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DISSERTATION

# The Risk of Developing Subsequent Primary Malignancies among Adult Patients with Lymphatic and Haematopoietic Malignancies in Germany: A Pooled Analysis of Cancer Registry Data (1990–2011)

zur Erlangung des akademischen Grades

Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät

Charité – Universitätsmedizin Berlin

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Datum der Promotion: **10.03.2017**

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# Abstract

**Background:** The increased risk of subsequent primary malignancies (SPM) in survivors of adult lymphohaematopoietic malignancies (LHM) remains a challenging clinical problem worldwide. In Germany, no national estimates exist until now for this risk. Based on the recently pooled German cancer registry data, we provide here detailed and up-to-date estimates of this risk.

**Methods:** We calculated the standardized incidence ratio (SIR) and excess absolute risk (EAR) for developing SPM in adult patients diagnosed with first LHM (ICD-10 C81-C96, N=238,525) from 1990 to 2011 in 14 German federal states. Risks for each subgroup of LHM as a subsequent cancer following selected first cancers were also calculated. The results were compared with data (1992-2011) obtained from the US Surveillance, Epidemiology, and End Results-program. Risks were compared across different groups of sex, age, latency and calendar periods of diagnosis (1990-2000 vs. 2001-2011).

**Results:** The SIR of any SPM was significantly increased: over twofold for Hodgkin lymphoma (HL), 1.5-fold for each non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukaemia (CLL), 1.4-fold for chronic myeloid leukaemia (CML), and 1.1-fold for multiple myeloma (MM) survivors. The EARs ranged from 15 to 68 excess SPM cases/10,000 person-years after MM and CLL, respectively. Overall, SIRs did not vary by gender, but were highest (7- to 10-fold) in patients below 30 years of age upon first diagnosis, within the first year of diagnosis, and the earlier calendar period. For solid SPM, overall SIRs were significantly elevated between 7% after MM and 79% after HL. Increased SIRs (≥1.5-fold) were found for several SPM after HL, NHL and CLL including cancers of the oropharynx, stomach, colon/rectum, thyroid, lung, skin melanoma, breast and kidney. Only NHL survivors were at significantly increased risk for liver, pancreas, testis, and brain. Following MM and CML, SIRs were only significantly elevated for oropharynx, melanoma, and kidney. For certain SPM, SIRs remained significantly elevated more than 10 years after HL and NHL diagnosis. Positive reciprocal associations were demonstrated between all LHM and several solid cancers underlined above. Recent US data showed overall SIRs to be slightly lower after all first malignancies, but patterns of risk were largely comparable to the German data.

**Conclusions:** The updated German data showed an increased risk of SPM in long-term survivors of adult LHM compared to the general population, particularly when diagnosed at a young age. Beside treatment effects, the reciprocal risks of lymphoid malignancies with some solid cancers suggest common etiologic factors.

# Zusammenfassung

**Hintergrund:** Das erhöhte Risiko von Zweitmalignomen (SPM) bei Erwachsenen mit lymphohämatopoetischen Malignomen (LHM) stellt weltweit nach wie vor ein schwieriges klinisches Problem dar. Für Deutschland existieren bislang noch keine nationalen Schätzungen zu diesem Risiko. Dieser Beitrag präsentiert aktuelle und detaillierte Risiko-Schätzungen auf der Basis gepoolter bundesdeutscher epidemiologischer Krebsregisterdaten.

**Methoden:** Zur Bewertung des Risikos für SPM wurden standardisierte Inzidenzquotienten (SIR) und die absolute Riskoerhöhung (EAR) für Erwachsene berechnet, bei denen zwischen 1990 und 2011 in 14 deutschen Bundesländern zunächst ein erstes LHM (ICD-10 C81-C96, N=238.525) diagnostiziert wurde. Das Risiko für LHM als Zweitmalignom nach ausgewählten Tumorerkrankungen wurde ebenfalls berechnet. Die Ergebnisse wurden mit Daten (1992-2011) aus dem „Surveillance, Epidemiologie und End Results"-Programm der USA nach Geschlecht, Alter, Latenzzeit und Kalenderperioden der Diagnose (1990-2000 vs. 2001-2011) verglichen.

**Ergebnisse:** Der SIR für SPM nach LHM war signifikant erhöht: über das Zweifache für Hodgkin-Lymphome (HL), 1,5-fach für Non-Hodgkin-Lymphome (NHL) und chronische lymphatische Leukämien (CLL), 1,4-fach für chronische myeloische Leukämien (CML), und 1,1-fach für Multiple Myelome (MM). Die EARs betrugen zwischen 15 (nach MM) und 68 (nach CLL) zusätzliche SPM-Fälle pro 10.000 Personenjahre. Hinsichtlich der SIRs konnten keine wesentlichen Geschlechts-Unterschiede beobachtet werden. Die Indikatoren waren am höchsten (7- bis 10-fach) bei Patienten unter 30 Jahren zum Zeitpunkt der ersten Diagnose, innerhalb des ersten Jahres nach Diagnose und der früheren Kalenderperiode. Für solide SPM waren die SIRs insgesamt signifikant erhöht zwischen 7% nach MM und 79% nach HL. Erhöhte SIRs (≥1,5-fach) wurden für mehrere SPM nach HL, NHL und CLL festgestellt, einschließlich Krebserkrankungen des Mund/Rachenraums, des Magens, des Dickdarm/Mastdarms, der Schilddrüse, der Lunge, des Haut-Melanoms, der Brust und der Nieren. Nur NHL-Überlebende hatten ein signifikant erhöhtes Risiko für Leber-, Pankreas-, Hoden- und bösartige Hirntumore. Nach MM und CML waren SIRs nur signifikant erhöht für Krebserkrankungen von Mundhöhle/Rachen, malignes Melanom und Nierenkrebs. Für bestimmte SPM blieben SIRs deutlich mehr als 10 Jahren nach HL- und NHL-Diagnose erhöht. Positive beiderseitige Assoziationen wurden zwischen allen LHM und den oben unterstrichenen soliden Tumoren gefunden. In den aktuellen USA-Daten zeigen sich insgesamt etwas geringere SIRs nach allen ersten malignen Erkrankungen, die Risikomuster waren jedoch weitgehend vergleichbar mit den hier untersuchten deutschen Daten.

**Schlussfolgerungen:** Die aktuellen deutschen Krebsregisterdaten zeigen ein erhöhtes Risiko von SPM bei langzeitüberlebenden Erwachsenen mit einem LHM im Vergleich zur allgemeinen Bevölkerung, besonders bei im jüngeren Alter Diagnostizierten. Neben Behandlungseffekten werden gemeinsame ätiologische Faktoren als Ursache für die wechselseitigen Risiken zwischen malignen Lymphomen und einigen soliden Tumoren vermutet.

# Introduction

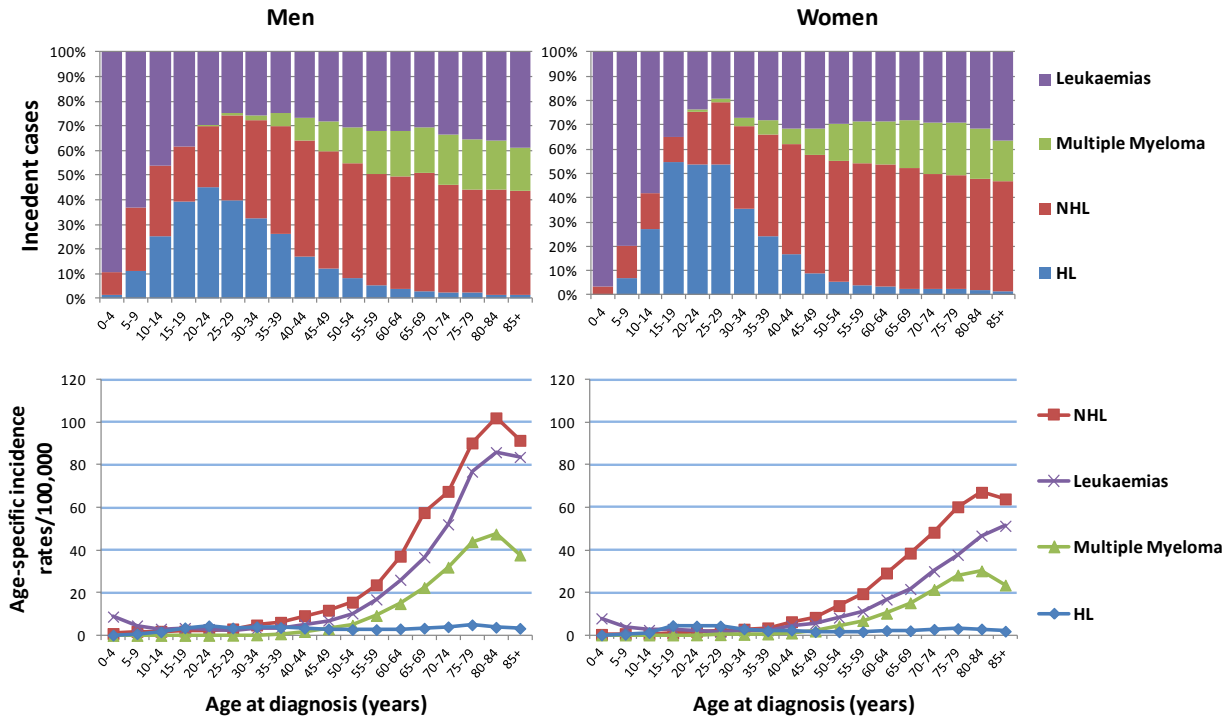
## Lymphatic and haematopoietic malignancies: an epidemiological overview

In Germany, cancer remains the second most common cause of death after cardiovascular diseases and represents 25% of all deaths [1]. An estimated 477,300 new cancer cases, excluding non-melanoma skin cancer, and approximately 218,258 deaths caused by cancer occur yearly in Germany [2]. According to the most recent incidence estimation for Germany, every second man or woman is expected to develop cancer within their lifespan. As a consequence of the increasing number of aged persons in Germany, the number of new cancer cases has increased by approximately 21% in men and by 14% in women between 2000 and 2010. This increase was also associated with a slight rise in the number of deaths from cancer by almost 8% among men during the same time period, but remained largely unchanged among women. With the exception of liver cancer in men and lung and vulvar cancers in women, age-standardized mortality rates have been declining for many cancer types in both genders as a result of improvements in life-expectancy and survival prospects of cancer patients over the recent years. As recently estimated, using most recent data for the period 2009-2010, more than half (>60%) of German cancer patients are expected to survive at least 5 years following diagnosis [2] compared to patient survival rates (<50%) three decades earlier.

Lymphatic and haematopoietic malignancies (LHM, ICD-10 C81-C96) are among the top 20 most common cancers and most common causes of cancer deaths in Germany. They account for over 7% of all new cancer cases and almost 8% of deaths due to cancer estimated to occur in both sexes after 15 years of age, which is relatively small compared with the proportions of other common cancers such as breast, prostate, lung, and colon and rectum [2]. In 2010, almost 36,130 cases were newly diagnosed with LHM, and of these, 17,396 died following diagnosis. Malignancies of the haematopoietic and lymphoid system constitute a complex type of cancer with diverse entities each has a different incidence, aetiology, clinical, histological and biological features, and, thus, variable treatment options and prognosis [3]. For most types, the main causes are primarily unknown. Hodgkin lymphoma (HL) is less frequent compared with other LHM but is very common in young adults, with most cases diagnosed before 50 years of age (**Figure 1** and **Figure 2**). Among all LHM in adults, HL is the most curable cancer with the most favourable prognosis, particularly if diagnosed and treated during the early stages (**Figure 3**). By contrast, non-Hodgkin lymphoma (NHL) is the most common type of LHM in adults, accounting for almost 45% of cases, but has a poorer prognosis that primarily depends on the histological type and grade of the disease. Some subtypes of NHL can now be cured with modern treatments

including aggressive lymphomas. Survival chances for multiple myeloma (MM) and some leukaemia forms such as chronic myeloid leukaemia (CML) are rather poor, and there is no cure even following allogeneic or autologous stem cell transplantation (SCT).

**Figure 1. Age-specific incidence according to type of primary LHM and sex, Germany, 2009–2010**

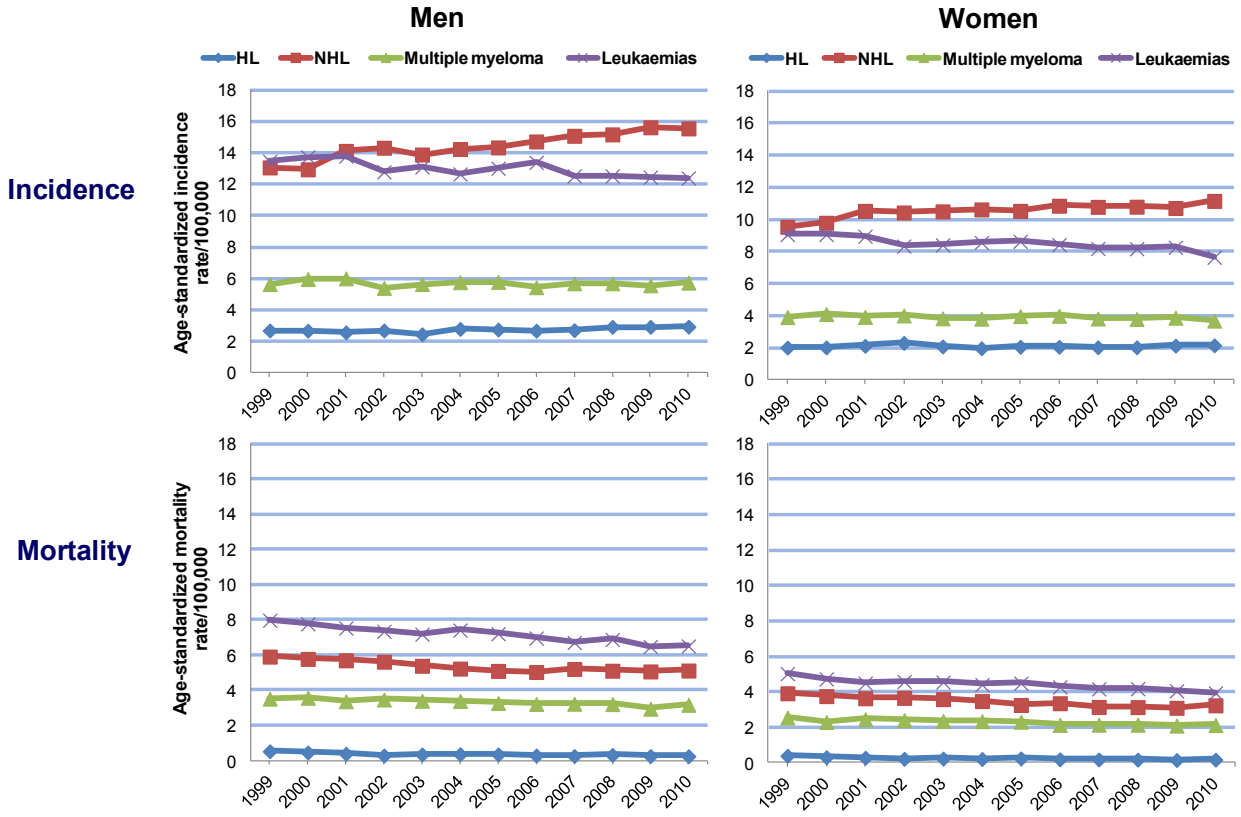



LHM: Lymphohaematopoietic malignancies; NHL: non-Hodgkin lymphoma; HL: Hodgkin lymphoma.
Source: Cancer in Germany 2009/2010 [2].

The temporal trends of age-standardized incidence rates of all subgroups of LHM appear to be constant over time, whereas incidence rates of NHL have been steadily increasing in Germany since the end of the 1990s (**Figure 2**). The increase in incidence cannot be entirely explained by improvements in diagnostic technologies and changes in the classification of NHL [4]. The age-standardized mortality rates of all subgroups have been declining over the last 10 years due to advances in diagnostic techniques and anti-cancer therapies, which have considerably improved survival rates, particularly after the introduction of radiotherapy and chemotherapy procedures in the 1960s and 1970s. The current standard initial treatment regimens for most LHM generally comprise of combinations of chemotherapies that are administered with or without radiation therapy for several months [5]. Treatment with high-dose chemotherapy (HDCT) followed by

autologous or allogeneic SCT is applied for most relapsed/refractory cases as a second line of treatment, but may also be considered as the first line of treatment for newly diagnosed cases with aggressive lymphomas. Salvage therapies are also administered for some cases to mobilize haematopoietic stem cells prior to HDCT and SCT. In MM and CML, maintenance therapy is also used to prevent disease progression.

**Figure 2. Time trend of age-standardized incidence and mortality rates according to type of primary LHM and sex, Germany, 1999–2010**



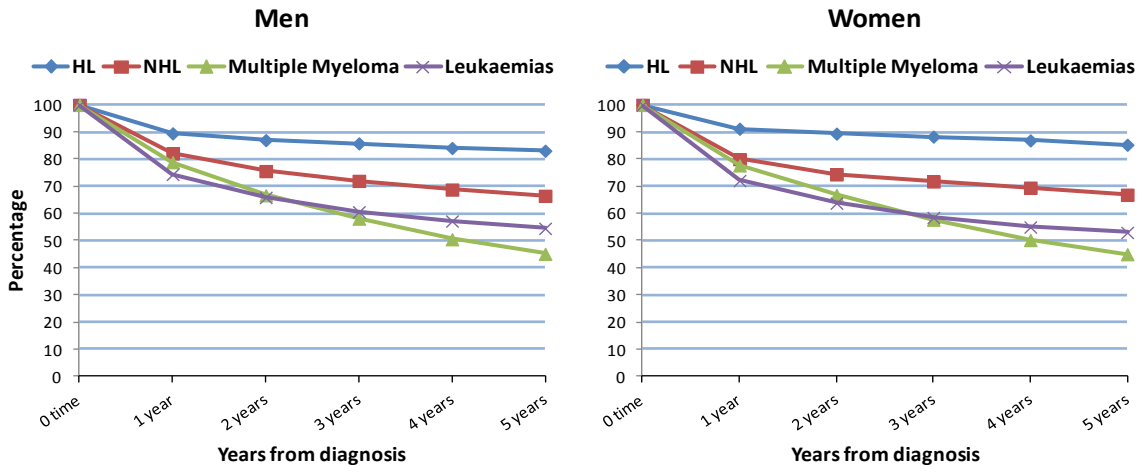

LHM: Lymphohaematopoietic malignancies; NHL: non-Hodgkin lymphoma; HL: Hodgkin lymphoma.
Source: Cancer in Germany 2009/2010 [2].

## Epidemiology of subsequent primary malignancies

There have been significant developments in cancer treatment, particularly LHM, over the past decades with substantial changes in treatment occurring in the late 1990s [6]. Chemotherapy regimens for HL have been changed from nitrogen mustard-based MOPP chemotherapy (combination of mechlorethamine, vincristine, procarbazine, and prednisone) to more effective regimens such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and recently etoposide-based BEACOPP chemotherapy (bleomycin, etoposide, doxorubicin,

cyclophosphamide, vincristine, procarbazine, and prednisone) for advanced HL [7, 8]. In the treatment protocols for chronic lymphocytic leukaemia (CLL), initial therapy has been changed from chlorambucil to nucleoside analogues (fludarabine/pentostatin/cladribine) that are usually administered in combination with alkylating agents such as cyclophosphamide (e.g. FC) [6]. For some NHL types, CVP (cyclophosphamide, vincristine, and prednisone) or CHOP chemotherapies (cyclophosphamide, doxorubicin, vincristine, and prednisone) were established in the 1970s as a standard initial treatment [6]. New regimens resulted in higher complete response (CR) rates and progression-free survival compared with previous combinations. Moreover, after the year 2000, the introduction of monoclonal antibodies (rituximab, anti-CD20 antibody), classically added to standard chemotherapy in the treatment of NHLs and CLL (R-CHOP, R-CVP, FCR) [6, 9], novel agents such as immunomodulatory drugs (IMiDs, thalidomide/lenalidomide/pomalidomide) and proteasome inhibitors (bortezomib/carfilzomib) in combination with melphalan and prednisone in MM treatment [5], as well as tyrosine-kinase inhibitors (TKIs, imatinib/dasatinib/nilotinib) in CML treatment [10, 11], have further improved the outcome of these malignancies and resulted in overall survival prolongation, which is the most important clinical goal in oncology. Over recent years, significant improvements in long-term population-based survival rates for lymphoma, myeloma, and leukaemia patients have also been reported [12–16]. Recent nationwide estimates of the 5-year relative survival in Germany [2] range from approximately 45% for male and female adult MM patients to 83% and 85% for male and female adult HL patients, respectively (**Figure 3**).

**Figure 3. Five-year relative survival rates (in percent) according to type of primary LHM and sex, Germany, 2009–2010**




LHM: Lymphohaematopoietic malignancies; NHL: non-Hodgkin lymphoma; HL: Hodgkin lymphoma. Source: Cancer in Germany 2009/2010 [2].

Although new therapies have improved survival rates, some of these therapies have been associated with an increased incidence of long-term toxicities, most importantly subsequent primary malignancies (SPM) that are now a major cause of morbidity among long-term survivors of LHM and have a large negative impact on survival [17–19]. Furthermore, some therapeutic regimens are associated with an increased incidence of a number of other long-term complications and most commonly include cardiovascular, pulmonary, neurologic, and endocrine dysfunctions, as well as infertility and psychiatric complications [20, 21].

As the survival rates of cancer patients continue to increase, the burden of SPM is expected to be higher and may constitute a major public health problem in the future, taking into account the projected increase in cancer incidence [2]. In the United States (US), it has been reported that the incidence of second cancers among adult cancer survivors has increased over the past four decades from 9% of all new cancer cases in 1975–1979 to 19% in 2005–2009 [22].

## Aetiology of subsequent primary malignancies

### *Treatment of first cancer*

Cancer treatment, primarily comprising chemotherapy, radiotherapy or hormonal therapy, has been demonstrated to be the major cause of an increased risk of SPM [23]. Radiotherapy for certain malignancies, particularly primary childhood malignancies, HL, and breast and testicular cancers, has long been recognized to induce carcinogenic changes via cell death and chromosomal damage in other normal tissues and organs, localized at or near radiation treatment fields due to direct or scatter radiation [24, 25]. Several secondary malignancies such as cancers of the thyroid, female breast, brain, non-melanoma skin, gastrointestinal tract, lung, urinary bladder, bone and soft tissues, and leukaemias have been attributed to therapeutic radiation exposure [25]. The risk appears following a long latency period of 10 years or more and depends on the dose and field of radiation, age of patient at exposure, sensitivity of organs under exposure, and interactions with other factors such as chemotherapy and genetics [26]. In addition to medical uses of ionizing radiations, exposure to atomic bomb irradiation has also been shown to be an important cause of an increased risk for most of these cancers [24]. Epidemiological studies of survivors of the atomic bombing in Japan have largely contributed to the understanding of the association of ionizing radiation with cancers in human populations [24, 27].

Several decades ago, cytotoxic therapy for cancer was demonstrated to be associated with an increased risk of acute myeloid leukaemia (AML)/myelodysplastic syndrome, the most lethal side effect of therapy, due to its myelosuppression and leukaemogenic potentials [17, 23, 26].

Chemotherapies such as alkylating agents (e.g. busulfan, carmustine, chlorambucil, cyclophosphamide, mechlorethamine, melphalan, and dihydroxybusulfan), topoisomerase II inhibitors (e.g. epipodophyllotoxins, etoposide, and teniposide), anthracyclines (e.g. doxorubicin), or antimetabolites (e.g. fludarabine and azathioprine) have been associated with an increased risk of therapy-related AML [23]. Furthermore, alkylating chemotherapy, alone or combined with radiotherapy, has been identified as a cause for the increased incidence of several secondary solid cancers such as stomach, lung, colon/rectum, bladder, bone sarcoma and thyroid [22, 28, 29]. The latency period for chemotherapy-induced cancers is relatively short (<10 years after treatment) and the risk for some SPM has been shown to be dose-dependent (e.g. AML). Recently, recipients of allogeneic and autologous haematopoietic stem cell transplantation (HCT), which are specifically offered to patients with high risk or refractory LHM, were shown to be at an increased risk of developing a number of secondary solid (e.g. melanoma) and haematological SPM compared with the general population [30, 31].

***Non-treatment related risk factors: host, lifestyle, and environment***

It has become apparent that the elevated risk for some specific types of secondary cancer cannot be solely explained by treatment effects. Several other potential risk factors for multiple primary malignancies have, therefore, been proposed besides long-term complications of treatment including shared immune defects, hormonal dysfunctions, genetic susceptibility and other host factors (age and sex), lifestyle (tobacco use, alcohol intake, or diet) or environmental risk factors (e.g. viral infections, sun exposure, contaminants, or occupational risks such as asbestos and radon), in addition to various interactions between these factors [29, 32]. A detailed overview of the influence of these factors has been recently reviewed by Travis and co-workers (2013) [23]. The aetiological role of gene-environment interactions of second cancers remains undefined; however, interaction between genetic susceptibility and treatment appears to be a key contributor to SPM in survivors of childhood cancer [22, 33]. On the other hand, the interaction between environmental and lifestyle risk factors appears to play a greater role among adult cancer survivors besides cancer therapies [22]. Interestingly, a recent study indicated that the proportion of second solid cancers attributed to radiotherapy in adult cancer survivors is relatively small (<10%), suggesting that a larger fraction of SPM may be due to other cancer risk factors [34].

Several epidemiological studies have reported on reciprocal associations among different groups of cancers, for example, tobacco-related cancers (oral cavity and pharynx, larynx, lung, pancreas, kidney, and urinary bladder) [35, 36] and hormone-related cancers (breast,

endometrial, ovarian, and colorectal cancers) [26, 37]. Additionally, several types of inherited neoplasms may present with multiple tumours that may develop either within the same organ (colon or skin), another organ pair (breast or ovary) of the first primary cancer, or in a different organ of the first primary cancer. For example, hereditary non-polyposis colon cancer (or Lynch syndrome) may be associated with gastric, pancreatic, small intestine, endometrial, ovarian, kidney, and urinary tract cancers. Li Fraumeni syndrome (a rare autosomal dominant hereditary syndrome involving germline mutation in the TP53 gene) has been shown to be associated with primary bone and soft tissue sarcoma, but is also associated with other primary cancers including breast, brain, urinary bladder, pancreatic, adrenocortical, gastrointestinal cancers, and leukaemia [26, 38]. Immune dysfunctions due to infection with human immunodeficiency virus or following organ transplantation have been described to be associated with an elevated risk of multiple infection-related malignancies such as NHL, Kaposi's sarcoma, HL, and melanoma [26], and reciprocal associations between these malignancies have also been reported in several studies [39, 40].

Moreover, surveillance effects (increased medical surveillance) require consideration when attempting to understand the associations between first and second primary cancers as, cancer patients are prone to accidental diagnosis of clinically inapparent cancers particularly during the initial medical diagnostic work-up. Nonetheless, differentiation between all of these risk factors poses a difficultly due to the potential overlapping nature.

**Subsequent primary malignancy risk reported by population-based cancer registries**

Currently, the increased risk of SPM is a significant and challenging clinical problem facing long-term cancer survivors worldwide. In general, cancer survivors are at a significantly higher risk (1.2- to 1.3-fold) of developing a new independent cancer when compared with the general population [26, 41].

Data from population-based cancer registries have been preferably used to quantify the SPM risk because of the very large populations of cancer patients in the regions under coverage and the longer period of follow-up, ensuring a more powerful and accurate risk estimation. Although data from most population-based cancer registries do not directly allow the assessment of the effects of cancer treatments, these data provide an opportunity to generate hypotheses concerning the late effects of therapies through specific statistical methods. Since the 1980s, several papers have been published from many international epidemiological cancer registries (see **Table 1** for selected studies). A number of these studies have documented the overall relative risk of

developing SPM following any first cancer diagnosis in addition to risks following specific cancer sites in multiple organ systems. The relative risk is usually statistically calculated as the ratio between the observed and expected SPM (O/E ratio) by applying general population incidence rates. The updated estimates of the overall relative risk (O/E ratio) of SPM in adult cancer survivors have been recently reported in several cancer registries from the US (National Cancer Institute's Surveillance, Epidemiology and End Results program, SEER) [22, 37], France [42], Italy (Italian Association of Cancer Registries, AIRTUM working group) [43], Australia [44, 45], and Japan [46], with 1.10- to 1.36-fold significantly increased risks compared with the general population.

Cancer registry-based studies have provided beneficial information to understand patterns of SPM risk via the ability of stratifying and comparing relative risks among different subgroups of patients according to their gender, age at diagnosis, follow-up length, and years of diagnosis, and in a few studies, by initial treatment categories with some limitations. Considerable variations in SPM risks have been reported with risks varying according to the first cancer type [42, 47], which was shown to predominantly depend on the age of the patients at diagnosis and prognosis of the first cancer, type of initial treatment(s), and other intrinsic factors related to the first cancer.

**Table 1. Overall relative risk of SPM in adult cancer survivors from selected population-based studies**

| Cancer registry (CR) data [ref.] | Study period | Prevalence of SPM (% of all cancer patients) | Overall O/E ratio | O/E ratio by sex | |
|---|---|---|---|---|---|
| | | | | Males | Females |
| Connecticut **[48]** | 1935–1982 | 6.6 | **1.31** | 1.19 | 1.42 |
| Finland **[49]** | 1953–1979 | - | - | **0.89** | **1.09** |
| Denmark **[50]** | 1943–1980 | 4 | **0.91** | - | - |
| England and Wales **[51]** | 1971–1981 | 3.3 | - | 0.77 | 0.80 |
| Switzerland (Vaud CR) **[52]** | 1974–1989 | 6.3 | **1.2** | **1.2** | **1.2** |
| Finland **[53]** | 1953–1991 | 4 | **1.12** | 1.0 | **1.25** |
| Italy (11CRs) **[54]** | 1980–1995 | 3.6 | **1.08** | - | - |
| Sweden **[55]** | 1958–1996 | 8.5 | - | **1.3** | **1.6** |
| USA (NCI 9 SEER) **[37]** | 1973–2000 | 9 | **1.14** | **1.11** | **1.17** |
| Australia (Victorian CR) **[44]** | 1982–2004 | M=11<br>F=9.4 | - | **1.03** | **1.26** |
| Australia (Queensland CR) **[45]** | 1982–2001 | 12 | - | **1.22** | **1.36** |
| Japan (Osaka CR) **[46]** | 1985–2004 | 3.8 | **1.21** | **1.17** | **1.31** |
| Italy (AIRTUM working group) **[43]** | 1976–2010 | 5.2 | **1.10** | **1.08** | **1.12** |
| France (10 CR) **[42]** | 1989–2004 | 7.3 | **1.36** | **1.38** | **1.32** |

SPM: subsequent primary malignancies; O/E: the ratio of observed to the expected number of subsequent malignancies.
Bold indicates a statistically significant O/E ratio (95% confidence interval did not include the value 1, *P <0.05*).

In general, the elevated overall risk for SPM has been frequently reported to be high following initial adult-onset cancers such as oral cavity/pharynx, larynx, lung, melanoma, thyroid, female breast, cervix, ovary, urinary bladder, colon/rectum, testis, and HL. Conversely, risks for SPM have been consistently shown to be reduced following cancers with low survival rates such as cancers originating in the pancreas, liver, and central nervous system (CNS)/brain [42, 43, 45, 46], possibly due to insufficient time at risk to develop SPM. In addition, significant differences in relative risks according to the age of patients with specific initial cancers have also been observed. The highest O/E ratios (ranged from 2- to 6-fold) were frequently reported for survivors of cancer of any type first diagnosed at a younger age (under 30 years) and lowest O/E ratios (1 or less) were reported for survivors first diagnosed at 70 years or older [22, 37].

## Research problem

In addition to the population-based studies depicted in **Table 1**, numerous studies have investigated the relative risks of developing SPM and have focused on the follow-up of survivors of adult-onset LHM. Significant contributions have been generally made by the US SEER program published reports [56–59], international multicentre studies [39], and the North American and European collaborative studies [60–66]. National and population-based cancer registry data were also reported from France [67], Sweden [68–71], Denmark [72–74], and Australia [75–77]. Among LHM, primary HL as a first cancer has been extensively investigated due to the early age of disease onset and the very favourable prognosis following treatment, allowing for longer follow-up periods throughout the patient's lifetime to precisely estimate long-term SPM risks.

A national report on SPM in childhood cancer survivors, including lymphoma and leukaemia, has been recently published by the German Childhood Cancer Registry [78, 79]. Until now, there has been no comprehensive national report on the risk of developing SPM in survivors of adult-onset LHM in Germany. Adult LHM survivors are expected to have different risk patterns compared with survivors of childhood LHM, particularly as treatment strategies are fundamentally different [5] and because of, as described above, variations in exposure to other risk factors [22].

Previous epidemiological studies, particularly the more recent ones, have demonstrated that long-term survivors of adult LHM are at an increased risk of developing SPM relative to the general population. Among lymphoma patients, the relative risk has been reported to reach to 2- to 4-fold higher compared with the general population [22, 66, 77, 80]. Relatively little data exists on SPM after diagnosis and treatment of other subtypes of LHM in adults such as MM and leukaemia. The relative risks of SPM after adult-onset MM and leukaemia appeared to be lower

(not exceeding 2-fold) than after lymphoma [37, 45, 59, 68], and is possibly influenced by lower survival, which affects time under risk for SPM.

Recent studies have suggested that several new types of therapies for LHM (primarily introduced after the year 2000) are associated with an increased incidence of SPM [8, 30, 67, 81–85] in adult survivors. Very few population-based studies have examined the change in risk (O/E ratios) of SPM over time [39, 72, 81] and very little is known on the temporal trend of SPM risk over the recent periods of diagnosis [59, 73, 81] to indirectly assess whether the use of new therapies is associated with an increased SPM incidence.

To examine the hypothesis of shared risk factors, population-based studies also provide a useful means of indirectly assessing the association between two cancer types via the assessment of reciprocal risks (bidirectional increased risk between two cancer sites). Common risk factors would be plausible if there is a positive bidirectional association between the first and second malignancy, which should be relatively stable over the complete follow-up period, whereas treatment effects appear likely if the association is unidirectional. The effect of chemotherapy (as a first-line treatment) may peak between 5 and 10 years, while effects of radiotherapy or any second-line or third-line therapy have a tendency to appear beyond 10 years following initial diagnosis and remain high [86].

Accordingly, many reports on SPM following different types of LHM pointed towards the reciprocal risk between HL and NHL [68, 77, 80], suggesting common aetiologies such as immune dysfunctions alongside treatment effects. However, there is little information available on reciprocal associations between these two lymphoma types and other cancers [37, 39], and also between MM or leukaemia and other cancers. On the other hand, some associations are, at times, difficult to explain by merely hypothesizing shared risk factors or treatment. For example, reciprocal associations between lymphoma, particularly NHL, and skin cancer (both melanoma and non-melanoma) have been consistently found in several epidemiological studies [37, 39, 87, 88], and a common mechanism related to immune suppression or exposure to ultraviolet radiations (UVR) has been suggested. However, a protective effect of UVR, a known risk factor for melanoma, was later demonstrated against lymphoma [89]. Furthermore, unidirectional associations should be interpreted carefully, as the time lag between exposure to a certain risk factor and cancer development may vary for different cancer types (haematological vs. solid).

## Study purposes and implications

The most important aim of this study was to provide detailed and up-to-date estimates of the risk of developing SPM amongst adult survivors of different types of LHM, utilising the recently pooled German cancer registry database. We analysed the relative and absolute excess risks of developing SPM by patients' sex and age at first diagnosis, length of follow-up, and calendar period of first cancer diagnosis to identify factors associated with increased SPM risk. The large German cancer registry database has also enabled us to further analyse the relative and absolute excess risks by type of SPM. Assessment of the excess absolute risk for each specific type of SPM may also possibly influence the decision regarding the type of follow-up care required in clinical practice [90]. Additionally, we addressed the association of different forms of LHM (lymphoma, myeloma, and leukaemia) with other cancers, particularly solid cancers, via estimation of the reciprocal relative risks. These associations have not received particular attention in previous epidemiological studies. This type of analysis is of clinical significance, as it may aid in better understanding the nature of these types of malignancies. Moreover, in the current study, we analysed the large and recent US SEER program cancer registry dataset to compare the relative risks of SPM following HL, NHL, myeloma, and chronic leukaemias in Germany with that in the US. Follow-up studies play a key role in the development of preventive and therapeutic strategies for the management and control of cancer. The present follow-up study provides a more detailed assessment of long-term SPM risks in a subset of patients with LHM that may assist oncologists and public health professionals in decision-making regarding required preventive measures, screening and therapeutic strategies to reduce the clinical burden of SPM in these survivors.

## Aims of the present thesis

### General objective

To estimate the risk of developing SPM (including a second or more primary cancers) among adult survivors of lymphatic and haematopoietic malignancies (LHM), utilising the recent national German cancer registry database.

### Specific objectives

- To determine the overall observed number (incidence), and the relative and absolute excess risks of SPM that develop after diagnosis of first HL, NHL, myeloma, and leukaemia.
- To study the distribution of observed SPM, and the relative and absolute excess risks by sex and age to determine any sex- or age-specific differences in risks among each subgroup with first primary HL, NHL, myeloma, and leukaemia.
- To analyse the observed numbers, and the relative and absolute excess risks of SPM after each subgroup of HL, NHL, myeloma, and leukaemia by the SPM type.
- To determine changes in risks (overall and site-specific) of SPM with increasing follow-up time after diagnosis (the latency time) of first primary HL, NHL, myeloma, and leukaemia.
- To determine temporal changes in risks (overall and site-specific) of SPM over time periods of diagnosis of each first cancer.
- To evaluate the relative risk of developing each subgroup of HL, NHL, myeloma, and leukaemia as a subsequent malignancy following other first cancers to assess whether positive reciprocal associations exist.
- To analyse the relative risks of SPM following each subgroup of first primary HL, NHL, myeloma, and leukaemia by the German epidemiologic cancer registry to assess regional variations in risks and to evaluate the quality of data.
- To compare overall results in Germany with results from the recent population-based cancer incidence data in the US.

# Methodology

## Data source

The database used in the present analysis was obtained from the German Centre for Cancer Registry Data (ZfKD). After the Federal Cancer Registry Data Act (Bundeskrebsregisterdatengesetz – BKRG) came into force in August 2009, the ZfKD was established as an independent division within the Robert Koch Institute (RKI), the German national public health institute. Since its establishment in 2010 [2], the centre annually collects anonymized cancer incidence and survival data from all federal states' cancer registries. It regularly publishes figures on nationwide cancer incidence, mortality and survival rates on its website (www. krebsdaten.de), and in the biannual report 'Cancer in Germany' (together with the Association of Population-based Cancer Registries in Germany – GEKID).

The registration now covers 100% of the total German population (about 82 million). The cancer registry in the federal state of Saarland has been continuously performing population-based cancer registration since 1967, while most of the remaining federal states in Germany followed between 1990 and 2009 [91]. The ZfKD annually estimates the degree of capture of new cancer cases in the German cancer registries (completeness of registration) which is a very important measure of data quality. The estimation of completeness is based on the mortality / incidence ratio (M / I index) [92], an internationally accepted method. Currently, the total completeness of cancer registration (all cancer sites) is 91% on average. This estimate varies across German registries from 70% to 100% (**Table 2**) for the year 2011, with nine federal states estimated to have over 90% completeness level. Data from seven German cancer registries were presented in the last edition of the World Health Organization (WHO)/International Agency for Research on Cancer (IARC) "Cancer Incidence in Five Continents" monograph.

Information that is routinely collected by epidemiologic cancer registries includes patient's date of birth, sex, date and site of diagnosis of primary cancer (according to 10$^{th}$ revision of the WHO International Classification of Disease, ICD-10 site codes), primary cancer morphology (according to the third edition of the International Classification of Diseases for Oncology, ICD-O-3 codes), type of diagnosis confirmation, cancer grade and stage, type of initial treatment, date and site of diagnosis of other cancers (ICD-10). Information on vital status and date of death is also obtained, as these data are routinely linked with the death certificate through record linkage in each region.

Data on 6,826,671 new cancer cases (up to 2011) were available; of these 360,587 cases were lymphohaematopoietic malignancies (LHM, ICD-10 C81-C96). In 2011, approximately 70% of all cases with LHM were microscopically/histologically confirmed as primary malignant tumour, and 16% were registered only from death certificate (DCO) sources. Details by cancer registry can be seen in **Table 2**.

**Table 2. Population-based cancer registries in Germany and data quality indicators**

| | Region | Symbol | Years of start registration | Years included in the analysis of second cancers | Follow-up years | Estimated completeness 2011* (all cancer sites) | Estimated completeness 2011* (C81-C96 group) | DCO 2011 (C81-C96 group) | Microscopically confirmed cases 2011 (C81-C96 group) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Schleswig-Holstein | SH | 1998 | 1998-2011 | 13 | 98% | 109% | 20% | 77% |
| 2 | Hamburg | HH | 1926 | 1990-2011 | 21 | 105% | 115% | 1% | 96% |
| 3 | Lower Saxony | NI | 2000 | 2003-2011 | 8 | 98% | 97% | 12% | 69% |
| 4 | Bremen | HB | 1998 | 1998-2011 | 13 | 98% | 104.35% | 6% | 93% |
| 55 | North Rhine-Westphalia (Muenster) | Muenster | 1986 | 1990-2011 | 21 | 102% | 98% | 10% | 71% |
| 5 | North Rhine-Westphalia (without Muenster) | NRW | 2005 | 2006-2011 | 5 | 95%-100% ** | 72%-84% | 20% | 65% |
| 6 | Hesse | HE | 2003/2007*** | -- | -- | 76% | 54% | 45% | 54% |
| 7 | Rhineland-Palatinate | RP | 1997 | 1998-2011 | 13 | 87% | 70% | 24% | 71% |
| 8 | Baden-Wuerttemberg | BW | 2009 | -- | -- | 70% | 64% | 0% | 35% |
| 9 | Bavaria | BY | 1998 | 2002-2011 | 9 | 95% | 84% | 16% | 79% |
| 10 | Saarland | SL | 1967 | 1990-2011 | 21 | 89% | 84% | 8% | 87% |
| 11 | Berlin (GKR)***** | BE | 1953/1995**** | 1995-2011 | 16 | 86% | 64% | 24% | 75% |
| 12 | Brandenburg (GKR) | BB | 1953 | 1995-2011 | 16 | 93% | 76% | 12% | 81% |
| 13 | Mecklenburg-Western Pomerania (GKR) | MV | 1953 | 1995-2011 | 16 | 88% | 84% | 13% | 86% |
| 14 | Saxony (GKR) | SN | 1953 | 1995-2011 | 16 | 96% | 94% | 10% | 88% |
| 15 | Saxony-Anhalt (GKR) | ST | 1953 | 1995-2011 | 16 | 75% | 64% | 24% | 75% |
| 16 | Thuringia (GKR) | TH | 1953 | 1995-2011 | 16 | 90% | 82% | 13% | 86 |
| | **Pooled data** | | | **1990-2011** | **5-21** | **91%** | **83%** | **16%** | **70%** |

* Degree of completeness for all cancer sites (ICD-10 C00-C97 without C44) and for all haematological malignancies (C81-C96). The presented percentage in each registry represents an average value of estimated completeness for males and females. The data was obtained from the RKI yearly sex-specific completeness estimation done according to law by the ZfKD.
**The average value for Detmold/Arnsberg and Duesseldorf/Cologne in North Rhine-Westphalia.
***2003 Darmstadt district, 2007 entire Hesse.
****1953 East Berlin, 1995 entire Berlin.
***** Common Cancer Registry (Gemeinsames Krebsregister) of the states: Berlin, Brandenburg, Mecklenburg-Western Pomerania, Saxony-Anhalt, Saxony and Thuringia.
Microscopically confirmed cases include both cytological and histological examination of tumours.
Source: Cancer in Germany 2009/2010 [2].

**Figure 4** shows cancer registries selected in the present study. Our analysis was based on data pooled from 15 German regions out of 9 different epidemiologic cancer registries. These registries comprise 65.697 million inhabitant representing 82% of the German population. Data from two newly established registries (Baden-Wuerttemberg and Hesse) were not included, as they did not have data on patients with a follow-up time of 5 years or more. The periods of

diagnosis varied by registry and were selected based on the years when the data was of good quality which is determined by completeness of registration for cancer overall (**Table 2**). Data from Saarland cancer registry, which are normally coded according to ICD-9, were converted to ICD-10 to avoid differences in coding between registries.

The routinely recorded information on the type of initial treatment is basic, and in some cancer registries it is incomplete, we therefore did not use information on therapy in this study. Similarly, information regarding stage at diagnosis of LHM is considered not complete for this analysis.

**Figure 4. German cancer registries included in the present study and selected years of registration**


## Multiple primary malignancies: definition and classification

The epidemiologic cancer registries in Germany apply the internationally standardized rules for coding multiple primary cancers as suggested by the IARC and the International Association of Cancer Registries (IACR) [93]. According to these rules, multiple primary cancers are defined as the diagnosis of two or more malignant tumours that are anatomically or morphologically different (regardless of the time passed between the diagnosis of the first and the later tumour) in the same person (**Appendix I**). Thus the new primary malignancy should not be a recurrence, extension or metastasis of the first cancer. Cancers arising in the same or paired organs must be counted as one single cancer unless they have been proven to have different histological

characteristics. Cancers of the lymphatic and hematopoietic system and other systemic (multicentric) cancers that involve many different organs such as Kaposi's sarcoma are exceptions, as they should be counted only once. For LHM, it is also possible that the same patient is registered with diagnosis of two different types of lymphoma because HL and NHL are considered histologically different and therefore counted as multiple primaries. Similarly, myeloid and lymphoid leukaemias are histologically different and thus counted as multiple tumours. In addition, within the NHL group, B-cell NHL differs histologically from T- or NK-cell NHL and should therefore be counted as multiple registrations in the same patient. The German cancer registries generally use the more detailed rules for coding multiple primaries of haematological malignancies of the National Cancer Institute's SEER program as recommended by the GEKID [94]. The pooled database in the current study was centrally checked for internal consistency. It was also verified that multiple primaries of haematological malignancies were accurately classified and coded by each cancer registry by applying the SEER-matrix [94].

## Study population

A defined cohort of 238,525 cancer patients, who had been diagnosed with first primary lymphoma, MM, and leukaemia during the period from 1990 to 2011, were examined (**Table 3**, **Table 4**, and **Figure 5**). Only patients aged 15 years or older were included. Neither in situ (D00-D09) nor benign tumours (D10-D36) or non-melanoma skin cancer (C44) incident cases were considered in the calculation of multiple primaries incidence. Cases reported to the cancer registries via DCO were also excluded from the overall analysis, as these cases usually lack any information on date of diagnosis.

**Table 3. Lymphoma, myeloma, and leukaemia patients' selection in Germany**

| Selection criteria | Cases up to 2011 |
|---|---|
| All invasive cancer cases in the database* | 6826671 |
| Only cases with lymphoma, myeloma, and leukaemia (C81-C96) | 360857 |
| After exclusion of ages <15 years old | 352572 |
| After the exclusion of DCO cases | 285748 |
| After the exclusion of HE and BW** | 271626 |
| After the exclusion of cancers diagnosed before 1990 | 265886 |
| After the exclusion of preceding tumours | 238525 |
| **Subjects included for final analysis** | **238525** |

* excluding non-melanoma skin cancer (C44), in situ and benign tumours (D-codes) incident cases.
**Hesse and Baden-Wuerttemberg cancer registries. DCO: death certificate only cases

**Table 4. Type of first primary malignancy included in the present study**

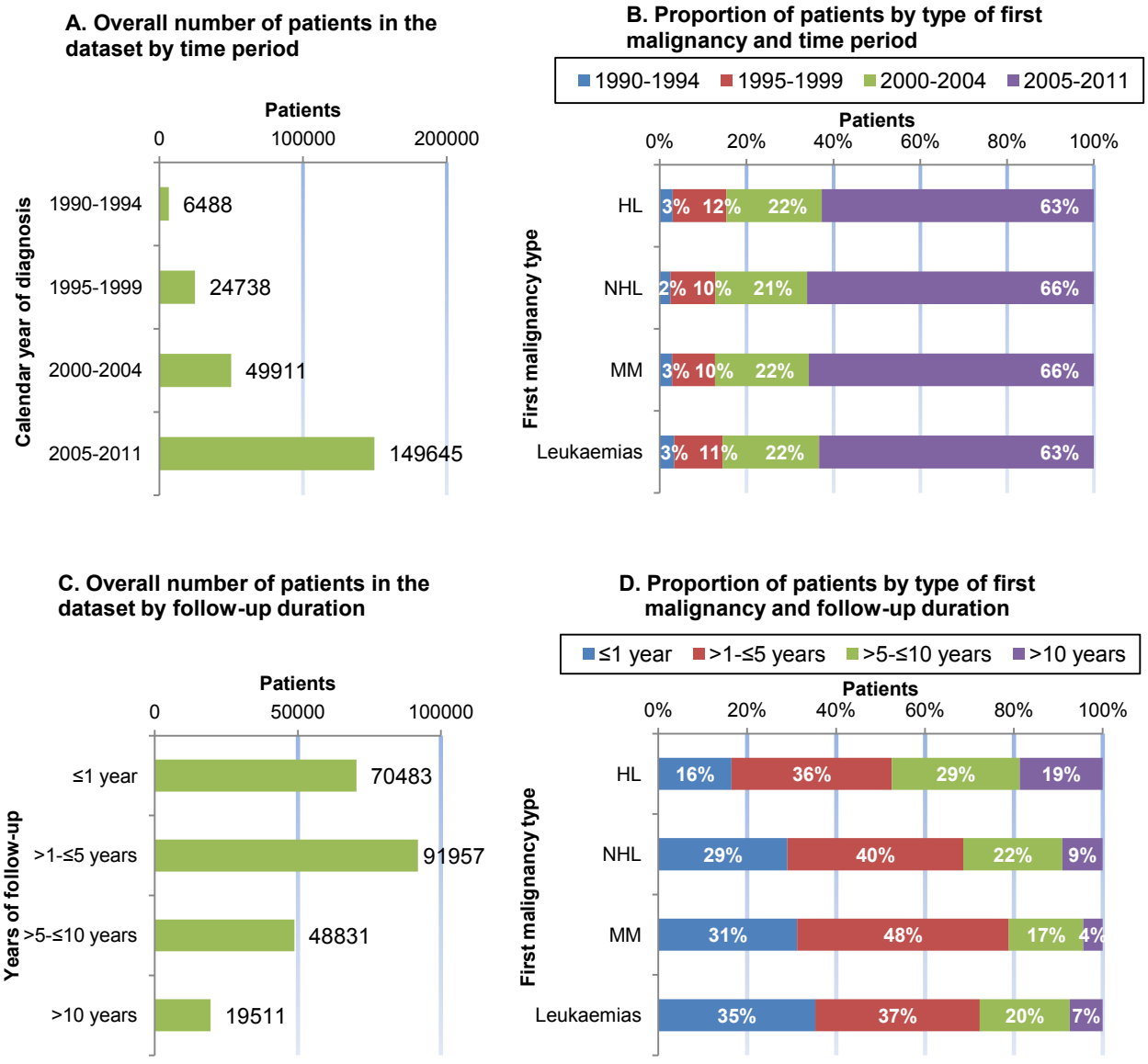
| First primary malignancy | Patients (%) | ICD-10 site code | ICD-O-3 morphology code |
|---|---|---|---|
| **Lymphoma, myeloma and leukaemia** | **238525 (100)** | **C81-C96** | **9590-9989** |
| **Lymphomas** | **118135 (49.53)** | **C81-C86** | **9590-9729** |
| Hodgkin lymphoma (HL) | 16826 (7.05) | C81 | 9650–9667 |
| Non-Hodgkin lymphoma (NHL) | 99829 (41.85) | C82-C85 | 9670-9729 |

**Table 4 continued**

| | | | |
|---|---|---|---|
| **Multiple myeloma (MM) or plasma cell neoplasm** | **39074 (16.38)** | **C90** | **9731-9734** |
| **Leukaemias** | **75053 (31.47)** | **C91-C95** | **9800-9948** |
| Lymphoid leukaemia (LL) | 38331 (16.07) | C91 | 9820-9837 |
| Acute lymphoblastic leukaemia (ALL) | 4132 (1.73) | C91.0 | |
| Chronic lymphocytic leukaemia (CLL) | 30878 (12.95) | C91.1 | |
| Myeloid leukaemia (ML) | 30518 (12.79) | C92 | 9840-9931 |
| Acute myeloblastic leukaemia (AML) | 16937 (7.10) | C92.0 | |
| Chronic myeloid leukaemia (CML) | 7900 (3.31) | C92.1 | |

ICD-10: 10th revision of the WHO International Classification of Disease.
ICD-O-3: 3rd edition of the WHO International classification of Diseases for Oncology.

**Figure 5. Characteristics of patients with first primary LHM (C81-C96), Germany (1990–2011)**




LHM: lymphohaematopoietic malignancies; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; MM: multiple myeloma.

## Study design and statistical analysis

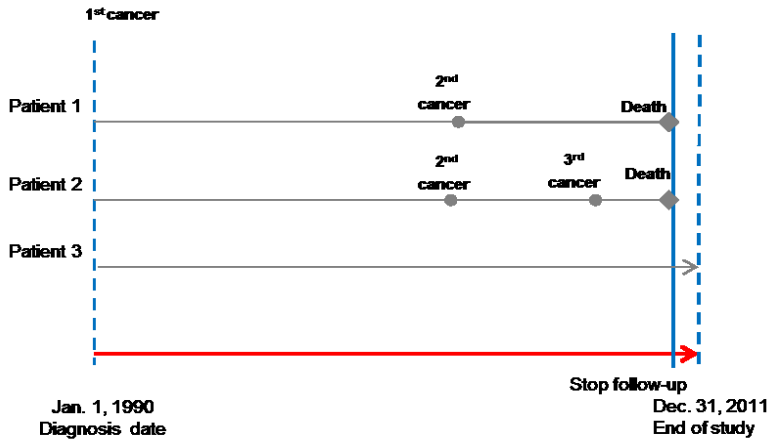
Following international studies, standardized incidence ratio (SIR) was used as a measure of relative risk of SPM which is generally calculated by indirect age-standardized method [95, 96]. The SIR (or O/E ratio) compares the observed number (O) of SPM in the cohort to the expected number (E) in the general population; assuming that patients with first primary cancer in the cohort and persons in the general population have similar cancer risks. The expected number of SPM cases was calculated by applying registry-, site-, sex-, age-, and calendar period-specific incidence rates in the general German population to the correspondingly stratified person-years at risk in the cohort according to the following formula:

$$\mathrm{SIR} = \frac{\sum_{j=1}^{J} \mathrm{O_j}}{\sum_{j=1}^{J} \mathrm{n_j} * \lambda_j} = \frac{\sum_{j=1}^{J} \mathrm{O_j}}{\sum_{j=1}^{J} \mathrm{E_j}} = \frac{\mathrm{O}}{\mathrm{E}}$$

**J**= stratum specific to site-, sex-, age-, and time period; $\mathbf{O_j}$= the observed numbers of cases of SPM in the jth cell of the J stratum; $\mathbf{E_j}$= the expected numbers of SPM for survivors in the jth cell of the J stratum; $\boldsymbol{\lambda_j}$= the population-based age-specific cancer incidence rates (from the reference German population) and **nj** = the person-years at risk in the jth cell of the J stratum.

To calculate the risk for all SPM (2nd, 3rd, 4th and more) in this cohort, the person-years at risk were accumulated for each person from the date of diagnosis of the first primary HL, NHL, MM, or leukaemia (January 1, 1990–2011) until date of death or the end of follow-up (December 31, 2011), whichever occurred first [96]. The observed number of SPM was similarly determined from the date of diagnosis of the first primary cancer to date of death or end of the study (**Figure 6**).

**Figure 6. Calculation of time at risk for subsequent malignancies**




Subsequent malignancies were ordered based on the date of the diagnosis. However, the date of diagnosis is recorded as the month and the year because cancer registries do not routinely register diagnosis day. The birthday, diagnosis day and death day were therefore approximated

to the 15th (middle) of the month for all cases in the dataset to facilitate the statistical computations. Missing data on month were substituted (imputed) to June (a value representing the middle of the year).

In contrast to many other studies, synchronous malignancies (i.e. concurrent or those diagnosed within two months of the first primary cancer) were included in our analysis. These cancers are usually excluded from data analyses to reduce the impact of detection bias (lead time bias), which is assumed to be high during the primary diagnostic work-up period of the initial cancer due to intense medical examinations. In fact, the effect of detection bias is not only limited to synchronous malignancies but it is also possible for metachronous malignancies (occurring after 2 months) because cancer patients undergo life-long medical examinations [38]. In addition, synchronous malignancies may also represent cancers that might have shared risk factors (e.g. genetic, tobacco smoking) which led to their simultaneous development. In our study, cancers diagnosed in the same month and year were randomly selected as being first or subsequent cancer. Unfortunately, there are no guidelines that help in determining which cancer is the first primary in this case [38].

The overall SIR for SPM (at any site) after HL, NHL, myeloma, or leukaemia was calculated from the registry-specific incidence rates of all cancer sites combined (C00–C97 without C44) in the general population. The SIRs for all solid SPM (C00–C75 without C44) and all haematological SPM (C81–C96) were similarly computed from the reference population rates.

The 95% confidence intervals (CI) of the SIRs were computed by assuming a Poisson distribution of the observed cases [95]:

Lower confidence limit:

$$SIR = \frac{O}{E} * \left(1 - \frac{1}{9 * O} - \frac{1.96}{\sqrt[3]{O}}\right)^3$$

Upper confidence limit:

$$SIR = \frac{O+1}{E} * \left(1 - \frac{1}{9 * (O+1)} + \frac{1.96}{\sqrt[3]{O+1}}\right)^3$$

Where **O=** the observed number of cases of SPM; **E=** the expected numbers of SPM; 1.96 is the $100_{\alpha}$ percentile of the standard normal distribution.

The excess or reduced relative risk is considered statistically significant if the CI does not include the value 1.00.

The excess absolute risk (EAR), another important measure of risk, was also calculated as the difference between observed and expected SPM cases (O - E) divided by the person-years at risk (excess number of cancer cases per 10,000 person-years). The EAR provides an accurate measure of the extent of excess morbidity and clinical burden of SPM.

The risk of developing SPM following the diagnosis of each first primary malignancy is described in detail in a specific section. Results on SPM following first primary of other/unspecified leukaemia forms (C93–C95, N=6,204), and other/unspecified malignancies of lymphoid, haematopoietic and related tissues (C96, N=6,263) are not presented specifically as the number of observed cases was not sufficient for the analysis. The observed number and SIRs of SPM are presented by the site of the SPM (24 sites sorted according to ICD-10 codes), sex, age at first primary diagnosis (15-44, 45-59, and ≥60 years), and years since diagnosis of first cancer (≤1 year, >1-≤5, >5-≤10, and >10 years). For the analysis of some specific first cancers, we combined the follow-up interval into wider categories (≤5 years or >5 years) due to the short follow-up time in some registries or small number of cases with longer follow-up. Sensitivity analysis was carried out by re-estimating the overall SIR after excluding SPM diagnosed in the two months and first year of follow-up.

To examine the SIR in relation to the calendar period of diagnosis (1990–2000 and 2001–2011), data from 4 population-based cancer registries were pooled (Hamburg, Muenster, Saarland, and GKR). These registries were selected based on the length of follow-up time (i.e. registries that started before the year 1996). In a separate chapter (**Pages 70–72**), comparison of SIRs among German epidemiologic cancer registries and results of sensitivity analysis are also shown.

We additionally evaluated the risk of developing HL, NHL, MM, CLL, and CML as a subsequent cancer following selected first cancers (solid and haematological) that had significantly elevated SIRs in the initial analysis. Thus, a trend of increase in risk with longer latency from diagnosis and a unidirectional increase in risk could indirectly indicate late side effects of therapy, whereas constantly elevated risk over time and bidirectional plausible associations (significantly elevated SIRs of a similar magnitude) could indirectly indicate common risk factors.

Further analysis was conducted for examining the relative risk of SPM following specific histological subtypes of first NHL. In particular, the updated Kiel classification [97] and the 2008 WHO classification of haematopoietic and lymphoid malignancies [3] (**Appendix II**) were used for classifying NHL as they take into account the grade of NHL (low-grade/indolent or high-grade/aggressive) and the type of cells (B- or T-cell), thus allowing comparisons to be made

among major NHL subgroups. The overall SIRs following more specific subtypes of NHL were also calculated when the number of cases was sufficient.

All statistical analyses were conducted by R software (version 3.2.2 [2015]) [98]. For comparison, we performed similar analyses using the most recent US cancer incidence data (1992–2011) from the SEER website. This data was pooled from 13 SEER cancer registries covering about 13.4% of the US population [99]. For this analysis (**Pages 73–84**), we used the SEER*STAT software (version 8.1.5 (Multiple Primary-SIR session)) [100].

## Ethical approval

Epidemiological cancer registration in Germany is regulated by law in each federal state, with case notification being mandatory in most states. Data transmission for the German Centre for Cancer Registry Data (ZfKD) is regulated by the National Law for Cancer Registry Data (BKRG). The BKRG provides for all analyses to be conducted as part of this thesis. Therefore, permission was not required from the German population-based registries. The study was based on anonymized cancer registry database, meaning that informed consent is not required as no individual patient was identified or contacted, and no individual data were directly linked to other data sources. The analyses follow the German guidelines for good epidemiological practice and good practice for analysis of secondary data.

# Results

## Subsequent malignancies following Hodgkin lymphoma (HL, C81)

### Descriptive statistics of patients with first primary HL

A total of 16,826 cases were registered with a diagnosis of HL as a first malignancy (56.5% were males) and were followed for 97,474.55 person-years between 1990 and 2011 (**Table 5**). About 75% of cases in HL cohort were aged less than 60 at the time of diagnosis. With a median follow-up time of 3.9 years in males and 4 years in females, a total of 953 (5.7%) SPM were observed after first HL diagnosis compared to 409.01 expected based on general population rates. The overall SIR for SPM at any site was 2.33 (95% CI=2.18–2.48) and the EAR was 55.81 cases per 10,000 person-years. Around 5% of patients had a second primary malignancy and 0.4% had two or more subsequent primaries. Overall, about 17% of the observed SPM occurred within two months of the first HL diagnosis, and 28% occurred during the first year.

**Table 5. Descriptive statistics of patients with first primary HL, Germany (1990–2011)**

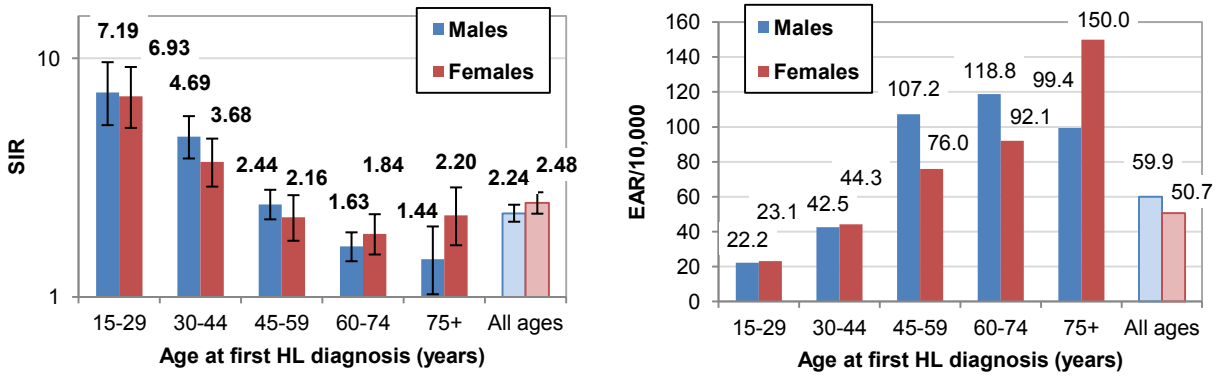
| | Males | | Females | | Total | |
|---|---|---|---|---|---|---|
| | Number | % | Number | % | Number | % |
| **Patients with first primary malignancy*** | **9499** | **100** | **7327** | **100** | **16826** | **100** |
| **Patients by age at first malignancy diagnosis** | | | | | | |
| 15-44 years old | 5291 | 55.70 | 4314 | 58.88 | 9605 | 57.08 |
| 45-59 years old | 2012 | 21.18 | 1046 | 14.28 | 3058 | 18.17 |
| 60-74 years old | 1650 | 17.37 | 1216 | 16.60 | 2866 | 17.03 |
| >75 years old | 546 | 5.75 | 751 | 10.25 | 1297 | 7.71 |
| **Patients by follow-up time** | | | | | | |
| ≤1 year | 1576 | 16.59 | 1194 | 16.30 | 2770 | 16.46 |
| >1 to ≤5 years | 3506 | 36.91 | 2561 | 34.95 | 6067 | 36.06 |
| >5 to ≤10 years | 2714 | 28.57 | 2130 | 29.07 | 4844 | 28.79 |
| >10 years | 1703 | 17.93 | 1442 | 19.68 | 3145 | 18.69 |
| **Patients with multiple primary malignancies** | | | | | | |
| 1 primary malignant tumour | 8960 | 94.33 | 6977 | 95.22 | 15937 | 94.72 |
| 2 primaries | 497 | 5.23 | 331 | 4.52 | 828 | 4.92 |
| 3 primaries | 39 | 0.41 | 19 | 0.26 | 58 | 0.34 |
| 4 or more primaries | 3 | 0.03 | 0 | 0.00 | 3 | 0.02 |
| **Person-years of observation** | **54065.79** | | **43408.76** | | **97474.55** | |
| **Median length of follow-up (years)** | | | | | | |
| **..All ages** | **3.87** | | **4.04** | | **-** | |
| 15-44 years old | 4.80 | | 5.21 | | - | |
| 45-59 years old | 3.63 | | 3.71 | | - | |
| 60-74 years old | 2.61 | | 2.61 | | - | |
| >75 years old | 0.81 | | 1.08 | | - | |
| **Observed number of subsequent malignancies** | **584** | **6.15** | **369** | **5.04** | **953** | **5.66** |
| Synchronous (<2 months)** | 99 | 16.95 | 65 | 17.62 | 164 | 17.21 |
| Metachronous (>2 months)** | 485 | 83.05 | 304 | 82.38 | 789 | 82.79 |
| **Expected number of subsequent malignancies** | **260.16** | | **148.85** | | **409.01** | |

HL: Hodgkin lymphoma.
*after excluding Death Certificate only (DCO) cases, preceding primary malignancies, and patients aged less than 15 years old
**after the diagnosis of the first primary malignant cancer

**Age-specific risks (15 years age group) of all subsequent malignancies by sex**

As **Figure 7** shows, the observed number of all SPM increased with increasing age at HL diagnosis and peaked at age 60-74 years in both women and men. However, the age-specific SIR was highest (7-fold) among survivors who were younger than 30 years old when first diagnosed with HL in both sexes, and decreased significantly with increasing age. The SIR of SPM remained however significantly elevated at age 75 years and older, and it was slightly higher in women compared to men. In addition, the estimated overall SIR for a subsequent malignancy was slightly higher in women than in men (2.48 vs. 2.24), but the difference was not statistically significant. The EAR was highest in men diagnosed with HL at ages 60-74 and women at age 75 years or older.

**Figure 7. Observed number, SIRs and EARs of all SPM by age at diagnosis of HL and sex**




**Observed number of SPM by age and sex**

| | 15-29 | 30-44 | 45-59 | 60-74 | 75+ | All ages |
|---|---|---|---|---|---|---|
| **Males** | 45 | 97 | 196 | 205 | 39 | 584 |
| **Females** | 48 | 76 | 84 | 107 | 53 | 369 |

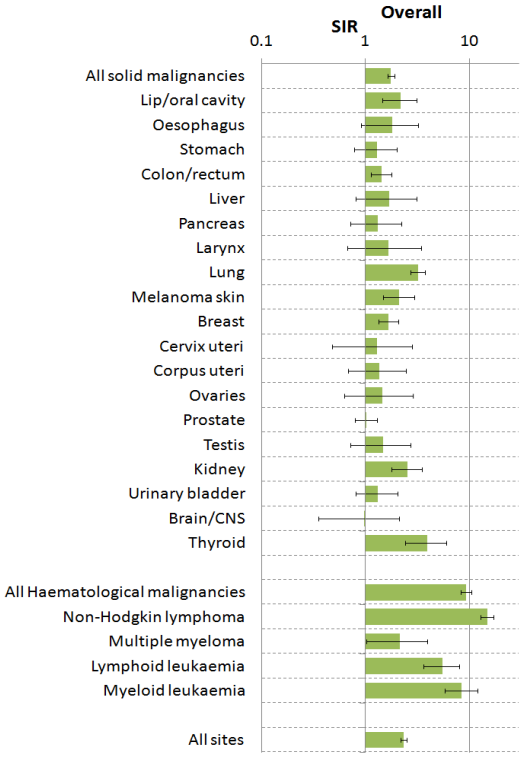
SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; EAR: excess absolute risk per 10,000 person-years; HL: Hodgkin lymphoma; SPM: subsequent primary malignancies.
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

**Site-specific risks by sex and age at first HL diagnosis**

A total of 653 (69%) solid malignancies occurred after first HL compared with 371.42 expected in the general population giving a statistically significant elevated SIR of 1.76 (95% CI=1.63–1.90) and EAR of 28.9/10,000 person-years in both sexes (**Figure 8**). About 87% of these cancers were metachronous (**Appendix III**, **Table 30**). The SIRs of all solid malignancies were slightly higher in females (1.90) than males (1.68), with both SIRs being significant. However, this variation was not observed to be statistically significant. In addition, there was a significant 9-fold

increase in the risk of developing other haematological SPM following HL in both sexes (SIR=9.29, 95% CI=8.23–10.43). In absolute numbers, SPM of lung, prostate, breast and colorectal cancers, and NHL were most frequently observed. Among solid malignancies, the highest EAR (10.65 cases/10,000 person per year) was found for subsequent lung cancer. For both sexes, SIRs were significantly elevated for subsequent NHL (14.91), ML (8.48, mainly due to AML), for cancers of the thyroid (3.93), lung (3.20), kidney (2.54), lip/oral cavity (2.17), skin melanoma (2.12), breast (1.67), and colon/rectum (1.42). A non-significant reduced risk was found for cancers of the brain/central nervous system (CNS). For some SPM, the SIRs were greatest (3- to 33-fold) among survivors who were younger than 45 years of age at HL diagnosis. These include: lip/oral cavity, stomach, colorectal, lung, kidney, melanoma, and breast cancers, NHL, myeloma and leukaemia all subtypes (**Figure 9** and **Table 28** in **Appendix III**). Subsequent risks for NHL, LL, and cancers of the lung and kidney were significantly high across all ages. Subsequent risk of LL and thyroid cancer seemed to be unrelated to the age of patients at time of first HL diagnosis.

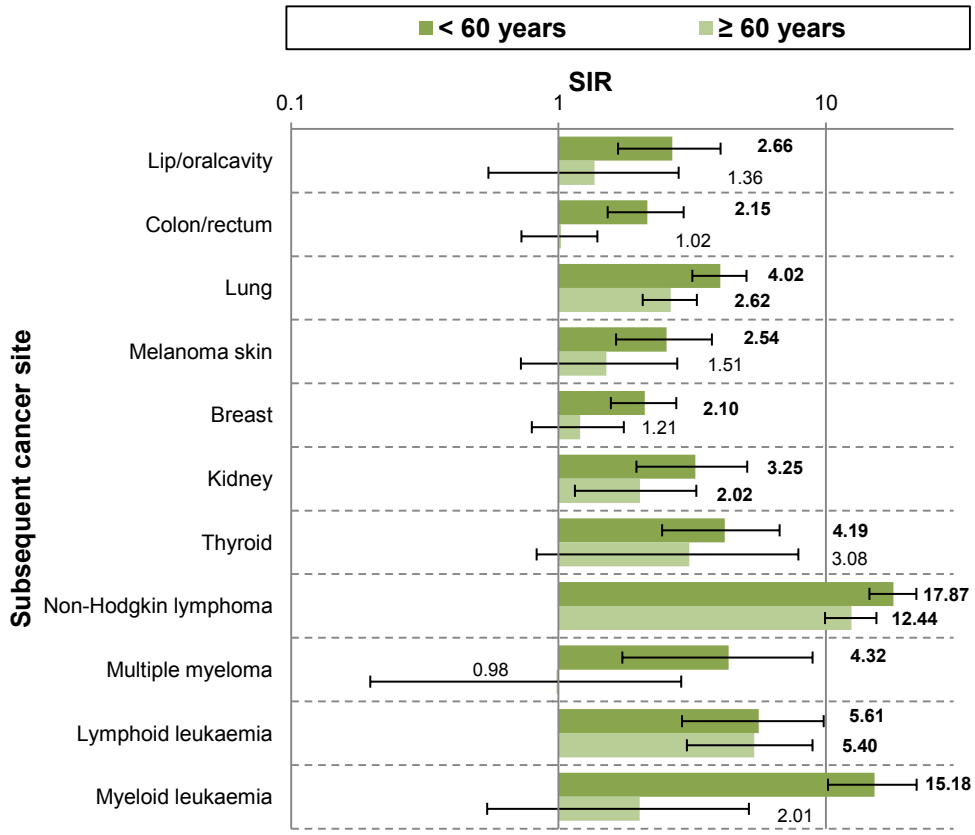
**Figure 8. Observed number, SIRs and EARs according to the type of SPM following HL by sex and overall**




| | Overall | | | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | SIR | O | EAR | O | SIR | 95% CI | EAR | O | SIR | 95% CI | EAR |
| All solid malignancies | **1.76** | 653 | 28.9 | 396 | **1.68** | **1.52-1.85** | 29.6 | 257 | **1.90** | **1.67-2.15** | 28.1 |
| Lip/oral cavity | **2.17** | 29 | 1.6 | 24 | **2.18** | **1.40-3.24** | 2.4 | 5 | 2.10 | 0.68-4.90 | 0.6 |
| Oesophagus | 1.81 | 11 | 0.5 | 8 | 1.53 | 0.66-3.01 | 0.5 | 3 | 3.57 | 0.72-10.44 | 0.5 |
| Stomach | 1.29 | 19 | 0.4 | 15 | 1.47 | 0.82-2.43 | 0.9 | 4 | 0.88 | 0.24-2.26 | -0.1 |
| Colon/rectum | **1.42** | 80 | 2.4 | 42 | 1.15 | 0.83-1.55 | 1.0 | 38 | **1.92** | **1.36-2.63** | 4.2 |
| Liver | 1.69 | 10 | 0.4 | 8 | 1.72 | 0.74-3.38 | 0.6 | 2 | 1.57 | 0.18-5.69 | 0.2 |
| Pancreas | 1.32 | 14 | 0.3 | 9 | 1.36 | 0.62-2.57 | 0.4 | 5 | 1.25 | 0.40-2.92 | 0.2 |
| Larynx | 1.67 | 7 | 0.3 | 7 | 1.81 | 0.72-3.73 | 0.6 | 0 | 0.00 | 0.00-11.47 | -0.1 |
| Lung | **3.20** | 151 | 10.6 | 122 | **3.26** | **2.71-3.90** | 15.7 | 29 | **2.95** | **1.97-4.23** | 4.4 |
| Melanoma skin | **2.12** | 35 | 1.9 | 16 | 1.69 | 0.96-2.74 | 1.2 | 19 | **2.71** | **1.63-4.24** | 2.8 |
| Breast | **1.67** | 79 | 3.3 | 0 | 0.00 | 0.00-6.32 | -0.1 | 79 | **1.70** | **1.34-2.11** | 7.5 |
| Cervix uteri | 1.30 | 6 | 0.1 | | | | | 6 | 1.30 | 0.47-2.82 | 0.3 |
| Corpus uteri | 1.37 | 11 | 0.3 | | | | | 11 | 1.37 | 0.68-2.45 | 0.7 |
| Ovaries | 1.46 | 8 | 0.3 | | | | | 8 | 1.46 | 0.63-2.87 | 0.6 |
| Prostate | 1.02 | 66 | 0.1 | 66 | 1.02 | 0.79-1.29 | 0.2 | | | | |
| Testis | 1.49 | 10 | 0.3 | 10 | 1.49 | 0.71-2.73 | 0.6 | | | | |
| Kidney | **2.54** | 35 | 2.2 | 19 | **1.92** | **1.15-3.00** | 1.7 | 16 | **4.10** | **2.34-6.66** | 2.8 |
| Urinary bladder | 1.32 | 20 | 0.5 | 19 | 1.54 | 0.93-2.40 | 1.2 | 1 | 0.35 | 0.00-1.96 | -0.4 |
| Brain/CNS | 0.97 | 6 | 0.0 | 5 | 1.23 | 0.40-2.88 | 0.2 | 1 | 0.47 | 0.01-2.60 | -0.3 |
| Thyroid | **3.93** | 21 | 1.6 | 9 | **4.74** | **2.16-8.99** | 1.3 | 12 | **3.48** | **1.80-6.08** | 2.0 |
| All Haematological malignancies | **9.29** | 282 | 25.8 | 176 | **9.05** | **7.76-10.49** | 29.0 | 106 | **9.71** | **7.95-11.74** | 21.9 |
| Non-Hodgkin lymphoma | **14.91** | 182 | 17.4 | 113 | **14.60** | **12.03-17.55** | 19.5 | 69 | **15.44** | **12.01-19.54** | 14.9 |
| Multiple myeloma | **2.14** | 10 | 0.5 | 9 | **2.98** | **1.36-5.66** | 1.1 | 1 | 0.61 | 0.01-3.37 | -0.2 |
| Lymphoid leukaemia | **5.49** | 27 | 2.3 | 18 | **5.28** | **3.13-8.34** | 2.7 | 9 | **5.96** | **2.72-11.32** | 1.7 |
| Myeloid leukaemia | **8.48** | 33 | 3.0 | 17 | **7.05** | **4.11-11.29** | 2.7 | 16 | **10.81** | **6.18-17.56** | 3.3 |
| All sites | **2.33** | 953 | 55.8 | 584 | **2.24** | **2.07-2.43** | 59.9 | 369 | **2.48** | **2.23-2.75** | 50.7 |

O: observed number of subsequent primary malignancies; SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; EAR: excess absolute risk/10,000 person per year; HL: Hodgkin lymphoma; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites and all solid cancers: excluding non-melanoma skin cancer (C44).

**Figure 9. SIRs according to the type of SPM following HL by age at diagnosis, for both sexes**



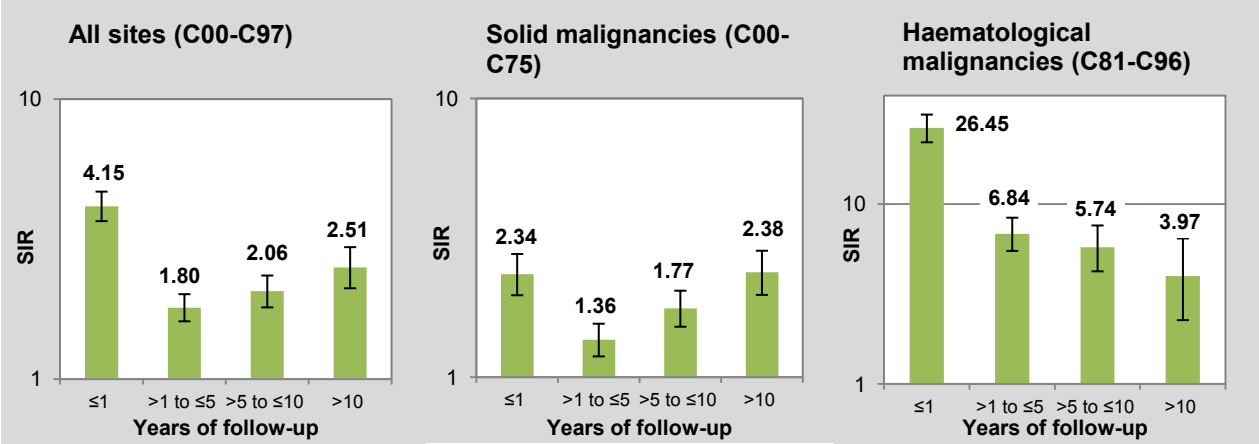

SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; HL: Hodgkin lymphoma; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

### Overall and site-specific risks in relation to time from HL diagnosis

The SIRs for all sites and for solid SPM were significantly elevated during the whole follow-up period, and increased with time from first HL diagnosis to reach 2.5-fold after 10 years (**Figure 10**). Trends in SIRs for selected SPM types are given in **Figure 11**. Risks for lip/oral cavity, kidney, and breast cancers were highest in the first year and more than 10 years after HL diagnosis (SIRs=2.8 to 3.3), whereas lung cancer risk increased steadily over the follow-up time (10-year SIR was 5.2). Colorectal and stomach cancer risks tended to occur in the later periods (SIR=2.3 to 4). The risk for malignant melanoma was highest in the first five years following diagnosis (SIR=2.8). For subsequent ML, SIR increased to 11-fold in the >5–≤10 years range and declined later. Risks for thyroid cancer, NHL, MM and LL were significantly highest within the first year following initial HL diagnosis and declined after that.

The analysis excluding the first year after HL diagnosis showed that the SIRs for subsequent cancers of the lip/oral cavity, colon/rectum, lung, skin melanoma, breast and thyroid, and NHL and ML remained significantly higher than the value one (**Appendix III, Table 30**). The SIR for all sites combined did not substantially change after exclusion of SPM detected during the first year after HL diagnosis (SIR=2.00, 95% CI=1.85–2.15 vs. SIR=2.33, 95% CI=2.18–2.48).

**Figure 10. Overall SIRs of SPM by follow-up duration following HL, for both sexes**




SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; HL: Hodgkin lymphoma; SPM: subsequent primary malignancies.
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites and all solid cancers: excluding non-melanoma skin cancer (C44).

