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ACTA REVIEW

Hormone replacement therapy and risk of breast cancer: the role of progestins

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Epidemiological studies have shown an increased risk of breast cancer associated with the use of hormone replacement therapy (HRT). This notion is mostly based on studies from the USA. During the last decades unopposed estrogen treatment has been used to a lesser extent, whereas the combined estrogen-progestin treatment regimen is now prescribed worldwide. In the USA the predominant compounds are conjugated estrogens and medroxyprogesterone-acetate, whereas oestradiol combined with testosterone-like progestins is commonly used in Europe. These differences are mainly the result of traditions. Recent studies originating from both the USA and Europe suggest that the combined treatment regimens with estrogen and progestin increase the risk of breast cancer beyond the risk following the use of unopposed estrogen. At present it is not known if progestins with different androgenecity influence the risk of breast cancer to a varying degree.

This review focuses on studies published after the latest meta-analysis in 1997, with special attention given to the type of progestin used and the treatment mode, i.e. cyclical or continuous regimen.

Keywords: breast cancer, breast neoplasm, epidemiology, estrogens, hormone replacement therapy, menopause, oral contraceptives, progesterone, progestins, sex steroids

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Epidemiological studies have shown an increased risk of breast cancer following the use of hormone replacement therapy (HRT). The latest pooled analysis published in 1997, found that the increased risk is confined to the current use or recent use of HRT. Furthermore, the magnitude of risk resembles the increased risk of breast cancer associated with a delayed natural menopause (1). The vast majority of studies in the pooled analysis originate from the USA, and data on the type of HRT is limited. Recent studies from both the USA and Europe suggest that the combined treatment regimens with estrogen plus progestin increase the risk of breast cancer beyond the risk following the use of unopposed estrogen treatment (2–7). Only two recent studies have estimated the effect of cyclical vs. continuous combined HRT, and these did not fully agree (2,5). The issue to be addressed is whether progestins with different androgenecity influence the risk of breast cancer to a varying degree.

In the USA women have traditionally been given equine conjugated estrogens (CE) as a substitution, i.e. oestrone- and dihydrooestrone-sulfate, equilin-sulfate and equilinin-sulfate.

Abbreviations:
HRT: hormone replacement therapy; ERT: estrogen replacement therapy; P: progestin; CE: conjugated estrogen; E: estrogen; MPA: medroxyprogestreroneacetate; NETA: norethistosteroneacetate; LNG: levonorgestrel; BMI: body mass index; SHBG: sex hormone binding globulin; BBD: benign breast disease; RR: relative risk; OR: odds ratio; CI: confidence interval; HR: hazard ratio; SIR: standardized incidence rate; SE: standard error.

During the past two decades the prescription of regimens opposed by progestins has increased worldwide. The progestin preferred in the USA is medroxyprogesterone-acetate (MPA), which resembles natural progesterone and is administered either cyclically or continuously. In Europe the predominant regimen prescribed is 17-β-oestradiaol opposed by testosterone-derived progestins, mainly norethistosteroneacetate (NETA) or levonorgestrel (LNG); while the less androgenic progestin MPA is used to a lesser extent. This treatment regimen has increasingly been administered in the continuous treatment mode. Previously, oestradiol injections combined with testosterone alone have been used as well (8). As a result of these traditional differences of prescription practices in USA and Europe, it has been difficult to assess the risk of breast cancer according to the type of progestin or treatment mode.

The aim of the present review was to evaluate and summarize the epidemiological evidence concerning the risk of breast cancer conferred by different HRT treatment regimens focusing on the combined estrogen plus progestin treatment, the impact of the different progestin compounds and the treatment mode, i.e. the cyclical or continuous administration of progestins.

