1. Methodological considerations

As a bridge science between pharmacology and epidemiology, pharmacoepidemiology means the study of the utilization and effects of drugs in large number of people [104]. One part of the task of clinical pharmacology studying effects of drugs in humans is to provide a risk to benefit assessment for the drug treatment in defined diseases. Epidemiology evaluates the distribution and determinants of diseases in populations. Pharmacoepidemiological studies benefit from the methodology developed in general epidemiology. Therefore, pharmacoepidemiology can also be defined as the application of epidemiological methods to pharmacological issues. Generally, epidemiology can be divided into two main types: 1) descriptive epidemiology, which mainly yields hypotheses without testing them, studies of drug utilization would generally fall under descriptive studies; and 2) analytical epidemiology, which can generate and test hypotheses, usually to detect causal associations between exposures and outcomes of interest, for example in clinical trials [105]. Case-control studies and cohort studies are the most important analytical epidemiological techniques. The former are retrospective observational studies that focus on inferring the exposure from existed outcomes, and the latter are prospective observational studies that focus on which outcomes could be observed after following-up the exposure of interest for a period of time. Data acquired from case-control studies depend, to a great extent, on the correct recall of study participants, which is prone to recall bias and can not be controlled. Cohort studies, however, can be well controlled by study design. Cohort studies, therefore, are more powerful in inferring causal associations between exposures and outcomes of interest than case-control studies.

From 1984 to 1999, five well-organized National Health Surveys T0, T1, T2, T3 and BGS98 had been conducted in Germany. National Health Surveys are in essence cross-sectional observational studies and are retrospective chronologically as the data acquired reflect merely the past and the status quo. Cross-sectional studies and case-control studies based on single one cross-sectional national health survey are limited in inferring causal associations between exposure and outcomes. Results of those studies, especially concerning causal inference, should be exploited discreetly

and considered the statistical association, biological rationality, possible bias and confounding factors comprehensively. In the first part of this dissertation, most results were from descriptive or comparative studies, and in the second part, 4 independent case-control studies derived from National Health Surveys were performed, all of them were based on cross-sectional data and therefore are relatively weak in any causal inferring.

National Health Surveys used to a stratified multistage probability cluster are designed to allow generalizability to the noninstitutionalized civilian population. Because the studied population of each survey was representative of the total German national population at that time, the study population of the four surveys as a whole (apart from T3) could be regarded as a cohort at large, reflecting roughly the dynamic change of health and diseases as well as drug utilization of the (western) German population from 1984 to 1999. Huge differences in social economic background existed between East Germany and West Germany and may exert potential impact on health and disease. In correspondence with the eastern survey T3 and the western part when necessary. Different trends between drug users and controls may reveal interesting results. In addition, BGS98 differed from the other four surveys in the age of study population, which additionally covered subjects aged 18-24 and 70-79. All above factors should be considered in the interpretation of the results of the five National Health Surveys.

Steroid hormone use in healthy women under ambulant care, either for contraception or for HRT, shows a clearly differring age distribution in the general population (Fig. 4). Contraceptive users are much younger compared with nonusers whereas HRT users are centralized in the age range of 50-59 years, in which women show of higher prevalence rates of climacteric symptoms. Age is generally closely related to the occurrence of disease. Many diseases, osteoporosis for example, occur more frequently in the elderly while some others may occur more frequently in the younger age groups. Since the use of oral contraceptives concentrates mainly on younger women, contraceptive users tend to be healthier with lower prevalence rates of diseases compared with on average older nonusers in the general population. Therefore, any comparison for the effects following steroid hormone use between

steroid hormone users and nonusers in a general population without matching on age may be of little significance, as any discrepancy might be attributed to the age difference of the two populations rather than to the researched factor of steroid hormone use. Unfortunately, this question has been neglected by some studies in the literature. Thus, it is necessary to choose age-matched controls of hormone users when the possible health-related outcomes of hormone users are studied. Body mass index is often regarded as another indicator for some diseases, however, it is highly correlated to age.

For a long time, the effect of so-called 'healthy users' in studies of oral contraceptives [106,107] and HRT use [108,109] has been recognized. HRT users have been thought to be different from nonusers in socioeconomic background with more favorable lifestyle [110]. For continuous parameters concerning blood lipids, coagulation, glycemic status and blood pressure from survey BGS98, three different methods were used to compare HRT users with controls in an effort to check the effect of the matching on age (Table 53). In Method A, which was used in this dissertation, controls were matched on age only; in Method B, HRT users were from West Germany only and controls were matched on age and social class (a comprehensive concept for education, household income and profession) and randomly chosen from nonusers in West Germany; In Method C, univariate covariance analysis was used while controlling for age, BMI, social class and region (West or East Germany). From Table 53, results of Method A were in line with the results of the other two methods except for DBP, suggesting the matching on age was effective.

In the first part of this dissertation, steroid hormone users were compared with their age-matched controls in aspects including sociodemographic factors, health-related lifestyle, prevalence of diseases and laboratory measurements, health service utilization, etc. in order to check the differences between users and their age-matched controls from the point of drug exposure to generate hypotheses. In the second part of this dissertation, 4 independent case-control studies derived from the five National Health Surveys were performed to check the differences of drug exposure (steroid hormone use) from established outcomes. This avoided the

possible effects of healthy users and the associations between steroid hormone use with the outcomes of interest could be confirmed.

2. Use of steroid hormone for contraception and for HRT in different general populations

Contraceptive use

Results of the German Cohort Study on Women's Health (Deutsche Kohortenstudie zur Frauengesundheit) showed that the prevalence of contraceptive use was 40.4% for fertile women aged 15-44, 66.3% for younger women aged 15-24 and 15% for elder women aged 45-54, respectively [111]. Another investigation of Oddens [112], which was conducted in a sample of 1466 women living in West Germany, showed that oral contraceptive use was 36.4% for women aged 20-49. The figures from younger women are comparable with the results of BGS98, but the figures for elderly women were much higher in these studies. In BGS98, the prevalence of OC use was only 4.9% (30/607) for women aged 45-54, 24.1% (324/1344) for women aged 20-49 in West Germany (calculated from Table 9), but 60.4% (67.2% in East and 57.2% in West) for women aged 20-24. Results of five German National Health Surveys suggested that age-stratified OC use rates were not so high particularly in the elderly German women though there was no obvious difference in younger women compared with the results of the above two studies. The study participants of German Cohort Study on Women's Health were volunteers, it is possible that a higher proportion of elderly oral contraceptive users would like to take part in such a study because they were more concerned about their health. It is also possible that women in the earlier times might use oral contraceptives as an alternative for hormone replacement therapy because of relatively high-dose estrogens contained in the earlier oral contraceptives formulations. Oddens' survey [112] was conducted in March/April,1995, right before the so-called 'pill crisis' from the results of the transnational study on oral contraceptives [113,114], which claimed that the third generation oral contraceptives were associated with an increased risk of venous thromboembolic disease [115]. 'Pill crisis' resulted in a dramatic decline in oral contraceptive use worldwide, including Germany [111]. Reanalysis of this study with more refined techniques and with an enhanced dataset confirmed later that it resulted most probably from bias and confounding [106,113]. The use of oral contraceptives showed still a declining trend after the pill crisis in Germany [111].

