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Estrogens in the causation of breast, endometrial and ovarian cancers — evidence and hypotheses from epidemiological findings

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Abstract

Estrogens along with progesterone/progestins, and other hormones, are important determinants of cancer in the breast, endometrium and ovary. Estrogens may increase the risk of breast cancer through various mechanisms and at various phases of life, with a possible synergistic effect of progesterone/progestins. Exposure to high doses of placental hormones, such as estrogens and/or progesterone, during pregnancy may play a pivotal role in reducing subsequent breast cancer susceptibility. Estrogens cause endometrial cancer, an effect that can be reduced, prevented or reversed by progesterone/progestin — if allowed to act for a sufficiently long period of each cycle. The role of sex hormones seems important for ovarian carcinogenesis. Intake of combined oral contraceptives has a substantial and well-documented protective effect on endometrial and ovarian cancer risks. Epidemiological observations and experimental data from an animal model indicate that estrogens may have an adverse effect, while progesterone/progestins have a risk reducing effect directly on the ovarian epithelium. Thus, estrogens and other sex hormones have potential effects on the three most important female cancers. Research has yet to define how some of the risk factors can be modified or treatment regimens can be improved to reduce these cancer risks. © 2000 Published by Elsevier Science Ltd.

Keywords: Estrogen; Breast cancer; Endometrial cancer; Ovarian cancer

1. Introduction

The exposure to estrogens during different phases of a woman's life can influence the risk of cancer in the main target organs, i.e. the breast, endometrium and ovary. Numerous epidemiological studies report associations between markers of ovarian or placental hormone production and cancer risks. In recent decades, also exogenous hormones — as in oral contraceptives and hormone replacement therapy — have been implicated as risk factors for cancer and also as preventive agents. Epidemiological observations give important clues as to the carcinogenetic role of sex hormones, but need support from clinical and basic research in order to verify and characterize their action in relevant pathways.

This presentation highlights some of the more recent epidemiological findings and their implications for research and for clinical practice.

2. Breast cancer

Breast cancer is the most frequent cancer among women world-wide, with approxinately a 5-fold higher incidence in some western countries as compared with Asian countries [1]. The cumulative incidence up to 74 years of age is as high as 7–9% in North America and other northern European countries [2]. The incidence has been rising in both developed and developing countries [3], whereas mortality in high-risk countries has been rather stable during past decades [4]. Migration studies reveal striking patterns; descendants of women moving from low-risk Asian countries to the US have been shown to adopt the incidence of breast cancer in the host country by the second and third generation [5]. The determinants of these patterns clearly deal with changes in aspects of lifestyle rather than genetic susceptibility. However, the actual causative mechanisms have remained elusive and no major means for primary prevention have yet been identified.

Nevertheless, epidemiological observations do give important leads in the search for etiological factors. For recent overviews, see Refs. [4,6,7].

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2.1. Intrauterine exposures

Evidence for a new paradigm in breast cancer etiology was recently presented, i.e. that breast cancer risk is influenced by intrauterine exposures of the fetus [8–10]. Daughters of mothers developing preeclampsia during pregnancy — a condition associated with impaired placental function and subnormal hormone levels — experienced a substantially reduced risk of breast cancer during their life-time [11]. Furthermore, birth weight, reflecting intra-uterine nutritional and hormonal exposures, has in some studies been positively related to breast cancer risk [11–13] and to mammography patterns linked to a high risk of breast cancer [14].

2.2. Endogenous hormones

Several risk factors have been established that pertain to differences and variations in endogenous hormones at different phases of life [4].

2.2.1. Sex

Women have a 100-fold greater risk to develop breast cancer as compared with men.

2.2.2. Age

Breast cancer is infrequent before the age of 35, it increases with increasing age, reaching a maximum at about the age of 65. An intriguing observation in the world-wide cancer statistics is the characteristic inflection of the breast cancer incidence curve around age 50, i.e. the time of menopause and reflecting cessation of ovarian hormone production.

