Hormone replacement therapy: pathobiological aspects of hormone-sensitive cancers in women relevant to epidemiological studies on HRT: a mini-review

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Hormone replacement therapy (HRT) has gained widespread and in some areas indiscriminate use. In reference to recent epidemiological studies which showed unexpected and controversial associations of HRT use with malignant tumours, here we review the current understanding of the dynamics of tumour growth. The pathomorphological characteristics and sex hormone sensitivity of cancers of the breast, endometrium, ovary and colon are discussed. The development of cancer from the first malignant tumour cell to clinical diagnosis takes many years. Hormones can influence tumour growth, but it is questionable whether hormones induce malignant tumours de novo. It is much more likely that hormones ‘merely’ promote the growth of already existing tumour cells. The long developmental process of tumours is in apparent contradiction to results of some epidemiological studies that describe an increased cancer risk, implying primary initiation, in HRT users within observation periods of 1–6 years. The mechanisms of initiation versus promotion of hormone-sensitive cancers, particularly breast cancer, are only partly understood. The conventional methods of epidemiological studies cannot detect potential risk factors without bias if they do not include a pathomorphological component on growth characteristics. The results of previous studies should be interpreted with great caution with regard to tumour biology.

Key words: cancer/endometrium/epidemiology/hormone receptors/pathomorphology

Introduction

Hormone replacement therapy (HRT) has gained widespread and in some areas indiscriminate use, in part due to the observation of protective effects on the cardiovascular system. Recent epidemiological studies with cohort and trial designs on HRT have reported unexpected results. These include previously unanticipated negative effects on cardiovascular disease (Manson et al., 2003), quality of life (Hays et al., 2003), cognition (LeBlanc et al., 2001; Rapp et al., 2003; Shumaker et al., 2003), and also on cancers (Chlebowski et al., 2003; Million Women Study Collaborators, 2003) and bone fractures (Rodriguez et al., 2001; Torgerson and Bell-Syer, 2001; Wells et al., 2002; Writing Group for the Women’s Health Initiative Investigators, 2002), which in their sum have created considerable discussion concerning methods, content and possible conclusions, and some rethinking concerning the general prescribing habits of HRT to menopausal women (Windler, 2002; Bailar, 2003; Beckmann et al., 2003; Braendle and Kuhl, 2003; Ena and Rozenberg, 2003; Gann and Morrow, 2003; Garbe et al., 2003; Goodman et al., 2003; Grady, 2003; Grodstein et al., 2003; Hertington and Howard, 2003; Luukkainen, 2003; Machens and Schmidt-Gollwitzer, 2003; Neves-e-Castro, 2003; Pedersen and Ottesen, 2003; Shapiro, 2003; Solomon and Dluhy, 2003).

Because these more recent studies appear to show some increased risks of cancers, in particular of breast cancer, a review of current understanding of the pathogenesis of such cancers would help to evaluate and position the results of these studies. The following is a review on the epidemiology, biology and growth dynamics of cancers associated with HRT use and a reflection of epidemiological results based on these insights.

Hormone replacement therapy

Approximately 40% of women suffer from menopausal symptoms severe enough to seek medical help (Grady, 2003). Among the spectrum of therapies prescribed for the various symptoms of these patients, hormone replacement has been shown to alleviate vasomotor changes, i.e. ‘hot flushes’ (Neves-e-Castro, 2003), mood disorders and genitourinary alterations, such as atrophic vaginitis (Schneider, 2000). Estrogens may even increase the cutaneous collagen
content, thus maintaining skin thickness and vascularity. The trends in formulation have moved from estrogen-only or unopposed replacement to combinations of estrogens and progestagens due to protective effects on the endometrium. Non-hormonal therapies have been reported to improve menopausal symptoms to a lesser degree than HRT, but have other beneficial effects (Breast Cancer Trialists’ Collaborative Group, 1998; Fisher et al., 1998; Cummings et al., 1999; Ettinger et al., 1999; Jordan, 2001).

