Safety of hormone therapy after breast cancer: a qualitative systematic review

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BACKGROUND: This qualitative review systematically analyses the safety of hormone therapy (HT) in breast cancer (BC) patients. METHODS: We systematically searched studies reporting the use of HT in BC patients. We selected 20 studies in which we evaluated the methodology, characteristics of the studied populations and outcomes in terms of mortality and recurrence rates (RRs). RESULTS: Many studies evaluating HT were uncontrolled and retrospective. Ten prospective and two randomized studies were found. These were characterized by heterogeneity in populations, tumour characteristics, prognostic factors and treatments. Two studies reported a reduced RR, and two reported lowered BC mortality rates in HT users. One randomized study reported an increased rate of new BC events in HT users. CONCLUSIONS: There are currently no reassuring data indicating the absence of a harmful effect of HT. Further studies should analyse whether some regimens are safer than others. There is a need for randomized trials assessing the safety of these regimens. In the meantime, patients should be informed about the absence of safety data.

Key words: hormone therapy/breast cancer/mortality/recurrence rates/treatments

Introduction

Breast cancer (BC) mortality has decreased in the last decades because of systematic screening and progress in the treatment of the disease (Ferlay et al., 2001; ACS, 2004; Berry et al., 2005). Quality of life has emerged as an important challenge in the management of BC. Many women affected by BC will, following chemotherapy or hormone therapy (HT), go through menopause and display climacteric symptoms at an earlier age, than other women (Goodwin et al., 1999; Lower et al., 1999). Some publications even reported a five times higher prevalence of menopausal symptoms in BC patients than that in the general population (Harris et al., 2002). An exacerbation of the symptoms can certainly be partially explained by the distress linked to the disease. On the contrary, HT is seldom prescribed for fear of increased risk of recurrence even though, in the last decade, the question has been raised whether HT is really contra-indicated in these patients (Cobleigh et al., 1994; Brzezinski, 1995). Various observations led to this hypothesis: (i) Women who have had BC and have decided to become pregnant do not appear to increase their risk of recurrence, although pregnancy is associated with a high estrogen climate; young pregnant women who are affected by BC have a similar prognosis as their age-related peers, and an abortion during pregnancy does not better their prognosis (Gorins et al., 1998); (ii) Some studies reported that mortality due to BC is similar or even lower in HT users or contraceptive-pill users than in non-users (Holli et al., 1998; Batur et al., 2006); (iii) Several small observational trials reported no increase in BC recurrences in patients using HT (DiSaia et al., 1996; Ursic-Vrscaj and Bebar, 1999; DiSaia et al., 2000; Marttunen et al., 2001; O’Meara et al., 2001; Durna et al., 2002; Natrajan and Gambrell, 2002; Vassilopoulou-Sellin et al., 2002; Decker et al., 2003). Nevertheless, the last two points have become controversial since the publication of the results of the Women’s Health Initiative (WHI) study (Chlebowski et al., 2003) and the reports of the HABITS trial (Holmberg and Anderson, 2004). Still, the situation is confusing for the clinician: for instance, recent review articles came to opposite conclusions (Col et al., 2005; Hickey et al., 2005; Batur et al., 2006). Hickey et al. (2005) concluded that HT should not be considered as first-line management for menopausal symptoms after BC. Similarly, Col et al. (2005) concluded that results from observational studies are discrepant from those of randomized trials and that the latter data suggest that HT increases the risk of recurrence in BC survivors. On the contrary, Batur et al. (2006) concluded that ‘menopausal hormone use in BC survivors was not associated with increased cancer recurrence, cancer-related mortality or total mortality’. Because BC affects an increasing number of women, the search for an effective and safe strategy to alleviate their climacteric symptoms has become essential.
This article evaluates whether it is safe for women with a personal history of BC to use HT. We systematically and thoroughly review the available data.

Materials and methods

To evaluate whether women with a history of BC increase their risk of disease recurrence when using HT, we identified all published trials assessing the alleviation of menopausal symptoms in BC patients. We conducted a Medline and an Embase search using the following key words: hormone replacement therapy, estrogen replacement therapy, breast cancer, breast neoplasm, breast cancer survivors, menopause and menopausal symptoms. The references from each identified study and from review articles were then cross-checked for other potentially relevant studies. We also searched other data bases (Cochrane Controlled Trials Register) and abstract books from recent conferences, on the subjects of menopause, HT or BC.

We established the following inclusion criteria: articles should be written in English or French, studies had to include the safety data of BC and survival in women with a history of invasive BC.