2.2.3. Age at menarche and menopause.

For an age at menarche around 12 years, as compared with 16 years or later, the risk of breast cancer is about 50–70% greater. Every 1-year increment in age at menopause confers an increase of breast cancer by approximately 3% [15]. Noteworthy is the marked protective effect from a premature oophorectomy performed before age 40, the risk of breast cancer being reduced by about 50%.

2.2.4. Parity and age at first full-term pregnancy

To give birth as compared with remaining nulliparous is associated with a considerable protective effect, which is greater the earlier the first-birth takes place. Each subsequent birth provides an additional protective effect. A novel observation is that a first full-term pregnancy actually gives rise to a dual effect, an initial risk increase during about 15 years after birth and a subsequent long-term decrease in risk. The later the first child is born, the more pronounced is the initial risk increase and the longer it takes before the protective effect occurs [16].

2.2.5. Stature

Height (tallness) has been consistently found to be a risk factor for breast cancer. It is believed to reflect the effects of nutritional status and action of hormones during the growth period of the adolescence.

2.2.6. Body build

A high body mass index (BMI) is linked to a lowered risk of premenopausal breast cancer, whereas there is an increased risk in postmenopausal women. Obesity is believed to act on breast cancer risk through the occurrence of unovulatory cycles in premenopausal women (less progesterone production), and in postmenopausal women through excessive extraglandular production of estrogens in the fat tissue. In some recent studies, weight gain in postmenopausal years has been suggested to be the key factor associated with an increase of breast cancer risk [17].

2.2.7. Alcohol intake

In several studies, regular intake of excessive amounts of alcohol has been associated with an higher risk, supposedly through elevations of endogenous estrogen levels [18].

2.2.8. Physical exercise

Some studies have reported a decreased risk following rigorous physical exercise during adolescence or during adult life. However, the evidence for this association is rather weak. Hypothesized mechanisms include a delay in menarche or reduced estrogen production by the ovaries [19,20].

2.2.9. Diet

Fat intake has been assumed to be a risk factor, but studies have failed to find any evidence of a link in adult life [21]. Aspects of nutrition may well be important during the adolescent period or intrauterine life; issues that are attracting increasing interest. There are indications that vegetables and fruits, olive oil and soy based foods may prevent breast cancer through anti-oxidant properties [21].

2.2.10. Serum hormone levels

Improved laboratory assays have enabled more accurate measurements of sex hormone levels in postmenopausal women. Both prospective cohort and retrospective case-control studies consistently show a positive relationship between serum levels of estradiol and estrone and post-menopausal breast cancer [22]. For androgens, results have been inconsistent.

2.3. Exogenous hormones

The use of exogenous hormones, both as combined oral contraceptives (COCs) in young women and for

replacement in postmenopausal women (HRT), has increased dramatically since the 1970s and become widespread. Because these treatments entail long-term exposure to potent estrogens (often combined with progestins) in healthy women, there is increasing concern of adverse effects on breast cancer risk.

2.3.1. COSs

The original data from some 50 epidemiological studies, including about 53 000 cases and 100 000 control subjects, were re-analyzed in a collaborative effort [23]. The key finding was a small, about 25%, increase in the risk of breast cancer for women under the age of 35 who had used COCs for 5 years or longer, predominantly for early types of tumours. The association vanished 5 years after cessation of the treatment. There were indications that use beginning before the age of 20 or before the first full-time pregnancy was linked to a stronger risk. The interpretation of these results is not clear-cut; the observed risk relationships may partly be explained by an earlier diagnosis of breast cancers in women taking COCs. These results, if valid, would translate into very minor effects in terms of absolute risks, i.e. among 10 000 women treated with COCs for 5 years between the ages of 25 and 29 years, five new cases may be attributed to the exposure.