Variance in the use of HRT

The number of women receiving HRT varies according to location, time and age group. Prescription of hormonal substitution with estrogens (ERT) became common in the USA in the 1960s, and some years later in Europe. The use of ERT declined in the mid-1970s, because of an observed increased risk of endometrial cancer. It was not until several years later that prescription of HRT increased again with a growing proportion of women receiving estrogen replacement therapy opposed by progestins (9). The use of HRT in women with an intact uterus is most frequent in women aged 50–54 years, who are often prescribed combined therapy regimens, while elderly women often prefer unopposed estrogen replacement therapy. A comparative study on the prescription of HRT in 1991/92 in USA and Europe based on pharmaceutical sales statistics, substantiated that the frequency of HRT use in women aged 45–54 years was highest in the USA (49%) followed by the UK and the Scandinavian countries (20–35%) and the lowest in continental Europe (1–15%) (10). These figures have been confirmed by others (11–16). A cohort study from the USA showed that in 1990–92, 46% of naturally menopausal women reported the ever-use of HRT, where the combined therapy with progestins accounted for 31% (13). In another population-based cohort the current use of HRT has increased from 10.3% in 1991 to 20.7% in 1995 (17). In Sweden in 1994, 24% of 54-year-old women were currently using HRT (18). In Denmark, a case-control study found that current use in 1993 was the highest in the age group 53–54 years (30%), where the combined treatment with estrogen and progestin accounted for two-thirds of cases (19). A recent Danish study based on a prescription database, 1990–95, reported an annual prevalence proportion of current use that was the highest in the age group 50–59 years and increased over time from 18% in 1991 to 25.5% in 1995, with a proportion of combined therapy regimens of approximately 60% (12). In Norway, one-third of Norwegian women aged 60 years or older are current or past users of HRT (20). The current use of HRT has been estimated in a random sample of Norwegian women to be increasing from 16.3% in 1994 to 19.1% in 1996 (21).

Meta-analyzes on HRT and risk of breast cancer

The first extensive meta-analysis on HRT and breast cancer was published in 1991 by Steinberg et al. and others have since followed. Even if the criteria for inclusion of studies may vary, later meta-analyses usually succeed the former ones by adding the newest studies available.

A pooled analysis on this topic was published in 1997 by the Collaborative Group on Hormonal Factors in Breast Cancer and the main results are summarized in Table I (1). The essential finding is an increased risk of breast cancer of 2.3% per year related to the current use of HRT, comparable to the risk associated with a delayed natural menopause. The summary estimate for the risk of breast cancer after more than 5 years of use is 1.35 (96% CI: 1.21–1.49). This increased risk of breast cancer diminishes with cessation of HRT and is similar to the risk among never-users 5 years later. Data on the type of HRT was only available for 39% of the HRT users included in the meta-analysis, out of which 80% used unopposed conjugated estrogens and 12% used estrogen combined with progestins. The type of progestin was not specified, although presumably MPA was the predominant compound used, as only a few European studies were included.

Two previously published meta-analyses have addressed differences between the USA and Europe in the risk of breast cancer following the use of HRT. Steinberg et al. found a mean proportional increase in risk per year of treatment

Table I. Relative risk of Breast Cancer following the use of HRT according to the latest pooled analysis (1).

Exposure	Duration of HRT use	Risk estimate		Estimated cumulative excess of breast cancer cases	
Current use or recent use 1–4 years before diagnosis		RR	SE	HRT use	Cases (95% CI)
CE $\leq$ 0.625 mg	$<$ 5 years	0.77	0.13	5 years	2/1000 (1–3)
	$>$ 5 years	1.64	0.25		
CE $\geq$ 1.85 mg	$<$ 5 years	0.94	0.17	10 years	6/1000 (3–9)
	$>$ 5 years	1.42	0.16		
Other Estrogen	$<$ 5 years	1.15	0.17	15 years	12/1000 (5–20)
	$>$ 5 years	1.26	0.21		
Estrogen + Progestin	$<$ 5 years	1.15	0.19		
	$>$ 5 years	1.53	0.33		

of 0.063 (0.035–0.092) based on the European studies compared with 0.010 (0.002–0.017) based on the studies from the USA (22). By extrapolation, this would result in a significant elevated relative risk of 2.5 (95%CI: 1.7–3.7) for the European women after more than 15 years of HRT use.

