HRT, breast and endometrial cancers: strategies and intervention options

Piero Sismondi a,*, Nicoletta Biglia a, Maurizia Giai a, Riccardo Ponzone a, Riccardo Roagna a, Luca Sgro a, Carlo Campagnoli b

a Department of Gynaecological Oncology, University of Turin, Mauriziano Umberto I Hospital, Largo Turati 62, 10128 Turin, Italy
b Department of Endocrinologic Gynaecology, S. Anna Hospital, Corso Spezia 60, 10126 Turin, Italy

Received 30 December 1997; received in revised form 17 February 1998; accepted 6 April 1998

Abstract

The demand for hormone replacement therapy (HRT) by women who enter the menopause is rapidly increasing in all developed countries. The concern that HRT may enhance morbidity and mortality from malignant diseases still limits the widespread adoption of hormonal treatments. Overall, epidemiological data on cancer incidence and HRT are reassuring, although long-term or inappropriate therapies may slightly increase the risk of developing malignant diseases. Many commercial hormonal compounds are currently available and the safest HRT regimen with regard to cancer risk must be identified. It is equally important that the best strategies for breast and endometrial surveillance in women commencing HRT be outlined, bearing in mind that the diffusion of hormonal therapies may be halted by unnecessary medical interventions. © 1998 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: HRT; Breast cancer; Gynecological cancer

1. Introduction

The diffusion of hormone replacement therapy (HRT) in menopause is mainly restrained by the concern that HRT may enhance morbidity and mortality from malignant diseases such as breast and endometrial cancer. Some epidemiological studies indicate that long term or inappropriate therapies are associated with a slightly increased risk of developing these tumours. On the other hand, it is long-term HRT that is most beneficial in terms of prevention of osteoporosis and cardiovascular diseases.

The majority of epidemiological data on cancer risk associated with hormonal treatments have been gathered from patients who took oral conjugated oestrogens unopposed by progestins.
The available information concerning progestin is essentially limited to the cyclic sequential regimen with medroxyprogesterone acetate (MPA) or to compounds with androgenic activity which are commonly used in Northern Europe.

A large number of commercial preparations containing oestrogens and progestins are currently available, with significant differences as far as hormonal activity, route of delivery, dose and duration of association are concerned. It is thus essential to analyse the available data from the literature with the aim of identifying the safest HRT regimens and specifically addressing the issue of the possible influence of these variables on cancer risk.

Furthermore, it is important that the best strategies to perform breast and endometrial surveillance of women on HRT be clearly outlined. This goal must be accomplished by limiting the number of medical interventions to those of proven value and avoiding excessive medicalization calling a halt to the diffusion of hormonal therapies.

2. Breast cancer

Breast cancer incidence is the most prevalent of the common malignant diseases in all developed countries and is steadily increasing all over the world. Therefore, even a weak causal link with HRT would have great public health impact.

Data from animal models and in vitro systems show that oestrogens are involved in the genesis and progression of breast tumours. Studies in premenopausal women indicate that breast mitotic activity peaks when endogenous progesterone level is highest, suggesting that progesterone may act synergistically with oestrogens to accelerate epithelial cell proliferation in breast tissue [1].

Overall, epidemiological data on breast cancer incidence and HRT are reassuring. Investigators substantially agree that short-term HRT, usually defined as 5 years or less, is not associated with an increased risk of breast cancer; a slight increase in risk, around 25–30%, has been found only for long-term treatments (> 5 years) [2–5].

The data regarding approximately 90% of the world-wide epidemiological evidence on HRT use and breast cancer risk have been recently re-analysed by the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) (Table 1) [6]. This study reports a relative risk (RR) for breast cancer of 1.35 (95% CI 1.21–1.49) for women who used HRT for 5 years or longer (average duration of use 11 years). The increase of breast cancer risk associated with long-term therapies was limited to current users or to women who stopped using it 1–4 years before the diagnosis; at five or more years after ceasing HRT there was no significant excess of breast cancer, overall or in relation to duration of use. For women whose last use was less than 5 years before diagnosis there was strong evidence of a trend of increasing risk with increasing duration of use (Table 2).