HRT alone or combined with physical exercise, vitamins, calcium, parathyroid hormone and bisphosphonates has a positive influence on the post-menopausal loss of bone mass and subsequent osteoporosis. Estrogens primarily maintain the bone structure, whereas most alternative treatments both increase bone mineralization and inhibit bone resorption (Wells et al., 2002). Early initiation and long duration of treatment seem to be essential for the prevention of fractures in the menopause and post-menopause.

There can be no general rule for the duration of HRT treatment, because even 18 years after menopause, ~16% of women still show considerable vasomotor and other complaints (Schneider, 2000). Nevertheless, women on HRT should be examined regularly to assess the need for continuous treatment or dose reduction. When discontinuing HRT, this should be done slowly to determine whether the patient suffers from prolonged vasomotor symptoms after menopause.

The sum of effects of HRT treatment in symptomatic women is therefore beneficial and likely to avert more serious health conditions. However, any therapeutic benefits have to be weighed against potential side effects and inherent risks which doctors have to be aware of and patients counselled about before any therapeutic decisions are made.

**Epidemiology and risk factors of conditions affecting post-menopausal women**

The diseases most often affecting peri- and post-menopausal women are cardiovascular and neoplastic. Cardiovascular events, e.g. myocardial infarcts, increase in frequency with age and are associated with case fatality of ~50% (Tunstall-Pedoe et al., 1994). Among the neoplastic diseases, breast cancer is the most frequent cancer in women of the Western world and accounts currently for ~26% of female cancers and ~18% of all female deaths in Germany (Arbeitsgemeinschaft Bevölkerungsbezogener Krebsregister in Deutschland, 1999). The annual breast cancer incidence in industrialized nations is high, ranging from 100 per 100,000 in France to 115.6 per 100,000 in the USA (International Agency for Research on Cancer, 2003). The rates for breast, ovarian and endometrial cancers are highest in industrialized nations and much lower in developing countries, with a lowest to highest incidence ratio of 1:20 for breast and endometrial cancer (American Institute for Cancer Research/World Cancer Research Fund, 2002).

The risk factors established or suspected as being associated with breast cancer include obesity, alcohol intake, low or late parity, dietary factors (Colditz et al., 1995; Magnusson et al., 1999; Schairer et al., 2000; American Institute for Cancer Research/World Cancer Research Fund, 2002; Endogenous Hormones and Breast Cancer Collaborative Group, 2002; Hankinson and Hunter, 2002; Brekelmans, 2003; La Vecchia and Fransesch, 2003; Olsson et al., 2003), genetic predisposition or family history (Grabrick et al., 2000; Friedenson and Friedenson, 2002; Ursin et al., 2002), and many others, including HRT use (Collaborative Group on Hormonal Factors in Breast Cancer, 1996, 1997; Li et al., 2003). Thus HRT use is one of a broad range of factors for which an association with breast cancer has been found. Although individual studies may show higher risk estimates for one or more of these factors, the most frequent risk estimates found are below 2, which is near the difference in population risks which an observational study is capable of detecting (see Tables I and II). While the general incidence of breast cancer is high, the case fatality (the proportion of people who have the disease and die from it) for breast cancer (just as for endometrial cancer) is much lower than that for colon and ovarian cancer.

The large differences in incidence estimates for breast cancer across countries worldwide raise the question of whether this is due to some causal agent, due to detection or diagnostic issues or due to environmental or genetic interactions. With a family history of breast cancer only present in 10–15% of first degree relatives of cancer patients and in ~5% of non-cancer controls, large intercultural differences are unlikely to be explained by genetic predisposition alone.

The majority of breast cancers occur sporadically, and the risk in genetically predisposed women changes after