Although not statistical significant, Colditz et al. found different pooled risk estimates for the ever-use of HRT, comparing three European studies (RR 1.31; CI 0.92–1.88) and 18 studies from the USA (RR 1.01; CI 0.92–1.11) (23). A comparative estimate for the long-term use has not been reported. One of the studies included in this meta-analysis is a Danish study, which showed an increased risk of breast cancer with a regimen that comprised of injections with oestradiol combined with testosterone; RR 2.31 (1.3–3.88) (8).

A recently published qualitative review concerning the risk of breast cancer and HRT stated that there is no association between the ever-use of HRT and breast cancer (24). The risk estimates were close to unity for the ever-use of both ERT and combined HRT. However, results may be questionable, as in this study confounding was not assessed, small studies were included and the different progesterone-types were not taken into account.

Risk of breast cancer according to HRT regimen and hormonal constituents

Since the publication of the latest pooled analysis, only a few studies including a sufficient number of cases and covering the different HRT treatment regimens have addressed the risk of breast cancer following the use of HRT. Table II summarizes these studies. Three studies originate from Sweden and four from the USA. The three Swedish studies have been conducted independently of each other, but the breast cancer cases will partly cover the same individuals, as the large population based case-control study by Magnusson et al. will cover most breast cancer cases in Sweden from 1993 to 1995. Oestradiol and conjugated estrogens have usually been considered as one exposure agent, as both are considered to be medium potent estrogens (9). This notion has been supported by the review by Bush et al. where the risk estimates for the use of oestradiol resembled those for conjugated estrogens (24). The risk estimates from the recent studies concerning the use of oestradiol and CE, respectively, are illustrated in Fig. 1. In these studies the risk estimates for the ever and long-term use of the two types of estrogens are very close to each other, and none of the compounds seems to confer a substantial increase in the risk of breast cancer.

The overall risk of breast cancer seems to increase with the use of combined therapy regimens. The risk estimates concerning the long-term use of combined estrogen plus progestin therapy regimens are presented in Fig. 2, according to the androgenecity of the progestin used. Only one study has analyzed the influence of both progesterone types on breast cancer risk (2). The other studies are entered into the figure according to the information on the predominant use of piogestin, which is NETA or LNG in the Swedish studies and MPA in the studies from the USA. The study by Persson et al. in 1999 found no increased risk for the long-term ever-use of combined estrogen/progestin treatment, while risk estimates for current users are increased as shown in Table II. Two studies do not provide data on duration for ever-users, and are entered into the figure with estimates for the ever-use of HRT (6,25). In the study by Schairer et al. the recent use of the combined treatment for 4 years or more showed increased risk estimates when stratified by BMI, with a risk estimate of 2.0 (1.3–3.0) for women with a BMI $<$ 24.5 kg/m*2 (6). No information on long-term use is available. Only one study observed no increased risk of

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Table II. Risk of Breast Cancer according to HRT type and regimen

Study Year of publication Land of origin	Study Design Number of participants	Aspect of use Ever use and recent/current use	Duration	Unopposed Estrogen treatment Type of estrogen Oestradiol or CE RR/OR (95% CI)	Combined Treatment with Progestin Type of progestin Progesterone-like or testosterone-like RR/OR (95% CI)
Persson (3) 1997 Sweden	Nested case-control in screening cohort. 436 cases/1740 controls.	Ever use.	1–10 years 11+ years	Estradiol mainly OR 0.5 (0.3–1.0) OR 1.3 (0.5–3.7)	Testosterone-like OR 1.4 (0.9–2.2) OR 2.4 (0.7–8.6)
Persson (4) 1999 Sweden	Cohort based on prescriptions. 11 472 women. Women born after 1918. 198 cases.	Ever use. Current use.	1–6 years 6+ years 1–6 years 6+ years	Estradiol RR 1.0 (0.6–1.7) RR 1.1 (0.6–2.0) RR 1.0 (0.2–5.9) RR 1.0 (0.3–3.4)	Mixed use. Testosterone and progesterone-like RR 0.9 (0.5–1.7) RR 1.0 (0.5–2.1) RR 2.8 (0.8–10.0) RR 1.9 (0.6–6.1)
Magnusson (2) 1999 Sweden	Case-control. Population controls. 3345 cases. 3454 controls.	Ever use. Ever use. Ever use. Ever use. 	 11+ years 1–5 years 5+ years 1–5 years 5+ years 10+ years Per 5 years 10+ years Per 5 years	Estradiol OR 1.94 (1.47–2.55) OR 2.70 (1.47–4.96)	Progesterone-like OR 1.14 (0.69–1.88) OR 1.41 (0.80–2.51) OR 0.79 (0.26–2.39) Testosterone-like OR 1.68 (1.39–2.03) OR 1.33 (1.05–1.68) OR 2.74 (1.99–3.78) Cyclic OR 1.48 (1.08–2.04) OR 2.45 (0.82–7.30) OR 1.16 (0.72–1.87) Continuous OR 1.41 (1.09–1.83) OR 5.36 (1.47–19.56) OR 2.44 (1.53–3.88)