Considering the lag response of OC use for the crisis, a higher prevalence rate of OC use than that of BGS98 observed by Oddens [112] *before* the 'pill crisis' was not a surprise.

The impact of pill crisis could not be reflected in the National Health Surveys because the crisis occurred just between survey T2 and BGS98. In the NHSs, the prevalence of contraceptive use remained almost constant among women in the western part from 1984 to 1999 whereas declined obviously in the eastern part of Germany from 1991 to 1999 (Table 9 and Fig. 3). The large difference in oral contraceptive use between western and eastern part of Germany was analyzed in detail and the reasons were also proposed in the study of Melchert and Knopf [116]. One of the most important reasons might be that oral contraceptives could be obtained free of charge in the former GDR before the reunification whereas must be paid after the reunification, which resulted in a dramatic decline for OC use in the eastern part of Germany (Fig. 3).

After more than 40 years of development, oral contraceptives have become much more safer with less adverse drug reactions than ever before. As one of the most effective and reliable birth-control measures, use of oral contraceptives has been widely accepted and became the most popularly used birth-control method among married couples in the developed countries (on average 17% in comparison with 5.9% in less developed countries, World Contraceptive Use 2001, by United Nations Population Division, http://www.un.org/). Generally, western European countries have a higher OC use than do central and eastern European countries. In France, oral contraceptives were more often used in women aged 20-44 with 28%, 34% and 40% in the years of 1978, 1988 and 1994, respectively [117] in comparison with 21%, 27% and 24% by German women of the same age in the years of 1984, 1987 and 1991, respectively (calculated from Table 9). While in Germany, 29% of women aged 18-49 used oral contraceptives in 1998/99 (calculated from Table 9), approximately 26% of Australian women of the same age range [118] and 18% of Canadian women aged 15-49 [119] did so in 1995 and in 1996/97, respectively. In the USA, the prevalence of oral contraceptive use among women in the reproductive age was 31% in 1988 and 27% in 1995 [3]. Interestingly, this small trend of decline in oral contraceptive use was similar to that in Germany from 1987 to 1998 (Table 9 and Fig. 3).

According to the age-stratified OC use rate in West Germany and East Germany from survey BGS98 (Table 9) and the age distribution of total German women population (Appendix 4, Federal Statistical Office Germany, *Statistisches Bundesamt*), it is estimated that totally 4.8 million German women (3.7 million in West Germany and 1.1 million in East Germany) aged 18-54 used oral contraceptives in 1998/1999. The first four German surveys covered only women over 25 years of age, which might underestimate the overall oral contraceptive use in Germany. In fact, young women aged 15-24 show usually the highest use rate of oral contraceptives [111]. Due to the lack of OC use data among teenagers in the five National Health Surveys, the overall OC use among all German fertile women should be much higher than the above estimate.

HRT use

In sharp contrast to the use of steroid hormones for contraception, which changed very little from 1984 to 1999, use of steroid hormones for HRT increased dramatically from 3.0% in 1984 to 21.2% in 1998 among women aged 40-69 in Germany. The dramatic increase of HRT use among German women was also reported in a study in the frame of the WHO-MONICA project, which was conducted in Augsburg, a city located in the south of Germany [110]. In this study, 1013 women aged 45-64 years in 1984/1985, 1496 and 1475 women aged 45-74 years in 1989/90 and 1994/95, respectively, were enrolled, representative of local approx. 80% female residents at the same age. HRT use rate from this study was 3%, 9% and 23% among women aged 45-64 years in 1984/85, 1990/91 and 1995/95, respectively [110], which is close to the results of National Health Survey T0 in 1984/85 (3.7%, calculated from Table 10) or somewhat lower than the result of survey T2 in 1990/91 (16.0%) and of survey BGS98 in 1998/99 (30.5%, in West Germany only) for women of the same age. It is unclear why the level of HRT use in Augsburg was lower than that of the overall West Germany since 1990/91, though the study sample of this investigation was representative of the population in a large city, in which a higher HRT use rate was more often reported than in small cities or in countryside. The results of Mueller [110] were representative for residents in Augsburg only, results of National Health Surveys are population-representative and reliable because their samples were stratified according to region and age distribution of the national total population.

Since the end of 1980s, use of HRT has mushroomed especially in western developed countries. Different levels of HRT use may be obtained from different studies conducted in different countries in different years. However, regarding HRT use in the general population, results of German National Health Surveys were comparable with the results of several population-representative studies from other European countries in similar survey years and focussing on similar age ranges of females [120-123]. Similar to the situation in Germany, HRT prevalence in UK was reported to increase tenfold since the middle of 1980s [122]. In 1987, HRT was used by an estimated 2.2% of women aged 40 to 64 years in England, and by 1.0% in Scotland. By 1994 this had risen to 21.7% in England, 20.4% in Scotland, and 21.3% in Wales [122]. While HRT use among German women aged 45-65 rose from 16% in 1991 to 30.5% in 1998 (calculated from Table 10), there were 18.4% of Danish women aged 45-65 using HRT in 1994 [124], and in Switzerland, it was estimated that 15-20% and 17-24% of women aged 45-69 were current HRT users in 1993 and 1996, respectively [125]. Studies in 18199 Norwegian women showed that HRT use rate was 31.9% among women aged 45-64 years in 1996/97 [126]. Yet, only 8.1% of French women aged 45-55 were using HRT in 1992 [120] in comparison with 18% of German women at the same age in 1990/91, but 20% of Finnish Women aged 45-64 were HRT users in 1989 [121] in comparison with 16% of German women in 1990/91. In Australia, HRT use in women aged 50 years and over rose from 13.2% in 1991 to 21.2% in 1993 and 26% in 1995 [127]. In the USA, 37.6% of women aged 50-74 were using HRT in 1995 [4], whereas only 28% of German women (calculated from Table 9) in the western part of Germany from survey BGS98. Notably, high HRT use rates were reported among American older women: 43%, 37% and 20% for women aged 60-70, 71-80 and over 80, respectively [128], by far exceeding the use rates of German women of comparable age.

According to the age-stratified HRT use rate in West Germany and East Germany from survey BGS98 and the age distribution of the German general population (Appendix 4), it is estimated that a total of 3.58 million German women (3.15 million in West Germany and 0.43 million in East Germany) under 80 years of age used HRT in 1998/99. This figure might rise to almost 5 million according to the estimate of Nimtz-Köster [91], but most probably may peak in 2002 when the first results of WHI

study were published, which suggested that the overall risks exceeded benefits for women using HRT for primary prevention against cardiovascular diseases [73].

3. Utilization of oral contraceptives and HRT in Germany

Oral contraceptive use

Since oral contraceptives were firstly marketed in 1960s, numerous oral contraceptive products have been developed and improved in their formulations and components by reducing the dose of estrogens, developing new progestins, adopting new schedules of administration in an effort to reduce side effects and enhance compliance. Compared with the earlier formulations, in which high-dose estrogens were often used, modern formulations have reduced the dose of estrogens by almost 80% [129], because estrogen has been presumed to be responsible for the serious thrombotic complications. Nowadays, the estrogen content (ethinyl estradiol) contained in oral contraceptives may be as low as 20 µg/pill, which remains efficacious in birth control, yet has low incidence of estrogen-related side effects [130]. Therefore, it is no wonder that use of contraceptives containing low-dose estrogens in Germany increased steadily from 1984 to 1999, the proportion of lowdose estrogen OCs accounted for 88% in 1998/99 (Fig.13). Subsequently it was found that the progestins contained in the pill could also play a thrombogenic role. Gestodene and desogestrel, two 'newly' developed progestins contained in the third generation contraceptives, were associated with increased risk of thromboembolism compared with progestins contained in the second generation contraceptives [115]. This resulted in a declined use of desogestrel and gestodene between survey T2 in 1990/91 and BGS98 in 1998/99 (Table 12). Levonorgestrel was the most often used progestin in combined oral contraceptives in all five surveys partly because it was associated with the lowest incidence of intermenstrual bleeding among three triphasic contraceptives in randomized controlled trials [131,132].