**Figure 11. SIRs for selected SPM by follow-up duration following HL, for both sexes**

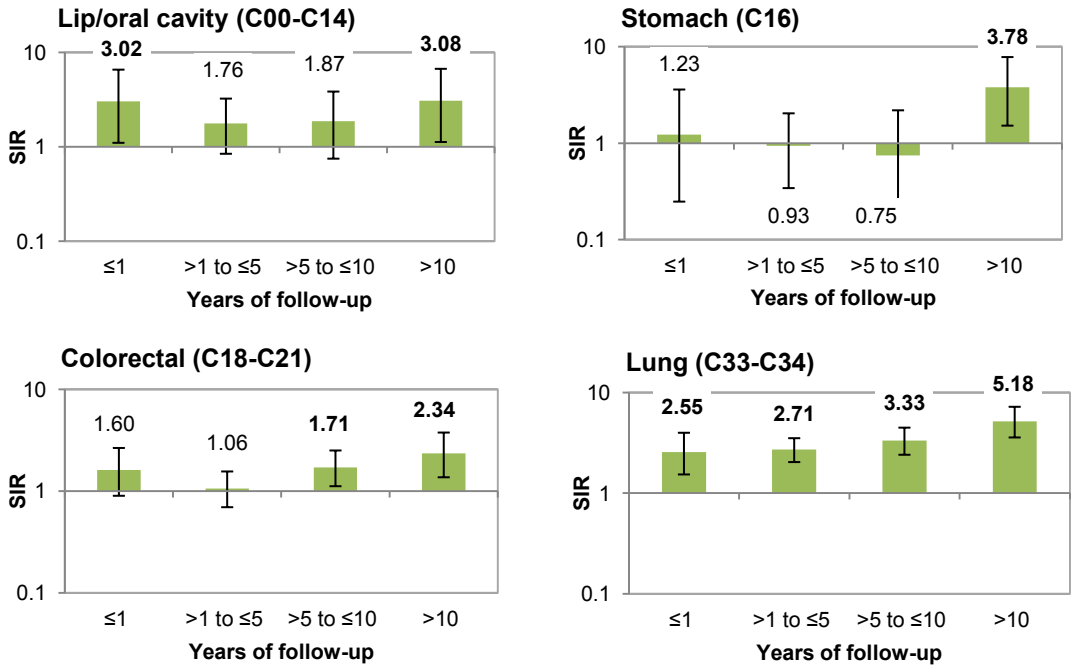
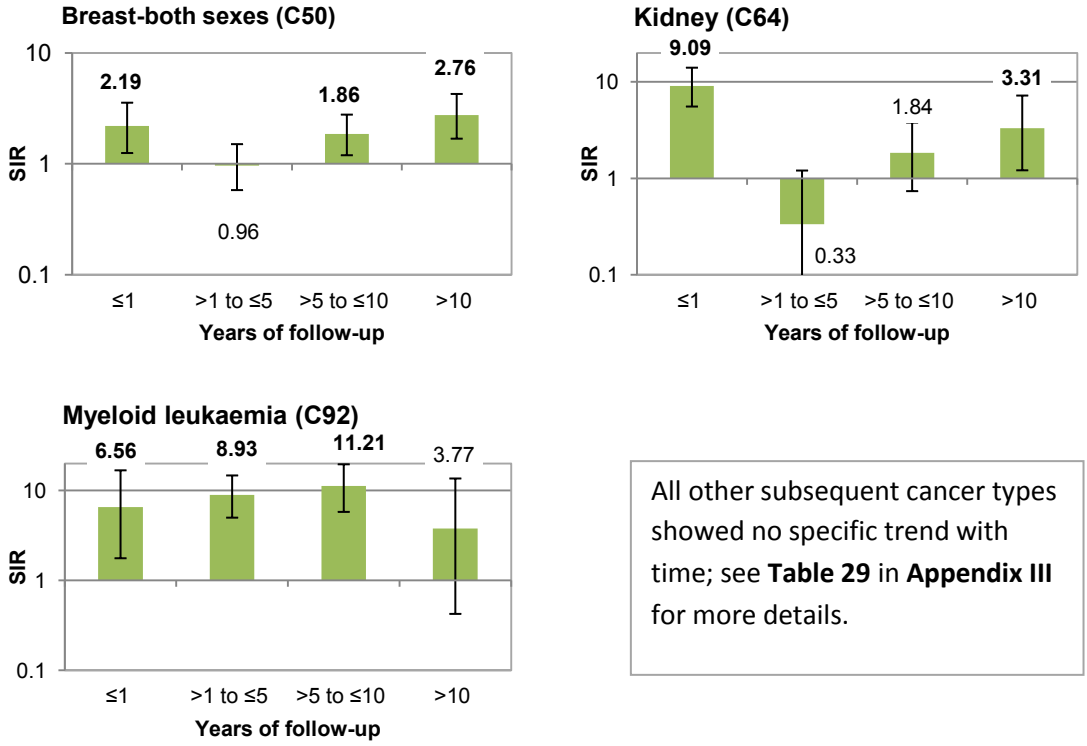


**Figure 11 continued**

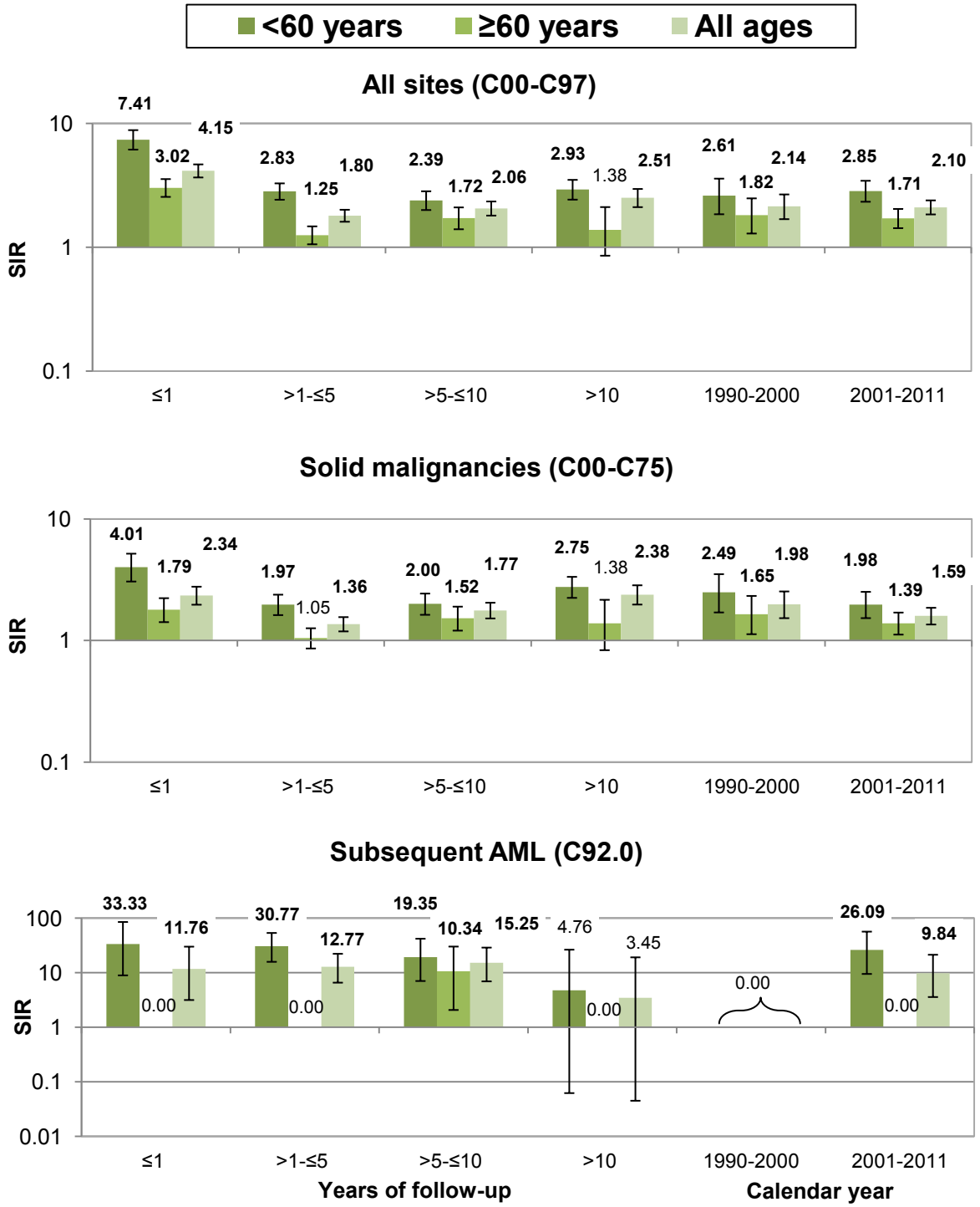



SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; HL: Hodgkin lymphoma; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

### Overall and site-specific risks in relation to time from HL diagnosis and calendar periods by age (<60 vs. ≥60 years old)

Trends in SIRs by patients' age at diagnosis (<60 vs. ≥60 years) are shown in **Figure 12**. Patients first diagnosed at ages less than 60 years had higher SIRs of SPM than patients diagnosed at an older age across all follow-up and calendar periods. In addition, the long-term 10 year-risk for all SPM was mainly increased in the younger age groups, whereas in older patients SIR was not significantly different from the general population rates of the same age group (≥60 years) after 10 years from HL diagnosis. This increase was prominent for subsequent solid malignancies including cancers of lip/oral cavity, stomach, colon/rectum, lung, breast, and kidney (**Appendix III**, **Table 31**). Among patients in either age group, there were no statistically significant differences in the overall risk (or of solid SPM) between the earlier (before 2000) and recent time period (after 2000). In contrast, the SIR for all haematological SPM has significantly increased over the most recent years, mainly due to increased incidence of subsequent AML. All cases (O=6) of AML from the included German population-based registries were diagnosed in the year 2000 or later (**Appendix III**, **Table 32**), and were observed in younger patients only.

**Figure 12. Overall SIRs of SPM by follow-up duration and calendar periods for HL survivors aged <60 vs. ≥60 years at diagnosis, for both sexes**




SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; HL: Hodgkin lymphoma; SPM: subsequent primary malignancies AML: acute myeloid leukaemia. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites and all solid cancers: excluding non-melanoma skin cancer (C44).

### Risk of HL subsequent to selected first cancers

The risk of developing HL as a new cancer following any primary malignancy (overall) was significantly increased by 66% (**Table 6**). The risk of HL increased significantly after first primary cancers of the colon/rectum, lung, skin melanoma, thyroid, and other haematological malignancies. The associations between HL and cancers of the lip/oral cavity, stomach, breast, kidney, and AML were unidirectional. Detailed analysis in relation to follow-up time can be found in **Appendix III** (**Table 33**). Following most first primary sites, the elevated risk of subsequent HL was only observed during the initial years of follow-up, except the risk of HL following NHL and CLL, which persisted for more than 5 years.

### Table 6. Risk of HL subsequent to other primary malignancies

| | | HL as a first cancer | | | | HL as a subsequent cancer | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Cancer site** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | **C00-C75** | 653 | 371.42 | **1.76** | **1.63-1.90** | 368 | 290.24 | **1.27** | **1.14-1.40** |
| Lip/oral cavity | C00-C14 | 29 | 13.39 | **2.17** | **1.45-3.11** | 14 | 8.86 | 1.58 | 0.86-2.65 |
| Colon/rectum | C18-C21 | 80 | 56.35 | **1.42** | **1.13-1.77** | 61 | 46.28 | **1.32** | **1.01-1.69** |
| Lung | C33-C34 | 151 | 47.23 | **3.20** | **2.71-3.75** | 34 | 15.24 | **2.23** | **1.54-3.12** |
| Melanoma of skin | C43 | 35 | 16.48 | **2.12** | **1.48-2.95** | 31 | 16.39 | **1.89** | **1.28-2.68** |
| Breast | C50 | 79 | 47.17 | **1.67** | **1.33-2.09** | 47 | 52.42 | 0.90 | 0.66-1.19 |
| Kidney | C64 | 35 | 13.8 | **2.54** | **1.77-3.53** | 15 | 12.8 | 1.17 | 0.66-1.93 |
| Thyroid | C73 | 21 | 5.35 | **3.93** | **2.43-6.00** | 15 | 5.25 | **2.86** | **1.60-4.71** |
| **All haematological malignancies** | **C81-C96** | 282 | 30.37 | **9.29** | **8.23-10.43** | 185 | 23.73 | **7.80** | **6.71-9.00** |
| NHL | C82-C85 | 182 | 12.21 | **14.91** | **12.82-17.24** | 137 | 10.09 | **13.58** | **11.40-16.05** |
| Multiple myeloma | C90 | 10 | 4.67 | **2.14** | **1.03-3.94** | 8 | 3.06 | **2.61** | **1.13-5.15** |
| Lymphoid leukaemia | C91 | 27 | 4.92 | **5.49** | **3.62-7.98** | 51 | 4.49 | **11.36** | **8.46-14.93** |
| ALL | C91.0 | 7 | 0.72 | **9.72** | **3.89-20.03** | 1 | 0.37 | 2.70 | 0.04-15.04 |
| CLL | C91.1 | 20 | 3.75 | **5.33** | **3.26-8.24** | 51 | 3.7 | **13.78** | **10.26-18.12** |
| Myeloid leukaemia | C92 | 33 | 3.89 | **8.48** | **5.84-11.91** | 6 | 2.02 | **2.97** | **1.08-6.47** |
| AML | C92.0 | 26 | 2.17 | **11.98** | **7.82-17.56** | 3 | 0.83 | 3.61 | 0.73-10.56 |
| **All sites**** | **C00-C97** | 953 | 409.01 | **2.33** | **2.18-2.48** | 526 | 316.16 | **1.66** | **1.52-1.81** |

O: observed number of subsequent primary malignancies; E: expected number of subsequent primary malignancies; SIR: standardized incidence ratio; 95% CI: 95% confidence intervals (lower-upper limits); HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; ALL: acute lymphoblastic leukaemia; CLL: chronic lymphocytic leukaemia; AML: acute myeloblastic leukaemia; ICD-10: the WHO International Classification of Diseases (10th revision).

*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96)

**excluding non-melanoma skin cancer (C44)

Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Subsequent malignancies following non-Hodgkin lymphoma (NHL, C82-C85)

### Descriptive statistics of patients with first primary NHL

A cohort of 99,829 cases (52% were men) with first primary NHL diagnosis were followed for 398490.79 person-years between 1990 and 2011 (**Table 7**). Nearly two-thirds of the identified NHL cases were older than 60 years at diagnosis. The median follow-up time was 2.3 years in men and 2.4 in women (range 0 to 21 years). During this follow-up time, a total of 6,788 (6.8%) SPM occurred after NHL, 21% of which were synchronous cancers. About 6.1% of patients had a second primary malignancy and 0.4% had two or more subsequent primaries.

**Table 7. Descriptive statistics of patients with first primary NHL, Germany (1990–2011)**

| | Males | | Females | | Total | |
|---|---|---|---|---|---|---|
| | Number | % | Number | % | Number | % |
| **Patients with first primary malignancy*** | **51860** | **100** | **47969** | **100** | **99829** | **100** |
| **Patients by age at first malignancy diagnosis** | | | | | | |
| 15-44 years old | 6274 | 12.10 | 4030 | 8.40 | 10304 | 10.32 |
| 45-59 years old | 11944 | 23.03 | 9019 | 18.80 | 20963 | 21.00 |
| 60-74 years old | 22206 | 42.82 | 19187 | 40.00 | 41393 | 41.46 |
| >75 years old | 11436 | 22.05 | 15733 | 32.80 | 27169 | 27.22 |
| **Patients by follow-up time** | | | | | | |
| ≤1 year | 15068 | 29.06 | 13935 | 29.05 | 29003 | 29.05 |
| >1 to ≤5 years | 20938 | 40.37 | 18558 | 38.69 | 39496 | 39.56 |
| >5 to ≤10 years | 11349 | 21.88 | 10912 | 22.75 | 22261 | 22.30 |
| >10 years | 4505 | 8.69 | 4564 | 9.51 | 9069 | 9.08 |
| **Patients with multiple primary malignancies** | | | | | | |
| 1 primary malignant tumour | 48027 | 92.61 | 45382 | 94.61 | 93409 | 93.57 |
| 2 primaries | 3591 | 6.92 | 2481 | 5.17 | 6072 | 6.08 |
| 3 primaries | 228 | 0.44 | 101 | 0.21 | 329 | 0.33 |
| 4 or more primaries | 14 | 0.03 | 5 | 0.01 | 19 | 0.02 |
| **Person-years of observation** | **203980.39** | | **194510.40** | | **398490.79** | |
| **Median length of follow-up (years)** | | | | | | |
| **..All ages** | **2.29** | | **2.38** | | **-** | |
| 15-44 years old | 3.87 | | 4.31 | | - | |
| 45-59 years old | 3.13 | | 3.63 | | - | |
| 60-74 years old | 2.34 | | 2.67 | | - | |
| >75 years old | 1.00 | | 1.08 | | - | |
| **Observed number of subsequent malignancies** | **4090** | **7.89** | **2698** | **5.62** | **6788** | **6.80** |
| Synchronous (<2 months)** | 830 | 20.29 | 591 | 21.91 | 1421 | 20.93 |
| Metachronous (>2 months)** | 3260 | 79.71 | 2107 | 78.09 | 5367 | 79.07 |
| **Expected number of subsequent malignancies** | **2738.36** | | **1785.59** | | **4523.95** | |

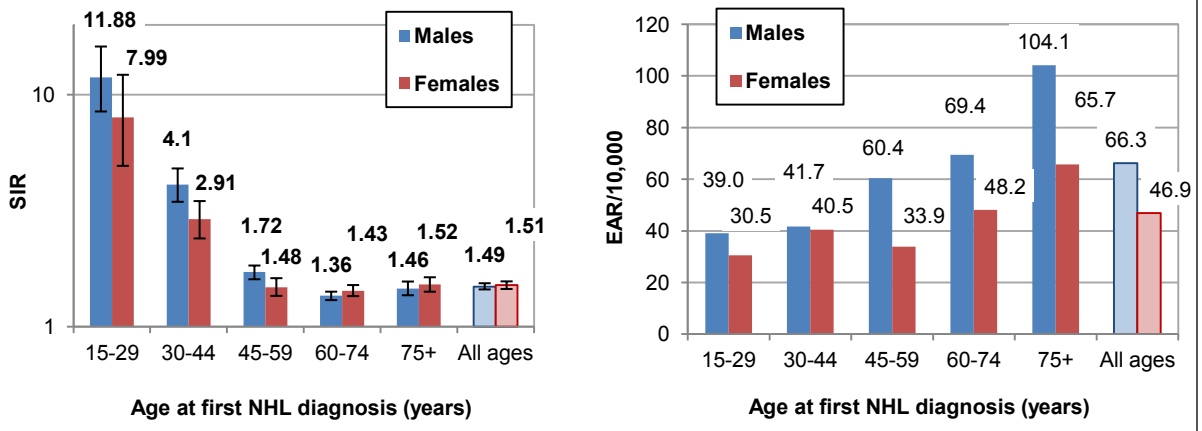
*after excluding Death Certificate only (DCO) cases, preceding primary malignancies, and patients aged less than 15 years old
**after the diagnosis of the first primary malignant cancer
NHL: non-Hodgkin lymphoma.

### Age-specific risks (15 years age group) of all subsequent malignancies by sex

Relative to the general population, adult patients with first primary NHL are at 1.5-fold increased risk to develop SPM at any site (SIR=1.50; 95% CI=1.46–1.54). An absolute excess risk of 56.82 cases/10,000 person-years was found overall. A significant steady decrease in the age-specific SIR with increasing age at first NHL diagnosis was demonstrated, and SIR was highest (about 12-fold in men and 8-fold in women) among survivors who were younger than 30 years old at first

diagnosis (**Figure 13**). Nevertheless, the SIR remained also slightly higher than expected at age 75 years or older. There was no overall significant gender difference in the SIR. The overall observed numbers of SPM and the EAR were slightly higher in men than women, particularly at age 75 years or older.

**Figure 13. Observed number, SIRs and EARs of all SPM by age at diagnosis of NHL and sex**




**Observed number of SPM by age and sex**

| | 15-29 | 30-44 | 45-59 | 60-74 | 75+ | All ages |
|---|---|---|---|---|---|---|
| **Males** | 40 | 146 | 840 | 222 | 841 | 4090 |
| **Females** | 21 | 117 | 509 | 1289 | 761 | 2698 |

SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; EAR: excess absolute risk per 10,000 person-years; NHL: non-Hodgkin lymphoma; SPM: subsequent primary malignancies.
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

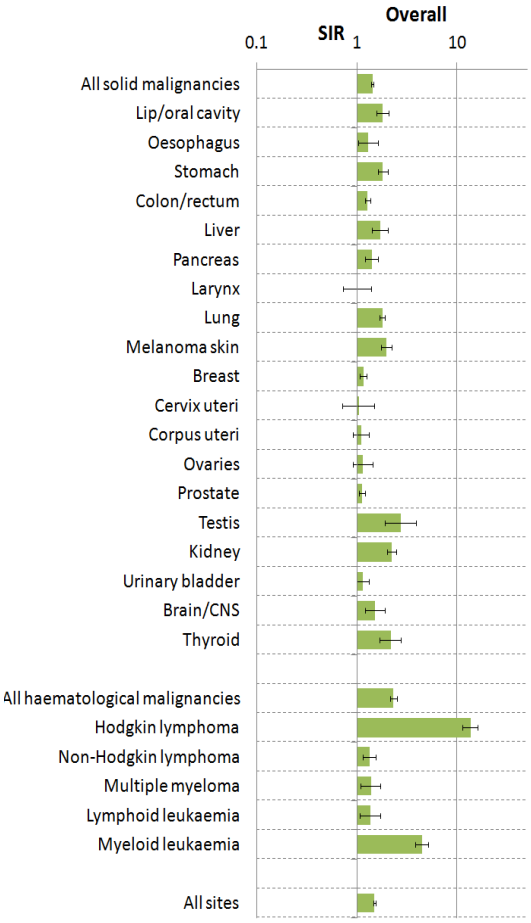
### Site-specific risks by sex and age at first NHL diagnosis

The majority of the observed SPM following NHL were solid cancers (87%), and most of these (80%) were metachronous. The relative risk of developing a solid cancer was significantly increased by 43% (SIR=1.43, 95% CI=1.39–1.47) compared with the general population of Germany, and there was no substantial gender difference in risk (**Figure 14**). Overall, cancers of prostate, lung, colorectal, and breast were the most frequently observed SPM. The EAR was highest for subsequent lung cancer (10.53 cases/10,000 patients per year) in both sexes. Also, there was a 2.3-fold relative increase in the risk of developing other haematological malignancies following first NHL (SIR=2.32, 95% CI=2.15–2.50).

For both sexes, SIRs were significantly high for HL (13.58), ML (4.44), and for cancers of testis, kidney, thyroid, and skin melanoma (ranging from 1.98 to 2.77), and moderately elevated for

stomach, lip/oral cavity, lung, liver and brain/CNS (ranging from 1.53 to 1.82). In addition, significant but slightly elevated SIRs for cancers of the oesophagus, colon/rectum, pancreas, urinary bladder, breast and prostate (<1.5) were observed. The risk of developing a subsequent NHL was also significantly elevated (SIR=1.33). Non-significant excess risk was found for cancers of the larynx and female gynaecologic organs. No SIR significantly lower than 1 was found.

**Figure 14. Observed number, SIRs and EARs according to the type of SPM following NHL by sex and overall**



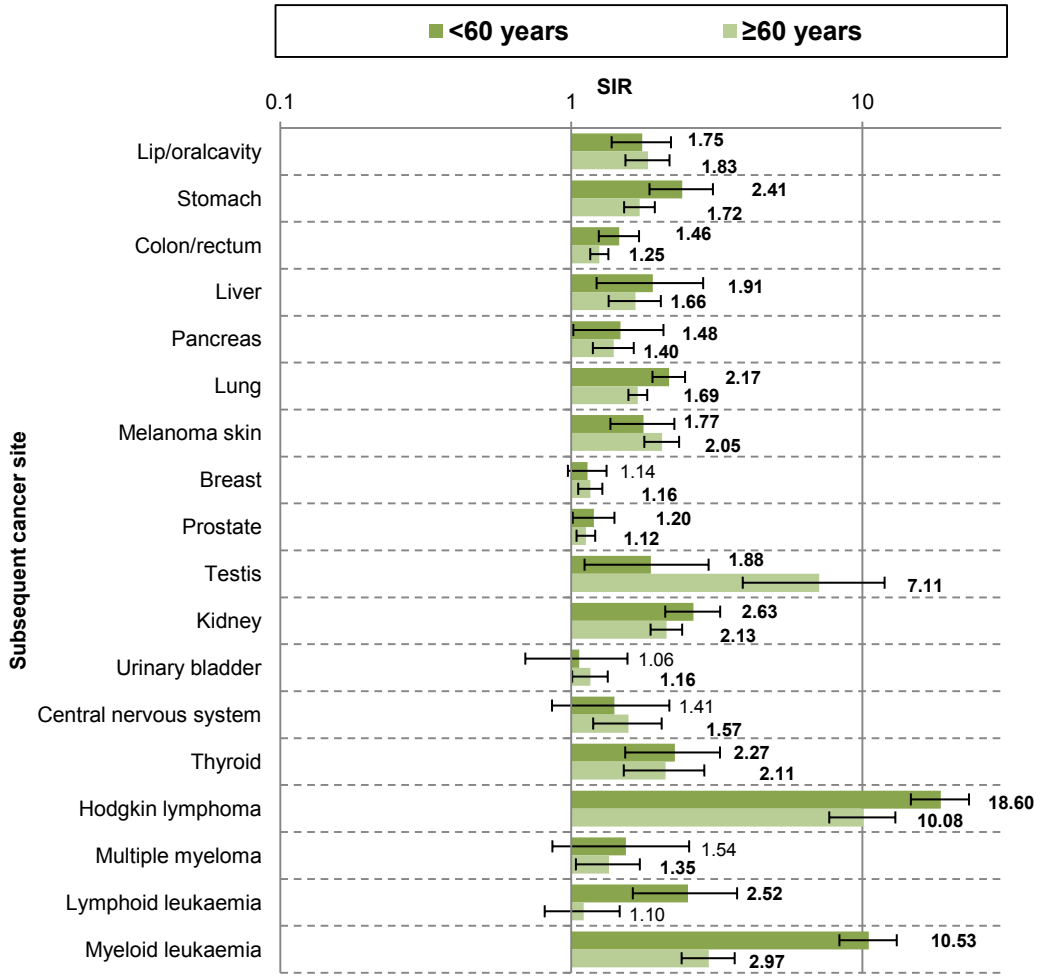

| | Overall | | | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | SIR | O | EAR | O | SIR | 95% CI | EAR | O | SIR | 95% CI | EAR |
| All solid malignancies | **1.43** | 5895 | 44.4 | 3573 | **1.42** | **1.38-1.47** | 52.2 | 2322 | **1.43** | **1.38-1.49** | 36.1 |
| Lip/oral cavity | **1.80** | 206 | 2.3 | 139 | **1.60** | **1.34-1.89** | 2.6 | 67 | **2.46** | **1.91-3.13** | 2.1 |
| Oesophagus | **1.30** | 81 | 0.5 | 60 | 1.19 | 0.91-1.53 | 0.5 | 21 | **1.79** | **1.11-2.73** | 0.5 |
| Stomach | **1.82** | 334 | 3.8 | 202 | **1.72** | **1.49-1.98** | 4.2 | 132 | **1.99** | **1.67-2.36** | 3.4 |
| Colon/rectum | **1.28** | 919 | 5.1 | 529 | **1.25** | **1.15-1.37** | 5.3 | 390 | **1.32** | **1.20-1.46** | 4.9 |
| Liver | **1.71** | 119 | 1.2 | 84 | **1.62** | **1.29-2.01** | 1.6 | 35 | **1.94** | **1.35-2.70** | 0.9 |
| Pancreas | **1.41** | 186 | 1.4 | 108 | **1.49** | **1.22-1.79** | 1.7 | 78 | **1.32** | **1.04-1.65** | 1.0 |
| Larynx | 1.01 | 40 | 0.0 | 38 | 1.06 | 0.75-1.46 | 0.1 | 2 | 0.55 | 0.06-1.97 | -0.1 |
| Lung | **1.79** | 949 | 10.5 | 689 | **1.71** | **1.58-1.84** | 14.0 | 260 | **2.07** | **1.83-2.34** | 6.9 |
| Melanoma skin | **1.98** | 274 | 3.4 | 168 | **2.04** | **1.74-2.37** | 4.2 | 106 | **1.89** | **1.55-2.28** | 2.6 |
| Breast | **1.16** | 604 | 2.1 | 6 | 0.94 | 0.34-2.04 | 0.0 | 598 | **1.16** | **1.07-1.26** | 4.3 |
| Cervix uteri | 1.05 | 31 | 0.0 | | | | | 31 | 1.05 | 0.71-1.49 | 0.1 |
| Corpus uteri | 1.10 | 117 | 0.3 | | | | | 117 | 1.10 | 0.91-1.32 | 0.6 |
| Ovaries | 1.15 | 75 | 0.3 | | | | | 75 | 1.15 | 0.91-1.45 | 0.5 |
| Prostate | **1.14** | 864 | 2.6 | 864 | **1.14** | **1.06-1.21** | 5.0 | | | | |
| Testis | **2.77** | 32 | 0.5 | 32 | **2.77** | **1.89-3.90** | 1.0 | | | | |
| Kidney | **2.23** | 340 | 4.7 | 221 | **2.20** | **1.92-2.51** | 5.9 | 119 | **2.30** | **1.91-2.76** | 3.5 |
| Urinary bladder | **1.15** | 227 | 0.7 | 177 | 1.15 | 0.99-1.34 | 1.2 | 50 | 1.14 | 0.84-1.50 | 0.3 |
| Brain/CNS | **1.53** | 76 | 0.7 | 46 | **1.54** | **1.13-2.06** | 0.8 | 30 | **1.50** | **1.01-2.14** | 0.5 |
| Thyroid | **2.18** | 71 | 1.0 | 29 | **2.47** | **1.66-3.55** | 0.9 | 42 | **2.01** | **1.45-2.72** | 1.1 |
| All haematological malignancies | **2.32** | 716 | 10.2 | 413 | **2.27** | **2.06-2.50** | 11.3 | 303 | **2.39** | **2.13-2.68** | 9.1 |
| Hodgkin lymphoma | **13.58** | 137 | 3.2 | 78 | **12.54** | **9.91-15.65** | 3.5 | 59 | **15.25** | **11.60-19.67** | 2.8 |
| Non-Hodgkin lymphoma | **1.33** | 174 | 1.1 | 93 | **1.25** | **1.01-1.54** | 0.9 | 81 | **1.44** | **1.14-1.79** | 1.3 |
| Multiple myeloma | **1.38** | 79 | 0.5 | 42 | 1.25 | 0.90-1.69 | 0.4 | 37 | **1.57** | **1.10-2.16** | 0.7 |
| Lymphoid leukaemia | **1.37** | 72 | 0.5 | 47 | **1.39** | **1.02-1.85** | 0.7 | 25 | 1.33 | 0.86-1.97 | 0.3 |
| Myeloid leukaemia | **4.44** | 171 | 3.3 | 108 | **4.84** | **3.97-5.84** | 4.2 | 63 | **3.90** | **3.00-4.99** | 2.4 |
| All sites | **1.50** | 6788 | 56.8 | 4090 | **1.49** | **1.45-1.54** | 66.3 | 2698 | **1.51** | **1.45-1.57** | 46.9 |

O: observed number of subsequent primary malignancies; SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; EAR: excess absolute risk/10,000 person per year; NHL: non-Hodgkin lymphoma; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites and all solid cancers: excluding non-melanoma skin cancer (C44).

Survivors under age 45 years had significantly elevated SIRs (ranging from 1.8- to 30-fold) for subsequent cancers of the lip/oral cavity, stomach, colon/rectum, lung, skin melanoma, breast, ovaries, prostate, kidney, and thyroid, and HL and leukaemia (all subtypes). However, the

relative risk for lip/oral cavity, melanoma, kidney, and thyroid did not substantially vary between the younger and older patients (**Figure 15** and **Table 34** in **Appendix III**).

**Figure 15. SIRs according to the type of SPM following NHL by age at diagnosis, for both sexes**




SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; NHL: Non-Hodgkin lymphoma; SPM: subsequent primary malignancies.
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

### Subsequent malignancies according to NHL histological subtypes

We checked if there is an overall difference in the relative risk between low-grade and high-grade NHL, but risks were nearly identical (SIR=1.54; 95% CI=1.49–1.59 and SIR=1.46; 95% CI=1.39–1.52; respectively). Increased risk for the following cancers was consistently observed: lip/oral cavity, stomach, colon/rectum, liver, lung, melanoma, kidney, thyroid, HL and ML (**Figure 16**).

We further stratified the SIR of SPM according to specific NHL cell type (B-cell vs. T-cell), summarized in **Table 8**. There was an overall significant difference in risk with highest SIR of SPM noted following NHL of T-cell type, particularly for the high-grade or aggressive form. The difference in risk was mainly due to higher risk for subsequent HL and leukaemia (both acute and chronic). The SIR of solid malignancies was significantly increased in all specific subtypes except in Burkitt lymphoma, and was highest in small cell B-cell lymphoma (1.52), CLL (1.47), and follicular lymphoma (FL) grade I/II,(1.41) (**Table 9** and **Table 10**). The risk for stomach, colon/rectum, lung, and melanoma was significantly elevated in all NHL subtypes except FL grade III, peripheral T-cell, and Burkitt lymphoma.

**Table 8. Overall SIRs of SPM following NHLs of different grades and histologies, for both sexes**

| | B-cell NHL | | | | T-cell NHL (and NK-cell) | | | |
|---|---|---|---|---|---|---|---|---|
| | O | E | SIR | 95%CI | O | E | SIR | 95%CI |
| **Low-grade** | 2905 | 1890.61 | **1.54** | **1.48-1.59** | 483 | 307.05 | **1.57** | **1.44-1.72** |
| CLL | 3022 | 2034.97 | **1.49** | **1.43-1.54** | | | | |
| Small cell B-cell lymphoma | 989 | 621.5 | **1.59** | **1.49-1.69** | | | | |
| FL grade I and II | 470 | 316.78 | **1.48** | **1.35-1.62** | | | | |
| MCL | 348 | 254.72 | **1.37** | **1.23-1.52** | | | | |
| Extranodal MALT | NA | | | | | | | |
| Immunocytoma/MW | NA | | | | | | | |
| Mycosis fungoides | | | | | 224 | 168.69 | **1.33** | **1.16-1.51** |
| Sezary disease | | | | | NA | | | |
| Peripheral T-cell lymphoma | | | | | 183 | 95.61 | **1.91** | **1.65-2.21** |
| SC panniculitis-like T-cell lymphoma | | | | | NA | | | |
| Extranodal NK/T-cell lymphoma | | | | | NA | | | |
| Hepatosplenic T-cell lymphoma | | | | | NA | | | |
| **High-grade** | 1902 | 1344.93 | **1.41** | **1.35-1.48** | 153 | 77.1 | **1.98** | **1.68-2.32** |
| DLBCL | 1688 | 1198.48 | **1.41** | **1.34-1.48** | | | | |
| FL grade III | 137 | 106.12 | **1.29** | **1.08-1.53** | | | | |
| Burkitt lymphoma | 51 | 34.4 | **1.48** | **1.10-1.95** | | | | |
| Mediastinal large B-cell lymphoma | NA | | | | | | | |
| Primary cutaneous CD30-positive T-cell | | | | | NA | | | |
| Enteropathy type T-cell lymphoma | | | | | NA | | | |
| Anaplastic T large cell lymphoma, ALK-positive | | | | | NA | | | |
| Angioimmunoblastic T-cell lymphoma | | | | | NA | | | |
| **Unspecified NHL (low- and high-grade/B- and T-cell)** | 1860 | 1218.92 | **1.53** | **1.46-1.60** | | | | |
| **Overall NHL** | 4798 | 3236.79 | **1.48** | **1.44-1.52** | 645 | 384.32 | **1.68** | **1.55-1.81** |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; standardized incidence ratio with 95% confidence intervals; NHL: non-Hodgkin lymphoma; CLL: chronic lymphocytic leukaemia; FL: follicular lymphoma; MCL: mantel cell lymphoma; DLBCL: diffuse large B-cell lymphoma; MALT-lrmphoma: marginal zone B-cell lymphoma of mucosa associated lymphoid tissue; MW: Morbus Waldenström macroglobulinaemia; SC panniculitis-like T-cell: Subcutancous panniculitis-like T-cell lymphoma; SPM: subsequent primary malignancies. NA: indicates that SIR was not estimated due to zero observed cases. For NHL subtypes classification please refer to **Appendix II**. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

**Table 9. Site-specific risks of SPM following low-grade NHL by histological subgroups**

| | CLL N=30878 | | Small B-cell N=10630 | | FL grade I/II N=7755 | | MCL N=5278 | | Mycosis F N=2596 | | Peripheral T-cell N=2741 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **O** | **SIR** | **O** | **SIR** | **O** | **SIR** | **O** | **SIR** | **O** | **SIR** | **O** | **SIR** |
| **All solid malignancies** | 2725 | **1.47** | 862 | **1.52** | 408 | **1.41** | 305 | **1.31** | 185 | **1.20** | 119 | **1.36** |
| Lip/oral cavity | 82 | **1.66** | 26 | **1.74** | 13 | 1.45 | 9 | 1.32 | 4 | 0.93 | 3 | 1.12 |
| Stomach | 124 | **1.43** | 39 | **1.52** | 17 | 1.52 | 13 | 1.23 | 14 | **2.02** | 3 | 0.77 |
| Colon/rectum | 488 | **1.49** | 127 | **1.27** | 59 | 1.28 | 60 | **1.49** | 25 | 0.95 | 9 | 0.60 |
| Liver | 45 | 1.34 | 24 | **2.46** | 7 | 1.52 | 6 | 1.40 | 2 | 0.72 | 2 | 1.28 |

## Table 9 continued

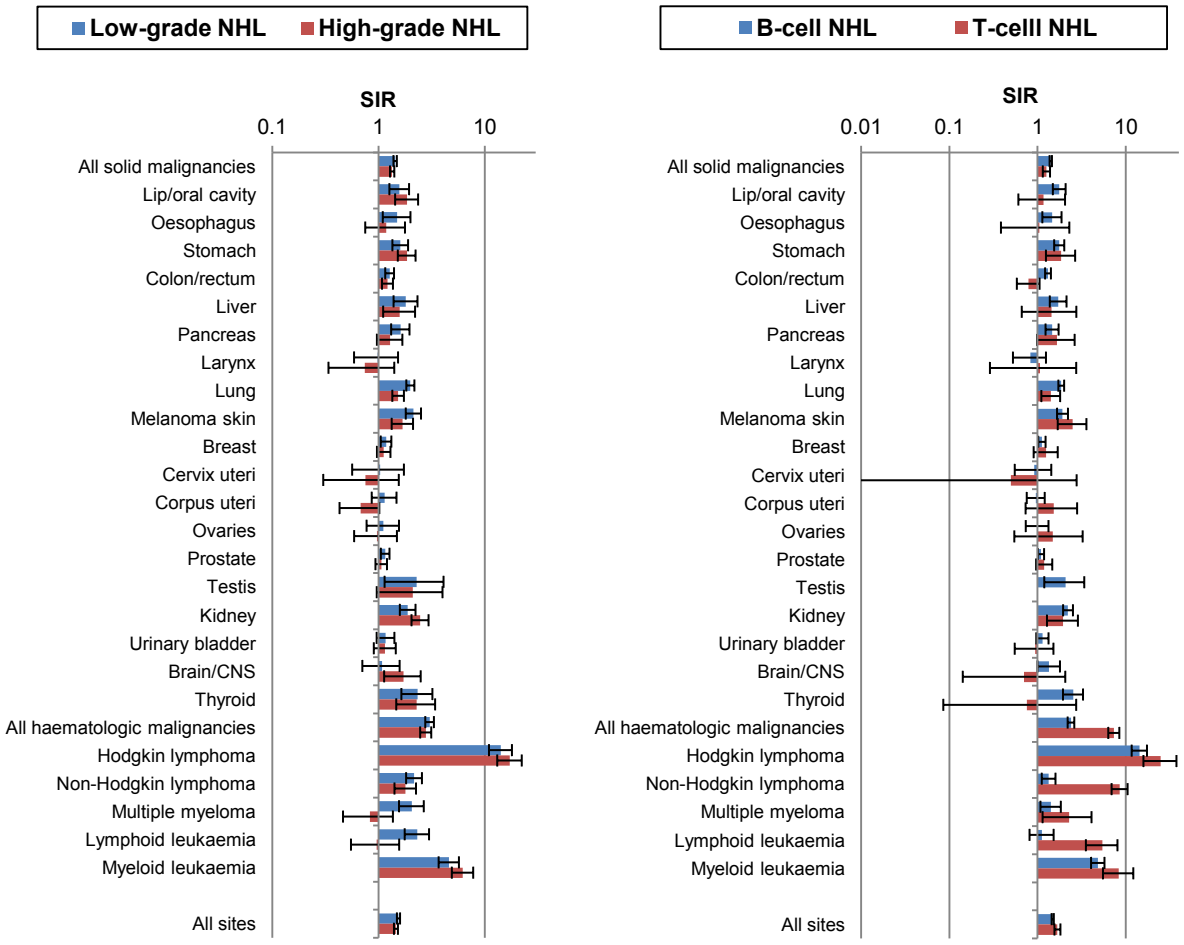
| | CLL N=30878 | | Small B-cell N=10630 | | FL grade I/II N=7755 | | MCL N=5278 | | Mycosis F N=2596 | | Peripheral T-cell N=2741 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pancreas | 74 | 1.23 | 29 | **1.57** | 15 | 1.66 | 10 | 1.39 | 7 | 1.47 | 7 | **2.56** |
| Larynx | 16 | 0.86 | 5 | 0.93 | 3 | 1.09 | 2 | 0.77 | 1 | 0.61 | 1 | 1.08 |
| Lung | 436 | **1.75** | 170 | **2.31** | 64 | **1.82** | 59 | **1.82** | 30 | 1.40 | 15 | 1.26 |
| Melanoma of skin | 173 | **2.96** | 42 | **2.28** | 16 | 1.47 | 24 | **3.13** | 14 | **2.70** | 7 | 2.37 |
| Breast | 204 | 1.14 | 74 | 1.14 | 44 | 0.92 | 22 | 1.27 | 14 | 1.11 | 19 | **2.06** |
| Prostate | 500 | **1.28** | 133 | 1.19 | 62 | 1.27 | 54 | 0.96 | 47 | 1.28 | 20 | 1.16 |
| Testis | 4 | 1.44 | 4 | **4.30** | 3 | 3.45 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| Kidney | 170 | **2.36** | 49 | **2.39** | 23 | **2.23** | 16 | **1.76** | 9 | 1.55 | 7 | 2.05 |
| Urinary bladder | 120 | **1.24** | 32 | 1.14 | 13 | 1.16 | 10 | 0.82 | 4 | 0.48 | 6 | 1.36 |
| Brain/CNS | 28 | 1.30 | 7 | 1.08 | 4 | 1.08 | 1 | 0.37 | 2 | 1.14 | 1 | 0.90 |
| Thyroid | 24 | **2.05** | 8 | 2.14 | 7 | 2.27 | 2 | 1.38 | 0 | 0.00 | 2 | 2.74 |
| **All haematological malignancies** | 221 | **1.59** | 109 | **2.53** | 54 | **2.60** | 29 | **1.71** | 33 | **2.89** | 61 | **9.43** |
| HL | 51 | **13.78** | 11 | **9.09** | 14 | **18.92** | 3 | **6.00** | 3 | **8.57** | 5 | **20.83** |
| NHL | 59 | 1.03 | 27 | 1.49 | 10 | 1.11 | 8 | 1.13 | 16 | **3.38** | 29 | **10.66** |
| MM | 22 | 0.83 | 25 | **3.07** | 3 | 0.79 | 3 | 0.94 | 2 | 0.93 | 4 | 3.39 |
| Lymphoid leukaemia | 5 | **0.20** | 12 | 1.60 | 6 | 1.79 | 5 | 1.63 | 8 | **3.92** | 8 | **7.08** |
| ALL | 3 | 2.63 | 2 | 5.56 | 1 | 4.76 | 1 | 7.14 | 0 | 0.00 | 5 | **83.33** |
| CLL | 0 | 0.00 | 5 | 0.76 | 5 | 1.73 | 4 | 1.49 | 8 | **4.47** | 2 | 2.04 |
| Myeloid leukaemia | 62 | **3.58** | 16 | **2.97** | 15 | **5.98** | 10 | **4.88** | 2 | 1.44 | 11 | **13.58** |
| AML | 16 | 1.59 | 13 | **4.13** | 10 | **6.94** | 8 | **6.72** | 2 | 2.53 | 9 | **19.15** |
| CML | 36 | **9.86** | 1 | 0.87 | 2 | 3.92 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| **All sites** | 3022 | **1.49** | 989 | **1.59** | 470 | **1.48** | 348 | **1.37** | 224 | **1.33** | 183 | **1.91** |

## Table 10. Site-specific risks of SPM following high-grade NHL by histological subgroups

| | DLBCL N=31036 | | FL grade III N=2273 | | Burkitt lymphoma N=1275 | |
|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **O** | **SIR** | **O** | **SIR** | **O** | **SIR** |
| **All solid malignancies** | 1464 | **1.34** | 119 | **1.23** | 38 | 1.21 |
| Lip/oral cavity | 59 | **2.02** | 5 | 1.77 | 0 | 0.00 |
| Stomach | 97 | **1.95** | 2 | 0.50 | 1 | 0.75 |
| Colon/rectum | 243 | **1.25** | 20 | 1.24 | 6 | 1.16 |
| Liver | 30 | **1.62** | 1 | 0.65 | 0 | 0.00 |
| Pancreas | 46 | 1.30 | 4 | 1.29 | 1 | 1.06 |
| Larynx | 7 | 0.70 | 0 | 0.00 | 1 | 3.03 |
| Lung | 206 | **1.52** | 18 | 1.48 | 4 | 0.96 |
| Melanoma of skin | 63 | **1.69** | 6 | 1.75 | 0 | 0.00 |
| Breast | 155 | 1.12 | 10 | 0.70 | 7 | 1.94 |
| Prostate | 205 | 1.03 | 19 | 1.13 | 8 | 1.31 |
| Testis | 7 | 2.23 | 1 | 4.00 | 1 | 3.03 |
| Kidney | 93 | **2.32** | 11 | **3.31** | 4 | 3.39 |
| Urinary bladder | 61 | 1.16 | 3 | 0.69 | 3 | 2.16 |
| Brain/CNS | 23 | **1.77** | 3 | 2.54 | 1 | 2.27 |
| Thyroid | 20 | **2.34** | 1 | 1.20 | 0 | 0.00 |
| **All haematological malignancies** | 173 | **2.11** | 16 | **2.19** | 9 | **3.75** |
| HL | 36 | **13.53** | 4 | **16.67** | 2 | **15.38** |
| NHL | 39 | 1.12 | 2 | 0.65 | 3 | 3.00 |
| MM | 9 | 0.59 | 2 | 1.48 | 1 | 2.38 |
| Lymphoid leukaemia | 7 | 0.51 | 0 | 0.00 | 1 | 2.50 |
| ALL | 3 | 3.90 | 0 | 0.00 | 0 | 0.00 |
| CLL | 0 | **0.00** | 0 | 0.00 | 1 | 3.03 |
| Myeloid leukaemia | 54 | **5.30** | 4 | **4.44** | 2 | 6.67 |
| AML | 37 | **6.28** | 1 | 1.92 | 1 | 5.88 |
| CML | 5 | 2.36 | 0 | 0.00 | 1 | 16.67 |
| **All sites** | 1688 | **1.41** | 137 | **1.29** | 51 | **1.48** |

O: observed number of subsequent primary malignancies; SIR: standardized incidence ratio; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; CLL: chronic lymphocytic leukaemia; FL: follicular lymphoma; MCL: Mantel cell lymphoma; DLBCL: diffuse large B-cell lymphoma; MM: multiple myeloma; ALL: acute lymphoblastic leukaemia; AML: acute myeloblastic leukaemia; CML: chronic myeloid leukaemia; SPM: subsequent primary malignancies.
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites and all solid cancers: excluding non-melanoma skin cancer (C44).

**Figure 16. Overall and site-specific risks of SPM by major NHL histological subgroups**




SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; NHL: non-Hodgkin lymphoma; SPM: subsequent primary malignancies. For more details on NHL subtypes classification please refer to **Appendix II.** All sites and all solid cancers: excluding non-melanoma skin cancer (C44).

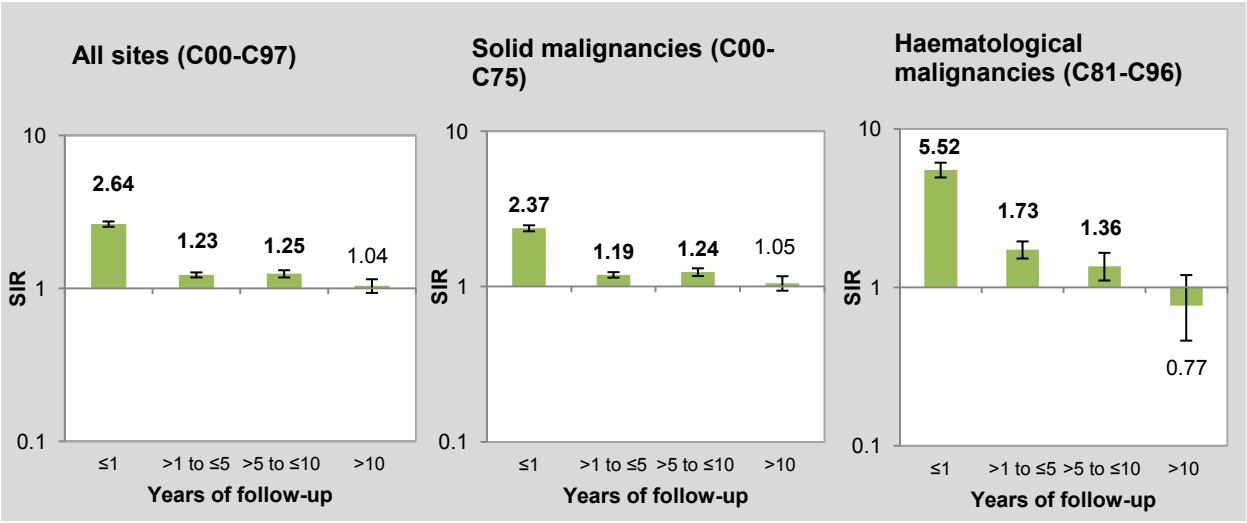
### Overall and site-specific risks in relation to time from NHL diagnosis

There appears to be no significant increase in overall SIRs for developing SPM at any site or for solid malignancies 10 years following NHL diagnosis (**Figure 17**). The SIRs for most SPM sites (**Figure 18**) were highest within the first year and were not significantly different from the population rates 10 years after first NHL diagnosis with the exception of subsequent stomach, liver, pancreatic and melanoma skin cancers, and HL and AML for which SIRs remained significantly elevated more than 10 years after NHL diagnosis.

The sensitivity analysis, excluding the first year after NHL diagnosis, showed that the SIRs for subsequent cancers of the lip/oral cavity, stomach, colon/rectum, liver, pancreas, lung, and skin (melanoma), and HL and ML remained significantly higher than the value one (**Appendix III**,

**Table 36**). However, the SIR for all sites declined significantly from 1.50 (95% CI=1.46–1.54) to 1.21 (95% CI=1.18–1.25).

**Figure 17. Overall SIRs of SPM by follow-up duration following NHL, for both sexes**




SIR: standardized incidence ratio with 95% confidence intervals shown in the graph, NHL: non-Hodgkin lymphoma; SPM: subsequent primary malignancies.
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites and all solid cancers: excluding non-melanoma skin cancer (C44).

**Figure 18. SIRs for selected SPM by follow-up duration following NHL, for both sexes**

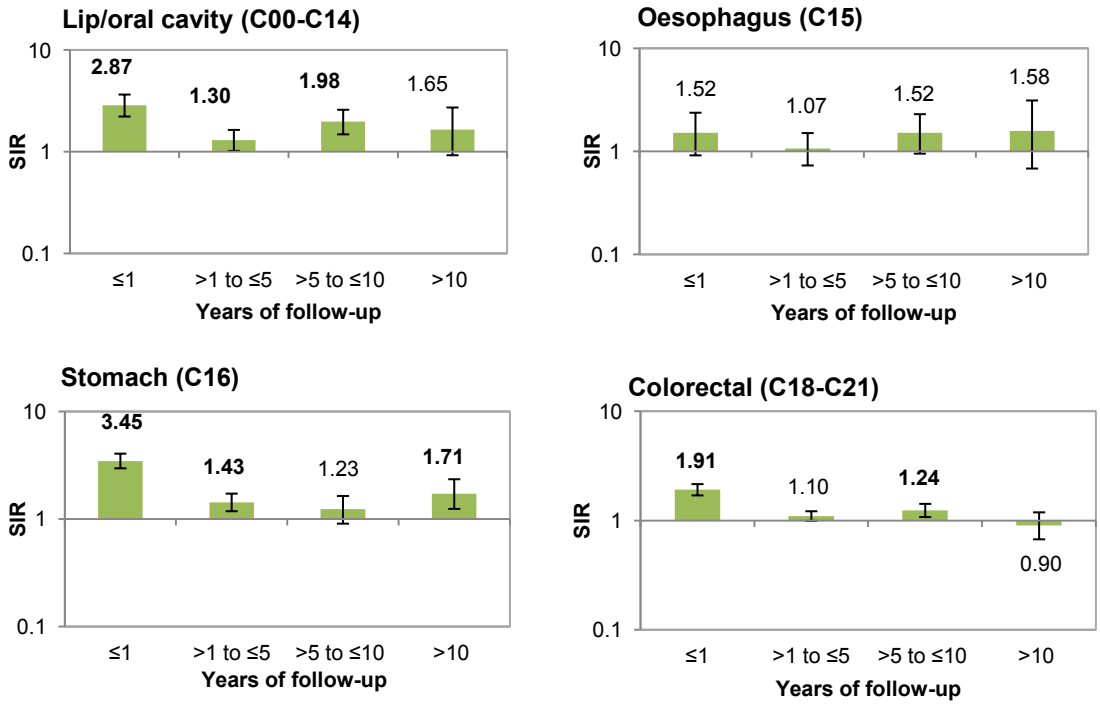
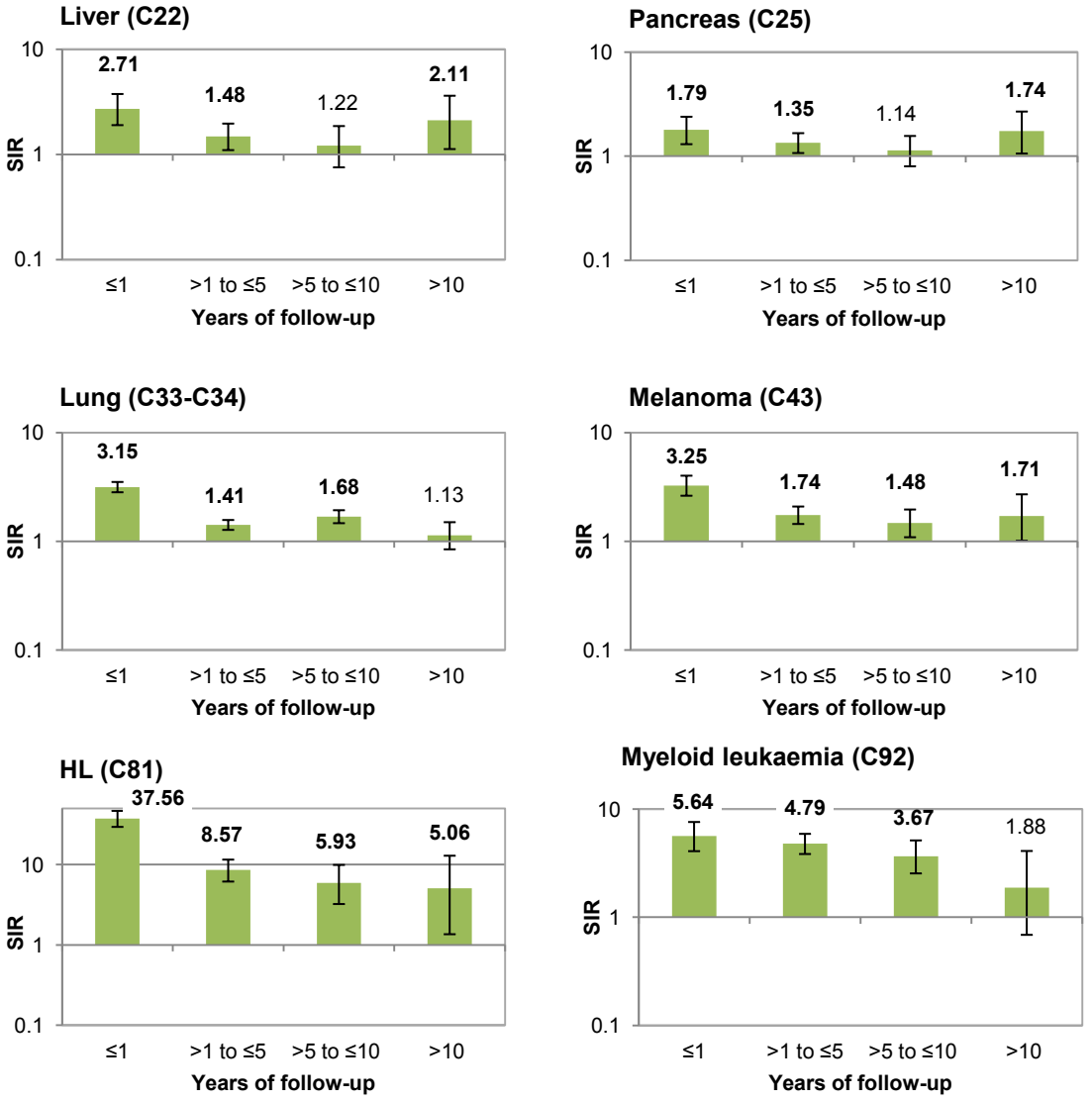


**Figure 18 continued**




All other subsequent cancer types showed no specific trend or declined with time; see **Table 35** in **Appendix III** for more details.

SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; NHL: non-Hodgkin lymphoma; HL: Hodgkin lymphoma; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

### Overall and site-specific risks in relation to time from NHL diagnosis and calendar periods by age (<60 vs. ≥60 years old)

Relative risks for SPM (overall and solid malignancies) similarly diminished with increasing intervals of follow-up among the younger and older patients and were not significantly different from the general population rates of the same age groups more than 10 years after NHL diagnosis (**Figure 19**). However, a substantial increase in SIR 10 years after NHL diagnosis was noted for liver and pancreas in the age group under 60 (**Appendix III, Table 37**). In this age

group, AML SIR was also significantly elevated across all follow-up intervals and peaked at the one to five years period. For all ages, the SIR for all sites' SPM significantly declined over time from 1.82 (95% CI=1.69–1.96) in 1990–2000 to 1.50 (95% CI=1.43–1.57) in 2001–2011, **Figure 19**. This decrease was mainly noted for subsequent solid malignancies; in particular the risk for colon/rectum cancer (**Appendix III, Table 38**). However, for some cancers such as melanoma, liver, pancreas, and testis, elevation of SIRs were limited to the period after 2000 only. For haematological SPM, SIR was slightly higher in the 2001–2011 compared with the earlier time period (1990–2000), especially for subsequent HL and other types of myeloid leukaemia, but not for AML. Generally, the trend of all SIRs over time did not greatly vary between NHL patients first diagnosed before or after age 60.

### Risk of NHL subsequent to selected first cancers

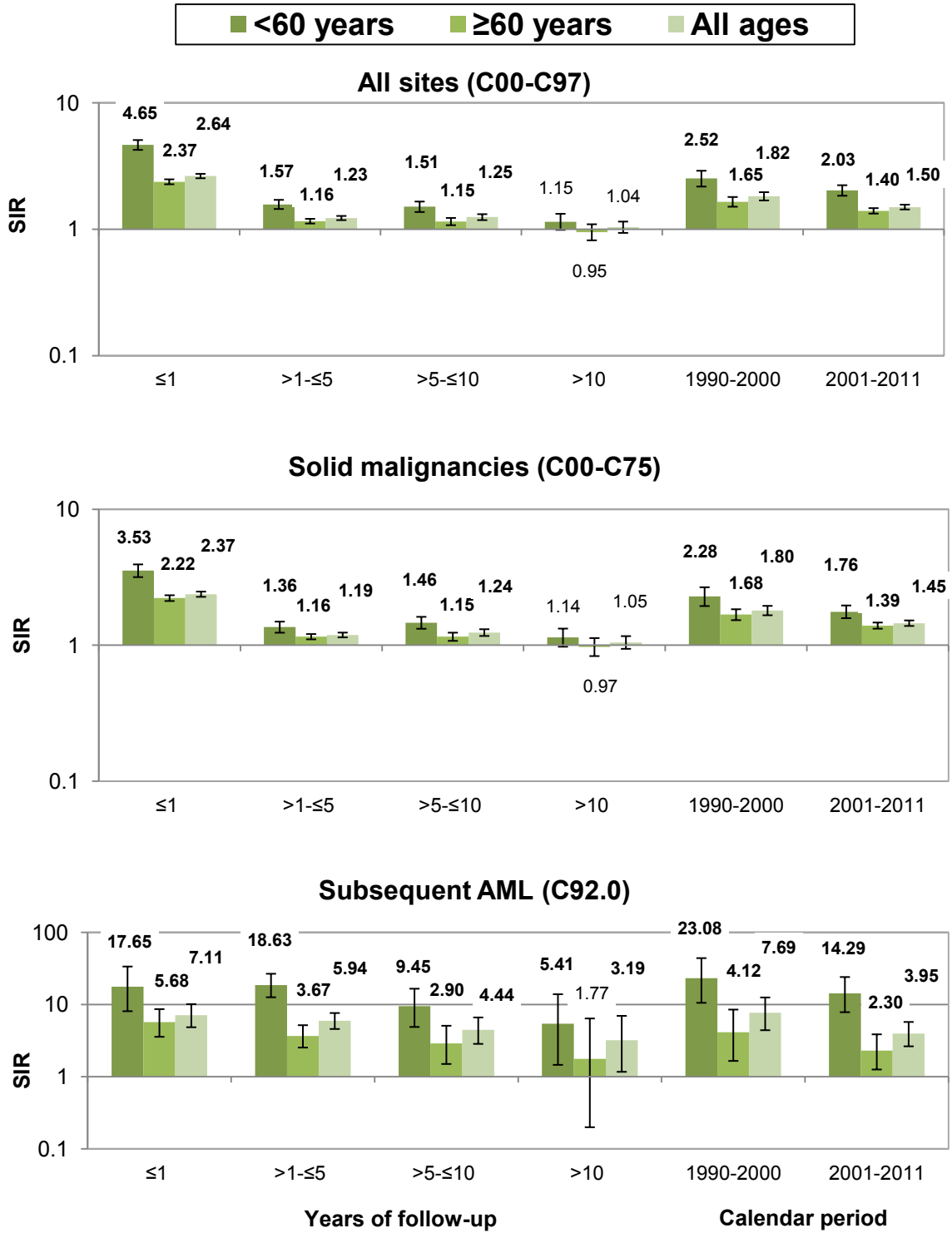
Significant bidirectional associations were found between NHL and all cancer sites included in the analysis (on the basis of associations observed in the initial analysis) except for cancers of the oesophagus and brain/CNS (**Table 11**). The risk of developing NHL after most of these first primary sites was only increased in the first year of follow-up and was highest following first primary HL (more details can be found in **Table 39, Appendix III**).

**Table 11. Risk of NHL subsequent to other primary malignancies**

| | | NHL as a first cancer | | | | NHL as a subsequent cancer | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Cancer site** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | **C00-C75** | 5895 | 4127.43 | **1.43** | **1.39-1.47** | 5721 | 4151.08 | **1.38** | **1.34-1.41** |
| Lip/oral cavity | C00-C14 | 206 | 114.17 | **1.80** | **1.57-2.07** | 186 | 102.76 | **1.81** | **1.56-2.09** |
| Oesophagus | C15 | 81 | 62.13 | **1.30** | **1.04-1.62** | 37 | 27.54 | 1.34 | 0.95-1.85 |
| Stomach | C16 | 334 | 183.57 | **1.82** | **1.63-2.03** | 211 | 116.98 | **1.80** | **1.57-2.06** |
| Colon/rectum | C18-C21 | 919 | 716.55 | **1.28** | **1.20-1.37** | 987 | 747.71 | **1.32** | **1.24-1.41** |
| Liver | C22 | 119 | 69.76 | **1.71** | **1.41-2.04** | 43 | 22.47 | **1.91** | **1.38-2.58** |
| Pancreas | C25 | 186 | 131.71 | **1.41** | **1.22-1.63** | 49 | 32.8 | **1.49** | **1.11-1.98** |
| Lung | C33-C34 | 949 | 529.43 | **1.79** | **1.68-1.91** | 375 | 215.12 | **1.74** | **1.57-1.93** |
| Melanoma of skin | C43 | 274 | 138.6 | **1.98** | **1.75-2.23** | 350 | 180.05 | **1.94** | **1.75-2.16** |
| Breast | C50 | 604 | 521.58 | **1.16** | **1.07-1.25** | 850 | 739.36 | **1.15** | **1.07-1.23** |
| Prostate | C61 | 864 | 761.23 | **1.14** | **1.06-1.21** | 1240 | 1040.4 | **1.19** | **1.13-1.26** |
| Testis | C62 | 32 | 11.57 | **2.77** | **1.89-3.90** | 70 | 18.31 | **3.82** | **2.98-4.83** |
| Kidney | C64 | 340 | 152.19 | **2.23** | **2.00-2.48** | 308 | 186.9 | **1.65** | **1.47-1.84** |
| Urinary bladder | C67 | 227 | 197.36 | **1.15** | **1.01-1.31** | 257 | 208.09 | **1.24** | **1.09-1.40** |
| Brain/CNS | C70-C72 | 76 | 49.8 | **1.53** | **1.20-1.91** | 28 | 19.31 | 1.45 | 0.96-2.10 |
| Thyroid | C73 | 71 | 32.62 | **2.18** | **1.70-2.75** | 75 | 45.7 | **1.64** | **1.29-2.06** |
| **All haematological malignancies** | **C81-C96** | 716 | 308.36 | **2.32** | **2.15-2.50** | 577 | 286.66 | **2.01** | **1.85-2.18** |
| HL | C81 | 137 | 10.09 | **13.58** | **11.40-16.05** | 182 | 12.21 | **14.91** | **12.82-17.24** |
| Multiple myeloma | C90 | 79 | 57.27 | **1.38** | **1.09-1.72** | 76 | 45.18 | **1.68** | **1.33-2.11** |
| Lymphoid leukaemia | C91 | 72 | 52.56 | **1.37** | **1.07-1.73** | 87 | 64.00 | **1.36** | **1.09-1.68** |
| ALL | C91.0 | 17 | 2.94 | **5.78** | **3.37-9.26** | 7 | 1.42 | **4.93** | **1.97-10.16** |
| Myeloid leukaemia | C92 | 171 | 38.48 | **4.44** | **3.80-5.16** | 50 | 19.99 | **2.50** | **1.86-3.30** |
| AML | C92.0 | 124 | 22.25 | **5.57** | **4.64-6.64** | 26 | 7.93 | **3.28** | **2.14-4.80** |
| **All sites**** | **C00-C97** | 6788 | 4523.95 | **1.50** | **1.46-1.54** | 6066 | 4468.11 | **1.36** | **1.32-1.39** |

O: observed number of subsequent primary malignancies; E: expected number of subsequent primary malignancies;
SIR: standardized incidence ratio with 95% confidence intervals (lower-upper limits); HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; ALL: acute lymphoblastic leukaemia; AML: acute myeloblastic leukaemia.
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96)
**excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

**Figure 19. Overall SIRs of SPM by follow-up duration and calendar periods for NHL survivors aged <60 vs. ≥60 years at diagnosis, for both sexes**




SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; NHL: non-Hodgkin lymphoma; SPM: subsequent primary malignancies; AML: acute myeloid leukaemia. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites and all solid cancers: excluding non-melanoma skin cancer(C44).

## Subsequent malignancies following multiple myeloma (MM, C90)

### Descriptive statistics of patients with first primary MM

Between 1990 and 2011, 39,074 cases (78% aged 60 years or older and only 3% aged 15 to 44) were registered with a diagnosis of MM as a first malignancy in Germany (**Table 12**). Approximately 17% (N=6,537) of MM cases had a follow-up time between five to ten years after their diagnosis, and only 4% (N=1,712) had a follow-up of 10 years or longer. The median follow-up time was 1.9 years in men and 2 years in women, amounting to 121,875.71 person-years in total. In both sexes, about 4.5% (N=1,761) of cases had developed SPM, most of these cases had a second subsequent primary malignancy.

**Table 12. Descriptive statistics of patients with first primary MM, Germany (1990–2011)**

| | Males | | Females | | Total | |
|---|---|---|---|---|---|---|
| | Number | % | Number | % | Number | % |
| **Patients with first primary malignancy*** | **20591** | **100** | **18483** | **100** | **39074** | **100** |
| **Patients by age at first malignancy diagnosis** | | | | | | |
| 15-44 years old | 754 | 3.66 | 494 | 2.67 | 1248 | 3.19 |
| 45-59 years old | 4265 | 20.71 | 2982 | 16.13 | 7247 | 18.55 |
| 60-74 years old | 10439 | 50.70 | 8551 | 46.26 | 18990 | 48.60 |
| >75 years old | 5133 | 24.93 | 6456 | 34.93 | 11589 | 29.66 |
| **Patients by follow-up time** | | | | | | |
| ≤1 year | 6435 | 31.25 | 5777 | 31.26 | 12212 | 31.25 |
| >1 to ≤5 years | 9882 | 47.99 | 8731 | 47.24 | 18613 | 47.64 |
| >5 to ≤10 years | 3394 | 16.48 | 3143 | 17.00 | 6537 | 16.73 |
| >10 years | 880 | 4.27 | 832 | 4.50 | 1712 | 4.38 |
| **Patients with multiple primary malignancies** | | | | | | |
| 1 primary malignant tumour | 19546 | 94.92 | 17846 | 96.55 | 37392 | 95.70 |
| 2 primaries | 997 | 4.84 | 609 | 3.29 | 1606 | 4.11 |
| 3 primaries | 45 | 0.22 | 27 | 0.15 | 72 | 0.18 |
| 4 or more primaries | 3 | 0.01 | 1 | 0.01 | 4 | 0.01 |
| **Person-years of observation** | **63711.34** | | **58164.37** | | **121875.71** | |
| **Median length of follow-up (years)** | | | | | | |
| **..All ages** | **1.92** | | **2.00** | | **-** | |
| 15-44 years old | 3.52 | | 4.13 | | - | |
| 45-59 years old | 2.80 | | 3.09 | | - | |
| 60-74 years old | 2.00 | | 2.25 | | - | |
| >75 years old | 1.08 | | 1.25 | | - | |
| **Observed number of subsequent malignancies** | **1095** | **5.32** | **666** | **3.60** | **1761** | **4.51** |
| Synchronous (<2 months)** | 259 | 23.65 | 144 | 21.62 | 403 | 22.88 |
| Metachronous (>2 months)** | 836 | 76.35 | 522 | 78.38 | 1358 | 77.12 |
| **Expected number of subsequent malignancies** | **994.88** | | **587.28** | | **1582.16** | |

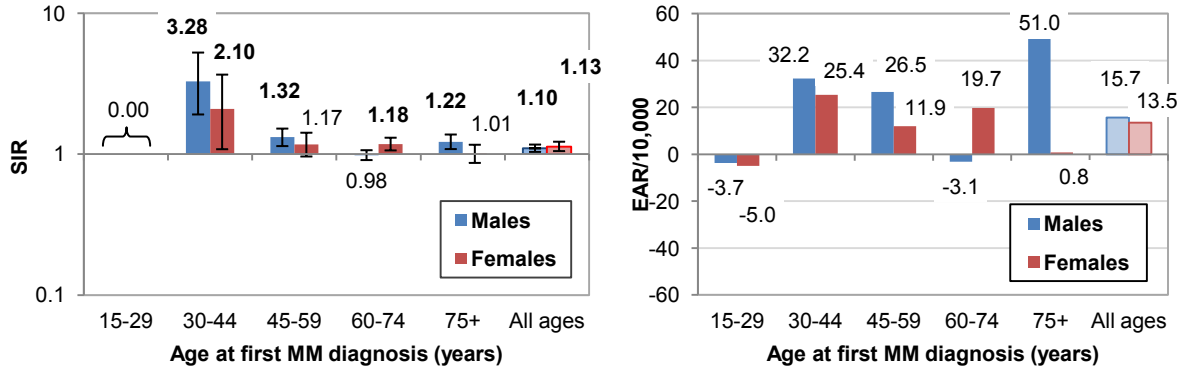
*after excluding Death Certificate only (DCO) cases, preceding primary tumours, and patients aged less than 15 years old
**after the diagnosis of the first primary cancer
MM: multiple myeloma.

### Age-specific risks (15 years age group) of all subsequent malignancies by sex

There was a small, but a statistically significant, increase in the overall relative risk of developing SPM in MM patients compared with the general population (SIR=1.11; 95% CI=1.06–1.17, EAR=14.67/10,000 person-years). Women had a slightly higher SIR than men (1.13 vs. 1.10), but the difference appeared to be not statistically significant (**Figure 20**). No SPM were observed

among patients who were aged under 30 at first MM diagnosis, possibly due to lower incidence of the first cancer at a young age in the general population. For those who were aged 30-44 years, the relative risk of all SPM was 2.7-fold higher than the general population in both sexes. However, it appeared that the SIR diminished with advancing age.

**Figure 20. Observed number, SIRs and EARs of all SPM by age at diagnosis of MM and sex**




**Observed number of SPM by age and sex**

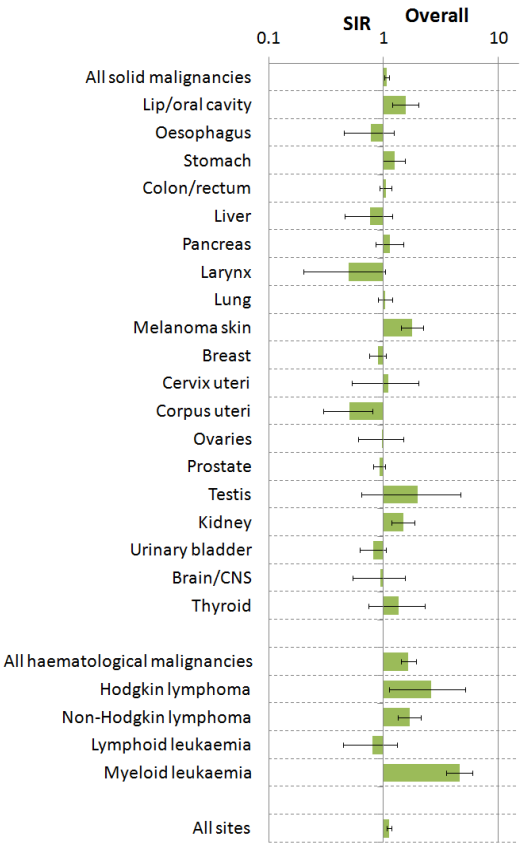
| | 15-29 | 30-44 | 45-59 | 60-74 | 75+ | All ages |
|---|---|---|---|---|---|---|
| **Males** | 0 | 17 | 195 | 603 | 280 | 1095 |
| **Females** | 0 | 12 | 107 | 366 | 181 | 666 |

SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; EAR: excess absolute risk per 10,000 person-years; MM: multiple myeloma; SPM: subsequent primary malignancies.
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

### Site-specific risks by sex and age at first MM diagnosis

In both sexes, the risk of subsequent solid malignancies in MM patients was marginally elevated compared with the general population (O=1,540, SIR=1.07; 95% CI=1.01–1.12, EAR=7.93/10,000) (**Figure 21**). Patients with MM were also found to be at 1.7-fold increased risk for other haematological malignancies, though they occurred less frequently than solid malignancies (O=178, SIR=1.65; 95% CI=1.41–1.91, EAR=5.74/10,000). There was a significantly higher risk of ML (4.6-fold), HL (2.8-fold), NHL (1.7-fold), and cancers of the skin melanoma (1.8-fold), lip/oral cavity (1.6-fold), and kidney (1.5-fold). For these subsequent malignancies, the EAR was also observed to be the highest. Risks for some other cancers were slightly elevated but not significantly different from expected risks. There was a significantly reduced risk of developing cancer of the uterus. The SIR of oral cavity (mainly lip) and lung cancer was elevated only in women, whereas men had slightly higher risks of melanoma skin and kidney cancer (but SIRs were not significantly different).

**Figure 21. Observed number, SIRs and EARs according to the type of SPM following MM by sex and overall**

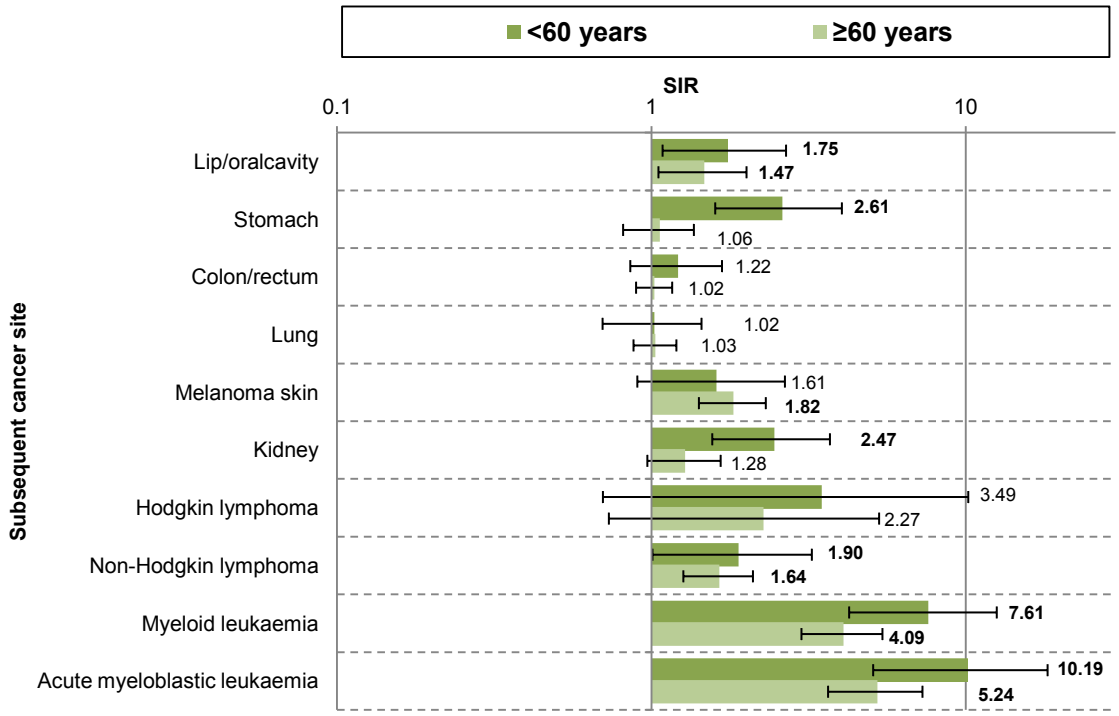



| | Overall | | | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | SIR | O | EAR | O | SIR | 95% CI | EAR | O | SIR | 95% CI | EAR |
| All solid malignancies | **1.07** | 1540 | 7.9 | 961 | 1.05 | 0.99-1.12 | 7.8 | 579 | 1.09 | 1.00-1.18 | 8.1 |
| Lip/oral cavity | **1.56** | 61 | 1.8 | 41 | 1.35 | 0.97-1.83 | 1.7 | 20 | **2.31** | **1.41-3.56** | 2.0 |
| Oesophagus | 0.77 | 17 | -0.4 | 12 | 0.66 | 0.34-1.16 | -1.0 | 5 | 1.29 | 0.42-3.01 | 0.2 |
| Stomach | 1.25 | 81 | 1.3 | 56 | 1.31 | 0.99-1.70 | 2.1 | 25 | 1.13 | 0.73-1.66 | 0.5 |
| Colon/rectum | 1.05 | 264 | 1.0 | 160 | 1.04 | 0.89-1.22 | 1.0 | 104 | 1.05 | 0.86-1.27 | 0.9 |
| Liver | 0.77 | 19 | -0.5 | 14 | 0.75 | 0.41-1.25 | -0.8 | 5 | 0.83 | 0.27-1.95 | -0.2 |
| Pancreas | 1.14 | 53 | 0.5 | 27 | 1.02 | 0.67-1.48 | 0.1 | 26 | 1.31 | 0.86-1.92 | 1.1 |
| Larynx | 0.50 | 7 | -0.6 | 6 | 0.47 | 0.17-1.02 | -1.1 | 1 | 0.84 | 0.01-4.68 | 0.0 |
| Lung | 1.03 | 194 | 0.4 | 136 | 0.92 | 0.77-1.09 | -1.8 | 58 | **1.42** | **1.08-1.83** | 2.9 |
| Melanoma skin | **1.78** | 83 | 3.0 | 56 | **1.94** | **1.46-2.51** | 4.3 | 27 | **1.53** | **1.01-2.23** | 1.6 |
| Breast | 0.89 | 150 | -1.5 | 5 | 2.15 | 0.69-5.01 | 0.4 | 145 | 0.87 | 0.74-1.03 | -3.7 |
| Cervix uteri | 1.10 | 10 | 0.1 | | | | | 10 | 1.10 | 0.53-2.03 | 0.2 |
| Corpus uteri | **0.51** | 18 | -1.4 | | | | | 18 | **0.51** | **0.30-0.80** | -3.0 |
| Ovaries | 0.97 | 21 | -0.1 | | | | | 21 | 0.97 | 0.60-1.48 | -0.1 |
| Prostate | 0.92 | 258 | -1.8 | 258 | 0.92 | 0.81-1.04 | -3.5 | | | | |
| Testis | 1.99 | 5 | 0.2 | 5 | 1.99 | 0.64-4.65 | 0.4 | | | | |
| Kidney | **1.49** | 80 | 2.1 | 54 | **1.48** | **1.11-1.94** | 2.8 | 26 | 1.49 | 0.98-2.19 | 1.5 |
| Urinary bladder | 0.81 | 58 | -1.1 | 45 | 0.80 | 0.58-1.07 | -1.8 | 13 | 0.88 | 0.47-1.51 | -0.3 |
| Brain/CNS | 0.94 | 16 | -0.1 | 8 | 0.77 | 0.33-1.51 | -0.4 | 8 | 1.22 | 0.53-2.40 | 0.3 |
| Thyroid | 1.35 | 14 | 0.3 | 6 | 1.51 | 0.55-3.29 | 0.3 | 8 | 1.26 | 0.54-2.47 | 0.3 |
| All haematological malignancies | **1.65** | 178 | 5.7 | 110 | **1.68** | **1.38-2.02** | 7.0 | 68 | **1.60** | **1.25-2.03** | 4.4 |
| Hodgkin lymphoma | **2.61** | 8 | 0.4 | 8 | **4.17** | **1.79-8.21** | 1.0 | 0 | 0.00 | 0.00-3.22 | -0.2 |
| Non-Hodgkin lymphoma | **1.68** | 76 | 2.5 | 43 | **1.62** | **1.17-2.18** | 2.6 | 33 | **1.77** | **1.22-2.48** | 2.5 |
| Lymphoid leukaemia | 0.80 | 15 | -0.3 | 6 | 0.48 | 0.18-1.05 | -1.0 | 9 | 1.41 | 0.64-2.68 | 0.5 |
| Myeloid leukaemia | **4.61** | 62 | 4.0 | 43 | **5.32** | **3.85-7.17** | 5.5 | 19 | **3.53** | **2.13-5.52** | 2.3 |
| All sites | **1.11** | 1761 | 14.7 | 1095 | **1.10** | **1.04-1.17** | 15.7 | 666 | **1.13** | **1.05-1.22** | 13.5 |

O: observed number of subsequent primary malignancies; SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; EAR: excess absolute risk/10,000 person per year; MM: multiple myeloma: SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites and all solid cancers: excluding non-melanoma skin cancer (C44).

