

Effects of estrogens and hormone replacement therapy on breast cancer risk and on efficacy of breast cancer therapies

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Abstract

This review summarises preclinical and clinical data on effects of endogenous and exogenous estrogens on probability of breast cancer diagnosis, and on the course and efficacy of breast cancer therapies. The data indicate that higher endogenous estrogen exposure (e.g. pregnancy, early menarche and late menopause, estrogen levels in future breast cancer patients, obesity) or exogenous estrogens (oral contraceptives; hormone replacement therapies) may be associated with an increased probability of breast cancer diagnosis. However, there is little evidence that estrogens have deleterious effects on the course of breast cancer. Moreover, increased incidence of breast cancer diagnosis after prolonged hormone replacement therapy (HRT) use seems to be associated with clinically less advanced disease. In studies assessing both diagnosis and mortality, HRT is frequently associated with reduced mortality compared to never users. The interaction of progestagens and estrogens on the probability of breast cancer diagnosis is complex and dependent on type of progestagens and regimens employed. Efficacy of current treatment modalities for breast cancer (surgery, irradiation, adjuvant therapy or chemotherapy) is not negatively influenced by estrogens at concentrations considerably higher than those attained with current HRT preparations. Although it cannot be excluded that estrogens increase the probability of breast cancer diagnosis, available data fail to demonstrate that, once breast cancer has been diagnosed, estrogens worsen prognosis, accelerate the course of the disease, reduce survival or interfere with the management of breast cancer. It may therefore be concluded that the prevalent opinion that estrogens and estrogen treatment are deleterious for breast cancer, needs to be revisited. However, results of ongoing prospective, randomised clinical trials with different HRT regimens in healthy women or breast cancer survivors are needed to provide more definite conclusions about risks and benefits of HRT. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

A common opinion is that estrogens may be detrimental in breast cancer, in respect both of the risk to develop breast cancer and of the prognosis once breast cancer has been diagnosed. The majority of breast cancers are considered to be due to sporadic events but about 10% are may be due to inherited genotypes. Estrogens are generally felt not to play a role in the malignant transformation, since experimental data show a lack of mutagenicity of estrogens. There is, however, ample evidence that estrogens may play a role in the promotion of tumour proliferation and that estrogens influence the expression and transcription of many growth factors, oncogenes and other factors involved in the physiological cell cycle [1–5]. These activities of estrogens on normal cells are also likely to play a role in the growth of breast cancer cells. That estrogens stimulate the proliferation of primary breast cancer cell cultures or cancer-derived cell lines also clearly points to the promotional effects of estrogens [2,6]. With respect to the process of metastasis, estrogens have been shown to affect the expression of membrane degrading enzymes and factors involved in angiogenesis [7–10]. In addition, the requirement of estrogens to support the growth of human estrogen receptor (ER)-positive breast cancer cells in nude mice provides further evidence for the estrogenic promotion of tumour proliferation [11].

On the assumption that these actions of estrogens in experimental conditions also play a role during the development of breast cancer in humans, continued exposure to estrogens, once breast cancer is diagnosed, would be to put ‘fuel on the fire’. Estrogens would also be considered incompatible with the anti-estrogenic treatment which is often instituted as adjunct to surgery and radiotherapy. Therefore, hormone replacement therapy (HRT¹) is today considered to be con-

traindicated for breast cancer survivors, and once a tumour is diagnosed, an ongoing treatment with HRT is to be discontinued.

In contrast to this general belief, there are also indications suggesting that estrogens may be indifferent or even favourable with respect to breast cancer development and prognosis. One indication is that the presence of ER-positive and/or progesterone receptor positive cells in breast cancer patients is usually associated with a higher differentiation and a lower metastatic potential of the cancer [12]. Observations in nude mice show that ER-positive human breast cancer cells are less metastatic compared to ER-negative cancer cells and that transfection of the estrogen receptor into ER-negative breast cancer cell lines decreases the metastatic and invasive potential [7,8,10].

It would, therefore, appear that there are both experimental and clinical data challenging the prevalent negative opinion on the relationship between estrogens and breast cancer. Recent clinical data also support the view that this opinion may need to be revisited and that the risk/benefit ratio of HRT has to be put into proper perspective [13–21].

In this paper, we review both experimental and clinical data on the association between endogenous and exogenous estrogens and the probability of breast cancer diagnosis. Relevant data are reviewed on the effects of continued exposure to estrogens on prognosis of breast cancer, once breast cancer has been diagnosed and on the treatments installed.