With the largest market share, monophasic oral contraceptives were the main preparations used in Germany, the use of which increased steadily from 1984 to 1999. Similar to the physiological menstrual cycle of women, bi- and triphasic contraceptives should have less side effects and be accepted more easily by many women. Nevertheless, there was a trend of decline for the use of biphasic contraceptives whereas the proportion of triphasic contraceptives changed little

though the absolute number of triphasic contraceptive use doubled from 1984 to 1999 (Fig. 11). Progestin-only contraceptives were used very seldom, accounting for less than 1% in all surveys. Numerous studies have been done to evaluate the contraceptive effectiveness, cycle control, bleeding patterns or discontinuation due to minor side effects such as weight gain with specific formulations. However, there is evidence of difference in contraceptive effectiveness among different no formulations, but the equivalence of all currently marked products or the superiority of any specific formulation in reducing the risk of any minor side effect of oral contraceptives has not been established yet. A review suggested that biphasic pills containing norethindrone had inferior cycle control compared with triphasic pills containing levonorgestrel, the odds ratio was 1.7 (95% Cl 1.3-2.2) for cycles with intermenstrual bleeding and 6.5 (95% CI 3.1-13) for cycles without withdraw bleeding [133]. However. biphasic contraceptives were comparable with triphasic contraceptives in cycle controls if the progestin contained in both of them was identical. The authors thus concluded that the choice of progestins may be more important than the phasic regime in determining bleeding patterns [133]. In another review from the same authors, no significant differences could be found between the biphasic and monophasic oral contraceptives in the intermenstrual bleeding, amenorrhea and study discontinuation due to intermenstrual bleeding [134].

HRT use

The main objective of HRT is to replace the reduced endogenous estrogen in women after menopause. Later it was found that estrogen alone increased the risk of endometrial proliferation in women with intact uterus [135] and progestogen was therefore added to oppose the partial effect of estrogen on the uterus. Women with an intact uterus are highly recommended to take an opposed regime of HRT and women with a hysterectomy are suggested to take unopposed ERT because the added progestin may also counteract some supposed benefits of estrogens, for example lipid profiles. In this dissertation, it is shown that the use of unopposed regime of ERT declined while the opposed regime of HRT increased from 1984 to 1999 (Fig. 16). However, the arm of opposed HRT in the WHI study was prematurely terminated on May 31, 2002 [73] because of more harms than benefits. Very recently, another arm of ERT regime of WHI study was also preterminated on Feb. 29, 2004 (planned to end in 2005) [74]. It seems that neither opposed regime of HRT

nor unopposed regime of ERT could provide enough cardioprotective effects for postmenopausal women in primary prevention against cardiovascular diseases.

4. Determinants of use of oral contraceptives and HRT and their change from 1984 to 1999

Education and social class

Many studies show that HRT users had a higher education level than nonusers [136,137]. In this dissertation, it was also found that HRT users had a higher proportion of college education than their age-matched controls. However, an increasing trend for HRT use rate along with school education in the five German National Health Surveys was not found (Fig. 6), suggesting that the overall HRT use was not more popular among women with higher education than among women with lower one. This could be explained from the following two aspects. Firstly, HRT use in Germany was more symptom-specified rather than for disease prevention or health promotion. In other words, HRT was used mainly for the relief of climacteric symptoms irrespective of women's education, which could be manifested by the bellshaped distribution of HRT use rate peaking around the climacteric ages. Secondly, many women with higher education were reluctant to use HRT for disease prevention because they doubted the preventive effects of HRT against cardiovascular diseases, which are still controversial and often discussed in special and/or in lay media. That women with a higher level of education were less willing to use HRT and did not more often use HRT than less educated was also documented in a study of Norwegian women [138].

However, along with the increase of household income, an increasing trend for HRT use was found in each survey, especially in surveys T2 and BGS98, in which relative large numbers of HRT users were found (Fig. 7). The same increasing trend of HRT use was also observed for social class, an integrated concept for education, profession and income [95], suggesting that economic factors may be important for choosing HRT. In line with the concept is that generally, HRT users had a significant lower average BMI and spent more hours per week on sports compared with controls. Also in the USA the household income was associated with the prevalence rate of HRT use in general populations, as a higher household income increased the likelihood of receiving HRT counseling [136].

Profiles of OC users differ of those of HRT users with respect to levels of education, social class and household income. No significant differences concerning the proportion of education and social class were found between contraceptive users and their age-matched controls in the first four surveys and in BGS98 if the special situation in East Germany was considered, where contraceptive use was very high. However, the use of contraceptives was more popular with a higher prevalence rate among women with middle or higher education, household income or social class than that among women with lower ones. This was specially true for the survey T3 in East Germany, which resulted in the significant differences of BGS98 compared with the first three surveys. Apart from the influences of contraceptive use in East Germany, the same changing trends for the proportion of education and social class were found in contraceptive users and in controls from 1984 to 1999 in West Germany. In other words, education and social class had little influence on the use of contraceptives from 1984 to 1999. This is guite understandable because the purpose of contraceptives is guite simple, birth control only rather than anything else (apart from short use for some gynecologic disorders). Women with middle and higher education or social class seem more likely to accept oral contraceptives, which could be seen from their higher prevalence rate of contraceptive use and the higher proportion among all contraceptive users. This may be due to the fact that the noncontraceptive benefits of oral contraceptives have been more recognized in recent years.

Body weight and body mass index

Generally, steroid hormone users, either for contraception or for HRT, had a significant lower body weight or body mass index on average compared with their controls particularly in the earlier surveys (Fig. 19). However, in the last survey BGS98, no difference in body weight or BMI was found between contraceptive users and controls. From Fig. 20, among all contraceptive users, less and less women were under-weighted and more and more women were over-weighted from 1984 to 1999; in contrast, among controls the proportion of 'under-weighted' changed very little. Different trends from 1984 to 1999 in body weight between contraceptive users and their age-matched controls suggested that use of oral contraceptives in the earlier surveys might increase the body weight of users. Weight gain was more often

observed with the older pills [139,140] since progestogen-related fluid retention can occasionally cause cyclical weight gain [141]. Changing to a contraceptive with a lower dose of progestogen or a different progestogen can help [142]. Weight gain is among the most common complaints of women using OC and often discourages continuation of oral contraceptives by many young women. A study indicated that approx. 8% pill users gave up this contraceptive method because of the problem of weight gain though women who complained about weight gain tended to be younger (< 25 years old) and new users [143]. More recent studies failed to confirm weight gain following pill use [141,144] and tend to conclude that current oral contraceptives do not contribute to weight gain [145,146]. Specially, 9 years of longitudinal data indicated that use of OCs in young women was not associated with weight gain and did not increase body fat either [147].