A total of 40 articles were found (Stoll, 1989; Wile et al., 1991; DiSaia et al., 1993; Marchant, 1993; Powles et al., 1993; Wile et al., 1993; Vassilopoulou-Sellin and Theriault, 1994; DiSaia et al., 1995; Eden et al., 1995; DiSaia et al., 1996; Peters and Jones, 1996; Decker et al., 1997; Vassilopoulou-Sellin et al., 1997; Bluming et al., 1998; Dew et al., 1998; Gorins et al., 1998; Bluming et al., 1999; Brewster et al., 1999; Espie et al., 1999; Guidozzi, 1999; Natrajan et al., 1999; Ursic-Vrscaj and Bebar, 1999; O’Meara, 2000; Peters and Jones, 2000; O’Meara et al., 2001; Marttunen et al., 2001; O’Meara et al., 2003; Peters, 2003; Peters and Jones, 2003; Durna et al., 2001; Durna et al., 2002; Decker et al., 2003; Dew et al., 2003; Gorins et al., 2003; Holmberg and Anderson, 2004; von Schoultz et al., 2005). One study was classified as a prospective, although the authors did not provide explicit information about the methodology used (Natrajan and Gambrell, 2002). Seven studies were uncontrolled: four of which were prospective and three retrospective (Supplementary Table I). It should also be noted that in some ‘prospective’ studies, only part of the methodology was truly prospective. We classified the selected studies using the levels of evidence (Spong and Scott, 2004). Two reports of studies were available only as abstracts (Bluming et al., 1999; Powles et al., 1993). In only six studies women exposed to HT were matched to controls for certain factors [age, date and stage of disease at diagnosis, tumour size, node involvement, type of surgery, length of follow-up, use of adjuvant treatment, and delay between diagnosis and the beginning of HT] (DiSaia et al., 1996; Ursic-Vrscaj and Bebar, 1999; DiSaia et al., 2000; O’Meara et al., 2001; Decker et al., 2003; Gorins et al., 2003; Holmberg and Anderson, 2004; von Schoultz et al., 2005). In the Holmberg study, patients who did not use HT were treated with at least one strategy involving Clonidine, Sotalol, psychological help, exercise or acupuncture. Eleven other studies were controlled, in which four were prospective and six retrospective (Supplementary Table I).

Results

Characteristics of the studies and of the populations (Supplementary Table I)

Among the 20 identified and selected studies, only two were randomized trials: the HABITS trial and the Stockholm trial (Holmberg and Anderson, 2004; von Schoultz et al., 2005). Both were open studies, and randomization occurred using a central computer program stratified for past use of HT and use of tamoxifen. In addition, stratification occurred for investigator centres in the HABITS trial and for the time since primary diagnosis in the Stockholm trial. In the Stockholm trial, it is not reported which medication was given to women with symptoms who did not use HT. In the Holmberg study, patients who were randomized not to receive HT were treated with at least one strategy involving Clonidine, Sotalol, psychological help, exercise or acupuncture. Eleven other studies were controlled, in which four were prospective and six retrospective (Supplementary Table I).

In four controlled studies, women exposed to HT were not matched to controls (Marttunen et al., 2001; Durna et al., 2002; Natrajan and Gambrell, 2002; Vassilopoulou-Sellin et al., 2002), but in the study of Durna et al. (2002), results were adjusted based on tumour size, age at the time of diagnosis and year of diagnosis. Among the four unadjusted studies, Natrajan and Gambrell (2002) do not mention whether the two populations were comparable; Beckmann et al. (2001) and Vassilopoulou-Sellin et al. (2002) report no difference in prognostic characteristics between the studied populations and controls. Marttunen et al. (2001) report an increased rate of node invasion among the controls compared with women exposed to HT.

Eight studies mentioned that the included patients were postmenopausal (Wile et al., 1993; Guidozzi, 1999; Marttunen et al., 2001; Durna et al., 2002; Vassilopoulou-Sellin et al., 2002; Gorins et al., 2003; Holmberg and Anderson, 2004; von Schoultz et al., 2005). The number of included patients varied between 24 and 1122 (Guidozzi, 1999; Durna et al., 2002) and the number of women using HT between 21 and 286 (Ursic-Vrscaj and Bebar, 1999; Durna et al., 2002).