2. Estrogens and breast cancer risk

Findings related to endogenous estrogen levels, pregnancy and use of combined oral contraceptives are discussed before addressing the issue of breast cancer and HRT. It should be realised that a breast cancer is usually present for many years (as long as 5–10 years) before it is clinically

¹ HRT is used as a general term, without differentiating between estrogen only (E) and estrogen combined with a progesterone (E + P) replacement therapy.

diagnosed (theory of the ‘dormant malignant cell’). This implies that breast cancer cells, during their subclinical period, are likely to have been exposed for a considerable time to endogenous and exogenous sex hormones. It should also be realised that the opinion that estrogens have an adverse influence on the risk of breast cancer has so far precluded prospective, randomised clinical studies with HRT in women at high risk for development of breast cancer or in breast cancer survivors. Trials with HRT in breast cancer survivors have been proposed [13,16,18,22] and are ongoing in USA, Sweden and UK, but have not yet been completed. Such studies may ultimately provide further evidence on the association of exogenous estrogens and breast cancer.

2.1. Endogenous estrogen levels and breast cancer risk

A number of prospective studies in postmenopausal women showed that increased probability (two to five times) of breast cancer diagnosis later in life is associated with slightly higher levels of estrogens (about 6.8–12 pmol/l higher; the estradiol levels being in the top third or fourth part in the total population studied) measured in blood samples collected 3–8 years before diagnosis [23–28]. In addition to estrogens, also the plasma levels of other hormones including testosterone are slightly increased. The observed estradiol concentrations in all studies are low compared to those in pre-menopausal women (100–2000 pmol/l) and in women on HRT (200–1000 pmol/l). In our opinion an alternative explanation for the association between the slightly increased levels of estrogens and increased probability of breast cancer diagnosis may be that breast cancer cells were already present in the patients at the time of the blood sampling and that the tumour cells are able to enhance the concentration of estrogens. It has been demonstrated that breast tumour stromal cells may indeed contribute to estrogen production [29–31]. These small increases in estrogen levels may, therefore, be more likely a consequence of the ‘spill-over’ of these locally-produced estrogens into the circulation. Prolonged exposure to much

higher endogenous estrogens (e.g. as in women with early menarche and late menopause) is associated with increased probability of breast cancer diagnosis and oophorectomy at an early age decreases this risk [32,33]. With respect to obesity, the situation is more complex. Due to peripheral aromatization in fat tissue, obesity is associated among other things with increased estrogen levels. Obesity has been associated with a lower probability of diagnosis of some breast cancers in premenopausal women, whereas after the menopause it is usually found to confer with a higher risk [34]. It remains to be established, however, whether the risk of breast cancer is associated also with other factors than estrogen levels (e.g. insulin-like growth factors, ovulatory disturbances).

The observations above support the hypothesis that (slightly) higher levels of endogenous estrogens in postmenopausal women may be associated with a higher probability of breast cancer. Whether the very small increase in estradiol levels as observed in some studies are a consequence of or a cause for breast cancer remains to be established. However, it should be noted that the prognosis of breast cancer diagnosed in premenopausal women (who have much higher endogenous estrogen levels) is more often better than in postmenopausal women when matched for stage at diagnosis [35].

2.2. Pregnancy and breast cancer

A number of observations illustrate the complex association between pregnancy with its very high levels of endogenous steroid hormones, e.g. estradiol > 40 000 pmol/l and the probability of breast cancer. Pregnancy, in particular pregnancy at early age, and parity are associated with a decreased probability of breast cancer diagnosis compared to the increased probability in nulliparous women. It has also been reported that pregnancy transiently increased the probability for breast cancer diagnosis after giving birth, with a reduced risk later in life [36]. Women who have been pregnant 1–2 years before or are pregnant at the time of their breast cancer diagnosis do not appear to have a worse prognosis than non-pregnant women when matched for age and stage

[15,37]. However, increased mortality from breast cancer diagnosed during pregnancy in young women (20–29 years of age) has also been reported [38]. Women becoming pregnant after treatment for their breast cancer have been reported to have similar or even improved prognosis in comparison with breast cancer survivors who subsequently never become pregnant [35].

The pregnant state has many effects on endogenous hormones. Levels of estrogens such as estrone, estradiol and estriol, levels of progesterone and other hormones are elevated (up to 1000 × the mid-cycle levels). It has been suggested that the differentiation of breast ductal tissue induced after a full term pregnancy renders the breast less susceptible for the development of malignancies [5,39]. This has also been proposed as an explanation for the observation that full-term pregnancy at an early age protects against breast cancer later in life. These observations suggest that very high levels of estrogens in combination with other hormones are not necessarily associated with an increased diagnosis or a worse prognosis of breast cancer. Whether or not a putative deleterious effect of estrogens is counteracted by other factors elevated during pregnancy is still an open question.

2.3. Oral contraceptives and breast cancer

A re-analysis [40] of the individual data of 53 297 women in 54 epidemiological studies on oral contraceptives (OC) and breast cancer showed that there is a small increase in the relative probability of having breast cancer diagnosed in current users: 1.24 (95% confidence limits: 1.15–1.39). This increase seemed not to be related to the duration of use, age at first use, and the dose and type of hormones in the OC preparation. Some association was found between an increased probability for breast cancer diagnosis and OC use at an early age before the first pregnancy. The OC preparations were predominantly a continuous combination of different doses of an estrogen and a progestagen during about 3 weeks followed by a pill-free interval of 1 week. The levels of ethinylestradiol, a considerably more potent estrogen than the estrogens

commonly used in HRT (e.g. estradiol or conjugated equine estrogens (CEE)), ranged from 30 to 500 pmol/l. The increased probability of breast cancer diagnosis gradually declined to that of non-users during the 10 years after cessation of OC use.