HRT users show the same trends on the proportion of BMI as controls from 1984 to 1999 (Fig. 21). However, in each single survey, HRT users had a much lower proportion for over-weighted, especially for the proportion of heavy over-weighted. The difference in body weight between HRT users and controls was often discussed as the evidence for healthier HRT users.

Smoking

It is well-known that smoking jeopardizes health. Smoking is a predictor of the risk of myocardial infarction [148], stroke [149] and venous thromboembolism [150] among contraceptive users. Oral contraceptive users aged >35 years who smoked were specially at risk for the above diseases and had a much greater risk of dying from circulatory diseases than nonsmoking OC users [151]. Therefore, pill users were often advised to give up smoking. This could be reflected from Table 21 and Fig. 28. Among contraceptive users, more and more women were nonsmokers from 1984 to 1999. In contrast, among controls, more and more women were current smokers and the proportion of nonsmokers remained almost constant.

For HRT users, the proportion of former smokers in each survey was much higher than that of controls, suggesting HRT users were more concerned about their health than the controls. On the other hand, there was an increasing trend for the proportion of current smokers from 1984 to 1999. From the viewpoint of smoking status, contraceptive users were becoming healthier whereas HRT users were not so healthy as before.

Multivariate logistic regression analysis showed that selected socioeconomic factors and personal lifestyle were closely associated with steroid hormone use. Women with normal or under-weighted body weight, women had quitted smoking, women from middle or upper social class and women who took part in sports actively were more likely to be HRT users. These determinants have been documented in other studies [110,121,123,124,152]. Women's health conditions, such as climacteric complaints, around the age of menopause, history of hysterectomy or oophorectomy were strong determinants of HRT use, too [123,124]. Determinants of HRT use tended to be associated with a healthy lifestyle that may favor a better health on one side, many HRT users were suffering more from postmenopausal symptoms on the other side. Contraceptive users showed no significant difference in education and social class from nonusers. However, determinants of steroid hormone use, either for contraception or fof HRT, may vary in different surveys along with time.

5. Possible effects following use of oral contraceptives and HRT in the general population

In this dissertation, many differences concerning health and disease and their correlates were found between steroid hormone users and their age-matched controls in the same survey or among different surveys. Reasons for these differences may be due to:

- the change of socioeconomic background. After reunification of the two parts of Germany, people in East Germany changed a lot in lifestyle, health and disease
 [96] including drug consumption [153].
- 2) the change of lifestyle along with time or after illness [154,155]. Mild diabetes, unfavorable blood lipids or blood pressures can usually be controlled without any medications by changing lifestyle such as diet, more physical activities, etc..
- 3) the effect of healthy users. In 2000, the World Health Organization (WHO) and American College of Obstetricians and Gynecologists (ACOG) published practice guidelines on medical eligibility for contraceptive use [156,157]. According to the guidelines, many women who are heavy smokers (particularly those older than 35 years), suffer from migraine, hypertension, have a history of stroke, ischemic

heart disease and venous thromboembolism or have a family history of breast cancer should not use oral contraceptives, which may result in the fact that contraceptive users are generally healthier than nonusers. And HRT users are often said to be healthier than nonusers because they are associated with higher education, social class, less weighted or being more active in physical activities than nonusers [110,121,123,124,152,158]. In Germany, women with characteristics associated with lower morbidity and mortality were more likely to use HRT [110].

- 4) steroid hormone use. As steroid hormone users, before initiation of therapy, appear similar to nonusers in health indicators [127,159], the differences found between steroid hormone users and controls should result most probably from the use of steroid hormones. For example, many studies have confirmed consistently that oral contraceptives can improve the blood level of ferric ions, ferritin and transferrin [160], as shown in Table 40, which is associated with a lower incidence of anemia in oral contraceptive users [161,162]. Favorable lipid profiles following HRT use were often documented in literature [163] and also in this dissertation, as shown in Table 35. Further, results of multivariate regression analysis (Table 43 and Table 44) show that sociodemographic data and personal lifestyle were not consistent for the use of steroid hormones among different surveys, suggesting that their effects may vary. The most probable reason for these differences observed between steroid hormone users and age-matched controls, therefore, should be the long-term use of steroid hormones, meanwhile other factors can not be excluded completely.
- 5) the effect of unhealthy users. HRT use peaks on the age ranged 50-59 years, in which most women experience their menopause and suffer from climacteric symptoms. Women are more likely to seek HRT medications when vasomotor symptoms such as hot flash, night sweat or sleep disturbance, etc. harass them and may affect their daily life. Moreover, women who use HRT to prevent or treat osteoporosis may be suffering from more body pain. All above seems to be associated with unhealthy HRT users, as shown by a study that women who use HRT were less healthy than nonusers when measured by a generic health status measure SF36 [164]. Results of BGS98 proved that HRT user had generally a lower score for all items of SF36 with significance in items of body pain and

vitality/energy compared with controls (Table 24). However, this conflicts somewhat with the so-called healthy HRT users.

Health status and health-related quality of life

Generally, there were no significant differences between steroid hormone users and controls regarding self-assessed health status as well as the overall health-related satisfaction with life in each survey. Oral contraceptive users, however, tended to have a better health status and were more satisfied with their health, whereas HRT users tended to have a worse health status and were less satisfied with their health compared with their age-matched controls (Fig. 31), which could be seen from the histories of specific and unspecific diseases/symptoms in the last 12 months (Table 25-29). During the last ten years from 1990 to 1999 when the use of HRT increased rapidly among German postmenopausal women, the score of satisfaction with health in HRT users, surprisingly, decreased significantly compared with controls (Table 23) and Fig. 31); the same trend was also observed for the overall satisfaction with life for HRT users in Western Germany (Fig. 30). This phenomenon could not be explained merely by the effect of unhealthy HRT users though HRT users may suffer from more menopausal symptoms [165] and therefore make a worse assessment for their health status. From Table 36, HRT users visited more frequently gynecologists and general practitioners than controls in the earlier surveys, but no significant difference could be found any more in the last survey BGS98, suggesting that HRT users were getting 'healthier' in the last survey BGS98 compared with the time before. Also, the above phenomenon is difficult to explain by SBP and the metabolic status (Table 32-35 and Table 41), since German HRT users had characteristics associated with lower morbidity, which strongly supported the results of a previous study [110]. Yet it may reflect the fact first described by the WHI study group that HRT use causes overall more harm than benefits [73,74].

Many women choose to use HRT based on the consideration that HRT may improve the quality of life besides the supposed benefits on the prevention of cardiovascular disease and osteoporosis, claiming that they feel better after taking hormones [166]. HRT may help users to improve quality of life by relieving menopausal symptoms [166,167]. However, a recent sub-study of WHI revealed that no significant effects could be found between HRT users and controls on general health, role-related

activities, vitality, social functioning and mental health etc. regarding health-related quality of life. HRT use could increase significantly only the score on terms of sleep disturbance, physical function and body pain, but with minor clinical meaning only [81]. Particularly, even among women aged 50-54 years who were suffering mostly from moderate-to-severe vasomotor symptoms, HRT had no benefits in terms of other outcomes concerning quality of life though it could improve vasomotor symptoms and -to some extent- also sleep disturbance [81]. Especially, the same results were reported in other clinical trials [168,169]. The assessment for health status and satisfaction with life and the measurement for quality of life depend largely on personal perception and socioeconomic background. For example, newly entering postmenopausal women tend to have a positive assessment for HRT use.