Ross (5) 2000 USA	Case-control Population based. 1897 cases. 1637 controls.	Duration of use. Ever-use or current use.	10+ years 15+ years Per 5 years of use	CE	OR 1.24 (not given) OR 1.06 (0.97–1.15)	Progesterone-like	OR 1.51 (CI not given) OR 1.24 (1.07–1.45)
			10+ years Per 5 years of use			Cyclic	OR 1.79 (CI not given) OR 1.38 (1.13–1.68)
			10+ years Per 5 years of use			Continuous	OR 1.23 (CI not given) OR 1.09 (0.88–1.35)
Schairer (6) 2000 USA	Screening cohort 1980–1995. 46 355 women. 2082 cases.	Ever-use Duration Current use. Duration. Recent use with BMI < 24.5 kg/m*2.	Increase per year. Trend significant. 16+ years 4+ years	CE	RR 1.1 (1.0–1.3) 0.01 (0.002–0.03) RR 1.1 (1.0–1.3) RR 1.6 (1.2–2.2)	Progesterone-like	RR 1.3 (1.0–1.6) 0.08 (0.002–0.16) RR 1.4 (1.1–1.9) RR 2.0 (1.3–3.0)
Colditz (7) 2000 USA	Cohort study. American nurses. 14 years follow up (1980–1994). 58 520 women for analysis. 1761 cases.	Use of conjugated estrogens from ages 50–60 years.	Cumulative risk of breast cancer at age 70 years. Nonlinear poisson-regression accounting for time.	CE	RR 1.23 (1.06–1.42)	Progesterone-like	RR 1.67 (1.18–2.36)
Moorman (25) 2000 USA	Case-control. Population based. 384 cases/420 controls. Caucasian: 217 cases/ 242 controls.	Ever use. Often short-term use.		Mainly CE	OR 0.9 (0.5–1.6)	Progesterone-like	OR 0.6 (0.4–1.0)

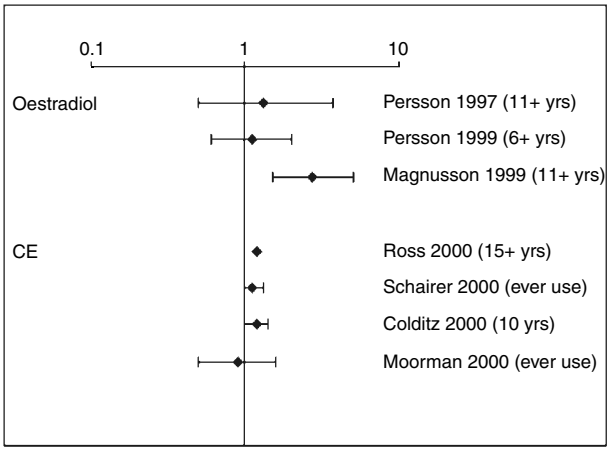

Fig. 1. Effect of the unopposed-ever and long-term use of oestradiol or conjugated estrogens on the risk of breast cancer.