An intriguing observation was that breast cancers diagnosed in current or past OC-users (up to 20 years after use of OC) were more likely to remain localised to the breast, to show fewer metastases and to be clinically less advanced than those diagnosed in never-users. These less advanced cancers were associated with an increased survival. Two reports have shown that use of OC within 1 year of breast cancer diagnosis does not diminish survival period after diagnosis [41,42]. Beral [40] concluded that it is not possible to infer from her re-analysis whether the increased probability of breast cancer diagnosis is due to an earlier diagnosis in ever-users or to the biological effects of OC or even to a combination of reasons.

2.4. HRT and the incidence of breast cancer

Only one small, prospective, randomised clinical trial has assessed the effects of HRT on the incidence of breast cancer [43,44]. One group of 84 postmenopausal women (mean age 55 years at entry) received 2.5 mg CEE per day and 10 mg medroxyprogesterone acetate (MPA) during 7 days of each month. The control group ($N=84$) received placebo. After 10 years, some women switched to other, lower dose CEE and progestagen regimens or to placebo. After 22 years, a total of six breast cancer patients had been diagnosed in the never HRT group, whereas no cases were found in the ever-HRT group; the difference being statistically significant. This study also found that ever-HRT use reduced the overall mortality [43,44]. These results should be viewed in the light of the very limited size of the study, but they nevertheless suggest no deleterious effects of this long-term, high estrogen/progestagen regimen on the incidence of breast cancer.

Many individual epidemiological studies on breast cancer and HRT have been re-analysed [45]. This re-analysis of the individual data of

52 705 women from 51 epidemiological studies found that the probability of having breast cancer diagnosed is increased by 2.3% per year of HRT use; (95% confidence limits 1.1–3.6%). For each year the menopause is delayed a similar increase in probability has been found: 2.8% (2.1–3.4%). This implies that the cumulative number of breast cancers diagnosed per 1000 women raises from 18 at the age of 50 years to 63 at 70 years if the women did not use HRT, and from 18 to 65, 69 and to 75 if they started HRT at the age of 50 and continued to use it for 5, 10 and 15 years, respectively. Five or more years after cessation of HRT, there is no significant excess of breast cancer diagnosis overall or in relation to duration of use. The stage of breast cancer diagnosed in ever-HRT users tended to be clinically less advanced. The majority of the observations has been made with oral preparations (predominantly with CEE) and this comprehensive re-analysis does not allow conclusions on dose nor on type of HRT. However, this re-analysis gives no reason to suspect that the probability for breast cancer diagnosis is different for specific types of HRT, route of administration or addition of a progestagen (see also section on progestagen addition). Two recent reports provide evidence that HRT users were younger at the time of their breast cancer diagnosis than women who never used HRT, thus supporting the hypothesis that estrogens accelerate the growth of pre-existing tumours [46,47]. Moreover, another report showed that postmenopausal women with a history of proliferative breast disease were at increased probability of a diagnosis of invasive breast carcinoma [48]. This increase depended on the histological classification of the benign breast disease, whereas the use of HRT did not significantly elevate the probability of diagnosis of invasive breast carcinoma in women with previous histologically defined benign breast disease. It was, therefore, concluded that HRT is not contraindicated in these women [48]. The results from the re-analysis by Beral [45] and other recent reports thus support the current belief of a relationship between use of HRT and an increase in probability for breast cancer diagnosis. However, these data do not allow a conclusion on the causality of the relationship. There is insufficient

information on the frequency of mammography or clinical examination which could falsely elevate the calculated risk and account for the increase in clinically less advanced cancers in HRT users.

2.5. HRT and prognosis of breast cancer

Since it takes many years for breast cancer to become clinically manifest, it is likely that breast cancer patients who are recent or past HRT users actually have been exposed to estrogens with or without progestagens before their disease became clinically manifest. In some studies the effects of HRT on both prognosis (mortality) and the probability of breast cancer diagnosis was investigated (Table 1)[49–63]. Whereas most of these studies also showed an increased probability of breast cancer diagnosis (see above), these same studies often indicated that the prognosis was considerably better for breast cancer patients on HRT than for never-HRT users (Table 1). Only two reports [49,50] showed a higher mortality in ever-HRT users. In a nested case-control study [51] among the participants in the Nurses' Health study the relative risk of dying from breast cancer tended to be decreased in current and past HRT users relative to never-users (0.76 (0.56–1.02) and 0.83 (0.69–1.09), respectively). This favourable effect tended to decrease with long-term use (> 10 years). These results do not seem to be in line with the results previously reported by Colditz [49] on the same study and population group (Table 1); an explanation has not been provided. In a recent analysis of ERT and breast cancer survival in a large screening study [52], it was concluded that the group of patients with breast cancer who were using estrogens at the time of diagnosis experienced reductions in breast cancer mortality which waned with the time since diagnosis. Cobleigh [17] found a better prognosis in patients on HRT < 1 year before diagnosis of their breast cancer compared to non-users.