Prevalence of disease histories

The differences of health status between steroid hormone users and controls could be mirrored in more details by comparing their specific disease histories and unspecific disease/symptoms. Compared with age-matched controls, contraceptive users did not show a higher prevalence of cardiovascular diseases such as myocardial infarction, myocardial ischemia and stroke, but show even a trend of lower prevalence rates in varicosity, thromboembolism and arterial occlusion in legs (Table 25). Usually, it has been believed that oral contraceptives are associated with increased risks of myocardial infarction [37-39], ischemic stroke [40,41] and venous thromboembolism [42,43,64]. However, these serious adverse health outcomes occur very rare in premenopausal women, the absolute increase in risks of these diseases is thus expected to be very small in general populations. It is therefore hard to find any difference for these outcomes between contraceptive users and controls who are under ambulant care in our study population. In addition, the trend of lower prevalence of vascular diseases in contraceptive users observed in this dissertation may be largely due to the medical choosing for contraceptive use. Women with a history of stroke, ischemic heart disease or venous thromboembolism are often excluded to use oral contraceptives, the risks in these women are unacceptable if they use oral contraceptives according to the guidelines of World Health Organization [156] or of American College of Obstetricians and Gynecologists [157]. Most of concerns regarding oral contraceptive use with association to serious adverse outcomes come usually from studies of oral contraceptives containing high-dose

estrogens. Studies of oral contraceptives containing low-dose estrogens tended to show no significant difference. Moreover, women are not at increased risk for these serious but rare adverse outcomes anymore after they cease taking OCs [170].

Diabetes

For self-reported diabetes, a lower trend of prevalence was found in contraceptive users (Table 25, Fig. 33). For fasting-glucose-defined diabetes, however, no significant differences were found between contraceptive users and controls (Table 33). Results of other studies concerning the association of oral contraceptive use with diabetes or fasting glucose level are controversial [171,172]. The association of contraceptive use with diabetes or glucose level has been less consistent, partially due to increased variability in insulin levels between and within subjects [173]. While some studies found that current use of oral contraceptives was associated with increased 2-hours-tolerance glucose [174], many studies tend to conclude that use of contraceptives did not influence the fasting glucose level and did not have an increased risk of diabetes [171,175,176].

It seems that HRT differs from oral contraceptives in glycemic control. It has been suggested that hyperandrogenicity is closely associated with insulin resistance and a risk factor of diabetes in postmenopausal women [177]. Estrogen replacement in postmenopausal women has been linked with decreased hyperandrogenicity and therefore markedly improved glucose homeostasis [178]. In this dissertation, it was found that HRT users had a significantly lower fasting glucose levels and a significantly lower prevalence rate of diabetes (survey T2 and BGS98) compared with controls (Fig. 49, Table 33), and use of HRT was associated with a lower risk of diabetes from the case-control study derived from the five national health surveys with OR 0.32 (0.13-0.78) and 0.81 (0.45-1.48) for BGS98 and survey T012 (the merging of survey T0, T1 and T2), respectively (Table 50). These findings were not only in agreement with many observational studies [179-181], but also with recently published results of HERS and WHI study, which suggested that use of HRT reduced the incidence of diabetes by 35% [182] and 21% [183], respectively. Before the HERS and WHI study, another large randomized controlled clinical trial PEPI study (Postmenopausal Estrogen/progestin Intervention) also found a statistically significant decrease in insulin level (16% lower) and mean fasting glucose levels (2.2 mg/dl lower) for HRT compared with placebo [184].

Blood pressure

From Table 32 and Fig. 48, contraceptive users usually had a significantly higher blood pressure and a significantly higher prevalence rate of hypertension whereas HRT users, on the contrary, had a trend of lower blood pressure and prevalence of hypertension with significance in the last survey BGS98. Oral contraceptives have been for a long time linked with increased blood pressures [185-187]. Even low-dose contraceptives (30 µg ethinyl estradiol) were found to be able to increase blood pressure in a small study monitoring 24-h ambulatory blood pressure [188]. According to a large population-based study, estrogens in contraceptives should be responsible for the increase of blood pressure, as combined oral contraceptives were found to be associated with, whereas progestin-only contraceptives were not [187]. A recent review of 3 prospective control trials and 1 cross-sectional study concerning progestogen-only contraceptives found no association of high blood pressure with contraceptive use for up to 2-3 years [189]. Physiologically, estrogens are involved in mediating the renin-angiotensin-aldosterone system, thereby affect blood pressure [190]. However, contraceptives-induced hypertension is usually mild (2-3 mm Hg for SBP, and clinically unimportant) and does not require any medication [191]. Moreover, increased blood pressure following OC use usually returns to normal levels in 3-6 months after termination of OC use [186]. Women with even mild elevation of blood pressure, however, should be very cautious of initiating contraceptive use as a small percentage of patients may develop severe, even lifethreatening hypertension. According to the guidelines of WHO, oral contraceptives are absolutely contraindicated for women with systolic blood pressure >160 mm Hg or diastolic blood pressure >90 mm Hg. For women with controlled marginal hypertension using contraceptives, risks usually outweighs benefits [156]. Progestogen-only contraceptives are an alternative for women who are at risk of cardiovascular disease due to increased blood pressure.

It seems that postmenopausal HRT does not affect blood pressure very much [192-196], though WHI study found a slightly increased SBP of 1-1.5 mm Hg in a subgroup of women taking HRT [73]. In fact, blood pressure was more often

observed to be lowered by HRT in the most of such studies [196] especially in those focussing on a transdermal product [197,198]. In a longitudinal observational study, it was found that after 5-10 years follow-up postmenopausal women taking HRT had a smaller increase in SBP over time than those not taking HRT. Therefore HRT may protect from increased blood pressure [199]. In this dissertation, significantly decreased SBP and the prevalence of hypertension was found in survey BGS98 for HRT users under 80 years of age (Table 32), but was not found for HRT users under 70 years of age (Fig. 48, Page 59 text) compared with controls, partly due to that HRT may protect from increased blood pressure especially in the elderly [199]. Important interindividual factors such as smoking, BMI, sodium intake and different HRT regimes used [200] may account for the inconsistent findings seen in studies examining the effects of HRT on blood pressure.

Blood lipids

In this dissertation, it was found in most surveys that contraceptive users had a significant higher prevalence of hyperlipidemia compared with age-matched controls (Fig. 50 and Table 35). That oral contraceptives can increase the levels of triglycerides and total cholesterol has been confirmed in numerous cross-sectional studies and randomized clinical trials [201-203]. The effect of oral contraceptives on lipid levels depends on the estrogen dose relative to the progestogen dose. Estrogens tend to have beneficial effects on lipids and progestogens seem to have opposite effects of estrogens. While combined contraceptives containing 'second generation' progestogens affect adversely lipid profiles by increasing total cholesterol, triglycerides and LDL-cholesterol, combined contraceptives containing 'third generation' progestogens show mostly beneficial effects on lipid profile by decreasing LDL-cholesterol and increasing HDL-cholesterol [204]. This may explain why hyperlipidemia was more often observed in earlier surveys in this dissertation (Table 48). The positive impact of desogestrel-containing oral contraceptives on HDL-C and LDL-C suggests that a potential cardioprotective benefit (rather than an atherosclerosis risk) may occur with prolonged use of such an OC [201,205]. Very recently, WHI study suggested that use of oral contraceptives could significantly reduce the risks of cardiovascular disease by 8% (p<0.001), myocardial infarction by 10% (p<0.008), angina by 9% (p<0.001) and peripheral artery disease by 12% (p<0.003) (http://www.nature.com/news/2004/041018/full/041018-13.html, accessed 25th, Oct., 2004).

