Eur J Cancer Clin Oncol, Vol. 25, No. 12, pp. 1961–1972, 1989.
Printed in Great Britain

0277-5379/89$3.00 + 0.00

The Role of Exogenous Hormones in the Epidemiology of Breast, Ovarian and Endometrial Cancer

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Abstract—*This review focuses on the effects of oral contraceptives (OC) and estrogen replacement therapy (ERT) on the risk of breast, ovarian and endometrial cancer. The relationship between OC and cancer risk is first placed in a historical perspective. Since* 1960, *when OC were introduced, the hormonal composition of OC as well as the characteristics of the OC user have changed considerably. Studies conducted in the* 1970*s were generally reassuring, but it was not until the* 1980*s that studies could evaluate the effect of prolonged OC use after an extended follow-up period.*

Although the relationship between breast cancer and OC has been investigated in about 40 *studies, the issue still remains essentially unresolved. Most studies report no association between ever use of OC and breast cancer risk. Several studies find increased risk for prolonged use and other studies report elevated risks for women who used OC very early in their reproductive years. The inconsistent results of recent studies are attributed to bias or to geographical variation in latency period elapsed, types of OC preparations, or prevalence of other risk factors.*

In contrast, the use of combined OC has consistently been shown to reduce the risk of ovarian and endometrial cancer. The risk further decreases with increasing duration of use and the protective effect seems to persist in ex-users for at least 5 *years. Some evidence indicates that higher parity reduces the protective effect.*

Though studies relating ERT to breast cancer are far from consistent, overall, there is evidence for a moderately increased risk with high dose and/or long duration. The effect seems to be modified by mode of administration (injections vs. pills) and by type of ERT, but this needs confirmation. The number of adequate studies on the relationship between ERT and ovarian cancer is too small to draw firm conclusions. The positive relationship between ERT and endometrial cancer is now well established. The ERT effect is dose- and duration-dependent and is characterized by a short latency period. The cyclic addition of progesterone (>10 *days/cycle) may reduce the risk increase.*

INTRODUCTION

OVERWHELMING EVIDENCE from both epidemiologic and experimental studies points to an important role of endogenous hormones in the genesis of certain human cancers [1, 2]. Regarding breast cancer, for example, a number of established risk factors emerging from epidemiologic studies, like age, late age at first birth, nulliparity, early age at menarche and late age at menopause, are related to endogenous hormone production and metabolism [3]. For this reason, the role of exogenous female hormones has been felt to be of considerable interest in understanding the etiology of gynecological cancers. Exogenous female hormones comprise oral contraceptives (OC), injectable contraceptives, estrogens used for replacement therapy (ERT) at and after menopause and drugs used for regulation of periods, infertility problems, pregnancy difficulties and suppression of lactation (among various conditions). Some of these hormones, such as OC and ERT, have been used by many millions of women, and, accordingly, assessment of their effect on cancer risk is of great public health importance. Other hormone preparations, such as those prescribed for infertility problems, have not been commonly used, and, as a consequence, reliable human data on their effect on cancer risk are sparse. This review will focus on the effects of oral contraceptives and estrogen replacement therapy. Emphasis will be placed on current controversies rather than on

Accepted 10 July 1989.
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This work was partly supported by a grant from the Netherlands Cancer Foundation.
Paper presented at the 7th Annual ECP Symposium 'Breast, Endometrial and Ovarian Cancer: Aetiological and Epidemiological Relationships', Bilthoven, The Netherlands, 1–2 May 1989.

established facts. By a critical evaluation of the studies conducted so far, we will identify several unanswered questions that should be the subject of further investigation.

ORAL CONTRACEPTIVES AND CANCER RISK IN A HISTORICAL PERSPECTIVE

'Consider the implications of the fact that more than fifty million women worldwide take regularly for contraceptive purposes a combination of hormones that essentially cuts off the function of their own ovaries' [4].

The above statement, made by MacMahon in 1979, has prompted the epidemiological community for more than two decades now to conduct numerous studies evaluating the effects of OC on cancer risk. Oral contraceptives, in the form of estrogen–progestogen combinations, were first introduced in the U.S.A. in 1959. Other countries soon followed and since 1960 there has been a tremendous increase in worldwide OC use. In 1980 it was estimated that about 150 million women in the world had ever used OC [5], while approximately 60 million women are current OC users [6]. For the interpretation of epidemiological studies on the association between OC use and cancer risk, it is of great importance to note that oral contraceptive practices have changed considerably over the years. First, the OC preparations have undergone remarkable changes, the major ones being a reduction of estrogen dosage and potency, the application of different progestagens and the introduction of completely new types of preparations, such as biphasic and triphasic pills and the progestagen-only pill [7].