A better prognosis of breast cancer in HRT users is compatible with the findings in the reanalysis study that cancer diagnosed in ever-users tended to be clinically less advanced than those diagnosed in never-users [45]. Similar findings have been found in epidemiological studies with OCs [40].

Table 1
Relative risk of breast cancer diagnosis and mortality in HRT users compared to never-users in case-control and cohort studies^a

Source	Design	Cases	RR of mortality of ever-HRT	RR of diagnosis in ever HRT
Bergkvist [53]	Cohort	261	Overall: 0.68 (0.52–0.87)	Overall: 1.1 (1.0–1.3)
Persson [54]	Same cohort	Mortality: 102; Incidence: 634	CEE/E2: 0.5 (0.4–0.7) E2+LNG: 0.6 (0.4–0.9) E3: 0.5 (0.4–0.8)	CEE/E2: 0.9 (0.8–1.1) E2+LNG: 1.3 (1.1–1.4) E3: 0.9 (0.7–1.0)
Schairer [55]	Same cohort	Mortality follow-up 10 years	Overall 0.72 (0.58 ± 0.89)	No data presented
Gambrell [56]	Cohort	50	0.53	
Gambrell [57]	Cohort	256	10 year mortality reduced from 50 to 30% in HRT users	0.7 (0.5–1.1) 0.3 (0.1–0.8) 0.8 (0.5–1.7)
Hunt [58] (Vessey [59])	Cohort	31	Years use <4 years: 0.38 (0.0–1.07) 5–9 years: 0.74 (0.27–1.21) >10 years: 0.97 (0.47–1.47) Total: 0.76 (0.45–1.06)	E only: E + P: P only:
Henderson [60]	Cohort	Not specified	0.81	No data presented
Criqui [61]	Cohort	42	0.73 (0.44–1.22)	No data presented
Colditz [49]	Cohort	359: Current users > 5 years: Current users < 5 years: Current users (all): Past users:	1.45 (1.01–2.09) 0.99 (0.66–1.48) 1.14 (0.85–1.51) 0.80 (0.60–1.07)	CEE alone 1.46 1.32 (1.14–1.52) 1.41 (1.15–1.74)

Table 1 (Continued)

Source	Design	Cases	RR of mortality of ever-HRT	RR of diagnosis in ever HRT
Folsom [62]	Cohort	468 cases per 12 9149 persons years	Overall mortality 0.75 (0.48–1.17) HRT use: ≤5 years: 0.79 (0.58–1.08) > 5 years:	HRT use: ≤5 years: 1.45 (1.03–2.06) > 5 years: 1.12 (1.12 (0.92–1.60))
Ettinger [50]	Case-control Study	232/222	1.89 (0.43–8.36) breast cancer 0.85 (0.46–1.58) all cancer	No data presented
Willis [63]	Cohort	422 373/1469 cases	0.84 (0.75–0.94) 0.59 (0.40–0.87), menopause <40 years	No data presented
Schairer [52]	Case-control	2614/486 cases/deaths Node negative: follow up < 12 years > 12 years: Node positive: follow up < 4 years: > 4 years	0.5 (0.3–0.8) 2.2 (0.9–5.2) 0.5 (0.3–0.8) 1.1 (0.7–1.7)	No data presented

^a RR, relative risk. The RR for mortality from breast cancer in never-HRT users is 1.0; CEE, conjugated equine estrogens; E+P, estrogen (E)-progestagen (P) combinations (type and regimes not specified); LNG, levonorgestrel (250 µg/d for 10/21 days) in combination with 2 mg/g estradiol (E2); ERT, estrogen replacement therapy; HRT, hormone replacement therapy; E3, estro; 95% confidence limits are between brackets (). The overall mortality as reported by Folsom, 1995 also includes mortality from other causes than breast cancer.

Whilst these findings could be explained by early detection of breast cancer due to better surveillance or healthy-user effects [20,35,64–67], some evidence shows that HRT may also have direct effects on breast cancer prognosis. Table 2 summarises the studies that have examined the characteristics of breast cancer diagnosed in HRT and non-HRT users. A prospective study [64] in a breast cancer screening unit (minimising surveillance bias) showed that women on HRT had lower grade breast cancer than breast cancer patients who did not use HRT. The lower grade in HRT users was confirmed by others [47,68]. Other studies [65,66,68] have reported that women taking HRT have a lower probability of being diagnosed with large tumours or positive axillary lymph nodes, whereas some studies did not show a difference [46]. Holli et al. [66] found a lower proliferation rate in the tumours from current users, indicating a lower aggressiveness of the tumours. Cobleigh [46] found in the specific population of current HRT users with ER positive cancer a higher percentage of women with a high S-phase. O'Connor [68] reported a difference in the expression of immunohistochemical markers (Bcl-2, p53 and E-Cadherin) between HRT and non-HRT users, whereas no difference in the expression of ER or PR was found.