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<th>Reference/study name</th>
<th>Estrogen-only HRT</th>
<th>Combined HRT</th>
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<td></td>
<td>Risk ratio</td>
<td>95% CI</td>
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<td>Observational designs</td>
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<tr>
<td>Million Women Study (2003)</td>
<td>1.30</td>
<td>1.21–1.40</td>
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<td>Colditz et al. (1995)</td>
<td>1.30</td>
<td>1.20–1.70</td>
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<td>Schairer et al. (2000)</td>
<td>1.20</td>
<td>1.00–1.40</td>
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<td>Li et al. (2003)</td>
<td>1.00</td>
<td>0.80–1.30</td>
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<td>Trial designs</td>
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<td>HERS II; Hulley et al. (2002)</td>
<td>1.38</td>
<td>0.82–2.31</td>
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<tr>
<td>Women’s Health Initiative; Chlebowski (2003)</td>
<td>1.40</td>
<td>1.20–1.70</td>
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migration into other social or lifestyle environments. Nonetheless, some studies of high risk families have demonstrated an impact on the occurrence of breast cancer and an interaction with hormone use at least in first degree relatives (Wiseman, 2000). Moreover, it has been suggested that the population-attributable risk of factors such as education, family history as well as individual reproductive and hormonal factors may explain up to 50% of the breast cancer risk—even if external hormone use is not considered (Henderson and Bernstein, 1996).

Growth dynamics of gynaecological tumours—the pathomorphological view

While the focus of this review is on breast cancer, other tumours such as endometrial, ovarian and colon cancers will be briefly mentioned.

HRT and endometrial cancer

Endometrial cancer is the most common invasive malignancy of the female genital tract (Greenlee et al., 2000). The known risk factors associated either with an increased or decreased risk for endometrial cancer are age, obesity, late first birth, nulliparity, alcohol use, oral contraception (OC) and HRT. A dualistic model of endometrial carcinogenesis has been proposed previously (Lax et al., 2000). In this model, there are two main types of endometrial carcinomas: a slowly developing, indolent form which develops in the setting of excess estrogen stimulation (type I) and a more aggressive variant arising in a relatively estrogen-deficient milieu (type II). The prototype of the former is the endometrioid or mucinous carcinoma, whereas the latter is typified by the serous–papillary and more rarely the clear-cell carcinoma (WHO Classification on Pathology and Genetics, 2003).

The 5-year survival rate for type II carcinoma is ~60% (Cirisano et al., 2000). The cause of this cancer, which primarily affects older women, is not known. Type I, the form of endometrial cancer potentially associated with HRT use, is less fatal, with a 5-year survival rate of 70–80% (WHO Classification on Pathology and Genetics, 2003).

Hyperestrogenism leads to endometrial hyperplasia and eventually to epithelial atypia which may be the primary lesion of endometrioid adenocarcinoma (Cirisano et al., 2000). A 2- to 3-fold risk of endometrial adenocarcinoma has been shown in post-menopausal women who have used estrogen-only HRT. By comparison, the familial (endometrioid) endometrium carcinomas show a 5-fold increased risk. The cancer risk is reduced when sequential HRTs are used. There is a downregulation of estrogen receptors and progesterone receptors with reduced hormone sensitivity. Thus progesterone application reduces estrogen stimulation and thereby cancer risk.

The Women’s Health Initiative (WHI) study included 22 women on HRT (0.05%) and 25 women on placebo (0.06%) with endometrial carcinoma (Writing Group for the Women’s Health Initiative Investigators, 2002), a statistically not significant difference. There was, however, a decrease of the detection of carcinomas in the treatment group after the fourth year, which was not observed in the placebo group. This has prompted speculations regarding tumour initiation and promotion under HRT, especially as the study showed a large number of endometrial carcinomas in the HRT group during the initial part of follow-up, levelling off later on, whereas the occurrence in the placebo group was continuous. This may indicate that HRT stimulates already existing lesions which show up earlier, and argues against tumour initiation by HRT.

Normally atypical hyperplasia precedes carcinoma, but it is unknown in which women this occurs, or how many carcinomas were preceded by hyperplasia. Based on generally accepted models of tumour growth (Tomlinson and Bodmer, 1995; Plotkin and Nowak, 2002), slowly growing tumours such as endometrial cancer will require a minimum time from induction to diagnosis of 5–10 years, and presumably much longer. The observations in the WHI study might therefore be either a random phenomenon, or else a reflection of study conduct or the specific features of the HRT user population. It is also possible that a different progesterone from that used in the WHI study might show different results. To resolve such issues of bias, an examination of the endometrium prior to therapy and prior to entry into an epidemiological study is needed.