2.3.2. HRT

The epidemiological data from about 50 studies including over 50 000 breast cancer cases and almost 110 000 control women were collaboratively analyzed and reported recently [24]. Intake of replacement estrogens (information on added progestins was mostly not available) for 5 years or more was associated with an elevated risk of about 50%, predominantly for early breast cancers. This risk relationship disappeared 5 years after treatment had been stopped. Further, the excess risk was only measurable in women with a normal or lean body build. These results imply that among 1000 women treated for 15 years, 12 new cases would be expected on account of this exposure.

Several original studies reported in latter years have provided more detailed data on the risk related to different estrogenic compounds, dosages and importantly to combinations with progestins (added to prevent endometrial malignancy). These studies confirm a duration dependent risk increase after current or recent intake, of both conjugated estrogens and estradiol compounds, with relative risk estimates ranging from 1.5 to 3 after 6–10 years of intake [22,25]. A growing number of studies show that added progestins do not seem to reduce or eliminate the excess risk associated with exogenous estrogens. One recently reported large Swedish case-control study suggests, for the first time, that the adverse effect may persist even a long time after discontinuation of treatment, and further that addition of progestins may enhance the risk above that for estrogens alone [25].

Data on the biological characteristics and prognosis of breast cancer occurring after HRT are scarce and difficult to interpret due to the possibility of lead-time bias. Data from some studies support that breast cancers occurring after HRT are predominantly estrogen receptor positive [26] and are associated with favourable survival and little or no effect on mortality.

The available evidence supports that the risk increase for breast cancer after HRT is causal [22]. This adverse effect of HRT may be a threat to women's health and needs to be considered when advising women on the long-term effects of HRT.

2.4. An etiological model

On the basis of epidemiological observations mentioned above and findings in animal research, a comprehensive etiological model for breast cancer has been proposed [9], with the following four components:

- The probability of breast cancer developing depends on the absolute amount of susceptible cells in the breast parenchyma. Indirect evidence is that mammography density (reflecting the amount of breast tissue) is a risk predictor [27]; that women with small breasts have a lowered risk, and that reduction mammoplasty may reduce breast cancer risk [28,29].
- The amount of cells and their sensitivity to hormonal carcinogenesis are influenced in early life, and perhaps in utero. Observations in support of this are that breast parenchyma of new-borns show different levels of structural development [30]; examinations of rat breasts indicate that breast cells developing in utero are undifferentiated and susceptible to carcinogens [31]; birth weight (reflecting placental function and hormone levels) is positively associated with breast cancer risk [13].

Mechanisms to explain such a possible link between perinatal factors and adult breast cancer risk entail the role of nutrition during pregnancy for placental function and the possibility for intrauterine genetic imprinting of target cells in the breast.

- A pregnancy stimulates growth of already transformed cells through placental hormones (chiefly estrogens?), leading to an initial risk increase of breast cancer, but yields a long-term protective effect through a differentiation of tubulo–glandular cells. Empirical evidence stems from rat models showing that a full-term pregnancy is followed by differentiation towards more mature and hypothetically more refractory glandular structures in which epithelial cells have a decreased rate of mitosis [32]. These changes would be expected to render cells less susceptible to malignant transformation.

- A number of mammotrophic hormones regulate the pool of target cells and cause receptor mediated responses [9]. Major hormonal factors are the ovarian estrogens and progesterone — both believed to increase proliferation of breast epithelial cells — but also, among others, prolactin and IGF-1 hormones. During adolescence, and in adult life, these may determine breast cancer risk by increasing the population of cells at risk prior to initiating events, affecting clonal expansion and promoting growth of an established tumour.

As mentioned, most of the risk factors would be expected to act through hormonal mechanisms, importantly estrogens and progesterone/progestins. Susceptibility to estrogenic effects may vary with the presence and type of receptors, e.g. for ERα and ERβ or for IGF-1. However, the regulation of cellular responses is certainly complex, since not only these receptor mediated endocrine but also paracrine, autocrine and intrauterine mechanisms are likely to be important [33]. Further, these hypothetical carcinogenetic pathways act indirectly through proliferative responses, whereas direct genotoxic effects of estrogens have been suggested — through metabolic activation of estradiol to catechol estrogens that may lead to adduct formation and increased mutagenesis [34].