Magnusson et al. [65] found, compared to never-users, that the reductions in probability of breast cancer diagnosis were more pronounced in women receiving E + P combinations than in all HRT (E and E + P) users. They also found a lower number of deaths due to breast cancer in HRT users compared to non-HRT users and did not detect a difference between the expression of ER or PR. The authors conclude that their findings may reflect a less aggressive biological behaviour of breast cancers in women receiving E + P compared to all HRT users or may in part be explained by the earlier detection of the tumours in these women. It remains to be determined whether (surveillance) bias explains the difference between the all HRT and the E + P combination groups or differential biological effects of estrogens or the E + P combination. Finally a recent paper by Capstur [69] provided evidence that the breast cancers found in patients

taking HRT usually were of a lower aggressive and less invasive type with a more favourable histology and prognosis.

The observations described above support the notion that compared to never use, HRT use is associated with more restricted, clinically less advanced, and histologically distinct breast cancer and thus with a more favourable prognosis. The finding that breast cancer diagnosed in premenopausal women (with their higher endogenous estrogen levels) is associated with a better prognosis than breast cancer diagnosed in age- and stage-matched postmenopausal women [35], also supports this argument.

Taken together, the data presented in this section do not point to an adverse effect of HRT on death due to breast cancer and on the prognosis of the disease.

2.6. HRT and recurrence in breast cancer survivors

Clinical studies of breast cancer survivors who have been prescribed HRT may provide an indication on the effects of HRT on breast cancer prognosis. An overview of available studies [14,16,22,70–81] is presented in Table 3. Although the number of breast cancer survivors treated with HRT in these observational studies is small and selection bias may interfere with valid conclusions, it should be noted that none of these studies demonstrated an increase in cancer progression. When the results of all studies (except those reported by Dew [75]) are combined the following recurrences can be calculated: 59/953 (6.2%) and 88/600 (29.3%) in HRT and no HRT users, respectively. However crude, these data appear to indicate that HRT seems to be associated with a reduced recurrence of breast cancer and with an improved prognosis. This is in line with the reduced (overall) mortality found in the studies by Eden [16], Dew [75] and Beckman [76].

On the other hand one anecdotal study [82] on four breast cancer survivors has reported that cessation of HRT halted the progression of breast cancer recurrence. In an ongoing study in the UK, 100 women with early stage of breast cancer were randomised to receive HRT or no treatment. Only

Table 2

Examination of breast cancer characteristics in HRT users compared to never-users in case-control and cohort studies^a

O'Connor [68] Author	number of patients Study design number of patients	Tumor size (>20 mm) Parameter assessed	29/98 (29.6%) HRT users	41/133 (30.8%) No HRT user	positive cancers were five times Remarks
Harding [64]	Prospective screen <i>N</i> = 108 HRT; <i>N</i> = 325 no HRT	Grade I: Grade II: Grade III:	45% 44% 10%	20% 64% 16%	Data from breast cancer screening unit
Holli [66]	Cohort; <i>N</i> = 477 total <i>N</i> = 171 HRT	Tumor size (>20 mm): Node positivity: % in S-phase	RR: 0.47 (0.3–0.7) RR: 0.73 (0.5–1.2) 7.8%	 10.3%	Past HRT 9.4%
O'Connor [68]	Case-control <i>N</i> = 31 HRT <i>N</i> = 29 no HRT	Tumor size: Grade I: Grade II: Grade III: Node metastases	17 mm 12/31 (39%) 13/31 (42%) 6/31 (19%) 6/23 (26%)	25 mm 4/29 (14%) 16/29 (55%) 9/29 (31%) 11/27 (41%)	HRT versus no HRT have a higher expression of Bcl-2 (87; 79%) and a lower expression of p53 (29; 45%) and E-Cadherin (48%; 72%)
Bilinora [47]	Prospective case-control; <i>N</i> = 140 HRT <i>N</i> = 202 no HRT	Age at diagnosis Tumor size (mm) Grade I: Grade II: Grade III: Node positivity	61.3 years 17.6 mm 28.5% 45.9% 25.6% 29/98 (29.6%)	66.4 years 17.2 mm 26.5% 36.5% 37% 41/133 (30.8%)	
Cobleigh [46]	Prospective cohort <i>N</i> = 142 current HRT <i>N</i> = 165 never HRT	Age at diagnosis: Tumor size (>20 mm) Node positivity: % in high S-phase: ER positive: PR positive:	56.6 years 47/123 (38%) 43/131 (33%) 37/68 (54%) 96/135 (71%) 47/133 (35%)	61.9 years 59/140 (42%) 47/132 (36%) 27/83 (33%) 114/159 (72%) 71/150 (47%)	Current HRT users with ER- positive cancers were five times more likely to have a high S-phase than never users
Magnusson [65]	Prospective case-control <i>N</i> = 121 HRT <i>N</i> = 1468 no HRT	Treatment: Tumor size (>20 mm) Node positivity: ER positive: PR positive:	All HRT 0.7 (0.5–1.1) 0.7 (0.4–1.1) 1.2 (0.8–1.9) 1.1 (0.7–1.9)	E + P: 0.4 (0.2–0.8) 0.5 (0.2–1.0) 0.9 (0.4–1.9) 1.5 (0.70–3.5)	Breast cancer deaths: (6–7 years follow-up); 19/121 (16%) all HRT; 310/1468 (21%) no HRT

^a See Table 1 for legend. ER, estrogen receptor; PR, progesterone receptor; *N* = number.