The observation that genital (excluding ovarian) and extra-genital endometriosis is rarely accompanied by endometrial hyperplasia or malignancy (Yantiss et al., 2000) suggests that women are probably under no increased risk of developing pre-cancers or cancers in their endometriotic lesions under progestogen-containing HRT.

HRT and ovarian cancer

As stated in the WHO Classification on Pathology and Genetics (2003), cancer of the ovary represents ~30% of all cancers of the female genital organs. In developed countries, it is about as common as cancers of the corpus uteri (35%) and invasive cancer of the cervix (27%). The age-adjusted incidence rates vary from <2 new cases per 100 000 women in most of Southeast Asia and Africa to >15 cases in Northern and Eastern Europe (American Institute for Cancer Research/World Cancer Research Fund, 2002). The economically advanced countries of North America, Europe, Australia, New Zealand and temperate South America show the highest rates. Incidence rates have been either stable or have shown slow increases in most Western countries, whereas they have risen steadily in parts of Eastern Asia.

### Table II. Pooled estimates of breast cancer risk associated with HRT from 51 observational studies and from studies with a trial design (with 95% CI)

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<th>Study Type</th>
<th>Risk ratio</th>
<th>SE/95% CI</th>
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<tr>
<td>Observational designs (Beral et al., 1997)</td>
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</tr>
<tr>
<td>Prospective (cohort) studies</td>
<td>1.09</td>
<td>SE: 0.047</td>
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<tr>
<td>Case–control studies, population controls</td>
<td>1.15</td>
<td>SE: 0.046</td>
</tr>
<tr>
<td>Case–control studies, hospital controls</td>
<td>1.27</td>
<td>SE: 0.091</td>
</tr>
<tr>
<td>All observational studies</td>
<td>1.14</td>
<td>SE: 0.031</td>
</tr>
<tr>
<td>Trial designs (Beral et al., 2002)</td>
<td>1.27</td>
<td>1.03–1.54</td>
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In the USA and Western Europe, 90% of these cancers are carcinomas of surface epithelial–stromal origin, whereas in Japan a significantly higher proportion (20%) of the cancers are malignant germ cell tumours. The incidence of ovarian carcinoma increases steadily with age. Two factors consistently associated with a reduced risk of the disease are high parity and OC use (WHO Classification on Pathology and Genetics, 2003). Several dietary factors have been related to ovarian cancer, but no definitive association has been established (American Institute for Cancer Research/World Cancer Research Fund, 2002). The protective effects of pregnancies and of OC suggest a direct role for ovulation in causing the disease. The mechanism which links a reduced rate of ovulations with malignant transformation was suggested to be a decrease in the number of small cysts which appear after ovulation, since most ovarian cancers are cystic lesions. Convincing evidence for this is lacking, however.

Histologically, surface epithelial–stromal tumours are the most common neoplasms of the ovary. They derive from the ovarian surface epithelium or its derivatives and occur in women of reproductive age and beyond. They are histologically composed of one or more distinctive type of epithelium, admixed with a variable amount of stroma. Their biological behaviour varies with histological type.

Because 50–60% of non-mucinous ovarian carcinomas have estrogen receptors (van Doorn et al., 2000), a relationship between HRT and occurrence of ovarian carcinoma is possible in principle (WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1988). A recent review of 20 pertinent studies (Risch, 2002) reached no satisfactory conclusion, as all studies differed in size, outcome and exposure, so that no reliable comparison is possible. Five studies described a slightly increased risk associated with HRT (Whittemore et al., 1992; Negri et al., 1999; Rodriguez et al., 2001; Gambacciani et al., 2002; Lacey et al., 2002), whereas 15 did not. As in the case of endometrial carcinoma, the question is again whether these findings are due to induction or to a previously undiscovered ovarian carcinoma which becomes apparent under therapy. Currently no increased risk of ovarian cancer associated with HRT use can be assumed, because the evidence is inconclusive.

Interestingly, OC use is associated with a decreased risk of both ovarian and endometrial cancer (Royer et al., 2001; International Agency for Research on Cancer, 2003), even after discontinuation for as long as 10–15 years. This may be due to a reduction of ovulatory events rather than to a direct effect. The reason why HRT apparently does not prevent ovarian or endometrial cancer may also be a change in the baseline conditions in the patients involved. In general, perimenopausal women tend to have less proliferative endometria and less frequently ovulating ovaries.