In summary, the proposed etiological model expands on previous theories and accommodates previously and newly reported risk factors. It gives a theoretical framework for the action of carcinogenic exposures from very early in life and perhaps for how environmental factors influence breast cancer risk.

3. Endometrial cancer

World-wide, endometrial cancer is the sixth most common cancer, accounting for about 2% of all incident cases in women. The incidence varies greatly between countries, being the highest in the USA and Northern Europe [35]. It generally has a favourable clinical course, the 5-year average survival being about 75% [3].

It is established that estrogens cause endometrial cancer. The key mechanism of carcinogenesis is an enhanced and long-standing proliferation of endometrial cells leading to a gradual development of the endometrium into hyperplasia, atypical hyperplasia and to cancer, in the vast majority of estrogen-related so-called type I tumours [36].

3.1. Endogenous estrogens

The preponderance of risk factors reflect exposure to excessive amounts of estrogens without an adequate opposition by progesterone [37].

3.1.1. Age

The incidence starts to increase at about 40 years of age and rises to a maximum at about 65–70 years [38]. Interestingly, the rate of incidence increase becomes slower at the age of 50, i.e. about the average time of menopause in Swedish women.

3.1.2. Parity

A large number of studies show an inverse relationship between parity and risk, an effect attributed to the high levels of progesterone during pregnancy. Nulliparity per se may be a risk factor, when associated with unovulatory infertility, i.e. exposure to unexposed estrogens [39].

3.1.3. Age at menopause

Together with irregular menstrual cycles, a late menopause is a marker for a prolonged period of progesterone unopposed estrogen exposure that gives rise to an increased risk.

3.1.4. Body build

Adult obesity is a strong and consistently reported risk factor. It most importantly acts through an enhanced extraglandular production of estrogens in postmenopausal women through transformation of precursor adrenal androgens in fat tissue.

3.1.5. Diabetes

Non-insulin dependent diabetes mellitus is associated with an increased risk that is independent of the BMI (obesity), indicating that some other (endocrine) condition affects endometrial cancer risk, hypothetically through elevated androgen and lowered SHBG levels [40].

3.1.6. Hypertension

Data from numerous studies fail to support that hypertension is an independent risk factor, rather being associated with a metabolic syndrome.

3.1.7. Physical activity

A few studies have reported a decrease in risk with increasing levels of physical activity, thought to act through weight reduction or by reducing ovarian estrogen production [41].

3.1.8. Cigarette smoking

The preponderance of evidence suggests that current cigarette smoking reduces endometrial cancer risk, the mechanism being an up-regulation of estrogen metabolic liver enzymes and reduced estrogen levels [42].

3.1.9. Tamoxifen

Tamoxifen has been classified as a carcinogen [43] due to its effect on increasing the incidence of endometrial cancer [44]. The mechanism of action is proposed to be an agonistic estrogenic effect selectively in the endometrium.

3.1.10. Endogenous estrogens

The PCO syndrome and estrogen secreting ovarian tumours, both entailing persistent production of unopposed estrogens, have been associated with an increased risk of endometrial cancer [42,45]. In recent studies, associations with endometrial cancer were observed for high levels of estradiol, estrone and androstendione in postmenopausal women [46].

3.2. Exogenous hormones

3.2.1. COCs

A remarkably consistent finding in the epidemiological literature is the up to 40% reduced risk of endometrial cancer after only a few years of COC intake, persisting long after the discontinuation of intake [47]. A recent case-control study of endometrial cancer in women aged 50–74 years verified a protective effect among post-menopausal women, i.e. decades after cessation of treatment [48]. The continuous addition of a potent synthetic progestin during 3 out of 4 weeks is believed to be responsible for this substantial beneficial effect.