Table 3
HRT use in breast cancer survivors and recurrence of breast cancer^a

Author	Type of study	Patients per treatment	Stage	Treatment duration (months)	Follow-up duration (months)	Number (%) of patients with recurrence; RR	Remarks
Stoll [70]	Open	65 HRT	III–IV	3–6	>24	0/65 (0%)	
Wile [71]	Case-control	25 HRT 50 no HRT	I–IV I–IV	24–36	24–82	4/25 (16%) HRT at 35 months 2/50 (4%) no HRT at 17 months	
DiSaia [72]	Open	77 HRT	I–IV	1–233	10–425	7/77 (9%) had recurrence	40% on tamoxifen
DiSaia [14]	Case-control	41 HRT 82 no HRT	I–IV I–IV			6/41 (15%) 7/82 (9%)	4 years survival: 69 ± 2% 4 years survival: 46 ± 1%
Powles [73]	Open	35 HRT	I–IV	1–44	1–238	2/35(6%)	
Eden [16]	Case-control	90 HRT 180 no HRT	I–III	3–144		6/90 (7%) 31/180 (19%) RR: 0.4 (0.17–0.93)	All cause deaths: 0/90 HRT; 80/811 no HRT
Eden [74]	Case-control	167 HRT 167 no HRT	I–II I–II	19	88	16/167 (10%) 31/167 (19%)	Partly same as Eden, 1995
Dew [75]	Cohort	167 HRT;	Not staged	3–264			For recurrence: corrected RR, 0.99 (0.40–2.47); deaths: 2/167 (1.2%; HRT); 169/1427 (11.5%; total) previously reported groups included
Peters [79]	Open	56 HRT	I–III?	2–192	1–454	0/56 (0%)	
Decker [80]	Open	114 HRT	I–III	1–210	Not known	7/114 (6%)	
Vassilopoulou [22]	Open	49 HRT	Not known	24–142	46–324	1/49 (2%)	
Bluming [81]	Open	146 HRT	I–III	1–52+	Not specified	4/146 (3%)	
Beckmann [76]	Case-control	64 HRT 121 no HRT	I–IV	6–45	0–60	6/64 (9%) 17/121 (14%)	Deaths: 4 (6%) Deaths: 15 (13%)
Guidozzi [77]	Open 24 HRT	Not known	24–44	32–134	0/24 (0%)		
Ursic [78]	Case-control	21 HRT 42 no HRT	Invasive	3–72	28–180	4/21 (19%) 5/42 (11%)	Deaths: 0 (0%) Deaths: 1 (2.4%)

^a HRT, hormone replacement therapy; RR, relative risk (95% confidence limits).

two women (one receiving no treatment, one HRT for 6 weeks) developed metastatic disease.

In agreement with other authors [14–17,84,85] we conclude that at present the available studies in breast cancer survivors fail to demonstrate adverse effects of HRT on breast cancer prognosis.

2.7. Influence of progestagen addition on breast cancer

The observational studies of the use of HRT and the probability to develop breast cancer generally do not distinguish between the effects on breast cancer by estrogens only or by combinations of estrogen and intermittent or continuous progestagen. It has been suggested that, in combination estrogens and progestagens either increase or alternatively decrease the risk of developing the disease. The observation that maximal mitotic activity in the normal breast has been found in the mid luteal phase until day 24 of the cycle (with its high concentrations of progesterone and estradiol) has been used to imply that progestagens may actually promote breast cancer [3]. However, this increased proliferation does not necessarily suggest malignant transformation since the end result is usually the transformation of the intermediate epithelial cell into a fully differentiated cell capable of secretory activity. As mentioned above, a pregnancy early in life (with among others high levels of estradiol and progesterone) is associated with a reduced incidence of breast cancer later in life which could be explained by the induction of differentiation in breast epithelial cells [39].

Although *in vitro* studies show that progestagen alone may induce proliferation, these observations also show that a continuous combination of estradiol and a progestagen reduces the proliferation of primary breast cell cultures and of various breast cancer cell lines in contrast to the stimulation by estradiol alone [2,6]. In addition, it has recently been demonstrated that progestagens induce apoptosis in breast cancer cell lines [86,87] and affect apoptosis-regulating proteins [88].