Incidence of cardiovascular diseases increases significantly in women after menopause. Part of the increase is due to atherogenic changes in plasma lipoproteins, i.e. increased level in LDL cholesterol and lipoprotein (A) and decreased level in HDL cholesterol [206,207]. Hormone replacement therapy may exert an antiatherogenic effect by influence on plasma lipoprotein fractions. The favorable lipid profiles following HRT use, i.e. a decrease in lipoprotein (A), LDL and total cholesterol and an increase in the ratio of HDL to total cholesterol, were consistently observed not only in this dissertation but also in many other cross-sectional studies as well as in randomized clinical trials [179,207,208]. A pooled analysis of 248 studies from 1974 to 2000 involving 42 different HRT regimes on lipid profiles indicated that all estrogen alone regimes raised HDL cholesterol and lowered total and LDL cholesterol; oral estrogen raised whereas transdermal 17β-estradiol lowered triglycerides; progestogens had little effect on estrogen-induced reduction in LDL and total cholesterol, but opposed estrogen-induced increase in HDL cholesterol and triglycerides to different degrees depending on different types of progestogens used [163]. In addition, treatment of postmenopausal women with CEE and MPA can also significantly reduce the levels of remnant lipoprotein particles, which have been suggested to be the most atherogenic particles among the triglyceride-rich lipoproteins [209]. Despite the ability of HRT to improve serum lipid profiles and the results of numerous observational and experimental studies, results of NHSs and other clinical trials as well [73,82], indicated that the improved lipid profile does not translate into less more cardiovascular diseases. Considering that LDL-C levels increased by approximately 15-25% around the time of menopause [206], 12% decrease of LDL-C following use of CEE and MPA [73,83] may not be very effective in modifying the progress of atherosclerosis [210]. Furthermore, the decrease of LDL-C in women undergoing HRT was mainly the decrease of less atherogenic LDL particles rather than the more atherogenic smaller denser LDL-C [210]. Statins, in contrast, can lower LDL-C including the small dense LDL-C significantly and therefore reduce the risks of cardiovascular diseases markedly [211]. Moreover, estrogens may enhance C-reactive protein [212,213], a crucial marker for cardiovascular disease, increase thrombin generation and decrease antithrombin III [214]. These effects affect adversely the development of cardiovascular diseases and may explain partially the null effect of HRT for prevention of cardiovascular disease. Besides, genetic variation in estrogen receptors may also play a roll.

Postmenopausal women with the ER-alpha IVS1-401 C/C genotype or several other closely linked genotypes have an augmented response of HDL cholesterol to estrogen or combined replacement therapy [215], suggesting that it may be necessary to individualize HRT use.

6. Risks of HRT

6.1 Cardiovascular risks

Despite the beneficial effects of HRT on lipid profiles and fibrinogen [192], a decreased morbidity of cardiovascular disease was not found either in HRT users compared with age-matched controls here or in HRT treated groups compared with placebo in clinical trials. This does not mean HRT users had no such increased risks. The reasons should be attributed to the small sample size of HRT users in NHSs and the small absolute risks of heart attack and stroke in general population. In fact, WHI study reported significantly increased cardiovascular events (nonfatal myocardial infarction and CHD death) (HR, 1.29, 95% CI: 1.02-1.63) [73] and ischemic and hemorrhagic stroke (HR 1.50, 95% CI: 1.08-2.08) [76], corresponding to 7 and 8 additional cases of heart attack and stroke in every 10000 person-year, respectively. It is therefore hard to find any difference in our small sample population. For women with established CHD, many clinical trials reported consistently a null effect of HRT on morbidity or mortality of cardiovascular diseases. In HERS study, active treatment group (CEE plus progesting) had a RR of myocardial infarction or CHD death 0.99 (0.81-1.22) in comparison with placebo after 4.1 years follow-up [82]. Additional two more years follow-up in the same study reconfirmed this null effect with RR 1.00 (0.77-1.29) [83]. In PHASE trial (Papworth HRT Atherosclerosis Study Enquiry), postmenopausal women receiving transdermal 17β-estradiol 2 mg/day for a mean of 30.8 months experienced unsignificantly more primary endpoints of hospitalization for unstable angina, myocardial infarction or death, with event rate ratio 1.49 (0.93-2.36) compared with placebo [216]. In WEST study (Women's Estrogen for Stroke Trial), 99 and 93 strokes or deaths were recorded in 664 women with a documented stroke or transient ischemic attack in the active treatment group (1 mg 17β -estradiol/day) and placebo group, respectively (RR 1.1, 95% CI: 0.8-1.4) when followed up for 2.8 years on average [217]. In another clinical trial, no significant difference in mean minimum coronary artery diameters could be found among the three groups (estrogen alone:1.87±0.02 mm, estrogen plus progestin: 1.84±0.02 mm, and placebo

1.87±0.02 mm). This holds also true with respect to CHD events (estrogen alone: 29 CHD/100, estrogen plus progestin: 28 CHD/104, placebo: 34 CHD/105, p=0.69) when 309 postmenopausal women with coronary stenosis were followed-up for 3.2 years on average [218].

Clearly, a large body of evidences both from clinical trials and from observational studies demonstrated that venous thromboembolic events (deep vein thrombosis and pulmonary embolism) occurred more frequently in HRT users than in nonusers, with the highest risks in the first year of use [73,84]. According to a meta-analysis of 12 studies, current HRT users had 2-fold increased risk of thromboembolism compared with nonusers [69], which was consistent with results of WHI study (34 vs. 16 venous thromboembolism per 10000 person-year) [73] and of HERS study (34 vs. 12 events, RR 2.89, 95% CI 1.5-5-58) [82].

All above-mentioned studies are long-term, middle-to-large scale, randomized controlled clinical trials examining HRT regimens including CEE and 17β-estradiol, which own the strongest power in casual inferring among epidemiological studies. Despite results of numerous observational studies and strong biological plausibilities. clinical trials do not support the hypothesis that HRT can reduce the risks of cardiovascular diseases. According to the results of clinical trials and of this dissertation, it may be concluded that HRT use does not induce any cardioprotective effect. On the contrary, HRT use increases the risk of cardiovascular diseases including stroke and thromboembolism in postmenopausal women with or without established CHD, and therefore should not be used for the primary or secondary prevention of cardiovascular diseases. As early as in 2001, based on the results of HERS and subsequent trials, American Heart Association has published a statement, opposing clearly the initiation of HRT for the secondary prevention of cardiovascular disease [219]. For primary prevention, clinical recommendation had to await the results of randomized clinical trials due to the lack of adequate data at that time. Results of WHI study now have given the answer [73,74]. Besides to WHI study for primary prevention, another large scale clinical trial, WISDOM study (Women's International Study of long Duration Oestrogen after Menopause), scheduled to end in 2012, was also early terminated [220]. Therefore the dispute concerning HRT use for the prevention of cardiovascular disease should be over now.