Second, the OC users themselves have changed. Over the past two decades women have tended to start OC use at a progressively younger age and to use OC to delay their first birth as well as to space or limit later births [8].

When reading reviews and editorials on OC in the 1960s and the early 1970s, it is of interest to note that early concerns in the scientific community about undesired effects of the pill did *not* focus on cancer, although the theoretical possibility of increased cancer risk was kept open [9–13]. Due to a variety of more or less serious short-term effects that became apparent soon after the introduction of OC, attention focused on their effects on the cardiovascular system (mainly thromboembolic phenomena) and on carbohydrate metabolism (most of these side-effects would largely disappear when OC with lower estrogen potency came into use). Several researchers in the cancer field, however, warned that a prolonged latent period of many years characterizes the behavior of most known carcinogens in man [14, 15] and that it might take 20 or 40 years to obtain conclusive results [9]. Hertz [14] ascribed the relative lack of concern about cancer risk to (a) the reassuring results regarding OC effects in animal experiments and (b) the fact that estrogen use during or after the menopause had so far not been associated with increased cancer risk. Hertz discarded both arguments by pointing out that extrapolation from animal experiments to humans suffers from many problems (as is now better recognized than in the 1960s). Further, estrogen studies in human beings showed serious limitations, e.g. by that time only four studies had been conducted that showed data on estrogen users who were treated for 4 years or more. Even these few data were not considered by Hertz to be relevant for the OC issue because OC users were much younger and also because the progestogen component in OC might change the estrogen effects.

In the seventies the first epidemiological studies of OC and cancer risk were published. Most studies examined breast cancer and their results were, with one exception, highly reassuring. The consistent finding that oral contraceptive use protected against benign breast lesions even led to the promising thought that, eventually, breast cancer risk might also be decreased in OC users [16]. By the end of the seventies large numbers of women had already entered their second decade after first exposure and it seemed justified to conclude that OC did not affect the growth of preexisting cancers nor exert an effect late in the promotional phase of carcinogenesis. The general feeling of reassurance is well reflected by the fact that we were unable to find more than one editorial in the major medical journals published from 1970–1979. As a comparison, in the same period 13 editorials appeared that discussed menopausal estrogens and cancer, while three editorials dealt with exogenous hormones in general, with an emphasis on estrogen risks.

In the beginning of the 1980s the picture changed completely. Many new studies were conducted that could evaluate the effect of prolonged OC use after an extended follow-up period. However, as will be shown below, this did not mean that consensus could be reached. Unexpected findings regarding the effect of OC on the risk of ovarian and endometrial cancer and highly controversial findings with regard to breast cancer led to no less than 15 editorials in major medical journals from 1980 up to May 1989.

BREAST CANCER

To our knowledge, the relationship between OC and breast cancer has been investigated in at least 32 case-control studies and seven cohort studies. Despite this vast number of studies, the issue still remains essentially unresolved. The first well-conducted, case-control study on the subject was published by Arthes *et al.* in 1971 [17]. No evidence was found for an association between OC and

development of breast cancer. It is of interest, however, that the authors already recognized a problem that would hinder the interpretation of all epidemiological studies in the next two decades, i.e. that an effect of OC, if real, might only become apparent after a prolonged latency period. As a modest purpose of their study Arthes *et al.* mentioned 'to provide a baseline measurement with which subsequent changes could be contrasted. The development of a relative risk for former users of OC would perhaps have greater significance if it were known that prior to the expiration of a period of latency the risk had been essentially unity.' This view turned out to be highly prescient. One of the strongest indications at present for a late acting effect of OC on breast cancer risk is the finding by three research groups of a positive association between OC and breast cancer risk in their recent studies, whereas earlier studies of the same groups, using almost identical methods, did not show an association [18–20].

Table 1 summarizes the main design features and results of major case-control studies that included cases diagnosed after 1980 [18, 19, 21–31]. Earlier case-control studies had been largely reassuring, although suspicions had been raised about adverse effects among women with increased baseline risk, such as those with a history of biopsy-proved benign breast disease [32–35] and with a family history of breast cancer [34, 36, 37].