Breast tissue is able to concentrate, produce and metabolise estrogens [3], resulting in local estrogen concentrations 10–40 times higher than in the circulation. If one assumes that estrogens may

promote the growth of breast cancer cells, reduction of the local estrogen levels or of the local estrogenic effects becomes interesting. Progestagens have the capacity to down-regulate the expression of estrogen receptors and to decrease the local estrogen concentration in the breast by reducing local aromatases and sulphatases [3,89–91] and by increasing estrogen-metabolising enzymes [1,92]. For these effects the continuous presence of progestagens would be required and this may explain the differences between the continuous and intermittent presence of progestagens as observed *in vitro* (see above [2,6]) and *in vivo* (see below [83,93,95]).

Two case-control studies [83,93] reported intriguing, but non-significant trends towards a lower relative risk with continuous progestagen addition than with intermittent addition (RR compared to non-HRT: 1.38 (1.13–1.68) and 1.41 (0.93–2.13) versus 1.09 (0.88–1.35) and 0.63 (0.26–1.53) for intermittent and continuous progestagen, respectively). On the other hand, Cline et al. [94] have shown increased mitosis in the breast in monkeys receiving HRT. Another variable is the type of progestagen included in the HRT. Although most studies do not allow differentiation between the types of progestagens, in a cohort study of 1150 pre-menopausal women with benign breast disease (thus being at a higher risk to develop subsequent breast cancer [48]), neither overall progestagen use nor the duration of their use was found to be significantly associated with the probability of breast cancer [95]. When the progestagens were classified into their structural categories (19-nortestosterone or C21 pregnane derivatives), 19-nortestosterone derivative use was found to be significantly associated with a lower probability of breast cancer (0.48 (95% confidence interval 0.25–0.90)). In addition, there was a linear trend in the decrease of the relative risk of breast cancer with the duration of use ($P = 0.02$).

2.8. Conclusion

HRT may be associated with a slightly increased probability of having breast cancer diagnosed, but there is little evidence that HRT has deleterious effects on the course and prognosis of breast

cancer. The slightly increased incidence of breast cancer diagnosis after prolonged HRT use seems to be associated with less advanced clinical disease. In studies assessing both the diagnosis and mortality, HRT is also frequently associated with a reduced mortality from breast cancer compared to never-users. The observations may be partly, but not completely attributed to biases. The interaction of progestagens and estrogens in relation to the probability of breast cancer is complex; however, the data do not seem to support the hypothesis that progestagens may increase the probability for breast cancer. The opinion that HRT and estrogens in particular are deleterious for breast cancer needs to be revisited. The American College of Obstetricians and Gynecologists Committee Opinion [96] states that in postmenopausal women with previously treated breast cancer, consideration of HRT is an option but must be viewed with caution. Any possible benefit must be balanced against the possible risks by a thorough explanation of current knowledge to the patients. Obviously, the results of well-conducted, prospective, randomised clinical trials that are ongoing in the USA, Sweden and UK have to be awaited for more definite answers.

3. Influence of estrogens on efficacy of therapies

The current therapies for breast cancer usually include surgery of the primary tumour, irradiation, chemotherapy or hormone therapy. The treatment of breast cancer depends on the stage, extent (node involvement) and nature (receptor status) of the tumour, together with the menopausal status and age of the patient at diagnosis (for review see [17,35,97]). The use of therapies to antagonise or suppress the production of endogenous estrogens is based on the observation about 100 years ago that oophorectomy induced clinical responses in some pre-menopausal breast cancer patients. Later studies have shown that ovarian ablation has a small but significant effect on disease-free interval and overall survival in premenopausal women, the effect being smaller if combined with cytotoxic chemotherapy [98]. Many of the treatment modalities for breast cancer induce estrogen deficiency

symptoms and may precipitate an early menopause in younger patients [15,16,99]. Despite the well-known short- and long-term benefits of HRT and the general lack of efficiency of nonhormonal alternatives in the alleviation of symptoms of estrogen deficiency [85,99], physicians are reluctant to prescribe HRT to breast cancer survivors. Unfortunately, no prospective, randomised clinical studies have yet been published that assess the possible interference of exogenous estrogens with therapies for breast cancer. Several observations, however, on endogenous estrogens and the management of breast cancer and its final outcome exist and are reviewed below.

3.1. Estrogens and tamoxifen

Treatment with tamoxifen is the adjuvant treatment of choice in women with ER-positive tumours [13,16,33,100]. Tamoxifen is a non-steroidal compound with anti-estrogenic effects on breast tissue and brain (gonadotrophins) and estrogenic effect on several other tissues (bone, endometrium). Tamoxifen competes for binding to the ER. Residual estrogens may, on a theoretical basis, be expected to interfere with the favourable effects of tamoxifen. Various observations assess the effects of tamoxifen in the presence of estrogens. Tamoxifen is an effective therapy for breast cancer in both postmenopausal and premenopausal women. In a large randomised trial with tamoxifen in node-negative, ER-positive breast cancer patients it was shown that premenopausal women derived greater benefit from tamoxifen than postmenopausal women [17,100]. The premenopausal women have higher endogenous estrogen levels indicating that tamoxifen retains and has even higher anti-tumour effects in the presence of estrogens. Premenopausal women with intact ovaries treated for breast cancer with tamoxifen frequently show a rise in estrogen levels due to central gonadotrophin stimulation [17,35,101,102]. The estrogen levels during tamoxifen treatment may be four to five times higher than those observed during certain phases of the normal menstrual cycle [17,101,102]. Obviously, this rise has not been found in postmenopausal women. It should be realised that the