The effect of age at first MM diagnosis on risk was particularly high for haematological malignancies (SIR=8.33 in <45 years old vs. SIR=1.50 in ≥60 years old, a statistically significant difference) (**Appendix III, Table 40**). For subsequent NHL, SIR was notably highest in younger survivors (7.89 in <45 years). However, the increased risk for AML was significant only among those aged 45 years or older. In addition, SIRs for lip/oral cavity and melanoma did not significantly differ between patients aged <60 and ≥60 years at initial MM diagnosis (**Figure 22**).

**Figure 22. SIRs according to the type of SPM following MM by age at diagnosis, for both sexes**

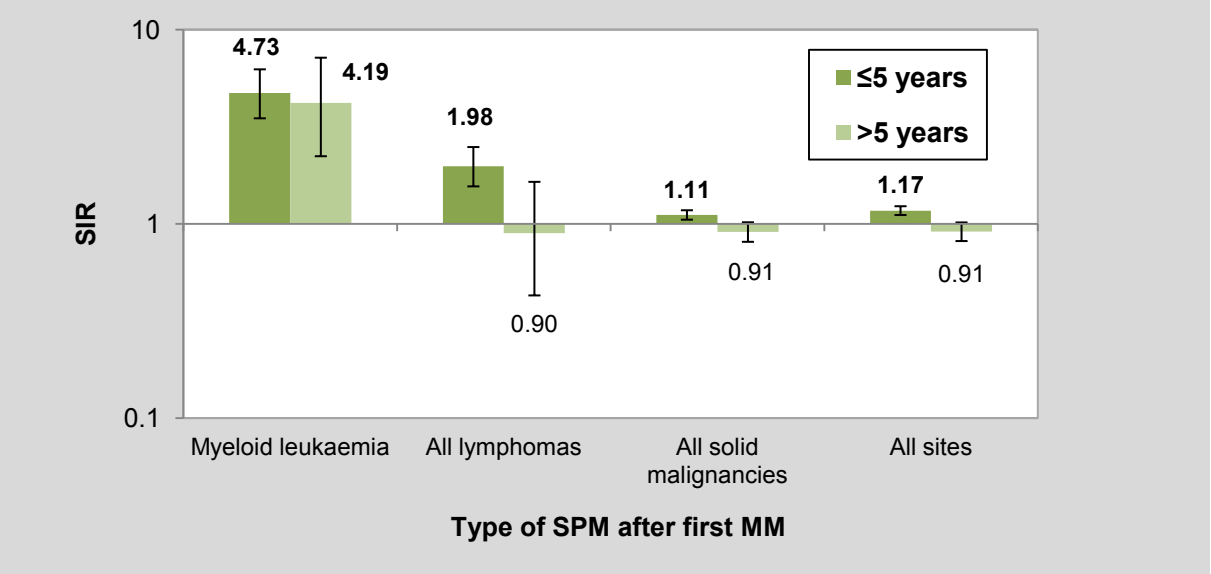



SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; MM: multiple myeloma; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

### Overall and site-specific risks in relation to time from MM diagnosis

The SIRs for all sites combined and specific cancer sites subsequent to MM by follow-up durations are presented **Figure 23** and in details in **Table 41** (**Appendix III**). The overall SIRs of SPM in the ≤1 year, >1 - ≤5, >5 - ≤10, and >10 years intervals following MM diagnosis were 1.70, 0.91, 1.00, and 0.62, respectively. For most SPM cancer sites (solid or haematological), the SIR was significantly highest during the first year and no significant excess risk was found beyond 10 years after first MM diagnosis. Risks for lip cancer and AML remained significantly elevated up to 10 years after diagnosis but not later. For malignant melanoma, the SIR was significantly higher within the initial 5 years of MM diagnosis. On the other hand, the risk for oesophagus, liver, breast, uterus, larynx, and urinary bladder was lower than expected in the general population among all matched age groups and follow-up intervals. When we excluded the initial 2 month period of the follow-up from the analysis, the SIR for all sites SPM dropped significantly from 1.11 to a value lower than expected in the general population (0.90), but risks remained significantly elevated for lip/oral cavity, melanoma, and AML (**Table 42, Appendix III**).

**Figure 23. Overall SIRs of SPM by follow-up duration (≤5 and >5 years) following MM, for both sexes**

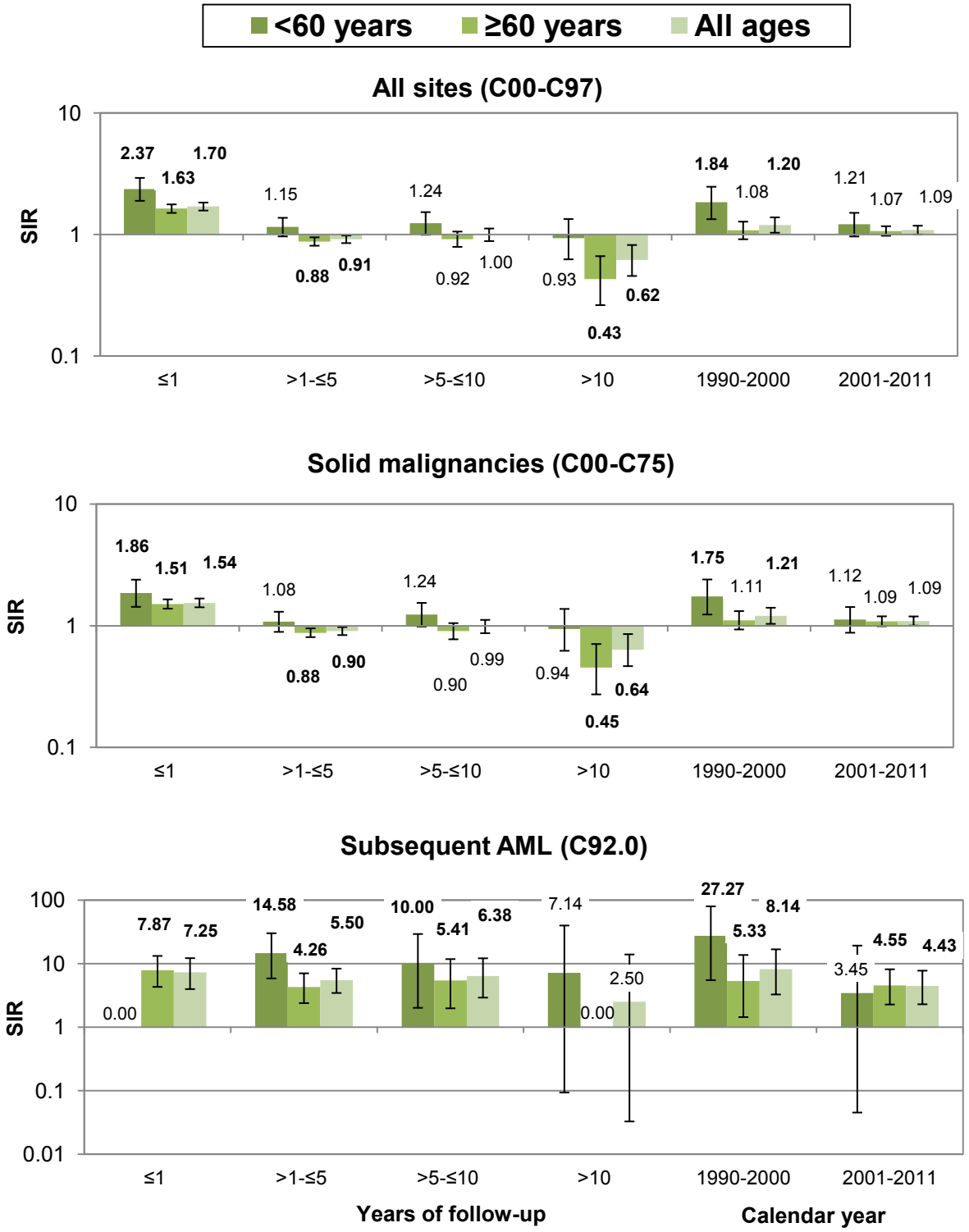



SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; MM: multiple myeloma; SPM: subsequent primary malignancies.
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites and all solid cancers: excluding non-melanoma skin cancer (C44). All lymphomas: include C81-C86.

### Overall and site-specific risks in relation to time from MM diagnosis and calendar periods by age (<60 vs. ≥60 years old)

A similar pattern of decreasing risk of SPM with follow-up time was observed in both the younger (<60 years) and older age group (≥60 years), **Figure 24**. The relative risk of developing subsequent AML was limited to the first ten years after the first MM diagnosis, and was highest (14.6-fold) in the >1-≤5 years follow-up interval among patients aged less than 60 years at first MM diagnosis. Trends of SIR by age for specific cancer sites can be seen in **Appendix IIII** (**Table 43**). The risk for SPM at any site (or for solid SPM) was slightly higher in the earlier calendar period than the recent period (SIR=1.20 vs. 1.09), but the difference was not statistically significant. After 2000, a slight increase in risk for lip/oral cavity cancer was observed; while the risk for other solid SPM has decreased (**Appendix III**, **Table 44**). Patients with MM were found to be at significantly increased risk for AML before and after the year 2000 with a higher risk noted in the earlier period, but the change were not statistically significant. However, SIRs for AML were notably decreased after 2000 in younger patients (<60 years), and remained constant in patients diagnosed with first MM at an older age (≥60 years).

**Figure 24. Overall SIRs of SPM by follow-up duration and calendar periods for MM survivors aged <60 vs. ≥60 years at diagnosis, for both sexes**




SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; MM: multiple myeloma; SPM: subsequent primary malignancies; AML: acute myeloid leukaemia. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites and all solid cancers: excluding non-melanoma skin cancer (C44).

### Risk of MM subsequent to selected first cancers

Bidirectional positive associations were found between MM and HL, ML, and cancers of the skin melanoma and kidney (**Table 13**). However, the occurrence of haematological malignancies such as HL, NHL, and ML after first MM was relatively higher than the occurrence of MM after these malignancies. In contrast, the occurrence of MM following any solid cancer, in particular kidney, was higher than in the opposite direction. The association of MM with lip/oral cavity was only unidirectional. In addition, MM occurred significantly in excess following but not preceding lung cancer (SIR=1.33 vs. 1.03). **Table 45** (**Appendix III**) summarizes the SIR for MM as a subsequent cancer in relation to time from diagnosis. The elevated risk of subsequent MM was only observed within the first year of diagnosis of other first cancers.

**Table 13. Risk of MM subsequent to other primary malignancies**

| | | MM as a first cancer | | | | MM as a subsequent cancer | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | **C00-C75** | 1540 | 1443.32 | **1.07** | **1.01-1.12** | 2193 | 1839.96 | **1.19** | **1.14-1.24** |
| Lip/oral cavity | C00-C14 | 61 | 39.09 | **1.56** | **1.19-2.00** | 45 | 44.8 | 1.00 | 0.73-1.34 |
| Stomach | C16 | 81 | 65.05 | 1.25 | 0.99-1.55 | 51 | 52.14 | 0.98 | 0.73-1.29 |
| Colon/rectum | C18-C21 | 264 | 252.4 | 1.05 | 0.92-1.18 | 356 | 331.88 | 1.07 | 0.96-1.19 |
| Lung | C33-C34 | 194 | 188.6 | 1.03 | 0.89-1.18 | 130 | 97.55 | **1.33** | **1.11-1.58** |
| Melanoma of skin | C43 | 83 | 46.57 | **1.78** | **1.42-2.21** | 108 | 77.36 | **1.40** | **1.15-1.69** |
| Kidney | C64 | 80 | 53.8 | **1.49** | **1.18-1.85** | 151 | 85.37 | **1.77** | **1.50-2.07** |
| **All haematological malignancies** | **C81-C96** | 178 | 108.04 | **1.65** | **1.41-1.91** | 130 | 127.12 | 1.02 | 0.85-1.21 |
| HL | C81 | 8 | 3.06 | **2.61** | **1.13-5.15** | 10 | 4.67 | **2.14** | **1.03-3.94** |
| NHL | C82-C85 | 76 | 45.18 | **1.68** | **1.33-2.11** | 79 | 57.27 | **1.38** | **1.09-1.72** |
| Myeloid leukaemia | C92 | 62 | 13.46 | **4.61** | **3.53-5.91** | 32 | 8.64 | **3.70** | **2.53-5.23** |
| AML | C92.0 | 46 | 7.75 | **5.94** | **4.35-7.92** | 11 | 3.41 | **3.23** | **1.61-5.77** |
| **All sites**** | **C00-C97** | 1761 | 1582.16 | **1.11** | **1.06-1.17** | 2271 | 1980.05 | **1.15** | **1.10-1.20** |

O: observed number of subsequent primary malignancies; E: expected number of subsequent primary malignancies; SIR: standardized incidence ratio; 95% confidence intervals (lower-upper limits); MM: multiple myeloma; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; AML: acute myeloblastic leukaemia; ICD-10: the WHO International Classification of Diseases (10th revision).

*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96)

**excluding non-melanoma skin cancer (C44)

Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Subsequent malignancies following leukaemia (C91-C95)

Overall, 75,053 cases were diagnosed with adult leukaemia, of which 38,331 cases were LL, and 30,518 cases were ML (**Table 14**). The majority of cases with LL and ML were diagnosed at ages older than 60 years. The overall median follow-up time was substantially shorter in patients with ML due to the unfavourable overall survival rates, with only 5.5% having a follow-up time of >10 years. Generally, SPM were observed in 6% (O=4,478) of cases who were diagnosed with first leukaemia between 1990 and 2011 (265,641.1 person-years). In both sexes, the relative risk of developing SPM at any site after being diagnosed with first leukaemia was significantly increased by 44% (SIR=1.44; 95% CI=1.39–1.48, EAR=51.17/10,000). Leukaemia comprises several types of malignancies that can also be classified according to the disease course into acute and chronic leukaemias. The relative and absolute risks of SPM were also analysed for the most common subtypes of acute leukaemias (ALL and AML) and chronic leukaemias (CLL and CML). However, due to insufficient number of SPM cases following acute leukaemias and unstable results, detailed analysis was not presented.

**Table 14. Descriptive statistics of patients with first primary leukaemia, Germany (1990–2011)**

| | LL (C91) | | ML (C92) | | All leukaemias (C91-C95) | |
|---|---|---|---|---|---|---|
| | Number | % | Number | % | Number | % |
| **Patients with first primary malignancy*** | **38331** | **100** | **30518** | **100** | **75053** | **100** |
| **Patients by sex** | | | | | | |
| Males | 22797 | 59.47 | 15898 | 52.09 | 42109 | 56.11 |
| Females | 15534 | 40.53 | 14620 | 47.91 | 32944 | 43.89 |
| **Patients by age at first malignancy diagnosis** | | | | | | |
| 15-44 years old | 3361 | 8.77 | 4685 | 15.35 | 8654 | 11.53 |
| 45-59 years old | 7548 | 19.69 | 6095 | 19.97 | 14510 | 19.33 |
| 60-74 years old | 17425 | 45.46 | 11634 | 38.12 | 31431 | 41.88 |
| >75 years old | 9997 | 26.08 | 8104 | 26.55 | 20458 | 27.26 |
| **Patients by follow-up time** | | | | | | |
| ≤1 year | 7763 | 20.25 | 15337 | 50.26 | 26498 | 35.31 |
| >1 to ≤5 years | 16074 | 41.93 | 9705 | 31.80 | 27781 | 37.02 |
| >5 to ≤10 years | 10825 | 28.24 | 3796 | 12.44 | 15189 | 20.24 |
| >10 years | 3669 | 9.57 | 1680 | 5.50 | 5585 | 7.44 |
| **Patients with multiple primary malignancies** | | | | | | |
| 1 primary malignant tumour | 35166 | 91.74 | 29639 | 97.12 | 70839 | 94.39 |
| 2 primaries | 2967 | 7.74 | 828 | 2.71 | 3964 | 5.28 |
| 3 primaries | 186 | 0.49 | 50 | 0.16 | 235 | 0.31 |
| 4 or more primaries | 12 | 0.03 | 1 | 0.00 | 15 | 0.02 |
| **Person-years of observation** | **174139.72** | | **78396.35** | | **265641.10** | |
| **Median length of follow-up (years)** | | | | | | |
| Males | 3.25 | | 0.92 | | 1.96 | |
| Females | 3.25 | | 0.84 | | 1.66 | |
| **Observed number of subsequent malignancies** | **3375** | **8.80** | **930** | **3.05** | **4478** | **5.97** |
| Synchronous (<2 months)** | 584 | 17.30 | 217 | 23.33 | 837 | 18.69 |
| Metachronous (>2 months)** | 2791 | 82.70 | 713 | 76.67 | 3641 | 81.31 |
| **Expected number of subsequent malignancies** | **2264.86** | | **703.24** | | **3118.63** | |

*after excluding Death Certificate only (DCO) cases, preceding primary malignancies, and patients aged less than 15 years old

**after the diagnosis of the first primary cancer

LL: Lymphoid leukaemia; ML: Myeloid leukaemia.

## Acute leukaemias

### Subsequent malignancies following acute lymphoblastic leukaemia (ALL, C91.0)

Estimates of the overall SIR and SIRs according to SPM localizations following ALL are given in **Table 15.** Patients with ALL (N=4,132) had a SPM risk that was 70% (O=80, SIR=1.71; 95% CI=1.36–2.13, EAR=25.72) higher in comparison to the general German population. The median follow-up time was 1.4 years in men and 1.2 years in women. Forty nine solid malignancies and 29 haematological malignancies occurred subsequent to ALL, but only the excess of other haematological was significantly higher than expected in the general population (SIR=8.03; 95% CI=5.38–11.54). Statistically significant SIRs were mainly seen for subsequent NHL (5-fold) and ML (33-fold). SIRs lower than 1 were observed for cancers of the stomach, larynx, lung, uterus, ovaries, prostate, and MM (none was significant). The relative risk of all types of SPM was significantly higher (7-fold) at early ages at onset of the first ALL, and rates declined steeply with advancing age.

### Subsequent malignancies following acute myeloblastic leukaemia (AML, C92.0)

There was overall a 28% (O=360, SIR=1.28; 95% CI=1.15–1.42, EAR=24.32) higher risk of developing SPM in patients (N=16,937) with first AML than the general German population (**Table 15**). Overall, median follow-up time was extremely short (nearly 6 months). The overall SIR for solid malignancies (O=277) was not significantly different from the expected incidence rates, however, significantly increased SIRs were noted for subsequent cancers of the lip, parotid glands, larynx, and lung (based on a small observed number). SIRs lower than 1 were observed for cancers of the stomach, liver, breast, cervix, prostate (significant), and brain/CNS. Significantly increased SIRs for all subsequent haematological malignancies, except for subsequent HL, were also observed. In general, the SIR of any SPM was significantly higher (3.8-fold) for patients who were first diagnosed with AML before the age of 45 than those diagnosed at an age older than 60 years (1.1-fold).

## Table 15. SIRs and EARs according to the type of SPM following first ALL and AML

| | | ALL N=4132 PYRs=12936.36 | | | | | AML N=16937 PYRs=32628.64 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **EAR** | **O** | **E** | **SIR** | **95% CI** | **EAR** |
| **All solid malignancies*** | **C00-C75** | 49 | 42.3 | 1.16 | 0.86-1.53 | 5.18 | 277 | 256.59 | 1.08 | 0.96-1.21 | 6.26 |
| Lip, oral cavity, and pharynx | C00-C14 | 2 | 1.48 | 1.35 | 0.15-4.88 | 0.40 | 12 | 8 | 1.50 | 0.77-2.62 | 1.23 |
| Lip | C00 | 1 | 0.05 | 20.00 | 0.26-111.28 | 0.73 | 3 | 0.32 | **9.38** | **1.88-27.39** | 0.82 |
| Tongue | C01-C02 | 1 | 0.29 | 3.45 | 0.05-19.19 | 0.55 | 3 | 1.56 | 1.92 | 0.39-5.62 | 0.44 |
| Gum/mouth | C03-C06 | 0 | 0.37 | 0.00 | 0.00-9.91 | -0.29 | 1 | 1.99 | 0.50 | 0.01-2.80 | -0.30 |
| Parotid/ other salivary gland | C07-C08 | 0 | 0.1 | 0.00 | 0.00-36.68 | -0.08 | 3 | 0.52 | **5.77** | **1.16-16.86** | 0.76 |
| Pharynx/other oral cavity | C09-C14 | 0 | 0.64 | 0 | 0.00-5.73 | -0.49 | 2 | 3.4 | 0.59 | 0.07-2.12 | -0.43 |
| Oesophagus | C15 | 1 | 0.65 | 1.54 | 0.02-8.56 | 0.27 | 6 | 4.04 | 1.49 | 0.54-3.23 | 0.60 |
| Stomach | C16 | 1 | 1.65 | 0.61 | 0.01-3.37 | -0.50 | 8 | 10.52 | 0.76 | 0.33-1.50 | -0.77 |
| Colon, rectum and anus | C18-C21 | 8 | 6.36 | 1.26 | 0.54-2.48 | 1.27 | 52 | 41.15 | 1.26 | 0.94-1.66 | 3.33 |
| Liver | C22 | 1 | 0.66 | 1.52 | 0.02-8.43 | 0.26 | 3 | 4.26 | 0.70 | 0.14-2.06 | -0.39 |
| Pancreas | C25 | 2 | 1.21 | 1.65 | 0.19-5.97 | 0.61 | 10 | 7.76 | 1.29 | 0.62-2.37 | 0.69 |
| Larynx | C32 | 0 | 0.44 | 0.00 | 0.00-8.34 | -0.34 | 9 | 2.69 | **3.35** | **1.53-6.35** | 1.93 |
| Lung | C33-C34 | 4 | 5.17 | 0.77 | 0.21-1.98 | -0.90 | 47 | 33.57 | **1.40** | **1.03-1.86** | 4.12 |
| Melanoma of skin | C43 | 4 | 1.85 | 2.16 | 0.58-5.54 | 1.66 | 10 | 9.18 | 1.09 | 0.52-2.00 | 0.25 |
| Breast | C50 | 7 | 6.19 | 1.13 | 0.45-2.33 | 0.63 | 24 | 35.09 | 0.68 | 0.44-1.02 | -3.40 |
| Cervix uteri | C53 | 1 | 0.5 | 2.00 | 0.03-11.13 | 0.39 | 1 | 2.38 | 0.42 | 0.01-2.34 | -0.42 |
| Corpus uteri | C54-C55 | 1 | 1.1 | 0.91 | 0.01-5.06 | -0.08 | 7 | 6.43 | 1.09 | 0.44-2.24 | 0.17 |
| Ovaries | C56 | 0 | 0.72 | 0.00 | 0.00-5.09 | -0.56 | 7 | 4.08 | 1.72 | 0.69-3.54 | 0.89 |
| Prostate | C61 | 3 | 6.71 | 0.45 | 0.09-1.31 | -2.87 | 28 | 46.7 | **0.60** | **0.40-0.87** | -5.73 |
| Testis | C62 | 4 | 0.85 | **4.71** | **1.27-12.05** | 2.43 | 2 | 1.25 | 1.60 | 0.18-5.78 | 0.23 |
| Kidney | C64 | 3 | 1.56 | 1.92 | 0.39-5.62 | 1.11 | 15 | 9.59 | 1.56 | 0.87-2.58 | 1.66 |
| Urinary bladder | C67 | 2 | 1.64 | 1.22 | 0.14-4.40 | 0.28 | 12 | 11.2 | 1.07 | 0.55-1.87 | 0.25 |
| Central nervous system | C70-C72 | 1 | 0.73 | 1.37 | 0.02-7.62 | 0.21 | 3 | 3.41 | 0.88 | 0.18-2.57 | -0.13 |
| Thyroid | C73 | 2 | 0.62 | 3.23 | 0.36-11.65 | 1.07 | 3 | 2.61 | 1.15 | 0.23-3.36 | 0.12 |
| **All haematological malignancies** | **C81-C96** | 29 | 3.61 | **8.03** | **5.38-11.54** | 19.63 | 67 | 18.97 | **3.53** | **2.74-4.49** | 14.72 |
| Hodgkin lymphoma | C81 | 1 | 0.37 | 2.70 | 0.04-15.04 | 0.49 | 3 | 0.83 | 3.61 | 0.73-10.56 | 0.67 |
| Non-Hodgkin lymphoma | C82-C85 | 7 | 1.42 | **4.93** | **1.97-10.16** | 4.31 | 26 | 7.93 | **3.28** | **2.14-4.80** | 5.54 |
| Multiple myeloma | C90 | 0 | 0.53 | 0.00 | 0.00-6.92 | -0.41 | 11 | 3.41 | **3.23** | **1.61-5.77** | 2.33 |
| Lymphoid leukaemia | C91 | 3 | 0.61 | 4.92 | 0.99-14.37 | 1.85 | 22 | 3.22 | **6.83** | **4.28-10.34** | 5.76 |
| Acute lymphoblastic | C91.0 | 1 | 0.13 | 7.69 | 0.10-42.80 | 0.67 | 13 | 0.23 | **56.52** | **30.07-96.66** | 3.91 |
| Chronic lymphocytic | C91.1 | 1 | 0.43 | 2.33 | 0.03-12.94 | 0.44 | 9 | 2.73 | **3.30** | **1.50-6.26** | 1.92 |
| Myeloid leukaemia | C92 | 15 | 0.46 | **32.61** | **18.24-53.79** | 11.24 | 0 | 2.45 | 0.00 | 0.00-1.50 | -0.75 |
| Acute myeloblastic | C92.0 | 9 | 0.26 | **34.62** | **15.80-65.72** | 6.76 | 0 | 1.43 | 0.00 | 0.00-2.57 | -0.44 |
| Chronic myeloid | C92.1 | 5 | 0.11 | **45.45** | **14.65-106.08** | 3.78 | 0 | 0.53 | 0.00 | 0.00-6.92 | -0.16 |
| **All sites**** | **C00-C97** | 80 | 46.73 | **1.71** | **1.36-2.13** | 25.72 | 360 | 280.65 | **1.28** | **1.15-1.42** | 24.32 |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); EAR: excess absolute risk per 10,000 person years; PYRs: person years of observation;
ALL: acute lymphocytic leukaemia; AML: acute myeloid leukaemia; SPM: subsequent primary malignancies; ICD-10: the WHO International Classification of Diseases (10th revision).
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Chronic leukaemias

## Subsequent malignancies following chronic lymphocytic leukaemia (CLL, C91.1)

### Descriptive statistics of patients with first primary CLL

A great proportion (79%) of patients with first CLL (N=30,878) were older than 60 years at time of diagnosis. The median follow-up time was 3.5 years in men and 3.6 years in women, and was lower for patients diagnosed at ages older than 75 years (**Table 16**). Approximately 60% of CLL patients had a follow-up time less than 5 years. In men and women, the observed number of SPM (O=3,022) was significantly higher than expected (E=2,034.97), the overall SIR being increased by 50% (95% CI=43%–54%) and the EAR was 68.10 excess cases/10,000 person-years.

**Table 16. Descriptive statistics of patients with first primary CLL, Germany (1990–2011)**

| | Males | | Females | | Total | |
|---|---|---|---|---|---|---|
| | Number | % | Number | % | Number | % |
| **Patients with first primary malignancy*** | **18158** | **100** | **12720** | **100** | **30878** | **100** |
| **Patients by age at first malignancy diagnosis** | | | | | | |
| 15-44 years old | 533 | 2.94 | 284 | 2.23 | 817 | 2.65 |
| 45-59 years old | 3757 | 20.69 | 2043 | 16.06 | 5800 | 18.78 |
| 60-74 years old | 9519 | 52.42 | 5807 | 45.65 | 15326 | 49.63 |
| >75 years old | 4349 | 23.95 | 4586 | 36.05 | 8935 | 28.94 |
| **Patients by follow-up time** | | | | | | |
| ≤1 year | 3098 | 17.06 | 2218 | 17.44 | 5316 | 17.22 |
| >1 to ≤5 years | 8062 | 44.40 | 5290 | 41.59 | 13352 | 43.24 |
| >5 to ≤10 years | 5459 | 30.06 | 3836 | 30.16 | 9295 | 30.10 |
| >10 years | 1539 | 8.48 | 1376 | 10.82 | 2915 | 9.44 |
| **Patients with multiple primary malignancies** | | | | | | |
| 1 primary malignant tumour | 16217 | 89.31 | 11821 | 92.93 | 28038 | 90.80 |
| 2 primaries | 1813 | 9.98 | 856 | 6.73 | 2669 | 8.64 |
| 3 primaries | 119 | 0.66 | 41 | 0.32 | 160 | 0.52 |
| 4 or more primaries | 9 | 0.05 | 2 | 0.02 | 11 | 0.04 |
| **Person-years of observation** | **83144.01** | | **61791.82** | | **144935.83** | |
| **Median length of follow-up (years)** | | | | | | |
| **All ages** | **3.46** | | **3.59** | | **-** | |
| 15-44 years old | 4.80 | | 4.19 | | - | |
| 45-59 years old | 4.54 | | 4.87 | | - | |
| 60-74 years old | 3.75 | | 4.29 | | - | |
| >75 years old | 2.04 | | 2.29 | | - | |
| **Observed number of subsequent malignancies** | **2078** | **11.44** | **944** | **7.42** | **3022** | **9.79** |
| Synchronous (<2 months)** | 323 | 15.54 | 191 | 20.23 | 514 | 17.01 |
| Metachronous (>2 months)** | 1755 | 84.46 | 753 | 79.77 | 2508 | 82.99 |
| **Expected number of subsequent malignancies** | **1388.01** | | **646.96** | | **2034.97** | |

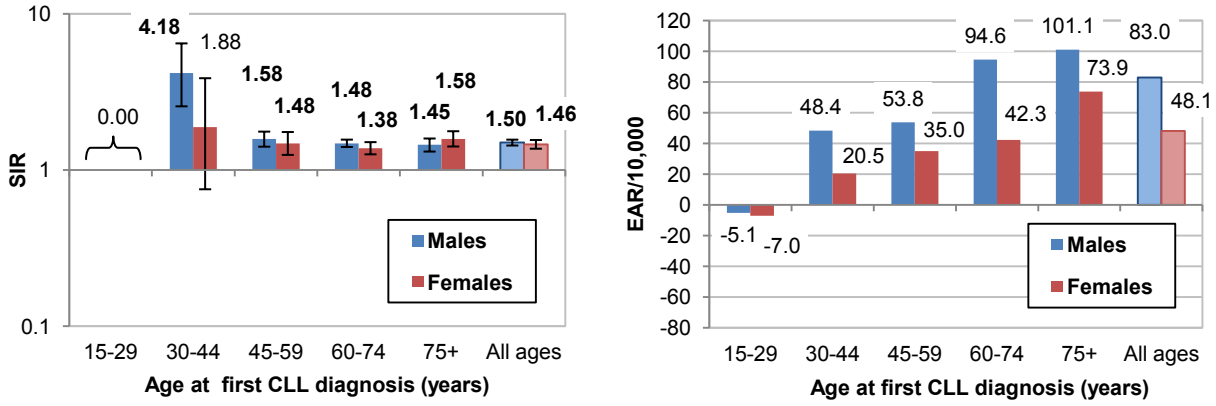
*after excluding Death Certificate only (DCO) cases, preceding primary malignancies, and patients aged less than 15 years old
**after the diagnosis of the first primary malignant cancer
CLL: chronic lymphocytic leukaemia.

### Age-specific risks (15 years age group) of all subsequent malignancies by sex

Generally, there is no significant gender difference in the overall relative risk of developing SPM (SIR 1.50 in men and 1.46 in women, both being significant) after CLL (**Figure 25**). No SPM

occurred in the 15-29 years age group in either sex. Men in the younger age group (30-44 years) had about 3 times the risk of men in the older age group (≥75 years). In women, SIR was not significantly different from that in the general population in the 30-44 age group. For all ages, men had higher incidence (O=2,078) and EAR of SPM (83 excess subsequent cancer cases per 10,000 patient per year) than women.

**Figure 25. Observed number, SIRs and EARs of all SPM by age at diagnosis of CLL and sex**




**Observed number of SPM by age and sex**

| | 15-29 | 30-44 | 45-59 | 60-74 | 75+ | All ages |
|---|---|---|---|---|---|---|
| **Males** | 0 | 20 | 320 | 1314 | 424 | 2078 |
| **Females** | 0 | 7 | 141 | 484 | 312 | 944 |

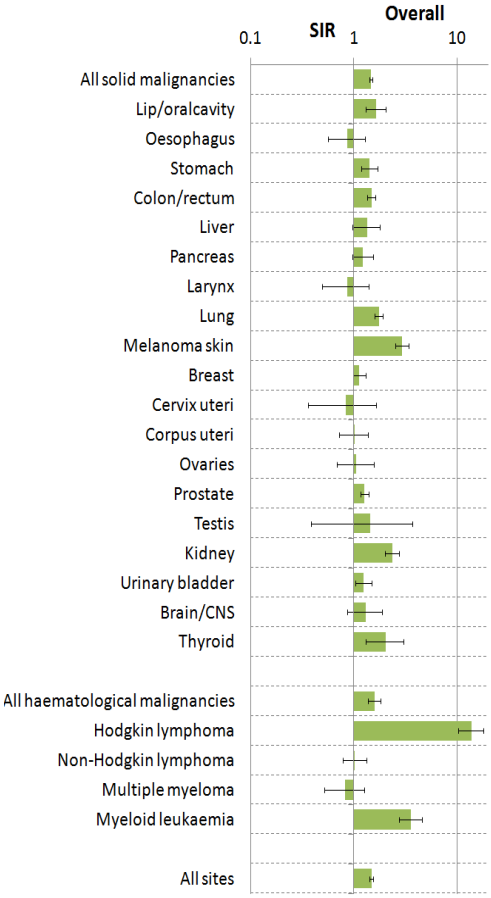
SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; EAR: excess absolute risk per 10,000 person-years; CLL: chronic lymphocytic leukaemia; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

### Site-specific risks by sex and age at first CLL diagnosis

**Figure 26** presents risks of SPM by sex and cancer type. Overall, there was no significant difference in SIR between solid malignancies (1.47) and haematological malignancies (1.59) after first CLL. However, subsequent solid malignancies (O=2,725) were more frequent compared with haematological malignancies (O=221). Cancers of the prostate, colon/rectum and lung were the most frequently observed of all solid SPM. In addition, highest EARs (6 to 12 excess cases per 10,000 person-years) were observed for subsequent cancers of the lung, colorectal, skin melanoma, prostate and kidney. SIRs were significantly elevated for subsequent HL (13.8), CML (9.9), and cancers of the skin melanoma (3.0), kidney (2.4), thyroid (2.1), lung (1.8), lip/oral cavity (1.7), colon/rectum (1.5), stomach (1.4), prostate (1.3), and urinary bladder (1.2, borderline).

Increased risk for stomach cancer was limited to men only, while increased risks for urinary bladder and thyroid were limited to women. Overall, no SPM occurred significantly lower than expected rates in either gender.

**Figure 26. Observed number, SIRs and EARs according to the type of SPM following CLL by sex and overall**

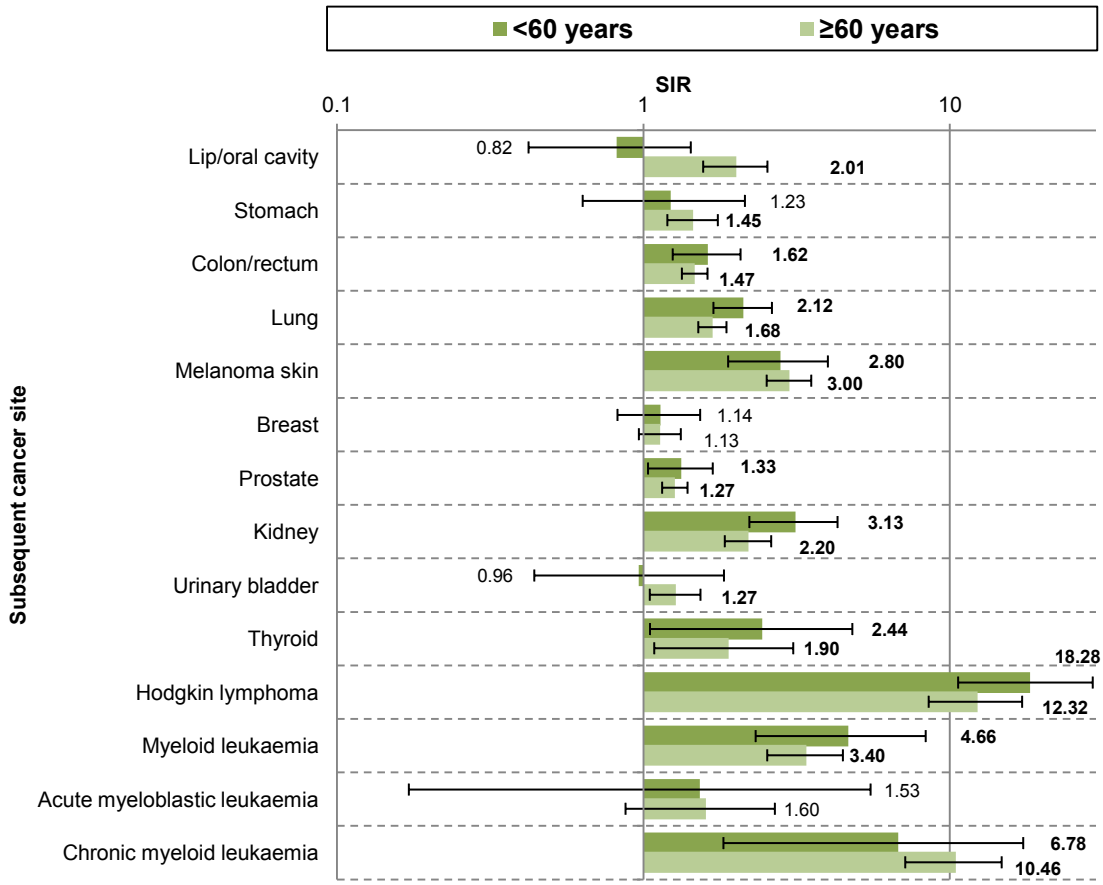



| | Overall | | | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | SIR | O | EAR | O | SIR | 95% CI | EAR | O | SIR | 95% CI | EAR |
| All solid malignancies | **1.47** | 2725 | 60.0 | 1891 | **1.49** | **1.42-1.56** | 74.5 | 834 | **1.43** | **1.33-1.53** | 40.4 |
| Lip/oralcavity | **1.66** | 82 | 2.2 | 63 | **1.56** | **1.20-2.00** | 2.7 | 19 | **2.05** | **1.24-3.21** | 1.6 |
| Oesophagus | 0.87 | 25 | -0.3 | 23 | 0.93 | 0.59-1.40 | -0.2 | 2 | 0.48 | 0.05-1.72 | -0.4 |
| Stomach | **1.43** | 124 | 2.6 | 89 | **1.46** | **1.17-1.79** | 3.4 | 35 | 1.36 | 0.95-1.89 | 1.5 |
| Colon/rectum | **1.49** | 488 | 11.1 | 295 | **1.37** | **1.22-1.53** | 9.5 | 193 | **1.73** | **1.49-1.99** | 13.1 |
| Liver | 1.34 | 45 | 0.8 | 35 | 1.32 | 0.92-1.83 | 1.0 | 10 | 1.45 | 0.70-2.67 | 0.5 |
| Pancreas | 1.23 | 74 | 1.0 | 43 | 1.15 | 0.83-1.55 | 0.7 | 31 | 1.37 | 0.93-1.94 | 1.3 |
| Larynx | 0.86 | 16 | -0.2 | 15 | 0.87 | 0.49-1.43 | -0.3 | 1 | 0.83 | 0.01-4.60 | 0.0 |
| Lung | **1.75** | 436 | 12.9 | 365 | **1.78** | **1.60-1.97** | 19.2 | 71 | **1.63** | **1.27-2.05** | 4.4 |
| Melanoma skin | **2.96** | 173 | 7.9 | 132 | **3.35** | **2.80-3.97** | 11.1 | 41 | **2.16** | **1.55-2.93** | 3.6 |
| Breast | 1.14 | 204 | 1.7 | 8 | **2.48** | **1.07-4.90** | 0.6 | 196 | 1.11 | 0.96-1.28 | 3.2 |
| Cervix uteri | 0.83 | 8 | -0.1 | | | | | 8 | 0.83 | 0.36-1.64 | -0.3 |
| Corpus uteri | 1.01 | 40 | 0.0 | | | | | 40 | 1.01 | 0.72-1.38 | 0.1 |
| Ovaries | 1.05 | 25 | 0.1 | | | | | 25 | 1.05 | 0.68-1.56 | 0.2 |
| Prostate | **1.28** | 500 | 7.5 | 500 | **1.28** | **1.17-1.39** | 13.0 | | | | |
| Testis | 1.44 | 4 | 0.1 | 4 | 1.44 | 0.39-3.70 | 0.2 | | | | |
| Kidney | **2.36** | 170 | 6.8 | 115 | **2.21** | **1.82-2.65** | 7.6 | 55 | **2.74** | **2.07-3.57** | 5.7 |
| Urinary bladder | **1.24** | 120 | 1.6 | 90 | 1.13 | 0.91-1.39 | 1.3 | 30 | **1.77** | **1.19-2.52** | 2.1 |
| Brain/CNS | 1.30 | 28 | 0.5 | 15 | 1.04 | 0.58-1.72 | 0.1 | 13 | 1.81 | 0.96-3.09 | 0.9 |
| Thyroid | **2.05** | 24 | 0.9 | 8 | 1.52 | 0.66-3.00 | 0.3 | 16 | **2.47** | **1.41-4.02** | 1.5 |
| All haematological malignancies | **1.59** | 221 | 5.7 | 137 | **1.50** | **1.26-1.77** | 5.5 | 84 | **1.76** | **1.40-2.18** | 5.9 |
| Hodgkin lymphoma | **13.78** | 51 | 3.3 | 34 | **13.71** | **9.49-19.16** | 3.8 | 17 | **13.93** | **8.11-22.31** | 2.6 |
| Non-Hodgkin lymphoma | 1.03 | 59 | 0.1 | 40 | 1.09 | 0.78-1.49 | 0.4 | 19 | 0.91 | 0.55-1.42 | -0.3 |
| Multiple myeloma | 0.83 | 22 | -0.3 | 14 | 0.81 | 0.44-1.35 | -0.4 | 8 | 0.88 | 0.38-1.73 | -0.2 |
| Myeloid leukaemia | **3.58** | 62 | 3.1 | 33 | **2.93** | **2.01-4.11** | 2.6 | 29 | **4.79** | **3.20-6.87** | 3.7 |
| All sites | **1.49** | 3022 | 68.1 | 2078 | **1.50** | **1.43-1.56** | 83.0 | 944 | **1.46** | **1.37-1.56** | 48.1 |

O: observed number of subsequent malignancies; SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; EAR: excess absolute risk/10,000 person per year; CLL: chronic lymphocytic leukaemia; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites and all solid cancers: excluding non-melanoma skin cancer (C44).

The estimated SIRs by age at first CLL diagnosis and cancer type, summed up for both sexes, are given in detail in **Table 46** (**Appendix III**) and summarized in **Figure 27**. Risks for kidney cancer and ML were significantly increased in all age groups, but were highest amongst patients in the diagnosis age group under 45 years. For men in this age group (under 45 years), SIRs were also significantly elevated for subsequent stomach and lung cancers. Risks for cancer at other organs appeared not to be related to age of patients at first CLL diagnosis.

**Figure 27. SIRs according to the type of SPM following CLL by age at diagnosis, for both sexes**

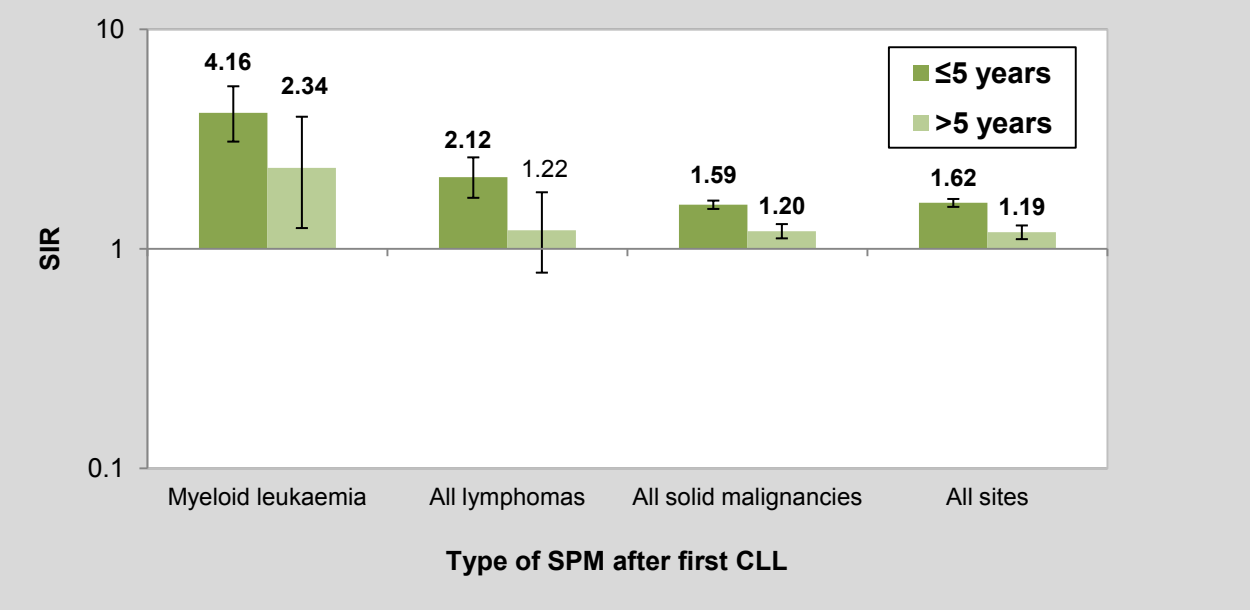



SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; CLL: chronic lymphocytic leukaemia; SPM: subsequent primary malignancies.
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

### Overall and site-specific risks in relation to time from CLL diagnosis

For all types of SPM (**Figure 28**), the SIR was significantly higher during the first five years of follow-up since the first CLL diagnosis than after 5 years. After 5 years, the SIR for solid cancers and for ML (mostly CML) remained significantly elevated, but not for subsequent lymphomas. Similar patterns of declining SIRs with longer follow-up (>5 years) can be seen for many specific cancer types in **Appendix III** (**Table 47**), except for subsequent lung and melanoma, for which SIRs remained significantly elevated beyond 5 years. After excluding the first year of follow-up from the overall analysis, the SIR for all sites SPM declined significantly from 1.49 (95% CI=1.43–1.54) to 1.25 (95% CI=1.20–1.31). This decline was also found for both solid and haematological SPM, SIRs remained however significantly elevated for cancers of the stomach, colon/rectum, lung, skin melanoma, kidney, HL, and CML (**Appendix III**, **Table 48**).

**Figure 28. Overall SIRs of SPM by follow-up duration (≤5 and >5 years) following CLL, for both sexes**

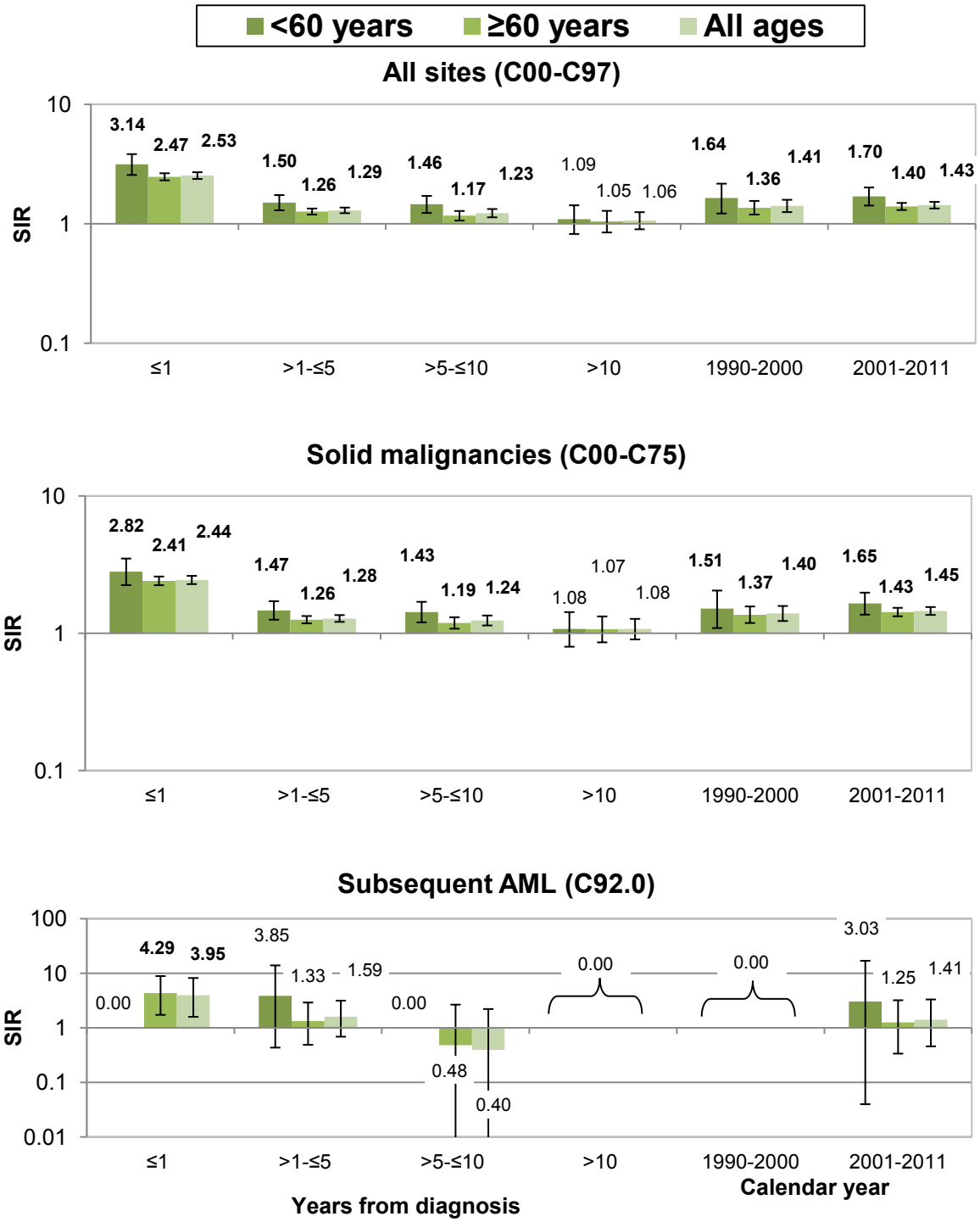



SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; CLL: chronic lymphocytic leukaemia; SPM: subsequent primary malignancies.
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites and all solid cancers: excluding non-melanoma skin cancer (C44). All lymphomas: include C81-C86.

### Overall and site-specific risks in relation to time from CLL diagnosis and calendar periods by age (<60 vs. ≥60 years old)

The overall risk and risk for solid SPM were significantly elevated up to 10 years after first CLL diagnosis, but not later. Similar trends in SIRs were seen in both the younger and older age groups, but SIRs were consistently higher in the younger age group. For solid malignancies, SIRs were slightly higher after the year 2000 compared to before 2000 (not statistically significantly different, **Figure 29**). Increased risk of subsequent AML was only limited to the first year of follow-up in older people and presented no specific trend over time (see also **Table 49** and **Table 50** in **Appendix IIII**).

**Figure 29. Overall SIRs of SPM by follow-up duration and calendar periods for CLL survivors aged <60 vs. ≥60 years at diagnosis, for both sexes**




SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; CLL: chronic lymphocytic leukaemia; SPM: subsequent primary malignancies; AML: acute myeloid leukaemia. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites and all solid cancers: excluding non-melanoma skin cancer (C44).

### Risk of CLL subsequent to selected first cancers

Reciprocal positive associations were observed between CLL and all first cancers analysed (**Table 17**). Following solid cancer, the increased risk of developing subsequent CLL was highest following first primary malignant melanoma of the skin and kidney cancer (SIR=2.56 and 2.06, respectively) with SRs being significantly greater than 1 within the first 10 years of follow-up only (**Appendix III, Table 51**).

### Table 17. Risk of CLL subsequent to other primary malignancies

| | | CLL as a first cancer | | | | CLL as a subsequent cancer | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Cancer site** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **O** | | **SIR** | **95% CI** |
| **All solid malignancies*** | **C00-C75** | 2725 | 1856.03 | **1.47** | **1.41-1.52** | 2102 | 1477.7 | **1.42** | **1.36-1.48** |
| Lip/oral cavity | C00-C14 | 82 | 49.51 | **1.66** | **1.32-2.06** | 66 | 37.47 | **1.76** | **1.36-2.24** |
| Stomach | C16 | 124 | 86.84 | **1.43** | **1.19-1.70** | 60 | 43.01 | **1.40** | **1.06-1.80** |
| Colon/rectum | C18-C21 | 488 | 327.7 | **1.49** | **1.36-1.63** | 331 | 267.74 | **1.24** | **1.11-1.38** |
| Lung | C33-C34 | 436 | 249.02 | **1.75** | **1.59-1.92** | 123 | 80.41 | **1.53** | **1.27-1.83** |
| Melanoma of skin | C43 | 173 | 58.44 | **2.96** | **2.54-3.44** | 160 | 62.4 | **2.56** | **2.18-2.99** |
| Prostate | C61 | 500 | 391.99 | **1.28** | **1.17-1.39** | 576 | 426.09 | **1.35** | **1.24-1.47** |
| Kidney | C64 | 170 | 72.08 | **2.36** | **2.02-2.74** | 149 | 72.42 | **2.06** | **1.74-2.42** |
| Urinary bladder | C67 | 120 | 96.42 | **1.24** | **1.03-1.49** | 121 | 82.01 | **1.48** | **1.22-1.76** |
| Thyroid | C73 | 24 | 11.72 | **2.05** | **1.31-3.05** | 24 | 14.12 | **1.70** | **1.09-2.53** |
| **All haematological malignancies** | **C81-C96** | 221 | 139.17 | **1.59** | **1.39-1.81** | 96 | 102.84 | 0.93 | 0.76-1.14 |
| HL | C81 | 51 | 3.7 | **13.78** | **10.26-18.12** | 20 | 3.75 | **5.33** | **3.26-8.24** |
| Myeloid leukaemia | C92 | 62 | 17.34 | **3.58** | **2.74-4.58** | 37 | 6.9 | **5.36** | **3.78-7.39** |
| CML | C92.1 | 36 | 3.65 | **9.86** | **6.91-13.66** | 26 | 3.1 | **8.39** | **5.48-12.29** |
| **All sites**** | **C00-C97** | 3022 | 2034.97 | **1.49** | **1.43-1.54** | 2080 | 1590.52 | **1.31** | **1.25-1.37** |

O: observed number of subsequent primary malignancies; E: expected number of subsequent primary malignancies; SIR: standardized incidence ratio; 95% confidence intervals (lower-upper); CLL: chronic lymphocytic leukaemia; SPM: subsequent primary malignancies; CML: chronic myeloid leukaemia; HL: Hodgkin lymphoma; ICD-10: the WHO International Classification of Diseases ($10^{th}$ revision).

*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96)

**excluding non-melanoma skin cancer (C44)

Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Subsequent malignancies following chronic myeloid leukaemia (CML, C92.1)

### Descriptive statistics of patients with first primary CML

Among patients who were first diagnosed with CML (N=7,900, **Table 18**), 5.5% (O=438) developed one or more subsequent malignant tumours (365 solid and 62 haematological malignancies). More than half of CML patients were older than 60 when first diagnosed. The median follow-up time was 2.7 in men and 2.8 in women and the accumulated person-years at risk in the whole cohort totalled 33,779.58. The proportion of patients that could be followed up for 10 years or longer was very small (10%).

**Table 18. Descriptive statistics of patients with first primary CML, Germany (1990–2011)**

| | Males | | Females | | Total | |
|---|---|---|---|---|---|---|
| | Number | % | Number | % | Number | % |
| **Patients with first primary malignancy*** | **4300** | **100** | **3600** | **100** | **7900** | **100** |
| **Patients by age at first malignancy diagnosis** | | | | | | |
| 15-44 years old | 955 | 22.21 | 605 | 16.81 | 1560 | 19.75 |
| 45-59 years old | 1045 | 24.30 | 845 | 23.47 | 1890 | 23.92 |
| 60-74 years old | 1515 | 35.23 | 1207 | 33.53 | 2722 | 34.46 |
| >75 years old | 785 | 18.26 | 943 | 26.19 | 1728 | 21.87 |
| **Patients by follow-up time** | | | | | | |
| ≤1 year | 1145 | 26.63 | 916 | 25.44 | 2061 | 26.09 |
| >1 to ≤5 years | 1701 | 39.56 | 1430 | 39.72 | 3131 | 39.63 |
| >5 to ≤10 years | 1039 | 24.16 | 867 | 24.08 | 1906 | 24.13 |
| >10 years | 415 | 9.65 | 387 | 10.75 | 802 | 10.15 |
| **Patients with multiple primary malignancies** | | | | | | |
| 1 primary malignant tumour | 4053 | 94.26 | 3441 | 95.58 | 7494 | 94.86 |
| 2 primaries | 224 | 5.21 | 151 | 4.19 | 375 | 4.75 |
| 3 primaries | 22 | 0.51 | 8 | 0.22 | 30 | 0.38 |
| 4 or more primaries | 1 | 0.02 | 0 | 0.00 | 1 | 0.01 |
| **Person-years of observation** | **18023.61** | | **15755.96** | | **33779.58** | |
| **Median length of follow-up (years)** | | | | | | |
| **All ages** | **2.66** | | **2.75** | | **-** | |
| 15-44 years old | 4.04 | | 4.67 | | - | |
| 45-59 years old | 3.38 | | 3.80 | | - | |
| 60-74 years old | 2.50 | | 2.92 | | - | |
| >75 years old | 0.92 | | 1.08 | | - | |
| **Observed number of subsequent malignancies** | **271** | **6.30** | **167** | **4.64** | **438** | **5.54** |
| Synchronous (<2 months)** | 43 | 15.87 | 37 | 22.16 | 80 | 18.26 |
| Metachronous (>2 months)** | 228 | 84.13 | 130 | 77.84 | 358 | 81.74 |
| **Expected number of subsequent malignancies** | **190.09** | | **120.51** | | **310.60** | |

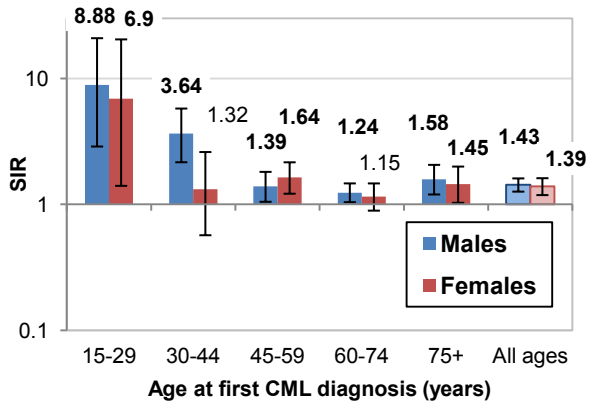
*after excluding Death Certificate only (DCO) cases, preceding primary malignancies, and patients aged less than 15 years old
**after the diagnosis of the first primary malignant cancer
CML: chronic myeloid leukaemia

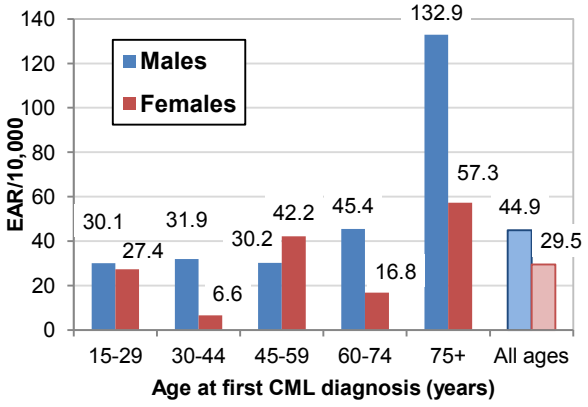
### Age-specific risks (15 years age group) of all subsequent malignancies by sex

There was a 41% increased relative risk of a SPM at any site among survivors of adult CML (SIR=1.41; 95% CI=1.28–1.55, EAR=37.72/10,000 person-years). Generally, males had a slightly higher relative risk of SPM than females (SIR=1.43 vs. 1.39), but the difference was not statistically significant (**Figure 30**). The SIR was five times higher for male and female survivors

who were under 30 years of age at first CML diagnosis than those who were aged 75 years or older (both sexes' SIR= 8.08 vs. 1.53, *P<0.05*). The excess absolute risk of all SPM cases was generally higher in men than women, especially those diagnosed at an older age (>75 years, EAR=132.9 vs. 57.3).

**Figure 30. Observed number, SIRs and EARs of all SPM by age at diagnosis of CML and sex**




**Observed number of SPM by age and sex**

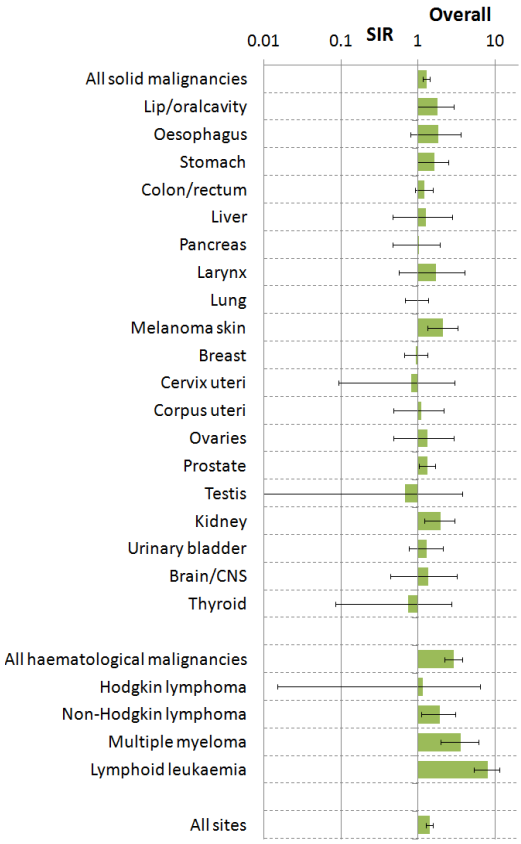
| | 15-29 | 30-44 | 45-59 | 60-74 | 75+ | All ages |
|---|---|---|---|---|---|---|
| **Males** | 5 | 18 | 55 | 136 | 56 | 271 |
| **Females** | 3 | 8 | 50 | 66 | 38 | 167 |

SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; EAR: excess absolute risk per 10,000 person-years; CML: chronic myeloid leukaemia; SPM: subsequent primary malignancies.
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

### Site-specific risks by sex and age at first CML diagnosis

Both male and female CML patients had an elevated relative risk for the following malignancies (**Figure 31**): LL (SIR=8.01, EAR=7.51), MM (SIR=3.63, EAR=3), NHL (SIR=1.91, EAR=2.39), and cancers of the skin melanoma (SIR=2.13, EAR=3.30), kidney (SIR=1.79, EAR=3.07), lip/oral cavity (SIR=1.78, EAR=1.49), and prostate (SIR=1.32, EAR=4.93). All the above SIRs were significantly greater than one. For cancers of the lung, testis, breast, cervix, and thyroid, SIRs were lower than expected (none was significant). The SIR for ALL was 12.5 (95% CI=2.51-36.52), based on 3 cases only. No cases with second ML were found. Detailed analysis of SIR by age and site of SPM is shown in **Table 52** (**Appendix III**) and **Figure 32**. For patients under age 45 years, significant SIRs were observed for malignant melanoma (5-fold) and other haematological malignancies (11-fold).

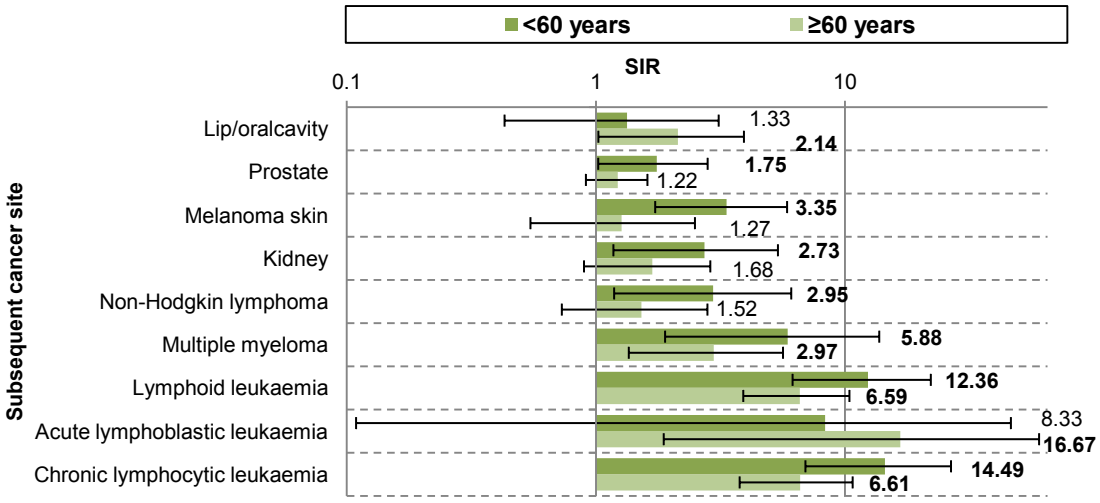
## Figure 31. Observed number, SIRs and EARs according to the type of SPM following CML by sex and overall




| | Overall | | | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | SIR | O | EAR | O | SIR | 95% CI | EAR | O | SIR | 95% CI | EAR |
| All solid malignancies | **1.29** | 365 | 24.1 | 228 | **1.31** | **1.15-1.49** | 30.1 | 137 | **1.25** | **1.05-1.48** | 17.4 |
| Lip/oralcavity | **1.78** | 15 | 1.9 | 11 | 1.68 | 0.84-3.01 | 2.5 | 4 | 2.12 | 0.57-5.42 | 1.3 |
| Oesophagus | 1.85 | 8 | 1.1 | 6 | 1.69 | 0.62-3.67 | 1.4 | 2 | 2.60 | 0.29-9.38 | 0.8 |
| Stomach | 1.63 | 20 | 2.3 | 11 | 1.36 | 0.68-2.43 | 1.6 | 9 | 2.15 | 0.98-4.09 | 3.1 |
| Colon/rectum | 1.21 | 57 | 2.9 | 33 | 1.15 | 0.79-1.61 | 2.4 | 24 | 1.30 | 0.83-1.93 | 3.5 |
| Liver | 1.27 | 6 | 0.4 | 4 | 1.12 | 0.30-2.87 | 0.2 | 2 | 1.75 | 0.20-6.33 | 0.6 |
| Pancreas | 1.03 | 9 | 0.1 | 6 | 1.20 | 0.44-2.60 | 0.5 | 3 | 0.80 | 0.16-2.34 | -0.5 |
| Larynx | 1.74 | 5 | 0.6 | 5 | 1.91 | 0.62-4.45 | 1.3 | 0 | 0.00 | 0.00-14.11 | -0.2 |
| Lung | 0.98 | 36 | -0.3 | 27 | 0.95 | 0.63-1.39 | -0.8 | 9 | 1.06 | 0.48-2.01 | 0.3 |
| Melanoma skin | **2.13** | 21 | 3.3 | 12 | 2.07 | 1.07-3.61 | 3.4 | 9 | **2.22** | **1.01-4.22** | 3.1 |
| Breast | 0.95 | 35 | -0.5 | 0 | 0.00 | 0.00-8.53 | -0.2 | 35 | 0.96 | 0.67-1.34 | -0.9 |
| Cervix uteri | 0.82 | 2 | -0.1 | | | | | 2 | 0.82 | 0.09-2.97 | -0.3 |
| Corpus uteri | 1.11 | 8 | 0.2 | | | | | 8 | 1.11 | 0.48-2.18 | 0.5 |
| Ovaries | 1.33 | 6 | 0.4 | | | | | 6 | 1.33 | 0.49-2.90 | 1.0 |
| Prostate | **1.32** | 68 | 4.9 | 68 | **1.32** | **1.03-1.68** | 9.2 | | | | |
| Testis | 0.68 | 1 | -0.1 | 1 | 0.68 | 0.01-3.81 | -0.3 | | | | |
| Kidney | **1.97** | 21 | 3.1 | 15 | **2.08** | **1.16-3.43** | 4.3 | 6 | 1.75 | 0.64-3.81 | 1.6 |
| Urinary bladder | 1.31 | 17 | 1.2 | 15 | 1.45 | 0.81-2.40 | 2.6 | 2 | 0.75 | 0.08-2.69 | -0.4 |
| Brain/CNS | 1.36 | 5 | 0.4 | 3 | 1.34 | 0.27-3.91 | 0.4 | 2 | 1.39 | 0.16-5.01 | 0.4 |
| Thyroid | 0.75 | 2 | -0.2 | 1 | 1.08 | 0.01-5.98 | 0.0 | 1 | 0.58 | 0.01-3.23 | -0.5 |
| All haematological malignancies | **2.91** | 62 | 12.0 | 37 | **2.87** | **2.02-3.95** | 13.4 | 25 | **2.97** | **1.92-4.38** | 10.5 |
| Hodgkin lymphoma | 1.15 | 1 | 0.0 | 1 | 1.82 | 0.02-10.12 | 0.3 | 0 | 0.00 | 0.00-11.46 | -0.2 |
| Non-Hodgkin lymphoma | **1.91** | 17 | 2.4 | 11 | **2.12** | **1.05-3.79** | 3.2 | 6 | 1.62 | 0.59-3.52 | 1.5 |
| Multiple myeloma | **3.63** | 14 | 3.0 | 7 | **3.02** | **1.21-6.22** | 2.6 | 7 | **4.55** | **1.82-9.37** | 3.5 |
| Lymphoid leukaemia | **8.01** | 29 | 7.5 | 17 | **7.08** | **4.12-11.34** | 8.1 | 12 | **9.84** | **5.08-17.18** | 6.8 |
| All sites | **1.41** | 438 | 37.7 | 271 | **1.43** | **1.26-1.61** | 44.9 | 167 | **1.39** | **1.18-1.61** | 29.5 |

O: observed number of subsequent primary malignancies; SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; EAR: excess absolute risk/10,000 person per year; CML: chronic myeloid leukaemia; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites and all solid cancers: excluding non-melanoma skin cancer (C44).

## Figure 32. SIRs according to the type of SPM following CML by age at diagnosis, for both sexes

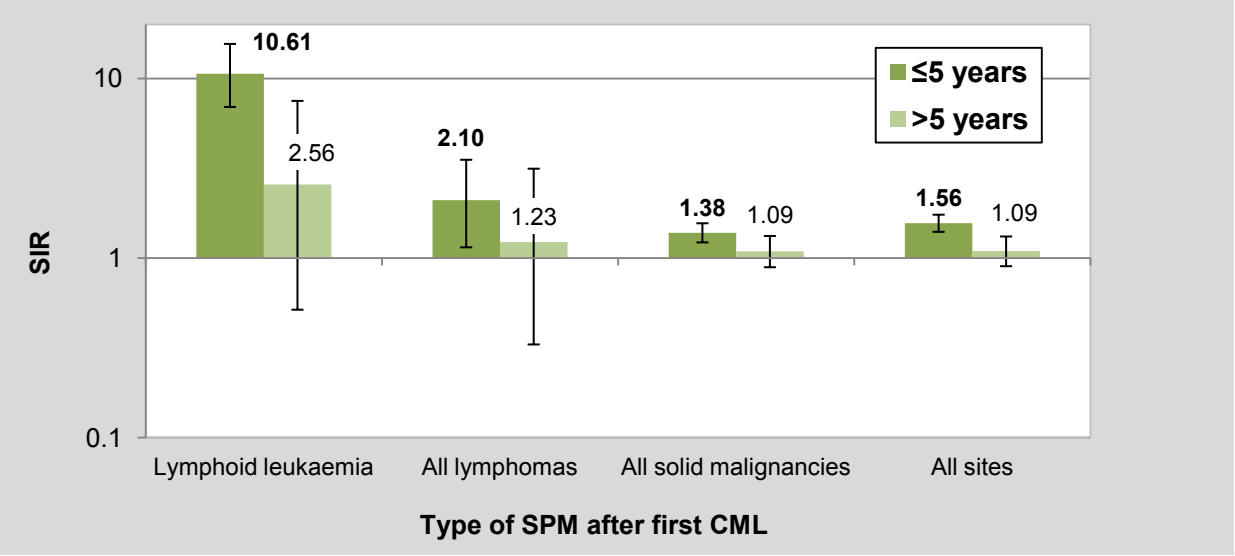



SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; CML: chronic myeloid leukaemia; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (significant SIR, *P<0.05*).

**Overall and site-specific risks in relation to time from CML diagnosis**

The overall risk of SPM tended to decrease as the time from CML diagnosis increased. Within the first five years of CML diagnosis, the SIR of subsequent LL was significantly higher than for all lymphomas and solid malignancies, while after 5 years all SIRs were nearly similar and were not significantly different from the general population rates (**Figure 33**). More detailed analysis of the SIRs for specific cancer types by follow-up period is presented in **Table 53** (**Appendix III**). The SIR for malignant melanoma peaked (3.6-fold) between 5 and 10 years, and dropped to normal levels afterwards. An elevated SIR for ALL was shown to be limited only to the first year period. The increased risk for CLL was observed within the first five years only. The risks for many other types of SPM such as HL, colon/rectum, lung, breast, cervix, CNS, and thyroid were not statistically significantly different from the incidence of cancer in the general population irrespective of sex, age, and follow-up time.

**Figure 33. Overall SIRs of SPM by follow-up duration (≤5 and >5 years) following CML, for both sexes**




SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; CML: chronic myeloid leukaemia; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites and all solid cancers: excluding non-melanoma skin cancer (C44). All lymphomas: include C81-C86.

When excluding SPM developing within first year (**Appendix III, Table 54**), the overall SIR, as well as solid and haematological malignancies SIRs, decreased and were no longer statistically significantly different from risk of the general population (SIR=1.13, 1.08, and 1.52, respectively). SIRs for subsequent melanoma skin cancer increased slightly (from 2.13 to 2.25); while for LL (mainly CLL), the SIR dropped from 8.01 to 3.21 (none of these changes was statistically significantly different).

**Overall and site-specific risks in relation to time from CML diagnosis and calendar periods by age (<60 vs. ≥60 years old)**

Patients first diagnosed with CML before age 60 years showed higher relative risk of developing SPM than older patients (aged 60 years or older) and their risks remained significantly elevated up to 10 years after initial CML diagnosis but not after that (**Figure 34**). This trend was mainly due to increased SIR for malignant melanoma and kidney cancer in the >5-≤10 years follow-up interval (**Appendix III**, **Table 55**). Generally, no significant differences in relative risks were found between patients diagnosed with first CML before 2000 (SIR=1.57) and those diagnosed in 2001 or later (SIR=1.45) (**Appendix III, Table 56**).

**Risk of CML subsequent to selected first cancers**

The risk of developing a subsequent CML was significantly elevated following first cancers at any site (SIR=1.56), as well as first solid and haematological malignancies (SIR=1.55 and 2.56, respectively). A significant bidirectional positive association was seen between CML and LL (acute and chronic), and between CML and kidney cancer (**Table 19**). The association of CML with melanoma was unidirectional. Of note, CML occurred subsequent to first primary oropharyngeal, colorectal, urinary bladder and kidney cancers at a rate higher than the occurrence of these cancers after first CML. The SIR of subsequent CML following kidney cancer and CLL tended to increase with latency (based on small numbers, **Table 57** in **Appendix III**).

**Table 19. Risk of CML subsequent to other primary malignancies**

| | | CML as a first cancer | | | | CML as a subsequent cancer | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Cancer site** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | **C00-C75** | 365 | 283.46 | **1.29** | **1.16-1.43** | 396 | 256.02 | **1.55** | **1.40-1.71** |
| Lip/oral cavity | C00-C14 | 15 | 8.43 | 1.78 | 1.00-2.93 | 14 | 6.68 | **2.10** | **1.14-3.52** |
| Stomach | C16 | 20 | 12.29 | 1.63 | 0.99-2.51 | 11 | 7.39 | 1.49 | 0.74-2.66 |
| Colon/rectum | C18-C21 | 57 | 47.26 | 1.21 | 0.91-1.56 | 63 | 45.48 | **1.39** | **1.06-1.77** |
| Lung | C33-C34 | 36 | 36.85 | 0.98 | 0.68-1.35 | 21 | 13.77 | 1.53 | 0.94-2.33 |
| Melanoma of skin | C43 | 21 | 9.86 | **2.13** | **1.32-3.26** | 17 | 11.3 | 1.50 | 0.88-2.41 |
| Prostate | C61 | 68 | 51.34 | **1.32** | **1.03-1.68** | 75 | 62.47 | 1.20 | 0.94-1.50 |
| Kidney | C64 | 21 | 10.64 | **1.97** | **1.22-3.02** | 25 | 11.66 | **2.14** | **1.39-3.17** |
| Urinary bladder | C67 | 17 | 13.01 | 1.31 | 0.76-2.09 | 25 | 13.44 | **1.86** | **1.20-2.75** |
| **All haematological malignancies** | **C81-C96** | 62 | 21.32 | **2.91** | **2.23-3.73** | 47 | 18.39 | **2.56** | **1.88-3.40** |
| NHL | C82-C85 | 17 | 8.91 | **1.91** | **1.11-3.06** | 13 | 8.2 | 1.59 | 0.84-2.71 |
| MM | C90 | 14 | 3.86 | **3.63** | **1.98-6.09** | 3 | 2.88 | 1.04 | 0.21-3.04 |
| Lymphoid leukaemia | C91 | 29 | 3.62 | **8.01** | **5.36-11.51** | 44 | 4.09 | **10.76** | **7.82-14.44** |
| ALL | C91.0 | 3 | 0.24 | **12.50** | **2.51-36.52** | 5 | 0.11 | **45.45** | **14.65-106.08** |
| CLL | C91.1 | 26 | 3.1 | **8.39** | **5.48-12.29** | 36 | 3.65 | **9.86** | **6.91-13.66** |
| **All sites**** | **C00-C97** | 438 | 310.6 | **1.41** | **1.28-1.55** | 432 | 276.31 | **1.56** | **1.42-1.72** |

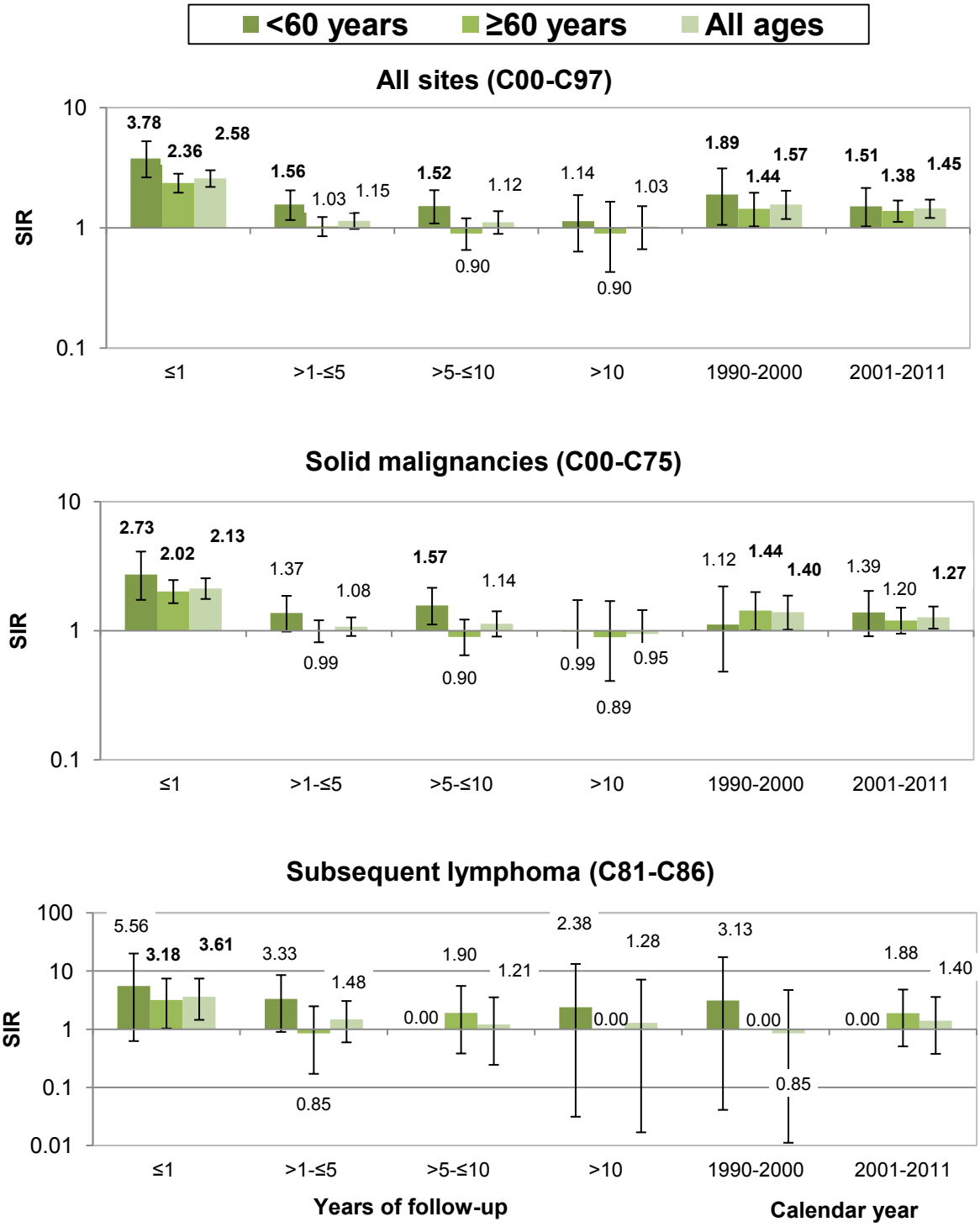
O: observed number of subsequent primary malignancies; E: expected number of subsequent primary malignancies; SIR: standardized incidence ratio; 95% confidence intervals (lower-upper limits); CML: chronic myeloid leukaemia; NHL: non-Hodgkin lymphoma; MM: multiple myeloma; ALL: acute lymphoblastic leukaemia; CLL: chronic lymphocytic leukaemia); ICD-10: the WHO International Classification of Diseases (10th revision).