6.2 Cancer risks

Breast cancer

Of large concern is also breast cancer following HRT use. Since many years breast cancer has occupied the first place of morbidity and mortality in all cancers in Germany [221]. Unfortunately, no information on it could be provided in this dissertation because the studied sample was from the general population under ambulant care, in which the incidence of breast cancer is very low. However, a growing body of evidence from the results of recent large scale studies and randomized controlled trials show consistently that use of HRT increases the risks of breast cancer. Up to now, the largest study examining the association of HRT use and breast cancer is the Million Women Study, in which 1084110 UK women aged 50-64 years were recruited between 1996 and 2001 and followed up for 2.6 to 4.1 years [86]. Results revealed that current users of HRT were more likely than never users to develop breast cancer (adjusted RR 1.66, 95% CI: 1.58-1.75) and die from it (RR 1.22, 95% CI 1.00-1.48). Both regimes of estrogen alone and estrogen plus progestins increased the risk of breast cancer, with the latter (RR 2.00, 1.88-2.12) having substantially greater risks than the former (RR 1.30, 1.21-1.40). In addition, the risk of breast cancer increased with total duration of use with each type of HRT while past users of HRT were not at an increased risk of incident or fatal disease, with RR 1.01 (0.94-1.09) and 1.05 (0.82-1.34, respectively [86].

Similarly, an earlier collaborative reanalysis of original data from 51 epidemiological studies involving 52705 women with and 108411 women without breast cancer indicated that ever use of HRT increased significantly the risk of breast cancer with RR 1.14 (p<0.0001) compared with never users. Current use of HRT for 5 years or more had a RR 1.35 (1.21-1.49), the risk of breast cancer increased with longer duration of HRT use, too. Yet, there was no significant increase of breast cancer after cessation of HRT use for 5 or more years [222]. The WHI study, too, showed that HRT increased the risk of breast cancer with a HR 1.26 (1.00-1.59) for women using combined estrogen plus progestin after 5.2 years [73,77]. Further, breast cancers diagnosed in HRT treated group were at more advanced stage compared with those in placebo group, suggesting that HRT may interfere with the early diagnosis of breast cancer [77]. In addition, a large cohort study of 46355 postmenopausal women showed that use of combined estrogen plus progestin or estrogen alone

within 4 years increased the risk of breast cancer with a RR 1.4 (1.1-1.8) and 1.2 (1.0-1.4), respectively [223]. Similar results of increased risk of breast cancer following HRT use were also reported in a nested case-control study, the incidence of breast cancer increased by 60% to 85% in recent long term HRT users [224]. Surprisingly, the recently published results of estrogen alone regime in WHI study suggested that estrogen alone (CEE) might reduce the incidence of breast cancer (HR 0.77, 95% CI: 0.59-1.01) [74]. The reasons are unclear and further investigations are needed.

Ovarian cancer

Ovarian cancer is a malignant gynecological cancer with a death rate exceeding other cancers in women. For the association of ovarian cancer and HRT use, epidemiological studies have yielded conflicting results. A meta-analysis of 15 case-control studies before the year 2000 did not find a significant association of estrogen replacement therapy and epithelial ovarian cancer (OR 1.1, 95% CI 0.9-1.3) [225].

Recent large scale studies, however, indicated that HRT use increased the risk of ovarian cancer. A large prospective study (211581 postmenopausal women were followed up from 1982 to 1996) reported that women who were using ERT at baseline had a higher death rate from ovarian cancer compared with nonusers with rate ratio 1.51 (1.16-1.96). For former ERT user, rate ratio was 1.16 (0.99-1.37) and duration of ERT use was associated with increased risk of mortality in both baseline and former users. Baseline users with 10 or more years of use had a RR of 2.20 (1.53-3.17), while former users with 10 or more years of use had a RR of 1.59 (1.13-2.25) [226]. Results of another large cohort study using the data of a nationwide breast cancer screening program (a total of 44241 postmenopausal women were followed-up from 1979 to 1998) were well in accordance. Ever use of ERT was significantly associated with ovarian cancer with rate ration 1.6 (1.2-2.0) comparing with nonuse. Duration response was also observed in this study: rate ratios for 10 to 19 years and 20 or more years of use were 1.8 (1.1-3.0) and 3.2 (1.7-5.7), respectively (P value for trend <.001). However, for the regime of estrogen plus progestins, the rate ratio was 1.1 (0.64-1.7) and no evidence of a duration response was found: the rate ratios for less than 2 years and 2 or more years of estrogenprogestin-only use were 1.6 (0.78-3.3) and 0.80 (0.35-1.8), respectively [227]. Very recently, a study including 31381 postmenopausal women followed-up for 15 years also suggested that women who were using ERT at baseline had an elevated multivariate-adjusted relative risk of ovarian cancer (1.7; 95% CI, 1.1-2.8) compared with never-users, and women who had used ERT at baseline for more than five years were at higher risk with RR 2.5 (1.4-4.5) [228].

In particular, an increased risk of ovarian cancer was observed in the WHI study. The hazard ratios (HR) in women assigned to estrogen plus progestin compared with placebo were 1.58 (0.77-3.24) and 0.81 (0.48-1.36) for invasive ovarian cancer and endometrial cancer, respectively, but more HRT women required endometrial biopsies (33% vs 6%; P<.001) [229]. While women with intact uterus should be prescribed an estrogen-progestin combination as it is unquestionable that estrogen alone without progestins can cause endometrial cancers in these women, it is still common for women who have had a hysterectomy (but who retain 1 or 2 ovaries) to be given estrogen only. Thus, based on the results of large cohort studies and WHI, it may be concluded that use of ERT in postmenopausal women is associated with increased morbidity and mortality of ovarian cancer, the association of HRT with ovarian cancer is scant and warrants further investigation.



6.3 Various risks



Other potential increased risks of HRT use include mild cognitive impairment and/or probable dementia in postmenopausal women aged 65 years or older (HR: 2.05, 95% CI:1.21-3.48, WHI study) [79] and cholecystitis, RRs of which were 1.8 (1.6-2.0) and 2.5 (2.0-2.9) according to a recent scientific review [69]. Compared with the benefits of HRT, i.e. reduced risks of colorectal cancer and osteoporotic fracture, the above-mentioned risks of HRT were overweighted (Fig. 51).

7. Non-contraceptive benefits of oral contraceptives

Apart from the primary effect of oral contraceptives, namely birth control, oral contraceptives show also many non-contraceptive health benefits for OC users. Many women tend to overestimate their risks while they are unaware of these non-contraceptive benefits. It seems necessary to summarize these non-contraceptive benefits following OCs use below.