HRT and colorectal carcinoma
Colorectal carcinomas vary considerably throughout the world, being one of the leading cancer sites (~8.5% of all new cancers) in the developed countries (World Health Organization, 2000). These cancers are associated with dietary and genetic factors (American Institute for Cancer Research/World Cancer Research Fund, 2002). Genetic susceptibility ranges from well-defined inherited syndromes, e.g. familial adenomatous polyposis, to ill-defined familial aggregations. Current data suggest two main tumorigenetic mechanisms: a mutational pathway, which involves the inactivation of tumour suppressor genes such as APC, and a microsatellite instability pathway exemplified by the syndromes of hereditary non-polyposis colon cancer (HNPCC).

All studies have shown a reduced risk of colon cancer with HRT (Herbert-Croteau, 1998; Gambacciani et al., 2002; Writing Group of the Women’s Health Initiative, 2002). This permits the conclusion that HRT can be given to patients with colon cancer. However, the pathogenetic mechanisms of estrogen action in colon cancer are unclear.

The dynamics of colon cancer development are very similar to those of the gynaecological tumours described above. It may take 10 or more years for a colon cancer to become invasive (Polyak et al., 1996). One explanation for the reduction in risk is that estrogen may retard the last step of progression from adenoma (‘polyp stage’) to adenocarcinoma (‘invasive growth’) (Lacey et al., 2002). The estrogen receptor genes of colonocytes are normally in a methylated, inactive state. Any estrogen-mediated demethylation may be instrumental in the observed reduction of risk (Issa et al., 1994). The HRT data are consistent with those for OCs, which also show lower colon cancer risk (Grodstein et al., 1999).

HRT and breast cancer
Some observational studies have been interpreted as suggesting a small but significant increase in the risk of breast cancer in women using estrogen or estrogen plus progestin therapy (Table I) (Colditz et al., 1995; Collaborative Group on Hormonal Factors in Breast Cancer, 1996, 1997; Magnusson et al., 1999; Schairer et al., 2000; American Institute for Cancer Research/World Cancer Research Fund, 2002; Endogenous Hormones and Breast Cancer Collaborative Group, 2002; Hankinson and Hunter, 2002; Porch et al., 2002; La Vecchia and Franceschi, 2003; Olsson et al., 2003; Brekelmans, 2003; Li et al., 2003). A collaborative re-analysis of data from 51 epidemiological studies dealing mainly with estrogen-only substitution (~80% of the included studies) showed an overall relative risk of breast cancer of 1.14 when HRT users were compared with never-users (Table II). Although small, this difference is statistically significant due to the large numbers of women included. From this, the authors estimated that an additional six cases per 1000 women treated with HRT would occur over a period of 10 years compared with non-treated groups (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). The WHI study found an overall risk of 1.24 of breast cancer when comparing HRT users against placebo users [hazard ratio (HR) 1.24; 95% confidence interval (CI) 1.01–1.54]. This group estimated eight additional cases for 10 000 women-years for conjugated equine estrogen (CEE) with medroxyprogesterone (MPA), which corresponds to the results of the collaborative re-analysis (Writing Group for the Women’s Health Initiative Investigators, 2002; Chlebowski et al., 2005).
et al., 2003). The Million Women Study (MWS) observed a relative risk of breast cancer in HRT users of up to 2.0 (Million Women Study Collaborators, 2003). None of these studies has conclusively ruled out various sources of bias. Most studies which have investigated mortality have shown improved breast cancer survival in women under hormone therapy (Willis et al., 1966; Hankinson et al., 1996; Sellers et al., 1997), possibly due to early diagnosis. The MWS showed a slightly increased risk of death for current users of HRT only after ex-users were excluded.

The main pathophysiological issues regarding the WHI and MWS studies [with average follow up of 5.2 years (Chlebowski et al., 2003), and 1.2 years from recruitment to breast cancer diagnosis (Million Women Study Collaborators, 2003), respectively] relate to the increased breast and endometrium cancer risks after relatively short periods of use and a decreased risk immediately after discontinuation. This constellation argues against any cancer-initiating effects as a basis for the associations found.