*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96)

**excluding non-melanoma skin cancer (C44)

Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

**Figure 34. Overall SIRs of SPM by follow-up duration and calendar periods for CML survivors aged <60 vs. ≥60 years at diagnosis, for both sexes**




SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; CML: chronic myeloid leukaemia; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites and all solid cancers: excluding non-melanoma skin cancer (C44).

## Estimated risk of subsequent malignancies following lymphoma, myeloma, and leukaemia in Germany by region: cancer registry-specific analysis

The pooled SIRs for SPM at any site and cancer registry-specific SIRs (ordered according to time periods) are presented in **Table 20**. Among all subgroups of LHM, higher SIRs were noted in Hamburg and NRW registry, whereas lowest SIRs were observed in Berlin, Brandenburg, and Saarland registries. No SIR significantly lower than 1 was noted among all German epidemiologic cancer registries following each first malignancy. Variations in risks between cancer registries may result from differences in time periods of diagnosis, length of follow-up, and completeness of incidence data. Of note, the Bavarian cancer registry contributed the largest number of patients (14% to 16%) and person-years at risk of developing SPM. **Table 20** also shows sensitivity analysis excluding data from selected registries. Overall SIRs for SPM did not significantly change when excluding data from Berlin and Saxony-Anhalt states (recognized to have lowest estimated completeness), although a slight increase in SIRs was observed. The analysis, which excludes data from cancer registries with a follow-up shorter than 10 years (Lower Saxony, Bavaria, and NRW), also showed no significant changes. Results for solid SPM were generally similar (**Table 58, Appendix III**). Additional analysis was carried out pooling data from 3 cancer registries with a stable long-term registration from 1990 to 2011 (Saarland, Hamburg, and Muenster), **Table 21**. Generally, results were identical to the first pooled analysis (overall and site-specific SPM risks), see **Figure 35**. Although overall SIRs were slightly higher than the previous results, none was statistically significantly different. Additionally, a separate long-term analysis was conducted from Saarland cancer registry for HL, NHL, myeloma, and leukaemia diagnosed between 1970 and 2011, the overall trend of SIR with follow-up time was largely similar to the previous analysis for the year of diagnosis 1990–2011 (data not shown).

**Table 20. Estimated overall SIRs for SPM following lymphoma (A), myeloma (B), and leukaemia (C) by region, Germany, 1990–2011**

**(A)**

| Region (years of diagnosis) | Hodgkin lymphoma | | | | | Non-Hodgkin lymphoma | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Patients | PYRs | O | SIR | 95% CI | Patients | PYRs | O | SIR | 95% CI |
| SL (1990+) | 550 | 4509.59 | 61 | **2.58** | **1.98-3.32** | 3512 | 17816.96 | 283 | **1.28** | **1.13-1.43** |
| HH (1990+) | 1020 | 8121.66 | 95 | **2.52** | **2.04-3.08** | 5621 | 29084.84 | 688 | **1.94** | **1.80-2.09** |
| BE (1995+) | 1181 | 7921.51 | 34 | 1.27 | 0.88-1.78 | 6139 | 31292.41 | 340 | **1.28** | **1.14-1.42** |
| BB (1995+) | 951 | 6719.49 | 54 | **1.83** | **1.37-2.38** | 5081 | 24041.71 | 339 | **1.28** | **1.15-1.42** |
| MV (1995+) | 596 | 4076.91 | 38 | **2.27** | **1.60-3.11** | 3744 | 16666.84 | 247 | **1.32** | **1.16-1.49** |
| SN (1995+) | 1642 | 11475.49 | 85 | **1.85** | **1.48-2.29** | 9590 | 41337.37 | 646 | **1.34** | **1.24-1.45** |
| ST (1995+) | 789 | 5525.95 | 37 | **1.88** | **1.32-2.59** | 4740 | 22048.09 | 280 | **1.31** | **1.16-1.47** |
| TH (1995+) | 722 | 4979.77 | 27 | **1.78** | **1.17-2.58** | 4685 | 21358.52 | 283 | **1.29** | **1.15-1.45** |
| SH (1998+) | 1011 | 5919.22 | 74 | **2.34** | **1.84-2.94** | 5834 | 25091.6 | 443 | **1.44** | **1.31-1.58** |
| HB (1998+) | 207 | 1172.66 | 15 | **2.48** | **1.39-4.10** | 1414 | 5249.079 | 125 | **1.72** | **1.44-2.05** |
| RP (1998+) | 949 | 5316.61 | 56 | **2.44** | **1.84-3.17** | 6089 | 25503.91 | 475 | **1.71** | **1.56-1.87** |
| NI (2003+) | 1533 | 5886.04 | 51 | **1.79** | **1.33-2.35** | 10848 | 34382.51 | 657 | **1.47** | **1.36-1.59** |
| BY (2002+) | 2686 | 11978.41 | 121 | **2.68** | **2.23-3.21** | 14846 | 51309.8 | 881 | **1.58** | **1.48-1.69** |

## Table 20 continued

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| NRW (2006+)* | 1815 | 4567.56 | 89 | **4.47** | **3.59-5.50** | 11146 | 23757.55 | 567 | **1.96** | **1.80-2.13** |
| Muenster (1990+) | 1174 | 9303.67 | 116 | **2.92** | **2.42-3.51** | 6540 | 29549.6 | 534 | **1.47** | **1.34-1.60** |
| **Pooled (1990-2011)** | 16826 | 97474.55 | 953 | **2.33** | **2.18-2.48** | 99829 | 398490.8 | 6788 | **1.50** | **1.46-1.54** |
| **Pooled (1990-2011), excluding BE and ST** | 14856 | 84027.08 | 882 | **2.43** | **2.27-2.60** | 88950 | 345150.3 | 6168 | **1.53** | **1.49-1.56** |
| **Pooled (1990-2011), excluding NRW, BY, and NI** | 10792 | 75042.54 | 692 | **2.19** | **2.03-2.36** | 62989 | 289040.93 | 4683 | **1.45** | **1.41-1.49** |

**(B)**

| Region (years of diagnosis) | Multiple myeloma | | | | |
|---|---|---|---|---|---|
| | Patients | PYRs | O | SIR | 95% CI |
| SL (1990+) | 1191 | 3971.625 | 64 | 1.16 | 0.89-1.48 |
| HH (1990+) | 2369 | 9216.473 | 205 | **1.5** | **1.3-1.72** |
| BE (1995+) | 2152 | 8493.314 | 76 | 0.88 | 0.69-1.1 |
| BB (1995+) | 2056 | 7160.703 | 86 | 0.94 | 0.75-1.16 |
| MV (1995+) | 1475 | 4920.121 | 71 | 1.12 | 0.88-1.41 |
| SN (1995+) | 4286 | 14130.72 | 183 | 1.01 | 0.87-1.16 |
| ST (1995+) | 1787 | 6494.514 | 60 | 0.83 | 0.63-1.07 |
| TH (1995+) | 1999 | 6381.763 | 75 | 1 | 0.78-1.25 |
| SH (1998+) | 2538 | 8798.899 | 125 | 1.03 | 0.86-1.23 |
| HB (1998+) | 544 | 1573.221 | 30 | 1.28 | 0.86-1.83 |
| RP (1998+) | 2099 | 6496.435 | 104 | **1.3** | **1.06-1.57** |
| NI (2003+) | 4455 | 11178.05 | 173 | 1.09 | 0.93-1.26 |
| BY (2002+) | 5344 | 15753.2 | 267 | **1.36** | **1.21-1.54** |
| NRW (2006+)* | 3784 | 7376.433 | 106 | 1.07 | 0.88-1.3 |
| Muenster (1990+) | 2995 | 9930.239 | 136 | 0.96 | 0.81-1.14 |
| **Pooled (1990-2011)** | 39074 | 121875.7 | 1761 | **1.11** | **1.06-1.17** |
| **Pooled (1990-2011), excluding BE and ST** | 35135 | 106887.9 | 1625 | **1.14** | **1.09-1.2** |
| **Pooled (1990-2011), excluding NRW, BY, and NI** | 25491 | 87568.03 | 1215 | **1.08** | **1.02-1.14** |

**(C)**

| Region (years of diagnosis) | Chronic lymphoid leukaemia | | | | | Chronic myeloid leukaemia | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Patients | PYRs | O | SIR | 95% CI | Patients | PYRs | O | SIR | 95% CI |
| SL (1990+) | 813 | 4758.32 | 82 | 1.09 | 0.87-1.35 | 332 | 1650.067 | 12 | 0.69 | 0.36-1.21 |
| HH (1990+) | 2040 | 11588.55 | 291 | **1.60** | **1.42-1.79** | 569 | 2526.86 | 59 | **2.27** | **1.73-2.92** |
| BE (1995+) | 1054 | 5639.27 | 89 | **1.41** | **1.14-1.74** | 501 | 2863.55 | 14 | 0.70 | 0.38-1.18 |
| BB (1995+) | 1907 | 10529.37 | 232 | **1.59** | **1.39-1.81** | 413 | 2167.28 | 20 | 0.97 | 0.60-1.51 |
| MV (1995+) | 1518 | 8075.99 | 161 | **1.38** | **1.18-1.61** | 303 | 1412.83 | 18 | 1.34 | 0.80-2.12 |
| SN (1995+) | 3878 | 20087.61 | 331 | **1.17** | **1.05-1.31** | 733 | 3293.73 | 48 | **1.48** | **1.09-1.96** |
| ST (1995+) | 1835 | 10136.45 | 159 | **1.32** | **1.12-1.54** | 384 | 2024.34 | 19 | 1.35 | 0.81-2.11 |
| TH (1995+) | 1864 | 9827.017 | 177 | **1.42** | **1.22-1.65** | 412 | 1937.94 | 22 | 1.36 | 0.85-2.07 |
| SH (1998+) | 1794 | 8849.73 | 162 | **1.25** | **1.06-1.45** | 390 | 1865.88 | 19 | 1.06 | 0.64-1.66 |
| HB (1998+) | 424 | 1936.37 | 52 | **1.66** | **1.24-2.17** | 87 | 377.03 | 2 | 0.51 | 0.06-1.83 |
| RP (1998+) | 1776 | 8742.38 | 183 | **1.59** | **1.37-1.84** | 522 | 2333.67 | 25 | 1.21 | 0.78-1.78 |
| NI (2003+) | 3269 | 10861.20 | 248 | **1.51** | **1.33-1.71** | 935 | 3104.15 | 43 | 1.31 | 0.94-1.76 |
| BY (2002+) | 4517 | 18323.04 | 497 | **1.99** | **1.82-2.18** | 1081 | 4305.51 | 69 | **1.80** | **1.40-2.28** |
| NRW (2006+)* | 2352 | 5788.37 | 170 | **2.04** | **1.75-2.37** | 599 | 1340.43 | 30 | **2.56** | **1.73-3.66** |
| Muenster (1990+) | 1837 | 9792.15 | 188 | **1.25** | **1.07-1.44** | 639 | 2576.32 | 38 | **1.50** | **1.06-2.06** |
| **Pooled (1990-2011)** | 30878 | 144935.83 | 3022 | **1.49** | **1.43-1.54** | 7900 | 33779.58 | 438 | **1.41** | **1.28-1.55** |
| **Pooled (1990-2011), excluding BE and ST** | 27989 | 129160.11 | 2774 | **1.50** | **1.44-1.56** | 7015 | 28891.6879 | 405 | **1.46** | **1.32-1.61** |
| **Pooled (1990-2011), excluding NRW, BY, and NI** | 20740 | 109963.22 | 2107 | **1.37** | **1.31-1.43** | 5285 | 25029.49 | 296 | **1.30** | **1.16-1.46** |

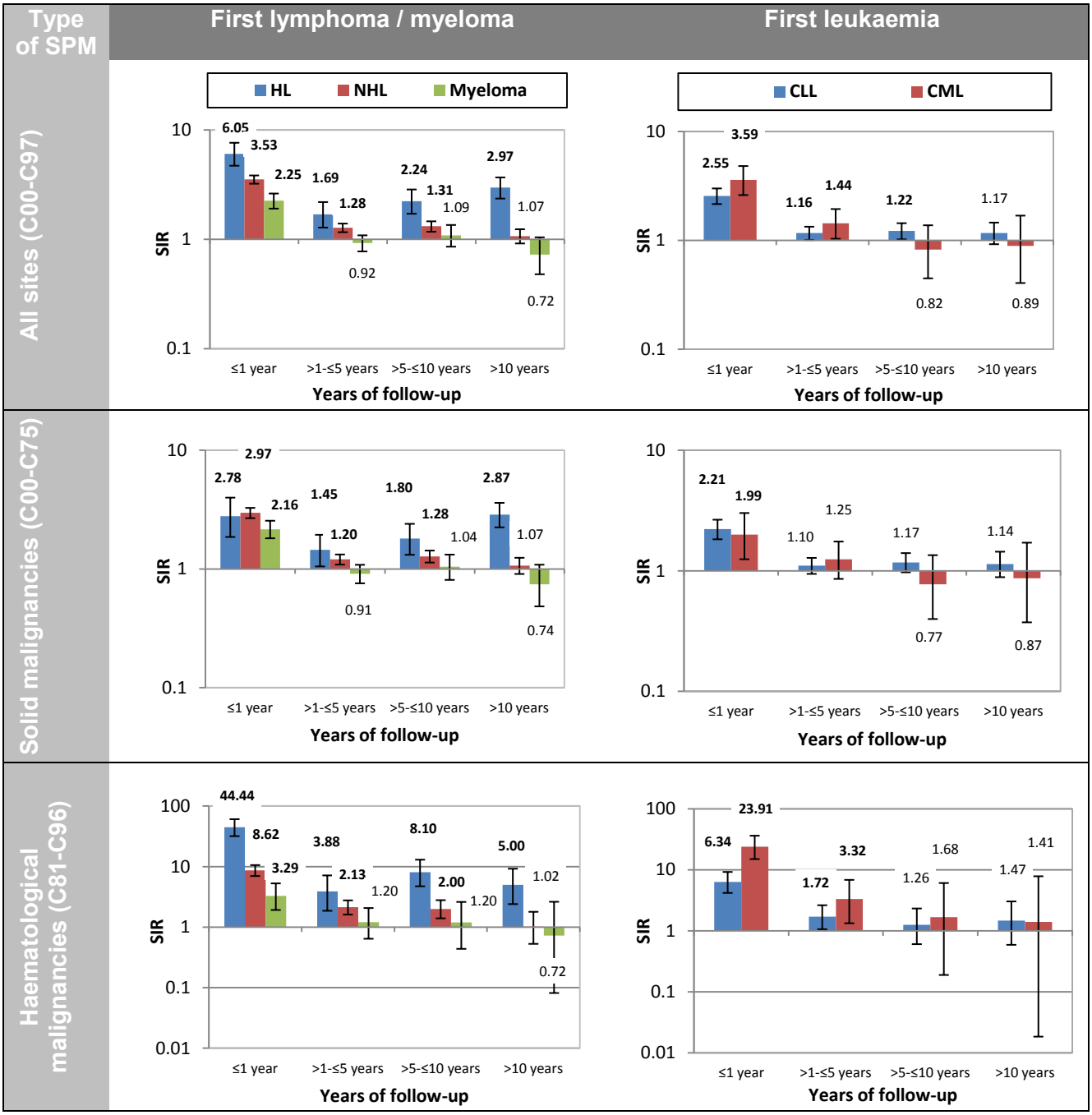
* excluding Muenster. PYRs: person-years at risk; SIR: standardized incidence ratio; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 21. Overall SIRs of SPM in data pooled from long-term German epidemiologic cancer registries: Saarland, Hamburg, and Muenster (1990–2011)

| First malignancy | Patients | O (% of all cases) | E | SIR | 95% CI |
|---|---|---|---|---|---|
| **HL (C81)** | 2744 | 272 (9.9%) | 100.98 | **2.69** | **2.38-3.03** |
| **NHL (C82-C85)** | 15673 | 1505 (9.6%) | 940.6 | **1.60** | **1.52-1.68** |
| **MM (C90)** | 6555 | 405 (6.2%) | 332.68 | **1.22** | **1.10-1.34** |
| **CLL (C91.1)** | 4690 | 561 (11.96%) | 408.26 | **1.37** | **1.26-1.49** |
| **CML (C92.1)** | 1540 | 109 (7.08%) | 68.72 | **1.59** | **1.30-1.91** |

O: observed number of subsequent primary malignancies; E: expected number of subsequent primary malignancies; SIR: standardized incidence ratio; 95% confidence intervals (lower-upper limits); SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

**Figure 35. Overall results from three pooled long-term German cancer registries: overall SIRs of SPM by type of first LHM and follow-up duration**




SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; SPM: subsequent primary malignancies; LHM: lymphohaematopoietic malignancies; HL: Hodgkin lymphoma; NHL non-Hodgkin lymphoma; CLL: chronic lymphoid leukaemia; CML: chronic myeloid leukaemia.
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites and all solid cancers: excluding non-melanoma skin cancer (C44).
For this analysis data was pooled from three long-term German epidemiologic cancer registries: Saarland, Hamburg, and Muenster (1990–2011)

# Comparisons of results with data derived from the United States' SEER cancer registries

## Lymphoma

Comparisons between the German and SEER data (the overall risks and risks for selected SPM stratified by follow-up durations) are shown on **pages 74–79**. In SEER data, overall SIRs were 1.86 (95% CI=1.76–1.97) in the HL and 1.39 (95% CI=1.36–1.41) in the NHL group (**Table 22** and **Table 23**). The estimated SPM SIRs (overall, sex- and age-specific) for the US are significantly lower than for Germany, especially for the younger age groups.

The time pattern of risk in the SEER data was generally similar to our results, although our estimated overall SIRs were significantly higher, particularly in the first year of follow-up after both types of lymphoma and for long-term survivors of HL (**Figure 36** and **Figure 39**).

Except for lip/oral cavity, thyroid, and kidney cancers, comparable trends with follow-up time from HL diagnosis were observed for all sites in both sets of data (**Figure 37**). After NHL, SEER data showed significantly elevated SIRs for lip/oral cavity, breast, and urinary bladder cancers >10 years from diagnosis, a finding that was not detected in the German data (**Figure 40**). In contrast, long-term risk was significantly elevated for melanoma, liver, and pancreatic cancer in the German data but not in SEER. Myeloid leukaemia risk after HL and NHL in SEER data was highest in the time period >1–≤5 years and remained significantly elevated in >10 years (**Figure 38** and **Figure 41**).

In relation to calendar year of diagnosis, increases in risk for subsequent haematological malignancies over time were observed in both data sets after NHL, but was significant only in the US data **(Figure 39)**. The observed increase in relative risk after the year 2000 in the US involved all specific subtypes of haematological malignancies following NHL. After HL, the risk for subsequent haematological malignancies was only significantly increased over the recent time (after 2000) in our data (**Figure 36**).

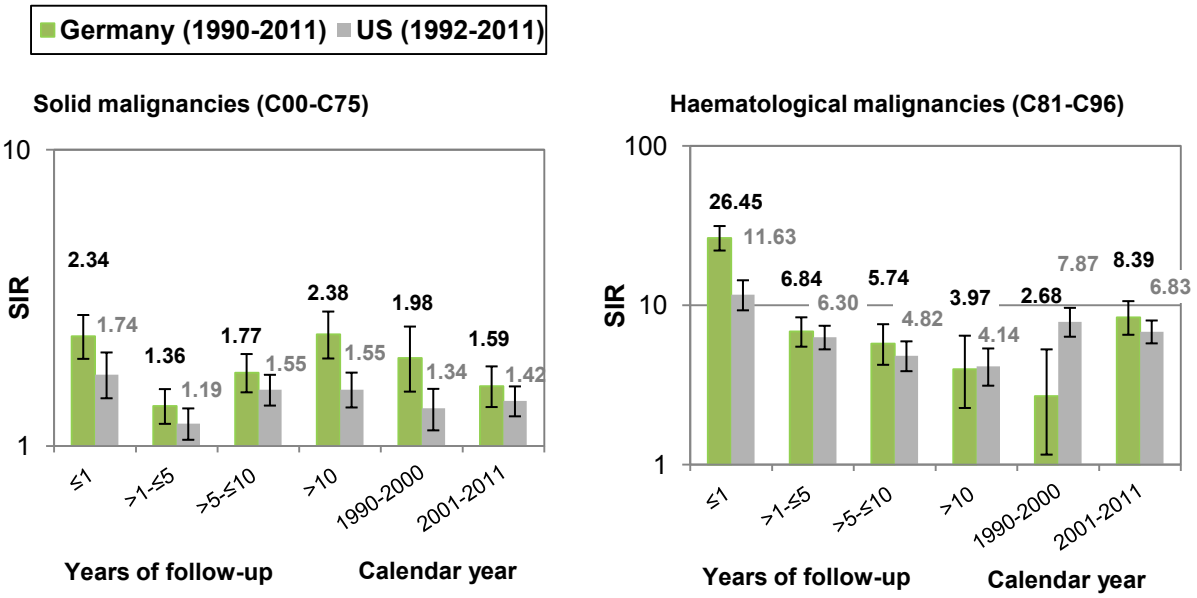
## Hodgkin lymphoma

### Table 22. Overall SIRs of SPM following first HL by age, sex, time from diagnosis and calendar periods in Germany and the US

| | Germany (1990–2011) N=16826 | | | US (1992–2011) N=18834 | | |
|---|---|---|---|---|---|---|
| | O | SIR | 95% CI | O | SIR | 95% CI |
| **Overall** | 953 | **2.33** | **2.18-2.48** | 1261 | **1.86** | **1.76-1.97** |
| **Sex** | | | | | | |
| Males | 584 | **2.24** | **2.07-2.43** | 703 | **1.77** | **1.64-1.90** |
| Females | 369 | **2.48** | **2.23-2.75** | 558 | **2.00** | **1.84-2.18** |
| **Age at first diagnosis (years)** | | | | | | |
| 15-29 | 93 | **7.05** | **5.69-8.64** | 155 | **3.29** | **2.79-3.85** |
| 30-44 | 173 | **4.18** | **3.58-4.86** | 291 | **2.27** | **2.01-2.54** |
| 45-59 | 280 | **2.35** | **2.08-2.64** | 359 | **1.76** | **1.58-1.95** |
| 60-74 | 312 | **1.69** | **1.51-1.89** | 343 | **1.59** | **1.43-1.77** |
| ≥75 | 92 | **1.80** | **1.45-2.21** | 113 | **1.39** | **1.15-1.68** |
| **Years of follow-up** | | | | | | |
| ≤1 | 269 | **4.15** | **3.66-4.67** | 213 | **2.65** | **2.31-3.03** |
| >1-≤5 | 317 | **1.80** | **1.61-2.01** | 395 | **1.66** | **1.50-1.84** |
| >5-≤10 | 231 | **2.06** | **1.80-2.34** | 372 | **1.85** | **1.66-2.04** |
| >10 | 140 | **2.51** | **2.11-2.96** | 281 | **1.79** | **1.59-2.01** |
| **Calendar year *** | | | | | | |
| 1990–2000 | 77 | **2.14** | **1.69-2.67** | 252 | **1.93** | **1.70-2.18** |
| 2001–2011 | 233 | **2.10** | **1.84-2.39** | 446 | **1.93** | **1.76-2.12** |

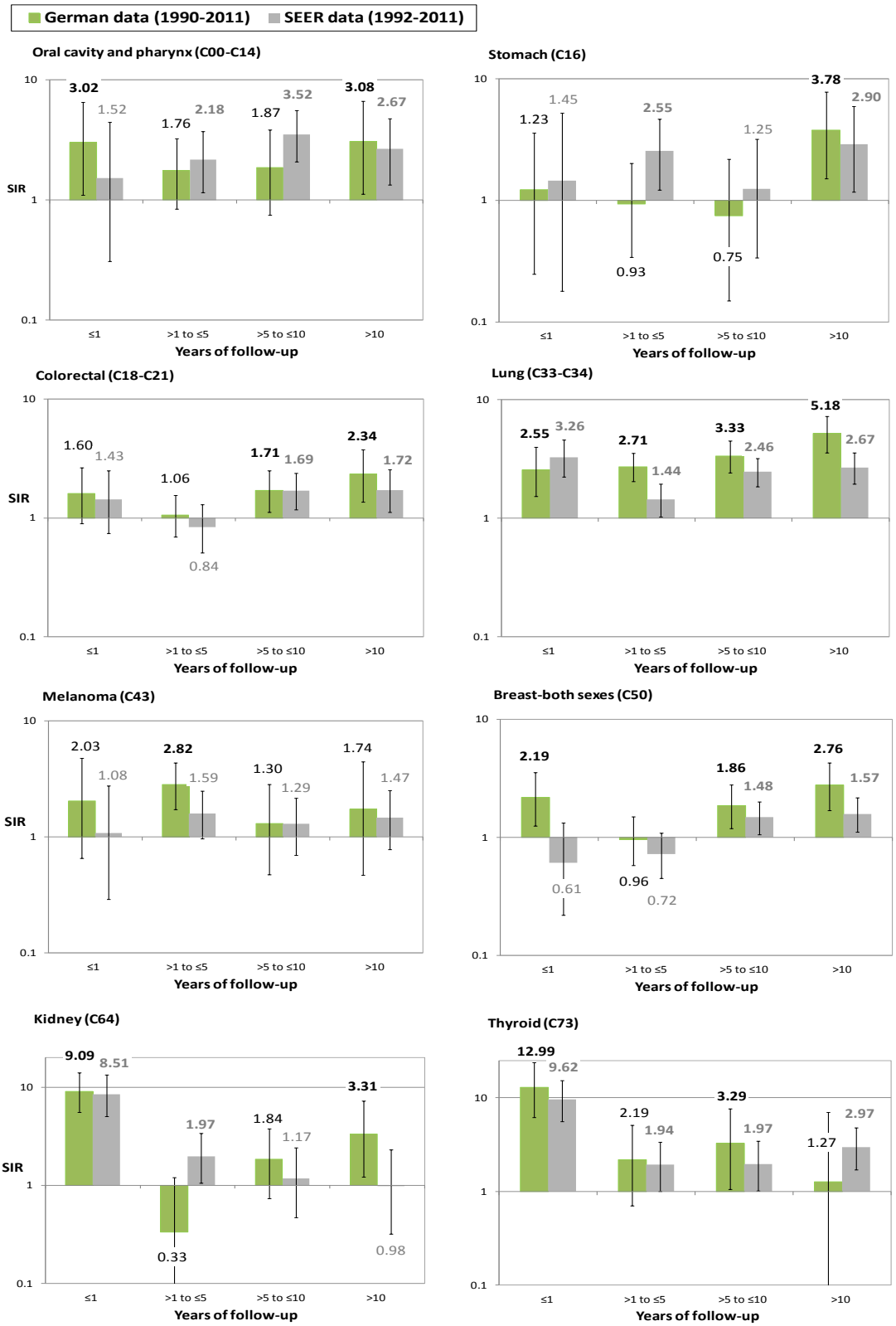
SIR: standardized incidence ratio; 95% CI: 95% confidence interval (lower-upper limits); HL: Hodgkin lymphoma; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).
*German data: for the analysis in relation to calendar year, data was pooled from 9 German regions (out of 4 epidemiologic cancer registries).

### Figure 36. Overall SIRs for solid and haematological SPM following HL by follow-up duration and calendar year in Germany and the US



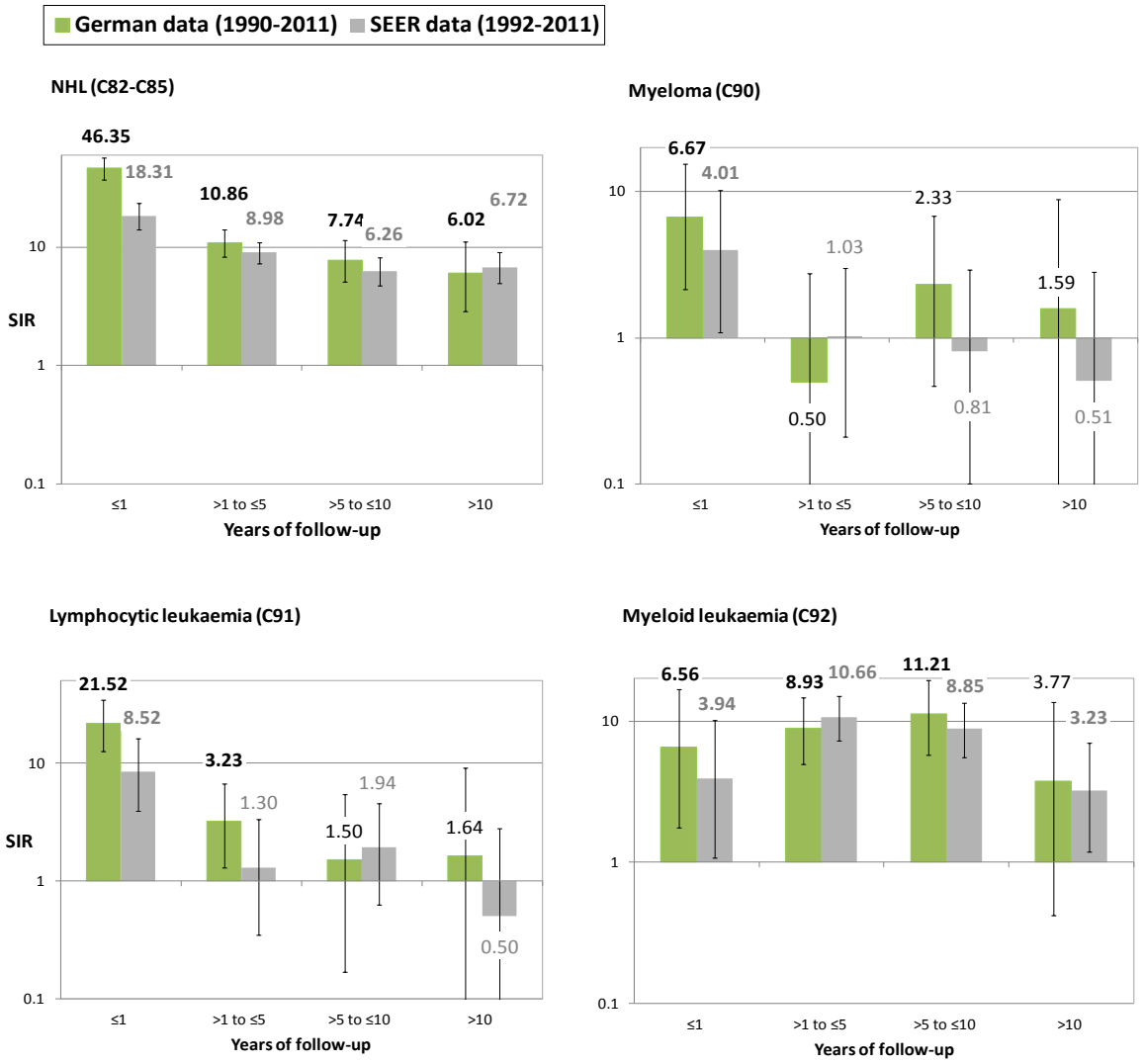

SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; HL: Hodgkin lymphoma; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).
German data: for the analysis in relation to calendar year, data was pooled from 9 German regions (out of 4 epidemiologic cancer registries).

## Figure 37. SIRs for selected solid SPM following HL in Germany and the US




SIR: standardized incidence ratio with 95% confidence intervals; HL: Hodgkin lymphoma; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Figure 38. SIRs for selected haematological SPM following HL in Germany and the US




SIR: standardized incidence ratio with 95% confidence intervals; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).
In the SEER data myeloid and monocytic leukaemia were combined together.

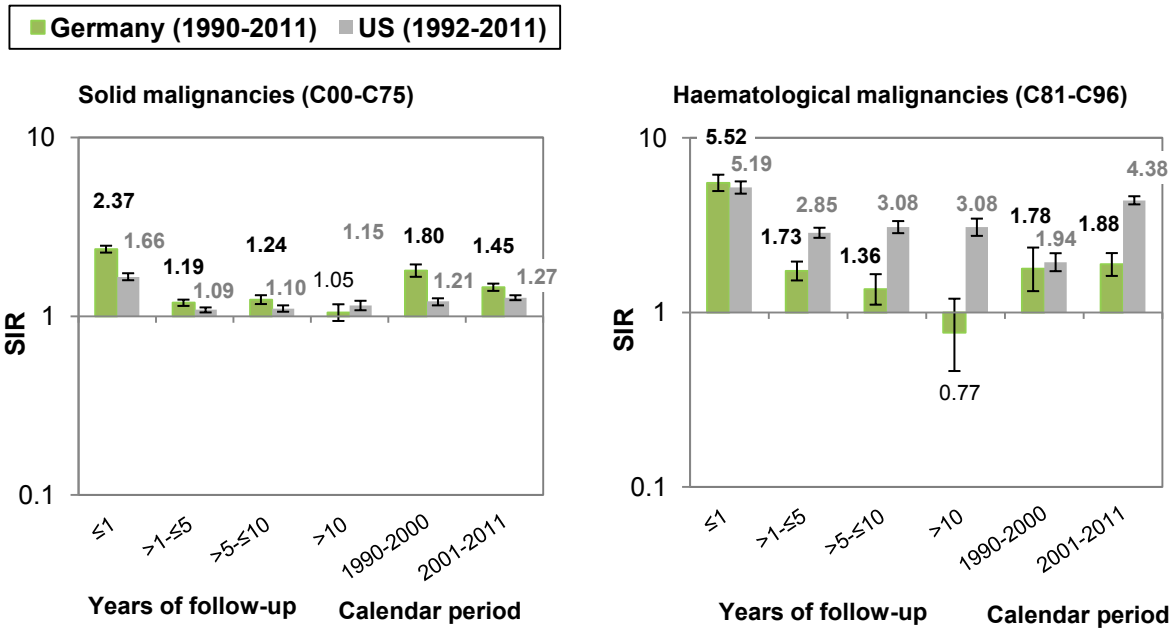
## Non-Hodgkin lymphoma

### Table 23. Overall SIRs of SPM following first NHL by age, sex, time from diagnosis and calendar periods in Germany and the US

| | Germany (1990–2011) N=99829 | | | US (1992–2011) N=118207 | | |
|---|---|---|---|---|---|---|
| | O | SIR | 95% CI | O | SIR | 95% CI |
| **Overall** | 6788 | **1.50** | **1.46-1.54** | 11337 | **1.39** | **1.36-1.41** |
| **Sex** | | | | | | |
| Males | 4090 | **1.49** | **1.45-1.54** | 6654 | **1.37** | **1.34-1.41** |
| Females | 2698 | **1.51** | **1.45-1.57** | 4683 | **1.40** | **1.36-1.45** |
| **Age at first diagnosis (years)** | | | | | | |
| 15-29 | 61 | **10.17** | **7.78-13.06** | 115 | **5.44** | **4.49-6.52** |
| 30-44 | 263 | **3.46** | **3.06-3.91** | 686 | **2.62** | **2.43-2.83** |
| 45-59 | 1349 | **1.62** | **1.54-1.71** | 2707 | **1.59** | **1.53-1.65** |
| 60-74 | 3511 | **1.38** | **1.34-1.43** | 5074 | **1.29** | **1.26-1.33** |
| ≥75 | 1602 | **1.49** | **1.42-1.57** | 2755 | **1.21** | **1.17-1.26** |
| **Years of follow-up** | | | | | | |
| ≤1 | 2410 | **2.64** | **2.53-2.74** | 2672 | **1.99** | **1.91-2.06** |
| >1-≤5 | 2684 | **1.23** | **1.18-1.27** | 4330 | **1.25** | **1.21-1.28** |
| >5-≤10 | 1326 | **1.25** | **1.18-1.32** | 2883 | **1.28** | **1.23-1.33** |
| >10 | 372 | 1.04 | 0.94-1.15 | 1452 | **1.32** | **1.25-1.39** |
| **Calendar year *** | | | | | | |
| 1990–2000 | 693 | **1.82** | **1.69-1.96** | 2326 | **1.29** | **1.24-1.34** |
| 2001–2011 | 2010 | **1.50** | **1.43-1.57** | 5376 | **1.56** | **1.51-1.60** |

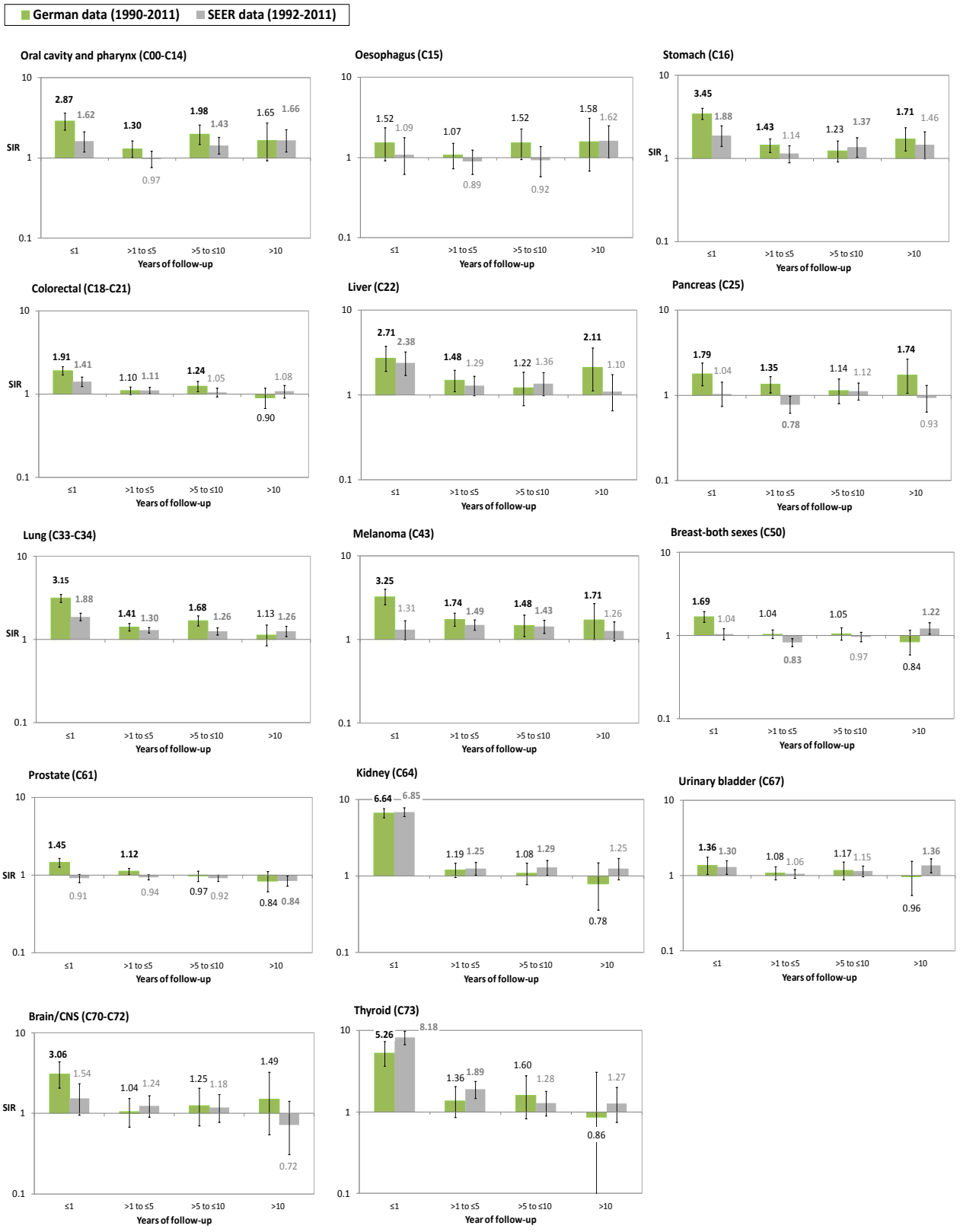
SIR: standardized incidence ratio; 95% confidence interval (lower-upper limits); NHL: non-Hodgkin lymphoma; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).
*German data: for the analysis in relation to calendar year, data was pooled from 9 German regions (out of 4 epidemiologic cancer registries).

### Figure 39. Overall SIRs for solid and haematological SPM following NHL by follow-up duration and calendar year in Germany and the US



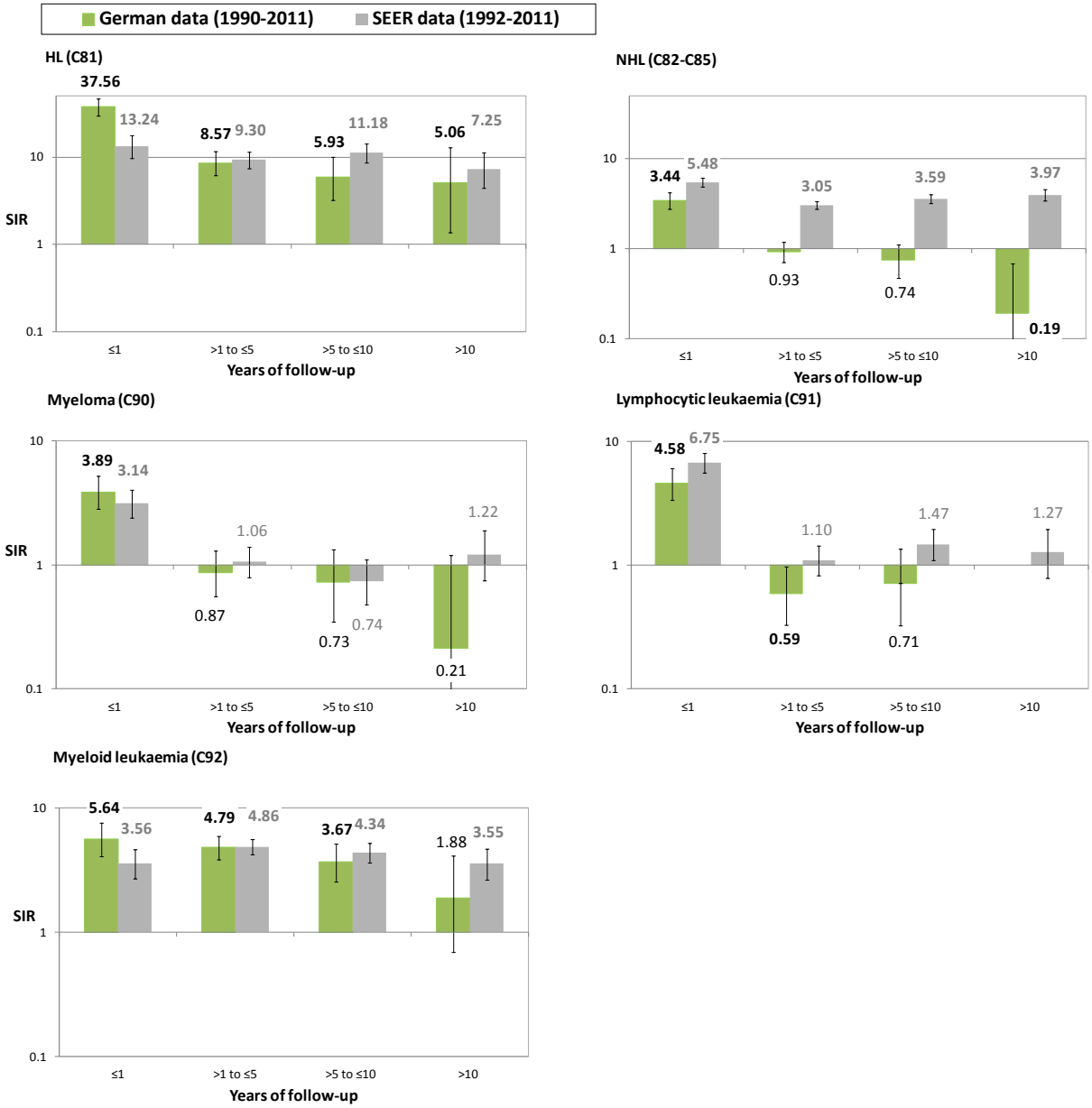

SIR: standardized incidence ratio with 95% confidence intervals; NHL: non-Hodgkin lymphoma; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).
German data: for the analysis in relation to calendar year, data was pooled from 9 German regions (out of 4 epidemiologic cancer registries).

## Figure 40. SIRs for selected solid SPM following NHL in Germany and the US




SIR: standardized incidence ratio with 95% confidence interval, NHL: non-Hodgkin lymphoma; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Figure 41. SIRs for selected haematological SPM following NHL in Germany and the US




SIR: standardized incidence ratio with 95% confidence intervals; NHL: non-Hodgkin lymphoma; HL: Hodgkin lymphoma; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).
In the SEER data myeloid and monocytic leukemia were combined together.

## Multiple myeloma

The relative risks of SPM (overall, and age-, sex-, and site-specific) following MM in Germany were generally comparable with those in the US (**Table 24)**. In the US, there was a borderline significant increase in the overall relative risk (SIR=1.09) of SPM following MM diagnosis compared with the general population. This risk was not significantly different from the estimated SIR for German MM survivors (SIR=1.11). A similarly increased risk of AML, NHL, and kidney cancer was observed in both data sets (**Figure 42**). Risks for subsequent HL, melanoma and lip/oral cavity cancers were elevated among German MM patients only. In Germany, the overall SIR was significantly higher during the first year following MM diagnosis and dropped below 1 after 10 years of follow-up (**Table 24**), while in the US the SIR was significantly higher 10 years after diagnosis (1.35-fold). This increase was mainly due to increased SIR for AML (>7-fold) after 10 years (**Figure 43**). In Germany, AML risk was limited to the first 10 years of follow-up only.

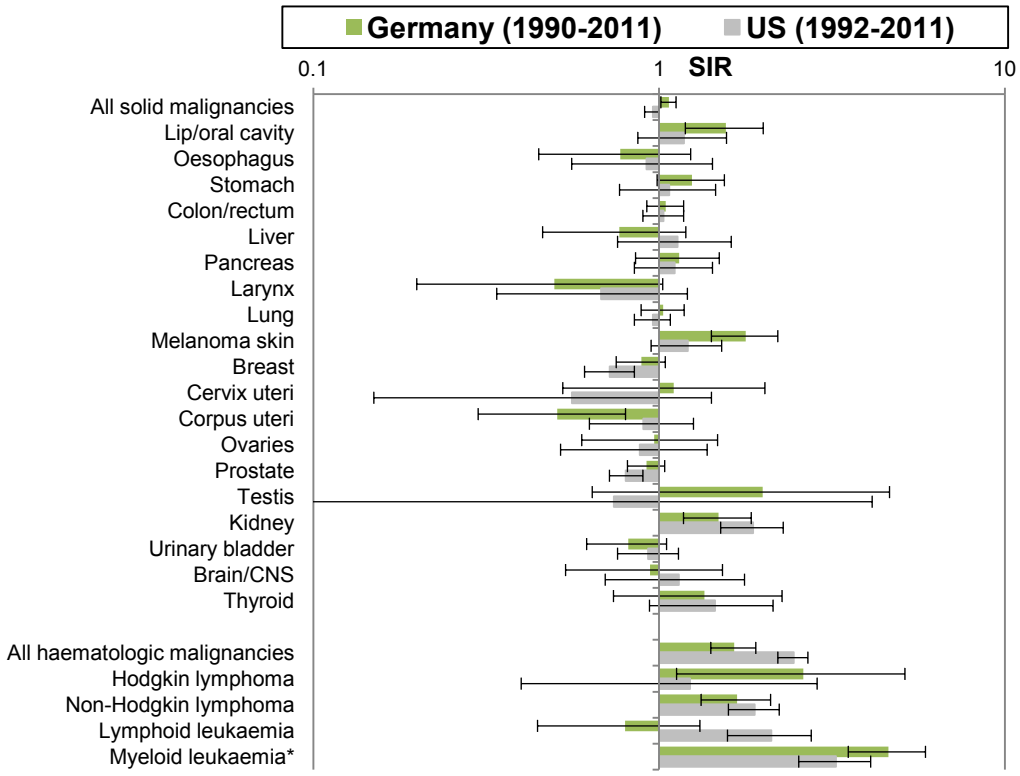
The overall SIR was higher in Germany during the previous years of diagnosis (1990–2000), while in the US it was higher in the most recent period; however, none of these differences was statistically significant. Similarly, no statistically significant differences in the SIRs for AML over the two calendar periods were observed in either database, and no change was noted for solid cancers.

**Table 24. Overall SIRs of SPM following first MM by age, sex, time from diagnosis and calendar periods in Germany and the US**

| | Germany (1990–2011) N=39074 | | | US (1992–2011) N=35462 | | |
|---|---|---|---|---|---|---|
| | O | SIR | 95% CI | O | SIR | 95% CI |
| **Overall** | 1761 | **1.11** | **1.06-1.17** | 2058 | **1.09** | **1.04-1.14** |
| **Sex** | | | | | | |
| Males | 1095 | **1.10** | **1.04-1.17** | 1278 | **1.07** | **1.01-1.13** |
| Females | 666 | **1.13** | **1.05-1.22** | 780 | **1.13** | **1.05-1.22** |
| **Age at first diagnosis (years)** | | | | | | |
| 15-29 | 0 | 0.00 | 0.00-22.93 | 2 | 5.27 | 0.64-19.04 |
| 30-44 | 29 | **2.66** | **1.78-3.82** | 48 | **2.09** | **1.54-2.76** |
| 45-59 | 302 | **1.26** | **1.12-1.41** | 404 | **1.23** | **1.12-1.36** |
| 60-74 | 969 | 1.05 | 0.98-1.12 | 1029 | **1.08** | **1.01-1.15** |
| ≥75 | 461 | **1.13** | **1.03-1.24** | 575 | 0.99 | 0.91-1.08 |
| **Years of follow-up** | | | | | | |
| ≤1 | 684 | **1.70** | **1.57-1.83** | 688 | **1.44** | **1.33-1.55** |
| >1-≤5 | 752 | **0.91** | **0.85-0.98** | 883 | **0.92** | **0.86-0.98** |
| >5-≤10 | 277 | 1.00 | 0.88-1.12 | 351 | 1.01 | 0.91-1.12 |
| >10 | 48 | **0.62** | **0.46-0.82** | 136 | **1.35** | **1.14-1.60** |
| **Calendar year *** | | | | | | |
| 1990–2000 | 188 | **1.20** | **1.03-1.38** | 1004 | 1.03 | 0.96-1.09 |
| 2001–2011 | 565 | 1.09 | 1.00-1.18 | 1054 | **1.16** | **1.09-1.23** |

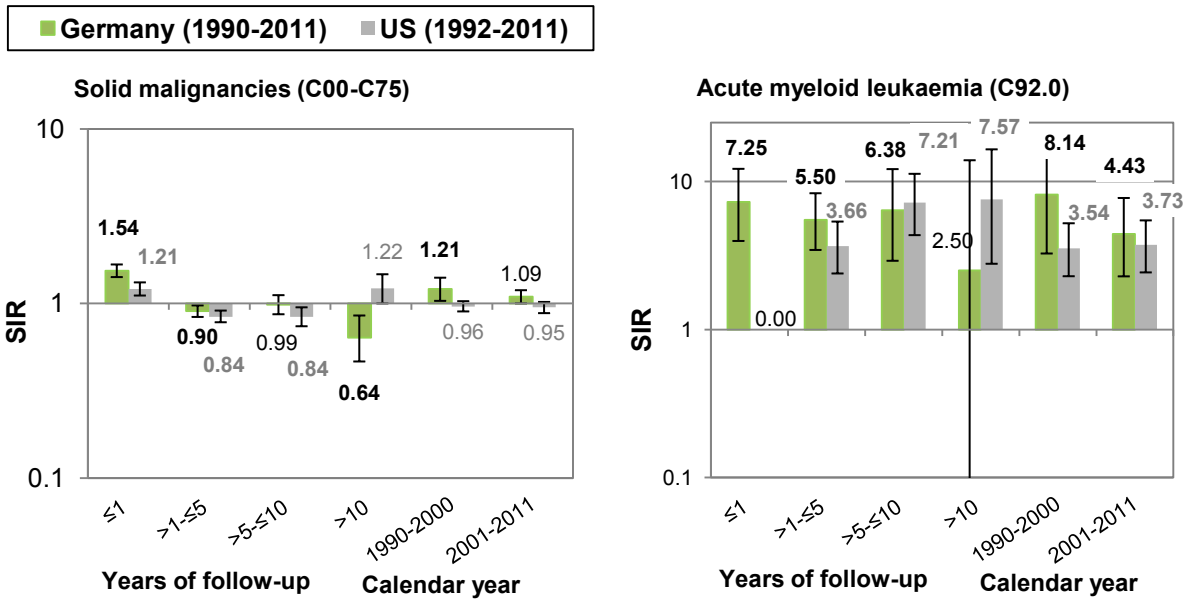
SIR: standardized incidence ratio; 95% confidence interval (lower-upper limits); MM: multiple myeloma; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).
*German data: for the analysis in relation to calendar year, data was pooled from 9 German regions (out of 4 epidemiologic cancer registries).

## Figure 42. SIRs by site of SPM following MM in Germany and the US




SIR: standardized incidence ratio with 95% confidence intervals; MM: multiple myeloma; SPM: subsequent primary malignancies.
*in the SEER data myeloid and monocytic leukemia were combined together

## Figure 43. SIRs for subsequent solid malignancies and acute myeloid leukaemia following MM by follow-up duration and calendar year in Germany and the US




SIR: standardized incidence ratio with 95% confidence intervals; MM: multiple myeloma; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). German data: for the analysis in relation to calendar year, data was pooled from 9 German regions (out of 4 epidemiologic cancer registries).

## Leukaemia

Following first CLL diagnosis, the US data revealed patterns of SPM risk (overall, and age-, sex-, and site-specific) similar to that seen in Germany (**Table 25)**, although overall SIR was significantly higher for patients in Germany than in the US (1.49 vs. 1.32). Elevated risks for the following SPM were consistent in both data: colorectal, lung, melanoma, kidney, urinary bladder, thyroid cancers, and HL and ML. Also trends in SIRs with time of follow-up and calendar year appeared to be similar in both databases (**Figure 44**). For AML, no specific trend could be observed probably due to the small numbers of cases. We did not find significant differences in risk overall or for AML over the two study time periods compared in the two data sets.

Regarding first CML, results from both data sets were largely comparable, but SIRs of SPM (overall and solid malignancies) during the first year of follow-up after CML diagnosis in the German data appeared to be significantly higher than that estimated in the US data (**Table 26**). In contrary to the German data, the US data showed significantly higher overall risks in the later time period (2001–2011), but the difference was not statistically significant (**Figure 45**).

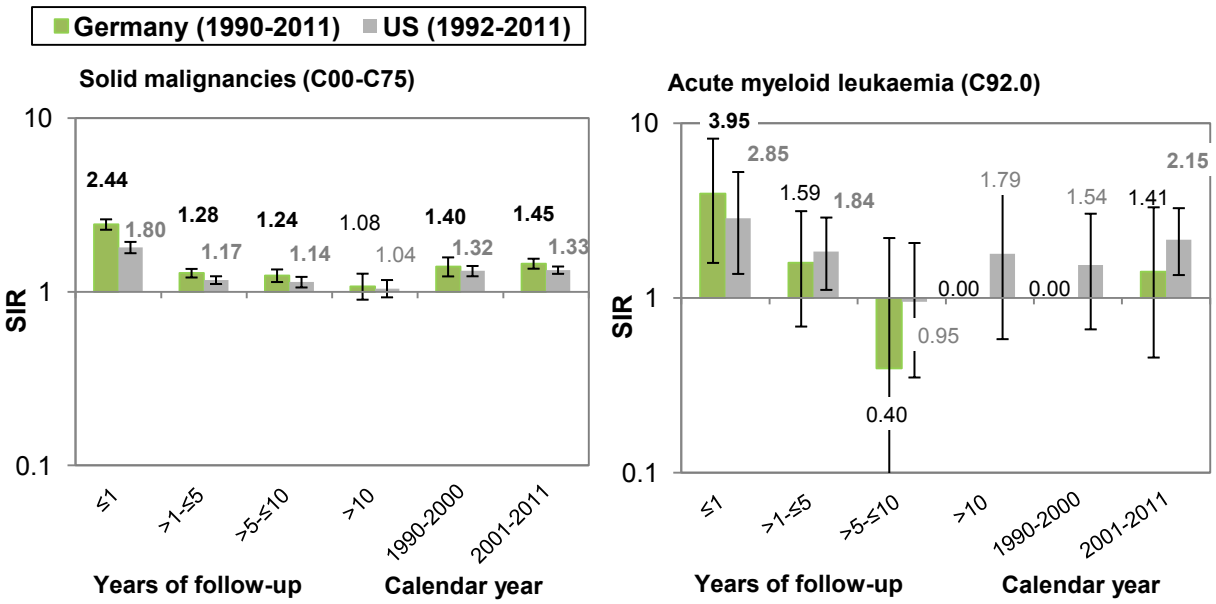
## Chronic lymphocytic leukaemia

### Table 25. Overall SIRs of SPM following first CLL by age, sex, time from diagnosis and calendar periods in Germany and the US

| | Germany (1990–2011) N=30878 | | | US (1992–2011) N=26742 | | |
|---|---|---|---|---|---|---|
| | O | SIR | 95% CI | O | SIR | 95% CI |
| **Overall** | 3022 | **1.49** | **1.43-1.54** | 3,776 | **1.32** | **1.28-1.36** |
| **Sex** | | | | | | |
| Males | 2078 | **1.50** | **1.43-1.56** | 2,485 | **1.3** | **1.25-1.35** |
| Females | 944 | **1.46** | **1.37-1.56** | 1,291 | **1.37** | **1.3-1.45** |
| **Age at first diagnosis (years)** | | | | | | |
| 15-29 | 0 | 0.00 | 0.00-28.22 | 0 | 0.00 | 0.00-65.75 |
| 30-44 | 27 | **3.17** | **2.09-4.62** | 33 | **1.82** | **1.25-2.56** |
| 45-59 | 461 | **1.55** | **1.41-1.69** | 654 | **1.57** | **1.45-1.69** |
| 60-74 | 1798 | **1.45** | **1.39-1.52** | 1,897 | **1.29** | **1.24-1.35** |
| ≥75 | 736 | **1.50** | **1.39-1.61** | 1,192 | **1.25** | **1.18-1.32** |
| **Years of follow-up** | | | | | | |
| ≤1 | 933 | **2.53** | **2.37-2.70** | 859 | **1.89** | **1.77-2.02** |
| >1-≤5 | 1331 | **1.29** | **1.22-1.36** | 1,603 | **1.23** | **1.17-1.29** |
| >5-≤10 | 611 | **1.23** | **1.13-1.33** | 949 | **1.22** | **1.15-1.30** |
| >10 | 147 | 1.06 | 0.90-1.25 | 365 | **1.13** | **1.02-1.26** |
| **Calendar year *** | | | | | | |
| 1990–2000 | 280 | **1.41** | **1.25-1.59** | 916 | **1.31** | **1.22-1.40** |
| 2001–2011 | 967 | **1.43** | **1.34-1.52** | 1,782 | **1.45** | **1.38-1.51** |

SIR: standardized incidence ratio; 95% confidence interval (lower-upper limits); CLL: chronic lymphocytic leukaemia; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).
*German data: for the analysis in relation to calendar year, data was pooled from 9 German regions (out of 4 epidemiologic cancer registries).

### Figure 44. SIRs for subsequent solid malignancies and acute myeloid leukaemia following CLL by follow-up duration and calendar year in Germany and the US




SIR: standardized incidence ratio; 95% confidence interval (bold indicates a statistically significant SIR, *P<0.05*); CLL: chronic lymphocytic leukaemia; SPM: subsequent primary malignancies. German data: for the analysis in relation to calendar year, data was pooled from 9 German regions (out of 4 epidemiologic cancer registries).

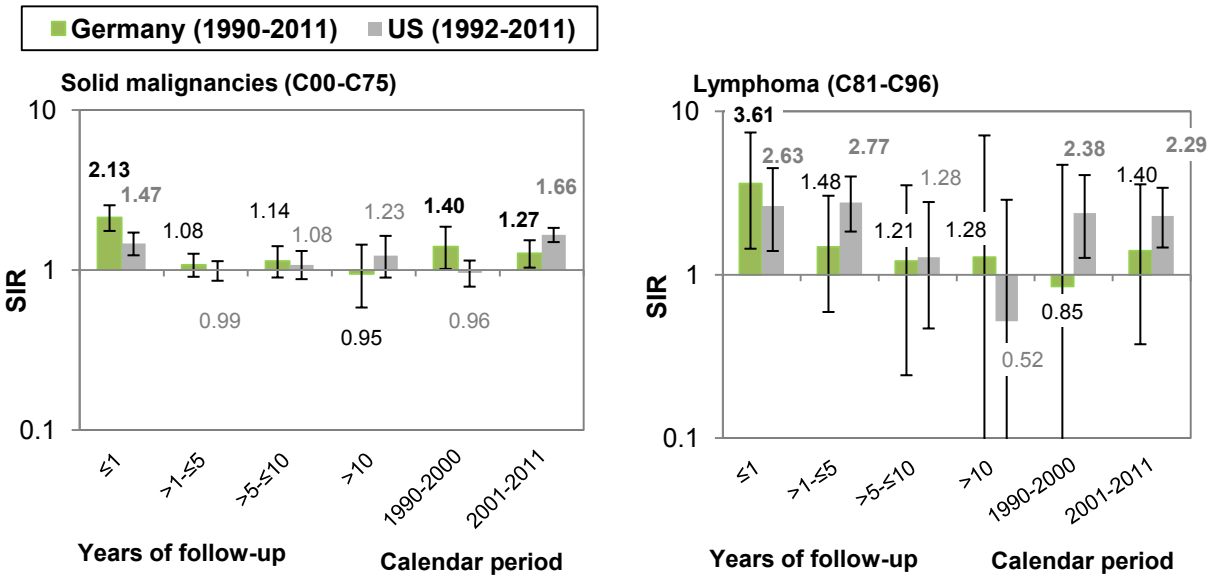
## Chronic myeloid leukaemia

### Table 26. Overall SIRs of SPM following first CML by age, sex, time from diagnosis and calendar periods in Germany and the US

| | Germany (1990–2011) N=7900 | | | US (1992–2011) N=10381 | | |
|---|---|---|---|---|---|---|
| | O | SIR | 95% CI | O | SIR | 95% CI |
| **Overall** | 438 | **1.41** | **1.28-1.55** | 660 | **1.38** | **1.27-1.49** |
| **Sex** | | | | | | |
| Males | 271 | **1.43** | **1.26-1.61** | 420 | **1.35** | **1.23-1.49** |
| Females | 167 | **1.39** | **1.18-1.61** | 240 | **1.42** | **1.25-1.61** |
| **Age at first diagnosis (years)** | | | | | | |
| 15-29 | 8 | **8.08** | **3.48-15.92** | 15 | **5.08** | **2.85-8.38** |
| 30-44 | 26 | **2.36** | **1.54-3.46** | 65 | **2.38** | **1.83-3.03** |
| 45-59 | 105 | **1.50** | **1.22-1.81** | 136 | **1.34** | **1.12-1.58** |
| 60-74 | 202 | **1.21** | **1.05-1.39** | 275 | **1.33** | **1.18-1.5** |
| ≥75 | 94 | **1.53** | **1.24-1.87** | 169 | **1.2** | **1.03-1.40** |
| **Years of follow-up** | | | | | | |
| ≤1 | 157 | **2.58** | **2.19-3.02** | 200 | **1.79** | **1.55-2.05** |
| >1-≤5 | 170 | 1.15 | 0.98-1.33 | 284 | **1.27** | **1.13-1.43** |
| >5-≤10 | 86 | 1.12 | 0.89-1.38 | 126 | **1.24** | **1.04-1.48** |
| >10 | 25 | 1.03 | 0.66-1.52 | 50 | 1.19 | 0.89-1.57 |
| **Calendar year *** | | | | | | |
| 1990–2000 | 56 | **1.57** | **1.18-2.04** | 143 | 1.08 | 0.91-1.28 |
| 2001–2011 | 130 | **1.45** | **1.21-1.72** | 370 | **1.67** | **1.51-1.85** |

SIR: standardized incidence ratio; 95% confidence interval (lower-upper limits); CML: chronic myeloid leukaemia; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).
*German data: for the analysis in relation to calendar year, data was pooled from 9 German regions (out of 4 epidemiologic cancer registries).

### Figure 45. SIRs for subsequent solid malignancies and lymphoma following CML by follow-up duration and calendar year in Germany and the US




SIR: standardized incidence ratio with 95% confidence interval; CML: chronic myeloid leukaemia; SPM: subsequent primary malignancies. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).
German data: for the analysis in relation to calendar year, data was pooled from 9 German regions (out of 4 epidemiologic cancer registries).

# Discussion

## Discussion of results

### Subsequent malignancies following lymphoma

The pooled German cancer registry data showed that long-term HL survivors have an over two-fold increased risk of developing a new SPM at any site and NHL survivors have a 1.5-fold risk compared with the general population. The increased risk was observed in both gender and amongst all age groups, but was significantly highest amongst survivors who were younger than 30 years of age upon their first lymphoma diagnosis. After the first HL, the overall risk was significantly elevated over the whole follow-up period and increased over the follow-up time, while it was only elevated within the first ten years after the first NHL.

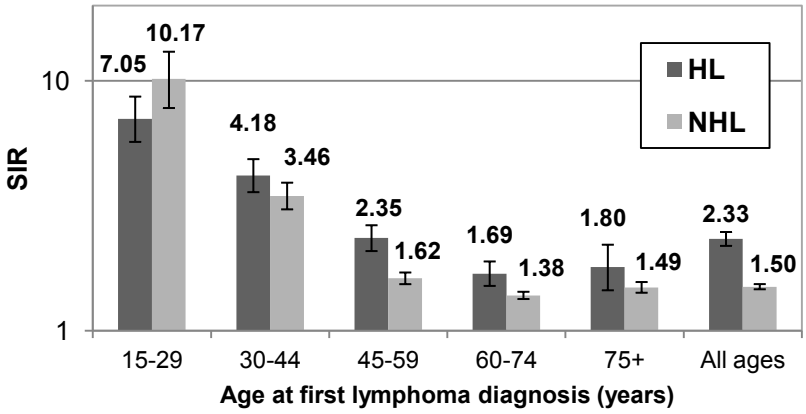
Our results are generally in agreement with previously published registry-based studies that have reported overall SIRs of second primary cancers ranging from 1.59 to 3.9 following HL [22, 42, 43, 62, 68, 77, 80] and from 1.12 to 2.0 following NHL [39, 42, 43, 57, 60, 66–68, 76, 77, 80]. In some studies, risks for subsequent solid malignancies were also reported to be significantly increased following HL (SIR= 1.4 [68] to 2.4 [62, 65]), and NHL (SIR= 1.11 [57] to 1.65 [69]), which are comparable to our estimates (SIR=1.76 and 1.43; respectively). However, no significant increased risk after NHL was reported by a Swedish study (SIR= 0.96, 95% CI=0.90–1.02) [68]. In contrast to HL, fewer registry-based studies on NHL have estimated the risk for subsequent solid cancers, which means that only very limited comparison can be made.

Differences between studies can be related to the use of different methods for the SIR calculation. For instance, some studies included the synchronous period [39, 66, 69], whereas many others excluded this period from the analysis, which also varied across studies (from one month to one year) [42, 57, 60, 62, 67, 68, 77, 80]. In particular, the exclusion of the initial time period after first cancer diagnosis has been applied by studies whose objective was to analyse the long-term effects of treatment mainly due to the fact that most of synchronous malignancies are more likely to have been identified through initial intensive medical investigations or other effects not related to treatment [38]. When we performed a sensitivity analysis excluding SPM that developed within the initial 2 months (most commonly applied time limit), a slight reduction in risks for solid malignancies by 18% following HL and 23% following NHL was demonstrated. This resulted in SIR of 1.58 (95% CI=1.45–1.72) and 1.20 (95% CI=1.17–1.24); respectively. However, despite this slight alteration from the initial analysis, our results remained comparable to studies cited above.

Other important reasons for variations of the estimated relative risks among studies might be related to differences in the study time periods, number of lymphoma survivors, database size or number of pooled registries, geographic variations, duration of the follow-up, and most importantly, rules applied for the definition and classification of multiple tumours. We implemented similar analyses (**Pages 74–79**) using the recent data from the US SEER program (with similar time period, data pool, and multiple primary cancer rules) [99] adjusting for age, sex, and start and duration of follow-up. Although the SEER data showed overall SIRs for all sites to be slightly lower (1.86 in HL and 1.39 in NHL) than our estimated SIRs, the patterns of risk were largely similar to the German data (as discussed in the following subsections).

A large number of clinical- or randomized trial-based studies on second cancer after treatment of HL/NHL have been published worldwide. Although they provide long-term follow-up, these studies are usually limited by small size and selection bias (e.g. age of patients or treatment groups) which result in higher risk estimates [18, 82, 83, 86, 101–103]. In addition, most of them often calculate person-years at risk starting one or 5 years after the initial treatment.

**Figure 46. SIRs for SPM at any site by age at diagnosis of first lymphoma**




SIR: standardized incidence ratio with 95% confidence intervals shown in the graph; SPM: subsequent primary malignancies; HL: Hodgkin lymphoma; NHL non-Hodgkin lymphoma. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). All sites SPM: excluding non-melanoma skin cancer (C44).

The significantly lower overall SIR for NHL compared to HL appears largely related to the later age of onset of NHL (median 70 for NHL vs. 40 for HL) and might be affected by the lower survival rates (5-year relative survival rates approx. 67% for NHL vs. 85% for HL) [2]. Lower survival results in lower person-years under risk for SPM over the follow-up time (9% of NHL vs. 19% of HL patients had a follow-up of more than 10 years). However, within the same age group, the overall results for HL and NHL were quite similar (**Figure 46**). Overall relative risk for all sites (and for solid cancers) was significantly higher (7.1- to 10.2-fold) in younger than older survivors

of both types of adult lymphoma, as demonstrated in several international studies [39, 57, 62, 65], indicating that age at first malignancy diagnosis is a very important risk factor for SPM. The corresponding SIRs in paediatric lymphoma up to age 21 years range from 6.9 to 12.5 [33, 78, 104, 105] for HL survivors and from 3.7 to 11 [33, 78, 104, 106] for NHL. This pattern likely suggests more intensive treatment (mainly combinations of chemo- and radiotherapy or stem cell transplantation), and/or possibly genetic predispositions in younger patients. Nevertheless, the incidence of SPM in older survivors is also very likely to be slightly underestimated because of the influence of co-morbid conditions and shorter life expectancy, suggesting SIRs should be interpreted with some caution [37].

The majority of the published long-term cohort studies reported increasing overall relative risks after HL and NHL with follow-up time [45, 60, 66, 67, 69, 86, 101, 107], whereas our data indicates an increasing risk with time following HL, but not following NHL. A similar finding has also been previously reported [68, 108]. Compared to results derived from the SEER data, our estimated SIRs were somewhat higher following HL across all follow-up intervals, but only in the first year after NHL diagnosis. Additionally, we did not observe an elevated SIR overall or for solid cancers following NHL in the German data beyond 10 years after diagnosis, whereas a small but significant increase was detectable in the SEER data. Moreover, our data demonstrates an increase in both the overall and solid cancer SIRs with follow-up time following HL diagnosis, which was not found in the SEER data. Although definitive conclusions cannot be made from this data, several reasons for the observed differences can be proposed. These may possibly include differences in treatment and survival. In recent years, it has been reported that five-year relative survival rates for HL patients in Germany were slightly higher in comparison to those in the US, particularly for younger patients [13]. These differences were linked to a potentially more intensive treatment approach used for advanced-stage HL in Germany than in the US (BEACOPP escalated vs. ABVD), which was introduced in the late 1990s by the German Hodgkin Lymphoma Study Group [7, 13]. There is evidence suggesting that BEACOPP escalated has more toxic effects than ABVD [8]. It has been especially associated with higher risk of secondary acute leukaemias, but the risk of solid SPM is not well defined. In both data sets, SIRs for solid malignancies did not significantly increase over the most recent calendar period (after 2000). Whether these differences in HL treatment regimens can also explain the elevated long-term risk of SPM in Germany compared to the US remains unclear and warrants further observation with longer follow-up periods. While the long-term risk for solid cancers after initial NHL was not significant in the German but was in the SEER data, the difference between the two estimates was relatively minor (1.05 vs. 1.15) and not statistically significant. Since NHL

treatment regimens are largely similar in Germany and the US [5, 109], difference in risk would not be expected. The striking differences in risk between the German and SEER data for developing haematological malignancies following NHL does not appear likely to be treatment-related, but may rather reflect differences in diagnosis and reporting practices, as they were mainly noted for secondary CLL (which may clinically overlap with NHL) and a second diagnosis of NHL.

In addition to the long-term effects of lymphoma treatment, common risk factors such as immune defects, genetic susceptibilities, lifestyle or environmental risk factors, as well as interactions between these factors have been discussed as potential mechanisms for SPM [29, 32]. Aside from these factors, surveillance effects and misclassification have to be considered as a potential source of increased SIR for lymphoma patients. Surveillance effects can be suspected when the SIR value is primarily increased in the first year following diagnosis, and decreases or normalizes over time. In this case, the SIR should not be interpreted as a relative risk of developing but rather as the likelihood of detecting a subsequent malignancy. Some cancer sites such as prostate, thyroid and, to some extent, breast are known to be potentially clinically inapparent over a long period of time and therefore prone to accidental diagnosis especially during the diagnostic work-up of the first malignancy. Similarly, misclassification caused by either diagnosis or coding errors, would likely be in effect during the first follow-up year. For instance, misclassification may play a role when HL and NHL or two different types of NHL are diagnosed in the same patient, but also for the typical sites for extranodal NHL (e.g. stomach) [39].

Given the limited information on treatment in our data, a direct assessment of therapy effects was not possible. However, the detailed analyses of overall and site-specific risks according to age at diagnosis, follow-up time intervals, and calendar year of diagnosis also provide valuable information about factors potentially associated with increased SPM risk. The analysis in relation to calendar period was implemented to assess the pattern of SPM risk after the introduction of new therapies. In an additional analysis, the risk of developing HL and NHL as a subsequent cancer was evaluated following selected cancers that were significantly increased after first primary HL and NHL in the first analysis. Thus, a trend of increase in risk for SPM with longer latency from diagnosis and a unidirectional association between the first and SPM site are suggestive (but not confirmatory) of late side effects of therapies, while shared risk factors would be suspected if there is a positive bidirectional association and the risk is constant over the complete follow-up intervals. It should be emphasized, however, that all these inferences can be made only indirectly. The positive associations observed in our study are explained for each HL

and NHL separately by applying the aforementioned principles and taking biological plausibility into account:

**Subsequent malignancies following HL**

The most commonly reported solid malignancies after HL are cancers of the lung, thyroid, female breast, stomach, oesophagus, colon, skin melanoma, lip/oral cavity, bone/soft tissue, and kidney [17, 42, 62, 65, 68, 77, 80, 110]. In addition, significant elevated risks for subsequent NHL, MM and leukaemia (both myeloid and lymphoid) have also been shown in several earlier and most recent reports [17, 42, 62, 68, 77, 80]. Our results also correspond to most of these studies. In contrast, we found no risk for urinary bladder and a non-significant decreased risk for brain/CNS, while other studies reported a positive association [62, 65, 68, 77].

Our data (and the US SEER data) suggest long-term effects of treatment for cancers of the lip/oral cavity, lung, female breast, and potentially for stomach and colorectal cancers because the SIRs for these sites increased at more than 10 years of follow-up and were higher at younger ages at diagnosis of HL. Additionally, the association of HL with these cancer sites was unidirectional, except for lung and colorectal cancers. Previous studies have also observed increasing SIRs of these cancers with time, started at 10 years after treatment of HL, which continued to increase for 20 years or longer [17, 62, 65, 80, 101, 107], and have linked the risk for these cancers to the long-term effects of radiotherapy (dose-dependent risks), or the combined radiation and chemotherapy effects [18, 25, 61, 80, 86, 101, 102, 111–115]. Moreover, most of these solid cancers are reported to be induced by exposure to radiation in the Life Span Study (LSS) of atomic bomb survivors [27].

The degree of risk related to radiotherapy appeared to be basically dependant on the amount of radiation, field size (extended field vs. involved field irradiation), and age of patients at time of exposure to irradiation. Some studies have indicated that most of the observed second solid malignancies were located at anatomical sites within or around the irradiation fields [18, 25, 101, 102, 105, 110], mostly involve cervical and chest/mediastinal areas. Until now, the effect of chemotherapy alone (e.g. cyclophosphamide, procarbazine, dacarbazine) on the risk of solid malignancies after HL remains unclear [18, 113, 115], but it is assumed to play a minor role. For instance, breast cancer risk has been found to increase with increasing radiation dose delivered to the breast, especially when administered at a younger age [112, 114, 116]. Conversely, a reduced risk of breast cancer following treatment of HL with alkylating chemotherapy (e.g. mechlorethamine and procarbazine containing therapy) has been shown in several studies [86, 101, 111, 112, 116]. The risk has been found to further decrease with increasing number of

cycles of alkylating agents [112] and was explained by the development of premature menopause caused by chemotherapy-induced ovarian failure.

Of real concern, a recent study indicates that the proportion of second solid cancers attributed to radiotherapy in adult cancer survivors is relatively small (<10%) suggesting that a larger fraction could be due to other cancer risk factors, such as lifestyle, environment or genetics [34], which probably interact with each other. An important example is subsequent lung cancer, where a combination of shared risk factors and treatment effect appears to be present in our data. In absolute terms, lung cancer was the most frequent subsequent solid cancer following initial HL in the current study, and the absolute excess for lung cancer risk was considerably higher than for all other solid cancers (10 subsequent lung cancer cases per 10,000 patients per year), particularly among men. Interestingly, it has been demonstrated that tobacco smoking has a multiplicative effect on treatment-related lung cancer (both radio- and chemotherapy) [61, 117]. This evidence effectively highlighted the possibility of interactions among several risk factors of SPM. Tobacco smoking could also be a potential shared risk factor between HL and lung cancer, particularly as there is evidence linking cigarette smoking to HL risk (mostly nodular sclerosis and mixed cellularity subtypes) [118]. However, the assumption of shared risks cannot yet be confirmed, as no similar mutual risk has been published in previous reports [119]. These results should be further investigated in larger studies that take into account the interaction between all potential risk factors, including treatment, lifestyle, environmental and socioeconomic factors.

Shared risk factors seem to be the most probable explanation for the elevated risk for melanoma. In previous studies, melanoma risk was only observed in the first 5 years of follow-up [68, 101, 111], which is in line with our study. The causes of increased risk of melanoma after HL are unknown. It has been suggested that the risk is related to shared immune dysfunctions and/or immunosuppressant effects of chemotherapy in the initial years. The occurrence of other lymphoid malignancies (NHL, CLL) following melanoma observed in other studies [37, 39, 40] and our own may also further suggest that the association with melanoma might be influenced by a common mechanism. Of particular interest, an inverse association between exposure to ultraviolet radiation (UVR) and HL risk has been recently confirmed in a large collaborative pooled analysis supported by the International Lymphoma Epidemiology Consortium (InterLymph) [120]. Thus, the role of UVR as a common aetiology cannot be suggested.

Surveillance effects can be suspected for kidney cancer. In contrast to the US data, our data also suggest a possible treatment effect for kidney cancer because of the increase in SIR over the follow-up time; however, this was based on a small observed number of cases. For thyroid

cancer risk, surveillance effects, probably in combination with shared risk factors, are also a likely explanation. An increase of 3- to 4-fold of thyroid cancer risk following HL has also been reported in some studies [62, 80]; it is higher particularly amongst younger patients. It is well known that thyroid cancer is induced by radiotherapy used in the treatment of childhood HL [105, 121, 122], but also adulthood HL [102]. Chemotherapy has also been reported to increase the risk of thyroid cancer among childhood cancer survivors [123]. However, long-term effects were not demonstrated in our data, but were in the US data. Strikingly, we found no risk for cancer of the brain/CNS, dissimilar to some studies that found significant increased risks in long-term survivors of adult HL [62, 65, 68, 77, 111] and childhood HL [33], which was also reported to be associated with radiotherapy.

The elevated risk for ML over the entire follow-up period, peaking between five and ten years (though somewhat earlier in SEER), may indicate a treatment effect which has been previously linked to the use of alkylating chemotherapy either alone [86, 124] or in combination with radiation [101, 102]. Of note, all subsequent AML cases in the German data were observed for HL patients initially diagnosed in the year 2000 or later (mainly in patients aged under 60 years at diagnosis), which may be related to the introduction of BEACOPP in the late 1990s [8]. The high SIRs (up to 46.4) in the first year for subsequent NHL, MM and LL likely indicate misclassifications, while surveillance effects may also add to these excesses. Subsequent NHL risk was significantly elevated in all ages and follow-up intervals in our study, but no change over follow-up time was seen. These results are in agreement with previous reports that also found that the elevated risk for NHL did not vary significantly with different treatment modalities [101, 111, 124], suggesting that the risk could also be associated with other risk factors in addition to HL treatment (e.g. immunosuppression state).

**Subsequent malignancies following NHL**

Increased relative risks for a number of SPM have been previously reported in NHL survivors: lung, skin (melanoma and non-melanoma), urinary bladder, kidney, lip/oral cavity, stomach, colon, brain/CNS and thyroid cancers, and HL and leukaemia [39, 42, 57, 60, 66, 69, 77, 80], which are in line with our findings. We additionally report increased risk for testis, liver, pancreas, breast, prostate, and MM. No cancer occurred in significantly lower than expected rates in our cohort.

Shared risk factors (most likely smoking, immune alterations, and viral infections) appear to generally explain the majority of the positive associations found between NHL and other SPM in our analysis, as the respective reciprocal SIRs were elevated to a similar degree. These findings

are highly consistent with findings from a previous international study that used registry data pooled from different countries [39]. The increased risks in the first year after NHL diagnosis for thyroid, melanoma, kidney and some other sites may also indicate additional surveillance effects, while for cancer of the stomach, the most affected organ in extranodal onset of NHL [3], misclassification may also occur.