7.1 Protection from ovarian cancer and endometrial cancer

A large body of evidence from case-control studies and several cohort-studies has indicated consistently that use of oral contraceptives can reduce the risk of ovarian cancers [55,56,59,60,230] and endometrial cancer [57,58,61]. As shown in the CASH study from the USA, the protection of oral contraceptives from ovarian cancer and endometrial cancer occurred in only 3-6 months after use of contraceptives, increased with duration of OC use and would persist for 10-15 years after termination of OC use [60]. A meta-analysis of 17 case-control studies and 3 cohort studies indicated that the risk of ovarian cancer declined by 10-12% after 1 year and by approximately 50% after 5 years of use [231]. Another meta-analysis showed that the risk of endometrial cancer before 60 years of age was reduced by 38%, 51%, 64% and 70% after the use of oral combined contraceptives for 2, 4, 8 and 12 years, respectively [232]. The net estimated effect of oral contraceptive use was 193 ovarian cancer and 197 endometrial cancer cases less occurred among 100000 women aged 20-54 after 8 years use [233]. The protecting effect of OC use from ovarian cancer may extend to women with family history of ovarian cancer [234], but not to women with a mutation in the BRCA1 and BRCA2 genes [235]. Nevertheless, in above studies, women have mostly used oral contraceptives containing high-dose sex hormones, which reduce the risk of endometrial cancer presumably by progestinmediated suppression of estrogen-induced proliferation of endometrial cells [236].

Newer formulations with modern low-dose estrogens have not been studied if these protective effects occur, but the presumed mechanism suggests that these formulation would reduce the risk, yet not so markedly [237].

7.2 Gynecological benefits

Well-established gynecological benefits following oral contraceptives use include a reduction in dysmenorrhea, menstrual blood loss, ecotopic pregnancy and pelvic inflammatory diseases [238,239]. Dysmenorrhea refers to the occurrence of painful menstrual cramps and is a common gynaecological complaint. The use of combined oral contraceptives for the treatment of primary dysmenorrhea has been advocated since the introduction of OCs for general use in 1960s. An earlier double-blinded study, in which combined oral contraceptives with medium-dose estrogen was used, confirmed the effect [240]. The involved mechanism for the treatment is supposed to inhibit ovulation and reduce the production of prostaglandins [241]. Menstrual fluid volume decreases along with the amount of prostaglandins produced, in turn effectively reducing dysmenorrhea by decreasing uterine motility, and thus uterine cramping. However, it is not clear if modern low-dose oral contraceptives are also effective in the treatment of primary dysmenorrhea. For the treatment of secondary dysmenorrhea due to endometriosis, low-dose OCs may be as effective as gonadotropin-releasing-hormone agonist [242].

Most OC users have shorter and more regular cycles compared with those using other contraceptive methods or no method [243,244]; and in this dissertation, significantly more OC users had regular menstrual cycles compared with their agematched controls (Table 30). This is because for OCs users menstrual cycles are artificial bleeding following the withdrawal of OCs and therefore are more regular. On average, healthy OC users lose only 50-60% as much blood per cycle as before after 3-6 months oral contraceptive medication [245]. Menorrhagia due to ovulatory dysfunctional uterine bleeding usually is well controlled by oral contraceptives. A randomized clinical trial has shown that combined triphasic contraceptives with either 20 µg or 35 µg estrogens significantly reduced dysfunctional uterine bleeding [246]. In addition, contraceptive use can significantly increase blood levels of iron, ferritin and transferrin (Table 40) and increased hemoglobin concentrations in anemic women, therefore, it is associated with a reduced prevalence of anemia [161,244,247].

Evidences also exist for the protective effect of contraceptive use against pelvic inflammatory disease. Chlamydial infection is one of the most common causes of pelvic inflammatory disease and this infection is associated with infertility and ectopic pregnancy. Though contraceptive users may be more susceptible to chlamydial infection than nonusers, as shown by some studies, OC users are less likely (OR 0.3-0.5) to experience acute symptomatic chlamydial salpingitis than women who use non-hormonal methods [248,249]. However, OC use does not protect from all forms of pelvic inflammatory disease such as gonococcal pelvic inflammatory disease [250].

7.3 Acne and hirsutism

Female acne patients are often found to have increased ovarian and adrenal androgen levels. Combined oral contraceptives can suppress the production of androgens in ovaries and in adrenals meanwhile raise sex hormone-binding globulin levels. This limits free testosterone, the presumed mechanism for the improvement of acne. Especially, modern low-dose combination oral contraceptives can decrease the concentration of free testosterone and are also effective in the management of acne [251,252]. The combination OCs containing cyproterone acetate is particularly effective, since cyproterone has a direct peripheral anti-androgenic action in blocking the androgen receptor [253]. The reduced testosterone levels associated with oral contraceptive use are also thought to be responsible for the improvement in hirsutism [253,254]. Without obvious difference in side effects from the placebo group, the efficacy of oral contraceptives for androgen-dependent disorders like acne and hirsutism has been confirmed by many multicenter randomized clinical trials [255-259]. Therefore, oral contraceptives are particularly useful for those women with androgen-dependent disorders who also require contraception.

7.4 Other possible benefits of oral contraceptives

It has been suggested that oral contraceptive use may decrease the risk of *colorectal cancer*. Results from several studies are inconsistent, however. The prospective Nurses' Health Study found that women who used oral contraceptives for 96 months

or longer had a 40% lower risk of developing colorectal cancer (RR 0.60; 95% CI 0.40-0.89) compared with women who never used oral contraceptives [260]. Similarly, combined data from a large multicenter case-control study of 1232 women with colorectal cancer and 2793 hospital controls suggested that ever use of oral contraceptives may reduce the risk of colorectal cancer by 36% (OR 0.63, 95% CI 0.49-0.85) [261]. A review of oral contraceptive use and colorectal cancer described a reduced risk in ever-users of oral contraceptives was found in three of four cohort studies and in five of eleven case-control studies and recent OC use with long duration appeared to be related to some risk reduction, too [262]. Yet, another prospective large study of 57529 women did not corroborate the hypothesis (RR 1.0, 95% CI 0.75-1.4) [263]. It can be concluded, however, that OC use does not increase the risk of colorectal cancer and may even have a favorable effect on either incidence or mortality of colorectal cancer. This holds true especially for modern low-dose contraceptives.

A cross-sectional retrospective study investigated risk factors for low bone mineral density in a group of 2297 women and found that oral contraceptive use may protect against low bone mass (OR 0.35, 95% CI 0.23-0.53) [264]. In a small randomized controlled clinical trial, bone density improved significantly in women with hypothalamic amenorrhea after oral contraceptive use for 12 months [265]. Further, higher bone mineral density was associated with increased duration of exposure, with a mean increase of 3.2% associated with the first 5 years and a further 0.2% with >/=5 years of exposure [266]. However, other studies failed to confirm the positive effect of oral contraceptives on the peak bone mass [267,268]. These studies vary in the age of study participants or in the bone sites. In addition, the conflicted results indicated that bone mass may be influenced by the compositions of various formulations of contraceptives. A review of 13 studies which focused on the low-dose contraceptives revealed that 9 of these studies showed a positive effect of OC use on BMD, and 4 did not [269]. Another review focussing on progestogen-only contraceptives showed that the average bone mineral density was even reduced in current users of depot medroxyprogesterone acetate compared with non-users, although density in users was within one standard deviation of the mean in non-users [270] This suggests strongly that estrogens contained in oral contraceptives play a critical role in the bone formation [271]. It should be noted that the benefits of

estrogen, with or without progestins, on bone mineral density, osteoporosis and colorectal cancer have been well documented in postmenopausal women.

The current lowest available dose of estrogen used for OCs is 20 μ g ethinyl estradiol. A review for this formulation with 20 μ g of ethinyl estradiol suggested that they are as efficacious as other OCs in birth control but have a lower incidence of estrogen-related side effects [130]. Both contraceptive and noncontraceptive benefits of OCs are available to most women from adolescence to menopause without complications [130].