Dynamics of proliferative breast disease

The exact pathogenetic mechanisms of breast cancer initiation and/or promotion are still poorly understood (Olsson et al., 1996; Adami et al., 1998; Hofseth et al., 1999; Li et al., 2000; Wiseman, 2000; Brekelmans, 2003). Therefore, no firm causal conclusions can be established from the associations found between risk factors, including hormone use, and breast cancer.

Hormones may well influence the progression of breast cancer at any time from the ‘primordial’ mutation to tumour diagnosis several years later (Anderson et al., 1989; Cutuli et al., 2001). The pathophysiological prerequisite for the appearance of cancer in menopausal and post-menopausal women and its association with hormone use is the presence of active estrogen receptors in the respective target tissues. Unfortunately, none of the studies which form the current view on the risk associated with HRT incorporate biochemical or immunopathological data on tumoral levels of estrogen receptor expression. Such information might have clarified some of the more troublesome observations made in these studies. The main issue these studies fail to resolve is whether the apparent associations are due to the facilitated detection of pre-existing small carcinomas growing more rapidly under HRT stimulation or to de novo malignant breast tumours brought about by an increased frequency of initiating mutations.

The tumour doubling time (TDT) is a useful concept for the elucidation of the duration of the pre-diagnostic stage of breast cancer and thereby its clinical course. It is defined as the time required for a tumour volume or cell number to double once, also referred to as net cell generations (Spratt et al., 1995). TDT is a function of many variables, encompassing the rate of cell division, the proportion of cells actively dividing, the rate of apoptoses, angiogenetic potency, the proportion of tumour composed of cells as opposed to fibrotic tissue, the intermitotic interval, the tumour burden, rates of desquamation, tumour dormancy and effects of therapy. This explains why estimations of TDT in breast cancer have varied. For early breast cancer, many experimental studies reported a median TDT of 40–128 days (Spratt et al., 1977; Shackney et al., 1978; Spratt and Spratt, 1985). Gershon-Cohen et al. (1963) reported that the average TDT was 128 days in patients with negative axillary node involvement and 85 days in patients with positive axillary node involvement. In addition, it appears to be relevant whether the TDT is being measured in early breast cancer or in late breast carcinoma. In a comprehensive study on this subject, Shackney et al. (1978) have shown that very early breast cancer has a mean TDT of 25 days, whereas late breast cancer has a mean TDT of 129 days. The difference in mean TDT in early and late breast cancer is statistically significant (P < 0.0001), providing convincing evidence for growth retarding processes in advanced human tumours, which is known as Gompertzian growth (Gompertz, 1825; Chabner and Longo). Another study shows that TDT of primary breast cancer varies from 23 to 209 days for early lesions, but in advanced lesions it may exceed 500 days (Haskell, 1985). Taken together, the current data show that a median TDT of 50–100 days can be assumed (Spratt et al., 1995).

There is general acceptance that 30–35 tumour doublings are required to achieve a tumour size of 1 cm diameter. This corresponds to 10⁷ cells, while a single tumour cell has an approximate volume of 10⁻⁶ mm³ (Spratt and Spratt, 1985). A size of 1 cm is more or less the smallest lesion to be diagnosed in the clinic. Assuming a median TDT of 50–100 days, a single malignant tumour cell requires ~1750–3500 days to grow to a clinically and/or mammographically detectable cell mass (Haskell, 1985). This means that on average, 5–10 years have passed from tumour initiation in a single cell to the diagnosis of a cancer consisting of 10⁷ cells. This calculation would only be true if every daughter cell from each generation would survive, which is not the case. It does not consider the cell loss by death and shedding of the tumor cells during the first 30–35 generations (Spratt et al., 1995). Further, there are no exact data on how often and for how long an invasive cancer goes through the non-invasive pre-cancerous stage of a carcinoma in situ (CIS) which will further prolong the period from initiation of the cellular alterations to detection. In reality, the time from initiation to a clinically relevant tumour might be much longer than 5–10 years.