In the German database, the patterns of risk with time since NHL diagnosis of cancers of stomach, liver, and pancreas were also consistent with treatment effects, but these results are based on very few cases and are not confirmed by the US SEER data. However, a time trend similar to ours for pancreatic cancer has been shown in a recent registry-based study from Nordic countries [66]. Of all long-term studies available on second cancer risk following NHL, relatively few have directly assessed the risk by the type of treatment [57, 58, 80, 82, 103, 108]. It is thus difficult in this case to make definite conclusions about treatment effects on secondary cancer risks. On the other hand, only the SEER data demonstrated significantly increased long-term risks for breast and urinary bladder cancer. A similar pattern to that of SEER was also reported in some studies [39, 66, 77], while many other studies reported that NHL survivors had no or reduced risk of breast and prostate cancer relative to the general population [39, 57, 60, 68, 69, 76, 108]. The reduced risk for breast cancer was also linked to the therapy-related early menopause due to chemotherapy and pelvic irradiation [57, 80, 108].

To our knowledge, only two studies found increased risk for liver cancer after NHL [39, 125] and have indicated a possible treatment effect as well as common mechanisms. The positive reciprocal association between NHL and liver cancer appears biologically plausible, as hepatitis C virus infection could play a role in the aetiology of both NHL (particularly B-cell NHL) and liver cancer [126] and might therefore be a potential shared risk factor. Unfortunately, data about hepatitis virus infection status were not available in our database. In addition, no data on population attributable risk of hepatitis for liver cancer or NHL risk in Germany has been published so far. On the other hand, alcohol intake, an important risk factor for liver cancer, appeared to be a protective factor for NHL [127].

Our study confirmed the reciprocal association between NHL (and HL) and melanoma consistently found in several epidemiologic studies [37, 39, 87, 88]. The underlying mechanism is not fully understood; however, the mutual risk is thought to be related to a common exposure such as chronic immune suppression. Exposure to UVR has also been described as a potential common risk factor for NHL and melanoma [87, 88] mainly due to its known systemic immunosuppressant effects. Currently, there is inconsistent evidence that an association

between UVR exposure and the risk of developing NHL exists, with results from several recent studies supporting a protective effect of UVR exposure on NHL risk [89], which increases the complexity of interpreting results.

Tobacco smoking could be a potential shared risk factor between NHL and lung cancer (as was noted previously between HL and lung cancer), especially as there is evidence to support a positive link between cigarette smoking and lymphoma (both types) risks [128, 129]. The joint effects of smoking with other potential risk factors, including interactions with NHL treatment, need to be assessed in future studies.

The biological mechanisms for the possible link between NHL and cancer of the thyroid or kidney remain unclear. Shared risks such as immune dysfunctions, genetic predisposition, environmental factors, and chromosomal abnormalities, have been proposed as potential risk factors [130, 131]. Thus, this observation requires additional investigation in future research.

Results for other haematological SPM after NHL were generally comparable to those following HL. The occurrence of ALL can also represent transformation of high-grade NHL. However, HL risk after initial NHL and vice versa [62, 68, 77] may also suggest a common aetiology, but misclassifications may also influence the results. The high risk for AML was linked to alkylating agents; either alone [132] or in combination with radiotherapy [108], as well as topoisomerase II inhibitors and nucleoside analogues. A trend of a slight decline (but not significant) in the risk for AML was seen over the recent time period (after 2000) in our study, dissimilar to other recent studies reporting increased risk of SPM following indolent NHLs treated in the recent time period after 2000 [67, 82]. This data suggests a possible role of rituximab or fludarabine (a nucleoside analogues), introduced in the late 1990s, which has been shown to be associated with the development of AML and other solid cancers. However, clearer conclusions can only be made with follow-up data covering a longer period.

Non-Hodgkin lymphoma has been recognized as a heterogeneous group of cancers that have diverse histology, clinical course, treatment, and prognosis. Therefore, different patterns of SPM risk would be expected after different NHL histological subtypes. Previous studies have reported either on the risk of SPM following treatment of indolent [82, 133] or aggressive NHLs [103]. A very limited number of studies, restricted only to the B-cell type, have compared the risk among patients with indolent and aggressive NHL subgroups [58, 108]. To our knowledge, only one cancer registry-based study assessed the risk in detail for common NHL subgroups of B- and T-cell type [67]. Our study is thus considered the second one that compared the risk of SPM between major cell types of NHL and different grades. Moreover, we were also able to estimate

the risk of SPM after more specific subtypes of NHL. Compared to low-grade or indolent NHLs, high-grade or aggressive NHLs are treated more intensively with multiphase chemotherapy (+/- radiotherapy) as they are more potentially curable. CHOP chemotherapy in combination with rituximab is the standard first line treatment for these lymphomas. Refractory cases have to be treated with high-dose chemo-radiotherapy and stem cell transplantation [5]. In contrast, low-grade NHLs, which account for the majority of NHLs (43%) in our database, are often treated with involved or extended field radiotherapy (+/- chemotherapy). The chemotherapy mostly includes fludarabine/chlorambucil and rituximab combinations (FCR). Previous studies have suggested overall differences in relative risks of SPM among NHL subtypes, but results were conflicting. Some studies indicated that CLL/SLL (small lymphocytic lymphoma) have a significantly higher risk of SPM compared to FL [133] or DLBCL [58], whereas other studies found that patients with DLBCL are at significantly highest risk of SPM compared to FL or lymphocytic NHL [108]. In the SEER registry-based study [58], more specifically increased risks for melanoma and lung cancer were noted after indolent NHLs (CLL and FL), but not after the more aggressive NHLs (DLBCL). While the reason for this difference remains unclear, long-term immune dysfunctions, genetic risk factors, and repeated exposure to treatment due to frequent relapses are proposed to play a role in indolent NHLs. Our data showed significantly increased SPM risk in all specific subtypes, but no significant difference in the overall SIR between low- and high-grade NHLs was noted, although the low-grade group tended to have a slightly higher risk overall and for some specific SPM (e.g. lung and melanoma) than high-grade NHL. When we further stratified the SIR according to NHL cell type (B-cell vs. T-cell), which have not been previously compared, we generally found that survivors of T-cell NHLs had a significantly higher risk of SPM than survivors of B-cell NHLs, particularly high-grade T-cell NHL. However, because of the rarity and poor survival of aggressive T-cell NHLs, the estimation of SIR following other more specific histological sub-sites was restricted. In a multivariate analysis adjusted for other confounding factors (including treatment), two recent studies [67, 82] found no significant difference in risk of SPM overall among different NHL histological subtypes, suggesting that the observed differences in risk might be related to confounding factors such age at diagnosis, follow-up time, or intrinsic characteristics of patients than to the histological NHL subtype.

**Subsequent malignancies following multiple myeloma**

German patients surviving MM are at increased risk (11%) of developing SPM compared with the general population. However, this risk was found to be substantially lower compared to SPM risk observed following lymphomas and leukaemia. Patients diagnosed under age 60 years with MM were found to have a slightly higher increased risk (30%) compared with the general population. The highest relative risk was generally observed for haematological malignancies (1.65-fold), mainly due to AML (6-fold), HL (2.6-fold), and NHL (1.7-fold). The overall relative risk of solid SPM was marginally increased (10%). Some types of subsequent solid malignancies occurred significantly more frequently than expected rates, including cancers of the skin melanoma, oral cavity, and kidney. These cancers accounted for the largest EAR in the MM cohort.

Little population-based data exist on SPM after MM, and the results are generally contradictory. Most population-based studies [59, 68, 80] with long-term follow-up reported a reduced overall risk of SPM or a risk that was not significantly different from the general population rates [42, 45]. By contrast, two more recent studies [71, 77] reported significantly elevated overall risks (SIR=1.55 and 1.26; respectively), which are somewhat higher than our estimated risk (SIR=1.11). In addition, results from these studies greatly varied with regard to the risk for solid malignancies, whereas results for increased risk of haematological malignancies were more or less consistent.

Increased risks for malignant melanoma and kidney cancer [59, 77, 80], NHL [59, 68, 134] and ML [59, 68, 71, 77, 80, 134] were also described in previous studies. In contrast to other studies, we observed an increased risk for HL, and cancers of the lip/oral cavity and lung (in females only). In addition, we did not find significant excess relative risks of CML, or of colorectal or urinary bladder cancers, as was indicated in some reports [59, 77, 80, 134]. The reduced risk for cancers of the oesophagus, larynx, breast, uterus, prostate, and LL after MM diagnosis observed in our cohort is similar to that described in most previous follow-up studies [59, 68, 80], but not all [77].

In most studies reviewed, no increases in overall SIRs with longer follow-up time after first MM diagnosis were reported [45, 59, 68, 77]. In our study, the SIR of SPM at any site (solid and haematological) was also found to be significantly lower than expected 10 years after MM diagnosis. This finding could be related to the advanced age of onset of MM (median 70 years) and the generally poor survival (e.g. 5-years relative survival of <45% in Germany) [2] that affect time under risk for SPM. Some caution is therefore warranted in interpreting these results because of the insufficient follow-up time and the small number of cases observed.

When we re-calculated the SIR by excluding the initial 2 months of MM diagnosis, no overall significant increase in risk for any new cancer was found (SIR=0.90, 95% CI=0.86–0.95). However, SIRs for subsequent ML and melanoma, did not significantly change from the initial analysis (SIR=3.99, 95% CI=2.97–5.25, and SIR=1.69, 95% CI=1.33–2.12, respectively), which is somewhat similar to the pattern of risk observed in other studies [59, 77].

The largest relative and absolute risk (SIR=5.94, EAR=3.14/10,000 person-years of follow-up) was found for subsequent AML in our study and in prior studies, SIR range from 5.4- to 11.5-fold [59, 68, 71, 77, 80] for ML as a one group. Myeloid leukaemia SIR has been reported to peak in 1-9 years [59, 68, 80] and in one study [77], SIR even continued to increase after 9 years from MM diagnosis (based on very small numbers). In our analysis, the SIR for ML was highest (10-fold) in younger MM patients (<60 years at first diagnosis), and was significantly elevated only within the first 10 years of follow-up. The long-term use of alkylating agents (e.g. melphalan and cyclophosphamide) for MM treatment has been associated with increased risk of AML/myelodysplastic syndrome in a number of studies [135, 136]. Generally, radiotherapy appears likely to play a minimal role in the aetiology of SPM in MM because it is only offered as a palliative therapy and for the curative treatment of solitary plasmacytoma (a rare subtype) [3, 5]. Melphalan, which has been used as standard therapy for MM since the 1960s (especially for older patients or patients who are not fit for SCT), was reported to have a greater toxic effect than cyclophosphamide [137]. In addition, new therapies for myeloma such as IMiDs (e.g. lenalidomide) have also been implicated in the aetiology of AML [84, 85], particularly when lenalidomide is administered in combination with melphalan. Genetic susceptibility has also been suspected to play a role in the development of AML/MDS after MM [135]. It remains unclear whether shared genetic risk factors could also explain the positive reciprocal association we found between MM and AML.

In the current pooled analysis, no trend of increase in AML SIR in the most recent calendar years (2001–2011) was found, the period of time during which IMiDs and targeted therapy with proteasome inhibitors were introduced, which is generally similar to other population-based studies [59, 71]. None of these two studies showed significant changes in the overall risk or for AML over the similar time periods. In addition, a pattern of decreasing relative risk over time among all ages was suggested. In relation to age of patients at diagnosis, we observed a notable decrease in AML SIR in the recent time period in younger patients (<60 years), while SIR remained constant in patients diagnosed at an older age (≥60 years). However, due to the very small number and limited follow-up durations, our findings should be interpreted with caution. Whether the decline in AML risk in younger MM patients is due to reduction of melphalan quantity

(shift from low- to high-dose melphalan with SCT) or the use of other more safe alkylators [81], is unclear and certainly further evaluations of this trend will be needed. By contrast, the unchanged risk of AML in older patients (in our cohort >70% of patients were 60 years or older) may indicate persistent toxic effects of some MM therapeutic agents (mainly melphalan). Definite conclusions cannot be made from registry-based data that usually lack information on type and dose of treatments. However, to confirm these findings, we performed a similar analysis using the recent SEER cancer data (1992–2011) stratifying the SIR by age, follow-up time, and calendar periods (**Pages 80–81)**. Results similar to ours were observed, in the US SIRs (overall and for AML) did not significantly rise over the recent time period in either age group (<60 and ≥60 years), and risks remained persistently high in older patients (data not shown).

The overall risk of subsequent melanoma was increased in both sexes but was limited to patients older than 60 years at diagnosis and the first five years of follow-up, a similar pattern was observed in some studies [59]. The reciprocal increased risk found in our data supports the role of immune dysfunctions or other common risk factors (genetic, environmental) [135, 136], but this positive association was not noted in the published US SEER report [80]. However, effects of medical surveillance can also play a role in increasing detection of melanoma in the initial years following diagnosis. Similarly, detection bias appears to explain part of the excesses for other solid malignancies such as kidney and oral cavity cancer, because the elevated risks were limited to the first year of follow-up [59, 80]. It is also possible that the apparently lower overall relative risk for all SPM 10 years after MM diagnosis might be influenced by increased medical surveillance.

The association of MM with other haematological malignancies such as HL and NHL should be carefully interpreted because of the possibility of diagnostic misclassifications (e.g. transformations of MM into NHL, or misdiagnosis of extramedullary plasmacytoma and extra-nodal NHLs) [3] given that relative risks for the two lymphoma types were only increased within the first year of MM diagnosis.

## Subsequent malignancies following leukaemia

**Acute leukaemias:** There are relatively few epidemiologic studies in the medical literature about SPM following adult-onset acute leukaemia [74, 138]. Most of previous cohort studies have evaluated the risk of SPM following childhood-onset acute leukaemia [33, 78, 104, 139]. In our study, survivors of adult AML had a 28% significantly increased relative risk for developing a new SPM, and survivors of ALL had a 71% significantly increased risk compared with the general population. Overall, no specific pattern of SPM risk could be observed over the follow-up periods of our study after first AML and ALL diagnosis, and the number of patients surviving more than 10 years was too small (< 10%). In the US SEER report [138], SPM SIRs were 0.94 (95% CI=0.79–1.09) and 1.55 (95% CI=1.20–1.98) for adult AML and ALL, respectively. Indeed, the risk following ALL in the SEER study was found to be limited to patients aged less than 17 years at first diagnosis. In Germany, patients aged under 30 years at first diagnosis had a 13.5-fold and 7.5-fold higher overall relative risks of developing SPM following initial AML and ALL, respectively, while patients aged over 60 years had relative risks of SPM that were not significantly different from general population risks. Among patients who were diagnosed before the age of 30 with first ALL, significantly elevated SIRs were noted for melanoma, breast, and AML. For patients aged 30 years or younger at first AML, significantly elevated SIRs were found for lip/oral cavity, lung, NHL, and ALL. Subsequent malignancy risk following adult acute leukaemias appears to be different from that in childhood. The corresponding overall SIRs for SPM following childhood-onset ALL (age under 21) were 4.4 to 12.7 [78, 104, 139, 140]. Elevated risks for brain/CNS, thyroid, bone and soft tissues sarcomas, oral cavity (including salivary glands), and NHL were consistently reported [33, 104, 139, 140]. Risks are largely attributed to exposure to radiation therapy particularly due to prophylactic/therapeutic cranio-spinal irradiation applied intensively in the 1970s–1980s. In addition, the increased risks have also been attributed to other risk factors such as previous chemotherapy, genetic predispositions (e.g. Li-Fraumeni syndrome), and relapse of primary ALL. The estimates of SPM risk following childhood AML varied among studies from non-significant increased SIR of 2.9 [139] to a significantly increased SIR ranging from 6.7 to 10.6 [78, 104] compared with children in the general population. No specific patterns by site of SPM were reported.

**Chronic leukaemias:**

### Subsequent malignancies following CLL

Following initial CLL, patterns of SPM risk were found to be similar to those observed after all NHLs. Recently, CLL and SLL (a low-grade NHL) have been considered to be one disease [3]. It

is characterized by a long-term course, with a lower rate of cure. Most cases of CLL may not need to receive medications until the disease progresses. In this case, combinations of alkylating chemotherapy (cyclophosphamide, chlorambucil, or bendamustin), purine analogues (fludarabine), and immunotherapy (rituximab) are included in the current initial therapeutic regimens [5]. Several studies have reported a significantly elevated relative risk, varying from 1.2- to 2.2-fold, for all SPM in patients with CLL compared with the general population [42, 56, 72, 75, 138, 141], which corresponds to our results (SIR=1.49). The increased risks seen in our study for many solid SPM involving cancers of the lip/oral cavity, stomach, colon/rectum, lung, skin melanoma, prostate, kidney, urinary bladder, and thyroid as well as for HL and ML were also consistent with other studies [75, 72, 56, 58, 133, 42, 141]. Unlike our results, increased risks for second cancers of the larynx, brain, and Kaposi sarcoma in patients with CLL have been indicated in some reports [56, 75, 138, 141].

There is little evidence regarding the effects of CLL/SLL treatment on the risk of SPM. Many previous reports showed no difference in risk for all SPM and specific sites by type of initial CLL treatment [56, 141, 142]. Moreover, the increased overall risk of SPM remained constant over all follow-up time intervals after CLL diagnosis in most long-term population-based studies [72, 75, 141]. In our study, the overall relative risk decreased with increased length of follow-up and the long-term risk (after 10 years of follow-up) for most solid SPM was not significantly different from expected rates in both younger and older age groups. Recently, there is evidence suggesting that therapies for indolent NHLs containing fludarabine (being in use since 1980s in Germany) [5] and rituximab (introduced in 2000s) are associated with increased risk of solid malignancies, but not of AML [82, 83, 143]. A slight significant increase in risk of solid SPM (SIR=1.45) over the recent calendar time period (2001–2011) was observed after initial CLL in our study, but this risk did not differ significantly from the risk of solid SPM (SIR=1.40) in CLL patients initially diagnosed during the earlier time period (1990–2000). This observation is similar to findings from a Danish cancer registry-based study that also reported no change in the overall second cancer risk over the two time periods compared (1943–1994 vs. 1994–2003) [72]. More detailed studies with large follow-up data sets covering lengthy periods are needed to assess if the incidence of solid SPM will significantly increase over time.

Elevated risks for Kaposi sarcoma and melanoma have been speculated to be associated with immune dysfunctions in CLL patients [56]. An overall 3-fold elevated SIR for subsequent melanoma (about 8 excess cases per 10,000 patients per year of follow-up) after CLL was found in our analysis. This risk was constantly increased across all follow-up intervals (peaked between one and five years) and both calendar time periods. In addition, the increased occurrence of

subsequent CLL following first melanoma observed in our cohort (SIR=2.56) supports the role of immunological impairments as a common mechanism. Similarly, the pattern of subsequent lung cancer risk after CLL was not consistent with the late effects of treatment in our study, as was demonstrated in other reports [75, 138]. Excesses of lung cancer were also observed following diagnosis of HL and NHL in our study. However, the mechanisms associated with the development of lung cancer after CLL are less clear. Several studies assumed that the causes for the increased risk of lung cancer after CLL are multifactorial. It has been hypothesized that radio- and chemotherapy (alone or in combination) for CLL can increase the effect of tobacco smoking for developing lung cancer in CLL patients like patients with other lymphoid malignancies [58, 72]. Other influences have also been discussed including treatment- or disease-related immunodeficiency state, and shared risk factors such as tobacco smoking, genetic, or environment (occupational: radon, asbestos). However, the shared risk factor of tobacco use between lung cancer and CLL/SLL seems to be not plausible. Cigarette smoking has very recently been found to have a protective effect in the development of CLL/SLL, based on a pooled analysis from 13 case-control studies published by the InterLymph Non-Hodgkin Lymphoma Subtypes Project [144]. In addition, data from two large studies that have examined the histological subtypes of second lung cancer in CLL/SLL patients reported that the relative risk for developing small-cell carcinoma of the lung, a subtype that is believed to be strongly related to tobacco smoking, was not significantly elevated [58, 72]. Detailed research is essential to assess the potential role of treatment and shared risk factors on SPM risk following CLL.

The increased risk for cancers of the lip/oral cavity, stomach, pancreas, kidney, and urinary bladder was confined to the first year of follow-up and appeared to be partly influenced by surveillance bias. No significantly elevated risk for developing cancers of the breast and female genital organs among CLL patients was found in our study, similar to findings from most population-based studies of CLL patients [56, 72, 138, 141] and NHL patients (see the NHL subsection). However, given that the majority of female patients (82%) in our cohort were diagnosed with first CLL at an age older than 60, slightly higher than NHL patients (72%), the protective effect of alkylating CLL/NHL chemotherapy on second breast cancer is an unlikely explanation for these reduced risks [72].

Histologic transformation of the first CLL into high-grade NHL (Richter syndrome) and ALL may occur [145], resulting in possible misclassifications of these diagnoses as SPM. An increased risk for secondary NHL was only noted within the first year of initial CLL diagnosis in our data. In contrast, diagnostic misclassification is an unlikely explanation for the elevated risk of subsequent HL because our analysis showed that the risk for this malignancy was constantly

increased over the entire follow-up time after initial CLL and did not vary between the two time periods (before/after 2000). In addition, the overall relative risk of HL did not significantly change after the exclusion of the first year of follow-up after CLL diagnosis (SIR remained at 13). The observed pattern supports the role of immune dysfunction and shared risk factors [138]. We found a 10-fold significantly increased SIR for subsequent CML after initial CLL (EAR=2.23 per 10,000 patients per year), but no significantly increased SIR was noted for AML. The excess risk for second CML has not been previously reported in other population-based studies on patients with CLL [75, 72, 56, 58, 42, 141]. We have no clear explanation for this association, but it is unlikely that ML is diagnostically misclassified as a SPM after CLL. Our results showed that the increased risk for CML persisted for more than 10 years after CLL diagnosis (based on very small observed numbers). The significantly increased risk for AML following SLL but not CLL observed in our study is consistent with a previous investigation [58] indicating that chemotherapy might be used more intensively in the treatment of SLL than CLL.

**Subsequent malignancies following CML**

The SIR of SPM was increased by 41% after diagnosis of first CML compared with the general population of Germany. Particularly, people who were under 60 years at first diagnosis were found to have a 1.7-fold significantly increased relative risk, while the risk of those who were over 60 years was only 1.3-fold. Generally, the overall risk decreases with follow-up time and the risk after 10 years from first CML diagnosis was found to be the same as the general population risk. There is an extreme lack of population-based data on second malignancies following CML in adults [42, 70, 73, 138], and many studies analysed the risk following ML as an entire group usually because of insufficient numbers of cases [45, 68, 77]. In the US [138] a 16% increased relative risk was found for all SPM sites, which was notably higher in female survivors of CML. Another Swedish registry-study reported an 82% significantly increased risk for patients diagnosed with CML between 1970 and 1995 [70]. In contrast, no significant increased risk was reported in a recent registry-based French study (during 1989–2004) [42].

In the present study, we found elevated risks for cancers of the skin melanoma, kidney, lip/oral cavity and prostate, and LL, MM and NHL, which are very similar to those previously reported in an Australian study [77]. By contrast, the Australian as well as the US SEER study has additionally observed increased risk for cancers of the lung and colon/rectum [77, 138]. No clear explanation could be found for these elevated risks. In addition, the authors of the Swedish study [70] pointed to an increased incidence of stomach cancer, but not of lung or prostate.

In our analysis, the SIR of solid malignancies remained significantly elevated up to 10 years after first CML in patients diagnosed before age 60 years, whereas elevated risks were confined to the first follow-up year in patients diagnosed after age 60 years. In younger survivors, the observed trend was mainly due to increased SIR for melanoma and kidney in the >5–≤10 years follow-up interval (based on few observed cases). In addition, the overall risk for subsequent NHL was significantly higher (3-fold) in younger patients, especially within the first five years of follow-up, than the risk in older patients. Whether the increased risk for melanoma and NHL is related to CML therapy, such as exposure to bone marrow transplant at a young age, remains to be clarified in more specific clinical research. There is evidence of increased risk of malignant lymphoma (B-cell) and a number of solid malignancies (e.g. melanoma, lung, and oral cavity) among adult allogeneic stem transplant recipients compared to the general population, with risk increasing over time [30]. In addition, risk factors such as total body irradiation, chronic graft-versus-host diseases, age at transplantation, genetic predispositions, immunosuppressive therapy and lifestyle were also identified to influence the risk of solid SPM.

We additionally examined changes in SIRs of SPM over two time periods from 1990 to 2000 and 2001 to 2011 (when major changes in CML therapies generally took place) for CML patients of all ages, and for patients aged <60 vs. ≥60 years. Generally, no significant differences in SIRs were noted between the two calendar periods (before/after 2000), and no indication of increasing risks in the later calendar period in younger patients were seen. Similar findings were also reported in a recent study [73] using the Danish cancer registry data (1977–2008). Nevertheless, more extended follow-up data will provide a more reliable estimate of the impact of new CML treatment in the future. Until now, still not much is known about the potential CML treatment-related long-term effects [146]. A more recent investigation of 221 CML patients did not find a positive association between imatinib and SPM [147]. Since 2000, imatinib (a tyrosine-kinase inhibitor, TKIs) is being used as a first line treatment for newly diagnosed CML in the chronic phase, but also in higher doses for accelerated/blastic phase, which led to significant improvement in its survival [10, 11]. Imatinib should be given over the entire life span of patients to prevent disease progression to advanced phases. Currently, second generation TKIs (e.g. nilotinib, dasatinib) and allogeneic stem cell transplant are being used in the second- and third-line treatment options.

The SIR of a subsequent ALL was 12.5 times higher than the expected risk, and was elevated in the first year only. Misclassifications of a subsequent ALL can occur especially because the initial CML may transform/progress during the blast phase to acute forms of leukaemia (myeloblastic or even lymphoblastic) [3]. No cases of AML were observed subsequent to CML in our analysis.

## Discussion of methods

### Limitations of the study

The major limitations of this study include the insufficient treatment data. We therefore were not able to assess treatment effects on SPM risk. However, our examination of the relative risk in relation to time from diagnosis and calendar period suggests that some SPM might be attributable to treatment due to increasing risk with time.

Generally, caution should be exercised in interpreting the overall risk of second haematological malignancies after initial HL/NHL (especially those of lymphoid cell types), but also of some cancer sites typically affected by extra-nodal onset of lymphoma (e.g. stomach cancer). For all these cancers, misclassification of diagnoses seems likely to contribute to the marked increase of SIR especially in the first year after initial diagnosis. Caution should also be applied in interpreting risks of subsequent NHL following initial MM/CLL (Richter syndrome), or subsequent AML/ALL following initial CML which might be a transformation of the first cancer and not a new cancer. It should be emphasised that even a small amount of misclassification during this period would greatly affect the SIR, as the expected number of a specific SPM within the first year tends to be very small. In a sensitivity analysis (**Appendix III**) excluding all haematological SPM diagnosed within a year of first HL or NHL diagnosis, the SIRs for these malignancies decreased significantly following both HL and NHL (from 9.29 to 6.03 and from 2.32 to 1.52, respectively). The decrease in SIRs was mainly noted for subsequent HL and NHL. The analysis excluding solid SPM diagnosed within a year of first HL showed results very similar to the initial analysis (SIR=1.76 vs.1.66), while solid SPM SIR significantly declined (from 1.43 to 1.19) following NHL, especially for stomach and kidney cancers. We repeated the sensitivity analysis for other groups of first MM, CLL, and CML, and found a similar significant SIR decline for haematological SPM by excluding the first year after diagnoses. The risk for solid SPM following first MM dropped significantly from 1.07 to a value lower than one (0.91) and decreased significantly from 1.47 to 1.25 following first CLL. Although the impact on the overall relative risk estimate seems to be relatively small, it is recommended to consider the estimate in each specific follow-up stratum and cancer site when interpreting and comparing results.

Incomplete registration of incident cases may bias the estimated SIR in our data, particularly if the completeness would vary between first and subsequent malignancies. According to own estimations based on the mortality / incidence ratio method [92], completeness between German registries may vary substantially between 80% to 100% [2]. However, in the sensitivity analysis the overall SIR for solid SPM following each diagnostic group did not substantially change when

data from two registries with the lowest estimated completeness were excluded (from 1.76 to 1.80 for HL, from 1.43 to 1.44 for NHL, from 1.07 to 1.09 for MM, remained at 1.47 for CLL, and from 1.29 to 1.32 for CML, all SIRs were significant), see **Appendix III** (**Table 58**). Moreover, these registries represent only 11% of cases in the current cohort. Thus, the estimated SIRs from 14 pooled cancer registries are considered quite robust. In addition, underestimation of SPM risk may result from incompleteness of follow-up data (missed events of death or migration) in some German registries, as this would result in an overestimation of time at risk.

We noted some regional variations in SPM risks between German cancer registries which are not likely to be influenced by regional differences in diagnosis and management of LHM, or their survival. To investigate whether these variations reflect a real difference in SIR, we compared individual data from Hamburg, Saarland, and Muenster with similar follow-up durations and time periods (1990-2011). For most subgroups of first LHM (except HL), the registry-specific analysis showed that the highest overall SIR was found in data from the Hamburg cancer registry, mainly in the <1 year time interval, but SIR did not significantly change over time before/after 2000 (data not shown). Whether this could be related to increased medical investigation in Hamburg compared to other states in Germany is still unclear.

On the other hand, the comparative analysis with the US population-based dataset derived from SEER registries provided a relevant control measure of data quality basically because this data is of relatively similar size, years of diagnosis, and the SEER registries follow the same coding rules for multiple primaries of haematological malignancies. In addition, we were able to adjust for age groups and include synchronous tumours in the analysis. However, especially for Germany, most registries started registration around the year 2000 or even later, the follow-up time is therefore still too short to fully evaluate the long-term risk of treatment-related cancers. A previous SEER-based study including the years 1973–2000 reported that relative risks continue to increase with increasing length of follow-up, reaching 3-fold and 1.5-fold in >20 years after HL and NHL diagnosis, respectively [80]. The overall results from Germany are based mainly on patients with a follow-up time of less than 10 years, while a large proportion of included patients were still alive and under risk at the end of the study period. Hence, the SIR by follow-up period may be the more appropriate measure for interpretation and comparison rather than the overall results.

In an exploratory analysis, we pooled data from three German cancer registries with a stable long-term registration over 21 years from 1990 to 2011 (Saarland, Hamburg, and Muenster) to investigate the long-term SPM risks following first primary lymphomas, myeloma and chronic

leukaemias. In general, similar findings to the main pooled analysis have been shown (**Pages 71–72**).

Caution should be exercised in interpreting the risk in relation to calendar time period, as the analysis was based on a very small number of observed cases and limited follow-up time, particularly in the recent time period. Therefore, these estimates might be less precise especially for solid cancers. Caution is also warranted in attempting to compare results regarding SPM risk following some rare types of leukaemia such as ALL or CML, because the analysis was also based on a limited sample size and small numbers of events resulting in lower statistical power. Also these malignancies have a poor prognosis, therefore the follow-up time is generally short, which adds to the lower statistical power.

Data on co-morbidities (viral infections, chronic auto-immune diseases, or other conditions) and their related initial treatments are also lacking in cancer registry data. In addition, we were unable to assess the impact of these conditions by using co-morbidity data from other sources as this was beyond the scope of the current study.

Finally, it is possible that some statistically significant results are due to random variations because of multiple testing [37].

**Strengths of the study**

The strengths of the present study include the large size of the study cohort, and the inclusion of all SPM (second or more). Whereas the majority of previous studies focused only on second cancer incidence, our data also showed that about 0.17% to 0.56% long-term survivors developed more than one subsequent malignancy. The large dataset also enabled us to execute stratified analyses of risk by sex, age, follow-up duration, and calendar year of diagnosis, as well as the calculation of bidirectional risk estimates, providing more accurate and detailed descriptions of the current risks of SPM. In addition, the study used pooled data which represent a large part of the German population. The application of standardized rules for coding multiple primary malignancies by the regional cancer registries has enabled the comparability of data, and the additional centralized check of the pooled data for multiple primaries at the RKI German Centre for Cancer Registry Data (ZfKD) has guaranteed high internal validity of the database. A comparison between major types of lymphoma and leukaemia, and within specific NHL histological subtypes, is another advantage of the present study. The reciprocal risks were also assessed in relation to follow-up time considering that cancers sharing similar risk factors might not be necessarily observed simultaneously because of different time of exposure and latency for different malignancies.

## Overall summary and conclusions

The main aim of the present work was to provide up-to-date estimates of the relative and absolute risk of developing SPM in survivors of adult-onset LHM in Germany using cancer registry data pooled from 14 German federal states. Indeed, this is the first registry-based study to date from Germany reporting on SPM risk following these malignancies in adults. Therefore, this study can be regarded as a provisional report on the current risks of SPM which should also be important as a basis for future comparisons.

The study population consisted of 230,782 patients (aged 15 years or older) who were diagnosed between 1990 and 2011 with one of the following malignancies classified according to ICD-10: HL (C81), NHL (C82-C85), MM (C90), and leukaemia (C91-C95). A detailed analysis was also performed for CLL (C91.1) and CML (C92.1), and by NHL histological subtypes. In addition, the overall results from the German data were compared with the recent US data (1992–2011) obtained from the SEER 13 registries. In Germany, about 19% of patients with HL were followed for more than 10 years, while this proportion was lower for other first cancers (≤10%). During the follow-up of all LHM patients, 4.5% to 9.8% developed second or more primary malignancies.

Based on the results of this study, long-term survivors of adult onset LHM are found to have significantly higher relative risks of developing SPM at any organ compared to the general population of Germany. These risks were more than 2-fold higher in HL patients, moderately increased in NHL and CLL patients (1.5-fold), and slightly increased in CML and MM patients (1.4-fold and 1.1-fold, respectively). The increased risks resulted in an excess absolute risk of 15 cases in MM to 68 cases in CLL per 10,000 person per year. There was no overall significant gender difference in risks. In general, patients aged below 30 years upon first diagnosis had the highest relative risks (7- to 10-fold).

Among all LHM groups, solid and other haematological SPM occurred significantly more than expected rates resulting in a 1.07-fold in MM to 1.79-fold in HL increased SIR for solid malignancies and a 1.7-fold in MM to 9-fold in HL increased SIR for haematological malignancies. Relative risks were significantly increased (≥1.5-fold) for many specific types of SPM (see **Table 27**). After HL, NHL and CLL, increased SIRs were consistently found for solid SPM of the oropharynx, stomach, colon/rectum, thyroid, lung, skin melanoma, breast and kidney. Only NHL survivors were at significantly increased risk for liver, pancreas, testis, and brain. Following MM and CML, SIRs were only significantly elevated for oropharynx, melanoma, and kidney. Overall, solid malignancies accounted for the greatest proportion of the observed number of SPM (69%–89%) and excess absolute risk (particularly lung, colon/rectum, and melanoma).

Following HL, the relative risk of SPM increased with follow-up time and reached 2.5-fold among patients who survived 10 years or longer after diagnosis. This trend was mainly noticed among patients who were first diagnosed before age 60 years with increased long-term risks observed for cancers of the lip/oral cavity, breast, stomach, colon/rectum, lung, and kidney. In contrary, for most sites risks declined with follow-up time and were no longer significantly different from the general population rates beyond 10 years after diagnosis of first NHL (and CLL) except for subsequent melanoma, stomach, pancreas, liver, HL, and CML risks, which persisted for more than 10 years. Following first MM and CML, risks even dropped below expected rates. The risk for AML peaked between 1 and 5 years in younger survivors of both lymphoma and myeloma. Over time, there appears to be no increasing trend in SPM risks overall over the most recent calendar years, with risks significantly decreasing after the year 2000 for solid malignancies particularly after NHL diagnosis. However, our data indicates a significantly increased risk in recent years for subsequent haematological malignancies, mainly for AML after diagnosis of HL in patients aged below 60 years. In addition, the elevated risk of AML in older patients with first MM remained constant over time.

To compare the estimated SIR in our study with other studies, we selected only registry-based studies because clinical or trial studies usually provide biased risk estimates. Very few registry-based studies are available in the literature and most of them were based on relatively old data (and different time periods) that represent a different treatment era. For this reason, we performed an analysis of the recent SEER database in order to get more comparable results that would also highlight differences or similarities in the current risks between Germany and the US. Recent SEER data showed overall SIRs to be slightly lower after all first malignancies, but patterns of risk were largely comparable to the German data.

Other interesting findings include positive reciprocal associations between all lymphoid malignancies and other solid cancers (**Table 27**, and **Table 59** in **Appendix III**), which likely suggest common aetiologies besides treatment effects rather than chance observations. Potential risk factors for some of these associations are not clear and need to be further investigated in future studies. An increased detection rate of other cancers due to intensive medical examination of patients is also expected to play a role. Identification of risk factors is very complicated as there can be many and they may overlap. In addition, epidemiologic cancer registries do not routinely collect data on cancer risk factors (including socio-economic status). Therefore, this limitation should be taken into account when drawing any conclusion from these results. Our results can be considered an up-to-date estimate of SPM risk in adult LHM survivors in Germany representing the current risks facing survivors of these cancers.

**Table 27. Risk of SPM according to the type of first LHM in Germany: overall summary**

| First malignancy | Patients developing SPM (%) | SIR for all SPM (95%CI) | EAR for all SPM | SIR for solid SPM (95%CI) | High risk (≥1.5) [a] | Low risk (<1) | Positive reciprocal risk [a] |
|---|---|---|---|---|---|---|---|
| HL (N=16,826) | 953 (5.7) | **2.33 (2.18-2.48)** | 55.81 | **1.76 (1.63-1.90)** | NHL, AML, ALL, CLL, MM, thyroid, lung, kidney, lip/oral cavity, melanoma, breast | Brain/CNS | NHL, CLL, thyroid, lung, melanoma, colon/rectum |
| NHL (N=99,829) | 6788 (6.8) | **1.50 (1.46-1.54)** | 56.82 | **1.43 (1.39-1.47)** | HL, AML, ALL, testis, kidney, thyroid, melanoma, stomach, lip/oral cavity, lung, liver, brain/CNS | CLL | HL, ALL, AML, testis, melanoma, liver, lip/oral cavity, stomach, lung, kidney, thyroid, colon/rectum, pancreas, breast, prostate, urinary bladder |
| MM (N=39,074) | 1761 (4.5) | **1.11 (1.06-1.17)** | 14.67 | **1.07 (1.01-1.12)** | AML, HL, NHL, melanoma, lip/oral cavity, kidney | Uterus [a], ovaries, brain/CNS, oesophagus, liver, larynx, breast, prostate, urinary bladder, CLL | AML, HL, NHL, kidney, melanoma |
| CLL (N=30,878) | 3022 (9.8) | **1.49 (1.43-1.54)** | 68.1 | **1.47 (1.41-1.52)** | HL, CML, melanoma, kidney, thyroid, lung, lip/oral cavity, colon/rectum | Larynx, œsophages, cervix, MM | CML, HL, melanoma, kidney, lip/oral cavity, thyroid, lung, urinary bladder, stomach, prostate, colon/rectum |
| CML (N=7,900) | 438 (5.5) | **1.41 (1.28-1.55)** | 37.72 | **1.29 (1.16-1.43)** | ALL, CLL, MM, NHL, melanoma, kidney, oral cavity (lip) | Lung, breast, cervix, thyroid, testis | ALL, CLL, kidney |

SIR: standardized incidence ration; CI: 95% confidence intervals; EAR excess absolute risk per 10,000 person-years; LHM: lymphohaematopoietic malignancies; SPM: subsequent primary malignancies; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; MM: multiple myeloma; CLL: chronic lymphocytic lymphoma; CML: chronic myeloid leukaemia.

[a] *P<0.05*

## Conclusions

We report an increased risk of developing SPM in long-term survivors of adult LHM compared to the general population in Germany, which is in agreement with the US data. As cancer registry data do not contain detailed information on treatments administered, we therefore were not able to directly assess their effects on SPM risk. However, the timing of the risk suggests that subsequent lip/oral cavity, breast, lung, stomach, colon/rectum, and ML might generally be attributable to treatment. The increased risks over the study period of AML in younger HL patients and the constantly elevated risk of AML in older MM patients may indicate toxic effects of some therapies. In addition, the reciprocal risks of lymphoid malignancies with some solid cancers likely suggest common etiologic factors that could be potentially related to life style, immunologic disturbance, and viral infections. However, no clear explanation could be found for some other associations, suggesting the need for further research to investigate potential shared mechanisms. Continuous follow-up of cancer survivors is a very essential preventive measure to detect SPM at an early stage.

## Recommendations for future research

Given that risks for some SPM were observed to continue to increase beyond 10 years of first LHM, physicians should consider regular clinical follow-up during the whole life of these patients for effective prevention and early detection of new SPM to reduce their burden in survivors of these malignancies. Physicians should also provide proper individual counselling for patients regarding possible changes in lifestyle. In addition, prevention efforts should especially focus on high-risk patients, it is highly recommended in particular in patients who received irradiations (to the neck, chest, abdomen, pelvic or whole body) as a part of therapy at a young age [148], as well as patients who received bone marrow transplant. Such early detection programs of SPM have recently been initiated in Germany for survivors of paediatric HL [105]. High-risk patients should also include those with a smoking history.

Although the current cancer therapy regimens resulted in survival prolongation and cure of some cancers, based on our findings, future oncologic research should also put more emphasis on development of new types of drugs that should essentially have both survival benefits and lesser toxic effects than current therapies, especially in the management of younger patients.

Future clinical and epidemiological research is also needed to explore the associations observed in our study for which no clear explanation can be provided.

Genomic research is also essential to identify genetic alterations and their mechanisms in the development of SPM and will play an important role in improving our understanding on the aetiology of SPM in cancer survivors.

The current study has also demonstrated the good comparability of the German cancer registry database to the US SEER database and other international studies. This should encourage the use of the German cancer registry data in international or European collaboration projects as a very important and reliable source of information on multiple primaries in cancer survivors.

In addition, linking morbidity data from other sources or integrating information on co-morbidity into cancer registry data is very important for epidemiologic studies. For example, information on lymphoma and HIV status as well as other infections (HCV) and autoimmune diseases is lacking in our data. This could greatly assist in improving our understanding of risk factors for the first and second cancers.

## Prospect/outlook

The increasing set of cancer registry data in Germany (with nationwide coverage achieved in 2009) and the inclusion of data from clinical registries, that will be built up nationwide until 2017 in accordance with the Cancer Screening and Registration Act [KFRG] [149], will provide more accurate results on long-term risks of SPM in the future. The addition of detailed treatment data from clinical cancer registries will enable more specific analysis on the harmful effects of chemo- and radiotherapy. Therefore, and as a consequence of recent modifications of treatment strategies of LHM, further examination of the risks using cancer registry data should be considered to assess the impact of new therapies on SPM incidence in Germany.

Subsequent malignancies may possibly constitute a relevant public health problem for future clinical research, especially as long-term survival rates for lymphoma, myeloma, and leukaemia patients continue to improve [12–15].

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# List of abbreviations and symbols

| Symbol | Description |
|---|---|
| ABVD | Combinations chemotherapy regimens of doxorubicin, bleomycin, vinblastine, and dacarbazine |
| ALL | Acute lymphoblastic leukaemia |
| AML | Acute myeloblastic leukaemia |
| BEACOPP | Combinations chemotherapy regimens of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone |
| BKRG | The National Law for Cancer Registry Data |
| CI | Confidence interval |
| CLL | Chronic lymphocytic leukaemia |
| CML | Chronic myeloid leukaemia |
| CNS | Central nervous system |
| CVP | Combinations chemotherapy regimens of cyclophosphamide, vincristine, and prednisone |
| DCO | Death Certificate only |
| DLBCL | Diffuse large B-cell lymphoma |
| EAR | Excess absolute risk |
| FCR | Combination of fludarabine and cyclophosphamide with rituximab |
| FL | Follicular lymphoma |
| GEKID | The German Association of Epidemiologic Cancer Registries |
| HDCT | High dose chemotherpay |
| HL | Hodgkin lymphoma |
| IARC | International Agency for Research on Cancer |
| IACR | International Association of Cancer Registries |
| ICD-10 | The tenth revision of the International Classification of Diseases |
| ICD-O-3 | The third edition of the International Classification of Diseases for Oncology |
| IMiDs | Immunomodulatory drugs |
| InterLymph | International Lymphoma Epidemiology Consortium |
| LHM | Lymphohaematopoietic malignancies |
| LL | Lymphocytic leukaemia |
| LSS | Life Span Study |
| ML | Myeloid leukaemia |
| MM | Multiple myeloma |
| MOPP | Combinations chemotherapy regimens of mechlorethamine, vincristine, procarbazine, and prednisone |
| NCI | National Cancer Institute |
| NHL | Non-Hodgkin lymphoma |
| R-CHOP | Combination of cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab |
| RKI | Robert Koch Institute |
| SCT | Stem cell transplantation (autologous or allogeneic) |
| SEER | Surveillance, Epidemiology, and End Results program |
| SIR | Standardized incidence ratio |
| SLL | Small lymphocytic lymphoma |
| SPM | Subsequent primary malignancies |
| TKIs | Tyrosine-kinase inhibitors |
| US | The United States of America |
| UVR | ultraviolet radiation |
| WHO | World Health Organization |
| ZfKD | German Centre for Cancer Registry Data (Zentrum für Krebsregisterdaten) |

## Declaration/Affidavit

"I, **Nadia Baras**, certify under penalty of perjury by my own signature that I have submitted the thesis on the topic: "**The Risk of Developing Subsequent Primary Malignancies among Adult Patients with Lymphatic and Haematopoietic Malignancies in Germany: A Pooled Analysis of Cancer Registry Data (1990–2011)**" I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The sections on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) correspond to the URM (see above) and are answered by me. My interests in any publications to this dissertation correspond to those that are specified in the following joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author correspond to the URM (see above) and I am solely responsible.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

Date: **20.04.2016** Signature:

*Nadia Baras*

## Curriculum vitae and publication list

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

For privacy reasons, my resume is not published in the electronic version of my dissertation.

## Publication list

**Baras N** and Kraywinkel K. Mortality trends for liver cancer in Germany. **Power point presentation**: Robert Koch Institute-RKI Intern, 22 Sept. 2011, Berlin.

**Baras N**. Liver and Intrahepatic Bile Ducts Cancer (ICD-10 C22) in Germany. **Master Thesis-Monograph**: Fakultät Life Science, HAW Hamburg, 28 März 2012, Hamburg.

**Baras N**, Dahm S, Haberland J, Wolf U, Bertz J, Kraywinkel K. The Risk of Developing Subsequent Primary Tumours among Adult Patients with Leukaemia and Lymphoma in Germany. **Poster presentation**: Diplomanden-Doktoranden-Treffen, Robert Koch Institute-RKI, 16 Nov. 2012, Berlin.

**Baras N**, Dahm S, Haberland J, Kraywinkel K, Salama A. The Risk of Developing Subsequent Primary Tumour among Adult Patients with Leukaemia and Lymphoma in Germany. **Poster presentation**: 8. Jahrestagung der Deutschen Gesellschaft für Epidemiologie und 1. International LIFE-Symposium (DGEpi), 2013, Leipzig.

**Baras N**, Dahm S, Haberland J, Kraywinkel K, Salama A. Subsequent Primary Tumour Risk after Hodgkin Lymphoma and Non-Hodgkin Lymphoma in Germany: A Nationwide Analysis from 1970 to 2010. **Poster presentation**: 31. Deutscher Krebskongress (DKK), 2014, Berlin.

**Baras N** and Kraywinkel K. Subsequent Primary Malignancies after Lymphoma and Leukaemia in Germany: from 1970 to 2010. **Power point presentation**: Robert Koch Institute-RKI Intern, 27 Mai 2014, Berlin.

**Baras N**, Kraywinkel K, Salama A. Subsequent Malignancies among Survivors of Multiple Myeloma in Germany: Cancer Registry Data-Based Analysis (1990-2011). **Poster presentation**: 2nd German-Arab Cancer Congress, 2015, Berlin.

Baras N and Haberland J. Schätzung des Anteils geheilter Patienten in Deutschland auf der Basis epidemiologischer Krebsregisterdaten. **Power point presentation**: AbteilungsKolloquium, Robert Koch Institut-RKI Intern, 16 Feb. 2016, Berlin.

**Baras N**, Kraywinkel K, Salama A. Subsequent Malignancies among Survivors of Multiple Myeloma in Germany: Cancer Registry Data-Based Analysis (1990-2011). **Poster presentation**: 32. Deutscher Krebskongress (DKK), 2016, Berlin.

**Baras N**, Dahm S, Haberland J, Janz M, Emrich K, Kraywinkel K, Salama A. Subsequent Malignancies among Long-term Survivors of Hodgkin Lymphoma and Non-Hodgkin Lymphoma: A Pooled Analysis of German Cancer Registry Data (1990-2012). **Paper Publication in preparation at time of thesis submission.** Submitted later to *British Journal of Haematology* on 28 July 2016; accepted for publication on 3 November 2016. DOI: 10.1111/bjh.14530.

**Contributions to some chapters in book**: Epidemiology of liver cancer, tumours of the gallbladder and extra hepatic biliary tract, leukaemia, and multiple myeloma in:

Robert Koch Institute (ed.) and the Association of population-based Cancer Registries in Germany (ed.). Cancer in Germany 2007/2008. 8th edition. 2012, Berlin.

Robert Koch Institute (ed.) and the Association of population-based Cancer Registries in Germany (ed.). Cancer in Germany 2009/2010. 9th edition. 2013, Berlin.

Robert Koch Institute (ed.), the Association of population-based Cancer Registries in Germany (ed.). Cancer in Germany 2011/2012. 10th edition. 2015, Berlin.

## Acknowledgement

I would like to express my highest gratitude to **Allah (S.W.T)** in the first place for His guidance and bless for me to complete the Thesis.

Then, I wish to express my deep thanks and gratitude to **Dr. med. Klaus Kraywinkel** at the Robert Koch Institute (RKI), who supervised the preparation of this thesis, for his encouragement and strong support in every stage of the research, in spite of his preoccupation he never stopped giving me advises and counsel in all time. He always provided me constructive feedback on epidemiological issues and provided me with all needed information resources that helped me in writing this Thesis.

I am deeply indebted to my first supervisor at the Charité University Hospital in Berlin, **Professor Dr. med. Abdulgabar Salama**, who accompanied me since the beginning of the study. His encouragement, guidance and constructive criticism have made this study a reality.

I am also pleased to extend my thanks to the **RKI** to give me the permission to use this diverse and of great value cancer registry data contained in the centre which is of great interest and confidentiality. So, thanks to them for giving me this confidence. More specifically, I would like to acknowledge hereby **all the German cancer registries** for provision of their data. Additionally, I am very grateful to the RKI for the financial support during my study and thesis writing in Berlin, which without their assistance the completion of this research would have not been possible.

I would not forget also to specifically show all my respect and special appreciation to all my **colleagues at the RKI**, especially at the German Centre for Cancer Registry Data (ZfKD), for their cooperation, valuable suggestions, kindness and great support. I am very thankful especially to the statistician; **Dr. Stefan Dahm** for his great help in statistical analysis and for good teamwork.

Finally, I would like to thank **my beloved family**, **parents**, **sisters** and **brothers**, **my husband**, **mother-in-law**, and **my friends** who in spite of the distance and the difficult circumstances have given me encouragement, moral and emotional support without them and their love, prayers and hopes I will not be able to continue study and carry out my research.

I bear full responsibility for any unintentional errors that may remain in this work.

*Nadia Baras*

# Appendix I

**IARC rules for multiple primary cancers (2004): groups of malignant neoplasms considered to be histologically different**

| Histological group | ICD-O-3 |
|---|---|
| **Carcinoma** | |
| 1. Squamous and transitional cell carcinoma | 8051-8084, 8120-8131 |
| 2. Basal cell carcinomas | 8090-8110 |
| 3. Adenocarcinomas | 8140-8149, 8160-8162, 8190-8221, 8260-8337, 8350-8551, 8570-8576, 8940-8941 |
| 4. Other specific carcinomas | 8030-8046, 8150-8157, 8170-8180, 8230-8255, 8340-8347, 8560-8562, 8580-8671 |
| 5. Unspecified carcinomas (NOS) | 8010-8015, 8020-8022, 8050 |
| 6. Sarcomas and soft tissue tumours | 8680-8713, 8800-8921, 8990-8991, 9040-9044, 9120-9125, 9130-9136, 9141-9252, 9370-9373, 9540-9582 |
| 7. **Mesothelioma** | 9050-9055 |
| **Tumours of haematopoietic and lymphoid tissues** | |
| 8. Myeloid | 9840, 9861-9931, 9945-9946, 9950, 9961-9964, 9980-9987 |
| 9. B-cell neoplasms | 9670-9699, 9728, 9731-9734, 9761-9767, 9769, 9823-9826, 9833, 9836, 9940 |
| 10. T-cell and NK-cell neoplasms | 9700-9719, 9729, 9768, 9827-9831, 9834, 9837, 9948 |
| 11. Hodgkin lymphoma | 9650-9667 |
| 12. Mast-cell tumours | 9740-9742 |
| 13. Histiocytes and accessory lymphoid cells | 9750-9758 |
| 14. Unspecified types | 9590-9591, 9596, 9727, 9760, 9800-9801, 9805, 9820, 9832, 9835, 9860, 9960, 9970, 9975, 9989 |
| 15. **Kaposi sarcoma** | 9140 |
| 16. **Other specified types of cancer** | 8720-8790, 8930-8936, 8950-8983, 9000-9030, 9060-9110, 9260-9365, 9380-9539 |
| 17. **Unspecified types of cancer** | 8000-8005 |

ICD-O-3: the WHO International Classification of Diseases for Oncology (3rd revision)

# Appendix II

## NHL subtypes based on the Kiel and WHO 2008 classification

| Lymphoma cell type | B-cell | | T-cell (and NK-cell) | |
|---|---|---|---|---|
| ***Grade*** | ***Subtype*** | ***ICD-10*** | ***Subtype*** | ***ICD-10*** |
| **Low-grade (indolent)** | Chronic lymphocytic leukaemia (CLL)/ small lymphocytic lymphoma (SLL) | C91.1 | Peripheral T-cell lymphoma, not classified | C84.4 |
| | Small cell B-cell lymphoma | C83.0 | Subcutaneous (SC) panniculitis-like T-cell lymphoma | C86.3 |
| | Follicular lymphoma (FL, grade I and II) | C82.0, C82.1 | Extranodal NK/T-cell lymphoma, nasal type | C86.0 |
| | Mantel cell lymphoma (MCL) | C83.1 | Mycosis fungoides | C84.0 |
| | Immunocytoma/Morbus Waldenström macroglobulinaemia (MV) | C88.0 | Sezary disease | C84.1 |
| | Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma) | C88.4 | Hepatosplenic T-cell lymphoma | C86.1 |
| **High-grade (aggressive)** | Lymphoblastic (diffuse) lymphoma | C83.5 | Lymphoblastic (diffuse) lymphoma | C83.5 |
| | Burkitt lymphoma | C83.7 | Primary cutaneous CD30-positive T-cell proliferations | C86.6 |
| | Follicular lymphoma (FL, grade III a and b) | C82.2, C82.3, C82.4 | Enteropathy-type (intestinal) T-cell lymphoma | C86.2 |
| | Diffuse large B-cell lymphoma (DLBCL all subtypes) | C83.3 | Anaplastic large cell lymphoma, ALK-positive | C84.6 |
| | Mediastinal (thymic) large B-cell lymphoma | C85.2 | Angioimmunoblastic T-cell lymphoma | C86.5 |
| **Lymphoma, unspecified Low- and high-grade** | Non-Hodgkin lymphoma, unspecified B-cell lymphoma NOs | C85.7, C85.9, C85.1 | | |

NHL: non-Hodgkin lymphoma; WHO: World Health Organization; ICD-10: the WHO International Classification of Diseases (10th revision); NK-cell: natural killer cells.

# Appendix III

## Hodgkin lymphoma

### Table 28. Observed number, SIRs and EARs of SPM following HL by age at diagnosis, for both sexes

| | | 15-44 years | | | | | 45-59 years | | | | | ≥ 60 years | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **EAR** | **O** | **E** | **SIR** | **95% CI** | **EAR** | **O** | **E** | **SIR** | **95% CI** | **EAR** |
| **All solid malignancies*** | **C00-C75** | 168 | 47.13 | **3.56** | **3.05-4.15** | 18.41 | 200 | 109.43 | **1.83** | **1.58-2.10** | 54.13 | 282 | 214.86 | **1.31** | **1.16-1.47** | 44.52 |
| Lip, oral cavity, and pharynx | C00-C14 | 7 | 1.99 | **3.52** | **1.41-7.25** | 0.76 | 15 | 6.27 | **2.39** | **1.34-3.95** | 5.22 | 7 | 5.13 | 1.36 | 0.55-2.81 | 1.24 |
| Lip | C00 | 0 | 0.03 | 0.00 | 0.00-122.27 | 0.00 | 0 | 0.1 | 0.00 | 0.00-36.68 | -0.06 | 0 | 0.32 | 0.00 | 0.00-11.46 | -0.21 |
| Tongue | C01-C02 | 3 | 0.41 | **7.32** | **1.47-21.38** | 0.39 | 4 | 1.18 | 3.39 | 0.91-8.68 | 1.69 | 3 | 1.01 | 2.97 | 0.60-8.68 | 1.32 |
| Gum, floor of mouth, other mouth | C03-C06 | 1 | 0.5 | 2.00 | 0.03-11.13 | 0.08 | 3 | 1.59 | 1.89 | 0.38-5.51 | 0.84 | 1 | 1.24 | 0.81 | 0.01-4.49 | -0.16 |
| Parotid and other salivary glands | C07-C08 | 0 | 0.19 | 0.00 | 0.00-19.31 | -0.03 | 0 | 0.22 | 0.00 | 0.00-16.67 | -0.13 | 0 | 0.43 | 0.00 | 0.00-8.53 | -0.29 |
| Pharynx and other oral cavity | C09-C14 | 4 | 0.73 | **5.48** | **1.47-14.03** | 0.50 | 7 | 2.9 | 2.41 | 0.97-4.97 | 2.45 | 3 | 2.2 | 1.36 | 0.27-3.98 | 0.53 |
| Oesophagus | C15 | 3 | 0.46 | **6.52** | **1.31-19.06** | 0.39 | 4 | 2.42 | 1.65 | 0.44-4.23 | 0.94 | 4 | 3.21 | 1.25 | 0.34-3.19 | 0.52 |
| Stomach | C16 | 6 | 1.17 | **5.13** | **1.87-11.16** | 0.74 | 3 | 3.74 | 0.80 | 0.16-2.34 | -0.44 | 10 | 9.83 | 1.02 | 0.49-1.87 | 0.11 |
| Colon, rectum, and anus | C18-C21 | 14 | 3.53 | **3.97** | **2.17-6.65** | 1.59 | 25 | 14.64 | **1.71** | **1.10-2.52** | 6.19 | 39 | 38.18 | 1.02 | 0.73-1.40 | 0.54 |
| Liver | C22 | 1 | 0.38 | 2.63 | 0.03-14.64 | 0.09 | 3 | 1.79 | 1.68 | 0.34-4.90 | 0.72 | 6 | 3.74 | 1.60 | 0.59-3.49 | 1.50 |
| Pancreas | C25 | 1 | 0.61 | 1.64 | 0.02-9.12 | 0.06 | 5 | 3.05 | 1.64 | 0.53-3.83 | 1.17 | 8 | 6.97 | 1.15 | 0.49-2.26 | 0.68 |
| Larynx | C32 | 0 | 0.37 | 0.00 | 0.00-9.91 | -0.06 | 4 | 1.82 | 2.20 | 0.59-5.63 | 1.30 | 3 | 2 | 1.50 | 0.30-4.38 | 0.66 |
| Lung | C33-C34 | 28 | 2.86 | **9.79** | **6.50-14.15** | 3.83 | 47 | 15.79 | **2.98** | **2.19-3.96** | 18.65 | 75 | 28.59 | **2.62** | **2.06-3.29** | 30.77 |
| Melanoma of skin | C43 | 21 | 5.54 | **3.79** | **2.35-5.79** | 2.35 | 4 | 4.32 | 0.93 | 0.25-2.37 | -0.19 | 10 | 6.62 | 1.51 | 0.72-2.78 | 2.24 |
| Breast | C50 | 30 | 9.44 | **3.18** | **2.14-4.54** | 3.13 | 22 | 15.32 | 1.44 | 0.90-2.17 | 3.99 | 27 | 22.4 | 1.21 | 0.79-1.75 | 3.05 |
| Cervix uteri | C53 | 1 | 2.54 | 0.39 | 0.01-2.19 | -0.23 | 4 | 1.01 | **3.96** | **1.07-10.14** | 1.79 | 1 | 1.09 | 0.92 | 0.01-5.10 | -0.06 |
| Corpus uteri | C54-C55 | 2 | 0.65 | 3.08 | 0.35-11.11 | 0.21 | 0 | 2.32 | 0.00 | 0.00-1.58 | -1.39 | 9 | 5.07 | 1.78 | 0.81-3.37 | 2.61 |
| Ovaries | C56 | 0 | 0.97 | 0.00 | 0.00-3.78 | -0.15 | 4 | 1.51 | 2.65 | 0.71-6.78 | 1.49 | 4 | 3 | 1.33 | 0.36-3.41 | 0.66 |
| Prostate | C61 | 2 | 1.26 | 1.59 | 0.18-5.73 | 0.11 | 29 | 18.68 | **1.55** | **1.04-2.23** | 6.17 | 35 | 45.08 | 0.78 | 0.54-1.08 | -6.68 |
| Testis | C62 | 10 | 5.84 | 1.71 | 0.82-3.15 | 0.63 | 0 | 0.75 | 0.00 | 0.00-4.89 | -0.45 | 0 | 0.15 | 0.00 | 0.00-24.45 | -0.10 |
| Kidney | C64 | 7 | 1.36 | **5.15** | **2.06-10.61** | 0.86 | 12 | 4.49 | **2.67** | **1.38-4.67** | 4.49 | 16 | 7.94 | **2.02** | **1.15-3.27** | 5.34 |
| Urinary bladder | C67 | 2 | 0.62 | 3.23 | 0.36-11.65 | 0.21 | 5 | 3.56 | 1.40 | 0.45-3.28 | 0.86 | 13 | 11.03 | 1.18 | 0.63-2.02 | 1.31 |
| Central nervous system | C70-C72 | 4 | 1.96 | 2.04 | 0.55-5.22 | 0.31 | 2 | 1.81 | 1.10 | 0.12-3.99 | 0.11 | 0 | 2.41 | 0.00 | 0.00-1.52 | -1.60 |
| Thyroid | C73 | 12 | 2.65 | **4.53** | **2.34-7.91** | 1.42 | 5 | 1.41 | **3.55** | **1.14-8.28** | 2.15 | 4 | 1.3 | 3.08 | 0.83-7.88 | 1.79 |
| **All haematological malignancies** | **C81-C96** | 95 | 6.76 | **14.05** | **11.37-17.18** | 13.44 | 73 | 7.71 | **9.47** | **7.42-11.91** | 39.02 | 114 | 15.9 | **7.17** | **5.91-8.61** | 65.04 |
| Hodgkin lymphoma | C81 | 0 | 2.08 | 0.00 | 0.00-1.76 | -0.32 | 0 | 0.41 | 0.00 | 0.00-8.95 | -0.25 | 0 | 0.42 | 0.00 | 0.00-8.73 | -0.28 |
| Non-Hodgkin lymphoma | C82-C85 | 54 | 2.25 | **24.00** | **18.03-31.32** | 7.88 | 45 | 3.29 | **13.68** | **9.98-18.30** | 24.93 | 83 | 6.67 | **12.44** | **9.91-15.43** | 50.61 |
| Multiple myeloma | C90 | 3 | 0.3 | **10.00** | **2.01-29.22** | 0.41 | 4 | 1.32 | 3.03 | 0.82-7.76 | 1.60 | 3 | 3.05 | 0.98 | 0.20-2.87 | -0.03 |
| Lymphoid leukaemia | C91 | 7 | 0.81 | **8.64** | **3.46-17.81** | 0.94 | 5 | 1.33 | **3.76** | **1.21-8.77** | 2.19 | 15 | 2.78 | **5.40** | **3.02-8.90** | 8.10 |
| Acute lymphoblastic | C91.0 | 5 | 0.49 | **10.20** | **3.29-23.81** | 0.69 | 1 | 0.1 | 10.00 | 0.13-55.64 | 0.54 | 1 | 0.12 | 8.33 | 0.11-46.37 | 0.58 |
| Chronic lymphocytic | C91.1 | 2 | 0.22 | **9.09** | **1.02-32.82** | 0.27 | 4 | 1.09 | 3.67 | 0.99-9.40 | 1.74 | 14 | 2.44 | **5.74** | **3.13-9.63** | 7.66 |
| Myeloid leukaemia | C92 | 19 | 0.97 | **19.59** | **11.79-30.59** | 2.75 | 10 | 0.94 | **10.64** | **5.09-19.57** | 5.42 | 4 | 1.99 | 2.01 | 0.54-5.15 | 1.33 |
| Acute myeloblastic | C92.0 | 16 | 0.49 | **32.65** | **18.65-53.03** | 2.36 | 7 | 0.52 | **13.46** | **5.39-27.74** | 3.87 | 3 | 1.15 | 2.61 | 0.52-7.62 | 1.23 |
| Chronic myeloid | C92.1 | 1 | 0.29 | 3.45 | 0.05-19.19 | 0.11 | 1 | 0.23 | 4.35 | 0.06-24.19 | 0.46 | 0 | 0.41 | 0.00 | 0.00-8.95 | -0.27 |
| **All sites**** | **C00-C97** | 266 | 54.54 | **4.88** | **4.31-5.50** | 32.20 | 280 | 119.15 | **2.35** | **2.08-2.64** | 96.14 | 404 | 235.32 | **1.72** | **1.55-1.89** | 111.84 |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); EAR: excess absolute risk per 10,000 person-years; SPM: subsequent primary malignancies; ICD-10: the WHO International Classification of Diseases (10th revision); HL: Hodgkin lymphoma.

*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)

Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 29. Observed number and SIRs of SPM following HL by follow-up time, for both sexes

| | | ≤1 year | | | | >1-≤5 years | | | | >5-≤10 years | | | | >10 years | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | **C00-C75** | 138 | 58.86 | **2.34** | **1.97-2.77** | 218 | 159.88 | **1.36** | **1.19-1.56** | 180 | 101.85 | **1.77** | **1.52-2.05** | 121 | 50.82 | **2.38** | **1.98-2.84** |
| Lip, oral cavity, and pharynx | C00-C14 | 6 | 1.99 | **3.02** | **1.10-6.56** | 10 | 5.68 | 1.76 | 0.84-3.24 | 7 | 3.75 | 1.87 | 0.75-3.85 | 6 | 1.95 | **3.08** | **1.12-6.70** |
| Lip | C00 | 0 | 0.08 | 0.00 | 0.00-45.85 | 0 | 0.2 | 0.00 | 0.00-18.34 | 0 | 0.12 | 0.00 | 0.00-30.57 | 0 | 0.06 | 0.00 | 0.00-1.13 |
| Tongue | C01-C02 | 2 | 0.39 | 5.13 | 0.58-18.52 | 3 | 1.1 | 2.73 | 0.55-7.97 | 3 | 0.74 | 4.05 | 0.81-11.85 | 2 | 0.39 | 5.13 | 0.58-8.52 |
| Gum, floor of mouth, other mouth | C03-C06 | 1 | 0.5 | 2.00 | 0.03-11.13 | 2 | 1.42 | 1.41 | 0.16-5.09 | 0 | 0.94 | 0.00 | 0.00-3.90 | 2 | 0.49 | 4.08 | 0.46-4.74 |
| Parotid gland, other salivary glands | C07-C08 | 0 | 0.13 | 0.00 | 0.00-28.22 | 0 | 0.36 | 0.00 | 0.00-10.19 | 0 | 0.23 | 0.00 | 0.00-15.95 | 0 | 0.11 | 0.00 | 0.00-3.35 |
| Pharynx and other oral cavity | C09-C14 | 3 | 0.82 | 3.66 | 0.74-10.69 | 5 | 2.47 | 2.02 | 0.65-4.72 | 4 | 1.64 | 2.44 | 0.66-6.24 | 1 | 0.84 | 1.19 | 0.02-6.62 |
| Oesophagus | C15 | 2 | 0.95 | 2.11 | 0.24-7.60 | 4 | 2.61 | 1.53 | 0.41-3.92 | 3 | 1.68 | 1.79 | 0.36-5.22 | 2 | 0.85 | 2.35 | 0.26-8.50 |
| Stomach | C16 | 3 | 2.44 | 1.23 | 0.25-3.59 | 6 | 6.42 | 0.93 | 0.34-2.03 | 3 | 4.01 | 0.75 | 0.15-2.19 | 7 | 1.85 | **3.78** | **1.52-7.80** |
| Colon, rectum, and anus | C18-C21 | 15 | 9.35 | 1.60 | 0.90-2.65 | 26 | 24.5 | 1.06 | 0.69-1.56 | 26 | 15.24 | **1.71** | **1.11-2.50** | 17 | 7.26 | **2.34** | **1.36-3.75** |
| Liver | C22 | 4 | 0.9 | **4.44** | **1.20-11.38** | 2 | 2.5 | 0.80 | 0.09-2.89 | 2 | 1.68 | 1.19 | 0.13-4.30 | 2 | 0.86 | 2.33 | 0.26-8.40 |
| Pancreas | C25 | 4 | 1.64 | 2.44 | 0.66-6.24 | 3 | 4.5 | 0.67 | 0.13-1.95 | 5 | 2.97 | 1.68 | 0.54-3.93 | 2 | 1.52 | 1.32 | 0.15-4.75 |
| Larynx | C32 | 3 | 0.67 | 4.48 | 0.90-13.08 | 2 | 1.83 | 1.09 | 0.12-3.95 | 2 | 1.14 | 1.75 | 0.20-6.33 | 0 | 0.55 | 0.00 | 0.00-6.67 |
| Lung | C33-C34 | 19 | 7.44 | **2.55** | **1.54-3.99** | 55 | 20.31 | **2.71** | **2.04-3.52** | 43 | 12.91 | **3.33** | **2.41-4.49** | 34 | 6.57 | **5.18** | **3.58-7.23** |
| Melanoma of skin | C43 | 5 | 2.46 | 2.03 | 0.66-4.74 | 20 | 7.1 | **2.82** | **1.72-4.35** | 6 | 4.61 | 1.30 | 0.48-2.83 | 4 | 2.3 | 1.74 | 0.47-4.45 |
| Breast | C50 | 16 | 7.31 | **2.19** | **1.25-3.55** | 19 | 19.74 | 0.96 | 0.58-1.50 | 24 | 12.87 | **1.86** | **1.19-2.77** | 20 | 7.25 | **2.76** | **1.68-4.26** |
| Cervix uteri | C53 | 1 | 0.64 | 1.56 | 0.02-8.69 | 3 | 1.88 | 1.60 | 0.32-4.66 | 2 | 1.36 | 1.47 | 0.17-5.31 | 0 | 0.75 | 0.00 | 0.00-4.89 |
| Corpus uteri | C54-C55 | 3 | 1.35 | 2.22 | 0.45-6.49 | 4 | 3.47 | 1.15 | 0.31-2.95 | 1 | 2.16 | 0.46 | 0.01-2.58 | 3 | 1.08 | 2.78 | 0.56-8.12 |
| Ovaries | C56 | 3 | 0.91 | 3.30 | 0.66-9.63 | 3 | 2.36 | 1.27 | 0.26-3.71 | 2 | 1.47 | 1.36 | 0.15-4.91 | 0 | 0.75 | 0.00 | 0.00-4.89 |
| Prostate | C61 | 14 | 10.44 | 1.34 | 0.73-2.25 | 21 | 28.45 | 0.74 | 0.46-1.13 | 23 | 17.77 | 1.29 | 0.82-1.94 | 8 | 8.35 | 0.96 | 0.41-1.89 |
| Testis | C62 | 0 | 0.94 | 0.00 | 0.00-3.90 | 8 | 2.91 | **2.75** | **1.18-5.42** | 2 | 1.96 | 1.02 | 0.11-3.68 | 0 | 0.92 | 0.00 | 0.00-3.99 |
| Kidney | C64 | 20 | 2.2 | **9.09** | **5.55-14.04** | 2 | 6 | 0.33 | 0.04-1.20 | 7 | 3.81 | 1.84 | 0.74-3.79 | 6 | 1.81 | **3.31** | **1.21-7.22** |
| Urinary bladder | C67 | 3 | 2.54 | 1.18 | 0.24-3.45 | 9 | 6.59 | 1.37 | 0.62-2.59 | 6 | 4.09 | 1.47 | 0.54-3.19 | 2 | 1.97 | 1.02 | 0.11-3.67 |
| Central nervous system | C70-C72 | 0 | 0.93 | 0.00 | 0.00-3.94 | 3 | 2.64 | 1.14 | 0.23-3.32 | 2 | 1.74 | 1.15 | 0.13-4.15 | 1 | 0.87 | 1.15 | 0.02-6.40 |
| Thyroid | C73 | 10 | 0.77 | **12.99** | **6.22-23.89** | 5 | 2.28 | 2.19 | 0.71-5.12 | 5 | 1.52 | **3.29** | **1.06-7.68** | 1 | 0.79 | 1.27 | 0.02-7.04 |
| **All haematological malignancies** | **C81-C96** | 128 | 4.84 | **26.45** | **22.06-31.45** | 90 | 13.16 | **6.84** | **5.50-8.41** | 48 | 8.36 | **5.74** | **4.23-7.61** | 16 | 4.03 | **3.97** | **2.27-6.45** |
| Non-Hodgkin lymphoma | C82-C85 | 89 | 1.92 | **46.35** | **37.22-57.04** | 57 | 5.25 | **10.86** | **8.22-14.07** | 26 | 3.36 | **7.74** | **5.05-11.34** | 10 | 1.66 | **6.02** | **2.88-11.08** |
| Multiple myeloma | C90 | 5 | 0.75 | **6.67** | **2.15-15.56** | 1 | 2.01 | 0.50 | 0.01-2.77 | 3 | 1.29 | 2.33 | 0.47-6.79 | 1 | 0.63 | 1.59 | 0.02-8.83 |
| Lymphoid leukaemia | C91 | 17 | 0.79 | **21.52** | **12.53-34.46** | 7 | 2.17 | **3.23** | **1.29-6.65** | 2 | 1.33 | 1.50 | 0.17-5.43 | 1 | 0.61 | 1.64 | 0.02-9.12 |
| Acute lymphoblastic | C91.0 | 2 | 0.12 | **16.67** | **1.87-60.17** | 4 | 0.33 | **12.12** | **3.26-31.03** | 1 | 0.18 | 5.56 | 0.07-30.91 | 0 | 0.07 | 0.00 | 0.00-52.40 |
| Chronic lymphocytic | C91.1 | 15 | 0.61 | **24.59** | **13.75-40.56** | 3 | 1.64 | 1.83 | 0.37-5.34 | 1 | 1.03 | 0.97 | 0.01-5.40 | 1 | 0.48 | 2.08 | 0.03-11.59 |
| Myeloid leukaemia | C92 | 4 | 0.61 | **6.56** | **1.76-16.79** | 15 | 1.68 | **8.93** | **4.99-14.73** | 12 | 1.07 | **11.21** | **5.79-19.59** | 2 | 0.53 | 3.77 | 0.42-13.62 |
| Acute myeloblastic | C92.0 | 4 | 0.34 | **11.76** | **3.17-30.12** | 12 | 0.94 | **12.77** | **6.59-22.30** | 9 | 0.59 | **15.25** | **6.96-28.96** | 1 | 0.29 | 3.45 | 0.05-19.19 |
| Chronic myeloid | C92.1 | 0 | 0.15 | 0.00 | 0.00-24.45 | 0 | 0.41 | 0.00 | 0.00-8.95 | 1 | 0.25 | 4.00 | 0.05-22.26 | 1 | 0.11 | 9.09 | 0.12-50.58 |
| **All sites**** | **C00-C97** | 269 | 64.89 | **4.15** | **3.66-4.67** | 317 | 176.12 | **1.80** | **1.61-2.01** | 231 | 112.16 | **2.06** | **1.80-2.34** | 140 | 55.84 | **2.51** | **2.11-2.96** |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); SPM: subsequent primary malignancies; ICD-10: the WHO International Classification of Diseases (10th revision); HL: Hodgkin lymphoma.
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 30. Overall and site-specific SIRs of SPM following HL (all intervals, excluding initial 2 months, and excluding first year)

| | | Overall | | | | Overall (excl. <2 months) | | | | Overall (excl. <1year) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | **C00-C75** | 653 | 371.42 | **1.76** | **1.63-1.90** | 569 | 359.98 | **1.58** | **1.45-1.72** | 519 | 312.55 | **1.66** | **1.52-1.81** |
| Lip, oral cavity, and pharynx | C00-C14 | 29 | 13.39 | **2.17** | **1.45-3.11** | 27 | 13.01 | **2.08** | **1.37-3.02** | 23 | 11.38 | **2.02** | **1.28-3.03** |
| Lip | C00 | 0 | 0.46 | 0.00 | 0.00-7.97 | 0 | 0.44 | 0.00 | 0.00-8.34 | 0 | 0.38 | 0.00 | 0.00-9.65 |
| Tongue | C01-C02 | 10 | 2.62 | **3.82** | **1.83-7.02** | 10 | 2.54 | **3.94** | **1.88-7.24** | 8 | 2.23 | **3.59** | **1.54-7.07** |
| Gum, floor of mouth, other mouth | C03-C06 | 5 | 3.34 | 1.50 | 0.48-3.49 | 4 | 3.24 | 1.23 | 0.33-3.16 | 4 | 2.85 | 1.40 | 0.38-3.59 |
| Parotid gland, other salivary glands | C07-C08 | 0 | 0.84 | 0.00 | 0.00-4.37 | 0 | 0.82 | 0.00 | 0.00-4.47 | 0 | 0.7 | 0.00 | 0.00-5.24 |
| Pharynx and other oral cavity | C09-C14 | 13 | 5.77 | **2.25** | **1.20-3.85** | 12 | 5.65 | **2.12** | **1.10-3.71** | 10 | 4.95 | 2.02 | 0.97-3.72 |
| Oesophagus | C15 | 11 | 6.08 | 1.81 | 0.90-3.24 | 9 | 5.9 | 1.53 | 0.70-2.90 | 9 | 5.14 | 1.75 | 0.80-3.32 |
| Stomach | C16 | 19 | 14.73 | 1.29 | 0.78-2.01 | 16 | 14.25 | 1.12 | 0.64-1.82 | 16 | 12.28 | 1.30 | 0.74-2.12 |
| Colon, rectum, and anus | C18-C21 | 80 | 56.35 | **1.42** | **1.13-1.77** | 69 | 54.49 | 1.27 | 0.99-1.60 | 69 | 47 | **1.47** | **1.14-1.86** |
| Liver | C22 | 10 | 5.93 | 1.69 | 0.81-3.10 | 6 | 5.75 | 1.04 | 0.38-2.27 | 6 | 5.04 | 1.19 | 0.43-2.59 |
| Pancreas | C25 | 14 | 10.64 | 1.32 | 0.72-2.21 | 12 | 10.32 | 1.16 | 0.60-2.03 | 10 | 8.99 | 1.11 | 0.53-2.05 |
| Larynx | C32 | 7 | 4.19 | 1.67 | 0.67-3.44 | 6 | 4.07 | 1.47 | 0.54-3.21 | 4 | 3.52 | 1.14 | 0.31-2.91 |
| Lung | C33-C34 | 151 | 47.23 | **3.20** | **2.71-3.75** | 140 | 45.78 | **3.06** | **2.57-3.61** | 132 | 39.79 | **3.32** | **2.78-3.93** |
| Melanoma of skin | C43 | 35 | 16.48 | **2.12** | **1.48-2.95** | 32 | 16.02 | **2.00** | **1.37-2.82** | 30 | 14.01 | **2.14** | **1.44-3.06** |
| Breast | C50 | 79 | 47.17 | **1.67** | **1.33-2.09** | 68 | 45.76 | **1.49** | **1.15-1.88** | 63 | 39.86 | **1.58** | **1.21-2.02** |
| Cervix uteri | C53 | 6 | 4.63 | 1.30 | 0.47-2.82 | 6 | 4.51 | 1.33 | 0.49-2.90 | 5 | 3.99 | 1.25 | 0.40-2.92 |
| Corpus uteri | C54-C55 | 11 | 8.05 | 1.37 | 0.68-2.45 | 10 | 7.78 | 1.29 | 0.62-2.36 | 8 | 6.71 | 1.19 | 0.51-2.35 |
| Ovaries | C56 | 8 | 5.49 | 1.46 | 0.63-2.87 | 6 | 5.31 | 1.13 | 0.41-2.46 | 5 | 4.58 | 1.09 | 0.35-2.55 |
| Prostate | C61 | 66 | 65.01 | 1.02 | 0.79-1.29 | 60 | 62.98 | 0.95 | 0.73-1.23 | 52 | 54.57 | 0.95 | 0.71-1.25 |
| Testis | C62 | 10 | 6.73 | 1.49 | 0.71-2.73 | 10 | 6.56 | 1.52 | 0.73-2.80 | 10 | 5.79 | 1.73 | 0.83-3.18 |
| Kidney | C64 | 35 | 13.8 | **2.54** | **1.77-3.53** | 23 | 13.37 | **1.72** | **1.09-2.58** | 15 | 11.62 | 1.29 | 0.72-2.13 |
| Urinary bladder | C67 | 20 | 15.19 | 1.32 | 0.80-2.03 | 19 | 14.68 | 1.29 | 0.78-2.02 | 17 | 12.65 | 1.34 | 0.78-2.15 |
| Central nervous system | C70-C72 | 6 | 6.19 | 0.97 | 0.35-2.11 | 6 | 6.01 | 1.00 | 0.36-2.17 | 6 | 5.25 | 1.14 | 0.42-2.49 |
| Thyroid | C73 | 21 | 5.35 | **3.93** | **2.43-6.00** | 13 | 5.2 | **2.50** | **1.33-4.28** | 11 | 4.59 | **2.40** | **1.19-4.29** |
| **All haematological malignancies** | **C81-C96** | 282 | 30.37 | **9.29** | **8.23-10.43** | 204 | 29.42 | **6.93** | **6.02-7.95** | 154 | 25.55 | **6.03** | **5.11-7.06** |
| Non-Hodgkin lymphoma | C82-C85 | 182 | 12.21 | **14.91** | **12.82-17.24** | 126 | 11.84 | **10.64** | **8.86-12.67** | 93 | 10.27 | **9.06** | **7.31-11.09** |
| Multiple myeloma | C90 | 10 | 4.67 | **2.14** | **1.03-3.94** | 8 | 4.52 | 1.77 | 0.76-3.49 | 5 | 3.93 | 1.27 | 0.41-2.97 |
| Lymphoid leukaemia | C91 | 27 | 4.92 | **5.49** | **3.62-7.98** | 16 | 4.77 | **3.35** | **1.92-5.45** | 10 | 4.11 | **2.43** | **1.16-4.47** |
| Acute lymphoblastic | C91.0 | 7 | 0.72 | **9.72** | **3.89-20.03** | 7 | 0.7 | **10.00** | **4.01-20.60** | 5 | 0.58 | **8.62** | **2.78-20.12** |
| Chronic lymphocytic | C91.1 | 20 | 3.75 | **5.33** | **3.26-8.24** | 9 | 3.63 | **2.48** | **1.13-4.71** | 5 | 3.15 | 1.59 | 0.51-3.70 |
| Myeloid leukaemia | C92 | 33 | 3.89 | **8.48** | **5.84-11.91** | 32 | 3.77 | **8.49** | **5.80-11.98** | 29 | 3.28 | **8.84** | **5.92-12.70** |
| Acute myeloblastic | C92.0 | 26 | 2.17 | **11.98** | **7.82-17.56** | 25 | 2.11 | **11.85** | **7.67-17.49** | 22 | 1.82 | **12.09** | **7.57-18.30** |
| Chronic myeloid | C92.1 | 2 | 0.93 | 2.15 | 0.24-7.76 | 2 | 0.9 | 2.22 | 0.25-8.02 | 2 | 0.77 | 2.60 | 0.29-9.38 |
| **All sites**** | **C00-C97** | 953 | 409.01 | **2.33** | **2.18-2.48** | 789 | 396.38 | **1.99** | **1.85-2.13** | 688 | 344.12 | **2.00** | **1.85-2.15** |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); SPM: subsequent primary malignancies; ICD-10: the WHO International Classification of Diseases (10th revision); HL: Hodgkin lymphoma.
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 31. Observed number and SIRs of SPM following HL by follow-up time for survivors aged <60 or ≥60 years, for both sexes