If further studies were to confirm that breast cancer risk returns to baseline levels after a few years of discontinuation of therapy, the following strategy could be proposed. HRT could be started soon after the onset of menopause and prescribed for no more than 5 years; this would allow the alleviation of neurovegetative and dystrophic menopausal symptoms and permit improvement in the quality of life of women, without significantly influencing their breast cancer risk. HRT could then be recommenced again for a similar length of time at an older age, when the risk of cardiovascular diseases and osteoporotic fractures is higher and the breast cancer risk associated with the previous HRT has returned to the baseline level. Nevertheless, as far as this last point is concerned, it must be underlined that the CGHFBC study provided little information about current or recent use of HRT beginning long after the menopause or about HRT use at older ages; 96% of users started HRT before age 60, 92% of users stopped HRT before age 65 and 97% were aged under 70 at the time of cancer diagnosis.

3. HRT regimens

In the CGHFBC study, information about the hormonal constituents of the preparations used was available for 39% of eligible women; no sig-
significant variation in the RR of breast cancer according to the type or the dose of oestrogen used was found. However, there is little evidence on the long-term effects of low-dose therapy. Data regarding the use of oestrogen in the USA show that most women took high dose CE, since a dosage of 1.25 mg/day or more was used by two out of three women in the 1970s and by one out of two women in the 1980s [7].

The diffusion of transdermal oestrogens started just a few years ago and it is unknown whether this route of administration may produce different effects on breast cancer risk as compared to oral CE. The hepatic metabolism of oral and transdermal compounds is different: oral oestrogens produce marked hepatocellular effects, such as increased serum levels of sex hormone binding globulin (SHBG) and reduced insulin-like growth factor I (IGF-I), which could partially counterbalance the unfavourable effects of oestrogen stimulation on breast tissue [8,9]. Transdermal oestradiol has virtually no hepatocellular effects and does not influence SHBG and IGF-1 serum levels [9]. Until epidemiological data on the long-term effects of parenterally administered oestrogen become available, it seems unwise to extrapolate information gathered on oral CE to transdermal preparations.

The epidemiological information available to assess whether progestin addition to ERT can modify breast cancer risk are limited, since many studies were carried out before such therapy became conventional. In the CGHFBC analysis there was no evidence of a marked difference between preparations containing oestrogen alone or oestrogen plus progestin, although only 12% of women for which the information was available used HRT regimens containing progestins [6].

The analysis of single studies provides inconsistent results: risk estimates for women using oestrogens plus progestins reported by American studies do not usually differ from those of women using oestrogen alone [10–12]. An increase of the risk with sequential HRT regimens, although not statistically significant, has been reported only in Northern Europe with the use of 19 nor-testosterone derivatives at high dosage [13,14]. Also a recent Swedish case–control study shows a trend for a higher breast cancer risk among women assuming combined treatments versus oestrogen alone, with overall risk ratios for more than 10 years of intake

### Table 1
Relative risk of breast cancer in ever-users compared with never-users of HRT

<table>
<thead>
<tr>
<th>Cases/controls</th>
<th>Ever-use</th>
<th>Never-use</th>
<th>RR</th>
<th>RR and 99% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective studies</td>
<td>1976/7798</td>
<td>2051/8147</td>
<td>1.09</td>
<td></td>
</tr>
<tr>
<td>Case–control studies (population controls)</td>
<td>2813/3362</td>
<td>5562/6880</td>
<td>1.15</td>
<td></td>
</tr>
<tr>
<td>Case control studies (hospital controls)</td>
<td>693/1188</td>
<td>4854/8541</td>
<td>1.27</td>
<td></td>
</tr>
<tr>
<td>All studies</td>
<td>5482/12348</td>
<td>12467/23568</td>
<td>1.14</td>
<td></td>
</tr>
</tbody>
</table>

*See Ref. [6].
Table 2
Relative risk (RR) of breast cancer according to time since last use

<table>
<thead>
<tr>
<th>Time since last use (years)</th>
<th>Cases/controls</th>
<th>RR</th>
<th>RR and 99% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never-user</td>
<td>12467/23568</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>1796/3814</td>
<td>1.21</td>
<td></td>
</tr>
<tr>
<td>1–4 years</td>
<td>702/1660</td>
<td>1.10</td>
<td></td>
</tr>
<tr>
<td>5–9 years</td>
<td>500/1239</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>10–14 years</td>
<td>346/821</td>
<td>1.05</td>
<td></td>
</tr>
<tr>
<td>≥15 years</td>
<td>416/729</td>
<td>1.12</td>
<td></td>
</tr>
</tbody>
</table>

* See Ref. [6].

being 2.4 (95% CI 0.7–8.6) and 1.3 (95% CI 0.5–3.7), respectively [15].