current HRT preparations provide estradiol levels (400–800 pmol/l) that are considerably lower than peak estradiol levels during the physiological cycle (1250–1750 pmol/l) or those observed with tamoxifen therapy (4000–5000 pmol/l). Since tamoxifen also has beneficial effects in estrogen receptor-negative breast tumours [13,35], it has been suggested that the therapeutic effects of tamoxifen may include biological activities unrelated to its proclivity for the estrogen receptor such as inhibition of the production of various growth factors involved in cancer growth [13]. Thus, the observation that part of the anti-tumour effects of tamoxifen is not related to its antiestrogenic effects may also explain its effectiveness in ER-negative patients also suggesting no interference with (endogenous) estrogens. In our opinion these observations indicate that tamoxifen retains its antitumor effects in the presence of endogenous as well as exogenous estrogens.

3.2. Estrogens in estrogen receptor negative breast cancer

In about 20–30% of postmenopausal women it is not possible to demonstrate the presence of steroid hormone (estrogen or progestagen) receptors in the breast tumour cells [103]. When ERs are absent, untoward effects of estrogens on the tumours in these patients are unlikely.

3.3. Estrogens and chemotherapy

An important question is whether estrogens interfere with the efficacy of cytotoxic chemotherapy in breast cancer patients and thus with breast cancer prognosis. Various observations provide information on this issue. The prognosis of premenopausal breast cancer patients treated with cytotoxic chemotherapy is not significantly different from that in postmenopausal women, irrespective of whether they develop premature ovarian failure or regain normal ovarian function [35]. Another study showed no significant difference between pre- and post-menopausal women in disease-free and overall survival in a 20-year follow-up of node-positive patients with operable disease

treated with cyclophosphamide, methotrexate and 5-fluorouracil [97]. In the same study chemotherapy-induced amenorrhea did not appear an important predictor of response to treatment in peri-menopausal women [97]. However, Pagani [104] showed that cessation of menses in premenopausal women,beit for a limited time period after diagnosis of breast cancer might be beneficial. In her review on ovarian ablation, Pritchard [98] showed that the improvement of disease-free interval and survival obtained with chemotherapy alone, was not further improved by ovarian ablation. Most of these observations would thus indicate that the endogenous levels of estrogens have no adverse effects on the efficacy of the chemotherapy.

The effects of exogenous estradiol were studied in a randomised trial [105] in advanced breast cancer patients. No differences in complete and partial remissions and nonresponders were found between chemotherapy (CT) alone or combined with estrogen (2 mg estradiol + 1 mg estriol given twice daily, starting on day 1 and continuing during six chemotherapeutic cycles in 40 weeks). The mean interval between study entry and patient death or last follow-up was 29 months in the CT + E group and 22 months in the CT only group. Although the authors concluded that estrogen priming in this cohort of patients with advanced breast cancer did not appear to add to the toxicity or palliative benefit of the chemotherapeutic regimen, their data indicate that estrogens do not adversely influence the beneficial effects of the chemotherapy.

3.4. Conclusion

The data presented above suggest that the efficacy of the management of breast cancer is not negatively influenced by the presence of estrogens at concentrations considerably higher than those attained with current HRT preparations.

4. Overall conclusion

Available preclinical and clinical data on the relationship between HRT and breast cancer has

been reviewed. Although it cannot be excluded that estrogens slightly increase the probability of breast cancer diagnosis, the available data fail to demonstrate that, once breast cancer has been diagnosed, estrogens worsen prognosis, accelerate the course of breast cancer or reduce survival. However, it should be borne in mind that larger, prospective, randomised clinical trials are needed for definite conclusions. The limited data currently available indicate that estrogens do not negatively affect the management of breast cancer nor interfere with the current therapeutic modalities.

It may, therefore, be concluded that the prevalent opinion that estrogens and estrogen treatment are deleterious for breast cancer, needs to be revisited. Awareness that currently available data suggest that both endogenous and exogenous estrogens have no impact on breast cancer and do not interfere with the therapeutic modalities may convince physicians that a proper risk-benefit assessment of HRT is warranted in patients with risk factors for breast cancer or in breast cancer patients also taking into account the favourable effects of HRT on bone and the reduced cardiovascular morbidity and mortality. Prospective, randomised clinical trials with different HRT regimens including cyclic or continuous combined estrogens and progestagens in healthy women and breast cancer survivors are now ongoing. The results of these trials are needed to provide more definitive conclusion about the risks and benefits of HRT, before it may be generally recommended for women with breast cancer or with risk factors for breast cancer.

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