| Under 60 years | | | ≤1 year | | | | >1-≤5 years | | | | >5-≤10 years | | | | >10 years | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | 59 | 14.7 | **4.01** | **3.06-5.18** | 108 | 54.75 | **1.97** | **1.62-2.38** | 100 | 50 | **2.00** | **1.63-2.43** | 102 | 37.09 | **2.75** | **2.24-3.34** |
| Lip/oral cavity | 2 | 0.85 | 2.35 | 0.26-8.50 | 8 | 3.07 | **2.61** | **1.12-5.13** | 6 | 2.63 | 2.28 | 0.83-4.97 | 6 | 1.7 | **3.53** | **1.29-7.68** |
| Oesophagus | 2 | 0.26 | 7.69 | 0.86-27.77 | 1 | 1.01 | 0.99 | 0.01-5.51 | 3 | 0.93 | 3.23 | 0.65-9.43 | 1 | 0.67 | 1.49 | 0.02-8.30 |
| Stomach | 1 | 0.46 | 2.17 | 0.03-12.10 | 1 | 1.73 | 0.58 | 0.01-3.22 | 2 | 1.58 | 1.27 | 0.14-4.57 | 5 | 1.15 | **4.35** | **1.40-10.15** |
| Colon/rectum | 8 | 1.6 | **5.00** | **2.15-9.85** | 10 | 6.16 | 1.62 | 0.78-2.99 | 11 | 5.88 | 1.87 | 0.93-3.35 | 11 | 4.54 | **2.42** | **1.21-4.34** |
| Lung | 7 | 1.6 | **4.38** | **1.75-9.01** | 21 | 6.21 | **3.38** | **2.09-5.17** | 16 | 6.02 | **2.66** | **1.52-4.32** | 31 | 4.82 | **6.43** | **4.37-9.13** |
| Melanoma of skin | 5 | 1.12 | **4.46** | **1.44-10.42** | 13 | 3.85 | **3.38** | **1.80-5.77** | 4 | 3.01 | 1.33 | 0.36-3.40 | 3 | 1.89 | 1.59 | 0.32-4.64 |
| Breast | 5 | 2.47 | 2.02 | 0.65-4.72 | 10 | 8.83 | 1.13 | 0.54-2.08 | 18 | 7.73 | **2.33** | **1.38-3.68** | 19 | 5.74 | **3.31** | **1.99-5.17** |
| Prostate | 4 | 1.23 | 3.25 | 0.87-8.33 | 6 | 5.77 | 1.04 | 0.38-2.26 | 14 | 6.86 | **2.04** | **1.11-3.42** | 7 | 6.08 | 1.15 | 0.46-2.37 |
| Kidney | 7 | 0.56 | **12.50** | **5.01-25.76** | 1 | 2.09 | 0.48 | 0.01-2.66 | 5 | 1.89 | 2.65 | 0.85-6.17 | 6 | 1.31 | **4.58** | **1.67-9.97** |
| Thyroid | 7 | 0.47 | **14.89** | **5.97-30.69** | 5 | 1.63 | 3.07 | 0.99-7.16 | 4 | 1.24 | 3.23 | 0.87-8.26 | 1 | 0.72 | 1.39 | 0.02-7.73 |
| **All haematological malignancies** | 64 | 1.64 | **39.02** | **30.05-49.83** | 60 | 5.5 | **10.91** | **8.32-14.04** | 30 | 4.43 | **6.77** | **4.57-9.67** | 14 | 2.91 | **4.81** | **2.63-8.07** |
| Non-Hodgkin lymphoma | 44 | 0.61 | **72.13** | **52.41-96.84** | 31 | 2.05 | **15.12** | **10.27-21.47** | 14 | 1.72 | **8.14** | **4.45-13.66** | 10 | 1.19 | **8.40** | **4.02-15.46** |
| Multiple myeloma | 4 | 0.13 | **30.77** | **8.28-78.78** | 1 | 0.55 | 1.82 | 0.02-10.12 | 2 | 0.53 | 3.77 | 0.42-13.62 | 0 | 0.41 | 0.00 | 0.00-8.95 |
| Lymphoid leukaemia | 6 | 0.26 | **23.08** | **8.43-50.23** | 5 | 0.83 | **6.02** | **1.94-14.06** | 1 | 0.65 | 1.54 | 0.02-8.56 | 0 | 0.42 | 0.00 | 0.00-8.73 |
| Acute lymphoblastic | 2 | 0.1 | **20.00** | **2.25-72.21** | 3 | 0.28 | **10.71** | **2.15-31.31** | 1 | 0.14 | 7.14 | 0.09-39.74 | 0 | 0.07 | 0.00 | 0.00-52.40 |
| Chronic lymphocytic | 4 | 0.11 | **36.36** | **9.78-93.10** | 2 | 0.45 | 4.44 | 0.50-16.05 | 0 | 0.43 | 0.00 | 0.00-8.53 | 0 | 0.31 | 0.00 | 0.00-11.83 |
| Myeloid leukaemia | 4 | 0.22 | **18.18** | **4.89-46.55** | 15 | 0.73 | **20.55** | **11.49-33.89** | 8 | 0.59 | **13.56** | **5.84-26.72** | 2 | 0.38 | 5.26 | 0.59-19.00 |
| Acute myeloblastic | 4 | 0.12 | **33.33** | **8.97-85.34** | 12 | 0.39 | **30.77** | **15.88-53.75** | 6 | 0.31 | **19.35** | **7.07-42.13** | 1 | 0.21 | 4.76 | 0.06-26.49 |
| **All sites**** | 123 | 16.61 | **7.41** | **6.15-8.84** | 173 | 61.19 | **2.83** | **2.42-3.28** | 132 | 55.25 | **2.39** | **2.00-2.83** | 119 | 40.64 | **2.93** | **2.43-3.50** |
| **60 years or older** | | | **≤1 year** | | | | **>1-≤5 years** | | | | **>5-≤10 years** | | | | **>10 years** | | | |
| **Subsequent cancer** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | 79 | 44.16 | **1.79** | **1.42-2.23** | 110 | 105.13 | 1.05 | 0.86-1.26 | 79 | 51.85 | **1.52** | **1.21-1.90** | 19 | 13.73 | 1.38 | 0.83-2.16 |
| Lip/oral cavity | 4 | 1.14 | 3.51 | 0.94-8.98 | 2 | 2.61 | 0.77 | 0.09-2.77 | 2 | 1.13 | 1.77 | 0.20-6.39 | 0 | 0.26 | 0.00 | 0.00-14.11 |
| Oesophagus | 0 | 0.68 | 0.00 | 0.00-5.39 | 3 | 1.61 | 1.86 | 0.37-5.44 | 0 | 0.74 | 0.00 | 0.00-4.96 | 1 | 0.19 | 5.26 | 0.07-29.28 |
| Stomach | 2 | 1.99 | 1.01 | 0.11-3.63 | 5 | 4.69 | 1.07 | 0.34-2.49 | 1 | 2.43 | 0.41 | 0.01-2.29 | 2 | 0.7 | 2.86 | 0.32-10.32 |
| Colon/rectum | 7 | 7.76 | 0.90 | 0.36-1.86 | 16 | 18.34 | 0.87 | 0.50-1.42 | 14 | 9.35 | 1.50 | 0.82-2.51 | 6 | 2.72 | 2.21 | 0.81-4.80 |
| Liver | 4 | 0.73 | **5.48** | **1.47-14.03** | 1 | 1.79 | 0.56 | 0.01-3.11 | 0 | 0.96 | 0.00 | 0.00-3.82 | 1 | 0.27 | 3.70 | 0.05-20.61 |
| Lung | 12 | 5.85 | **2.05** | **1.06-3.58** | 34 | 14.1 | **2.41** | **1.67-3.37** | 27 | 6.9 | **3.91** | **2.58-5.69** | 3 | 1.74 | 1.72 | 0.35-5.04 |
| Melanoma of skin | 0 | 1.35 | 0.00 | 0.00-2.72 | 7 | 3.25 | 2.15 | 0.86-4.44 | 2 | 1.6 | 1.25 | 0.14-4.51 | 1 | 0.42 | 2.38 | 0.03-13.25 |
| Breast | 11 | 4.86 | **2.26** | **1.13-4.05** | 9 | 10.91 | 0.82 | 0.38-1.57 | 6 | 5.13 | 1.17 | 0.43-2.55 | 1 | 1.51 | 0.66 | 0.01-3.68 |
| Kidney | 13 | 1.64 | **7.93** | **4.22-13.56** | 1 | 3.9 | 0.26 | 0.00-1.43 | 1 | 1.91 | 0.52 | 0.01-2.91 | 0 | 0.5 | 0.00 | 0.00-7.34 |
| Thyroid | 3 | 0.29 | **10.34** | **2.08-30.23** | 0 | 0.65 | 0.00 | 0.00-5.64 | 1 | 0.28 | 3.57 | 0.05-19.87 | 0 | 0.06 | 0.00 | 0.00-61.13 |
| **All haematological malignancies** | 64 | 3.2 | **20.00** | **15.40-25.54** | 30 | 7.65 | **3.92** | **2.65-5.60** | 18 | 3.93 | **4.58** | **2.71-7.24** | 2 | 1.13 | 1.77 | 0.20-6.39 |
| Non-Hodgkin lymphoma | 45 | 1.33 | **33.83** | **24.68-45.27** | 26 | 3.21 | **8.10** | **5.29-11.87** | 12 | 1.65 | **7.27** | **3.75-12.70** | 0 | 0.47 | 0.00 | 0.00-7.80 |
| Multiple myeloma | 1 | 0.61 | 1.64 | 0.02-9.12 | 0 | 1.46 | 0.00 | 0.00-2.51 | 1 | 0.76 | 1.32 | 0.02-7.32 | 1 | 0.21 | 4.76 | 0.06-26.49 |
| Lymphoid leukaemia | 11 | 0.56 | **19.64** | **9.79-35.15** | 2 | 1.34 | 1.49 | 0.17-5.39 | 1 | 0.69 | 1.45 | 0.02-8.06 | 1 | 0.19 | 5.26 | 0.07-29.28 |
| Acute lymphoblastic | 0 | 0.02 | 0.00 | 0.00-183.40 | 1 | 0.06 | 16.67 | 0.22-92.73 | 0 | 0.03 | 0.00 | 0.00-122.27 | 0 | 0.01 | 0.00 | 0.00-366.81 |
| Chronic lymphocytic | 11 | 0.49 | **22.45** | **11.19-40.17** | 1 | 1.19 | 0.84 | 0.01-4.68 | 1 | 0.61 | 1.64 | 0.02-9.12 | 1 | 0.16 | 6.25 | 0.08-34.77 |
| Myeloid leukaemia | 0 | 0.4 | 0.00 | 0.00-9.17 | 0 | 0.95 | 0.00 | 0.00-3.86 | 4 | 0.49 | **8.16** | **2.20-20.90** | 0 | 0.15 | 0.00 | 0.00-24.45 |
| Acute myeloblastic | 0 | 0.22 | 0.00 | 0.00-16.67 | 0 | 0.56 | 0.00 | 0.00-6.55 | 3 | 0.29 | **10.34** | **2.08-30.23** | 0 | 0.09 | 0.00 | 0.00-40.76 |
| **All sites**** | 146 | 48.29 | **3.02** | **2.55-3.56** | 144 | 114.93 | **1.25** | **1.06-1.48** | 98 | 56.91 | **1.72** | **1.40-2.10** | 21 | 15.2 | 1.38 | 0.85-2.11 |

## Table 32. Observed number, SIRs and EARs of SPM following HL by calendar period, for both sexes

| | | 1990–2000 HL patients=3374 PYRs=11147.56 | | | | | 2001–2011 HL patients=5304 PYRs=51486.49 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **EAR** | **O** | **E** | **SIR** | **95% CI** | **EAR** |
| **All solid malignancies*** | **C00-C75** | 64 | 32.28 | **1.98** | **1.53-2.53** | 28.45 | 160 | 100.54 | **1.59** | **1.35-1.86** | 11.55 |
| Lip, oral cavity, and pharynx | C00-C14 | 2 | 1.24 | 1.61 | 0.18-5.82 | 0.68 | 4 | 3.76 | 1.06 | 0.29-2.72 | 0.05 |
| Oesophagus | C15 | 1 | 0.52 | 1.92 | 0.03-10.70 | 0.43 | 4 | 1.69 | 2.37 | 0.64-6.06 | 0.45 |
| Stomach | C16 | 4 | 1.58 | 2.53 | 0.68-6.48 | 2.17 | 6 | 3.98 | 1.51 | 0.55-3.28 | 0.39 |
| Colon, rectum, and anus | C18-C21 | 5 | 5.13 | 0.97 | 0.31-2.27 | -0.12 | 18 | 15.08 | 1.19 | 0.71-1.89 | 0.57 |
| Liver | C22 | 2 | 0.45 | 4.44 | 0.50-16.05 | 1.39 | 3 | 1.83 | 1.64 | 0.33-4.79 | 0.23 |
| Pancreas | C25 | 1 | 0.86 | 1.16 | 0.02-6.47 | 0.13 | 4 | 3.14 | 1.27 | 0.34-3.26 | 0.17 |
| Larynx | C32 | 2 | 0.47 | 4.26 | 0.48-15.36 | 1.37 | 3 | 1.14 | 2.63 | 0.53-7.69 | 0.36 |
| Lung | C33-C34 | 18 | 4.75 | **3.79** | **2.24-5.99** | 11.89 | 34 | 13.69 | **2.48** | **1.72-3.47** | 3.94 |
| Melanoma of skin | C43 | 4 | 1.1 | 3.64 | 0.98-9.31 | 2.60 | 5 | 3.9 | 1.28 | 0.41-2.99 | 0.21 |
| Breast | C50 | 4 | 3.95 | 1.01 | 0.27-2.59 | 0.04 | 17 | 11.84 | 1.44 | 0.84-2.30 | 1.00 |
| Cervix uteri | C53 | 1 | 0.56 | 1.79 | 0.02-9.94 | 0.39 | 1 | 1.16 | 0.86 | 0.01-4.80 | -0.03 |
| Corpus uteri | C54-C55 | 0 | 0.81 | 0.00 | 0.00-4.53 | -0.73 | 4 | 2.13 | 1.88 | 0.51-4.81 | 0.36 |
| Ovaries | C56 | 2 | 0.63 | 3.17 | 0.36-11.46 | 1.23 | 2 | 1.35 | 1.48 | 0.17-5.35 | 0.13 |
| Prostate | C61 | 4 | 4.01 | 1.00 | 0.27-2.55 | -0.01 | 17 | 17.68 | 0.96 | 0.56-1.54 | -0.13 |
| Testis | C62 | 2 | 0.61 | 3.28 | 0.37-11.84 | 1.25 | 5 | 1.61 | 3.11 | 1.00-7.25 | 0.66 |
| Kidney | C64 | 4 | 1.31 | 3.05 | 0.82-7.82 | 2.41 | 9 | 4.02 | **2.24** | **1.02-4.25** | 0.97 |
| Urinary bladder | C67 | 1 | 1.63 | 0.61 | 0.01-3.41 | -0.57 | 7 | 4.36 | 1.61 | 0.64-3.31 | 0.51 |
| Central nervous system | C70-C72 | 0 | 0.57 | 0.00 | 0.00-6.44 | -0.51 | 1 | 1.72 | 0.58 | 0.01-3.23 | -0.14 |
| Thyroid | C73 | 2 | 0.37 | 5.41 | 0.61-19.52 | 1.46 | 6 | 1.36 | **4.41** | **1.61-9.60** | 0.90 |
| **All haematological malignancies** | **C81-C96** | 8 | 2.98 | **2.68** | **1.16-5.29** | 4.50 | 69 | 8.22 | **8.39** | **6.53-10.62** | 11.81 |
| Non-Hodgkin lymphoma | C82-C85 | 5 | 1.17 | **4.27** | **1.38-9.97** | 3.44 | 48 | 3.27 | **14.68** | **10.82-19.46** | 8.69 |
| Multiple myeloma | C90 | 1 | 0.44 | 2.27 | 0.03-12.65 | 0.50 | 3 | 1.31 | 2.29 | 0.46-6.69 | 0.33 |
| Lymphoid leukaemia | C91 | 2 | 0.5 | 4.00 | 0.45-14.44 | 1.35 | 4 | 1.35 | 2.96 | 0.80-7.59 | 0.51 |
| Acute lymphoblastic | C91.0 | 0 | 0.09 | 0.00 | 0.00-40.76 | -0.08 | 1 | 0.18 | 5.56 | 0.07-30.91 | 0.16 |
| Chronic lymphocytic | C91.1 | 2 | 0.38 | 5.26 | 0.59-19.00 | 1.45 | 3 | 1.04 | 2.88 | 0.58-8.43 | 0.38 |
| Myeloid leukaemia | C92 | 0 | 0.4 | 0.00 | 0.00-9.17 | -0.36 | 9 | 1.07 | **8.41** | **3.84-15.97** | 1.54 |
| Acute myeloblastic | C92.0 | 0 | 0.22 | 0.00 | 0.00-16.67 | -0.20 | 6 | 0.61 | **9.84** | **3.59-21.41** | 1.05 |
| Chronic myeloid | C92.1 | 0 | 0.12 | 0.00 | 0.00-30.57 | -0.11 | 0 | 0.23 | 0.00 | 0.00-15.95 | -0.04 |
| other myeloid leukaemia | C92.2-C92.9 | 0 | 0.07 | 0.00 | 0.00-52.40 | -0.06 | 3 | 0.24 | **12.50** | **2.51-36.52** | 0.54 |
| **All sites**** | **C00-C97** | 77 | 36.02 | **2.14** | **1.69-2.67** | 36.76 | 233 | 110.79 | **2.10** | **1.84-2.39** | 23.74 |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); EAR: excess absolute risk per 10,000 person-years; PYRs: person-years of observation; SPM: subsequent primary malignancies; ICD-10: the WHO International Classification of Diseases (10th revision); HL: Hodgkin lymphoma.
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 33. Risk of HL subsequent to other primary malignancies by follow-up time, for both sexes

| | ≤1 year | | | >1-≤5 years | | | >5-≤10 years | | | >10 years | | | Overall | | | Overall (excl. <2 months) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Site of first primary cancer** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** |
| **All solid malignancies*** | 172 | **2.77** | **2.37-3.21** | 124 | 0.88 | 0.73-1.04 | 61 | 0.92 | 0.70-1.18 | 11 | **0.54** | **0.27-0.97** | 368 | **1.27** | **1.14-1.40** | 255 | 0.92 | 0.81-1.04 |
| Lip/oral cavity | 9 | **4.25** | **1.94-8.06** | 2 | 0.47 | 0.05-1.71 | 3 | 1.58 | 0.32-4.61 | 0 | 0.00 | 0.00-5.92 | 14 | 1.58 | 0.86-2.65 | 8 | 0.95 | 0.41-1.87 |
| Stomach | 6 | **2.76** | **1.01-6.02** | 2 | 0.58 | 0.06-2.08 | 1 | 0.68 | 0.01-3.78 | 0 | 0.00 | 0.00-7.34 | 9 | 1.18 | 0..54-2.25 | 4 | 0.56 | 0.15-1.44 |
| Colon/ rectum | 34 | **3.39** | **2.35-4.74** | 17 | 0.73 | 0.43-1.17 | 9 | 0.88 | 0.40-1.68 | 1 | 0.35 | 0.00-1.94 | 61 | **1.32** | **1.01-1.69** | 36 | 0.81 | 0.57-1.12 |
| Lung | 23 | **4.00** | **2.53-6.00** | 8 | 1.24 | 0.53-2.45 | 3 | 1.31 | 0.26-3.83 | 0 | 0.00 | 0.00-4.83 | 34 | **2.23** | **1.54-3.12** | 18 | 1.30 | 0.77-2.06 |
| Melanoma of skin | 7 | 2.30 | 0.92-4.73 | 15 | **1.88** | **1.05-3.10** | 7 | 1.74 | 0.70-3.59 | 2 | 1.49 | 0.17-5.39 | 31 | **1.89** | **1.28-2.68** | 26 | **1.64** | **1.07-2.41** |
| Breast (females) | 19 | **2.03** | **1.22-3.17** | 17 | 0.67 | 0.39-1.07 | 10 | 0.77 | 0.37-1.42 | 1 | 0.21 | 0.00-1.19 | 47 | 0.90 | 0.66-1.19 | 33 | **0.65** | **0.45-0.91** |
| Kidney | 9 | **3.78** | **1.73-7.18** | 5 | 0.82 | 0.26-1.92 | 1 | 0.31 | 0.00-1.72 | 0 | 0.00 | 0.00-3.30 | 15 | 1.17 | 0.66-1.93 | 9 | 0.73 | 0.33-1.38 |
| Thyroid | 12 | **13.04** | **6.73-22.79** | 3 | 1.19 | 0.24-3.48 | 0 | 0.00 | 0.00-2.76 | 0 | 0.00 | 0.00-7.49 | 15 | **2.86** | **1.60-4.71** | 3 | 0.59 | 0.12-1.73 |
| **All haematological malignancies** | 71 | **14.34** | **11.20-18.09** | 78 | **6.76** | **5.35-8.44** | 30 | **5.51** | **3.72-7.87** | 6 | **3.31** | **1.21-7.22** | 185 | **7.80** | **6.71-9.00** | 138 | **6.07** | **5.10-7.17** |
| Non-Hodgkin lymphoma | 77 | **37.56** | **29.64-46.95** | 42 | **8.57** | **6.18-11.59** | 14 | **5.93** | **3.24-9.95** | 4 | **5.06** | **1.36-12.96** | 137 | **13.58** | **11.40-16.05** | 73 | **7.53** | **5.90-9.47** |
| Multiple myeloma | 6 | **7.59** | **2.77-16.53** | 1 | 0.62 | 0.01-3.46 | 1 | 1.89 | 0.02-10.50 | 0 | 0.00 | 0.00-26.20 | 8 | **2.61** | **1.13-5.15** | 3 | 1.03 | 0.21-3.02 |
| Lymphoid leukaemia | 11 | **12.94** | **6.45-23.16** | 25 | **11.11** | **7.19-16.40** | 13 | **12.04** | **6.40-20.59** | 2 | 6.25 | 0.70-22.57 | 51 | **11.36** | **8.46-14.93** | 44 | **10.16** | **7.38-13.64** |
| Acute lymphoblastic | 0 | 0.00 | 0.00-45.85 | 1 | 5.88 | 0.08-32.73 | 0 | 0.00 | 0.00-40.76 | 0 | 0.00 | 0.00-122.27 | 1 | 2.70 | 0.04-15.04 | 1 | 2.86 | 0.04-15.90 |
| Chronic lymphocytic | 12 | **17.14** | **8.85-29.95** | 24 | **12.77** | **8.18-19.00** | 13 | **14.77** | **7.86-25.26** | 2 | 8.33 | 0.94-30.09 | 51 | **13.78** | **10.26-18.12** | 42 | **11.76** | **8.48-15.90** |
| Myeloid leukaemia | 5 | **9.80** | **3.16-22.88** | 1 | 1.08 | 0.01-5.98 | 0 | 0.00 | 0.00-8.53 | 0 | 0.00 | 0.00-24.45 | 6 | **2.97** | **1.08-6.47** | 4 | 2.09 | 0.56-5.36 |
| Acute myeloblastic | 2 | 8.00 | 0.90-28.88 | 1 | 2.78 | 0.04-15.46 | 0 | 0.00 | 0.00-24.45 | 0 | 0.00 | 0.00-52.40 | 3 | 3.61 | 0.73-10.56 | 3 | 3.90 | 0.78-11.38 |
| Chronic myeloid | 1 | 5.56 | 0.07-30.91 | 0 | 0.00 | 0.00-8.73 | 0 | 0.00 | 0.00-17.47 | 0 | 0.00 | 0.00-52.40 | 1 | 1.15 | 0.02-6.40 | 1 | 1.20 | 0.02-6.70 |
| **All sites**** | 218 | **3.21** | **2.80-3.67** | 200 | **1.30** | **1.12-1.49** | 91 | **1.26** | **1.02-1.55** | 17 | 0.76 | 0.44-1.22 | 526 | **1.66** | **1.52-1.81** | 391 | **1.29** | **1.17-1.43** |

O: observed number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); HL: Hodgkin lymphoma.
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Non-Hodgkin lymphoma

### Table 34. Observed number, SIRs and EARs of SPM following NHL by age at diagnosis, for both sexes

| | | 15-44 years | | | | | 45-59 years | | | | | ≥60 years | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **EAR** | **O** | **E** | **SIR** | **95% CI** | **EAR** | **O** | **E** | **SIR** | **95% CI** | **EAR** |
| **All solid malignancies*** | **C00-C75** | 218 | 73.01 | **2.99** | **2.60-3.41** | 23.85 | 1126 | 766.39 | **1.47** | **1.38-1.56** | 33.59 | 4549 | 3288.03 | **1.38** | **1.34-1.42** | 54.67 |
| Lip, oral cavity and pharynx | C00-C14 | 9 | 3.6 | **2.50** | **1.14-4.75** | 0.89 | 65 | 38.62 | **1.68** | **1.30-2.15** | 2.46 | 132 | 71.96 | **1.83** | **1.53-2.18** | 2.60 |
| Lip | C00 | 0 | 0.04 | 0.00 | 0.00-91.70 | -0.01 | 3 | 0.7 | 4.29 | 0.86-12.52 | 0.21 | 10 | 5.07 | 1.97 | 0.94-3.63 | 0.21 |
| Tongue | C01-C02 | 3 | 0.75 | 4.00 | 0.80-11.69 | 0.37 | 10 | 7.41 | 1.35 | 0.65-2.48 | 0.24 | 22 | 14.12 | 1.56 | 0.98-2.36 | 0.34 |
| Gum, floor of mouth, other mouth | C03-C06 | 3 | 0.94 | 3.19 | 0.64-9.32 | 0.34 | 20 | 9.79 | **2.04** | **1.25-3.16** | 0.95 | 29 | 17.73 | **1.64** | **1.10-2.35** | 0.49 |
| Parotid gland, other salivary glands | C07-C08 | 2 | 0.24 | 8.33 | 0.94-30.09 | 0.29 | 7 | 1.44 | **4.86** | **1.95-10.02** | 0.52 | 27 | 6.92 | **3.90** | **2.57-5.68** | 0.87 |
| Pharynx and other oral cavity | C09-C14 | 1 | 1.54 | 0.65 | 0.01-3.61 | -0.09 | 23 | 18.24 | 1.26 | 0.80-1.89 | 0.44 | 42 | 26.49 | **1.59** | **1.14-2.14** | 0.67 |
| Oesophagus | C15 | 2 | 0.86 | 2.33 | 0.26-8.40 | 0.19 | 16 | 15.2 | 1.05 | 0.60-1.71 | 0.07 | 63 | 46.06 | **1.37** | **1.05-1.75** | 0.73 |
| Stomach | C16 | 12 | 2 | **6.00** | **3.10-10.48** | 1.64 | 53 | 25.02 | **2.12** | **1.59-2.77** | 2.61 | 269 | 156.55 | **1.72** | **1.52-1.94** | 4.88 |
| Colon, rectum, and anus | C18-C21 | 23 | 6.18 | **3.72** | **2.36-5.58** | 2.77 | 135 | 101.86 | **1.33** | **1.11-1.57** | 3.10 | 760 | 608.52 | **1.25** | **1.16-1.34** | 6.57 |
| Liver | C22 | 3 | 0.69 | 4.35 | 0.87-12.70 | 0.38 | 21 | 11.89 | **1.77** | **1.09-2.70** | 0.85 | 95 | 57.18 | **1.66** | **1.34-2.03** | 1.64 |
| Pancreas | C25 | 4 | 1.15 | 3.48 | 0.94-8.91 | 0.47 | 29 | 21.2 | 1.37 | 0.92-1.96 | 0.73 | 153 | 109.35 | **1.40** | **1.19-1.64** | 1.89 |
| Larynx | C32 | 2 | 0.7 | 2.86 | 0.32-10.32 | 0.21 | 11 | 11.11 | 0.99 | 0.49-1.77 | -0.01 | 27 | 27.66 | 0.98 | 0.64-1.42 | -0.03 |
| Lung | C33-C34 | 30 | 5.68 | **5.28** | **3.56-7.54** | 4.00 | 209 | 104.62 | **2.00** | **1.74-2.29** | 9.75 | 710 | 419.13 | **1.69** | **1.57-1.82** | 12.61 |
| Melanoma of skin | C43 | 14 | 6.83 | **2.05** | **1.12-3.44** | 1.18 | 50 | 29.33 | **1.70** | **1.27-2.25** | 1.93 | 210 | 102.44 | **2.05** | **1.78-2.35** | 4.66 |
| Breast | C50 | 32 | 17.11 | **1.87** | **1.28-2.64** | 2.45 | 139 | 133.16 | 1.04 | 0.88-1.23 | 0.55 | 432 | 371.31 | **1.16** | **1.06-1.28** | 2.63 |
| Cervix uteri | C53 | 5 | 3.51 | 1.42 | 0.46-3.32 | 0.25 | 8 | 8.12 | 0.99 | 0.42-1.94 | -0.01 | 18 | 17.85 | 1.01 | 0.60-1.59 | 0.01 |
| Corpus uteri | C54-C55 | 1 | 1.35 | 0.74 | 0.01-4.12 | -0.06 | 21 | 20.84 | 1.01 | 0.62-1.54 | 0.01 | 95 | 83.69 | 1.14 | 0.92-1.39 | 0.49 |
| Ovaries | C56 | 5 | 1.53 | **3.27** | **1.05-7.63** | 0.57 | 15 | 13.37 | 1.12 | 0.63-1.85 | 0.15 | 55 | 50.05 | 1.10 | 0.83-1.43 | 0.21 |
| Prostate | C61 | 8 | 2.62 | **3.05** | **1.31-6.02** | 0.88 | 139 | 120.17 | 1.16 | 0.97-1.37 | 1.76 | 717 | 638.44 | **1.12** | **1.04-1.21** | 3.41 |
| Testis | C62 | 11 | 6.29 | 1.75 | 0.87-3.13 | 0.77 | 7 | 3.31 | 2.11 | 0.85-4.36 | 0.34 | 14 | 1.97 | **7.11** | **3.88-11.92** | 0.52 |
| Kidney | C64 | 7 | 2.38 | **2.94** | **1.18-6.06** | 0.76 | 79 | 30.33 | **2.60** | **2.06-3.25** | 4.55 | 254 | 119.48 | **2.13** | **1.87-2.40** | 5.83 |
| Urinary bladder | C67 | 1 | 1.15 | 0.87 | 0.01-4.84 | -0.02 | 25 | 23.27 | 1.07 | 0.70-1.59 | 0.16 | 201 | 172.95 | **1.16** | **1.01-1.33** | 1.22 |
| Central nervous system | C70-C72 | 6 | 2.32 | 2.59 | 0.94-5.63 | 0.61 | 14 | 11.9 | 1.18 | 0.64-1.97 | 0.20 | 56 | 35.57 | **1.57** | **1.19-2.04** | 0.89 |
| Thyroid | C73 | 9 | 3.2 | **2.81** | **1.28-5.34** | 0.95 | 21 | 10.01 | **2.10** | **1.30-3.21** | 1.03 | 41 | 19.42 | **2.11** | **1.51-2.86** | 0.94 |
| **All haematological malignancies** | **C81-C96** | 98 | 7.83 | **12.52** | **10.16-15.25** | 14.83 | 185 | 52.43 | **3.53** | **3.04-4.08** | 12.38 | 433 | 248.1 | **1.75** | **1.58-1.92** | 8.02 |
| Hodgkin lymphoma | C81 | 37 | 1.77 | **20.90** | **14.72-28.81** | 5.79 | 40 | 2.37 | **16.88** | **12.06-22.98** | 3.52 | 60 | 5.95 | **10.08** | **7.69-12.98** | 2.34 |
| Non-Hodgkin lymphoma | C82-C85 | 15 | 2.99 | **5.02** | **2.81-8.27** | 1.98 | 49 | 22.58 | **2.17** | **1.61-2.87** | 2.47 | 110 | 104.98 | 1.05 | 0.86-1.26 | 0.22 |
| Multiple myeloma | C90 | 2 | 0.56 | 3.57 | 0.40-12.89 | 0.24 | 13 | 9.18 | 1.42 | 0.75-2.42 | 0.36 | 64 | 47.52 | **1.35** | **1.04-1.72** | 0.71 |
| Lymphoid leukaemia | C91 | 12 | 0.93 | **12.90** | **6.66-22.54** | 1.82 | 13 | 9.01 | 1.44 | 0.77-2.47 | 0.37 | 47 | 42.61 | 1.10 | 0.81-1.47 | 0.19 |
| Acute lymphoblastic | C91.0 | 7 | 0.38 | **18.42** | **7.38-37.96** | 1.09 | 3 | 0.68 | 4.41 | 0.89-12.89 | 0.22 | 7 | 1.89 | **3.70** | **1.48-7.63** | 0.22 |
| Chronic lymphocytic | C91.1 | 3 | 0.4 | **7.50** | **1.51-21.91** | 0.43 | 8 | 7.51 | 1.07 | 0.46-2.10 | 0.05 | 24 | 37.75 | **0.64** | **0.41-0.95** | -0.60 |
| Myeloid leukaemia | C92 | 26 | 1.14 | **22.81** | **14.89-33.42** | 4.09 | 53 | 6.36 | **8.33** | **6.24-10.90** | 4.36 | 92 | 30.98 | **2.97** | **2.39-3.64** | 2.65 |
| Acute myeloblastic | C92.0 | 17 | 0.57 | **29.82** | **17.36-47.75** | 2.70 | 38 | 3.55 | **10.70** | **7.57-14.69** | 3.22 | 69 | 18.13 | **3.81** | **2.96-4.82** | 2.21 |
| Chronic myeloid | C92.1 | 3 | 0.36 | **8.33** | **1.67-24.35** | 0.43 | 3 | 1.57 | 1.91 | 0.38-5.58 | 0.13 | 7 | 6.27 | 1.12 | 0.45-2.30 | 0.03 |
| **All sites**** | **C00-C97** | 324 | 81.91 | **3.96** | **3.54-4.41** | 39.81 | 1349 | 832.25 | **1.62** | **1.54-1.71** | 48.27 | 5113 | 3609.79 | **1.42** | **1.38-1.46** | 65.18 |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); EAR: excess absolute risk per 10,000 person-years; SPM: subsequent primary malignancies; ICD-10: the WHO International Classification of Diseases (10th revision); NHL: non-Hodgkin lymphoma.

*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)

Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 35. Observed number and SIRs of SPM following NHL by follow-up time, for both sexes

| | | ≤1 year | | | | >1-≤5 years | | | | >5-≤10 years | | | | >10 years | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | **C00-C75** | 1980 | 834.42 | **2.37** | **2.27-2.48** | 2376 | 1997.71 | **1.19** | **1.14-1.24** | 1201 | 969.27 | **1.24** | **1.17-1.31** | 342 | 326.02 | 1.05 | 0.94-1.17 |
| Lip, oral cavity, and pharynx | C00-C14 | 66 | 23 | **2.87** | **2.22-3.65** | 72 | 55.3 | **1.30** | **1.02-1.64** | 53 | 26.79 | **1.98** | **1.48-2.59** | 15 | 9.08 | 1.65 | 0.92-2.72 |
| Lip | C00 | 4 | 1.14 | 3.51 | 0.94-8.98 | 5 | 2.76 | 1.81 | 0.58-4.23 | 4 | 1.41 | 2.84 | 0.76-7.26 | 0 | 0.49 | 0.00 | 0.00-7.49 |
| Tongue | C01-C02 | 11 | 4.48 | **2.46** | **1.22-4.39** | 8 | 10.77 | 0.74 | 0.32-1.46 | 14 | 5.24 | **2.67** | **1.46-4.48** | 2 | 1.79 | 1.12 | 0.13-4.03 |
| Gum, floor of mouth, other mouth | C03-C06 | 13 | 5.78 | **2.25** | **1.20-3.85** | 21 | 13.83 | 1.52 | 0.94-2.32 | 11 | 6.61 | 1.66 | 0.83-2.98 | 7 | 2.26 | **3.10** | **1.24-6.38** |
| Parotid gland, other salivary glands | C07-C08 | 12 | 1.72 | **6.98** | **3.60-12.19** | 14 | 4.15 | **3.37** | **1.84-5.66** | 8 | 2.03 | **3.94** | **1.70-7.77** | 2 | 0.7 | 2.86 | 0.32-10.32 |
| Pharynx and other oral cavity | C09-C14 | 24 | 9.3 | **2.58** | **1.65-3.84** | 23 | 22.41 | 1.03 | 0.65-1.54 | 15 | 10.91 | 1.37 | 0.77-2.27 | 4 | 3.67 | 1.09 | 0.29-2.79 |
| Oesophagus | C15 | 19 | 12.52 | 1.52 | 0.91-2.37 | 32 | 30.03 | 1.07 | 0.73-1.50 | 22 | 14.52 | 1.52 | 0.95-2.29 | 8 | 5.06 | 1.58 | 0.68-3.12 |
| Stomach | C16 | 130 | 37.73 | **3.45** | **2.88-4.09** | 127 | 88.86 | **1.43** | **1.19-1.70** | 53 | 42.94 | 1.23 | 0.92-1.61 | 24 | 14.04 | **1.71** | **1.09-2.54** |
| Colon, rectum, and anus | C18-C21 | 280 | 146.28 | **1.91** | **1.70-2.15** | 381 | 346.62 | 1.10 | 0.99-1.22 | 207 | 167.2 | **1.24** | **1.08-1.42** | 51 | 56.46 | 0.90 | 0.67-1.19 |
| Liver | C22 | 36 | 13.29 | **2.71** | **1.90-3.75** | 49 | 33.03 | **1.48** | **1.10-1.96** | 21 | 17.27 | 1.22 | 0.75-1.86 | 13 | 6.16 | **2.11** | **1.12-3.61** |
| Pancreas | C25 | 45 | 25.16 | **1.79** | **1.30-2.39** | 84 | 62.45 | **1.35** | **1.07-1.67** | 37 | 32.58 | 1.14 | 0.80-1.57 | 20 | 11.51 | **1.74** | **1.06-2.68** |
| Larynx | C32 | 14 | 8.31 | 1.68 | 0.92-2.83 | 15 | 19.36 | 0.77 | 0.43-1.28 | 11 | 8.91 | 1.23 | 0.62-2.21 | 0 | 2.9 | 0.00 | 0.00-1.26 |
| Lung | C33-C34 | 333 | 105.87 | **3.15** | **2.82-3.50** | 359 | 254.14 | **1.41** | **1.27-1.57** | 211 | 125.34 | **1.68** | **1.46-1.93** | 50 | 44.08 | 1.13 | 0.84-1.50 |
| Melanoma of skin | C43 | 90 | 27.65 | **3.25** | **2.62-4.00** | 118 | 67.85 | **1.74** | **1.44-2.08** | 48 | 32.54 | **1.48** | **1.09-1.96** | 18 | 10.55 | **1.71** | **1.01-2.70** |
| Breast | C50 | 176 | 104.21 | **1.69** | **1.45-1.96** | 263 | 252.42 | 1.04 | 0.92-1.18 | 130 | 123.39 | 1.05 | 0.88-1.25 | 35 | 41.56 | 0.84 | 0.59-1.17 |
| Cervix uteri | C53 | 15 | 6.05 | **2.48** | **1.39-4.09** | 12 | 14.32 | 0.84 | 0.43-1.46 | 3 | 6.88 | 0.44 | 0.09-1.27 | 1 | 2.23 | 0.45 | 0.01-2.50 |
| Corpus uteri | C54-C55 | 37 | 21.33 | **1.73** | **1.22-2.39** | 45 | 51.43 | 0.87 | 0.64-1.17 | 27 | 25.23 | 1.07 | 0.71-1.56 | 8 | 7.9 | 1.01 | 0.44-2.00 |
| Ovaries | C56 | 25 | 13.18 | **1.90** | **1.23-2.80** | 29 | 31.54 | 0.92 | 0.62-1.32 | 18 | 15.29 | 1.18 | 0.70-1.86 | 3 | 4.95 | 0.61 | 0.12-1.77 |
| Prostate | C61 | 228 | 157.18 | **1.45** | **1.27-1.65** | 419 | 373.04 | **1.12** | **1.02-1.24** | 170 | 174.88 | 0.97 | 0.83-1.13 | 47 | 56.14 | 0.84 | 0.62-1.11 |
| Testis | C62 | 22 | 2.36 | **9.32** | **5.84-14.11** | 8 | 5.67 | 1.41 | 0.61-2.78 | 2 | 2.66 | 0.75 | 0.08-2.71 | 0 | 0.88 | 0.00 | 0.00-4.17 |
| Kidney | C64 | 204 | 30.72 | **6.64** | **5.76-7.62** | 88 | 74.01 | 1.19 | 0.95-1.46 | 39 | 35.99 | 1.08 | 0.77-1.48 | 9 | 11.47 | 0.78 | 0.36-1.49 |
| Urinary bladder | C67 | 55 | 40.33 | **1.36** | **1.03-1.78** | 102 | 94.36 | 1.08 | 0.88-1.31 | 54 | 46.06 | 1.17 | 0.88-1.53 | 16 | 16.61 | 0.96 | 0.55-1.56 |
| Central nervous system | C70-C72 | 30 | 9.8 | **3.06** | **2.06-4.37** | 25 | 23.94 | 1.04 | 0.68-1.54 | 15 | 12.02 | 1.25 | 0.70-2.06 | 6 | 4.03 | 1.49 | 0.54-3.24 |
| Thyroid | C73 | 35 | 6.65 | **5.26** | **3.67-7.32** | 22 | 16.14 | 1.36 | 0.85-2.06 | 12 | 7.49 | 1.60 | 0.83-2.80 | 2 | 2.33 | 0.86 | 0.10-3.10 |
| **All haematological malignancies** | **C81-C96** | 341 | 61.79 | **5.52** | **4.95-6.14** | 256 | 148.21 | **1.73** | **1.52-1.95** | 100 | 73.56 | **1.36** | **1.11-1.65** | 19 | 24.8 | 0.77 | 0.46-1.20 |
| Hodgkin lymphoma | C81 | 77 | 2.05 | **37.56** | **29.64-46.95** | 42 | 4.9 | **8.57** | **6.18-11.59** | 14 | 2.36 | **5.93** | **3.24-9.95** | 4 | 0.79 | **5.06** | **1.36-12.96** |
| Non-Hodgkin lymphoma | C82-C85 | 91 | 26.46 | **3.44** | **2.77-4.22** | 58 | 62.64 | 0.93 | 0.70-1.20 | 23 | 30.94 | 0.74 | 0.47-1.12 | 2 | 10.5 | **0.19** | **0.02-0.69** |
| Multiple myeloma | C90 | 44 | 11.32 | **3.89** | **2.82-5.22** | 24 | 27.54 | 0.87 | 0.56-1.30 | 10 | 13.77 | 0.73 | 0.35-1.34 | 1 | 4.66 | 0.21 | 0.00-1.19 |
| Lymphoid leukaemia | C91 | 48 | 10.48 | **4.58** | **3.38-6.07** | 15 | 25.39 | **0.59** | **0.33-0.97** | 9 | 12.6 | 0.71 | 0.33-1.36 | 0 | 4.09 | **0.00** | **0.00-0.90** |
| Acute lymphoblastic | C91.0 | 10 | 0.58 | **17.24** | **8.25-31.71** | 7 | 1.43 | **4.90** | **1.96-10.09** | 0 | 0.7 | 0.00 | 0.00-5.24 | 0 | 0.24 | 0.00 | 0.00-15.28 |
| Chronic lymphocytic | C91.1 | 25 | 9.1 | **2.75** | **1.78-4.06** | 3 | 22.05 | **0.14** | **0.03-0.40** | 7 | 10.94 | 0.64 | 0.26-1.32 | 0 | 3.57 | 0.00 | 0.00-1.03 |
| Myeloid leukaemia | C92 | 43 | 7.63 | **5.64** | **4.08-7.59** | 88 | 18.39 | **4.79** | **3.84-5.90** | 34 | 9.27 | **3.67** | **2.54-5.13** | 6 | 3.19 | 1.88 | 0.69-4.09 |
| Acute myeloblastic | C92.0 | 31 | 4.36 | **7.11** | **4.83-10.09** | 63 | 10.6 | **5.94** | **4.57-7.60** | 24 | 5.41 | **4.44** | **2.84-6.60** | 6 | 1.88 | **3.19** | **1.17-6.95** |
| Chronic myeloid | C92.1 | 6 | 1.72 | **3.49** | **1.27-7.59** | 5 | 3.98 | 1.26 | 0.40-2.93 | 2 | 1.9 | 1.05 | 0.12-3.80 | 0 | 0.6 | 0.00 | 0.00-6.11 |
| Monocytic leukaemia | C93 | 6 | 1.06 | **5.66** | **2.07-12.32** | 10 | 2.65 | **3.77** | **1.81-6.94** | 2 | 1.36 | 1.47 | 0.17-5.31 | 4 | 0.49 | **8.16** | **2.20-20.90** |
| **All sites**** | **C00-C97** | 2410 | 914.15 | **2.64** | **2.53-2.74** | 2684 | 2188.17 | **1.23** | **1.18-1.27** | 1326 | 1063.42 | **1.25** | **1.18-1.32** | 372 | 358.21 | 1.04 | 0.94-1.15 |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); SPM: subsequent primary malignancies; ICD-10: the WHO International Classification of Diseases (10th revision); NHL: non-Hodgkin lymphoma.
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 36. Overall and site-specific SIRs of SPM following NHL (all intervals, excluding initial 2 months, and excluding first year)

| | | Overall | | | | Overall (excl. <2 months) | | | | Overall (excl. <1 year) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | **C00-C75** | 5895 | 4127.43 | **1.43** | **1.39-1.47** | 4761 | 3961.15 | **1.20** | **1.17-1.24** | 3919 | 3293 | **1.19** | **1.15-1.23** |
| Lip, oral cavity, and pharynx | C00-C14 | 206 | 114.17 | **1.80** | **1.57-2.07** | 168 | 109.66 | **1.53** | **1.31-1.78** | 140 | 91.17 | **1.54** | **1.29-1.81** |
| Lip | C00 | 13 | 5.8 | **2.24** | **1.19-3.83** | 13 | 5.57 | **2.33** | **1.24-3.99** | 9 | 4.66 | 1.93 | 0.88-3.67 |
| Tongue | C01-C02 | 35 | 22.27 | **1.57** | **1.09-2.19** | 28 | 21.39 | 1.31 | 0.87-1.89 | 24 | 17.8 | 1.35 | 0.86-2.01 |
| Gum, floor of mouth, other mouth | C03-C06 | 52 | 28.47 | **1.83** | **1.36-2.40** | 47 | 27.33 | **1.72** | **1.26-2.29** | 39 | 22.7 | **1.72** | **1.22-2.35** |
| Parotid gland, other salivary glands | C07-C08 | 36 | 8.6 | **4.19** | **2.93-5.80** | 28 | 8.25 | **3.39** | **2.25-4.91** | 24 | 6.88 | **3.49** | **2.23-5.19** |
| Pharynx and other oral cavity | C09-C14 | 66 | 46.28 | **1.43** | **1.10-1.81** | 50 | 44.47 | 1.12 | 0.83-1.48 | 42 | 36.99 | 1.14 | 0.82-1.53 |
| Oesophagus | C15 | 81 | 62.13 | **1.30** | **1.04-1.62** | 73 | 59.65 | 1.22 | 0.96-1.54 | 62 | 49.61 | 1.25 | 0.96-1.60 |
| Stomach | C16 | 334 | 183.57 | **1.82** | **1.63-2.03** | 256 | 175.93 | **1.46** | **1.28-1.64** | 204 | 145.84 | **1.40** | **1.21-1.60** |
| Colon, rectum, and anus | C18-C21 | 919 | 716.55 | **1.28** | **1.20-1.37** | 744 | 687.09 | **1.08** | **1.01-1.16** | 639 | 570.28 | **1.12** | **1.04-1.21** |
| Liver | C22 | 119 | 69.76 | **1.71** | **1.41-2.04** | 104 | 67.13 | **1.55** | **1.27-1.88** | 83 | 56.46 | **1.47** | **1.17-1.82** |
| Pancreas | C25 | 186 | 131.71 | **1.41** | **1.22-1.63** | 163 | 126.68 | **1.29** | **1.10-1.50** | 141 | 106.54 | **1.32** | **1.11-1.56** |
| Larynx | C32 | 40 | 39.48 | 1.01 | 0.72-1.38 | 33 | 37.84 | 0.87 | 0.60-1.22 | 26 | 31.17 | 0.83 | 0.54-1.22 |
| Lung | C33-C34 | 949 | 529.43 | **1.79** | **1.68-1.91** | 783 | 508.37 | **1.54** | **1.43-1.65** | 620 | 423.56 | **1.46** | **1.35-1.58** |
| Melanoma of skin | C43 | 274 | 138.6 | **1.98** | **1.75-2.23** | 231 | 133.15 | **1.73** | **1.52-1.97** | 184 | 110.94 | **1.66** | **1.43-1.92** |
| Breast | C50 | 604 | 521.58 | **1.16** | **1.07-1.25** | 484 | 501.05 | 0.97 | 0.88-1.06 | 428 | 417.37 | 1.03 | 0.93-1.13 |
| Cervix uteri | C53 | 31 | 29.48 | 1.05 | 0.71-1.49 | 22 | 28.29 | 0.78 | 0.49-1.18 | 16 | 23.43 | 0.68 | 0.39-1.11 |
| Corpus uteri | C54-C55 | 117 | 105.89 | 1.10 | 0.91-1.32 | 94 | 101.66 | 0.92 | 0.75-1.13 | 80 | 84.56 | 0.95 | 0.75-1.18 |
| Ovaries | C56 | 75 | 64.96 | 1.15 | 0.91-1.45 | 59 | 62.34 | 0.95 | 0.72-1.22 | 50 | 51.78 | 0.97 | 0.72-1.27 |
| Prostate | C61 | 864 | 761.23 | **1.14** | **1.06-1.21** | 737 | 729.96 | 1.01 | 0.94-1.09 | 636 | 604.06 | 1.05 | 0.97-1.14 |
| Testis | C62 | 32 | 11.57 | **2.77** | **1.89-3.90** | 14 | 11.12 | 1.26 | 0.69-2.11 | 10 | 9.21 | 1.09 | 0.52-2.00 |
| Kidney | C64 | 340 | 152.19 | **2.23** | **2.00-2.48** | 218 | 146.09 | **1.49** | **1.30-1.70** | 136 | 121.47 | 1.12 | 0.94-1.32 |
| Urinary bladder | C67 | 227 | 197.36 | **1.15** | **1.01-1.31** | 195 | 189.17 | 1.03 | 0.89-1.19 | 172 | 157.03 | 1.10 | 0.94-1.27 |
| Central nervous system | C70-C72 | 76 | 49.8 | **1.53** | **1.20-1.91** | 61 | 47.88 | 1.27 | 0.97-1.64 | 46 | 39.99 | 1.15 | 0.84-1.53 |
| Thyroid | C73 | 71 | 32.62 | **2.18** | **1.70-2.75** | 54 | 31.33 | **1.72** | **1.29-2.25** | 36 | 25.96 | 1.39 | 0.97-1.92 |
| **All haematological malignancies** | **C81-C96** | 716 | 308.36 | **2.32** | **2.15-2.50** | 477 | 295.94 | **1.61** | **1.47-1.76** | 375 | 246.57 | **1.52** | **1.37-1.68** |
| Hodgkin lymphoma | C81 | 137 | 10.09 | **13.58** | **11.40-16.05** | 73 | 9.69 | **7.53** | **5.90-9.47** | 60 | 8.05 | **7.45** | **5.69-9.59** |
| Non-Hodgkin lymphoma | C82-C85 | 174 | 130.56 | **1.33** | **1.14-1.55** | 111 | 125.2 | 0.89 | 0.73-1.07 | 83 | 104.08 | **0.80** | **0.64-0.99** |
| Multiple myeloma | C90 | 79 | 57.27 | **1.38** | **1.09-1.72** | 47 | 55.01 | 0.85 | 0.63-1.14 | 35 | 45.97 | 0.76 | 0.53-1.06 |
| Lymphoid leukaemia | C91 | 72 | 52.56 | **1.37** | **1.07-1.73** | 39 | 50.47 | 0.77 | 0.55-1.06 | 24 | 42.08 | **0.57** | **0.37-0.85** |
| Acute lymphoblastic | C91.0 | 17 | 2.94 | **5.78** | **3.37-9.26** | 11 | 2.83 | **3.89** | **1.94-6.96** | 7 | 2.37 | **2.95** | **1.18-6.09** |
| Chronic lymphocytic | C91.1 | 35 | 45.65 | 0.77 | 0.53-1.07 | 19 | 43.83 | **0.43** | **0.26-0.68** | 10 | 36.56 | **0.27** | **0.13-0.50** |
| Myeloid leukaemia | C92 | 171 | 38.48 | **4.44** | **3.80-5.16** | 149 | 36.95 | **4.03** | **3.41-4.73** | 128 | 30.85 | **4.15** | **3.46-4.93** |
| Acute myeloblastic | C92.0 | 124 | 22.25 | **5.57** | **4.64-6.64** | 111 | 21.38 | **5.19** | **4.27-6.25** | 93 | 17.89 | **5.20** | **4.20-6.37** |
| Chronic myeloid | C92.1 | 13 | 8.2 | 1.59 | 0.84-2.71 | 7 | 7.85 | 0.89 | 0.36-1.84 | 7 | 6.48 | 1.08 | 0.43-2.23 |
| Monocytic leukaemia | C93 | 22 | 5.56 | **3.96** | **2.48-5.99** | 20 | 5.35 | **3.74** | **2.28-5.77** | 16 | 4.5 | **3.56** | **2.03-5.77** |
| **All sites**** | **C00-C97** | 6788 | 4523.95 | **1.50** | **1.46-1.54** | 5367 | 4341.61 | **1.24** | **1.20-1.27** | 4382 | 3609.8 | **1.21** | **1.18-1.25** |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); SPM: subsequent primary malignancies; ICD-10: the WHO International Classification of Diseases (10th revision); NHL: non-Hodgkin lymphoma.

*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)

Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 37. Observed number and SIRs of SPM following NHL by follow-up time for survivors aged <60 or ≥60 years, for both sexes

| Under 60 years | ≤1 year | | | | >1-≤5 years | | | | >5-≤10 years | | | | >10 years | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | 341 | 96.48 | **3.53** | **3.17-3.93** | 448 | 329.5 | **1.36** | **1.24-1.49** | 387 | 264.37 | **1.46** | **1.32-1.62** | 170 | 149.07 | 1.14 | 0.98-1.33 |
| Lip/oral cavity | 18 | 5.76 | **3.13** | **1.85-4.94** | 22 | 18.03 | 1.22 | 0.76-1.85 | 26 | 12.51 | **2.08** | **1.36-3.05** | 8 | 5.9 | 1.36 | 0.58-2.67 |
| Stomach | 31 | 3.15 | **9.84** | **6.69-13.97** | 17 | 10.64 | 1.6 | 0.93-2.56 | 10 | 8.47 | 1.18 | 0.57-2.17 | 7 | 4.76 | 1.47 | 0.59-3.03 |
| Colon/rectum | 26 | 11.71 | **2.22** | **1.45-3.25** | 59 | 41.43 | **1.42** | **1.08-1.84** | 50 | 34.54 | **1.45** | **1.07-1.91** | 24 | 20.36 | 1.18 | 0.76-1.75 |
| Liver | 2 | 1.23 | 1.63 | 0.18-5.87 | 8 | 4.59 | 1.74 | 0.75-3.43 | 5 | 4.16 | 1.2 | 0.39-2.80 | 9 | 2.6 | **3.46** | **1.58-6.57** |
| Pancreas | 4 | 2.22 | 1.8 | 0.48-4.61 | 9 | 8.19 | 1.1 | 0.50-2.09 | 8 | 7.35 | 1.09 | 0.47-2.14 | 12 | 4.6 | **2.61** | **1.35-4.56** |
| Lung | 55 | 12 | **4.58** | **3.45-5.97** | 82 | 42.15 | **1.95** | **1.55-2.41** | 79 | 35.2 | **2.24** | **1.78-2.80** | 23 | 20.93 | 1.1 | 0.70-1.65 |
| Melanoma of skin | 13 | 4.96 | **2.62** | **1.39-4.48** | 32 | 15.4 | **2.08** | **1.42-2.93** | 14 | 10.51 | 1.33 | 0.73-2.24 | 5 | 5.28 | 0.95 | 0.31-2.21 |
| Breast | 31 | 19.38 | **1.6** | **1.09-2.27** | 60 | 62.41 | 0.96 | 0.73-1.24 | 56 | 45.24 | 1.24 | 0.93-1.61 | 25 | 23.23 | 1.08 | 0.70-1.59 |
| Prostate | 12 | 9.86 | 1.22 | 0.63-2.13 | 61 | 42.25 | **1.44** | **1.10-1.85** | 50 | 43.23 | 1.16 | 0.86-1.52 | 24 | 27.46 | 0.87 | 0.56-1.30 |
| Testis | 13 | 1.87 | **6.95** | **3.70-11.89** | 4 | 4.64 | 0.86 | 0.23-2.21 | 1 | 2.3 | 0.43 | 0.01-2.42 | 0 | 0.8 | 0 | 0.00-4.59 |
| Kidney | 39 | 3.9 | **10** | **7.11-13.67** | 24 | 13.14 | **1.83** | **1.17-2.72** | 19 | 10.29 | **1.85** | **1.11-2.88** | 4 | 5.39 | 0.74 | 0.20-1.90 |
| Central nervous system | 8 | 1.88 | **4.26** | **1.83-8.39** | 6 | 5.86 | 1.02 | 0.37-2.23 | 2 | 4.29 | 0.47 | 0.05-1.68 | 4 | 2.19 | 1.83 | 0.49-4.68 |
| Thyroid | 13 | 2.02 | **6.44** | **3.42-11.01** | 11 | 5.98 | 1.84 | 0.92-3.29 | 5 | 3.66 | 1.37 | 0.44-3.19 | 1 | 1.55 | 0.65 | 0.01-3.59 |
| **All haematological malignancies** | 129 | 7.41 | **17.41** | **14.53-20.69** | 103 | 23.95 | **4.3** | **3.51-5.22** | 40 | 18.5 | **2.16** | **1.54-2.94** | 11 | 10.39 | 1.06 | 0.53-1.89 |
| Hodgkin lymphoma | 42 | 0.67 | **62.69** | **45.17-84.74** | 25 | 1.86 | **13.44** | **8.70-19.84** | 8 | 1.11 | **7.21** | **3.10-14.20** | 2 | 0.49 | 4.08 | 0.46-14.74 |
| Multiple myeloma | 6 | 1.03 | **5.83** | **2.13-12.68** | 6 | 3.66 | 1.64 | 0.60-3.57 | 3 | 3.16 | 0.95 | 0.19-2.77 | 0 | 1.9 | 0 | 0.00-1.93 |
| Lymphoid leukaemia | 16 | 1.16 | **13.79** | **7.88-22.40** | 5 | 3.95 | 1.27 | 0.41-2.95 | 4 | 3.13 | 1.28 | 0.34-3.27 | 0 | 1.7 | 0 | 0.00-2.16 |
| Acute lymphoblastic | 6 | 0.18 | **33.33** | **12.17-72.55** | 4 | 0.48 | **8.33** | **2.24-21.34** | 0 | 0.29 | 0 | 0.00-12.65 | 0 | 0.13 | 0 | 0.00-28.22 |
| Chronic lymphocytic | 6 | 0.84 | **7.14** | **2.61-15.55** | 1 | 3.06 | 0.33 | 0.00-1.82 | 4 | 2.55 | 1.57 | 0.42-4.02 | 0 | 1.44 | 0 | 0.00-2.55 |
| Myeloid leukaemia | 14 | 0.94 | **14.89** | **8.14-24.99** | 45 | 3 | **15** | **10.94-20.07** | 16 | 2.26 | **7.08** | **4.04-11.50** | 4 | 1.3 | 3.08 | 0.83-7.88 |
| Acute myeloblastic | 9 | 0.51 | **17.65** | **8.05-33.50** | 30 | 1.61 | **18.63** | **12.57-26.60** | 12 | 1.27 | **9.45** | **4.88-16.51** | 4 | 0.74 | **5.41** | **1.45-13.84** |
| Chronic myeloid | 3 | 0.3 | **10** | **2.01-29.22** | 2 | 0.85 | 2.35 | 0.26-8.50 | 1 | 0.54 | 1.85 | 0.02-10.30 | 0 | 0.25 | 0 | 0.00-14.67 |
| **All sites**** | 491 | 105.62 | **4.65** | **4.25-5.08** | 565 | 359.19 | **1.57** | **1.45-1.71** | 433 | 287.3 | **1.51** | **1.37-1.66** | 186 | 162.05 | 1.15 | 0.99-1.33 |
| **60 years or older** | **≤1 year** | | | | **>1-≤5 years** | | | | **>5-≤10 years** | | | | **>10 years** | | | |
| **Subsequent cancer** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | 1639 | 737.96 | **2.22** | **2.11-2.33** | 1928 | 1668.21 | **1.16** | **1.10-1.21** | 814 | 704.89 | **1.15** | **1.08-1.24** | 172 | 176.96 | 0.97 | 0.83-1.13 |
| Lip/oral cavity | 48 | 17.21 | **2.79** | **2.06-3.70** | 50 | 37.28 | 1.34 | 1.00-1.77 | 27 | 14.28 | **1.89** | **1.25-2.75** | 7 | 3.18 | 2.2 | 0.88-4.54 |
| Stomach | 99 | 34.59 | **2.86** | **2.33-3.48** | 110 | 78.2 | **1.41** | **1.16-1.70** | 43 | 34.49 | 1.25 | 0.90-1.68 | 17 | 9.27 | **1.83** | **1.07-2.94** |
| Colon/rectum | 254 | 134.58 | **1.89** | **1.66-2.13** | 322 | 305.18 | 1.06 | 0.94-1.18 | 157 | 132.66 | **1.18** | **1.01-1.38** | 28 | 36.09 | 0.78 | 0.52-1.12 |
| Liver | 34 | 12.06 | **2.82** | **1.95-3.94** | 41 | 28.44 | **1.44** | **1.03-1.96** | 16 | 13.11 | 1.22 | 0.70-1.98 | 4 | 3.56 | 1.12 | 0.30-2.88 |
| Pancreas | 41 | 22.94 | **1.79** | **1.28-2.42** | 75 | 54.27 | **1.38** | **1.09-1.73** | 29 | 25.23 | 1.15 | 0.77-1.65 | 8 | 6.9 | 1.16 | 0.50-2.28 |
| Lung | 278 | 93.85 | **2.96** | **2.62-3.33** | 277 | 211.99 | **1.31** | **1.16-1.47** | 132 | 90.14 | **1.46** | **1.23-1.74** | 26 | 23.15 | 1.12 | 0.73-1.65 |
| Melanoma of skin | 77 | 22.69 | **3.39** | **2.68-4.24** | 86 | 52.45 | **1.64** | **1.31-2.02** | 34 | 22.03 | **1.54** | **1.07-2.16** | 13 | 5.28 | **2.46** | **1.31-4.21** |
| Breast | 145 | 84.8 | **1.71** | **1.44-2.01** | 203 | 190.01 | 1.07 | 0.93-1.23 | 74 | 78.15 | 0.95 | 0.74-1.19 | 10 | 18.33 | 0.55 | 0.26-1.00 |
| Prostate | 216 | 147.32 | **1.47** | **1.28-1.68** | 358 | 330.8 | 1.08 | 0.97-1.20 | 120 | 131.64 | 0.91 | 0.76-1.09 | 23 | 28.67 | 0.8 | 0.51-1.20 |
| Testis | 9 | 0.5 | **18** | **8.21-34.17** | 4 | 1.03 | **3.88** | **1.04-9.94** | 1 | 0.37 | 2.7 | 0.04-15.04 | 0 | 0.08 | 0 | 0.00-45.85 |
| Kidney | 165 | 26.83 | **6.15** | **5.25-7.16** | 64 | 60.87 | 1.05 | 0.81-1.34 | 20 | 25.7 | 0.78 | 0.48-1.20 | 5 | 6.09 | 0.82 | 0.26-1.92 |
| Central nervous system | 22 | 7.93 | **2.77** | **1.74-4.20** | 19 | 18.08 | 1.05 | 0.63-1.64 | 13 | 7.73 | 1.68 | 0.89-2.88 | 2 | 1.84 | 1.09 | 0.12-3.92 |
| Thyroid | 22 | 4.64 | **4.74** | **2.97-7.18** | 11 | 10.16 | 1.08 | 0.54-1.94 | 7 | 3.83 | 1.83 | 0.73-3.77 | 1 | 0.78 | 1.28 | 0.02-7.13 |
| **All haematological malignancies** | 212 | 54.38 | **3.9** | **3.39-4.46** | 153 | 124.25 | **1.23** | **1.04-1.44** | 60 | 55.06 | 1.09 | 0.83-1.40 | 8 | 14.41 | 0.56 | 0.24-1.09 |
| Hodgkin lymphoma | 35 | 1.38 | **25.36** | **17.66-35.27** | 17 | 3.04 | **5.59** | **3.26-8.95** | 6 | 1.24 | **4.84** | **1.77-10.53** | 2 | 0.29 | 6.9 | 0.77-24.90 |
| Multiple myeloma | 38 | 10.29 | **3.69** | **2.61-5.07** | 18 | 23.86 | 0.75 | 0.45-1.19 | 7 | 10.61 | 0.66 | 0.26-1.36 | 1 | 2.76 | 0.36 | 0.00-2.02 |
| Lymphoid leukaemia | 32 | 9.32 | **3.43** | **2.35-4.85** | 10 | 21.43 | **0.47** | **0.22-0.86** | 5 | 9.47 | 0.53 | 0.17-1.23 | 0 | 2.4 | 0 | 0.00-1.53 |
| Acute lymphoblastic | 4 | 0.41 | **9.76** | **2.62-24.98** | 3 | 0.95 | 3.16 | 0.63-9.23 | 0 | 0.41 | 0 | 0.00-8.95 | 0 | 0.11 | 0 | 0.00-33.35 |
| Chronic lymphocytic | 19 | 8.25 | **2.3** | **1.39-3.60** | 2 | 18.99 | **0.11** | **0.01-0.38** | 3 | 8.39 | 0.36 | 0.07-1.04 | 0 | 2.12 | 0 | 0.00-1.73 |
| Myeloid leukaemia | 29 | 6.69 | **4.33** | **2.90-6.23** | 43 | 15.39 | **2.79** | **2.02-3.76** | 18 | 7.01 | **2.57** | **1.52-4.06** | 2 | 1.89 | 1.06 | 0.12-3.82 |
| Acute myeloblastic | 22 | 3.87 | **5.68** | **3.56-8.61** | 33 | 8.99 | **3.67** | **2.53-5.16** | 12 | 4.14 | **2.9** | **1.50-5.06** | 2 | 1.13 | 1.77 | 0.20-6.39 |
| Chronic myeloid | 3 | 1.43 | 2.1 | 0.42-6.13 | 3 | 3.14 | 0.96 | 0.19-2.79 | 1 | 1.35 | 0.74 | 0.01-4.12 | 0 | 0.35 | 0 | 0.00-10.48 |
| **All sites**** | 1919 | 808.52 | **2.37** | **2.27-2.48** | 2119 | 1828.99 | **1.16** | **1.11-1.21** | 893 | 776.12 | **1.15** | **1.08-1.23** | 186 | 196.16 | 0.95 | 0.82-1.09 |

## Table 38. Observed number, SIRs and EARs of SPM following NHL by calendar period, for both sexes

| | | 1990–2000 NHL patients=17152 PYRs=41149.02 | | | | | 2001–2011 NHL patients=33330 PYRs=192047.32 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **EAR** | **O** | **E** | **SIR** | **95% CI** | **EAR** |
| **All solid malignancies*** | **C00-C75** | 618 | 343.2 | **1.80** | **1.66-1.95** | 66.78 | 1774 | 1220.93 | **1.45** | **1.39-1.52** | 28.80 |
| Lip, oral cavity, and pharynx | C00-C14 | 25 | 10.14 | **2.47** | **1.60-3.64** | 3.61 | 55 | 34.17 | **1.61** | **1.21-2.10** | 1.08 |
| Oesophagus | C15 | 7 | 5 | 1.40 | 0.56-2.88 | 0.49 | 20 | 18.23 | 1.10 | 0.67-1.69 | 0.09 |
| Stomach | C16 | 47 | 18.58 | **2.53** | **1.86-3.36** | 6.91 | 99 | 53.78 | **1.84** | **1.50-2.24** | 2.35 |
| Colon, rectum, and anus | C18-C21 | 108 | 61.13 | **1.77** | **1.45-2.13** | 11.39 | 248 | 205.96 | **1.20** | **1.06-1.36** | 2.19 |
| Liver | C22 | 3 | 5.11 | 0.59 | 0.12-1.72 | -0.51 | 48 | 23.86 | **2.01** | **1.48-2.67** | 1.26 |
| Pancreas | C25 | 6 | 10.23 | 0.59 | 0.21-1.28 | -1.03 | 66 | 42.61 | **1.55** | **1.20-1.97** | 1.22 |
| Larynx | C32 | 10 | 4.27 | **2.34** | **1.12-4.31** | 1.39 | 9 | 11.28 | 0.80 | 0.36-1.51 | -0.12 |
| Lung | C33-C34 | 93 | 51.59 | **1.80** | **1.45-2.21** | 10.06 | 315 | 165.24 | **1.91** | **1.70-2.13** | 7.80 |
| Melanoma of skin | C43 | 14 | 8 | 1.75 | 0.96-2.94 | 1.46 | 66 | 37.3 | **1.77** | **1.37-2.25** | 1.49 |
| Breast | C50 | 65 | 43.08 | **1.51** | **1.16-1.92** | 5.33 | 176 | 149.68 | **1.18** | **1.01-1.36** | 1.37 |
| Cervix uteri | C53 | 7 | 4.02 | 1.74 | 0.70-3.59 | 0.72 | 8 | 8.77 | 0.91 | 0.39-1.80 | -0.04 |
| Corpus uteri | C54-C55 | 12 | 10.2 | 1.18 | 0.61-2.06 | 0.44 | 41 | 32.25 | 1.27 | 0.91-1.72 | 0.46 |
| Ovaries | C56 | 12 | 6.94 | 1.73 | 0.89-3.02 | 1.23 | 22 | 18.42 | 1.19 | 0.75-1.81 | 0.19 |
| Prostate | C61 | 65 | 45.81 | **1.42** | **1.10-1.81** | 4.66 | 243 | 216.16 | 1.12 | 0.99-1.27 | 1.40 |
| Testis | C62 | 2 | 1.06 | 1.89 | 0.21-6.81 | 0.23 | 11 | 3.32 | **3.31** | **1.65-5.93** | 0.40 |
| Kidney | C64 | 45 | 13.73 | **3.28** | **2.39-4.39** | 7.60 | 101 | 49.82 | **2.03** | **1.65-2.46** | 2.66 |
| Urinary bladder | C67 | 23 | 19.23 | 1.20 | 0.76-1.79 | 0.92 | 70 | 60.3 | 1.16 | 0.90-1.47 | 0.51 |
| Central nervous system | C70-C72 | 13 | 4.33 | **3.00** | **1.60-5.13** | 2.11 | 28 | 15.97 | **1.75** | **1.16-2.53** | 0.63 |
| Thyroid | C73 | 16 | 2.61 | **6.13** | **3.50-9.96** | 3.25 | 28 | 9.63 | **2.91** | **1.93-4.20** | 0.96 |
| **All haematological malignancies** | **C81-C96** | 50 | 28.07 | **1.78** | **1.32-2.35** | 5.33 | 176 | 93.42 | **1.88** | **1.62-2.18** | 4.30 |
| Hodgkin lymphoma | C81 | 6 | 1.01 | **5.94** | **2.17-12.93** | 1.21 | 44 | 2.91 | **15.12** | **10.99-20.30** | 2.14 |
| Non-Hodgkin lymphoma | C82-C85 | 16 | 11.54 | 1.39 | 0.79-2.25 | 1.08 | 41 | 38.88 | 1.05 | 0.76-1.43 | 0.11 |
| Multiple myeloma | C90 | 1 | 5.28 | 0.19 | 0.00-1.05 | -1.04 | 8 | 17.72 | **0.45** | **0.19-0.89** | -0.51 |
| Lymphoid leukaemia | C91 | 3 | 4.94 | 0.61 | 0.12-1.77 | -0.47 | 11 | 16.51 | 0.67 | 0.33-1.19 | -0.29 |
| Acute lymphoblastic | C91.0 | 0 | 0.29 | 0.00 | 0.00-12.65 | -0.07 | 1 | 0.91 | 1.10 | 0.01-6.11 | 0.00 |
| Chronic lymphocytic | C91.1 | 3 | 4.31 | 0.70 | 0.14-2.03 | -0.32 | 7 | 14.34 | 0.49 | 0.20-1.01 | -0.38 |
| Myeloid leukaemia | C92 | 20 | 3.9 | **5.13** | **3.13-7.92** | 3.91 | 51 | 11.91 | **4.28** | **3.19-5.63** | 2.04 |
| Acute myeloblastic | C92.0 | 16 | 2.08 | **7.69** | **4.39-12.49** | 3.38 | 28 | 7.08 | **3.95** | **2.63-5.72** | 1.09 |
| Chronic myeloid | C92.1 | 3 | 1.11 | 2.70 | 0.54-7.90 | 0.46 | 5 | 2.27 | 2.20 | 0.71-5.14 | 0.14 |
| Monocytic leukaemia | C93 | 0 | 0.33 | 0.00 | 0.00-11.12 | -0.08 | 10 | 1.65 | **6.06** | **2.90-11.15** | 0.43 |
| **All sites**** | **C00-C97** | 693 | 380.08 | **1.82** | **1.69-1.96** | 76.05 | 2010 | 1341.43 | **1.50** | **1.43-1.57** | 34.81 |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); EAR: excess absolute risk per 10,000 person-years; PYRs: person-years of observation; NHL: non-Hodgkin lymphoma; SPM: subsequent primary malignancies; ICD-10: the WHO International Classification of Diseases (10th revision).
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 39. Risk of NHL subsequent to other primary malignancies by follow-up time, for both sexes

| | ≤1 year | | | >1-≤5 years | | | >5-≤10 years | | | >10 years | | | Overall | | | Overall (excl. <2 months) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Site of first primary cancer** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** |
| **All Solid malignancies*** | 2175 | **2.59** | **2.49-2.71** | 2120 | **1.07** | **1.02-1.12** | 1104 | **1.10** | **1.04-1.17** | 322 | 0.98 | 0.87-1.09 | 5721 | **1.38** | **1.34-1.41** | 4349 | **1.09** | **1.06-1.12** |
| Lip/oral cavity | 92 | **4.11** | **3.31-5.04** | 63 | **1.31** | **1.01-1.68** | 23 | 0.97 | 0.61-1.45 | 8 | 0.93 | 0.40-1.84 | 186 | **1.81** | **1.56-2.09** | 123 | **1.25** | **1.04-1.49** |
| Oesophagus | 24 | **2.43** | **1.55-3.61** | 7 | 0.58 | 0.23-1.20 | 5 | 1.17 | 0.38-2.73 | 1 | 0.75 | 0.01-4.15 | 37 | 1.34 | 0.95-1.85 | 20 | 0.79 | 0.48-1.23 |
| Stomach | 125 | **3.94** | **3.28-4.70** | 48 | 0.92 | 0.68-1.22 | 29 | 1.20 | 0.81-1.73 | 9 | 1.01 | 0.46-1.91 | 211 | **1.80** | **1.57-2.06** | 113 | 1.03 | 0.85-1.24 |
| Colon/rectum | 392 | **2.58** | **2.33-2.84** | 348 | 0.95 | 0.85-1.05 | 201 | 1.15 | 1.00-1.33 | 46 | 0.86 | 0.63-1.14 | 987 | **1.32** | **1.24-1.41** | 723 | 1.01 | 0.93-1.08 |
| Liver | 23 | **2.64** | **1.68-3.97** | 16 | 1.62 | 0.93-2.64 | 3 | 1.03 | 0.21-3.01 | 1 | 1.01 | 0.01-5.62 | 43 | **1.91** | **1.38-2.58** | 26 | 1.29 | 0.84-1.89 |
| Pancreas | 37 | **2.32** | **1.64-3.20** | 8 | 0.68 | 0.29-1.33 | 4 | 1.06 | 0.29-2.72 | 0 | 0.00 | 0.00-2.80 | 49 | **1.49** | **1.11-1.98** | 18 | 0.64 | 0.38-1.01 |
| Lung | 229 | **2.95** | **2.58-3.35** | 99 | 1.10 | 0.89-1.34 | 40 | 1.16 | 0.83-1.58 | 7 | 0.55 | 0.22-1.13 | 375 | **1.74** | **1.57-1.93** | 204 | 1.04 | 0.90-1.20 |
| Melanoma of skin | 128 | **4.06** | **3.39-4.83** | 148 | **1.74** | **1.47-2.04** | 54 | 1.17 | 0.88-1.53 | 20 | 1.16 | 0.71-1.79 | 350 | **1.94** | **1.75-2.16** | 287 | **1.65** | **1.46-1.85** |
| Breast (females) | 245 | **2.03** | **1.78-2.30** | 315 | 0.91 | 0.81-1.01 | 206 | 1.06 | 0.92-1.21 | 84 | 1.10 | 0.88-1.36 | 850 | **1.15** | **1.07-1.23** | 689 | 0.96 | 0.89-1.03 |
| Prostate | 373 | **1.97** | **1.77-2.18** | 548 | 1.02 | 0.93-1.10 | 270 | 1.05 | 0.93-1.18 | 49 | 0.90 | 0.67-1.20 | 1240 | **1.19** | **1.13-1.26** | 1058 | 1.05 | 0.99-1.12 |
| Testis | 33 | **15.87** | **10.92-22.28** | 22 | **3.10** | **1.94-4.70** | 10 | 1.75 | 0.84-3.22 | 5 | 1.46 | 0.47-3.40 | 70 | **3.82** | **2.98-4.83** | 51 | **2.84** | **2.12-3.74** |
| Kidney | 127 | **4.01** | **3.35-4.78** | 106 | **1.23** | **1.01-1.49** | 56 | 1.11 | 0.84-1.45 | 19 | 1.00 | 0.60-1.56 | 308 | **1.65** | **1.47-1.84** | 220 | **1.22** | **1.06-1.39** |
| Urinary bladder | 69 | **1.62** | **1.26-2.05** | 119 | **1.22** | **1.01-1.46** | 53 | 1.05 | 0.79-1.37 | 16 | 0.92 | 0.53-1.50 | 257 | **1.24** | **1.09-1.40** | 229 | 1.15 | 1.00-1.31 |
| Central nervous system | 17 | **2.40** | **1.40-3.85** | 4 | 0.55 | 0.15-1.42 | 3 | 0.89 | 0.18-2.59 | 4 | 2.42 | 0.65-6.21 | 28 | 1.45 | 0.96-2.10 | 17 | 0.97 | 0.57-1.56 |
| Thyroid | 29 | **4.26** | **2.86-6.13** | 24 | 1.18 | 0.76-1.76 | 13 | 1.00 | 0.53-1.71 | 9 | 1.60 | 0.73-3.03 | 75 | **1.64** | **1.29-2.06** | 59 | **1.33** | **1.01-1.71** |
| **All haematological malignancies** | 272 | **4.51** | **3.99-5.08** | 204 | **1.46** | **1.27-1.68** | 82 | 1.25 | 1.00-1.55 | 19 | 0.88 | 0.53-1.38 | 577 | **2.01** | **1.85-2.18** | 416 | **1.52** | **1.37-1.67** |
| Hodgkin lymphoma | 89 | **46.35** | **37.22-57.04** | 57 | **10.86** | **8.22-14.07** | 26 | **7.74** | **5.05-11.34** | 10 | **6.02** | **2.88-11.08** | 182 | **14.91** | **12.82-17.24** | 126 | **10.64** | **8.86-12.67** |
| Multiple myeloma | 45 | **3.95** | **2.88-5.29** | 22 | 0.94 | 0.59-1.42 | 7 | 0.87 | 0.35-1.80 | 2 | 0.87 | 0.10-3.15 | 76 | **1.68** | **1.33-2.11** | 50 | 1.17 | 0.86-1.54 |
| Lymphoid leukaemia | 42 | **3.65** | **2.63-4.93** | 34 | 1.07 | 0.74-1.49 | 9 | 0.57 | 0.26-1.07 | 2 | 0.42 | 0.05-1.52 | 87 | **1.36** | **1.09-1.68** | 56 | 0.91 | 0.68-1.18 |
| Acute lymphoblastic | 3 | **7.32** | **1.47-21.38** | 4 | **6.67** | **1.79-17.07** | 0 | 0.00 | 0.00-13.10 | 0 | 0.00 | 0.00-30.57 | 7 | **4.93** | **1.97-10.16** | 4 | 3.03 | 0.82-7.76 |
| Myeloid leukaemia | 23 | **4.14** | **2.62-6.21** | 18 | **2.03** | **1.20-3.21** | 6 | 1.46 | 0.53-3.19 | 3 | 2.04 | 0.41-5.96 | 50 | **2.50** | **1.86-3.30** | 36 | **1.93** | **1.35-2.67** |
| Acute myeloblastic | 13 | **4.74** | **2.52-8.11** | 8 | **2.47** | **1.06-4.87** | 3 | 2.21 | 0.44-6.45 | 2 | 3.39 | 0.38-12.24 | 26 | **3.28** | **2.14-4.80** | 19 | **2.64** | **1.59-4.12** |
| **All sites**** | 2198 | **2.42** | **2.32-2.52** | 2341 | **1.10** | **1.05-1.14** | 1185 | **1.11** | **1.05-1.17** | 342 | 0.97 | 0.87-1.08 | 6066 | **1.36** | **1.32-1.39** | 4793 | **1.12** | **1.09-1.15** |