As is shown in Table 1, most studies reported no association between ever use of OC and breast cancer risk. However, the most recent study published by Miller *et al.* [18] did find a two-fold increased risk [95% confidence interval (CI): 1.4–2.9] for ever use, and even a four times increased risk for 10 or more years of use in women diagnosed with breast cancer under age 45. These observations are in contrast with earlier findings from the same group. Since almost the same methods were used in both studies, bias seems to be an unlikely explanation of the results and it is tempting to hypothesize that only in the latest study had enough time elapsed for the effects of OC use to emerge. However, Miller *et al.* were unable to detect a clear increase of risk with increasing time interval following five years of use.

Some support for an overall increased risk in young breast cancer patients comes from the recent update of the Royal College of General Practitioners (RCGP) cohort study [20]. In this study, which follows a cohort from 1968 onwards, a relative risk of 3.33 was observed for ever use of OC in women aged 30–34 years at diagnosis. An analysis by time since stopping OC use showed a significant trend in all ever users (regardless age), but the trend was steeper for women aged 30–34 at diagnosis.

A study conducted in Yugoslavia, where OC use has been much lower than in the U.S.A. and Western Europe, also showed an increased risk for ever use, with a positive trend for duration of use [31]. However, the authors indicate that their hospital control group may not have been fully appropriate.

In a carefully matched study conducted in Scandinavia, no increased risk was observed for ever use, but long-term use (≥12 years) in women younger than 45 years was associated with a more than two-fold risk (RR = 2.2; 95% CI: 1.2–4.0) [26].

Nearly all the studies in Table 1 show significantly elevated risks in one or more subgroups. Most attention has been focused on the subgroup of women who use OC very early in their reproductive years. Three studies conducted in the late 1970s already observed an increased risk in women using OC before their first full-term pregnancy [38–40]. In the 1980s this finding was reproduced in the studies in the U.K. [19, 29]. Pike *et al.* [21] reported that OC use before age 25 rather than use before first pregnancy was the relevant determinant for breast cancer risk. These findings seemed of particular relevance in the light of what is already known about the biology and epidemiology of breast cancer. Age at menarche and age at first full-term pregnancy have convincingly been shown to influence breast cancer risk as much as three or four decades later [41]. Also, among atomic bomb survivors in Japan, the highest risk of breast cancer was experienced by women aged 10–19 [42]. These observations have led to the general belief that the breast is most susceptible to carcinogenic influences during adolescent years, when breast tissue is rapidly developing.

However, most studies in Table 1 did not observe any increased breast cancer risk in women using OC before first pregnancy or at young ages. In the Scandinavian study a relative risk of 4.4 (95% CI: 1.2–15.5) was found in the Swedish cases less than 40 years of age (n = 195), who are closely matched for age and age at first birth, but the investigators pointed out that OC use before age at first birth might be a proxy variable for the total duration of OC use [26]. These two variables were strongly correlated in their series, but the data indicated that total duration of use was the crucial determinant of risk. The recent update from the RCGP cohort showed a significant trend relating to duration of use and time since last OC use for women who had only one child at diagnosis [20]. Age at first birth was not known in this study, but the authors postulated that the greater part of OC use in women with only one child probably occurred before their first pregnancy, which would lend support to the hypothesis that exposure before first birth is crucial. This explanation of the RCGP results, however, though plausible, remains unproven so far.