3.2.2. HRT

A substantial duration-dependent increase in the risk of endometrial cancer is well documented for women taking estrogens without added progestins [37]. Numerous studies reported from the late 1970s show that the risk of predominantly early and well-differentiated endometrial cancer is increased by about 10-fold after 10 years intake of estrogens alone. Women developing tumours after HRT had no measurable effect on their survival.

Since the 1980s, progestins have been increasingly added to estrogens in order to protect the endometrium from the development of hyperplasia and neoplasia. Different regimens have been applied, e.g. cyclic addition for seven–12 days of the cycle resulting in withdrawal bleedings, or continuous addition all days of the cycle in order to avoid menstrual bleedings. A limited number of studies have had the opportunity to evaluate the effects on endometrial cancer risk of these combined regimens. In the most recent studies, cyclic addition for less than ten days was associated with a risk increase compared with non-users [49], the addition for ten days still yielded a small excess risk with long-term treatment, whereas continuous addition eliminated the risk increase [50]. The recent Swedish case-control study confirmed the risk increase with many years of unopposed estrogen treatment. Further, it showed evidence of a 60% excess risk, also with the addition for ten days of a potent progestin, but a lower risk compared with untreated women when the progestin had been added during all days of the treatment cycle. Thus, these data evidence that progestins can counteract the carcinogenic effect of estrogens on the endometrium, partially, entirely, or even reversing the risk to an absolute protective effect, depending on the number of days the progestins are added.

In summary, estrogens cause endometrial cancer. When giving HRT this adverse effect can be eliminated by opposing the estrogenic effects by an adequately long addition of a progestin.

4. Ovarian cancer

Globally, ovarian cancer is the fifth most common cancer among women. Incidence rates are the highest in Scandinavia, with intermediate rates in the USA and with the lowest, but increasing, rates in Japan [51]. Since most of the invasive cancers are diagnosed at an advanced stage, the prognosis is poor, with an average 5-year survival of less than 40% [51]. The non-invasive, borderline subtype, comprising about 20%t of all tumours, is associated with a considerably better prognosis.

4.1. Etiological hypothesis

The etiology of ovarian cancer is overall poorly understood, although it is established that reproductive (hormonal) factors are commonly involved.

Risk factors observed in epidemiological studies have been considered compatible with two main mechanistic hypotheses, i.e. the incessant ovulation theory [52] and the gonadotropin theory [53]. The former suggests that each ovulation traumatizes the ovarian epithelium and that the healing process entails increased cell division activity and an increased likelihood for entrapment of epithelial cells in ovarian stroma that is rich in growth factors. The latter theory predicts that high levels of gonadotropins increase cancer risk by directly stimulating growth of the epithelium through receptors. Other, newer hypotheses imply that retrograde menstruations carry carcinogens to the ovary [54]; and that the sex hormones exert direct effects on the ovarian epithelium, i.e. as suggested that ‘pregnancy hormones’ clear the ovary of premalignant cells [55] or androgens enhance while progesterone reduces epithelial proliferation [56].

4.2. Reproductive risk factors

A number of hormonally related factors have been evaluated in epidemiological studies [57].

4.2.1. Age at menarche and menopause

Several studies found a weak increase with menarche at young age, others found no link. An increased risk for late age at menopause has been reported in retrospective studies, but not in two cohort studies. These divergent results cannot give support to any of the etiological theories.

4.2.2. Parity and pregnancy

A consistent finding is the preventive effect of a full-term pregnancy. Parous women have a 30–70% lower risk as compared with nulliparous women. This major risk determinant is consistent with the incessant ovulation and direct hormonal effect theories. Infertility, especially among women failing to become pregnant, seems to be associated with an increased risk [58]. A late age at birth of a first child has been reported to confer a greater protective effect as compared with an early age [55], a finding however without confirmation in other studies.