O: observed number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); NHL: non-Hodgkin lymphoma.
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Multiple myeloma

### Table 40. Observed number, SIRs and EARs of SPM following MM by age at diagnosis, for both sexes

| | | 15-44 years | | | | | 45-59 years | | | | | ≥60 years | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **EAR** | **O** | **E** | **SIR** | **95% CI** | **EAR** | **O** | **E** | **SIR** | **95% CI** | **EAR** |
| **All solid malignancies*** | **C00-C75** | 19 | 9.95 | **1.91** | **1.15-2.98** | 13.93 | 261 | 220.11 | **1.19** | **1.05-1.34** | 13.20 | 1260 | 1213.26 | 1.04 | 0.98-1.10 | 5.54 |
| Lip, oral cavity, and pharynx | C00-C14 | 2 | 0.53 | 3.77 | 0.42-13.62 | 2.26 | 19 | 11.44 | 1.66 | 1.00-2.59 | 2.44 | 40 | 27.13 | **1.47** | **1.05-2.01** | 1.52 |
| Lip | C00 | 2 | 0 | 0.00 | 0.00-0.00 | 3.08 | 1 | 0.19 | 5.26 | 0.07-29.28 | 0.26 | 15 | 1.82 | **8.24** | **4.61-13.59** | 1.56 |
| Tongue | C01-C02 | 0 | 0.11 | 0.00 | 0.00-33.35 | -0.17 | 5 | 2.18 | 2.29 | 0.74-5.35 | 0.91 | 4 | 5.3 | 0.75 | 0.20-1.93 | -0.15 |
| Gum, floor of mouth, other mouth | C03-C06 | 0 | 0.15 | 0.00 | 0.00-24.45 | -0.23 | 6 | 2.89 | 2.08 | 0.76-4.52 | 1.00 | 6 | 6.65 | 0.90 | 0.33-1.96 | -0.08 |
| Parotid gland, other salivary glands | C07-C08 | 0 | 0.03 | 0.00 | 0.00-122.27 | -0.05 | 0 | 0.42 | 0.00 | 0.00-8.73 | -0.14 | 1 | 2.55 | 0.39 | 0.01-2.18 | -0.18 |
| Pharynx and other oral cavity | C09-C14 | 0 | 0.23 | 0.00 | 0.00-15.95 | -0.35 | 7 | 5.46 | 1.28 | 0.51-2.64 | 0.50 | 14 | 10.22 | 1.37 | 0.75-2.30 | 0.45 |
| Oesophagus | C15 | 0 | 0.13 | 0.00 | 0.00-28.22 | -0.20 | 6 | 4.52 | 1.33 | 0.48-2.89 | 0.48 | 11 | 17.35 | 0.63 | 0.32-1.13 | -0.75 |
| Stomach | C16 | 2 | 0.28 | 7.14 | 0.80-25.79 | 2.65 | 18 | 7.37 | **2.44** | **1.45-3.86** | 3.43 | 61 | 57.39 | 1.06 | 0.81-1.37 | 0.43 |
| Colon, rectum, and anus | C18-C21 | 0 | 0.86 | 0.00 | 0.00-4.27 | -1.32 | 37 | 29.54 | 1.25 | 0.88-1.73 | 2.41 | 227 | 221.99 | 1.02 | 0.89-1.16 | 0.59 |
| Liver | C22 | 0 | 0.1 | 0.00 | 0.00-36.68 | -0.15 | 0 | 3.46 | 0.00 | 0.00-1.06 | -1.12 | 19 | 21.24 | 0.89 | 0.54-1.40 | -0.27 |
| Pancreas | C25 | 0 | 0.17 | 0.00 | 0.00-21.58 | -0.26 | 7 | 6.08 | 1.15 | 0.46-2.37 | 0.30 | 46 | 40.1 | 1.15 | 0.84-1.53 | 0.70 |
| Larynx | C32 | 0 | 0.1 | 0.00 | 0.00-36.68 | -0.15 | 2 | 3.34 | 0.60 | 0.07-2.16 | -0.43 | 5 | 10.61 | 0.47 | 0.15-1.10 | -0.66 |
| Lung | C33-C34 | 1 | 0.82 | 1.22 | 0.02-6.79 | 0.28 | 31 | 30.47 | 1.02 | 0.69-1.44 | 0.17 | 162 | 157.31 | 1.03 | 0.88-1.20 | 0.56 |
| Melanoma of skin | C43 | 1 | 0.89 | 1.12 | 0.01-6.25 | 0.17 | 14 | 8.41 | 1.66 | 0.91-2.79 | 1.80 | 68 | 37.28 | **1.82** | **1.42-2.31** | 3.64 |
| Breast | C50 | 1 | 2.43 | 0.41 | 0.01-2.29 | -2.20 | 35 | 35.64 | 0.98 | 0.68-1.37 | -0.21 | 114 | 130.48 | 0.87 | 0.72-1.05 | -1.95 |
| Cervix uteri | C53 | 0 | 0.45 | 0.00 | 0.00-8.15 | -0.69 | 2 | 2.19 | 0.91 | 0.10-3.30 | -0.06 | 8 | 6.42 | 1.25 | 0.54-2.46 | 0.19 |
| Corpus uteri | C54-C55 | 1 | 0.19 | 5.26 | 0.07-29.28 | 1.25 | 4 | 5.58 | 0.72 | 0.19-1.84 | -0.51 | 13 | 29.72 | **0.44** | **0.23-0.75** | -1.98 |
| Ovaries | C56 | 0 | 0.2 | 0.00 | 0.00-18.34 | -0.31 | 2 | 3.6 | 0.56 | 0.06-2.01 | -0.52 | 19 | 17.9 | 1.06 | 0.64-1.66 | 0.13 |
| Prostate | C61 | 0 | 0.37 | 0.00 | 0.00-9.91 | -0.57 | 29 | 35.99 | 0.81 | 0.54-1.16 | -2.26 | 229 | 243.85 | 0.94 | 0.82-1.07 | -1.76 |
| Testis | C62 | 2 | 0.71 | 2.82 | 0.32-10.17 | 1.99 | 2 | 1.02 | 1.96 | 0.22-7.08 | 0.32 | 1 | 0.77 | 1.30 | 0.02-7.23 | 0.03 |
| Kidney | C64 | 2 | 0.34 | 5.88 | 0.66-21.24 | 2.55 | 21 | 8.99 | **2.34** | **1.45-3.57** | 3.88 | 57 | 44.46 | 1.28 | 0.97-1.66 | 1.49 |
| Urinary bladder | C67 | 0 | 0.17 | 0.00 | 0.00-21.58 | -0.26 | 4 | 6.83 | 0.59 | 0.16-1.50 | -0.91 | 54 | 64.17 | 0.84 | 0.63-1.10 | -1.20 |
| Central nervous system | C70-C72 | 1 | 0.28 | 3.57 | 0.05-19.87 | 1.11 | 4 | 3.45 | 1.16 | 0.31-2.97 | 0.18 | 11 | 13.26 | 0.83 | 0.41-1.48 | -0.27 |
| Thyroid | C73 | 1 | 0.4 | 2.50 | 0.03-13.91 | 0.92 | 1 | 2.82 | 0.35 | 0.00-1.97 | -0.59 | 12 | 7.13 | 1.68 | 0.87-2.94 | 0.58 |
| **All haematological malignancies** | **C81-C96** | 8 | 0.96 | **8.33** | **3.59-16.42** | 10.83 | 32 | 15.19 | **2.11** | **1.44-2.97** | 5.43 | 138 | 91.89 | **1.50** | **1.26-1.77** | 5.46 |
| Hodgkin lymphoma | C81 | 0 | 0.17 | 0.00 | 0.00-21.58 | -0.26 | 3 | 0.69 | 4.35 | 0.87-12.70 | 0.75 | 5 | 2.2 | 2.27 | 0.73-5.30 | 0.33 |
| Non-Hodgkin lymphoma | C82-C85 | 3 | 0.38 | **7.89** | **1.59-23.07** | 4.03 | 10 | 6.48 | 1.54 | 0.74-2.84 | 1.14 | 63 | 38.3 | **1.64** | **1.26-2.10** | 2.93 |
| Multiple myeloma | C90 | 0 | 0.08 | 0.00 | 0.00-45.85 | -0.12 | 0 | 2.68 | 0.00 | 0.00-1.37 | -0.87 | 0 | 17.96 | **0.00** | **0.00-0.20** | -2.13 |
| Lymphoid leukaemia | C91 | 1 | 0.11 | 9.09 | 0.12-50.58 | 1.37 | 0 | 2.68 | 0.00 | 0.00-1.37 | -0.87 | 14 | 16.02 | 0.87 | 0.48-1.47 | -0.24 |
| Acute lymphoblastic | C91.0 | 1 | 0.03 | 33.33 | 0.44-185.46 | 1.49 | 0 | 0.2 | 0.00 | 0.00-18.34 | -0.06 | 0 | 0.7 | 0.00 | 0.00-5.24 | -0.08 |
| Chronic lymphocytic | C91.1 | 0 | 0.06 | 0.00 | 0.00-61.13 | -0.09 | 0 | 2.22 | 0.00 | 0.00-1.65 | -0.72 | 13 | 14.19 | 0.92 | 0.49-1.57 | -0.14 |
| Myeloid leukaemia | C92 | 1 | 0.14 | 7.14 | 0.09-39.74 | 1.32 | 14 | 1.83 | **7.65** | **4.18-12.84** | 3.93 | 47 | 11.5 | **4.09** | **3.00-5.43** | 4.21 |
| Acute myeloblastic | C92.0 | 1 | 0.07 | 14.29 | 0.19-79.48 | 1.43 | 10 | 1.01 | **9.90** | **4.74-18.21** | 2.90 | 35 | 6.68 | **5.24** | **3.65-7.29** | 3.36 |
| Chronic myeloid | C92.1 | 0 | 0.05 | 0.00 | 0.00-73.36 | -0.08 | 1 | 0.45 | 2.22 | 0.03-12.36 | 0.18 | 2 | 2.37 | 0.84 | 0.09-3.05 | -0.04 |
| **All sites**** | **C00-C97** | 29 | 11.06 | **2.62** | **1.76-3.77** | 27.61 | 302 | 239.18 | **1.26** | **1.12-1.41** | 20.28 | 1430 | 1331.93 | **1.07** | **1.02-1.13** | 11.62 |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); EAR: excess absolute risk per 10,000 person-years; SPM: subsequent primary malignancies; ICD-10: the WHO International Classification of Diseases (10th revision); MM: multiple myeloma.
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 41. Observed number and SIRs of SPM following MM by follow-up time, for both sexes

| | | ≤1 year | | | | >1-≤5 years | | | | >5-≤10 years | | | | >10 years | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | **C00-C75** | 566 | 367.43 | **1.54** | **1.42-1.67** | 679 | 751.6 | **0.90** | **0.84-0.97** | 250 | 253.69 | 0.99 | 0.87-1.12 | 45 | 70.61 | **0.64** | **0.46-0.85** |
| Lip, oral cavity, and pharynx | C00-C14 | 18 | 9.87 | **1.82** | **1.08-2.88** | 28 | 20.44 | 1.37 | 0.91-1.98 | 12 | 6.93 | 1.73 | 0.89-3.02 | 3 | 1.85 | 1.62 | 0.33-4.74 |
| Lip | C00 | 10 | 0.5 | **20.00** | **9.57-36.78** | 4 | 1.04 | **3.85** | **1.03-9.85** | 3 | 0.36 | **8.33** | **1.67-24.35** | 1 | 0.11 | 9.09 | 0.12-50.58 |
| Tongue | C01-C02 | 1 | 1.92 | 0.52 | 0.01-2.90 | 4 | 3.98 | 1.01 | 0.27-2.57 | 4 | 1.34 | 2.99 | 0.80-7.64 | 0 | 0.36 | 0.00 | 0.00-10.19 |
| Gum, floor of mouth, other mouth | C03-C06 | 2 | 2.46 | 0.81 | 0.09-2.94 | 6 | 5.06 | 1.19 | 0.43-2.58 | 4 | 1.7 | 2.35 | 0.63-6.02 | 0 | 0.45 | 0.00 | 0.00-8.15 |
| Parotid gland, other salivary glands | C07-C08 | 0 | 0.75 | 0.00 | 0.00-4.89 | 1 | 1.55 | 0.65 | 0.01-3.59 | 0 | 0.53 | 0.00 | 0.00-6.92 | 0 | 0.15 | 0.00 | 0.00-24.45 |
| Pharynx and other oral cavity | C09-C14 | 5 | 3.99 | 1.25 | 0.40-2.92 | 13 | 8.32 | 1.56 | 0.83-2.67 | 1 | 2.82 | 0.35 | 0.00-1.97 | 2 | 0.75 | 2.67 | 0.30-9.63 |
| Oesophagus | C15 | 7 | 5.57 | 1.26 | 0.50-2.59 | 7 | 11.43 | 0.61 | 0.25-1.26 | 2 | 3.9 | 0.51 | 0.06-1.85 | 1 | 1.11 | 0.90 | 0.01-5.01 |
| Stomach | C16 | 31 | 16.76 | **1.85** | **1.26-2.63** | 32 | 33.75 | 0.95 | 0.65-1.34 | 13 | 11.35 | 1.15 | 0.61-1.96 | 5 | 3.18 | 1.57 | 0.51-3.67 |
| Colon, rectum, and anus | C18-C21 | 85 | 64.68 | **1.31** | **1.05-1.63** | 120 | 130.92 | 0.92 | 0.76-1.10 | 50 | 44.01 | 1.14 | 0.84-1.50 | 9 | 12.81 | 0.70 | 0.32-1.33 |
| Liver | C22 | 6 | 6.03 | 1.00 | 0.36-2.17 | 8 | 12.76 | 0.63 | 0.27-1.24 | 5 | 4.63 | 1.08 | 0.35-2.52 | 0 | 1.36 | 0.00 | 0.00-2.70 |
| Pancreas | C25 | 20 | 11.3 | **1.77** | **1.08-2.73** | 22 | 23.89 | 0.92 | 0.58-1.39 | 8 | 8.6 | 0.93 | 0.40-1.83 | 3 | 2.55 | 1.18 | 0.24-3.44 |
| Larynx | C32 | 4 | 3.68 | 1.09 | 0.29-2.78 | 2 | 7.37 | **0.27** | **0.03-0.98** | 0 | 2.38 | 0.00 | 0.00-1.54 | 1 | 0.62 | 1.61 | 0.02-8.97 |
| Lung | C33-C34 | 84 | 47.63 | **1.76** | **1.41-2.18** | 77 | 97.83 | **0.79** | **0.62-0.98** | 28 | 33.53 | 0.84 | 0.55-1.21 | 5 | 9.59 | 0.52 | 0.17-1.22 |
| Melanoma of skin | C43 | 25 | 11.71 | **2.13** | **1.38-3.15** | 44 | 24.49 | **1.80** | **1.31-2.41** | 11 | 8.19 | 1.34 | 0.67-2.40 | 3 | 2.18 | 1.38 | 0.28-4.02 |
| Breast | C50 | 48 | 42.81 | 1.12 | 0.83-1.49 | 72 | 88.18 | 0.82 | 0.64-1.03 | 27 | 29.58 | 0.91 | 0.60-1.33 | 3 | 7.99 | 0.38 | 0.08-1.10 |
| Cervix uteri | C53 | 4 | 2.38 | 1.68 | 0.45-4.30 | 6 | 4.75 | 1.26 | 0.46-2.75 | 0 | 1.55 | 0.00 | 0.00-2.37 | 0 | 0.39 | 0.00 | 0.00-9.41 |
| Corpus uteri | C54-C55 | 5 | 9.11 | 0.55 | 0.18-1.28 | 11 | 18.65 | 0.59 | 0.29-1.06 | 1 | 6.18 | **0.16** | **0.00-0.90** | 1 | 1.55 | 0.65 | 0.01-3.59 |
| Ovaries | C56 | 9 | 5.6 | 1.61 | 0.73-3.05 | 8 | 11.36 | 0.70 | 0.30-1.39 | 3 | 3.74 | 0.80 | 0.16-2.34 | 1 | 0.99 | 1.01 | 0.01-5.62 |
| Prostate | C61 | 101 | 72.09 | **1.40** | **1.14-1.70** | 105 | 146.85 | **0.72** | **0.58-0.87** | 47 | 48.53 | 0.97 | 0.71-1.29 | 5 | 12.75 | **0.39** | **0.13-0.92** |
| Testis | C62 | 2 | 0.67 | 2.99 | 0.34-10.78 | 2 | 1.34 | 1.49 | 0.17-5.39 | 1 | 0.41 | 2.44 | 0.03-13.57 | 0 | 0.09 | 0.00 | 0.00-40.76 |
| Kidney | C64 | 34 | 13.75 | **2.47** | **1.71-3.46** | 35 | 28.21 | 1.24 | 0.86-1.73 | 11 | 9.43 | 1.17 | 0.58-2.09 | 0 | 2.41 | 0.00 | 0.00-1.52 |
| Urinary bladder | C67 | 15 | 18.17 | 0.83 | 0.46-1.36 | 36 | 36.43 | 0.99 | 0.69-1.37 | 7 | 12.6 | 0.56 | 0.22-1.14 | 0 | 3.98 | **0.00** | **0.00-0.92** |
| Central nervous system | C70-C72 | 7 | 4.26 | 1.64 | 0.66-3.39 | 7 | 8.87 | 0.79 | 0.32-1.63 | 2 | 3.07 | 0.65 | 0.07-2.35 | 0 | 0.81 | 0.00 | 0.00-4.53 |
| Thyroid | C73 | 5 | 2.68 | 1.87 | 0.60-4.35 | 7 | 5.5 | 1.27 | 0.51-2.62 | 2 | 1.76 | 1.14 | 0.13-4.10 | 0 | 0.41 | 0.00 | 0.00-8.95 |
| **All haematological malignancies** | **C81-C96** | 96 | 27.42 | **3.50** | **2.84-4.28** | 59 | 56 | 1.05 | 0.80-1.36 | 20 | 19.23 | 1.04 | 0.64-1.61 | 3 | 5.41 | 0.55 | 0.11-1.62 |
| Hodgkin lymphoma | C81 | 6 | 0.79 | **7.59** | **2.77-16.53** | 1 | 1.61 | 0.62 | 0.01-3.46 | 1 | 0.53 | 1.89 | 0.02-10.50 | 0 | 0.14 | 0.00 | 0.00-26.20 |
| Non-Hodgkin lymphoma | C82-C85 | 45 | 11.39 | **3.95** | **2.88-5.29** | 22 | 23.46 | 0.94 | 0.59-1.42 | 7 | 8.03 | 0.87 | 0.35-1.80 | 2 | 2.29 | 0.87 | 0.10-3.15 |
| Lymphoid leukaemia | C91 | 10 | 4.75 | **2.11** | **1.01-3.87** | 5 | 9.79 | 0.51 | 0.16-1.19 | 0 | 3.37 | 0.00 | 0.00-1.09 | 0 | 0.91 | 0.00 | 0.00-4.03 |
| Acute lymphoblastic | C91.0 | 0 | 0.23 | 0.00 | 0.00-15.95 | 1 | 0.48 | 2.08 | 0.03-11.59 | 0 | 0.16 | 0.00 | 0.00-22.93 | 0 | 0.05 | 0.00 | 0.00-73.36 |
| Chronic lymphocytic | C91.1 | 10 | 4.16 | **2.40** | **1.15-4.42** | 3 | 8.58 | 0.35 | 0.07-1.02 | 0 | 2.95 | 0.00 | 0.00-1.24 | 0 | 0.79 | 0.00 | 0.00-4.64 |
| Myeloid leukaemia | C92 | 22 | 3.41 | **6.45** | **4.04-9.77** | 27 | 6.96 | **3.88** | **2.56-5.64** | 12 | 2.41 | **4.98** | **2.57-8.70** | 1 | 0.69 | 1.45 | 0.02-8.06 |
| Acute myeloblastic | C92.0 | 14 | 1.93 | **7.25** | **3.96-12.17** | 22 | 4 | **5.50** | **3.45-8.33** | 9 | 1.41 | **6.38** | **2.91-12.12** | 1 | 0.4 | 2.50 | 0.03-13.91 |
| Chronic myeloid | C92.1 | 2 | 0.76 | 2.63 | 0.30-9.50 | 1 | 1.49 | 0.67 | 0.01-3.73 | 0 | 0.5 | 0.00 | 0.00-7.34 | 0 | 0.13 | 0.00 | 0.00-28.22 |
| **All sites**** | **C00-C97** | 684 | 402.67 | **1.70** | **1.57-1.83** | 752 | 823.46 | **0.91** | **0.85-0.98** | 277 | 278.32 | 1.00 | 0.88-1.12 | 48 | 77.71 | **0.62** | **0.46-0.82** |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); SPM: subsequent primary malignancies; ICD-10: the WHO International Classification of Diseases (10th revision); MM: multiple myeloma.
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 42. Overall and site-specific SIRs of SPM following MM (all intervals, excluding initial 2 months, and excluding first year)

| | | Overall | | | | Overall (excl. <2 months) | | | | Overall (excl. <1 year) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | **C00-C75** | 1540 | 1443.32 | **1.07** | **1.01-1.12** | 1211 | 1369.97 | **0.88** | **0.83-0.94** | 974 | 1075.9 | **0.91** | **0.85-0.96** |
| Lip, oral cavity, and pharynx | C00-C14 | 61 | 39.09 | **1.56** | **1.19-2.00** | 51 | 37.14 | **1.37** | **1.02-1.81** | 43 | 29.22 | **1.47** | **1.06-1.98** |
| Lip | C00 | 18 | 2.02 | **8.91** | **5.28-14.08** | 11 | 1.92 | **5.73** | **2.86-10.25** | 8 | 1.51 | **5.30** | **2.28-10.44** |
| Tongue | C01-C02 | 9 | 7.59 | 1.19 | 0.54-2.25 | 9 | 7.21 | 1.25 | 0.57-2.37 | 8 | 5.68 | 1.41 | 0.61-2.78 |
| Gum, floor of mouth, other mouth | C03-C06 | 12 | 9.69 | 1.24 | 0.64-2.16 | 12 | 9.2 | 1.30 | 0.67-2.28 | 10 | 7.21 | 1.39 | 0.66-2.55 |
| Parotid gland, other salivary glands | C07-C08 | 1 | 2.99 | 0.33 | 0.00-1.86 | 1 | 2.84 | 0.35 | 0.00-1.96 | 1 | 2.23 | 0.45 | 0.01-2.50 |
| Pharynx and other oral cavity | C09-C14 | 21 | 15.87 | 1.32 | 0.82-2.02 | 18 | 15.09 | 1.19 | 0.71-1.89 | 16 | 11.89 | 1.35 | 0.77-2.19 |
| Oesophagus | C15 | 17 | 22.01 | 0.77 | 0.45-1.24 | 12 | 20.9 | 0.57 | 0.30-1.00 | 10 | 16.44 | 0.61 | 0.29-1.12 |
| Stomach | C16 | 81 | 65.05 | 1.25 | 0.99-1.55 | 65 | 61.66 | 1.05 | 0.81-1.34 | 50 | 48.28 | 1.04 | 0.77-1.37 |
| Colon, rectum, and anus | C18-C21 | 264 | 252.4 | 1.05 | 0.92-1.18 | 214 | 239.4 | 0.89 | 0.78-1.02 | 179 | 187.74 | 0.95 | 0.82-1.10 |
| Liver | C22 | 19 | 24.78 | 0.77 | 0.46-1.20 | 15 | 23.57 | 0.64 | 0.36-1.05 | 13 | 18.75 | 0.69 | 0.37-1.19 |
| Pancreas | C25 | 53 | 46.34 | 1.14 | 0.86-1.50 | 42 | 44.08 | 0.95 | 0.69-1.29 | 33 | 35.04 | 0.94 | 0.65-1.32 |
| Larynx | C32 | 7 | 14.05 | 0.50 | 0.20-1.03 | 5 | 13.32 | **0.38** | **0.12-0.88** | 3 | 10.37 | **0.29** | **0.06-0.85** |
| Lung | C33-C34 | 194 | 188.6 | 1.03 | 0.89-1.18 | 139 | 179.1 | **0.78** | **0.65-0.92** | 110 | 140.95 | **0.78** | **0.64-0.94** |
| Melanoma of skin | C43 | 83 | 46.57 | **1.78** | **1.42-2.21** | 75 | 44.25 | **1.69** | **1.33-2.12** | 58 | 34.86 | **1.66** | **1.26-2.15** |
| Breast | C50 | 150 | 168.56 | 0.89 | 0.75-1.04 | 128 | 160.05 | **0.80** | **0.67-0.95** | 102 | 125.75 | **0.81** | **0.66-0.98** |
| Cervix uteri | C53 | 10 | 9.07 | 1.10 | 0.53-2.03 | 7 | 8.59 | 0.81 | 0.33-1.68 | 6 | 6.69 | 0.90 | 0.33-1.95 |
| Corpus uteri | C54-C55 | 18 | 35.5 | **0.51** | **0.30-0.80** | 15 | 33.69 | **0.45** | **0.25-0.73** | 13 | 26.38 | **0.49** | **0.26-0.84** |
| Ovaries | C56 | 21 | 21.7 | 0.97 | 0.60-1.48 | 17 | 20.58 | 0.83 | 0.48-1.32 | 12 | 16.09 | 0.75 | 0.38-1.30 |
| Prostate | C61 | 258 | 280.22 | 0.92 | 0.81-1.04 | 197 | 265.88 | **0.74** | **0.64-0.85** | 157 | 208.13 | **0.75** | **0.64-0.88** |
| Testis | C62 | 5 | 2.51 | 1.99 | 0.64-4.65 | 4 | 2.38 | 1.68 | 0.45-4.30 | 3 | 1.84 | 1.63 | 0.33-4.76 |
| Kidney | C64 | 80 | 53.8 | **1.49** | **1.18-1.85** | 57 | 51.06 | 1.12 | 0.85-1.45 | 46 | 40.05 | 1.15 | 0.84-1.53 |
| Urinary bladder | C67 | 58 | 71.19 | 0.81 | 0.62-1.05 | 52 | 67.52 | 0.77 | 0.58-1.01 | 43 | 53.01 | 0.81 | 0.59-1.09 |
| Central nervous system | C70-C72 | 16 | 17 | 0.94 | 0.54-1.53 | 13 | 16.15 | 0.80 | 0.43-1.38 | 9 | 12.75 | 0.71 | 0.32-1.34 |
| Thyroid | C73 | 14 | 10.34 | 1.35 | 0.74-2.27 | 9 | 9.8 | 0.92 | 0.42-1.74 | 9 | 7.67 | 1.17 | 0.54-2.23 |
| **All haematological malignancies** | **C81-C96** | 178 | 108.04 | **1.65** | **1.41-1.91** | 118 | 102.52 | 1.15 | 0.95-1.38 | 82 | 80.64 | 1.02 | 0.81-1.26 |
| Hodgkin lymphoma | C81 | 8 | 3.06 | **2.61** | **1.13-5.15** | 3 | 2.9 | 1.03 | 0.21-3.02 | 2 | 2.28 | 0.88 | 0.10-3.17 |
| Non-Hodgkin lymphoma | C82-C85 | 76 | 45.18 | **1.68** | **1.33-2.11** | 50 | 42.91 | 1.17 | 0.86-1.54 | 31 | 33.78 | 0.92 | 0.62-1.30 |
| Multiple myeloma | C90 | 0 | 20.72 | **0.00** | **0.00-0.18** | 0 | 19.61 | **0.00** | **0.00-0.19** | 0 | 15.35 | **0.00** | **0.00-0.24** |
| Lymphoid leukaemia | C91 | 15 | 18.81 | 0.80 | 0.45-1.32 | 7 | 17.86 | **0.39** | **0.16-0.81** | 5 | 14.07 | **0.36** | **0.11-0.83** |
| Acute lymphoblastic | C91.0 | 1 | 0.93 | 1.08 | 0.01-5.98 | 1 | 0.89 | 1.12 | 0.01-6.25 | 1 | 0.69 | 1.45 | 0.02-8.06 |
| Chronic lymphocytic | C91.1 | 13 | 16.48 | 0.79 | 0.42-1.35 | 5 | 15.65 | **0.32** | **0.10-0.75** | 3 | 12.32 | **0.24** | **0.05-0.71** |
| Myeloid leukaemia | C92 | 62 | 13.46 | **4.61** | **3.53-5.91** | 51 | 12.77 | **3.99** | **2.97-5.25** | 40 | 10.06 | **3.98** | **2.84-5.41** |
| Acute myeloblastic | C92.0 | 46 | 7.75 | **5.94** | **4.35-7.92** | 41 | 7.37 | **5.56** | **3.99-7.55** | 32 | 5.81 | **5.51** | **3.77-7.78** |
| Chronic myeloid | C92.1 | 3 | 2.88 | 1.04 | 0.21-3.04 | 1 | 2.73 | 0.37 | 0.00-2.04 | 1 | 2.12 | 0.47 | 0.01-2.62 |
| **All sites**** | **C00-C97** | 1761 | 1582.16 | **1.11** | **1.06-1.17** | 1358 | 1501.73 | **0.90** | **0.86-0.95** | 1077 | 1179.49 | **0.91** | **0.86-0.97** |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); SPM: subsequent primary malignancies; MM: multiple myeloma; ICD-10: the WHO International Classification of Diseases (10th revision).
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 43. Observed number and SIRs of SPM following MM by follow-up time for survivors aged <60 or ≥60 years, for both sexes

| Under 60 years | | | ≤1 year | | | | >1-≤5 years | | | | >5-≤10 years | | | | >10 years | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies *** | 62 | 33.28 | **1.86** | **1.43-2.39** | 111 | 102.73 | 1.08 | 0.89-1.3 | 81 | 65.42 | 1.24 | 0.98-1.54 | 27 | 28.62 | 0.94 | 0.62-1.37 |
| Lip/oral cavity | 3 | 2.07 | 1.45 | 0.29-4.23 | 9 | 5.75 | 1.57 | 0.71-2.97 | 8 | 3.06 | 2.61 | 1.13-5.15 | 1 | 1.09 | 0.92 | 0.01-5.1 |
| Stomach | 5 | 1.12 | **4.46** | **1.44-10.42** | 9 | 3.44 | **2.62** | **1.19-4.97** | 4 | 2.14 | 1.87 | 0.50-4.79 | 3 | 0.94 | 3.19 | 0.64-9.32 |
| Lung | 7 | 4.39 | 1.59 | 0.64-3.29 | 16 | 13.82 | 1.16 | 0.66-1.88 | 6 | 8.97 | 0.67 | 0.24-1.46 | 3 | 4.1 | 0.73 | 0.15-2.14 |
| Melanoma of skin | 3 | 1.56 | 1.92 | 0.39-5.62 | 6 | 4.37 | 1.37 | 0.50-2.99 | 5 | 2.41 | 2.07 | 0.67-4.84 | 1 | 0.94 | 1.06 | 0.01-5.92 |
| Kidney | 10 | 1.41 | **7.09** | **3.40-13.04** | 8 | 4.27 | 1.87 | 0.81-3.69 | 5 | 2.61 | 1.92 | 0.62-4.47 | 0 | 1.05 | 0.00 | 0.00-3.49 |
| **All haematological malignancies** | 19 | 2.45 | **7.76** | **4.67-12.11** | 15 | 7.25 | **2.07** | **1.16-3.41** | 4 | 4.46 | 0.90 | 0.24-2.3 | 2 | 1.97 | 1.02 | 0.11-3.67 |
| Hodgkin lymphoma | 3 | 0.16 | **18.75** | **3.77-54.78** | 0 | 0.42 | 0.00 | 0.00-8.73 | 0 | 0.2 | 0.00 | 0.00-18.34 | 0 | 0.08 | 0.00 | 0.00-45.85 |
| Non-Hodgkin lymphoma | 7 | 1.04 | **6.73** | **2.70-13.87** | 5 | 3.09 | 1.62 | 0.52-3.78 | 0 | 1.89 | 0.00 | 0.00-1.94 | 1 | 0.84 | 1.19 | 0.02-6.62 |
| Leukaemia | 6 | 0.76 | **7.89** | **2.88-17.18** | 10 | 2.29 | **4.37** | **2.09-8.03** | 4 | 1.43 | 2.80 | 0.75-7.16 | 1 | 0.62 | 1.61 | 0.02-8.97 |
| Lymphoid leukaemia | 0 | 0.41 | 0.00 | 0.00-8.95 | 1 | 1.25 | 0.80 | 0.01-4.45 | 0 | 0.8 | 0.00 | 0.00-4.59 | 0 | 0.34 | 0.00 | 0.00-10.79 |
| Acute lymphoblastic | 0 | 0.03 | 0.00 | 0.00-122.27 | 1 | 0.11 | 9.09 | 0.12-50.58 | 0 | 0.05 | 0.00 | 0.00-73.36 | 0 | 0.02 | 0.00 | 0.00-183.4 |
| Chronic lymphocytic | 0 | 0.32 | 0.00 | 0.00-11.46 | 0 | 1.01 | 0.00 | 0.00-3.63 | 0 | 0.67 | 0.00 | 0.00-5.47 | 0 | 0.29 | 0.00 | 0.00-12.65 |
| Myeloid leukaemia | 2 | 0.32 | 6.25 | 0.70-22.57 | 8 | 0.89 | **8.99** | **3.87-17.71** | 4 | 0.54 | **7.41** | **1.99-18.96** | 1 | 0.24 | 4.17 | 0.05-23.18 |
| Acute myeloblastic | 0 | 0.17 | 0.00 | 0.00-21.58 | 7 | 0.48 | **14.58** | **5.84-30.05** | 3 | 0.3 | **10** | **2.01-29.22** | 1 | 0.14 | 7.14 | 0.09-39.74 |
| Chronic myeloid | 1 | 0.1 | 10.00 | 0.13-55.64 | 0 | 0.24 | 0.00 | 0.00-15.28 | 0 | 0.13 | 0.00 | 0.00-28.22 | 0 | 0.05 | 0.00 | 0.00-73.36 |
| **All sites**** | 86 | 36.36 | **2.37** | **1.89-2.92** | 129 | 111.8 | 1.15 | 0.96-1.37 | 88 | 70.99 | 1.24 | 0.99-1.53 | 29 | 31.1 | 0.93 | 0.62-1.34 |
| **60 years or older** | | | **≤1 year** | | | | **>1-≤5 years** | | | | **>5-≤10 years** | | | | **>10 years** | | | |
| **Subsequent cancer** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | 504 | 334.11 | **1.51** | **1.38-1.65** | 568 | 648.87 | **0.88** | **0.80-0.95** | 170 | 188.27 | 0.90 | 0.77-1.05 | 19 | 41.99 | **0.45** | **0.27-0.71** |
| Lip/oral cavity | 15 | 7.81 | **1.92** | **1.07-3.17** | 19 | 14.68 | 1.29 | 0.78-2.02 | 4 | 3.86 | 1.04 | 0.28-2.65 | 2 | 0.76 | 2.63 | 0.30-9.50 |
| Stomach | 26 | 15.63 | **1.66** | **1.09-2.44** | 23 | 30.31 | 0.76 | 0.48-1.14 | 10 | 9.21 | 1.09 | 0.52-2.00 | 2 | 2.23 | 0.90 | 0.10-3.24 |
| Colon/ rectum | 81 | 60.48 | **1.34** | **1.06-1.66** | 104 | 117.53 | 0.88 | 0.72-1.07 | 36 | 35.23 | 1.02 | 0.72-1.41 | 6 | 8.76 | 0.68 | 0.25-1.49 |
| Lung | 77 | 43.25 | **1.78** | **1.40-2.23** | 61 | 84.01 | **0.73** | **0.56-0.93** | 22 | 24.56 | 0.90 | 0.56-1.36 | 2 | 5.5 | 0.36 | 0.04-1.31 |
| Melanoma of skin | 22 | 10.14 | **2.17** | **1.36-3.29** | 38 | 20.13 | **1.89** | **1.34-2.59** | 6 | 5.78 | 1.04 | 0.38-2.26 | 2 | 1.23 | 1.63 | 0.18-5.87 |
| Kidney | 24 | 12.33 | **1.95** | **1.25-2.90** | 27 | 23.94 | 1.13 | 0.74-1.64 | 6 | 6.82 | 0.88 | 0.32-1.91 | 0 | 1.36 | 0.00 | 0.00-2.70 |
| **All haematological malignancies** | 77 | 24.95 | **3.09** | **2.44-3.86** | 44 | 48.76 | 0.9 | 0.66-1.21 | 16 | 14.76 | 1.08 | 0.62-1.76 | 1 | 3.43 | 0.29 | 0.00-1.62 |
| Hodgkin lymphoma | 3 | 0.61 | 4.92 | 0.99-14.37 | 1 | 1.18 | 0.85 | 0.01-4.72 | 1 | 0.33 | 3.03 | 0.04-16.86 | 0 | 0.07 | 0.00 | 0.00-52.4 |
| Non-Hodgkin lymphoma | 38 | 10.34 | **3.68** | **2.60-5.04** | 17 | 20.36 | 0.83 | 0.49-1.34 | 7 | 6.14 | 1.14 | 0.46-2.35 | 1 | 1.45 | 0.69 | 0.01-3.84 |
| Leukaemia | 33 | 8.22 | **4.01** | **2.76-5.64** | 26 | 16.15 | **1.61** | **1.05-2.36** | 8 | 4.95 | 1.62 | 0.70-3.18 | 0 | 1.16 | 0.00 | 0.00-3.16 |
| Lymphoid leukaemia | 10 | 4.34 | **2.3** | **1.10-4.24** | 4 | 8.53 | 0.47 | 0.13-1.2 | 0 | 2.58 | 0.00 | 0.00-1.42 | 0 | 0.57 | 0.00 | 0.00-6.44 |
| Acute lymphoblastic | 0 | 0.2 | 0.00 | 0.00-18.34 | 0 | 0.37 | 0.00 | 0.00-9.91 | 0 | 0.11 | 0.00 | 0.00-33.35 | 0 | 0.03 | 0.00 | 0.00-122.27 |
| Chronic lymphocytic | 10 | 3.85 | **2.6** | **1.24-4.78** | 3 | 7.56 | 0.4 | 0.08-1.16 | 0 | 2.28 | 0.00 | 0.00-1.61 | 0 | 0.5 | 0.00 | 0.00-7.34 |
| Myeloid leukaemia | 20 | 3.1 | **6.45** | **3.94-9.96** | 19 | 6.07 | **3.13** | **1.88-4.89** | 8 | 1.89 | **4.23** | **1.82-8.34** | 0 | 0.45 | 0.00 | 0.00-8.15 |
| Acute myeloblastic | 14 | 1.78 | **7.87** | **4.30-13.2** | 15 | 3.52 | **4.26** | **2.38-7.03** | 6 | 1.11 | **5.41** | **1.97-11.77** | 0 | 0.27 | 0.00 | 0.00-13.59 |
| Chronic myeloid | 1 | 0.67 | 1.49 | 0.02-8.30 | 1 | 1.24 | 0.81 | 0.01-4.49 | 0 | 0.37 | 0.00 | 0.00-9.91 | 0 | 0.09 | 0.00 | 0.00-40.76 |
| **All sites**** | 598 | 366.32 | **1.63** | **1.50-1.77** | 623 | 711.66 | **0.88** | **0.81-0.95** | 190 | 207.34 | 0.92 | 0.79-1.06 | 20 | 46.6 | **0.43** | **0.26-0.66** |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); SPM: subsequent primary malignancies; MM: multiple myeloma.
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 44. Observed number, SIRs and EARs of SPM following MM by calendar period, for both sexes

| | | 1990–2000 MM patients=6773 PYRs=14271.50 | | | | | 2001–2011 MM patients=13870 PYRs=56266.63 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **EAR** | **O** | **E** | **SIR** | **95% CI** | **EAR** |
| **All solid malignancies*** | **C00-C75** | 171 | 141.43 | **1.21** | **1.03-1.40** | 20.72 | 517 | 473.21 | 1.09 | 1.00-1.19 | 7.78 |
| Lip, oral cavity, and pharynx | C00-C14 | 5 | 3.96 | 1.26 | 0.41-2.95 | 0.73 | 27 | 13.05 | **2.07** | **1.36-3.01** | 2.48 |
| Oesophagus | C15 | 0 | 2.04 | 0.00 | 0.00-1.80 | -1.43 | 5 | 7.2 | 0.69 | 0.22-1.62 | -0.39 |
| Stomach | C16 | 8 | 7.83 | 1.02 | 0.44-2.01 | 0.12 | 21 | 21.01 | 1.00 | 0.62-1.53 | 0.00 |
| Colon, rectum, and anus | C18-C21 | 28 | 25.54 | 1.10 | 0.73-1.58 | 1.72 | 74 | 79.9 | 0.93 | 0.73-1.16 | -1.05 |
| Liver | C22 | 1 | 2.17 | 0.46 | 0.01-2.56 | -0.82 | 14 | 9.46 | 1.48 | 0.81-2.48 | 0.81 |
| Pancreas | C25 | 3 | 4.39 | 0.68 | 0.14-2.00 | -0.97 | 23 | 16.57 | 1.39 | 0.88-2.08 | 1.14 |
| Larynx | C32 | 3 | 1.74 | 1.72 | 0.35-5.04 | 0.88 | 3 | 4.49 | 0.67 | 0.13-1.95 | -0.26 |
| Lung | C33-C34 | 21 | 21.47 | 0.98 | 0.61-1.50 | -0.33 | 76 | 65.33 | 1.16 | 0.92-1.46 | 1.90 |
| Melanoma of skin | C43 | 6 | 3.07 | 1.95 | 0.71-4.25 | 2.05 | 26 | 14.02 | **1.85** | **1.21-2.72** | 2.13 |
| Breast | C50 | 17 | 17.02 | 1.00 | 0.58-1.60 | -0.01 | 49 | 52.46 | 0.93 | 0.69-1.23 | -0.61 |
| Cervix uteri | C53 | 3 | 1.49 | 2.01 | 0.40-5.88 | 1.06 | 5 | 2.91 | 1.72 | 0.55-4.01 | 0.37 |
| Corpus uteri | C54-C55 | 5 | 4.22 | 1.18 | 0.38-2.77 | 0.55 | 5 | 11.76 | **0.43** | **0.14-0.99** | -1.20 |
| Ovaries | C56 | 4 | 2.86 | 1.40 | 0.38-3.58 | 0.80 | 5 | 6.65 | 0.75 | 0.24-1.75 | -0.29 |
| Prostate | C61 | 25 | 19.31 | 1.29 | 0.84-1.91 | 3.99 | 88 | 89.92 | 0.98 | 0.78-1.21 | -0.34 |
| Testis | C62 | 2 | 0.26 | 7.69 | 0.86-27.77 | 1.22 | 2 | 0.83 | 2.41 | 0.27-8.70 | 0.21 |
| Kidney | C64 | 13 | 5.57 | **2.33** | **1.24-3.99** | 5.21 | 23 | 19.79 | 1.16 | 0.74-1.74 | 0.57 |
| Urinary bladder | C67 | 10 | 8.24 | 1.21 | 0.58-2.23 | 1.23 | 16 | 23.95 | 0.67 | 0.38-1.08 | -1.41 |
| Central nervous system | C70-C72 | 4 | 1.73 | 2.31 | 0.62-5.92 | 1.59 | 6 | 6.09 | 0.99 | 0.36-2.14 | -0.02 |
| Thyroid | C73 | 1 | 0.97 | 1.03 | 0.01-5.74 | 0.02 | 6 | 3.4 | 1.76 | 0.64-3.84 | 0.46 |
| **All haematological malignancies** | **C81-C96** | 14 | 11.72 | 1.19 | 0.65-2.00 | 1.60 | 31 | 35.97 | 0.86 | 0.59-1.22 | -0.88 |
| Hodgkin lymphoma | C81 | 1 | 0.35 | 2.86 | 0.04-15.90 | 0.46 | 1 | 0.97 | 1.03 | 0.01-5.74 | 0.01 |
| Non-Hodgkin lymphoma | C82-C85 | 4 | 4.68 | 0.85 | 0.23-2.19 | -0.48 | 9 | 14.71 | 0.61 | 0.28-1.16 | -1.01 |
| Lymphoid leukaemia | C91 | 0 | 2.09 | 0.00 | 0.00-1.76 | -1.46 | 1 | 6.57 | **0.15** | **0.00-0.85** | -0.99 |
| Acute lymphoblastic | C91.0 | 0 | 0.11 | 0.00 | 0.00-33.35 | -0.08 | 0 | 0.33 | 0.00 | 0.00-11.12 | -0.06 |
| Chronic lymphocytic | C91.1 | 0 | 1.85 | 0.00 | 0.00-1.98 | -1.30 | 1 | 5.73 | **0.17** | **0.00-0.97** | -0.84 |
| Myeloid leukaemia | C92 | 8 | 1.66 | **4.82** | **2.08-9.50** | 4.44 | 17 | 4.57 | **3.72** | **2.17-5.96** | 2.21 |
| Acute myeloblastic | C92.0 | 7 | 0.86 | **8.14** | **3.26-16.77** | 4.30 | 12 | 2.71 | **4.43** | **2.29-7.74** | 1.65 |
| Chronic myeloid | C92.1 | 1 | 0.46 | 2.17 | 0.03-12.10 | 0.38 | 0 | 0.87 | 0.00 | 0.00-4.22 | -0.15 |
| other myeloid leukaemia | C92.2-C92.9 | 0 | 0.33 | 0.00 | 0.00-11.12 | -0.23 | 5 | 1 | **5.00** | **1.61-11.67** | 0.71 |
| **All sites**** | **C00-C97** | 188 | 156.88 | **1.20** | **1.03-1.38** | 21.81 | 565 | 519.6 | 1.09 | 1.00-1.18 | 8.07 |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); SPM: subsequent primary malignancies; EAR: excess absolute risk per 10,000 person-years; PYRs: person-years of observation; MM: multiple myeloma; ICD-10: the WHO International Classification of Diseases (10th revision).
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 45. Risk of MM subsequent to other primary malignancies by follow-up time, for both sexes

| | ≤1 year | | | >1-≤5 years | | | >5-≤10 years | | | >10 years | | | Overall | | | Overall (excl. < 2 months) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Site of first primary cancer** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** |
| **All solid malignancies*** | 753 | **2.06** | **1.91-2.21** | 865 | 0.99 | 0.92-1.06 | 441 | 0.98 | 0.89-1.07 | 134 | 0.91 | 0.76-1.08 | 2193 | **1.19** | **1.14-1.24** | 1814 | 1.03 | 0.98-1.07 |
| Lip/oral cavity | 16 | 1.68 | 0.96-2.74 | 17 | 0.82 | 0.48-1.31 | 9 | 0.84 | 0.38-1.60 | 3 | 0.77 | 0.16-2.26 | 45 | 1.00 | 0.73-1.34 | 37 | 0.86 | 0.61-1.19 |
| Lung | 80 | **2.30** | **1.82-2.86** | 37 | 0.91 | 0.64-1.25 | 9 | 0.56 | 0.26-1.06 | 4 | 0.68 | 0.18-1.73 | 130 | **1.33** | **1.11-1.58** | 80 | 0.90 | 0.71-1.12 |
| Melanoma of skin | 34 | **2.56** | **1.78-3.58** | 45 | 1.24 | 0.90-1.66 | 21 | 1.04 | 0.64-1.59 | 8 | 1.06 | 0.45-2.08 | 108 | **1.40** | **1.15-1.69** | 93 | 1.24 | 1.00-1.52 |
| Kidney | 65 | **4.62** | **3.57-5.89** | 53 | **1.36** | **1.02-1.78** | 23 | 0.98 | 0.62-1.47 | 10 | 1.11 | 0.53-2.05 | 151 | **1.77** | **1.50-2.07** | 122 | **1.48** | **1.23-1.76** |
| **All haematological malignancies** | 62 | **2.33** | **1.79-2.99** | 46 | **0.75** | **0.55-0.99** | 18 | **0.61** | **0.36-0.97** | 4 | 0.42 | 0.11-1.08 | 130 | 1.02 | 0.85-1.21 | 94 | **0.77** | **0.62-0.94** |
| Hodgkin lymphoma | 5 | **6.67** | **2.15-15.56** | 1 | 0.50 | 0.01-2.77 | 3 | 2.33 | 0.47-6.79 | 1 | 1.59 | 0.02-8.83 | 10 | **2.14** | **1.03-3.94** | 8 | 1.77 | 0.76-3.49 |
| Non-Hodgkin lymphoma | 44 | **3.89** | **2.82-5.22** | 24 | 0.87 | 0.56-1.30 | 10 | 0.73 | 0.35-1.34 | 1 | 0.21 | 0.00-1.19 | 79 | **1.38** | **1.09-1.72** | 47 | 0.85 | 0.63-1.14 |
| Myeloid leukaemia | 23 | **9.43** | **5.97-14.14** | 7 | 1.84 | 0.74-3.79 | 1 | 0.56 | 0.01-3.14 | 1 | 1.61 | 0.02-8.97 | 32 | **3.70** | **2.53-5.23** | 16 | **1.99** | **1.14-3.23** |
| Acute myeloid | 8 | **6.67** | **2.87-13.14** | 3 | 2.17 | 0.44-6.35 | 0 | 0.00 | 0.00-6.32 | 0 | 0.00 | 0.00-4.67 | 11 | **3.23** | **1.61-5.77** | 5 | 1.62 | 0.52-3.78 |
| **All sites**** | 757 | **1.91** | **1.77-2.05** | 913 | 0.97 | 0.91-1.03 | 463 | 0.96 | 0.87-1.05 | 138 | 0.87 | 0.73-1.03 | 2271 | **1.15** | **1.10-1.20** | 1917 | 1.01 | 0.96-1.05 |

O: observed number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); MM: multiple myeloma.
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Chronic lymphocytic leukaemia

### Table 46. Observed number, SIRs and EARs of SPM following CLL by age at diagnosis, for both sexes

| | | 15-44 years | | | | | 45-59 years | | | | | ≥60 years | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **EAR** | **O** | **E** | **SIR** | **95% CI** | **EAR** | **O** | **E** | **SIR** | **95% CI** | **EAR** |
| **All solid malignancies*** | **C00-C75** | 20 | 7.74 | **2.58** | **1.58-3.99** | 24.68 | 412 | 274.09 | **1.50** | **1.36-1.66** | 39.53 | 2293 | 1574.18 | **1.46** | **1.40-1.52** | 68.41 |
| Lip, oral cavity, and pharynx | C00-C14 | 0 | 0.51 | 0.00 | 0.00-7.19 | -1.03 | 12 | 14.18 | 0.85 | 0.44-1.48 | -0.62 | 70 | 34.84 | **2.01** | **1.57-2.54** | 3.35 |
| Lip | C00 | 0 | 0 | 0.00 | 0.00-0.00 | 0.00 | 2 | 0.27 | 7.41 | 0.83-26.74 | 0.50 | 14 | 2.56 | **5.47** | **2.99-9.18** | 1.09 |
| Tongue | C01-C02 | 0 | 0.1 | 0.00 | 0.00-36.68 | -0.20 | 2 | 2.68 | 0.75 | 0.08-2.69 | -0.19 | 12 | 6.72 | 1.79 | 0.92-3.12 | 0.50 |
| Gum, floor of mouth, other mouth | C03-C06 | 0 | 0.14 | 0.00 | 0.00-26.20 | -0.28 | 2 | 3.55 | 0.56 | 0.06-2.03 | -0.44 | 7 | 8.35 | 0.84 | 0.34-1.73 | -0.13 |
| Parotid gland, other salivary glands | C07-C08 | 0 | 0.03 | 0.00 | 0.00-122.27 | -0.06 | 3 | 0.51 | **5.88** | **1.18-17.19** | 0.71 | 16 | 3.33 | **4.80** | **2.74-7.80** | 1.21 |
| Pharynx and other oral cavity | C09-C14 | 0 | 0.23 | 0.00 | 0.00-15.95 | -0.46 | 3 | 6.76 | 0.44 | 0.09-1.30 | -1.08 | 21 | 13.06 | 1.61 | 0.99-2.46 | 0.76 |
| Oesophagus | C15 | 1 | 0.12 | 8.33 | 0.11-46.37 | 1.77 | 3 | 5.85 | 0.51 | 0.10-1.50 | -0.82 | 21 | 22.82 | 0.92 | 0.57-1.41 | -0.17 |
| Stomach | C16 | 2 | 0.24 | 8.33 | 0.94-30.09 | 3.54 | 10 | 9.54 | 1.05 | 0.50-1.93 | 0.13 | 112 | 77.07 | **1.45** | **1.20-1.75** | 3.32 |
| Colon, rectum, and anus | C18-C21 | 1 | 0.71 | 1.41 | 0.02-7.84 | 0.58 | 62 | 38.15 | **1.63** | **1.25-2.08** | 6.84 | 425 | 288.84 | **1.47** | **1.33-1.62** | 12.96 |
| Liver | C22 | 0 | 0.09 | 0.00 | 0.00-40.76 | -0.18 | 2 | 4.59 | 0.44 | 0.05-1.57 | -0.74 | 43 | 28.82 | **1.49** | **1.08-2.01** | 1.35 |
| Pancreas | C25 | 0 | 0.15 | 0.00 | 0.00-24.45 | -0.30 | 11 | 7.91 | 1.39 | 0.69-2.49 | 0.89 | 63 | 52.08 | 1.21 | 0.93-1.55 | 1.04 |
| Larynx | C32 | 1 | 0.11 | 9.09 | 0.12-50.58 | 1.79 | 2 | 4.27 | 0.47 | 0.05-1.69 | -0.65 | 13 | 14.14 | 0.92 | 0.49-1.57 | -0.11 |
| Lung | C33-C34 | 3 | 0.69 | 4.35 | 0.87-12.70 | 4.65 | 81 | 38.91 | **2.08** | **1.65-2.59** | 12.06 | 352 | 209.4 | **1.68** | **1.51-1.87** | 13.57 |
| Melanoma of skin | C43 | 2 | 0.67 | 2.99 | 0.34-10.78 | 2.68 | 28 | 10.04 | **2.79** | **1.85-4.03** | 5.15 | 143 | 47.74 | **3.00** | **2.52-3.53** | 9.07 |
| Breast | C50 | 2 | 1.58 | 1.27 | 0.14-4.57 | 0.85 | 41 | 36.25 | 1.13 | 0.81-1.53 | 1.36 | 161 | 141.9 | 1.13 | 0.97-1.32 | 1.82 |
| Cervix uteri | C53 | 2 | 0.31 | 6.45 | 0.72-23.29 | 3.40 | 3 | 2.16 | 1.39 | 0.28-4.06 | 0.24 | 3 | 7.14 | 0.42 | 0.08-1.23 | -0.39 |
| Corpus uteri | C54-C55 | 0 | 0.13 | 0.00 | 0.00-28.22 | -0.26 | 4 | 6.02 | 0.66 | 0.18-1.70 | -0.58 | 36 | 33.35 | 1.08 | 0.76-1.49 | 0.25 |
| Ovaries | C56 | 0 | 0.13 | 0.00 | 0.00-28.22 | -0.26 | 2 | 3.78 | 0.53 | 0.06-1.91 | -0.51 | 23 | 19.79 | 1.16 | 0.74-1.74 | 0.31 |
| Prostate | C61 | 0 | 0.35 | 0.00 | 0.00-10.48 | -0.70 | 69 | 51.53 | **1.34** | **1.04-1.69** | 5.01 | 431 | 340.11 | **1.27** | **1.15-1.39** | 8.65 |
| Testis | C62 | 1 | 0.62 | 1.61 | 0.02-8.97 | 0.76 | 1 | 1.11 | 0.90 | 0.01-5.01 | -0.03 | 2 | 1.04 | 1.92 | 0.22-6.94 | 0.09 |
| Kidney | C64 | 4 | 0.3 | **13.33** | **3.59-34.14** | 7.45 | 34 | 11.83 | **2.87** | **1.99-4.02** | 6.35 | 132 | 59.94 | **2.20** | **1.84-2.61** | 6.86 |
| Urinary bladder | C67 | 1 | 0.14 | 7.14 | 0.09-39.74 | 1.73 | 8 | 9.19 | 0.87 | 0.37-1.72 | -0.34 | 111 | 87.09 | **1.27** | **1.05-1.53** | 2.28 |
| Central nervous system | C70-C72 | 0 | 0.22 | 0.00 | 0.00-16.67 | -0.44 | 6 | 4.24 | 1.42 | 0.52-3.08 | 0.50 | 22 | 17.09 | 1.29 | 0.81-1.95 | 0.47 |
| Thyroid | C73 | 0 | 0.28 | 0.00 | 0.00-13.10 | -0.56 | 8 | 3 | **2.67** | **1.15-5.25** | 1.43 | 16 | 8.43 | **1.90** | **1.08-3.08** | 0.72 |
| **All haematological malignancies** | **C81-C96** | 7 | 0.78 | **8.97** | **3.60-18.49** | 12.52 | 40 | 19.09 | **2.10** | **1.50-2.85** | 5.99 | 174 | 119.32 | **1.46** | **1.25-1.69** | 5.20 |
| Hodgkin lymphoma | C81 | 2 | 0.14 | **14.29** | **1.60-51.58** | 3.74 | 15 | 0.79 | **18.99** | **10.62-31.32** | 4.07 | 34 | 2.76 | **12.32** | **8.53-17.21** | 2.97 |
| Non-Hodgkin lymphoma | C82-C85 | 2 | 0.32 | 6.25 | 0.70-22.57 | 3.38 | 11 | 8.01 | 1.37 | 0.68-2.46 | 0.86 | 46 | 49.13 | 0.94 | 0.69-1.25 | -0.30 |
| Multiple myeloma | C90 | 1 | 0.07 | 14.29 | 0.19-79.48 | 1.87 | 0 | 3.42 | 0.00 | 0.00-1.07 | -0.98 | 21 | 23 | 0.91 | 0.56-1.40 | -0.19 |
| Myeloid leukaemia | C92 | 2 | 0.11 | **18.18** | **2.04-65.65** | 3.80 | 9 | 2.25 | **4.00** | **1.83-7.59** | 1.93 | 51 | 14.98 | **3.40** | **2.53-4.48** | 3.43 |
| Acute myeloblastic | C92.0 | 0 | 0.05 | 0.00 | 0.00-73.36 | -0.10 | 2 | 1.26 | 1.59 | 0.18-5.73 | 0.21 | 14 | 8.75 | 1.60 | 0.87-2.68 | 0.50 |
| Chronic myeloid | C92.1 | 2 | 0.04 | **50.00** | **5.62-180.52** | 3.94 | 2 | 0.55 | 3.64 | 0.41-13.13 | 0.42 | 32 | 3.06 | **10.46** | **7.15-14.76** | 2.75 |
| **All sites**** | **C00-C97** | 27 | 8.64 | **3.13** | **2.06-4.55** | 36.95 | 461 | 298.01 | **1.55** | **1.41-1.69** | 46.72 | 2534 | 1728.32 | **1.47** | **1.41-1.52** | 76.67 |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); EAR: excess absolute risk per 10,000 person-years; SPM: subsequent primary malignancies; CLL: chronic lymphocytic leukaemia; ICD-10: the WHO International Classification of Diseases (10th revision).

*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)

Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 47. Observed number and SIRs of SPM following CLL by follow-up time, for both sexes

| | | ≤1 year | | | | >1-≤5 years | | | | >5-≤10 years | | | | >10 years | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | **C00-C75** | 823 | 336.71 | **2.44** | **2.28-2.62** | 1204 | 939.6 | **1.28** | **1.21-1.36** | 563 | 454.17 | **1.24** | **1.14-1.35** | 135 | 125.56 | 1.08 | 0.90-1.27 |
| Lip, oral cavity, and pharynx | C00-C14 | 35 | 9.27 | **3.78** | **2.63-5.25** | 28 | 25.42 | 1.10 | 0.73-1.59 | 16 | 11.78 | 1.36 | 0.78-2.21 | 3 | 3.03 | 0.99 | 0.20-2.89 |
| Lip | C00 | 9 | 0.51 | **17.65** | **8.05-33.50** | 4 | 1.42 | 2.82 | 0.76-7.21 | 3 | 0.72 | 4.17 | 0.84-12.17 | 0 | 0.2 | 0.00 | 0.00-18.34 |
| Tongue | C01-C02 | 8 | 1.77 | **4.52** | **1.95-8.91** | 4 | 4.88 | 0.82 | 0.22-2.10 | 2 | 2.27 | 0.88 | 0.10-3.18 | 0 | 0.58 | 0.00 | 0.00-6.32 |
| Gum, floor of mouth, other mouth | C03-C06 | 3 | 2.27 | 1.32 | 0.27-3.86 | 5 | 6.19 | 0.81 | 0.26-1.89 | 1 | 2.84 | 0.35 | 0.00-1.96 | 0 | 0.75 | 0.00 | 0.00-4.89 |
| Parotid and other salivary glands | C07-C08 | 7 | 0.7 | **10.00** | **4.01-20.60** | 4 | 1.95 | 2.05 | 0.55-5.25 | 7 | 0.95 | **7.37** | **2.95-15.18** | 1 | 0.27 | 3.70 | 0.05-20.61 |
| Pharynx/other oral cavity | C09-C14 | 8 | 3.78 | 2.12 | 0.91-4.17 | 11 | 10.33 | 1.06 | 0.53-1.91 | 3 | 4.75 | 0.63 | 0.13-1.85 | 2 | 1.19 | 1.68 | 0.19-6.07 |
| Oesophagus | C15 | 3 | 5.28 | 0.57 | 0.11-1.66 | 15 | 14.64 | 1.02 | 0.57-1.69 | 6 | 6.97 | 0.86 | 0.31-1.87 | 1 | 1.92 | 0.52 | 0.01-2.90 |
| Stomach | C16 | 31 | 15.89 | **1.95** | **1.33-2.77** | 58 | 44.07 | 1.32 | 1.00-1.70 | 25 | 21.14 | 1.18 | 0.77-1.75 | 10 | 5.73 | 1.75 | 0.84-3.21 |
| Colon, rectum, and anus | C18-C21 | 161 | 59.44 | **2.71** | **2.31-3.16** | 205 | 165.52 | **1.24** | **1.07-1.42** | 101 | 79.92 | **1.26** | **1.03-1.54** | 21 | 22.83 | 0.92 | 0.57-1.41 |
| Liver | C22 | 11 | 5.72 | 1.92 | 0.96-3.44 | 18 | 16.68 | 1.08 | 0.64-1.71 | 14 | 8.63 | 1.62 | 0.89-2.72 | 2 | 2.47 | 0.81 | 0.09-2.92 |
| Pancreas | C25 | 20 | 10.27 | **1.95** | **1.19-3.01** | 34 | 29.78 | 1.14 | 0.79-1.60 | 15 | 15.49 | 0.97 | 0.54-1.60 | 5 | 4.62 | 1.08 | 0.35-2.53 |
| Larynx | C32 | 6 | 3.58 | 1.68 | 0.61-3.65 | 5 | 9.6 | 0.52 | 0.17-1.22 | 3 | 4.26 | 0.70 | 0.14-2.06 | 2 | 1.06 | 1.89 | 0.21-6.81 |
| Lung | C33-C34 | 114 | 45.09 | **2.53** | **2.09-3.04** | 205 | 126.03 | **1.63** | **1.41-1.87** | 96 | 60.96 | **1.57** | **1.28-1.92** | 21 | 16.95 | 1.24 | 0.77-1.89 |
| Melanoma of skin | C43 | 29 | 10.5 | **2.76** | **1.85-3.97** | 93 | 29.74 | **3.13** | **2.52-3.83** | 42 | 14.36 | **2.92** | **2.11-3.95** | 9 | 3.84 | **2.34** | **1.07-4.45** |
| Breast | C50 | 68 | 32.12 | **2.12** | **1.64-2.68** | 89 | 89.6 | 0.99 | 0.80-1.22 | 40 | 44.75 | 0.89 | 0.64-1.22 | 7 | 13.26 | 0.53 | 0.21-1.09 |
| Cervix uteri | C53 | 2 | 1.82 | 1.10 | 0.12-3.97 | 4 | 4.85 | 0.82 | 0.22-2.11 | 2 | 2.29 | 0.87 | 0.10-3.15 | 0 | 0.64 | 0.00 | 0.00-5.73 |
| Corpus uteri | C54-C55 | 10 | 7.05 | 1.42 | 0.68-2.61 | 21 | 19.73 | 1.06 | 0.66-1.63 | 6 | 9.94 | 0.60 | 0.22-1.31 | 3 | 2.77 | 1.08 | 0.22-3.16 |
| Ovaries | C56 | 10 | 4.27 | **2.34** | **1.12-4.31** | 11 | 11.83 | 0.93 | 0.46-1.66 | 2 | 5.87 | 0.34 | 0.04-1.23 | 2 | 1.74 | 1.15 | 0.13-4.15 |
| Prostate | C61 | 153 | 72.33 | **2.12** | **1.79-2.48** | 220 | 201.23 | 1.09 | 0.95-1.25 | 107 | 94.51 | 1.13 | 0.93-1.37 | 20 | 23.91 | 0.84 | 0.51-1.29 |
| Testis | C62 | 0 | 0.6 | 0.00 | 0.00-6.11 | 3 | 1.48 | 2.03 | 0.41-5.92 | 1 | 0.57 | 1.75 | 0.02-9.76 | 0 | 0.12 | 0.00 | 0.00-30.57 |
| Kidney | C64 | 77 | 13.13 | **5.86** | **4.63-7.33** | 62 | 36.78 | **1.69** | **1.29-2.16** | 23 | 17.65 | 1.30 | 0.83-1.96 | 8 | 4.52 | 1.77 | 0.76-3.49 |
| Urinary bladder | C67 | 38 | 17.56 | **2.16** | **1.53-2.97** | 53 | 48.49 | 1.09 | 0.82-1.43 | 23 | 23.43 | 0.98 | 0.62-1.47 | 6 | 6.94 | 0.86 | 0.32-1.88 |
| Central nervous system | C70-C72 | 9 | 3.86 | **2.33** | **1.06-4.43** | 11 | 10.88 | 1.01 | 0.50-1.81 | 6 | 5.38 | 1.12 | 0.41-2.43 | 2 | 1.43 | 1.40 | 0.16-5.05 |
| Thyroid | C73 | 11 | 2.23 | **4.93** | **2.46-8.83** | 6 | 6.1 | 0.98 | 0.36-2.14 | 6 | 2.74 | 2.19 | 0.80-4.77 | 1 | 0.65 | 1.54 | 0.02-8.56 |
| **All haematological malignancies** | **C81-C96** | 90 | 25.02 | **3.60** | **2.89-4.42** | 90 | 69.87 | **1.29** | **1.04-1.58** | 31 | 34.5 | 0.90 | 0.61-1.28 | 10 | 9.78 | 1.02 | 0.49-1.88 |
| Hodgkin lymphoma | C81 | 12 | 0.7 | **17.14** | **8.85-29.95** | 24 | 1.88 | **12.77** | **8.18-19.00** | 13 | 0.88 | **14.77** | **7.86-25.26** | 2 | 0.24 | 8.33 | 0.94-30.09 |
| Non-Hodgkin lymphoma | C82-C85 | 26 | 10.28 | **2.53** | **1.65-3.71** | 24 | 28.89 | 0.83 | 0.53-1.24 | 7 | 14.24 | 0.49 | 0.20-1.01 | 2 | 4.07 | 0.49 | 0.06-1.77 |
| Multiple myeloma | C90 | 11 | 4.69 | **2.35** | **1.17-4.20** | 8 | 13.26 | 0.60 | 0.26-1.19 | 3 | 6.64 | 0.45 | 0.09-1.32 | 0 | 1.89 | 0.00 | 0.00-1.94 |
| Myeloid leukaemia | C92 | 29 | 3.08 | **9.42** | **6.30-13.52** | 20 | 8.69 | **2.30** | **1.41-3.55** | 7 | 4.31 | 1.62 | 0.65-3.35 | 6 | 1.25 | **4.80** | **1.75-10.45** |
| Acute myeloblastic | C92.0 | 7 | 1.77 | **3.95** | **1.58-8.15** | 8 | 5.03 | 1.59 | 0.68-3.13 | 1 | 2.53 | 0.40 | 0.01-2.20 | 0 | 0.74 | 0.00 | 0.00-4.96 |
| Chronic myeloid | C92.1 | 20 | 0.69 | **28.99** | **17.70-44.77** | 8 | 1.86 | **4.30** | **1.85-8.48** | 4 | 0.86 | **4.65** | **1.25-11.91** | 4 | 0.24 | **16.67** | **4.48-42.67** |
| **All sites**** | **C00-C97** | 933 | 368.86 | **2.53** | **2.37-2.70** | 1331 | 1029.36 | **1.29** | **1.22-1.36** | 611 | 498.42 | **1.23** | **1.13-1.33** | 147 | 138.33 | 1.06 | 0.90-1.25 |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); SPM: subsequent primary malignancies; CLL: chronic lymphocytic leukaemia; ICD-10: the WHO International Classification of Diseases (10th revision).
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 48. Overall and site-specific SIRs of SPM following CLL (all intervals, excluding initial 2 months, and excluding first year)

| | | Overall | | | | Overall (excl. <2 months) | | | | Overall (excl. <1 year) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | **C00-C75** | 2725 | 1856.03 | **1.47** | **1.41-1.52** | 2291 | 1794.32 | **1.28** | **1.23-1.33** | 1902 | 1519.33 | **1.25** | **1.20-1.31** |
| Lip, oral cavity, and pharynx | C00-C14 | 82 | 49.51 | **1.66** | **1.32-2.06** | 59 | 47.81 | 1.23 | 0.94-1.59 | 47 | 40.23 | 1.17 | 0.86-1.55 |
| Lip | C00 | 16 | 2.84 | **5.63** | **3.22-9.15** | 9 | 2.74 | **3.28** | **1.50-6.24** | 7 | 2.34 | **2.99** | **1.20-6.16** |
| Tongue | C01-C02 | 14 | 9.5 | 1.47 | 0.80-2.47 | 10 | 9.18 | 1.09 | 0.52-2.00 | 6 | 7.73 | 0.78 | 0.28-1.69 |
| Gum, floor of mouth, other mouth | C03-C06 | 9 | 12.04 | 0.75 | 0.34-1.42 | 8 | 11.63 | 0.69 | 0.30-1.36 | 6 | 9.78 | 0.61 | 0.22-1.34 |
| Parotid and other salivary glands | C07-C08 | 19 | 3.87 | **4.91** | **2.95-7.67** | 15 | 3.74 | **4.01** | **2.24-6.62** | 12 | 3.17 | **3.79** | **1.95-6.61** |
| Pharynx/other oral cavity | C09-C14 | 24 | 20.05 | 1.20 | 0.77-1.78 | 17 | 19.36 | 0.88 | 0.51-1.41 | 16 | 16.27 | 0.98 | 0.56-1.60 |
| Oesophagus | C15 | 25 | 28.8 | 0.87 | 0.56-1.28 | 23 | 27.83 | 0.83 | 0.52-1.24 | 22 | 23.53 | 0.93 | 0.59-1.42 |
| Stomach | C16 | 124 | 86.84 | **1.43** | **1.19-1.70** | 104 | 83.92 | **1.24** | **1.01-1.50** | 93 | 70.94 | **1.31** | **1.06-1.61** |
| Colon, rectum, and anus | C18-C21 | 488 | 327.7 | **1.49** | **1.36-1.63** | 393 | 316.78 | **1.24** | **1.12-1.37** | 327 | 268.27 | **1.22** | **1.09-1.36** |
| Liver | C22 | 45 | 33.49 | 1.34 | 0.98-1.80 | 40 | 32.45 | 1.23 | 0.88-1.68 | 34 | 27.78 | 1.22 | 0.85-1.71 |
| Pancreas | C25 | 74 | 60.14 | 1.23 | 0.97-1.54 | 67 | 58.26 | 1.15 | 0.89-1.46 | 54 | 49.89 | 1.08 | 0.81-1.41 |
| Larynx | C32 | 16 | 18.5 | 0.86 | 0.49-1.40 | 11 | 17.84 | 0.62 | 0.31-1.10 | 10 | 14.92 | 0.67 | 0.32-1.23 |
| Lung | C33-C34 | 436 | 249.02 | **1.75** | **1.59-1.92** | 372 | 240.75 | **1.55** | **1.39-1.71** | 322 | 203.94 | **1.58** | **1.41-1.76** |
| Melanoma of skin | C43 | 173 | 58.44 | **2.96** | **2.54-3.44** | 164 | 56.52 | **2.90** | **2.47-3.38** | 144 | 47.94 | **3.00** | **2.53-3.54** |
| Breast | C50 | 204 | 179.71 | 1.14 | 0.98-1.30 | 164 | 173.81 | 0.94 | 0.80-1.10 | 136 | 147.61 | 0.92 | 0.77-1.09 |
| Cervix uteri | C53 | 8 | 9.6 | 0.83 | 0.36-1.64 | 8 | 9.27 | 0.86 | 0.37-1.70 | 6 | 7.78 | 0.77 | 0.28-1.68 |
| Corpus uteri | C54-C55 | 40 | 39.49 | 1.01 | 0.72-1.38 | 35 | 38.2 | 0.92 | 0.64-1.27 | 30 | 32.44 | 0.92 | 0.62-1.32 |
| Ovaries | C56 | 25 | 23.7 | 1.05 | 0.68-1.56 | 20 | 22.92 | 0.87 | 0.53-1.35 | 15 | 19.44 | 0.77 | 0.43-1.27 |
| Prostate | C61 | 500 | 391.99 | **1.28** | **1.17-1.39** | 440 | 378.77 | **1.16** | **1.06-1.28** | 347 | 319.65 | 1.09 | 0.97-1.21 |
| Testis | C62 | 4 | 2.77 | 1.44 | 0.39-3.70 | 4 | 2.66 | 1.50 | 0.40-3.85 | 4 | 2.17 | 1.84 | 0.50-4.72 |
| Kidney | C64 | 170 | 72.08 | **2.36** | **2.02-2.74** | 122 | 69.68 | **1.75** | **1.45-2.09** | 93 | 58.95 | **1.58** | **1.27-1.93** |
| Urinary bladder | C67 | 120 | 96.42 | **1.24** | **1.03-1.49** | 106 | 93.19 | 1.14 | 0.93-1.38 | 82 | 78.86 | 1.04 | 0.83-1.29 |
| Central nervous system | C70-C72 | 28 | 21.55 | 1.30 | 0.86-1.88 | 23 | 20.84 | 1.10 | 0.70-1.66 | 19 | 17.69 | 1.07 | 0.65-1.68 |
| Thyroid | C73 | 24 | 11.72 | **2.05** | **1.31-3.05** | 16 | 11.31 | 1.41 | 0.81-2.30 | 13 | 9.49 | 1.37 | 0.73-2.34 |
| **All haematological malignancies** | **C81-C96** | 221 | 139.17 | **1.59** | **1.39-1.81** | 152 | 134.55 | 1.13 | 0.96-1.32 | 131 | 114.15 | 1.15 | 0.96-1.36 |
| Hodgkin lymphoma | C81 | 51 | 3.7 | **13.78** | **10.26-18.12** | 42 | 3.57 | **11.76** | **8.48-15.90** | 39 | 3 | **13.00** | **9.24-17.77** |
| Non-Hodgkin lymphoma | C82-C85 | 59 | 57.47 | 1.03 | 0.78-1.32 | 39 | 55.58 | **0.70** | **0.50-0.96** | 33 | 47.2 | **0.70** | **0.48-0.98** |
| Multiple myeloma | C90 | 22 | 26.48 | 0.83 | 0.52-1.26 | 13 | 25.62 | **0.51** | **0.27-0.87** | 11 | 21.79 | **0.50** | **0.25-0.90** |
| Myeloid leukaemia | C92 | 62 | 17.34 | **3.58** | **2.74-4.58** | 38 | 16.78 | **2.26** | **1.60-3.11** | 33 | 14.25 | **2.32** | **1.59-3.25** |
| Acute myeloblastic | C92.0 | 16 | 10.07 | 1.59 | 0.91-2.58 | 11 | 9.75 | 1.13 | 0.56-2.02 | 9 | 8.3 | 1.08 | 0.49-2.06 |
| Chronic myeloid | C92.1 | 36 | 3.65 | **9.86** | **6.91-13.66** | 19 | 3.53 | **5.38** | **3.24-8.41** | 16 | 2.96 | **5.41** | **3.09-8.78** |
| **All sites**** | **C00-C97** | 3022 | 2034.97 | **1.49** | **1.43-1.54** | 2508 | 1967.33 | **1.27** | **1.23-1.33** | 2089 | 1666.11 | **1.25** | **1.20-1.31** |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); SPM: subsequent primary malignancies; CLL: chronic lymphocytic leukaemia; ICD-10: the WHO International Classification of Diseases (10th revision).
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 49. Observed number and SIRs of SPM following CLL by follow-up time for survivors aged <60 or ≥60 years, for both sexes