Androgenic progestins such as norethisterone acetate, unlike progestins without androgenic action like MPA that are commonly prescribed in the USA, oppose the hepatocellular effects of oral oestrogens that are potentially protective to the breast [16]. Different androgenic actions could, therefore, account for the conflicting results. Moreover, progestins show, on breast tissue, a direct progesterone-like effect whose consequences could be different depending both on the doses and activity of the progestin and on the schedule of progestin addition, sequentially or continuously combined to oestrogen. Some data suggest that this latter regimen could reduce breast stimulation. Nineteen-nortestosterone derivatives could also act directly on breast tissue in androgen-like and oestrogen-like ways [17].

These biological findings seem to suggest that the type of HRT associated with the lowest breast cancer risk is represented by oral oestrogen plus non-androgenic progestin in a continuous combined regimen. Nevertheless, it is essential to obtain more information on the biological and epidemiological aspects of this issue, with particular regard to the newest associations which are actually those more frequently prescribed.

4. Breast surveillance

The recommendations for breast surveillance in women receiving HRT are the same as in the general population over 50 years of age, and include periodic clinical examinations and mammography at least every 2 years [18].

HRT generates an increase of mammographic breast density or a change of the parenchymal pattern in a significant proportion of postmenopausal women (17–73% depending on the criteria adopted for the measurement of changes). A recent retrospective cohort study conducted on 8779 women indicated that the current use of oestrogen replacement therapy (ERT) is associated with lower specificity (82 versus 86% in never users) and sensitivity (69 versus 94% in never users) of mammography. The RR of a false-positive reading for current users versus never users
Table 3
Mammography in women treated with HRT (positive defined as any abnormal reading) \(a\)

<table>
<thead>
<tr>
<th></th>
<th>Never users ((n = 3826))</th>
<th>Former users ((n = 2853))</th>
<th>Current users ((n = 2100))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity (%)</td>
<td>86 (84–88)</td>
<td>86 (84–87)</td>
<td>82* (80–84)</td>
</tr>
<tr>
<td>False positive RR</td>
<td>1.0</td>
<td>1.0 (0.87–1.15)</td>
<td>1.33 (1.15–1.54)</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>94 (80–99)</td>
<td>94 (69–99)</td>
<td>69% ‡ (38–91)</td>
</tr>
<tr>
<td>False negative RR</td>
<td>1.0</td>
<td>1.06 (0.1–10.87)</td>
<td>5.23† (1.09–25.02)</td>
</tr>
</tbody>
</table>

\(a\) See Ref. [24].

* \(P = 0.006\) vs. never users; \(P = 0.001\) vs. former users.

‡ \(P = 0.04\) vs. never users; \(P = 0.05\) vs. former users.

\(\dagger\) \(P < 0.001\) vs. never users; \(P < 0.001\) vs. former users.

\(\ddagger\) \(P = 0.04\) vs. never users.

was 1.33 (95% CI 1.15–1.54) and the RR of a false-negative reading for current users versus never users was 5.23 (95% CI 1.09–25.02) (Table 3) [19].

In this study the authors were unable to explore the relationship between total duration of ERT use and changes in mammographic performance characteristics; this analysis represents an important area for further study. Future studies should also focus on the benefit of short-term withdrawal of ERT prior to screening mammograms. A retrospective study shows that short-term cessation of hormonal treatments for 2 weeks can induce a regression of hormone-induced mammographic changes, thus reducing the hazard of unnecessary biopsies [20].

Some of the false-negative examinations reported among current users might be explained by the presence of tumours that have grown rapidly under stimulation by exogenous oestrogens. This acceleration in the growth of spontaneously occurring cancers would lead to an effective shortening of the lead time to diagnosis among current users. This phenomenon could be probably reduced by adopting a 1-year versus 2-year interval as the gold standard definition.

An increase in breast density was seen with different types of treatment and was noted as early as 4 months after the beginning of treatment [21]. Nevertheless, it is unclear whether the type of regimen (sequential or continuous) or the dose can influence the accuracy of mammography. It has been reported that the specificity of mammography in women treated with continuous combined HRT is lower that in women treated with other regimens [22]. In a recent study mammographic breast density increased in 10% of women who received oestradiol plus sequential progestin and in 28% of women treated with a continuous oestradiol plus progestin combination [23].

Another study suggests that breast tissue density could be influenced by the dose of progestin [24]: in the lower-dose group (2.5 mg/day MPA) breast density increased by 4.8%, while in the higher-dose group (5 mg/day MPA) it increased by 9.3%. Multivariate analysis indicated that the lower tissue density is before treatment, the greater the increase of density is after treatment.