Compared with highly aggressive, rapidly dividing tumours, breast carcinomas detected in association with HRT are mostly well differentiated, showing a relatively low mitotic rate. The majority of invasive ductal and tubular (grade 1) breast cancers, 60 and 90%, respectively, are estrogen receptor positive. These tumours may be influenced by HRT, but are unlikely to grow fast enough to become detectable within 1–4 years. In general, the low grade, low malignancy invasive breast cancers are estrogen receptor positive. These usually do not metastasize early and have a good prognosis. They therefore have no significant impact on mortality. Even highly proliferative grade 3 tumours with 50% of the tumour cells in the mitotic phase would take several years to develop from de novo.
These data show that the time between the theoretically possible initiation of malignant breast tumours by HRT and clinical detection is at least 5 years, and presumably 10 years or even longer. All the studies showing associations between HRT and breast cancer are based on far shorter observational periods. Finally, since HRT more or less mimics a physiological situation with low hormone concentrations, there is no biologically or theoretically plausible mechanism which would convey to HRT the capability to initiate the cascade of mutations necessary to induce unlimited growth. Although the data are sparse, the WHI study shows the risk of breast and colorectal cancer beginning to diverge after ~3.5 years, for example (Writing Group for the Women's Health Initiative Investigators, 2002). The rates for placebo and HRT groups are in parallel for the first 3.5 years of follow-up for breast cancer and cross to show an apparent acceleration of breast cancer development among HRT users compared with placebo users. No such phenomenon is observed for colon cancer, which shows a continuous linear acceleration of breast cancer development among HRT users and in situ breast cancer remains the same for both exposure groups (Chlebowski et al., 2003).

All of this indicates that the increased risks reported in the MWS and WHI are more likely to be the result of accelerated growth with attendant earlier detection and not of primary initiation. This raises the question of whether it is an advantage or disadvantage to have early detection of breast cancer due to accelerated growth of small, at present undetectable, but already present breast cancer foci. Although these studies show an increased risk of breast cancer among women taking HRT, the same patients survive longer than women with breast cancer who did not take HRT. This implies a propensity for early detection of breast cancer among HRT users in these studies, indicating not only bias but also a benefit of early breast cancer detection. This observation also supports the notion that the results of these studies are most probably based on discovery, not on cancer initiation by the treatment. In theory, an alternative scenario is that there may be an enhanced discovery in the short term, and induction of cancer in the long term, or that HRT induces a more benign form of proliferation than that found without hormone substitution. The present studies, however, were not designed to resolve such questions.

Not only do the studies show an increase of breast cancer immediately after starting HRT, they also show a decline immediately after the discontinuation of therapy. The immediate decline was found after \( \leq 1 \) year in the MWS (Million Women Study Collaborators, 2003) and \( \leq 5 \) years in the Collaborative re-analysis (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). This observation, if not due to selective detection, implies growth acceleration of present breast cancer and deceleration after HRT is stopped, and again is indicative for a discovery phenomenon rather than an induction process. This is also supported by the failure of these studies to show an increase in CIS. Therefore, if for the sake of the argument the assumption is made that the increased risks in the MWS and WHI are not fully accounted for by bias, then it could be that they are related to enhanced growth with early detection.

The observation that all studies demonstrate an increase in a magnitude expected for menopause at age 55 or 58, coupled with the notion that early menarche and late menopause are associated with a higher risk of breast cancer, provides for an alternative explanation. HRT might simulate hormonal conditions analogous to late menopause. Perhaps there is a population of 'dormant' tumour cells waiting to be propagated into breast cancer cells when HRT is given and which is removed when HRT is discontinued. However, it may be difficult to resolve the conceptual problems concerning 'dormant' cancers on the basis of these very small increases in risk.

Due to their lack of initial diagnostic status, well-documented follow-up and history of prior hormonal therapy, these studies are by design restricted in their ability to address the questions surrounding their rather surprising results.