| Under 60 years | | | ≤1 year | | | | >1-≤5 years | | | | >5-≤10 years | | | | >10 years | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies *** | 82 | 29.08 | **2.82** | **2.24-3.5** | 166 | 112.97 | **1.47** | **1.25-1.71** | 135 | 94.34 | **1.43** | **1.20-1.69** | 49 | 45.44 | 1.08 | 0.80-1.43 |
| Lip/oral cavity | 3 | 1.95 | 1.54 | 0.31-4.5 | 4 | 6.69 | 0.60 | 0.16-1.53 | 3 | 4.43 | 0.68 | 0.14-1.98 | 2 | 1.61 | 1.24 | 0.14-4.49 |
| Oesophagus | 0 | 0.66 | 0.00 | 0.00-5.56 | 2 | 2.54 | 0.79 | 0.09-2.84 | 1 | 1.93 | 0.52 | 0.01-2.88 | 1 | 0.83 | 1.2 | 0.02-6.7 |
| Stomach | 1 | 1.04 | 0.96 | 0.01-5.35 | 8 | 3.98 | 2.01 | 0.87-3.96 | 3 | 3.22 | 0.93 | 0.19-2.72 | 0 | 1.54 | 0.00 | 0.00-2.38 |
| Colon/rectum | 10 | 3.85 | **2.60** | **1.24-4.78** | 22 | 15.4 | 1.43 | 0.89-2.16 | 24 | 13.07 | **1.84** | **1.18-2.73** | 7 | 6.55 | 1.07 | 0.43-2.2 |
| Lung | 13 | 4.02 | **3.23** | **1.72-5.53** | 32 | 15.82 | **2.02** | **1.38-2.86** | 30 | 13.24 | **2.27** | **1.53-3.23** | 9 | 6.52 | 1.38 | 0.63-2.62 |
| Melanoma of skin | 2 | 1.3 | 1.54 | 0.17-5.55 | 17 | 4.58 | **3.71** | **2.16-5.94** | 8 | 3.3 | **2.42** | **1.04-4.78** | 3 | 1.49 | 2.01 | 0.40-5.88 |
| Breast | 14 | 4.48 | **3.13** | **1.71-5.24** | 15 | 15.85 | 0.95 | 0.53-1.56 | 11 | 12.1 | 0.91 | 0.45-1.63 | 3 | 5.39 | 0.56 | 0.11-1.63 |
| Kidney | 16 | 1.35 | **11.85** | **6.77-19.25** | 14 | 5.09 | **2.75** | **1.50-4.62** | 5 | 3.98 | 1.26 | 0.40-2.93 | 3 | 1.71 | 1.75 | 0.35-5.13 |
| Urinary bladder | 2 | 0.87 | 2.30 | 0.26-8.3 | 3 | 3.56 | 0.84 | 0.17-2.46 | 4 | 3.16 | 1.27 | 0.34-3.24 | 0 | 1.74 | 0.00 | 0.00-2.11 |
| Central nervous system | 2 | 0.52 | 3.85 | 0.43-13.89 | 2 | 1.91 | 1.05 | 0.12-3.78 | 1 | 1.42 | 0.70 | 0.01-3.92 | 1 | 0.61 | 1.64 | 0.02-9.12 |
| Thyroid | 4 | 0.47 | **8.51** | **2.29-21.79** | 0 | 1.55 | 0.00 | 0.00-2.37 | 4 | 0.94 | **4.26** | **1.14-10.89** | 0 | 0.32 | 0.00 | 0.00-11.46 |
| **All haematological malignancies** | 14 | 2.19 | **6.39** | **3.49-10.73** | 19 | 8.04 | **2.36** | **1.42-3.69** | 10 | 6.44 | 1.55 | 0.74-2.86 | 4 | 3.17 | 1.26 | 0.34-3.23 |
| Hodgkin lymphoma | 4 | 0.14 | **28.57** | **7.69-73.15** | 7 | 0.43 | **16.28** | **6.52-33.54** | 4 | 0.26 | **15.38** | **4.14-39.39** | 2 | 0.11 | **18.18** | **2.04-65.65** |
| Non-Hodgkin lymphoma | 4 | 0.93 | **4.30** | **1.16-11.01** | 5 | 3.39 | 1.47 | 0.48-3.44 | 3 | 2.68 | 1.12 | 0.22-3.27 | 1 | 1.32 | 0.76 | 0.01-4.22 |
| Multiple myeloma | 1 | 0.34 | 2.94 | 0.04-16.36 | 0 | 1.35 | 0.00 | 0.00-2.72 | 0 | 1.18 | 0.00 | 0.00-3.11 | 0 | 0.61 | 0.00 | 0.00-6.01 |
| Myeloid leukaemia | 3 | 0.28 | **10.71** | **2.15-31.31** | 4 | 0.96 | **4.17** | **1.12-10.67** | 3 | 0.76 | 3.95 | 0.79-11.53 | 1 | 0.39 | 2.56 | 0.03-14.27 |
| Acute myeloblastic | 0 | 0.14 | 0.00 | 0.00-26.2 | 2 | 0.52 | 3.85 | 0.43-13.89 | 0 | 0.43 | 0.00 | 0.00-8.53 | 0 | 0.22 | 0.00 | 0.00-16.67 |
| Chronic myeloid | 3 | 0.07 | **42.86** | **8.61-125.22** | 0 | 0.26 | 0.00 | 0.00-14.11 | 1 | 0.17 | 5.88 | 0.08-32.73 | 0 | 0.08 | 0.00 | 0.00-45.85 |
| **All sites**** | 100 | 31.8 | **3.14** | **2.56-3.82** | 185 | 123.02 | **1.5** | **1.29-1.74** | 149 | 102.39 | **1.46** | **1.23-1.71** | 54 | 49.43 | 1.09 | 0.82-1.43 |
| **60 years and older** | | | **≤1 year** | | | | **>1-≤5 years** | | | | **>5-≤10 years** | | | | **>10 years** | | | |
| **Subsequent cancer sites** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | 741 | 307.63 | **2.41** | **2.24-2.59** | 1038 | 826.63 | **1.26** | **1.18-1.33** | 428 | 359.83 | **1.19** | **1.08-1.31** | 86 | 80.11 | 1.07 | 0.86-1.33 |
| Lip/oral cavity | 32 | 7.32 | **4.37** | **2.99-6.17** | 24 | 18.74 | 1.28 | 0.82-1.91 | 13 | 7.34 | 1.77 | 0.94-3.03 | 1 | 1.42 | 0.70 | 0.01-3.92 |
| Stomach | 30 | 14.87 | **2.02** | **1.36-2.88** | 50 | 40.09 | 1.25 | 0.93-1.64 | 22 | 17.92 | 1.23 | 0.77-1.86 | 10 | 4.19 | **2.39** | **1.14-4.39** |
| Colon/rectum | 151 | 55.6 | **2.72** | **2.30-3.19** | 183 | 150.11 | 1.22 | 1.05-1.41 | 77 | 66.85 | 1.15 | 0.91-1.44 | 14 | 16.28 | 0.86 | 0.47-1.44 |
| Liver | 11 | 5.3 | **2.08** | **1.03-3.71** | 17 | 14.9 | 1.14 | 0.66-1.83 | 13 | 6.99 | 1.86 | 0.99-3.18 | 2 | 1.63 | 1.23 | 0.14-4.43 |
| Pancreas | 18 | 9.52 | **1.89** | **1.12-2.99** | 29 | 26.71 | 1.09 | 0.73-1.56 | 12 | 12.71 | 0.94 | 0.49-1.65 | 4 | 3.14 | 1.27 | 0.34-3.26 |
| Lung | 101 | 41.08 | **2.46** | **2.00-2.99** | 173 | 110.21 | **1.57** | **1.34-1.82** | 66 | 47.71 | **1.38** | **1.07-1.76** | 12 | 10.42 | 1.15 | 0.59-2.01 |
| Melanoma of skin | 27 | 9.19 | **2.94** | **1.94-4.27** | 76 | 25.16 | **3.02** | **2.38-3.78** | 34 | 11.05 | **3.08** | **2.13-4.3** | 6 | 2.35 | 2.55 | 0.93-5.56 |
| Breast | 54 | 27.63 | **1.95** | **1.47-2.55** | 74 | 73.75 | 1.00 | 0.79-1.26 | 29 | 32.65 | 0.89 | 0.59-1.28 | 4 | 7.86 | 0.51 | 0.14-1.3 |
| Ovaries | 10 | 3.81 | **2.62** | **1.26-4.83** | 10 | 10.2 | 0.98 | 0.47-1.8 | 1 | 4.63 | 0.22 | 0.00-1.2 | 2 | 1.15 | 1.74 | 0.20-6.28 |
| Prostate | 146 | 68.6 | **2.13** | **1.80-2.5** | 194 | 182.86 | 1.06 | 0.92-1.22 | 81 | 74.98 | 1.08 | 0.86-1.34 | 10 | 13.66 | 0.73 | 0.35-1.35 |
| Kidney | 61 | 11.78 | **5.18** | **3.96-6.65** | 48 | 31.68 | **1.52** | **1.12-2.01** | 18 | 13.67 | 1.32 | 0.78-2.08 | 5 | 2.81 | 1.78 | 0.57-4.15 |
| Urinary bladder | 36 | 16.67 | **2.16** | **1.51-2.99** | 50 | 44.94 | 1.11 | 0.83-1.47 | 19 | 20.26 | 0.94 | 0.56-1.46 | 6 | 5.22 | 1.15 | 0.42-2.5 |
| Central nervous system | 7 | 3.33 | 2.10 | 0.84-4.33 | 9 | 8.98 | 1.00 | 0.46-1.9 | 5 | 3.95 | 1.27 | 0.41-2.95 | 1 | 0.82 | 1.22 | 0.02-6.79 |
| Thyroid | 7 | 1.76 | **3.98** | **1.59-8.2** | 6 | 4.55 | 1.32 | 0.48-2.87 | 2 | 1.8 | 1.11 | 0.12-4.01 | 1 | 0.34 | 2.94 | 0.04-16.36 |
| **All haematological malignancies** | 76 | 22.85 | **3.33** | **2.62-4.16** | 71 | 61.82 | 1.15 | 0.90-1.45 | 21 | 28.06 | 0.75 | 0.46-1.14 | 6 | 6.6 | 0.91 | 0.33-1.98 |
| Hodgkin lymphoma | 8 | 0.57 | **14.04** | **6.04-27.66** | 17 | 1.46 | **11.64** | **6.78-18.64** | 9 | 0.62 | **14.52** | **6.62-27.56** | 0 | 0.12 | 0.00 | 0.00-30.57 |
| Non-Hodgkin lymphoma | 22 | 9.34 | **2.36** | **1.48-3.57** | 19 | 25.5 | 0.75 | 0.45-1.16 | 4 | 11.55 | **0.35** | **0.09-0.89** | 1 | 2.74 | 0.36 | 0.00-2.03 |
| Multiple myeloma | 10 | 4.35 | **2.30** | **1.10-4.23** | 8 | 11.91 | 0.67 | 0.29-1.32 | 3 | 5.47 | 0.55 | 0.11-1.6 | 0 | 1.27 | 0.00 | 0.00-2.89 |
| Myeloid leukaemia | 26 | 2.83 | **9.19** | **6.00-13.46** | 16 | 7.73 | **2.07** | **1.18-3.36** | 4 | 3.55 | 1.13 | 0.30-2.88 | 5 | 0.86 | **5.81** | **1.87-13.57** |
| Acute myeloblastic | 7 | 1.63 | **4.29** | **1.72-8.85** | 6 | 4.51 | 1.33 | 0.49-2.9 | 1 | 2.1 | 0.48 | 0.01-2.65 | 0 | 0.52 | 0.00 | 0.00-7.05 |
| Chronic myeloid | 17 | 0.62 | **27.42** | **15.96-43.9** | 8 | 1.59 | **5.03** | **2.17-9.91** | 3 | 0.69 | 4.35 | 0.87-12.7 | 4 | 0.17 | **23.53** | **6.33-60.24** |
| **All sites**** | 833 | 337.05 | **2.47** | **2.31-2.65** | 1146 | 906.33 | **1.26** | **1.19-1.34** | 462 | 396.03 | **1.17** | **1.06-1.28** | 93 | 88.9 | 1.05 | 0.84-1.28 |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); SPM: subsequent primary malignancies; CLL: chronic lymphocytic leukaemia.
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 50. Observed number, SIRs and EARs of SPM following CLL by calendar period, for both sexes

| | | 1990–2000 CLL patients=5761 PYRs=16716.36 | | | | | 2001–2011 CLL patients=11266 PYRs=73691.18 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **EAR** | **O** | **E** | **SIR** | **95% CI** | **EAR** |
| **All solid malignancies*** | **C00-C75** | 250 | 179.14 | **1.40** | **1.23-1.58** | 42.39 | 895 | 615.79 | **1.45** | **1.36-1.55** | 37.89 |
| Lip, oral cavity, and pharynx | C00-C14 | 5 | 5.12 | 0.98 | 0.31-2.28 | -0.07 | 28 | 16.54 | **1.69** | **1.12-2.45** | 1.56 |
| Oesophagus | C15 | 1 | 2.67 | 0.37 | 0.00-2.08 | -1.00 | 7 | 9.54 | 0.73 | 0.29-1.51 | -0.34 |
| Stomach | C16 | 11 | 10.16 | 1.08 | 0.54-1.94 | 0.50 | 43 | 28.57 | **1.51** | **1.09-2.03** | 1.96 |
| Colon, rectum, and anus | C18-C21 | 46 | 32.51 | **1.41** | **1.04-1.89** | 8.07 | 171 | 105.18 | **1.63** | **1.39-1.89** | 8.93 |
| Liver | C22 | 5 | 2.77 | 1.81 | 0.58-4.21 | 1.33 | 15 | 12.76 | 1.18 | 0.66-1.94 | 0.30 |
| Pancreas | C25 | 10 | 5.46 | 1.83 | 0.88-3.37 | 2.72 | 17 | 21.57 | 0.79 | 0.46-1.26 | -0.62 |
| Larynx | C32 | 2 | 2.32 | 0.86 | 0.10-3.11 | -0.19 | 4 | 5.95 | 0.67 | 0.18-1.72 | -0.26 |
| Lung | C33-C34 | 57 | 28.59 | **1.99** | **1.51-2.58** | 17.00 | 155 | 86.47 | **1.79** | **1.52-2.10** | 9.30 |
| Melanoma of skin | C43 | 10 | 3.79 | **2.64** | **1.26-4.85** | 3.71 | 48 | 18.17 | **2.64** | **1.95-3.50** | 4.05 |
| Breast | C50 | 24 | 17.87 | 1.34 | 0.86-2.00 | 3.67 | 53 | 55.29 | 0.96 | 0.72-1.25 | -0.31 |
| Cervix uteri | C53 | 0 | 1.55 | 0.00 | 0.00-2.37 | -0.93 | 2 | 2.99 | 0.67 | 0.08-2.42 | -0.13 |
| Corpus uteri | C54-C55 | 2 | 4.49 | 0.45 | 0.05-1.61 | -1.49 | 10 | 12.83 | 0.78 | 0.37-1.43 | -0.38 |
| Ovaries | C56 | 0 | 3.02 | 0.00 | 0.00-1.21 | -1.81 | 5 | 7.12 | 0.70 | 0.23-1.64 | -0.29 |
| Prostate | C61 | 34 | 27.59 | 1.23 | 0.85-1.72 | 3.83 | 178 | 129.98 | **1.37** | **1.18-1.59** | 6.52 |
| Testis | C62 | 0 | 0.29 | 0.00 | 0.00-12.65 | -0.17 | 0 | 0.93 | 0.00 | 0.00-3.94 | -0.13 |
| Kidney | C64 | 15 | 7.28 | **2.06** | **1.15-3.40** | 4.62 | 61 | 26.66 | **2.29** | **1.75-2.94** | 4.66 |
| Urinary bladder | C67 | 14 | 11.08 | 1.26 | 0.69-2.12 | 1.75 | 40 | 32.77 | 1.22 | 0.87-1.66 | 0.98 |
| Central nervous system | C70-C72 | 2 | 2.11 | 0.95 | 0.11-3.42 | -0.07 | 11 | 7.69 | 1.43 | 0.71-2.56 | 0.45 |
| Thyroid | C73 | 1 | 1.13 | 0.88 | 0.01-4.92 | -0.08 | 6 | 3.79 | 1.58 | 0.58-3.45 | 0.30 |
| **All haematological malignancies** | **C81-C96** | 19 | 14.6 | 1.30 | 0.78-2.03 | 2.63 | 55 | 47.04 | 1.17 | 0.88-1.52 | 1.08 |
| Hodgkin lymphoma | C81 | 5 | 0.42 | **11.90** | **3.84-27.78** | 2.74 | 18 | 1.15 | **15.65** | **9.27-24.74** | 2.29 |
| Non-Hodgkin lymphoma | C82-C85 | 2 | 5.82 | 0.34 | 0.04-1.24 | -2.29 | 15 | 18.92 | 0.79 | 0.44-1.31 | -0.53 |
| Multiple myeloma | C90 | 0 | 2.83 | 0.00 | 0.00-1.30 | -1.69 | 0 | 9.13 | **0.00** | **0.00-0.40** | -1.24 |
| Myeloid leukaemia | C92 | 11 | 2.05 | **5.37** | **2.67-9.60** | 5.35 | 15 | 5.92 | **2.53** | **1.42-4.18** | 1.23 |
| Acute myeloblastic | C92.0 | 0 | 1.09 | 0.00 | 0.00-3.37 | -0.65 | 5 | 3.54 | 1.41 | 0.46-3.30 | 0.20 |
| Chronic myeloid | C92.1 | 11 | 0.58 | **18.97** | **9.45-33.94** | 6.23 | 9 | 1.11 | **8.11** | **3.70-15.39** | 1.07 |
| **All sites**** | **C00-C97** | 280 | 198.45 | **1.41** | **1.25-1.59** | 48.78 | 967 | 676.43 | **1.43** | **1.34-1.52** | 39.43 |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); EAR: excess absolute risk per 10,000 person-years; PYRs: person-years of observation; SPM: subsequent primary malignancies; CLL: chronic lymphocytic leukaemia; ICD-10: the WHO International Classification of Diseases (10th revision).
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 51. Risk of CLL subsequent to other primary malignancies by follow-up time, for both sexes

| | ≤1 year | | | >1-≤5 years | | | >5-≤10 years | | | >10 years | | | Overall | | | Overall (excl. <2 months) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Site of first primary cancer** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** |
| **All solid malignancies*** | 948 | **3.17** | **2.97-3.38** | 649 | **0.92** | **0.85-0.99** | 396 | 1.11 | 1.00-1.22 | 109 | 0.98 | 0.80-1.18 | 2102 | **1.42** | **1.36-1.48** | 1455 | 1.03 | 0.97-1.08 |
| Lip/oral cavity | 38 | **4.71** | **3.34-6.47** | 20 | 1.14 | 0.70-1.76 | 7 | 0.79 | 0.32-1.63 | 1 | 0.33 | 0.00-1.84 | 66 | **1.76** | **1.36-2.24** | 36 | 1.00 | 0.70-1.39 |
| Stomach | 31 | **2.66** | **1.81-3.78** | 18 | 0.93 | 0.55-1.47 | 8 | 0.90 | 0.39-1.77 | 3 | 0.96 | 0.19-2.81 | 60 | **1.40** | **1.06-1.80** | 34 | 0.84 | 0.58-1.18 |
| Colon/rectum | 166 | **3.06** | **2.61-3.56** | 93 | **0.70** | **0.57-0.86** | 53 | 0.84 | 0.63-1.10 | 19 | 1.02 | 0.62-1.60 | 331 | **1.24** | **1.11-1.38** | 215 | **0.84** | **0.73-0.96** |
| Lung | 91 | **3.11** | **2.51-3.82** | 23 | 0.68 | 0.43-1.02 | 7 | 0.54 | 0.22-1.11 | 2 | 0.45 | 0.05-1.61 | 123 | **1.53** | **1.27-1.83** | 53 | **0.73** | **0.54-0.95** |
| Melanoma of skin | 65 | **6.06** | **4.68-7.72** | 60 | **2.03** | **1.55-2.62** | 27 | **1.66** | **1.10-2.42** | 8 | 1.35 | 0.58-2.66 | 160 | **2.56** | **2.18-2.99** | 131 | **2.17** | **1.81-2.57** |
| Prostate | 209 | **2.70** | **2.35-3.09** | 223 | 1.01 | 0.88-1.15 | 124 | 1.17 | 0.98-1.40 | 20 | 0.90 | 0.55-1.39 | 576 | **1.35** | **1.24-1.47** | 446 | 1.08 | 0.98-1.19 |
| Kidney | 53 | **4.42** | **3.31-5.78** | 52 | **1.57** | **1.17-2.06** | 35 | **1.75** | **1.22-2.44** | 9 | 1.22 | 0.56-2.32 | 149 | **2.06** | **1.74-2.42** | 111 | **1.58** | **1.30-1.91** |
| Urinary bladder | 56 | **3.43** | **2.59-4.46** | 38 | 0.99 | 0.70-1.36 | 23 | 1.13 | 0.71-1.69 | 4 | 0.59 | 0.16-1.50 | 121 | **1.48** | **1.22-1.76** | 92 | 1.17 | 0.94-1.43 |
| Thyroid | 11 | **5.37** | **2.67-9.60** | 6 | 0.96 | 0.35-2.09 | 6 | 1.46 | 0.53-3.18 | 1 | 0.58 | 0.01-3.25 | 24 | **1.70** | **1.09-2.53** | 14 | 1.02 | 0.56-1.71 |
| **All haematological malignancies** | 62 | **2.86** | **2.19-3.66** | 19 | **0.38** | **0.23-0.59** | 13 | **0.55** | **0.29-0.94** | 2 | **0.27** | **0.03-0.98** | 96 | 0.93 | 0.76-1.14 | 59 | **0.60** | **0.46-0.77** |
| Hodgkin lymphoma | 15 | **24.59** | **13.75-40.56** | 3 | 1.83 | 0.37-5.34 | 1 | 0.97 | 0.01-5.40 | 1 | 2.08 | 0.03-11.59 | 20 | **5.33** | **3.26-8.24** | 9 | **2.48** | **1.13-4.71** |
| Myeloid leukaemia | 28 | **14.14** | **9.39-20.44** | 5 | 1.62 | 0.52-3.79 | 3 | 2.16 | 0.43-6.31 | 1 | 2.22 | 0.03-12.36 | 37 | **5.36** | **3.78-7.39** | 14 | **2.18** | **1.19-3.66** |
| Chronic myeloid | 18 | **29.51** | **17.48-46.64** | 5 | **3.36** | **1.08-7.83** | 2 | 2.60 | 0.29-9.38 | 1 | 4.35 | 0.06-24.19 | 26 | **8.39** | **5.48-12.29** | 9 | **3.02** | **1.38-5.73** |
| **All sites**** | 893 | **2.76** | **2.58-2.94** | 669 | **0.88** | **0.81-0.95** | 407 | 1.06 | 0.96-1.17 | 111 | 0.93 | 0.76-1.12 | 2080 | **1.31** | **1.25-1.37** | 1516 | 0.99 | 0.94-1.05 |

O: observed number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); CLL: chronic lymphocytic leukaemia.
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Chronic myeloid leukaemia

### Table 52. Observed number, SIRs and EARs of SPM following CML by age at diagnosis, for both sexes

| | | 15-44 years | | | | | 45-59 years | | | | | ≥60 years | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **EAR** | **O** | **E** | **SIR** | **95% CI** | **EAR** | **O** | **E** | **SIR** | **95% CI** | **EAR** |
| **All solid malignancies*** | **C00-C75** | 21 | 10.66 | **1.97** | **1.22-3.01** | 10.93 | 91 | 64.55 | **1.41** | **1.14-1.73** | 27.21 | 250 | 208.25 | **1.20** | **1.06-1.36** | 28.60 |
| Lip, oral cavity, and pharynx | C00-C14 | 2 | 0.49 | 4.08 | 0.46-14.74 | 1.60 | 3 | 3.26 | 0.92 | 0.18-2.69 | -0.27 | 10 | 4.68 | **2.14** | **1.02-3.93** | 3.64 |
| Lip | C00 | 1 | 0 | 0.00 | 0.00-0.00 | 1.06 | 0 | 0.05 | 0.00 | 0.00-73.36 | -0.05 | 2 | 0.33 | 6.06 | 0.68-21.88 | 1.14 |
| Tongue | C01-C02 | 1 | 0.1 | 10.00 | 0.13-55.64 | 0.95 | 2 | 0.63 | 3.17 | 0.36-11.46 | 1.41 | 1 | 0.91 | 1.10 | 0.01-6.11 | 0.06 |
| Gum, floor of mouth, other mouth | C03-C06 | 0 | 0.13 | 0.00 | 0.00-28.22 | -0.14 | 0 | 0.83 | 0.00 | 0.00-4.42 | -0.85 | 2 | 1.14 | 1.75 | 0.20-6.33 | 0.59 |
| Parotid gland, other salivary glands | C07-C08 | 0 | 0.03 | 0.00 | 0.00-122.27 | -0.03 | 0 | 0.13 | 0.00 | 0.00-28.22 | -0.13 | 1 | 0.42 | 2.38 | 0.03-13.25 | 0.40 |
| Pharynx and other oral cavity | C09-C14 | 0 | 0.21 | 0.00 | 0.00-17.47 | -0.22 | 1 | 1.55 | 0.65 | 0.01-3.59 | -0.57 | 3 | 1.76 | 1.70 | 0.34-4.98 | 0.85 |
| Oesophagus | C15 | 1 | 0.11 | 9.09 | 0.12-50.58 | 0.94 | 2 | 1.24 | 1.61 | 0.18-5.82 | 0.78 | 4 | 2.97 | 1.35 | 0.36-3.45 | 0.71 |
| Stomach | C16 | 1 | 0.28 | 3.57 | 0.05-19.87 | 0.76 | 2 | 2.1 | 0.95 | 0.11-3.44 | -0.10 | 17 | 9.9 | 1.72 | 1.00-2.75 | 4.86 |
| Colon, rectum, and anus | C18-C21 | 1 | 0.87 | 1.15 | 0.02-6.40 | 0.14 | 10 | 8.45 | 1.18 | 0.57-2.18 | 1.59 | 46 | 37.93 | 1.21 | 0.89-1.62 | 5.53 |
| Liver | C22 | 0 | 0.09 | 0.00 | 0.00-40.76 | -0.10 | 0 | 0.98 | 0.00 | 0.00-3.74 | -1.01 | 6 | 3.64 | 1.65 | 0.60-3.59 | 1.62 |
| Pancreas | C25 | 0 | 0.16 | 0.00 | 0.00-22.93 | -0.17 | 2 | 1.76 | 1.14 | 0.13-4.10 | 0.25 | 7 | 6.84 | 1.02 | 0.41-2.11 | 0.11 |
| Larynx | C32 | 0 | 0.09 | 0.00 | 0.00-40.76 | -0.10 | 2 | 0.93 | 2.15 | 0.24-7.76 | 1.10 | 3 | 1.86 | 1.61 | 0.32-4.71 | 0.78 |
| Lung | C33-C34 | 2 | 0.78 | 2.56 | 0.29-9.26 | 1.29 | 10 | 8.66 | 1.15 | 0.55-2.12 | 1.38 | 24 | 27.43 | 0.87 | 0.56-1.30 | -2.35 |
| Melanoma of skin | C43 | 5 | 1.07 | **4.67** | **1.51-10.90** | 4.15 | 7 | 2.51 | **2.79** | **1.12-5.75** | 4.62 | 8 | 6.31 | 1.27 | 0.55-2.50 | 1.16 |
| Breast | C50 | 0 | 2.57 | 0.00 | 0.00-1.43 | -2.72 | 17 | 11.85 | 1.43 | 0.84-2.30 | 5.30 | 17 | 22.4 | 0.76 | 0.44-1.22 | -3.70 |
| Cervix uteri | C53 | 1 | 0.55 | 1.82 | 0.02-10.12 | 0.48 | 0 | 0.77 | 0.00 | 0.00-4.76 | -0.79 | 1 | 1.11 | 0.90 | 0.01-5.01 | -0.08 |
| Corpus uteri | C54-C55 | 0 | 0.19 | 0.00 | 0.00-19.31 | -0.20 | 4 | 1.88 | 2.13 | 0.57-5.45 | 2.18 | 4 | 5.14 | 0.78 | 0.21-1.99 | -0.78 |
| Ovaries | C56 | 0 | 0.23 | 0.00 | 0.00-15.95 | -0.24 | 2 | 1.2 | 1.67 | 0.19-6.02 | 0.82 | 4 | 3.07 | 1.30 | 0.35-3.34 | 0.64 |
| Prostate | C61 | 1 | 0.3 | 3.33 | 0.04-18.55 | 0.74 | 16 | 9.39 | 1.70 | 0.97-2.77 | 6.80 | 51 | 41.65 | 1.22 | 0.91-1.61 | 6.41 |
| Testis | C62 | 1 | 1 | 1.00 | 0.01-5.56 | 0.00 | 0 | 0.33 | 0.00 | 0.00-11.12 | -0.34 | 0 | 0.13 | 0.00 | 0.00-28.22 | -0.09 |
| Kidney | C64 | 1 | 0.33 | 3.03 | 0.04-16.86 | 0.71 | 7 | 2.6 | **2.69** | **1.08-5.55** | 4.53 | 13 | 7.72 | 1.68 | 0.90-2.88 | 3.62 |
| Urinary bladder | C67 | 0 | 0.15 | 0.00 | 0.00-24.45 | -0.16 | 2 | 1.9 | 1.05 | 0.12-3.80 | 0.10 | 15 | 10.95 | 1.37 | 0.77-2.26 | 2.77 |
| Central nervous system | C70-C72 | 1 | 0.35 | 2.86 | 0.04-15.90 | 0.69 | 1 | 1.02 | 0.98 | 0.01-5.45 | -0.02 | 3 | 2.31 | 1.30 | 0.26-3.79 | 0.47 |
| Thyroid | C73 | 1 | 0.49 | 2.04 | 0.03-11.35 | 0.54 | 0 | 0.92 | 0.00 | 0.00-3.99 | -0.95 | 1 | 1.24 | 0.81 | 0.01-4.49 | -0.16 |
| **All haematological malignancies** | **C81-C96** | 13 | 1.16 | **11.21** | **5.96-19.17** | 12.51 | 11 | 4.44 | **2.48** | **1.24-4.43** | 6.75 | 38 | 15.7 | **2.42** | **1.71-3.32** | 15.28 |
| Hodgkin lymphoma | C81 | 0 | 0.28 | 0.00 | 0.00-13.10 | -0.30 | 0 | 0.21 | 0.00 | 0.00-17.47 | -0.22 | 1 | 0.38 | 2.63 | 0.03-14.64 | 0.42 |
| Non-Hodgkin lymphoma | C82-C85 | 5 | 0.45 | **11.11** | **3.58-25.93** | 4.81 | 2 | 1.92 | 1.04 | 0.12-3.76 | 0.08 | 10 | 6.56 | 1.52 | 0.73-2.80 | 2.36 |
| Multiple myeloma | C90 | 2 | 0.08 | **25.00** | **2.81-90.26** | 2.03 | 3 | 0.77 | 3.90 | 0.78-11.38 | 2.29 | 9 | 3.03 | **2.97** | **1.36-5.64** | 4.09 |
| Lymphoid leukaemia | C91 | 5 | 0.14 | **35.71** | **11.51-83.35** | 5.14 | 6 | 0.75 | **8.00** | **2.92-17.41** | 5.40 | 18 | 2.73 | **6.59** | **3.91-10.42** | 10.46 |
| Acute lymphoblastic | C91.0 | 1 | 0.06 | 16.67 | 0.22-92.73 | 0.99 | 0 | 0.06 | 0.00 | 0.00-61.13 | -0.06 | 2 | 0.12 | **16.67** | **1.87-60.17** | 1.29 |
| Chronic lymphocytic | C91.1 | 4 | 0.06 | **66.67** | **17.94-170.68** | 4.16 | 6 | 0.63 | **9.52** | **3.48-20.73** | 5.53 | 16 | 2.42 | **6.61** | **3.78-10.74** | 9.30 |
| **All sites**** | **C00-C97** | 34 | 11.99 | **2.84** | **1.96-3.96** | 23.26 | 105 | 70.12 | **1.50** | **1.22-1.81** | 35.89 | 296 | 228.48 | **1.30** | **1.15-1.45** | 46.26 |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); EAR: excess absolute risk per 10,000 person-years; SPM: subsequent primary malignancies; CML: chronic myeloid leukaemia; ICD-10: the WHO International Classification of Diseases (10th revision).

*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)

Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 53. Observed number and SIRs of SPM following CML by follow-up time, for both sexes

| | | ≤1 year | | | | >1-≤5 years | | | | >5-≤10 years | | | | >10 years | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer site** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | **C00-C75** | 118 | 55.46 | **2.13** | **1.76-2.55** | 146 | 135.39 | 1.08 | 0.91-1.27 | 80 | 70.4 | 1.14 | 0.90-1.41 | 21 | 22.21 | 0.95 | 0.59-1.45 |
| Lip, oral cavity, and pharynx | C00-C14 | 5 | 1.58 | **3.16** | **1.02-7.39** | 6 | 4.03 | 1.49 | 0.54-3.24 | 3 | 2.14 | 1.40 | 0.28-4.10 | 1 | 0.69 | 1.45 | 0.02-8.06 |
| Lip | C00 | 1 | 0.08 | 12.50 | 0.16-69.55 | 1 | 0.18 | 5.56 | 0.07-30.91 | 1 | 0.1 | 10.00 | 0.13-55.64 | 0 | 0.03 | 0.00 | 0.00-122.27 |
| Tongue | C01-C02 | 1 | 0.31 | 3.23 | 0.04-17.95 | 0 | 0.78 | 0.00 | 0.00-4.70 | 2 | 0.42 | 4.76 | 0.53-17.19 | 1 | 0.14 | 7.14 | 0.09-39.74 |
| Gum, floor of mouth, other mouth | C03-C06 | 0 | 0.4 | 0.00 | 0.00-9.17 | 2 | 1.01 | 1.98 | 0.22-7.15 | 0 | 0.53 | 0.00 | 0.00-6.92 | 0 | 0.17 | 0.00 | 0.00-21.58 |
| Parotid and other salivary glands | C07-C08 | 1 | 0.11 | 9.09 | 0.12-50.58 | 0 | 0.28 | 0.00 | 0.22-13.10 | 0 | 0.14 | 0.00 | 0.00-26.20 | 0 | 0.05 | 0.00 | 0.00-73.36 |
| Pharynx and other oral cavity | C09-C14 | 2 | 0.63 | 3.17 | 0.36-11.46 | 2 | 1.68 | 1.19 | 0.13-4.30 | 0 | 0.9 | 0.00 | 0.00-4.08 | 0 | 0.27 | 0.00 | 0.00-13.59 |
| Oesophagus | C15 | 3 | 0.83 | 3.61 | 0.73-10.56 | 2 | 2.07 | 0.97 | 0.11-3.49 | 3 | 1.09 | 2.75 | 0.55-8.04 | 0 | 0.34 | 0.00 | 0.00-10.79 |
| Stomach | C16 | 8 | 2.53 | **3.16** | **1.36-6.23** | 6 | 5.89 | 1.02 | 0.37-2.22 | 6 | 2.96 | 2.03 | 0.74-4.41 | 0 | 0.91 | 0.00 | 0.00-4.03 |
| Colon, rectum, and anus | C18-C21 | 16 | 9.56 | 1.67 | 0.96-2.72 | 24 | 22.67 | 1.06 | 0.68-1.58 | 12 | 11.41 | 1.05 | 0.54-1.84 | 5 | 3.61 | 1.39 | 0.45-3.23 |
| Liver | C22 | 2 | 0.88 | 2.27 | 0.26-8.21 | 4 | 2.2 | 1.82 | 0.49-4.65 | 0 | 1.23 | 0.00 | 0.00-2.98 | 0 | 0.41 | 0.00 | 0.00-8.95 |
| Pancreas | C25 | 2 | 1.64 | 1.22 | 0.14-4.40 | 2 | 4.11 | 0.49 | 0.05-1.76 | 3 | 2.27 | 1.32 | 0.27-3.86 | 2 | 0.75 | 2.67 | 0.30-9.63 |
| Larynx | C32 | 1 | 0.57 | 1.75 | 0.02-9.76 | 4 | 1.4 | 2.86 | 0.77-7.31 | 0 | 0.69 | 0.00 | 0.00-5.32 | 0 | 0.2 | 0.00 | 0.00-18.34 |
| Lung | C33-C34 | 13 | 7.2 | 1.81 | 0.96-3.09 | 15 | 17.5 | 0.86 | 0.48-1.41 | 5 | 9.18 | 0.54 | 0.18-1.27 | 3 | 2.97 | 1.01 | 0.20-2.95 |
| Melanoma of skin | C43 | 3 | 1.85 | 1.62 | 0.33-4.74 | 8 | 4.75 | 1.68 | 0.73-3.32 | 9 | 2.5 | **3.60** | **1.64-6.83** | 1 | 0.76 | 1.32 | 0.02-7.32 |
| Breast | C50 | 12 | 6.88 | 1.74 | 0.90-3.05 | 12 | 17.53 | 0.68 | 0.35-1.20 | 9 | 9.32 | 0.97 | 0.44-1.83 | 2 | 3.09 | 0.65 | 0.07-2.34 |
| Cervix uteri | C53 | 0 | 0.47 | 0.00 | 0.00-7.80 | 2 | 1.17 | 1.71 | 0.19-6.17 | 0 | 0.6 | 0.00 | 0.00-6.11 | 0 | 0.19 | 0.00 | 0.00-19.31 |
| Corpus uteri | C54-C55 | 4 | 1.39 | 2.88 | 0.77-7.37 | 3 | 3.46 | 0.87 | 0.17-2.53 | 1 | 1.81 | 0.55 | 0.01-3.07 | 0 | 0.57 | 0.00 | 0.00-6.44 |
| Ovaries | C56 | 4 | 0.88 | **4.55** | **1.22-11.64** | 1 | 2.16 | 0.46 | 0.01-2.58 | 1 | 1.11 | 0.90 | 0.01-5.01 | 0 | 0.35 | 0.00 | 0.00-10.48 |
| Prostate | C61 | 19 | 10.15 | **1.87** | **1.13-2.92** | 36 | 24.68 | **1.46** | **1.02-2.02** | 9 | 12.78 | 0.70 | 0.32-1.34 | 4 | 3.74 | 1.07 | 0.29-2.74 |
| Testis | C62 | 1 | 0.28 | 3.57 | 0.05-19.87 | 0 | 0.72 | 0.00 | 0.00-5.09 | 0 | 0.36 | 0.00 | 0.00-10.19 | 0 | 0.11 | 0.00 | 0.00-33.35 |
| Kidney | C64 | 10 | 2.05 | **4.88** | **2.34-8.97** | 5 | 5.11 | 0.98 | 0.32-2.28 | 6 | 2.66 | 2.26 | 0.82-4.91 | 0 | 0.8 | 0.00 | 0.00-4.59 |
| Urinary bladder | C67 | 9 | 2.69 | **3.35** | **1.53-6.35** | 3 | 6.15 | 0.49 | 0.10-1.43 | 5 | 3.12 | 1.60 | 0.52-3.74 | 0 | 1.06 | 0.00 | 0.00-3.46 |
| Central nervous system | C70-C72 | 2 | 0.69 | 2.90 | 0.33-10.47 | 3 | 1.75 | 1.71 | 0.34-5.01 | 0 | 0.95 | 0.00 | 0.00-3.86 | 0 | 0.3 | 0.00 | 0.00-12.23 |
| Thyroid | C73 | 0 | 0.49 | 0.00 | 0.00-7.49 | 2 | 1.27 | 1.57 | 0.18-5.69 | 0 | 0.68 | 0.00 | 0.00-5.39 | 0 | 0.21 | 0.00 | 0.00-17.47 |
| **All haematological malignancies** | **C81-C96** | 36 | 4.2 | **8.57** | **6.00-11.87** | 17 | 10.15 | 1.67 | 0.98-2.68 | 6 | 5.31 | 1.13 | 0.41-2.46 | 3 | 1.65 | 1.82 | 0.37-5.31 |
| Hodgkin lymphoma | C81 | 1 | 0.18 | 5.56 | 0.07-30.91 | 0 | 0.42 | 0.00 | 0.00-8.73 | 0 | 0.21 | 0.00 | 0.00-17.47 | 0 | 0.07 | 0.00 | 0.00-52.40 |
| Non-Hodgkin lymphoma | C82-C85 | 6 | 1.74 | **3.45** | **1.26-7.51** | 7 | 4.25 | 1.65 | 0.66-3.39 | 3 | 2.22 | 1.35 | 0.27-3.95 | 1 | 0.71 | 1.41 | 0.02-7.84 |
| Multiple myeloma | C90 | 8 | 0.76 | **10.53** | **4.53-20.74** | 4 | 1.84 | 2.17 | 0.58-5.57 | 1 | 0.97 | 1.03 | 0.01-5.74 | 1 | 0.3 | 3.33 | 0.04-18.55 |
| Lymphoid leukaemia | C91 | 20 | 0.71 | **28.17** | **17.20-43.51** | 6 | 1.74 | **3.45** | **1.26-7.51** | 2 | 0.91 | 2.20 | 0.25-7.94 | 1 | 0.26 | 3.85 | 0.05-21.40 |
| Acute lymphoblastic | C91.0 | 2 | 0.03 | **66.67** | **7.49-240.70** | 1 | 0.12 | 8.33 | 0.11-46.37 | 0 | 0.06 | 0.00 | 0.00-61.13 | 0 | 0.02 | 0.00 | 0.00-183.40 |
| Chronic lymphocytic | C91.1 | 18 | 0.61 | **29.51** | **17.48-46.64** | 5 | 1.49 | **3.36** | **1.08-7.83** | 2 | 0.77 | 2.60 | 0.29-9.38 | 1 | 0.23 | 4.35 | 0.06-24.19 |
| **All sites**** | **C00-C97** | 157 | 60.86 | **2.58** | **2.19-3.02** | 170 | 148.31 | 1.15 | 0.98-1.33 | 86 | 77.11 | 1.12 | 0.89-1.38 | 25 | 24.34 | 1.03 | 0.66-1.52 |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); SPM: subsequent primary malignancies; CML: chronic myeloid leukaemia; ICD-10: the WHO International Classification of Diseases (10th revision).
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 54. Overall and site-specific SIRs of SPM following CML (all intervals, excluding initial 2 months, and excluding first year)

| | | Overall | | | | Overall (excl. <2 months) | | | | Overall (excl. <1 year) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer sites** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | **C00-C75** | 365 | 283.46 | **1.29** | **1.16-1.43** | 315 | 272.66 | **1.16** | **1.03-1.29** | 247 | 228 | 1.08 | 0.95-1.23 |
| Lip, oral cavity, and pharynx | C00-C14 | 15 | 8.43 | 1.78 | 1.00-2.93 | 12 | 8.13 | 1.48 | 0.76-2.58 | 10 | 6.86 | 1.46 | 0.70-2.68 |
| Lip | C00 | 3 | 0.38 | **7.89** | **1.59-23.07** | 2 | 0.36 | 5.56 | 0.62-20.06 | 2 | 0.31 | 6.45 | 0.72-23.29 |
| Tongue | C01-C02 | 4 | 1.64 | 2.44 | 0.66-6.24 | 3 | 1.58 | 1.90 | 0.38-5.55 | 3 | 1.34 | 2.24 | 0.45-6.54 |
| Gum, floor of mouth, other mouth | C03-C06 | 2 | 2.11 | 0.95 | 0.11-3.42 | 2 | 2.03 | 0.99 | 0.11-3.56 | 2 | 1.71 | 1.17 | 0.13-4.22 |
| Parotid gland, other salivary glands | C07-C08 | 1 | 0.58 | 1.72 | 0.02-9.59 | 0 | 0.56 | 0.00 | 0.00-6.55 | 0 | 0.47 | 0.00 | 0.00-7.80 |
| Pharynx and other oral cavity | C09-C14 | 4 | 3.51 | 1.14 | 0.31-2.92 | 4 | 3.42 | 1.17 | 0.31-2.99 | 2 | 2.85 | 0.70 | 0.08-2.53 |
| Oesophagus | C15 | 8 | 4.33 | 1.85 | 0.80-3.64 | 6 | 4.17 | 1.44 | 0.53-3.13 | 5 | 3.5 | 1.43 | 0.46-3.33 |
| Stomach | C16 | 20 | 12.29 | 1.63 | 0.99-2.51 | 16 | 11.79 | 1.36 | 0.78-2.20 | 12 | 9.76 | 1.23 | 0.63-2.15 |
| Colon, rectum, and anus | C18-C21 | 57 | 47.26 | 1.21 | 0.91-1.56 | 53 | 45.38 | 1.17 | 0.87-1.53 | 41 | 37.69 | 1.09 | 0.78-1.48 |
| Liver | C22 | 6 | 4.71 | 1.27 | 0.47-2.77 | 6 | 4.54 | 1.32 | 0.48-2.88 | 4 | 3.84 | 1.04 | 0.28-2.67 |
| Pancreas | C25 | 9 | 8.77 | 1.03 | 0.47-1.95 | 8 | 8.45 | 0.95 | 0.41-1.87 | 7 | 7.13 | 0.98 | 0.39-2.02 |
| Larynx | C32 | 5 | 2.88 | 1.74 | 0.56-4.05 | 4 | 2.78 | 1.44 | 0.39-3.68 | 4 | 2.29 | 1.75 | 0.47-4.47 |
| Lung | C33-C34 | 36 | 36.85 | 0.98 | 0.68-1.35 | 31 | 35.44 | 0.87 | 0.59-1.24 | 23 | 29.65 | 0.78 | 0.49-1.16 |
| Melanoma of skin | C43 | 21 | 9.86 | **2.13** | **1.32-3.26** | 20 | 9.51 | **2.10** | **1.28-3.25** | 18 | 8.01 | **2.25** | **1.33-3.55** |
| Breast | C50 | 35 | 36.81 | 0.95 | 0.66-1.32 | 28 | 35.5 | 0.79 | 0.52-1.14 | 23 | 29.94 | 0.77 | 0.49-1.15 |
| Cervix uteri | C53 | 2 | 2.43 | 0.82 | 0.09-2.97 | 2 | 2.34 | 0.85 | 0.10-3.09 | 2 | 1.96 | 1.02 | 0.11-3.68 |
| Corpus uteri | C54-C55 | 8 | 7.22 | 1.11 | 0.48-2.18 | 6 | 6.95 | 0.86 | 0.32-1.88 | 4 | 5.84 | 0.68 | 0.18-1.75 |
| Ovaries | C56 | 6 | 4.51 | 1.33 | 0.49-2.90 | 4 | 4.34 | 0.92 | 0.25-2.36 | 2 | 3.62 | 0.55 | 0.06-1.99 |
| Prostate | C61 | 68 | 51.34 | **1.32** | **1.03-1.68** | 62 | 49.35 | 1.26 | 0.96-1.61 | 49 | 41.2 | 1.19 | 0.88-1.57 |
| Testis | C62 | 1 | 1.46 | 0.68 | 0.01-3.81 | 1 | 1.41 | 0.71 | 0.01-3.95 | 0 | 1.19 | 0.00 | 0.00-3.08 |
| Kidney | C64 | 21 | 10.64 | **1.97** | **1.22-3.02** | 14 | 10.25 | 1.37 | 0.75-2.29 | 11 | 8.57 | 1.28 | 0.64-2.30 |
| Urinary bladder | C67 | 17 | 13.01 | 1.31 | 0.76-2.09 | 13 | 12.48 | 1.04 | 0.55-1.78 | 8 | 10.33 | 0.77 | 0.33-1.53 |
| Central nervous system | C70-C72 | 5 | 3.68 | 1.36 | 0.44-3.17 | 5 | 3.55 | 1.41 | 0.45-3.29 | 3 | 3 | 1.00 | 0.20-2.92 |
| Thyroid | C73 | 2 | 2.65 | 0.75 | 0.08-2.72 | 2 | 2.55 | 0.78 | 0.09- 2.83 | 2 | 2.16 | 0.93 | 0.10-3.34 |
| **All haematological malignancies** | **C81-C96** | 62 | 21.32 | **2.91** | **2.23-3.73** | 34 | 20.5 | **1.66** | **1.15-2.32** | 26 | 17.11 | 1.52 | 0.99-2.23 |
| Hodgkin lymphoma | C81 | 1 | 0.87 | 1.15 | 0.02-6.40 | 1 | 0.83 | 1.20 | 0.02-6.70 | 0 | 0.7 | 0.00 | 0.00-5.24 |
| Non-Hodgkin lymphoma | C82-C85 | 17 | 8.91 | **1.91** | **1.11-3.06** | 13 | 8.57 | 1.52 | 0.81-2.59 | 11 | 7.18 | 1.53 | 0.76-2.74 |
| Multiple myeloma | C90 | 14 | 3.86 | **3.63** | **1.98-6.09** | 10 | 3.71 | **2.70** | **1.29-4.96** | 6 | 3.11 | 1.93 | 0.70-4.20 |
| Lymphoid leukaemia | C91 | 29 | 3.62 | **8.01** | **5.36-11.51** | 10 | 3.48 | **2.87** | **1.38-5.28** | 9 | 2.91 | **3.09** | **1.41-5.87** |
| Acute lymphoblastic | C91.0 | 3 | 0.24 | **12.50** | **2.51-36.52** | 1 | 0.24 | 4.17 | 0.05-23.18 | 1 | 0.2 | 5.00 | 0.07-27.82 |
| Chronic lymphocytic | C91.1 | 26 | 3.1 | **8.39** | **5.48-12.29** | 9 | 2.98 | **3.02** | **1.38-5.73** | 8 | 2.49 | **3.21** | **1.38-6.33** |
| **All sites**** | **C00-C97** | 438 | 310.6 | **1.41** | **1.28-1.55** | 358 | 298.74 | **1.20** | **1.08-1.33** | 281 | 249.76 | 1.13 | 1.00-1.26 |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); SPM: subsequent primary malignancies; CML: chronic myeloid leukaemia; ICD-10: the WHO International Classification of Diseases (10th revision).
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 55. Observed number and SIRs of SPM following CML by follow-up time for survivors aged <60 or ≥60 years, for both sexes

| Under 60 years | ≤1 year | | | | >1-≤5 years | | | | >5-≤10 years | | | | >10 years | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | 23 | 8.41 | **2.73** | **1.73-4.10** | 41 | 29.86 | 1.37 | 0.99-1.86 | 39 | 24.8 | **1.57** | **1.12-2.15** | 12 | 12.14 | 0.99 | 0.51-1.73 |
| Lip/oral cavity | 1 | 0.49 | 2.04 | 0.03-11.35 | 1 | 1.6 | 0.63 | 0.01-3.48 | 3 | 1.18 | 2.54 | 0.51-7.43 | 0 | 0.49 | 0.00 | 0.00-7.49 |
| Oesophagus | 1 | 0.15 | 6.67 | 0.09-37.09 | 0 | 0.55 | 0 | 0.00-6.67 | 3 | 0.45 | **6.67** | **1.34-19.48** | 0 | 0.21 | 0.00 | 0.00-17.47 |
| Stomach | 1 | 0.28 | 3.57 | 0.05-19.87 | 0 | 0.96 | 0 | 0.00-3.82 | 2 | 0.78 | 2.56 | 0.29-9.26 | 0 | 0.38 | 0.00 | 0.00-9.65 |
| Colon/rectum | 2 | 0.99 | 2.02 | 0.23-7.29 | 6 | 3.62 | 1.66 | 0.61-3.61 | 2 | 3.12 | 0.64 | 0.07-2.31 | 1 | 1.6 | 0.63 | 0.01-3.48 |
| Lung | 3 | 0.97 | 3.09 | 0.62-9.04 | 4 | 3.63 | 1.1 | 0.30-2.82 | 3 | 3.17 | 0.95 | 0.19-2.77 | 2 | 1.63 | 1.23 | 0.14-4.43 |
| Melanoma of skin | 1 | 0.48 | 2.08 | 0.03-11.59 | 5 | 1.55 | **3.23** | **1.04-7.53** | 6 | 1.09 | **5.5** | **2.01-11.98** | 1 | 0.45 | 2.22 | 0.03-12.36 |
| Breast | 5 | 1.74 | 2.87 | 0.93-6.71 | 4 | 5.93 | 0.67 | 0.18-1.73 | 7 | 4.58 | 1.53 | 0.61-3.15 | 2 | 2.15 | 0.93 | 0.10-3.36 |
| Ovaries | 2 | 0.18 | **11.11** | **1.25-40.12** | 0 | 0.59 | 0 | 0.00-6.22 | 0 | 0.46 | 0 | 0.00-7.97 | 0 | 0.21 | 0.00 | 0.00-17.47 |
| Prostate | 2 | 0.75 | 2.67 | 0.30-9.63 | 8 | 3.38 | **2.37** | **1.02-4.66** | 4 | 3.62 | 1.1 | 0.30-2.83 | 3 | 1.95 | 1.54 | 0.31-4.5 |
| Kidney | 3 | 0.34 | **8.82** | **1.77-25.78** | 1 | 1.19 | 0.84 | 0.01-4.68 | 4 | 0.96 | **4.17** | **1.12-10.67** | 0 | 0.45 | 0.00 | 0.00-8.15 |
| Urinary bladder | 0 | 0.19 | 0.00 | 0.00-19.31 | 1 | 0.76 | 1.32 | 0.02-7.32 | 1 | 0.7 | 1.43 | 0.02-7.95 | 0 | 0.38 | 0.00 | 0.00-9.65 |
| **All haematological malignancies** | 11 | 0.69 | **15.94** | **7.95-28.53** | 9 | 2.29 | **3.93** | **1.79-7.46** | 2 | 1.79 | 1.12 | 0.13-4.03 | 2 | 0.84 | 2.38 | 0.27-8.6 |
| Hodgkin lymphoma | 0 | 0.07 | 0.00 | 0.00-52.40 | 0 | 0.23 | 0 | 0.00-15.95 | 0 | 0.13 | 0.00 | 0.00-28.22 | 0 | 0.05 | 0.00 | 0.00-73.36 |
| Non-Hodgkin lymphoma | 2 | 0.3 | 6.67 | 0.75-24.07 | 4 | 0.95 | **4.21** | **1.13-10.78** | 0 | 0.76 | 0.00 | 0.00-4.83 | 1 | 0.37 | 2.70 | 0.04-15.04 |
| Multiple myeloma | 1 | 0.08 | 12.5 | 0.16-69.55 | 3 | 0.32 | **9.38** | **1.88-27.39** | 1 | 0.29 | 3.45 | 0.05-19.19 | 0 | 0.15 | 0.00 | 0.00-24.45 |
| Lymphoid leukaemia | 7 | 0.11 | **63.64** | **25.49-131.12** | 2 | 0.37 | 5.41 | 0.61-19.52 | 1 | 0.29 | 3.45 | 0.05-19.19 | 1 | 0.13 | 7.69 | 0.10-42.8 |
| Acute lymphoblastic | 1 | 0.02 | 50.00 | 0.65-278.19 | 0 | 0.05 | 0 | 0.00-73.36 | 0 | 0.03 | 0.00 | 0.00-122.27 | 0 | 0.02 | 0.00 | 0.00-183.4 |
| Chronic lymphocytic | 6 | 0.06 | **100** | **36.52-217.66** | 2 | 0.27 | 7.41 | 0.83-26.74 | 1 | 0.23 | 4.35 | 0.06-24.19 | 1 | 0.11 | 9.09 | 0.12-50.58 |
| **All sites**** | 35 | 9.26 | **3.78** | **2.63-5.26** | 51 | 32.66 | **1.56** | **1.16-2.05** | 41 | 27.01 | **1.52** | **1.09-2.06** | 15 | 13.2 | 1.14 | 0.64-1.87 |
| **60 years or older** | **≤1 year** | | | | **>1-≤5 years** | | | | **>5-≤10 years** | | | | **>10 years** | | | |
| **Subsequent cancer** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** | **O** | **E** | **SIR** | **95% CI** |
| **All solid malignancies*** | 95 | 47.05 | **2.02** | **1.63-2.47** | 105 | 105.54 | 0.99 | 0.81-1.20 | 41 | 45.59 | 0.90 | 0.65-1.22 | 9 | 10.07 | 0.89 | 0.41-1.70 |
| Lip/oral cavity | 4 | 1.11 | 3.60 | 0.97-9.23 | 5 | 2.43 | 2.06 | 0.66-4.80 | 0 | 0.96 | 0.00 | 0.00-3.82 | 1 | 0.18 | 5.56 | 0.07-30.91 |
| Oesophagus | 2 | 0.68 | 2.94 | 0.33-10.62 | 2 | 1.51 | 1.32 | 0.15-4.78 | 0 | 0.64 | 0.00 | 0.00-5.73 | 0 | 0.14 | 0.00 | 0.00-26.2 |
| Stomach | 7 | 2.26 | **3.10** | **1.24-6.38** | 6 | 4.94 | 1.21 | 0.44-2.64 | 4 | 2.17 | 1.84 | 0.50-4.72 | 0 | 0.53 | 0.00 | 0.00-6.92 |
| Colon/rectum | 14 | 8.58 | 1.63 | 0.89-2.74 | 18 | 19.05 | 0.94 | 0.56-1.49 | 10 | 8.3 | 1.20 | 0.58-2.22 | 4 | 2.01 | 1.99 | 0.54-5.09 |
| Lung | 10 | 6.21 | 1.61 | 0.77-2.96 | 11 | 13.86 | 0.79 | 0.40-1.42 | 2 | 6.01 | 0.33 | 0.04-1.20 | 1 | 1.34 | 0.75 | 0.01-4.15 |
| Melanoma of skin | 2 | 1.37 | 1.46 | 0.16-5.27 | 3 | 3.2 | 0.94 | 0.19-2.74 | 3 | 1.41 | 2.13 | 0.43-6.22 | 0 | 0.31 | 0.00 | 0.00-11.83 |
| Breast | 7 | 5.13 | 1.36 | 0.55-2.81 | 8 | 11.6 | 0.69 | 0.30-1.36 | 2 | 4.72 | 0.42 | 0.05-1.53 | 0 | 0.93 | 0.00 | 0.00-3.94 |
| Ovaries | 2 | 0.71 | 2.82 | 0.32-10.17 | 1 | 1.57 | 0.64 | 0.01-3.54 | 1 | 0.66 | 1.52 | 0.02-8.43 | 0 | 0.14 | 0.00 | 0.00-26.2 |
| Prostate | 17 | 9.4 | **1.81** | **1.05-2.90** | 28 | 21.31 | 1.31 | 0.87-1.90 | 5 | 9.16 | 0.55 | 0.18-1.27 | 1 | 1.79 | 0.56 | 0.01-3.11 |
| Kidney | 7 | 1.73 | **4.05** | **1.62-8.34** | 4 | 3.93 | 1.02 | 0.27-2.61 | 2 | 1.7 | 1.18 | 0.13-4.25 | 0 | 0.35 | 0.00 | 0.00-10.48 |
| Urinary bladder | 9 | 2.49 | **3.61** | **1.65-6.86** | 2 | 5.38 | 0.37 | 0.04-1.34 | 4 | 2.42 | 1.65 | 0.44-4.23 | 0 | 0.66 | 0.00 | 0.00-5.56 |
| **All haematological malignancies** | 25 | 3.51 | **7.12** | **4.61-10.51** | 8 | 7.86 | 1.02 | 0.44-2.01 | 4 | 3.52 | 1.14 | 0.31-2.91 | 1 | 0.81 | 1.23 | 0.02-6.87 |
| Hodgkin lymphoma | 1 | 0.09 | 11.11 | 0.15-61.82 | 0 | 0.2 | 0.00 | 0.00-18.34 | 0 | 0.08 | 0.00 | 0.00-45.85 | 0 | 0.02 | 0.00 | 0.00-183.4 |
| Non-Hodgkin lymphoma | 4 | 1.45 | 2.76 | 0.74-7.06 | 3 | 3.29 | 0.91 | 0.18-2.66 | 3 | 1.48 | 2.03 | 0.41-5.92 | 0 | 0.34 | 0.00 | 0.00-10.79 |
| Multiple myeloma | 7 | 0.66 | **10.61** | **4.25-21.85** | 1 | 1.51 | 0.66 | 0.01-3.68 | 0 | 0.68 | 0.00 | 0.00-5.39 | 1 | 0.16 | 6.25 | 0.08-34.77 |
| Lymphoid leukaemia | 13 | 0.6 | **21.67** | **11.53-37.05** | 4 | 1.38 | 2.90 | 0.78-7.42 | 1 | 0.61 | 1.64 | 0.02-9.12 | 0 | 0.13 | 0.00 | 0.00-28.22 |
| Acute lymphoblastic | 1 | 0.02 | 50.00 | 0.65-278.19 | 1 | 0.06 | 16.67 | 0.22-92.73 | 0 | 0.02 | 0.00 | 0.00-183.4 | 0 | 0.00 | 0.00 | 0.00-0.00 |
| Chronic lymphocytic | 12 | 0.55 | **21.82** | **11.26-38.11** | 3 | 1.22 | 2.46 | 0.49-7.18 | 1 | 0.54 | 1.85 | 0.02-10.3 | 0 | 0.12 | 0.00 | 0.00-30.57 |
| **All sites**** | 122 | 51.6 | **2.36** | **1.96-2.82** | 119 | 115.65 | 1.03 | 0.85-1.23 | 45 | 50.1 | 0.90 | 0.66-1.20 | 10 | 11.14 | 0.90 | 0.43-1.65 |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); SPM: subsequent primary malignancies; CML: chronic myeloid leukaemia.
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 56. Observed number, SIRs and EARs of SPM following CML by calendar period, for both sexes

| | | 1990–2000 CML patients=1933 PYRs=4388.98 | | | | | 2001–2011 CML patients=2422 PYRs=16063.93 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subsequent cancer site** | **ICD-10** | **O** | **E** | **SIR** | **95% CI** | **EAR** | **O** | **E** | **SIR** | **95% CI** | **EAR** |
| **All solid malignancies*** | **C00-C75** | 45 | 32.19 | **1.40** | **1.02-1.87** | 29.19 | 104 | 81.83 | **1.27** | **1.04-1.54** | 13.80 |
| Lip, oral cavity, and pharynx | C00-C14 | 1 | 0.97 | 1.03 | 0.01-5.74 | 0.07 | 3 | 2.55 | 1.18 | 0.24-3.44 | 0.28 |
| Oesophagus | C15 | 0 | 0.47 | 0.00 | 0.00-7.80 | -1.07 | 4 | 1.3 | 3.08 | 0.83-7.88 | 1.68 |
| Stomach | C16 | 4 | 1.74 | 2.30 | 0.62-5.89 | 5.15 | 7 | 3.5 | 2.00 | 0.80-4.12 | 2.18 |
| Colon, rectum, and anus | C18-C21 | 9 | 5.64 | 1.60 | 0.73-3.03 | 7.66 | 13 | 13.25 | 0.98 | 0.52-1.68 | -0.16 |
| Liver | C22 | 1 | 0.47 | 2.13 | 0.03-11.84 | 1.21 | 3 | 1.58 | 1.90 | 0.38-5.55 | 0.88 |
| Pancreas | C25 | 0 | 0.94 | 0.00 | 0.00-3.90 | -2.14 | 2 | 2.76 | 0.72 | 0.08-2.62 | -0.47 |
| Larynx | C32 | 0 | 0.42 | 0.00 | 0.00-8.73 | -0.96 | 1 | 0.83 | 1.20 | 0.02-6.70 | 0.11 |
| Lung | C33-C34 | 5 | 4.93 | 1.01 | 0.33-2.37 | 0.16 | 12 | 11.38 | 1.05 | 0.54-1.84 | 0.39 |
| Melanoma of skin | C43 | 1 | 0.75 | 1.33 | 0.02-7.42 | 0.57 | 4 | 2.59 | 1.54 | 0.42-3.95 | 0.88 |
| Breast | C50 | 6 | 4.02 | 1.49 | 0.55-3.25 | 4.51 | 6 | 9.7 | 0.62 | 0.23-1.35 | -2.30 |
| Cervix uteri | C53 | 1 | 0.4 | 2.50 | 0.03-13.91 | 1.37 | 0 | 0.65 | 0.00 | 0.00-5.64 | -0.40 |
| Corpus uteri | C54-C55 | 1 | 0.94 | 1.06 | 0.01-5.92 | 0.14 | 1 | 1.96 | 0.51 | 0.01-2.84 | -0.60 |
| Ovaries | C56 | 1 | 0.64 | 1.56 | 0.02-8.69 | 0.82 | 0 | 1.16 | 0.00 | 0.00-3.16 | -0.72 |
| Prostate | C61 | 7 | 4.27 | 1.64 | 0.66-3.38 | 6.22 | 28 | 14.87 | **1.88** | **1.25-2.72** | 8.17 |
| Testis | C62 | 0 | 0.15 | 0.00 | 0.00-24.45 | -0.34 | 1 | 0.42 | 2.38 | 0.03-13.25 | 0.36 |
| Kidney | C64 | 4 | 1.31 | 3.05 | 0.82-7.82 | 6.13 | 5 | 3.34 | 1.50 | 0.48-3.49 | 1.03 |
| Urinary bladder | C67 | 1 | 1.79 | 0.56 | 0.01-3.11 | -1.80 | 6 | 3.96 | 1.52 | 0.55-3.30 | 1.27 |
| Central nervous system | C70-C72 | 1 | 0.43 | 2.33 | 0.03-12.94 | 1.30 | 1 | 1.13 | 0.88 | 0.01-4.92 | -0.08 |
| Thyroid | C73 | 0 | 0.26 | 0.00 | 0.00-14.11 | -0.59 | 0 | 0.73 | 0.00 | 0.00-5.02 | -0.45 |
| **All haematological malignancies** | **C81-C96** | 11 | 2.65 | **4.15** | **2.07-7.43** | 19.02 | 22 | 6.26 | **3.51** | **2.20-5.32** | 9.80 |
| Hodgkin lymphoma | C81 | 0 | 0.11 | 0.00 | 0.00-33.35 | -0.25 | 1 | 0.25 | 4.00 | 0.05-22.26 | 0.47 |
| Non-Hodgkin lymphoma | C82-C85 | 1 | 1.06 | 0.94 | 0.01-5.25 | -0.14 | 3 | 2.58 | 1.16 | 0.23-3.40 | 0.26 |
| Multiple myeloma | C90 | 2 | 0.49 | 4.08 | 0.46-14.74 | 3.44 | 2 | 1.15 | 1.74 | 0.20-6.28 | 0.53 |
| Lymphoid leukaemia | C91 | 8 | 0.47 | **17.02** | **7.33-33.54** | 17.16 | 16 | 1.1 | **14.55** | **8.31-23.62** | 9.28 |
| Acute lymphoblastic | C91.0 | 1 | 0.03 | 33.33 | 0.44-185.46 | 2.21 | 1 | 0.07 | 14.29 | 0.19-79.48 | 0.58 |
| Chronic lymphocytic | C91.1 | 7 | 0.41 | **17.07** | **6.84-35.18** | 15.01 | 15 | 0.94 | **15.96** | **8.92-26.32** | 8.75 |
| **All sites**** | **C00-C97** | 56 | 35.7 | **1.57** | **1.18-2.04** | 46.25 | 130 | 89.81 | **1.45** | **1.21-1.72** | 25.02 |

O: observed number of subsequent malignancies; E: expected number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); EAR: excess absolute risk per 10,000 person-years; PYRs: person-years of observation; SPM: subsequent primary malignancies; CML: chronic myeloid leukaemia; ICD-10: the WHO International Classification of Diseases (10th revision).

*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)

Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 57. Risk of CML subsequent to other primary malignancies by follow-up time, for both sexes

| | ≤1 year | | | >1-≤5 years | | | >5-≤10 years | | | >10 years | | | Overall | | | Overall (excl. <2 months) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Site of first primary cancer** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** | **O** | **SIR** | **95% CI** |
| **All solid malignancies*** | 88 | **1.60** | **1.28-1.97** | 201 | **1.63** | **1.41-1.87** | 87 | **1.47** | **1.17-1.81** | 20 | 1.08 | 0.66-1.67 | 396 | **1.55** | **1.40-1.71** | 347 | **1.42** | **1.27-1.57** |
| Lip/oral cavity | 5 | **3.21** | **1.03-7.48** | 3 | 0.95 | 0.19-2.77 | 5 | **3.40** | **1.10-7.94** | 1 | 2.04 | 0.03-11.35 | 14 | **2.10** | **1.14-3.52** | 12 | 1.88 | 0.97-3.29 |
| Stomach | 2 | 0.94 | 0.11-3.41 | 6 | 1.82 | 0.66-3.96 | 2 | 1.37 | 0.15-4.95 | 1 | 2.00 | 0.03-11.13 | 11 | 1.49 | 0.74-2.66 | 11 | 1.60 | 0.80-2.86 |
| Lung | 7 | 1.33 | 0.53-2.74 | 10 | 1.75 | 0.84-3.22 | 4 | 1.90 | 0.51-4.88 | 0 | 0.00 | 0.00-5.17 | 21 | 1.53 | 0.94-2.33 | 15 | 1.21 | 0.67-1.99 |
| Melanoma of skin | 5 | 2.43 | 0.78-5.66 | 8 | 1.47 | 0.63-2.90 | 4 | 1.41 | 0.38-3.61 | 0 | 0.00 | 0.00-3.78 | 17 | 1.50 | 0.88-2.41 | 15 | 1.37 | 0.77-2.27 |
| Prostate | 16 | 1.33 | 0.76-2.15 | 40 | 1.24 | 0.88-1.69 | 16 | 1.08 | 0.62-1.75 | 3 | 0.91 | 0.18-2.67 | 75 | 1.20 | 0.94-1.50 | 66 | 1.10 | 0.85-1.39 |
| Kidney | 7 | **3.32** | **1.33-6.84** | 8 | 1.47 | 0.63-2.90 | 5 | 1.65 | 0.53-3.85 | 5 | **4.63** | **1.49-10.80** | 25 | **2.14** | **1.39-3.17** | 20 | **1.78** | **1.09-2.75** |
| Urinary bladder | 11 | **3.83** | **1.91-6.86** | 13 | **2.06** | **1.10-3.52** | 1 | 0.31 | 0.00-1.75 | 0 | 0.00 | 0.00-3.43 | 25 | **1.86** | **1.20-2.75** | 19 | 1.48 | 0.89-2.31 |
| **All haematological malignancies** | 19 | **4.66** | **2.80-7.27** | 16 | **1.78** | **1.02-2.89** | 7 | 1.73 | 0.69-3.56 | 5 | **3.97** | **1.28-9.26** | 47 | **2.56** | **1.88-3.40** | 33 | **1.88** | **1.29-2.64** |
| Non-Hodgkin lymphoma | 6 | **3.49** | **1.27-7.59** | 5 | 1.26 | 0.40-2.93 | 2 | 1.05 | 0.12-3.80 | 0 | 0.00 | 0.00-6.11 | 13 | 1.59 | 0.84-2.71 | 7 | 0.89 | 0.36-1.84 |
| Multiple myeloma | 2 | 2.63 | 0.30-9.50 | 1 | 0.67 | 0.01-3.73 | 0 | 0.00 | 0.00-7.34 | 0 | 0.00 | 0.00-28.22 | 3 | 1.04 | 0.21-3.04 | 1 | 0.37 | 0.00-2.04 |
| Lymphoid leukaemia | 27 | **34.18** | **22.52-49.73** | 9 | **4.39** | **2.00-8.33** | 4 | **4.12** | **1.11-10.56** | 4 | **14.29** | **3.84-36.57** | 44 | **10.76** | **7.82-14.44** | 21 | **5.33** | **3.30-8.15** |
| Acute lymphoblastic | 4 | **200.0** | **53.81-512.04** | 1 | 20.00 | 0.26-111.28 | 0 | 0.00 | 0.00-183.40 | 0 | 0.00 | 0.00-366.81 | 5 | **45.45** | **14.65-106.08** | 2 | **18.18** | **2.04-65.65** |
| Chronic lymphocytic | 20 | **28.99** | **17.70-44.77** | 8 | **4.30** | **1.85-8.48** | 4 | **4.65** | **1.25-11.91** | 4 | **16.67** | **4.48-42.67** | 36 | **9.86** | **6.91-13.66** | 19 | **5.38** | **3.24-8.41** |
| **All sites**** | 96 | **1.61** | **1.30-1.96** | 216 | **1.62** | **1.41-1.86** | 95 | **1.49** | **1.21-1.82** | 25 | 1.26 | 0.81-1.86 | 432 | **1.56** | **1.42-1.72** | 380 | **1.44** | **1.30-1.59** |

O: observed number of subsequent malignancies; SIR: standardized incidence ratio; 95% CIs: 95% confidence intervals (lower-upper limits); CML: chronic myeloid leukaemia.
*excluding non-melanoma skin cancer (C44) and haematological malignancies (C81-C96) **excluding non-melanoma skin cancer (C44)
Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).

## Table 58. SIR for subsequent solid malignancies following lymphoma and myeloma (A), and leukaemia (B) by region, Germany, 1990–2011

**(A)**

| Region (years of diagnosis) | Abbreviation | Hodgkin lymphoma | | | | Non-Hodgkin lymphoma | | | | Multiple myeloma | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | O | E | SIR | 95% CI | O | E | SIR | 95% CI | O | E | SIR | 95% CI |
| Saarland (1990+) | SL | 45 | 21.47 | **2.10** | **1.53-2.80** | 251 | 201.99 | **1.24** | **1.09-1.41** | 56 | 50.21 | 1.12 | 0.84-1.45 |
| Hamburg (1990+) | HH | 72 | 33.94 | **2.12** | **1.66-2.67** | 578 | 319.94 | **1.81** | **1.66-1.96** | 183 | 123.08 | **1.49** | **1.28-1.72** |
| Berlin (1995+) | BE | 31 | 24.28 | 1.28 | 0.87-1.81 | 322 | 243.83 | **1.32** | **1.18-1.47** | 70 | 79.14 | 0.88 | 0.69-1.12 |
| Brandenburg (1995+) | BB | 46 | 27.09 | **1.70** | **1.24-2.27** | 318 | 243.46 | **1.31** | **1.17-1.46** | 82 | 84.57 | 0.97 | 0.77-1.20 |
| Mecklenburg-Western Pomerania (1995+) | MV | 32 | 15.1 | **2.12** | **1.45-2.99** | 232 | 169.04 | **1.37** | **1.20-1.56** | 63 | 57.36 | 1.10 | 0.84-1.41 |
| Saxony (1995+) | SN | 69 | 41.36 | **1.67** | **1.30-2.11** | 599 | 436.39 | **1.37** | **1.26-1.49** | 172 | 164.44 | 1.05 | 0.90-1.21 |
| Saxony-Anhalt (1995+) | ST | 29 | 17.88 | **1.62** | **1.09-2.33** | 265 | 195.6 | **1.35** | **1.20-1.53** | 56 | 66.16 | 0.85 | 0.64-1.10 |
| Thuringia (1995+) | TH | 21 | 13.73 | 1.53 | 0.95-2.34 | 266 | 199.25 | **1.34** | **1.18-1.51** | 73 | 68.45 | 1.07 | 0.84-1.34 |
| Schleswig-Holstein (1998+) | SH | 38 | 28.76 | 1.32 | 0.93-1.81 | 348 | 281.72 | **1.24** | **1.11-1.37** | 108 | 111.06 | 0.97 | 0.80-1.17 |
| Bremen (1998+) | HB | 9 | 5.46 | 1.65 | 0.75-3.13 | 108 | 65.52 | **1.65** | **1.35-1.99** | 25 | 21.17 | 1.18 | 0.76-1.74 |
| Rhineland-Palatinate (1998+) | RP | 36 | 21.09 | **1.71** | **1.20-2.36** | 424 | 256.59 | **1.65** | **1.50-1.82** | 84 | 74.01 | 1.13 | 0.91-1.41 |
| Lower Saxony (2003+) | NI | 41 | 25.89 | **1.58** | **1.14-2.15** | 577 | 405.87 | **1.42** | **1.31-1.54** | 137 | 144.98 | 0.94 | 0.79-1.12 |
| Bavaria (2002+) | BY | 69 | 41.16 | **1.68** | **1.30-2.12** | 759 | 511.33 | **1.48** | **1.38-1.59** | 235 | 180 | **1.31** | **1.14-1.48** |
| North Rhine-Westphalia (2006+)* | NRW | 41 | 18.18 | **2.26** | **1.62-3.06** | 422 | 265.65 | **1.59** | **1.44-1.75** | 78 | 90.71 | 0.86 | 0.68-1.07 |
| Muenster (1990+) | Muenster | 74 | 36.02 | **2.05** | **1.61-2.58** | 426 | 331.27 | **1.29** | **1.17-1.41** | 118 | 127.99 | 0.92 | 0.76-1.10 |
| **Pooled (1990–2011)** | | 653 | 371.41 | **1.76** | **1.63-1.90** | 5895 | 4127.45 | **1.43** | **1.39-1.47** | 1540 | 1443.33 | **1.07** | **1.01-1.12** |
| **Pooled (1990–2011), excluding BE and ST** | | 593 | 329.25 | **1.80** | **1.66-1.95** | 5308 | 3688.02 | **1.44** | **1.40-1.48** | 1414 | 1298.03 | **1.09** | **1.03-1.15** |
| **Pooled (1990–2011), excluding NRW, BY, and NI** | | 502 | 286.18 | **1.75** | **1.60-1.91** | 4137 | 2944.6 | **1.40** | **1.36-1.45** | 1090 | 1027.64 | 1.06 | 1.00-1.13 |

**(B)**

| Region (years of diagnosis) | Abbreviation | Chronic lymphocytic leukaemia | | | | Chronic myeloid leukaemia | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | O | E | SIR | 95% CI | O | E | SIR | 95% CI |
| Saarland (1990+) | SL | 66 | 68.53 | 0.96 | 0.74-1.23 | 9 | 15.79 | 0.57 | 0.26-1.08 |
| Hamburg (1990+) | HH | 243 | 164.01 | **1.48** | **1.30-1.68** | 39 | 23.47 | **1.66** | **1.18-2.27** |
| Berlin (1995+) | BE | 87 | 57.47 | **1.51** | **1.21-1.87** | 14 | 18.22 | 0.77 | 0.42-1.29 |
| Brandenburg (1995+) | BB | 222 | 134.49 | **1.65** | **1.44-1.88** | 19 | 18.87 | 1.01 | 0.61-1.57 |
| Mecklenburg-Western Pomerania (1995+) | MV | 150 | 105.59 | **1.42** | **1.20-1.67** | 15 | 12.15 | 1.23 | 0.69-2.04 |
| Saxony (1995+) | SN | 319 | 255.61 | **1.25** | **1.11-1.39** | 43 | 29.4 | **1.46** | **1.06-1.97** |
| Saxony-Anhalt (1995+) | ST | 154 | 110.59 | **1.39** | **1.18-1.63** | 18 | 12.85 | 1.40 | 0.83-2.21 |
| Thuringia (1995+) | TH | 170 | 113.39 | **1.50** | **1.28-1.74** | 22 | 14.71 | 1.50 | 0.94-2.26 |
| Schleswig-Holstein (1998+) | SH | 131 | 118.95 | 1.10 | 0.92-1.31 | 14 | 16.34 | 0.86 | 0.47-1.44 |
| Bremen (1998+) | HB | 41 | 28.35 | **1.45** | **1.04-1.96** | 2 | 3.58 | 0.56 | 0.06-2.02 |
| Rhineland-Palatinate (1998+) | RP | 164 | 106.34 | **1.54** | **1.32-1.80** | 21 | 19.12 | 1.10 | 0.68-1.68 |
| Lower Saxony (2003+) | NI | 166 | 137.16 | **1.21** | **1.03-1.41** | 27 | 22.99 | 1.17 | 0.77-1.71 |
| Bavaria (2002+) | BY | 232 | 149.67 | **1.55** | **1.36-1.76** | 39 | 30.02 | 1.30 | 0.92-1.78 |
| North Rhine-Westphalia (2006+)* | NRW | 440 | 229.23 | **1.92** | **1.74-2.11** | 59 | 35.21 | **1.68** | **1.28-2.16** |
| Muenster (1990+) | Muenster | 140 | 76.62 | **1.83** | **1.54-2.16** | 24 | 10.74 | **2.23** | **1.43-3.33** |
| **Pooled (1990–2011)** | | 2725 | 1856 | **1.47** | **1.41-1.52** | 365 | 283.46 | **1.29** | **1.16-1.43** |
| **Pooled (1990–2011), excluding BE and ST** | | 2484 | 1687.94 | **1.47** | **1.41-1.53** | 333 | 252.39 | **1.32** | **1.18-1.47** |
| **Pooled (1990–2011), excluding NRW, BY, and NI** | | 1913 | 1400.48 | **1.37** | **1.31-1.43** | 243 | 207.49 | **1.17** | **1.03-1.33** |

SIR: standardized incidence ratio. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*). * excluding Muenster

## Table 59. Subsequent melanoma skin (A) and lung (B) cancer risk according to the type of first LHM in relation to patients characteristics in Germany, 1990–2011

**A. Subsequent melanoma skin cancer risk**

| | HL SIR (95% CI) | NHL SIR (95% CI) | MM SIR (95% CI) | CLL SIR (95% CI) | CML SIR (95% CI) |
|---|---|---|---|---|---|
| **Overall** | **2.12 (1.48-2.95)** | **1.98 (1.75-2.23)** | **1.78 (1.42-2.21)** | **2.96 (2.54-3.44)** | **2.13 (1.32-3.26)** |
| **Sex** | | | | | |
| Males | 1.69 (0.96-2.74) | **2.04 (1.74-2.37)** | **1.94 (1.46-2.51)** | **3.35 (2.80-3.97)** | **2.07 (1.07-3.61)** |
| Females | **2.71 (1.63-4.24)** | **1.89 (1.55-2.28)** | **1.53 (1.01-2.23)** | **2.16 (1.55-2.93)** | **2.22 (1.01-4.22)** |
| **Age at diagnosis** | | | | | |
| 15-44 years old | **3.79 (2.35-5.79)** | **2.05 (1.12-3.44)** | 1.12 (0.01-2.29) | 2.99 (0.34-10.78) | **4.67 (1.51-10.90)** |
| 45-59 years old | 0.93 (0.25-2.37) | **1.70 (1.27-2.25)** | 1.66 (0.91-2.79) | **2.79 (1.85-4.03)** | **2.79 (1.12-5.75)** |
| ≥60 years old | 1.51 (0.72-2.78) | **2.05 (1.78-2.35)** | **1.82 (1.42-2.31)** | **3.00 (2.52-3.53)** | 1.27 (0.55-2.50) |
| **Follow-up time** | | | | | |
| ≤1 year | 2.03 (0.66-4.74) | **3.25 (2.62-4.00)** | **2.13 (1.38-3.15)** | **2.76 (1.85-3.97)** | 1.62 (0.33-4.74) |
| >1-≤5 years | **2.82 (1.72-4.35)** | **1.74 (1.44-2.08)** | **1.80 (1.31-2.41)** | **3.13 (2.52-3.83)** | 1.68 (0.73-3.32) |
| >5-≤10 years | 1.30 (0.48-2.83) | **1.48 (1.09-1.96)** | 1.34 (0.67-2.40) | **2.92 (2.11-3.95)** | **3.60 (1.64-6.83)** |
| >10 years | 1.74 (0.47-4.45) | **1.71 (1.01-2.70)** | 1.38 (0.28-4.02) | **2.34 (1.07-4.45)** | 1.32 (0.02-7.32) |
| **Calendar period** | | | | | |
| 1990-2000 | 3.64 (0.98-9.31) | 1.75 (0.96-2.94) | 1.95 (0.71-4.25) | **2.64 (1.26-4.85)** | 1..33 (0.02-7.42) |
| 2001-2011 | 1.28 (0.41-2.99) | **1.77 (1.37-2.25)** | **1.85 (1.21-2.72)** | **2.64 (1.95-3.50)** | 1.54 (0.42-3.95) |
| **Reciprocal risk** | **1.89 (1.28-2.68)** | **1.94 (1.75-2.16)** | **1.40 (1.15-1.69)** | **2.56 (2.18-2.99)** | 1.50 (0.88-2.41) |

**B. Subsequent lung cancer risk**

| | HL SIR (95% CI) | NHL SIR (95% CI) | MM SIR (95% CI) | CLL SIR (95% CI) | CML SIR (95% CI) |
|---|---|---|---|---|---|
| **Overall** | **3.20 (2.71-3.75)** | **1.79 (1.68-1.91)** | 1.03 (0.89-1.18) | **1.75 (1.59-1.92)** | 0.98 (0.68-1.35) |
| **Sex** | | | | | |
| Males | **3.26 (2.71-3.90)** | **1.71 (1.58-1.84)** | 0.92 (0.77-1.09) | **1.78 (1.60-1.97)** | 0.95 (0.63-1.39) |
| Females | **2.95 (1.97-4.23)** | **2.07 (1.83-2.34)** | **1.42 (1.08-1.83)** | **1.63 (1.27-2.05)** | 1.06 (0.48-2.01) |
| **Age at diagnosis** | | | | | |
| 15-44 years old | **9.79 (6.50-14.15)** | **5.28 (3.56-7.54)** | 1.22 (0.02-6.79) | 4.35 (0.87-12.70) | 2.56 (0.29-9.26) |
| 45-59 years old | **2.98 (2.19-3.96)** | **2.00 (1.74-2.29)** | 1.02 (0.69-1.44) | **2.08 (1.65-2.59)** | 1.15 (0.55-2.12) |
| ≥60 years old | **2.62 (2.06-3.29)** | **1.69 (1.57-1.82)** | 1.03 (0.88-1.20) | **1.68 (1.51-1.87)** | 0.87 (0.56-1.30) |
| **Follow-up time** | | | | | |
| ≤1 year | **2.55 (1.54-3.99)** | **3.15 (2.82-3.50)** | **1.76 (1.41-2.18)** | **2.53 (2.09-3.04)** | 1.81 (0.96-3.09) |
| >1-≤5 years | **2.71 (2.04-3.52)** | **1.41 (1.27-1.57)** | **0.79 (0.62-0.98)** | **1.63 (1.41-1.87)** | 0.86 (0.48-1.41) |
| >5-≤10 years | **3.33 (2.41-4.49)** | **1.68 (1.46-1.93)** | 0.84 (0.55-1.21) | **1.57 (1.28-1.92)** | 0.54 (0.18-1.27) |
| >10 years | **5.18 (3.58-7.23)** | 1.13 (0.84-1.50) | 0.52 (0.17-1.22) | 1.24 (0.77-1.89) | 1.01 (0.20-2.95) |
| **Calendar period** | | | | | |
| 1990-2000 | **3.79 (2.24-5.99)** | **1.80 (1.45-2.21)** | 0.98 (0.61-1.50) | **1.99 (1.51-2.58)** | 1.01 (0.33-2.37) |
| 2001-2011 | **2.48 (1.72-3.47)** | **1.91 (1.70-2.13)** | 1.16 (0.92-1.46) | **1.79 (1.52-2.10)** | 1.05 (0.54-1.84) |
| **Reciprocal risk** | **2.23 (1.54-3.12)** | **1.74 (1.57-1.93)** | **1.33 (1.11-1.58)** | **1.53 (1.27-1.83)** | 1.53 (0.94-2.33) |

Standardized incidence ratio; LHM: lymphohaematopoietic malignancies; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; MM: multiple myeloma; CLL: chronic lymphocytic leukaemia; CML: chronic myeloid leukaemia. Bold indicates that the 95% confidence interval did not include the value 1 (statistically significant SIR, *P<0.05*).