Table 1. Recent case-control studies of breast cancer and OC

First author, year of publication [reference], country	Age of cases (years)	Years cases diagnosed	No. of cases	No. of controls	Nature of controls	Results*
McPherson 1983 [19] U.K.	<45	1980–1983	247	247	Hospital	RR of 3.1 for those using OC for more than 4 years before FFTP
Pike 1983 [21] U.S.A. (Los Angeles)	<37	1972–1982	314	314	Population (neighborhood)	RR of 4.9 for those using OC for more than 4 years before age 25
Rosenberg 1984 [22], Miller, 1986 [23] U.S.A.	20–59	1976–1981	1191	5026	Hospital	RR = 2.6 for age group 30–39; use ≥5 years that began ≥15 years ago (finding attributed to chance)
Cancer and Steroid Hormone Study 1985 [24], 1986 [25] U.S.A.	20–44 45–54	1980–1982	2088 2623	2065 2611	Population	No increased risk in any subgroup
Meirik, 1986 [26] Sweden and Norway	<45	1984–1985	422	722	Population	RR = 2.2 for long-term use (≥12 years), regardless of whether OC use began before FFTP; RR = 2.2 for ≥8 years use in Swedish subgroup <40 years of age
Paul, 1986 [27] New Zealand	25–54	1983–1985	433	897	Population	No increased risk in any subgroup
LaVecchia 1986 [28] Italy	<60	1982–1985	776	1282	Hospital	RR = 1.45 for any use that started ≥10 years ago
McPherson 1987 [29] U.K.	16–64	1980–1984	1125	1125	Hospital	RR = 2.6 for those aged <45 years who used OC for more than 4 years before FFTP; 'latency effect' for pills containing EO
Lee 1987 [30] Costa Rica	25–58	1982–1984	171	826	Population	RR = 2.0 for those using OC 3–5 years; RR = 2.6 for ever use of DMPA
Ravnihar 1988 [31] Yugoslavia	20–54	1980–1983	534	1989	Hospital	RR = 1.6 for ever use; positive trend with increasing duration of use; RR = 2.4 for ≥7 years use
Miller 1989 [18] U.S.A.	<45	1983–1986	407	424	Hospital	RR = 2.0 for ever use; RR = 4.1 for ≥10 years use.

*Results with a P value > 0.05 are not mentioned.
Abbreviations: EO = ethinyl estradiol; FFTP = first full term pregnancy; RR = relative risk; DMPA = injectable depot medroxyprogesterone acetate.

The Cancer and Steroid Hormone (CASH) Study has so far been the largest single study on OC and breast cancer [24, 25]. This population-based study was carried out in eight geographic areas of the U.S.A. Although in this study the numbers in the exposure categories with both long-term use and a long interval since first use did not appear to be less than in the positive studies from Sweden and the U.K., no patterns of increased risk emerged. The same holds true for the study from New Zealand [27]. In 1986 McPherson *et al.* offered an interesting explanation for the discrepancies between studies [43]. They postulated that the controversy was due to the considerable variation between countries in the lapse of time since OCs were widely used and, thus, in the possible latency period. For example, there are strong indications that the prevalence of OC use before first pregnancy (or at an early age) in the U.S.A. lagged at least 5 years behind as compared to the U.K. [44]. The 'latency hypothesis', as it has been called since then, requires a different type of analysis, in which all exposure during the presumed latency period (= x years before the date of diagnosis) is excluded from analysis. If a latency effect is present in the data, successive calculations of relative risks will show an increase when the assumed latency period is approaching the true latency period. So far, such analyses have only been carried out by McPherson's group, the New Zealand group [45] and, in a slightly modified way, by the investigators of the CASH study [46]. Contrary to the situation in the U.K., no latent effect appeared from either the New Zealand or the CASH data, so that the latency hypothesis cannot reconcile the conflicting results of recent studies. Despite this, it is recommended that future studies

analyse their data as proposed by McPherson *et al.* [43]. This will enable us to detect prolonged latency effects (which might take 15 years or more to emerge), and will thereby provide insight into the biological mechanism of an OC effect, if any, on breast cancer risk.

Numerous other explanations have been offered to explain the discrepancies between studies. Epidemiological studies have seldom been so vigorously scrutinized as the latest OC–breast cancer studies, and, since all of them are observational studies, it is not surprising that many methodological shortcomings could be found. For example, the Scandinavian study [26] was accused of recall bias since the aim of the study was explained to the women interviewed, and the CASH study [25] has been criticized with regard to selection bias, due to the use of the random digit dialing method for control selection [47]. Two types of bias merit further attention since they are, to a greater or less extent, applicable to all studies. *Information bias* (or recall bias), in this case meaning that cases overestimate their OC use as compared to controls, could not be examined in a single study. It is most important that future studies attempt to compare women's OC histories with physicians' records. *Detection* or *surveillance bias* was only recently mentioned by Skegg [47] as a potential problem in studies of breast cancer and OC. Such bias might arise if OC users are more likely than non-users to examine their breasts frequently (or to have them examined in a medical setting). Skegg postulated that this might lead to an apparent excess of OC use among cases, assuming that an appreciable proportion of breast tumors progresses very slowly, or behaves in a biologically benign manner, even though histologically malignant. Although a number of studies [18, 31, 48] lend some support to this interesting hypothesis, other evidence is inconsistent [49, 50] and at present the extent of this bias, if it exists, cannot be assessed. Future studies should collect information about clinical stage, symptoms at diagnosis and breast self-examination by the woman or her physician.