**Considerations on epidemiological results**

In order to evaluate properly the results of the recent studies (WHI and MWS) which investigate the associations of HRT use with cancers in post-menopausal women, it is important to understand their limitations (Braendle and Kuhl, 2003). Although the WHI study was conceived as a randomized controlled trial, its results must be interpreted like those of an observational study for a number of reasons (McDonough, 2002; Machens and Schmidt-Gollwitzer, 2003; Shapiro, 2003). First, after randomization, the women were at liberty to decide whether they continue their assigned treatment, or whether they undergo diagnostic procedures or not. This means that the WHI is prone to the same issues of selection bias as any other observational study. Secondly, the WHI study had a 45% unblinding rate among HRT recipients, so that almost half the women were aware of their treatment regimen. This compounds the issue of self-selection for diagnostic procedures. Thirdly, several warnings were sent about the detection of increased risks of myocardial infarction, stroke and pulmonary embolism in the course of the study, but the participants were asked to continue to use their medication. This introduces biases which are unlikely to occur in most observational studies which do not allocate treatments. The WHI study is not compatible with a randomized placebo-controlled situation, because neither exposure nor the discovery of outcomes were standardized, so that its results are those of an observational study with all attendant limitations. The MWS is a volunteer study of women invited to breast cancer screening, so that it is even more selective than the WHI and has many more formal problems. From the perspective of an epidemiologist, neither the size nor design of these studies lends their results preference over those of other observational studies.

Most importantly, neither of these studies contained standardized clinical or pathology diagnostic modules, nor did they consider previous use of hormones. These components must be included in any future study which wishes to address
hysterectomized women, there was no breakthrough bleeding and the unblinding rate was only 1.7% (100 in the estrogen and 83 in the placebo group), in contrast to 45% among women who received combined estrogen–progestin therapy. Some power is lost in this study component because 53.8% of the women had already stopped taking study medications at the time of study termination. The WHI authors state in their abstract that this possible reduction in breast cancer risk requires further investigation.

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Addendum

A further publication from the WHI that has appeared after the Kloster Andechs Workshop was held (Anderson et al., 2004). In this publication, no increase in the risk of breast cancer was found among women who used conjugated estrogens only (HR 0.77; 95% CI 0.59–1.01). As the accompanying editorial points out, these results differ markedly from the findings of the HERS and WHI estrogen plus progestin trials (Hulley and Grady, 2004). Although the authors of the editorial suggest that these results indicate that estrogen alone has advantages over estrogen plus progestin for treating postmenopausal women, not for the prevention of diseases, but for the short-term treatment of menopausal symptoms, they ascribe the breast cancer results to chance.

However, the alternative explanations of these findings are that unopposed estrogens may not increase the risk of breast cancer, or that they might, as the WHI authors themselves speculate (Anderson et al., 2004), be associated with a possible reduction in breast cancer risk. In some aspects, this study component, which includes data on 10793 women with prior hysterectomy, is methodologically stronger than the other WHI components. The comparisons in this estrogen-only arm of the WHI were confined to the issues of plausibility arising from the results of the currently available studies.

Conclusion

The currently available information from epidemiological studies concerning the association between HRT use and cancer occurrence is controversial and leaves many questions unanswered. Any future epidemiological study on breast cancer should require the pathological examination of the breast specimens so that a correlation between epidemiology and morphology can be made. It needs to address the phenomenon that risk increases with HRT and then decreases with cessation of HRT. Information on the pharmacological levels achieved under HRT would also be valuable. For other gynaecological cancers, it is necessary to have a status of the endometrium before therapy, which can be done with uterus sonography. The diagnosis of ovarian cancer can be difficult and should follow standardized formats as HRT use might increase the probability of diagnosis of ovarian cancer. In addition, the various studies have yielded inconsistent results. Given the current evidence of early risk after HRT, marker studies are needed. Further, and in extension of this, genotype studies which identify populations at increased risk are advisable. The issue of colon cancer is also of interest, as the mortality is higher than that for breast cancer, and there seems to be no public discussion on the potential benefit of HRT on this. Lastly, the ‘state-of-the-art’ of epidemiological studies should in the future be defined by a close cooperation with clinicians, pathologists and members of related disciplines in order to meet the requirements of evidence-based medical research and to avoid creating anxiety by overemphasizing the risk for women using HRT.
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