Finally, annual two-view mammography may be recommended for HRT users with a higher risk of breast cancer because of a previous biopsy for atypical benign breast disease or a family history of breast cancer.

5. Endometrial cancer

5.1. Treatment with oestrogen alone

More than 20 years ago it was noted that the use of oestrogens alone in menopause was associated with a significant increase of the risk of developing endometrial cancer. Almost all epidemiological studies of endometrial cancer in ERT users have observed a positive association. In a meta-analysis of 29 epidemiological studies published between 1970 and 1994, the summary RR of endometrial cancer for ever-users of unopposed oestrogen compared to non-users was 2.3 (95% CI 2.1–2.5) [25]. The increase of the risk
was directly related to the dosage of oestrogen, but the RR was elevated also for low-dose CE (0.3 mg/day). Endometrial cancer risk increased substantially with long duration of treatment. With short-term use of unopposed oestrogen for 1–5 years the summary data suggest a 3-fold increase in endometrial cancer risk, while the risk may be increased 10-fold for treatment lasting more than 10 years.

5.2. Progestin association

Progestins are added to ERT to prevent the development of endometrial hyperplasia and adenocarcinoma; sequential therapy promotes a regular and predictable bleeding.

The oestrogen–progestin association is now the standard therapy for menopausal patients who did not undergo hysterectomy, yet before 1990 fewer than 20% of women were receiving the combined therapy. This may account for the limited and conflicting data available regarding the risk for endometrial cancer among oestrogen plus progestin users. A further obstacle to the collection of information is represented by the wide heterogeneity of compounds and regimens that have been used in the past. Besides, it should be noted that many of the cases of endometrial cancer that occurred in patients receiving combined HRT have been reported in women previously treated with unopposed oestrogens.

In the meta-analysis the overall RR for endometrial cancer among women using combined therapy was 0.8 (95% CI 0.6–1.2); the direction of the effect is different in cohort (RR = 0.4; CI 0.2–0.6) versus case–control studies (RR = 1.8; CI 1.1–3.1). Only two studies included in the meta-analysis specifically considered the duration of progestin use: in the study by Voigt et al [26] women who took progestin for fewer than 10 days/month had an RR for endometrial cancer of 2.0 compared to an RR of 0.9 for those who took progestin for at least 10 days/month. In the study by Brinton et al [27] the RR for endometrial cancer associated with the combined regimen was 1.8 and did not vary by the duration of progestin use.

Table 4

<table>
<thead>
<tr>
<th>Hormonal regimen</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERT</td>
<td>2.17</td>
<td>1.91–2.47</td>
</tr>
<tr>
<td>Sequential HRT (progestin&lt;10</td>
<td>1.87</td>
<td>1.32–2.65</td>
</tr>
<tr>
<td>days/month)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequential HRT (progestin&gt;10</td>
<td>1.07</td>
<td>0.82–1.41</td>
</tr>
<tr>
<td>days/month)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous combined HRT</td>
<td>1.07</td>
<td>0.80–1.43</td>
</tr>
</tbody>
</table>

*ERT: Oestrogen replacement therapy; HRT: Hormone replacement therapy; see Ref. [28].

Some concern has been raised by the coincident publication of another large American case–control study reporting a 3-fold increase of endometrial cancer risk in HRT users who used progestins for less than 10 days per month. The excess risk may be reduced, but not fully eliminated, by prolonging the use of progestin to between 10 and 21 days (RR = 1.3) [29]. In the latter group of women the risk was not increased for less than 5 year periods of use (RR = 0.6; 95% CI
The results of the PEPI trial have confirmed that dose and duration of progestins association are crucial in providing endometrial protection to women who use oestrogens [30]. In this randomised placebo-controlled trial the histological findings of the endometrium of 596 women who were randomly assigned to placebo, oestrogen only or three different E + P regimens were compared. After 3 years of therapy, 62% of the women who received oestrogens alone developed some type of endometrial hyperplasia and 34% had complex hyperplasia or atypia; there was no difference in the occurrence of abnormal biopsy specimens between women who received placebo and those who received combined continuous regimen (CE with MPA at the low dose of 2.5 mg/day) or sequential regimens with MPA for 12 days every month at dosage of 10 mg/day.