4.2.3. Tubal ligation and hysterectomy

Several studies show that these procedures protect against ovarian cancer. The mechanism is, however, unclear, one theory implies that ovarian hormone production is compromised, another that ovulations are diminished, a third that the retrograde blood flow is prevented.

4.2.4. Lactation

Most studies have found a weekly decreased risk with lactation. Lactation can cause both anovulation and lowered gonadotropins levels while on-going, thus providing support for both these theories.

4.3. Exogenous hormones

4.3.1. COCs

One of the most important findings for COCs is the consistently reported substantial and persistent protective effect against ovarian cancer risk. Protection is observed after only a few years of intake and is seemingly present regardless of age at diagnosis. Uncertainties regard the effect for subtypes of tumours, prevention has not been clearly established for borderline or mucinous tumours. Further, the impact of modern low-dose COCs has not yet been characterized.

An overview of available studies reveals that 5 years of COC intake confers a 50% reduced risk, the preventive effect persisting at least for 10 years after use has been stopped [59].

Even though these data give support of the incessant ovulation theory, the observed protective effect is stronger than could be explained from inhibition of ovulations alone [56].

4.3.2. HRT

Replacement hormones may influence ovarian cancer risk, because of their gonadotropin lowering, or possible direct hormonal, effects.

The results of nine epidemiological studies were evaluated in a recent meta-analysis [60]. Among the original studies, eight case-control studies and one cohort study, two showed a 70–80% increased risk of invasive cancer after about 10 years intake of estrogens [61,62], while the remainder showed a weaker positive effect or no risk change. The meta-analysis yielded a joint risk estimate of about a 30% increased risk. These data, pertaining to replacement with estrogens alone, do not allow for a firm conclusion to be drawn about the effects of HRT on ovarian cancer risk. However, because of the newly arisen concern, larger studies need to be done that can provide more details.

4.3.3. Infertility treatment

Hormonal regimens introduced in the early 1970s to induce ovulations in infertile women are being evaluated, the concern being a suspected adverse effect on ovarian cancer risk. From a pooled analysis of three case-control studies conducted in the US, a vastly increased risk of ovarian cancer was reported for women exposed to unspecified 'fertility drugs' and never succeeding to complete a birth [63]. The report was heavily criticized on a number of methodological grounds but sparked great concern. One subsequent cohort study, with a small number of mixed ovarian tumours, showed a small excess risk after Chlomiphene intake [64]. Another cohort study of relatively young women who had received IVF treatments, found no risk increase linked to such treatment [65]. Lastly, two relatively large case-control studies in Canada [66] and Denmark [58] failed to find any association between hormonal infertility treatment and ovarian cancer risk. A crucial problem in these studies was the difficulty of separating the effects of infertility itself from that of the hormonal treatment.

Even if the latest reported studies give reassuring results, no firm conclusions can be drawn at present. Furthermore, there are yet no meaningful data on the consequences of the modern highly dosed IVF treatment regimens.

4.3.4. Animal data on progestin effects

It has been hypothesized that the marked protective effects associated with COC exposure and completed pregnancies are mediated partially or entirely through direct effects of progesterone/progestins on the ovarian epithelium [56]. This theory received support from an

experimental study in cynomologus monkeys, showing that the expression of an immunohistochemical apoptosis marker was related to administered sex hormones. In animals receiving progestins alone, 25% of the ovarian surface cells expressed an apoptotic response, in those receiving an oral contraceptive regimen 15%, as compared with 2% for estrogens alone or 4% for placebo treatment [67]. Given that apoptosis is a pathway for clearance of premalignant cells, these findings provide a possible explanation why progestins may have a protective effect on ovarian cancer risk. Clearly, this issue needs to be evaluated with a high priority.

In summary, ovarian carcinogenesis may involve the action of hormones through several mechanisms. The protective effects of pregnancy and particularly of COCs are important from a public health point of view and give clues to prevention, whereas some data on hormonal infertility drugs give reason for concern.

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