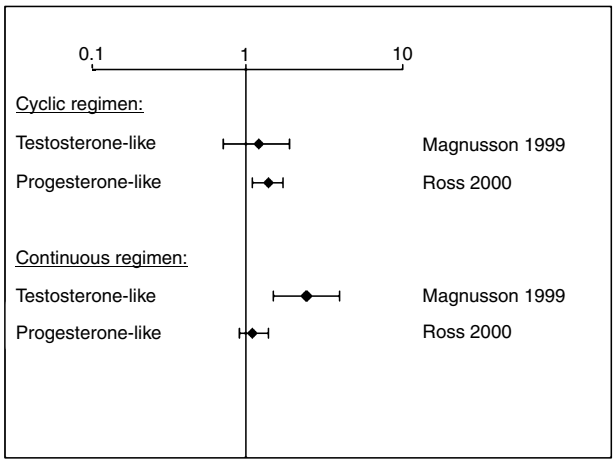

Fig. 3. Risk of breast cancer per 5 years of hormone replacement therapy use according to the estrogen/progestin treatment mode, i.e. cyclic or continuous progestin administration.

breast cancer with either HRT regimen (25). The low-risk estimates in this particular study might be because of fewer long-term users or the hormonal constituents of the compounds used. The use of testosterone-like progestins may be associated with a higher risk of breast cancer than the use of progesterone-like progestins, but the number of studies to provide data is small (Fig. 2).

Two studies have addressed the differential impact on breast cancer risk according to treatment mode, i.e. cyclic or continuous combined HRT (2,5). The risk estimates are presented in Fig. 3. Magnusson et al. found a 5-fold increased breast cancer risk with the continuous treatment with NETA/LNG after more than 10 years of use as compared with never-users. This was not found for the continuous treatment with MPA in the study by Ross et al. The risk estimates for the cyclic treatment regimens, though, were close to each other regardless the androgenecity of the progestin. The Swedish study excluded women with mixed use of HRT over time, and the data have recently been re-analyzed in order to investigate the role of additional risk factors for breast cancer. However, the more extensive analysis did not improve the model or alter the risk estimates (26).

Other recent studies have not been able to distinguish between unopposed estrogen therapy and combined estrogen/progestin therapy. A cohort study from USA based on 219 breast cancer cases, where exposure data are derived from a question concerning the ever-use of 'hormone pills for reasons related to menopause', did not find any association between HRT and risk of breast cancer, with RR 0.8 (0.6–1.3) (27). As mentioned previously, unopposed estrogen therapy with conjugated estrogens or oestradiol does not seem to increase the risk of breast cancer substantially, and studies not considering the

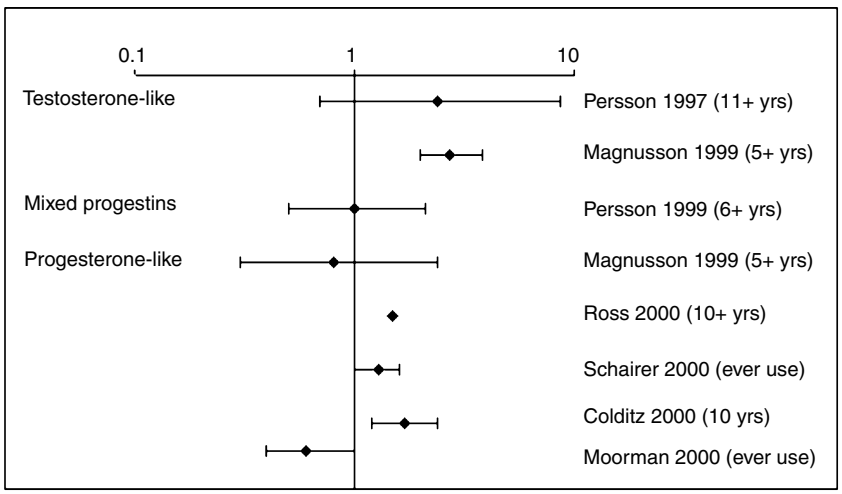

Fig. 2. Effect of the ever and long-term use of combined estrogen/progestin treatment according to the androgenecity of the progestin.

different hormonal constituents in the HRT regimen and treatment mode, tend to produce lower risk estimates. A recent Swedish cohort study found increased risk estimates for the ever-use of HRT which increased further with duration, SIR 1.35 (1.09–1.64), and after 5 years the estimate was SIR 1.78 (1.26–2.51) for women with a natural menopause. Again there was no specific analysis regarding the type of HRT, but the authors stated that the predominant therapy regimen in the study base was estrogen combined with progestin in either a cyclic or a continuous mode of treatment (28).