In our opinion, the above mentioned biases cannot explain more than a small part of the differences between studies. Accordingly, for the time being, the issue of whether OC use increases breast cancer risk remains unresolved. Other explanations for the conflicting results may be sought, such as geographic variation in the OC preparations available on the market. So far, only few studies have investigated the type of preparations, with inconsistent results, and geographical differences in OC formulations have not been carefully examined, although it is generally known that mestranol-containing OC are much more common in the U.S.A. than in Europe. A more promising, but also more difficult, approach might be to consider the prevalence of breast cancer risk factors other than OC in the various countries. Epidemiologists tend to forget that, strictly speaking, relative risks cannot be compared over populations, since the reference categories may substantially vary with regard to the prevalence of other risk factors [51].

Since it has been estimated that only 25% of breast cancer cases can be accounted for by known risk factors [52], it seems possible that at least part of the discrepancies between studies might be explained by variations in the prevalence of known and unknown breast cancer risk factors.

Taking a more pessimistic approach, it may be that only time will eventually throw light on this confused area. In this respect, it should also be kept in mind that new preparations were introduced in the 1970s. Therefore, it would be surprising if the final word on breast cancer and OC will be said before the year 2000.

OVARIAN CANCER

Contrary to the situation with breast cancer, epidemiological studies of OC and ovarian cancer have shown uniform results. Oral contraceptives have clearly been shown to reduce the risk of ovarian cancer. The protective effect of OC has been observed in at least 13 case-control studies [28, 53–64] and was also confirmed in the cohort study of the Oxford Family Planning Association [65]. Based on the studies published before 1987, Prentice and Thomas [66] calculated a summary relative risk of 0.6 for ever use of OC, indicating a risk reduction of about 40% for women who ever used combined OC.

In a number of studies risk of ovarian cancer was shown to decrease with increasing duration of use [28, 54, 59, 60, 62, 64]. In the CASH study, that included 546 cases and 4228 population controls, the relative risk even decreased to 0.2 (95% CI: 0.1–0.4) for women who used OC for 10 or more years [64]. Even women who used OC for a short period have been shown to experience decreased risk; in the CASH study even use of 3–6 months conferred a risk reduction. Risk was also shown to decrease with increasing interval since first use, and the CASH data suggest that a latency period of 5–10 years is needed before the protective effect is manifested [64].

More recent studies could investigate the persistence of the protective effect in ex-users. In three studies [60, 62, 64] the risk estimates remained significantly reduced for at least 10 years after OC use was stopped. An Italian study [28] reported that the effect persisted for at least 5 years and the latest CASH data even show a protective effect for women who had last used OC 15 or more years previously (RR = 0.5; 95% CI: 0.4–0.8) [64].

The remarkable consistency of results from various studies as shown above should not lead us to think that the epidemiological relationship between OC use and ovarian cancer has been fully unraveled. A couple of points need further clarification, such as risk modification by age at diagnosis, parity and age at first use. Cramer *et al.* [62] reported that in their data the risk reduction was restricted to women under 40 years of age at diagnosis of ovarian cancer. However, this finding was not confirmed by a number of other studies [28, 58, 60, 64]. Nulliparity is a known risk factor of ovarian cancer and thus, because of its likely association with OC use, a potential confounder in studies of OC and ovarian cancer.