In the literature, to our knowledge, there is just one study evaluating the safety of a sequential regimen with progestins at a lower dose (MPA 5 mg/day) than generally recommended [31]. After 1 year of therapy with CE 0.625 mg/day + MPA 2.5 and 5 mg/day in continuous combined regimens and MPA 5 and 10 mg/day for 14 days in sequential regimens, the occurrence of endometrial hyperplasia is less than 1% in all groups of treatment.

The relevance attributable to progestin dose in influencing the risk of endometrial cancer may also be derived from the update of a Swedish study after 13 years of follow-up [32]. In a cohort of 22,597 women receiving a fixed oestrogen–progestin brand (2 mg oestradiol) combined with a potent progestin at high dosage (levonorgestrel 250 µg for 10–21 days), risk estimates for endometrial cancer were at baseline.

The addition of a progestin to oestrogen therapy every 3 months (quarterly regimen) has been suggested to reduce the frequency of bleeding. Nevertheless, this regimen is not recommended: during the oestrogen-only phase the endometrium becomes increasingly proliferative and simple or cystic hyperplasia may develop as rapidly as after only 12 weeks of therapy. The Scandinavian Long Cycle Study in which 240 postmenopausal women were randomly assigned to monthly or quarterly cyclic HRT (2 mg oestradiol on days 1–84 with 1 mg of norethindrone on days 69–78) was stopped after 3 years because of the unacceptably high rate of endometrial pathology in the quarterly compared with the monthly cycle group (6.2 versus 0.8%; P = 0.004) [33].

5.3. Gynaecological surveillance

One of the most controversial aspects related to HRT therapy is represented by the optimal gynaecological surveillance strategy.

The information deriving from the meta-analysis and the PEPI trial was consistent with the opinion that menopausal women receiving a combined HRT had the same endometrial cancer risk of women belonging to the general population. Consequently, there was no rationale for prescribing periodical investigations to examine the endometrium of asymptomatic women.

As the latest studies of sequential HRT and endometrial cancer risk have produced conflicting results, the optimal duration of progestin association requires further study; Beresford et al. [29] have shown that even an adequate sequential HRT regimen may be associated with an increase of endometrial cancer risk after 5 years.

It is then probably wise to prescribe a baseline transvaginal pelvic sonography before commencing the treatment to exclude a pre-existing endometrial alteration; pelvic sonography should be repeated every 12–18 months during sequential HRT, particularly in the case of long-term treatments. Any alteration of the bleeding pattern during the treatment may be carefully evaluated with an endometrial biopsy or hysteroscopy. The occurrence of non hormone-dependent endometrial cancers in combined HRT users, such as serous papilliferous and clear cell adenocarcinomas, has been reported. These rare histotypes are not considered hormone-dependent tumours and may develop from an atrophic en-
dometrium that is very difficult to assess by ultrasound scanning.

Women who have used ERT should continue to undergo careful gynaecological surveillance for several years after the discontinuation of therapy. The risk of endometrial cancer persists after unopposed oestrogen is suspended; after 5 or more years of stopping the RR for endometrial cancer is still increased more than 2-fold. This finding suggests that the neoplastic process induced by oestrogen may continue after therapy is stopped, but may require several years to appear clinically.

6. Conclusion

An extensive analysis of the epidemiological data gathered during the last 20 years has shown that current or recent HRT use for more than 5 years can increase breast cancer risk by 35%.

Nevertheless, this information is derived from therapeutic schemes that differ from those currently used, both in terms of hormonal compounds and hormonal regimens prescribed. The effect of the addition of progestins and the possible influence of the type of progestin on breast cancer risk deserve attention and further study.

Any information on the efficacy and risks of commencing HRT long after the onset of menopause and on the potential favourable effects of a free interval between two periods of treatment in older women is not presently available.

The possibility that the accuracy of mammography in HRT users may be improved by adopting regimens with the least influence on breast density or by performing mammography during short periods of treatment suspension should not be neglected.

Long-term use of oestrogen preparations unopposed by progestins is associated with an increase of endometrial cancer risk. The use of progestin at an adequate dose in a combined continuous regimen and for at least 10 days per month in a sequential regimen should restore endometrial cancer risk to baseline levels. Nevertheless, this opinion is now being questioned by recent data suggesting that a modest increase of the risk after long periods of treatment also exists for adequate sequential regimens. Until this aspect has been fully elucidated it seems advisable for HRT users to undergo periodical transvaginal pelvic sonography even in the absence of ‘unexpected’ vaginal bleeding.

References