Discussion

Progestins started to be added to estrogens in HRT treatment regimen in the 1980s, in order to reduce the risk of endometrial cancer following the use of unopposed HRT. While successful for this purpose, it has now become evident, that the addition of progestins to the HRT treatment with estrogen is not protective against breast cancer. On the contrary, the latest studies indicate that the risk of breast cancer is increased for the combined therapy regimens compared with the treatment with estrogen only. Hypothetically, the testosterone-derived progestins might confer an increased risk beyond the risk known from the studies in the USA, where the progesterone-like progestin MPA is the most frequently used progestin. More evidence and studies addressing this issue are needed. Whether the cyclic vs. the continuous combined treatment regimen is most harmful with respect to breast cancer needs further investigation also. The effect might be different according to the androgenecity of the progestin, where the testosterone-like progestins, particularly when administered in a continuous treatment regimen, may be more harmful with respect to the risk of breast cancer.

When assessing the risk of breast cancer subsequent to HRT treatment with or without progestins, it must be noticed that the indications for prescription of these different regimens are not the same. Age is an important determinant for the choice of HRT regimen, as older women often are prescribed estrogen-only therapy. The combined estrogen/progestin replacement therapy is prescribed to women with an intact uterus, whereas the unopposed treatment with estrogen is prescribed to women who have had a hysterectomy. These women may not be representative or comparable with other women on HRT and may be at a lower baseline risk. Furthermore, these women often have had their ovaries removed, which places them at a lower risk per se (29). In order to deal with this issue, some studies have excluded women with a simple hysterectomy or have assumed that these women are comparable with respect to breast cancer risk factors and adjusted for hysterectomy in the multivariate model. Still, this represents a bias because exposure is related differently in these two groups. Hence it can be difficult to compare the risk estimates in the literature.

The meta-analyses have shown that current users of HRT experience an excess risk of breast cancer compared with never-users. The later studies have emphasized the fact that the risk of breast cancer may vary with the different compounds used, especially with the addition of progestins. The growing evidence of differential changes in mammographic density with different HRT regimens is supportive of the notion of a higher risk of breast cancer following the use of combined estrogen/progestin treatment. Mammographic parenchymal density increases with the use of combined estrogen and progestin as compared with the use of unopposed estrogen (30–33). Furthermore, increased mammographic density has been associated with an increased risk of breast cancer (34). A Swedish study found the relative risk of increased density with oestradiol-only treatment to be RR 1.5 (0.7–3.6), whereas oestradiol combined with cyclical or continuous administered progestin corresponded to a relative risk of 3.6 (1.6–7.7) and 12.4 (6.3–24.4), respectively. The type of progestin was not specified (35). A later Swedish study, where women were taking testosterone-like progestins in a cyclical or continuous regimen, showed that the densities increased 52% for women using the combined estrogen/continuous progestin treatment, while the density in women using the cyclic regimen increased 13% and for estrogen-only users (both oestradiol and conjugated estrogens) the density increased 18% (33). These findings are close to results from the USA, where the percentages for increased mammographic densities were 3.5% (1.0–12.0) for the CE group, 23.5% (11.9–35.1) in the CE plus cyclic MPA group, and 19.4% (9.9–28.9) in the CE help daily MPA group. The corresponding adjusted odds ratio for increased mammographic densities after 12 months were 13.1 (2.4–73.3) for the cyclic combined regimen and 9.0 (1.6–50.1) for the continuous combined regimen vs. CE (30). A study evaluating both the testosterone-like and progesterone-like progestins showed, as did some of the other studies, a significant higher risk associated with the continuous combined regimen compared with the cyclic progestin regimen. The increased mammographic densities in continuous combined regimen were associated with the androgenecity of