Impaired fertility has also been mentioned as a risk factor of ovarian cancer [67, 68] and, since infertile women who are aware of their condition are less likely to use OC, this might lead to a spurious negative association between OC use and ovarian cancer. Infertility and subfecundity are difficult to measure in epidemiological studies and therefore, in order to examine the above possibility, most studies stratified by parity in their analysis. If the association between OC use and ovarian cancer is an indirect effect of infertility one would expect that the protective effect of OC would only occur in nulliparous and not in parous women. Four studies convincingly showed that this is not the case [58, 60, 62, 64]. However, parity does seem to modify the protective effect of OC use and studies have not been consistent about the direction of the effect. In two studies significantly reduced risk was only reported for parous and not for nulliparous women [28, 62]. In contrast, the CASH data showed by far the greatest risk reduction for nulliparous women (the risk estimates for all nulliparous women and for those who practiced contraception and had no history of subfecundity did not differ) [69]. In the latest CASH report no association between OC and ovarian cancer was observed among women with a parity of five or more and interaction with parity was shown to be of borderline statistical significance [64]. In a recent case-control study from Canada reduced risk was only found for women of parity 1–3 [70]. It was pointed out that the protective effect of OC remains to be proven for nulliparous women who started on the pill young, since they have not yet reached the age of highest incidence of ovarian cancer.

Two biological explanations have been offered for the apparent protective effect of OC on ovarian cancer. First, OC might act through suppression of ovulation and thus prevent 'incessant ovulation' that has been incriminated as an etiologic factor in ovarian cancer [54]. This seems unlikely, however, since very short-term OC use, leading to approximately 2% less ovulations, has been shown to already materially reduce risk [71]. Also the persistence of the protective effect after OC use has stopped, is incompatible with this mechanism. Second, OC might exert their effect through their ability to reduce levels of gonadotropins that have also been positively associated with ovarian cancer risk [71]. This hypothesis will gain credibility if it is more convincingly shown that OC use leads to a permanent, or at least long lasting suppression of gonadotropin secretion.

Future studies of OC and ovarian cancer need to focus attention on (a) the persistence of the effect more than 10 years after OC use has ended; (b) the modifying effect of parity and (c) the effect of different formulations. With regard to the last issue, higher dose oral contraceptives may suppress gonadotropin secretion more than the lower dose ones do [72–74]. Thus, the results of separate analyses for different pill types might increase our biological understanding of ovarian cancer. Also, if the more recent low-dose pills confer less protection than the older high-dose formulations, then the ultimate risk reduction by OC use might be less than the 40% estimated from studies conducted so far.

ENDOMETRIAL CANCER

As with ovarian cancer, the results of studies examining the effect of OC on endometrial cancer development are largely in agreement. However, contrary to the situation with ovarian, and also with breast cancer, combined and sequential oral contraceptives have consistently been observed to exert an opposite effect on endometrial cancer risk. Use of *combined* oral contraceptives has been shown to reduce risk of endometrial cancer in at least eight case-control studies [28, 75–81]. The results of these studies suggest that the risk among women who ever used combination-type OC is half that of never-users of OC [8, 66]. In several studies, the risk of endometrial cancer decreased with increasing duration of use [76, 77, 79, 80]. The minimum period of OC use that was already associated with lowered risk was 1 year [76, 77, 80].

Endometrial cancer is rare, especially below the age of 45 years. Therefore, studies conducted so far have had difficulty including enough women who had the opportunity of using combined OC at an earlier age. Accordingly, the power of the present studies has not been high and the upper confidence limit sometimes included 1. The rarity of endometrial cancer in premenopausal years also implies that the protective effect of combined OC use will only have public health significance if it persists many years after OC use ends. Only two studies so far could study the persistence of the effect over a longer period. In one study the risk estimate remained

reduced for at least 15 years after OC use was stopped [80], while the other demonstrated a protective effect after at least 5 years [76].

As with ovarian cancer, it has been suggested that the protective effect of combined OC may be due to confounding with infertility, since nulliparity has long been associated with an increased risk of endometrial cancer. The CASH study convincingly showed that this is not the case [82]. The relative risk of ever use of combined OC for nulliparous women, after control for infertility and subfecundity, indicated a risk of 0.2 (95% CI: 0.1–0.6).

Risk modification by parity has not yet been clarified. Some studies indicate that the protective effect of combined OC wanes with increasing parity. For example, the CASH study did not detect a decreased risk in women with five or more children and risk was lowest for nulliparous women [80]. Another study did not observe any protective effect in women with three or more children [79]. Risk modification by other factors has also been described. Henderson *et al.* [79] did not observe reduced risk due to OC use in obese women and Weiss and Sayvetz [75] showed that the protective effect of OC could be undone by subsequent use of menopausal estrogens. The latter finding, if confirmed, has considerable public health impact and should be investigated in detail in further studies. In the WHO study, which included 130 cases and 835 controls from seven developing and two developed countries, it was possible to investigate whether the assumed protective effect of combined OC is the same in countries with varying incidence rates of endometrial cancer (and thus with different patterns of risk factors) [81]. Risk reduction was shown to be somewhat stronger in developing countries (RR = 0.49 vs. RR = 0.81). However, numbers were small in this study and none of the above risk estimates was significantly different from 1.0.