the progestin used, as the testosterone-like progestin accounted for an increase in density of 34.1%, followed by the progesterone-like progestin in 23.5% (32). These findings support the hypothesis of an increased risk of breast cancer following the combined use of estrogen/progestin, especially for the continuous combined treatment mode. This increased risk may be even more pronounced for the testosterone-like progestins. This could partly explain why the study by Ross et al. did not show the same increased risk with the combined regimen as the study by Magnuson et al., as the effect of the long-term and continuous administration of MPA might be different from the effect of the testosterone-like progestins (2,5).

The impact of sex steroids, especially estrogen, has been acknowledged for many years. More recently, the 'estrogen augmented by progestin' hypothesis has been put forward. It assumes that estrogen and progesterone in combination would produce a higher mitotic rate in the breast epithelium than estrogen alone (36). Supportive of this notion is the study by Longacre & Bartow, who studied the morphology of the breast during menstrual cycles and found that breasts in the secretory phase, where progesterone levels are high, are characterized by increased size of lobules, more terminal duct structures, and a higher rate of mitosis (37). Furthermore, breast morphology has been seen to change with pregnancy, when both estrogen and progesterone levels are high and result in differentiation of the mammary alveolus and gland, and a long-term risk reduction with respect to breast cancer (38–41).

Apparently there is a paradox as the incidence of breast cancers, which are ovarian hormone responsive, increases in the postmenopausal state when ovarian function has ceased and hormone levels are low. Long-term deprivation of ovarian hormones could be a major contributing factor to higher breast cancer risk, as it increases the sensitivity of the mammary tissue to estrogen and the combination of estrogen and progestin (42).

Progesterone in high doses has been used as second-line treatment of advanced breast cancer, and has shown inhibitory effects in the metabolism of estrogens *in vitro* (43). Furthermore, progesterone has been reported to both stimulate and inhibit the growth of experimental tumors (44). The effect of a progestin together with estrogen might differ with respect to the cyclical or continuous administration, as the acute effect of progesterone seems to be a stimulus of mitosis followed later on by growth inhibition and a higher degree of cellular differentiation (36,45–47). This may explain why breast cancer developing in women using HRT seems to have more favorable prognostic characteristics. The influence of progesterone, especially the testosterone-like progestins on mammary gland proliferation, may partly be the result of its estrogenic actions. Testosterone has estrogenic actions, and the high affinity for SHBG might contribute to higher levels of bio-available estrogen (48,49). The elevated risk of breast cancer after the use of combined HRT may thus be the result of the possible acute increase in cell division mediated by progestins, and hence in increased risk of mutation.

The pathophysiology and mechanisms by which endogenous and exogenous sex steroids are in the causal pathway of breast cancer is still not fully understood. Observational studies have added to the evidence of an increased risk of breast cancer following exogenous sex steroids, but this risk may be restricted to specific types of HRT, i.e. the continuous combined regimen with testosterone-like progestins.

Conclusion

Overall there seems to be evidence for an increased risk of breast cancer with the combined use of estrogen and progestins, and this risk might be different for the testosterone-like and progesterone-like progestins. Currently available epidemiological evidence, and studies on the mammographic density, suggest an increased risk of breast cancer following the use of the continuous combined regimens. However, whether the continuous combined regimen is more harmful than the cyclical regimen, remains to be further elucidated. The role of long-term combined HRT with testosterone-like progestins represents a challenge for further investigations not only with regard to incidence, but also in tumor features, stage of disease and survival. The personal identification number in the Nordic countries together with the population-based registers offers excellent opportunities for register linkage, as well as validation and follow up. As treatment modalities for postmenopausal hormonal substitution vary worldwide, we encourage European investigators to design further studies to provide the body of evidence necessary for the development of recommendations for the future prescription of HRT for women in Europe, taking into account various differences in genetic susceptibility, reproductive- and lifestyle factors.

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