Use of sequential OC involves exposure to estrogen alone for approximately 15 days of the menstrual cycle, approximately 5 days of an estrogen plus a progestogen, followed by cessation for a week (with a resultant withdrawal bleeding). At least four case-control studies observed a two-fold increased risk of endometrial cancer in women using sequential OC [75, 79, 82, 83]. This increased risk has been explained by the net estrogenic effect that sequential OC, as opposed to combined OC, exert on the endometrium.

In this respect it is of interest that some studies of combined OC and endometrial cancer reported that the greatest reduction in risk was found for women using strongly progestogenic pills [77]. This finding, if real, lends further support to the hypothesis that combined OC exert their beneficial effect on the endometrium through their progestogen content. It will be difficult to prove, however, since OC preparations contain different progestagens with varying potencies which are difficult to compare.

ESTROGEN REPLACEMENT THERAPY

General

Estrogen preparations came into use in the U.S.A. in the 1930s [84]. ERT is aimed at relieving the 'menopausal syndrome' and at preventing the development of osteoporosis. ERT has been prescribed much more frequently in the U.S.A. than in European countries. In the U.S.A. the drugs generally used for ERT are the conjugated equine estrogens. As a consequence, this type of ERT was either the only exposure investigated in several American studies [85–87] or it had been used by a high percentage of the study population (84% in the studies of Kaufman *et al.* [88] and Brinton *et al.* [89]). In two European populations the use of conjugated estrogens was far less common: in Italy this drug had been prescribed for 53% of ERT users [90], and in Denmark estrogens alone (including the conjugated estrogens) had been taken by 43% of the women on ERT [91]. Other types of estrogens (estriol, estradiol) or combinations of estrogens with progestagens or androgens have been used as ERT relatively more frequently in Europe than in the U.S.A.

Breast cancer

The relationship between breast cancer and ERT has received much attention in the literature. A review of epidemiologic studies published prior to 1980 showed no association [92]. Since then, at least 14 case-control studies and one cohort study have been published [85–91, 93–100]. Overall, these studies show a moderately increased relative risk of breast cancer (range: 1.5–2.0) when estrogens are administered at high doses for long periods of time. However, the findings of a dose–response relationship and of a duration–response relationship are contradictory. A dose–response relationship was present in several studies [85, 86], but not in all [87, 91, 95]. A duration–response relationship was found in some studies [86, 89–91], but again this was not a uniform finding [87, 88, 94, 95, 98, 100]. In addition, the effect of ERT in postmenopausal women with or without ovaries is not clear. Some studies showed the highest risk in the former group [85, 90, 93, 95], whereas other studies reported the highest risk in the latter group [86, 89, 99]. Moreover, several studies found no difference between the two groups at all [87–89, 91, 94, 100].

An increased overall risk in postmenopausal women was found in four studies [86, 90, 91, 95].

Among these studies are the only two European studies, which might suggest that geographic differences are present. As indicated above, the type of drug used for ERT differs among countries and, thus, ERT type might be one of the factors modifying breast cancer risk. The Denmark study showed a relative risk of 1.4 (95% CI: 0.9–2.1) for HRT and a relative risk of 2.3 (95% CI: 1.4–3.9) for combined treatment of injected estrogens and androgens [91]. In the study by Hulka *et al.* it was found that the use of injectable estrogens produced a four-fold increase in risk [95]. This suggests that the mode of administration is crucial. Compared to oral estrogens the injected hormone acts directly on breast tissue and may give higher and more continuously elevated blood levels. However, no difference of type of ERT on breast cancer risk was found in the Italian study [90] nor in two American studies [88, 94].

It is of interest to note here that two American studies found markedly increased risks for diethylstilbestrol (DES) [89, 97], which is in accordance with the effect of DES when used during pregnancy to prevent abortion [101, 102].

Ovarian cancer

In the very few case-control studies that have related ERT to ovarian cancer no association was found or a moderately increased risk was reported (range: 1.5–3.0) for longer duration of use [103, 104]. Rates for ovarian cancer in the U.S.A. over the time period 1969–1977 showed no change in the overall incidence of ovarian cancer, whereas the incidence of clear cell tumors increased [105]. This increment paralleled the increase in the incidence of endometrial cancer, suggesting that the relationship between ERT and these specific ovarian tumors needs further clarification.

Endometrial cancer

In the time period 1963–1973 the sales of drugs used for ERT rose four-fold in the U.S.A. [106]. Following this increase a marked rise in the incidence of endometrial cancer was observed between 1969 and 1973 [106]. U.S. data show a decline in ERT prescriptions in the late 1970s [107], followed by a decline in endometrial cancer incidence within 1 year [108].

Due to problems of selection bias, case-control studies of endometrial cancer and ERT have been one of the most hotly debated topics in epidemiology in the late seventies. In the period 1975–1980 no less than 12 editorials in major journals were devoted to the subject and it was not before 1981–1982 that the subject was settled [109–111]. At least 18 case-control studies and two cohort studies have consistently shown elevated relative risks (range: 2.0–7.0 [8]). The risk has been demonstrated to increase with both duration of use and estrogen dose. Latency seems to be relatively short, suggesting ERT to be a promoting factor in endometrial carcinogenesis. Risk declines with time since cessation of use, but few data are available on the interval sufficient to eliminate the excess risk. Both very short time intervals of 6 months to 2 years [112, 113] and long time intervals of 10 years after cessation [114] have been reported.

It has repeatedly been suggested that the cyclic addition of progestagens to estrogens (hormone replacement therapy, HRT) might reduce or even eliminate the risk. Progestagens added for at least 10 days of each treatment cycle have been shown to protect against endometrial hyperplasia [115]. Recently, a cohort study with a follow-up period of 6 years has shown that, indeed, the use of progestagens either removes the increased risk or delays its onset [116].

COMMENT

As indicated above, the OC–breast cancer relationship is still highly controversial, whereas a long duration of ERT use at high doses seems to slightly increase the risk of breast cancer. The risk of ovarian cancer is reduced by OC whereas the effect of ERT has not yet been adequately studied. Finally, the risk of endometrial cancer is reduced by combined OC, whereas it is clearly increased by ERT.

The 'unopposed estrogen' hypothesis has proved to be very successful in explaining and predicting the effect of exogenous hormones on endometrial cancer risk. The hypothesis postulates that estrogens increase the risk of endometrial cancer by increasing the rate of endometrial cell division. This estrogen effect is opposed by progestagens. Conjugated estrogens used for ERT increase the risk whereas addition of progestagen for half or more of the duration of estrogen seems to counteract this effect. It seems likely that the 5 days of progestagen addition to each cycle of sequential OC apparently does not adequately oppose the estrogen effect. Combined OC may reduce the risk of endometrial cancer because they shorten the period of endometrial exposure to unopposed estrogens from the 14 days of a normal follicular phase to the 7 days per 28 day cycle during which OC are not used.

Recently, Key and Pike [117] have indicated that the 'unopposed estrogen' hypothesis is not very plausible for breast cancer, since the hypothesis does not predict the small increase in risk observed with ERT. Furthermore, the hypothesis would predict a protection by OC and not the observed lack of association or increased risk. Key and Pike propose two alternative hypotheses: the 'estrogen plus progestagen' hypothesis and the 'estrogen

alone' hypothesis. The first implies that an increased exposure to estrogens alone carries some increased breast cancer risk, whereas the combination of estrogens and progestagens increases the risk much more. The 'estrogen alone' hypothesis implies that estrogens alone increase risk and that progestagens are irrelevant. Both hypotheses are consistent with the observed effects of ERT and OC on breast cancer risk. In contrast to the 'estrogen alone' hypothesis, however, the 'estrogen plus progestagen' hypothesis predicts that HRT will increase risk more than ERT. This is consistent with the recent Danish findings [91], but needs further confirmation. If so, HRT, as compared to ERT, might prove to reduce risk of endometrial cancer, whereas it might increase risk of breast cancer. In addition, both hypotheses clearly differ in their expectations of the effect of 'progestagen only' OC and of depot medroxyprogesterone acetate (DMPA). Adequate studies on the effect of these hormone preparations may reveal which of the two hypotheses is most plausible.

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