Exclusion criteria were mentioned in all but three studies (Bluming et al., 1999; Guidozzi, 1999; Beckmann et al., 2001) but were heterogenous: Some studies involved only invasive
The length of HT use varied from 1.2 to 3.7 years (Vassilopoulou-Sellin et al., 2000; O'Meara et al., 2001). The mean age at diagnosis was mentioned in all of the studies except two (Bluming et al., 1999; Decker et al., 2003), and in two trials the age was provided at the time of the inclusion but not at the time of diagnosis (Guidozzi, 1999; Beckmann et al., 2001). Gorins et al. (2003) mentioned only the age of patients using HT. Beckmann et al. (2001) and Durna et al. (2002) reported that women using HT were significantly younger than untreated women. Finally, two authors reported only the mean age of the participating women (DiSaia et al., 2000; O'Meara et al., 2001). The data were not stratified by the menopausal status at BC diagnosis. The average time between diagnosis and the start of HT varied from 1.3 to 9 years (Vassilopoulou-Sellin et al., 2002; von Schoultz et al., 2005). The length of HT use varied from 1.2 to 3.7 years (Powles et al., 1993; Decker et al., 2003) and the length of follow-up from 2.1 to 12 years (Vassilopoulou-Sellin et al., 1997; Holmberg and Anderson, 2004). In some studies, the length of follow-up was significantly longer in HT users than in non-users (Durna et al., 2002).

Tumour characteristics and treatments used after diagnosis of BC (Supplementary Table II)

The stage of disease was not reported in the only two randomized trials, but advanced stages were excluded (Holmberg and Anderson, 2004; von Schoultz et al., 2005). Six studies of the eleven controlled trials compared the women exposed to HT with the controlled group for the initial stage of the disease (DiSaia et al., 1996; Beckmann et al., 2001; Marttunen et al., 2001; O'Meara et al., 2001; Durna et al., 2002; Decker et al., 2003). Among them, Durna et al. (2002) were the only ones who reported a more favourable stage in the HT users compared with the control group. Two studies did not provide information regarding the stage of the disease (DiSaia et al., 2000; Gorins et al., 2003), and one included only stage I disease (Natrajan and Gambrell, 2002), whereas Vassilopoulou-Sellin et al. (2002) excluded advanced stages (higher than stage II).

In the randomized trials reported by von Schoultz et al. (2005) and Holmberg and Anderson, (2004), there was no difference regarding the nodal involvement between women using HT and controls (not using HT). Only one controlled study reported an increased number of patients with nodal invasion in the untreated group (Durna et al., 2002), but some authors do not provide information about this point (Gorins et al., 2003). Uncontrolled studies tended to mainly include women with a favourable prognosis (low stages, less node involvement) (Supplementary Table II).

Only four controlled studies stratified treated and untreated women for the BC grade (Ursic-Vrscaj and Bebar, 1999; Beckmann et al., 2001; Marttunen et al., 2001; Decker et al., 2003), whereas Gorins et al. (2003) reported only the grades of women using HT after BC.

No difference in receptor status was reported in the two randomized trials (Holmberg and Anderson, 2004; von Schoultz et al., 2005). In one controlled trial of six (Decker et al., 2003), HT users had tumours with positive estrogen receptors more often than did controls, but one author did not provide data about this parameter (Gorins et al., 2003) and another provided data for both groups but not separately (Natrajan and Gambrell, 2002). A wide variability characterized the hormonal receptor status of patients in the uncontrolled studies.

No (randomized or controlled) study reported a difference between the oncological management of the HT treated and untreated patients, but one study provided an incomplete report regarding the control group (Gorins et al., 2003).

The data about tamoxifen were very heterogeneous throughout the studies. Seven of 20 studies did not provide data about tamoxifen use (Wile et al., 1993; Vassilopoulou-Sellin et al., 1997; Bluming et al., 1999; DiSaia et al., 2000; Peters et al., 2001; Natrajan and Gambrell, 2002; Vassilopoulou-Sellin et al., 2002). Three studies of 13 specified that tamoxifen was used before the use of HT (Guidozzi, 1999; Decker et al., 2003; Gorins et al., 2003), but some authors provided no data regarding tamoxifen use in patients who were not taking HT (control group) (Gorins et al., 2003). In some studies, more women from the control group had used tamoxifen (Decker et al., 2003). Six of thirteen studies did not specify whether tamoxifen was taken before the start of the study (Ursic-Vrscaj and Bebar, 1999; Beckmann et al., 2001; Marttunen et al., 2001; O'Meara et al., 2001; Durna et al., 2002; Holmberg and Anderson, 2004), but in four studies tamoxifen was used simultaneously with HT (Powles et al., 1993; DiSaia et al., 1996; Brewster et al., 1999; von Schoultz et al., 2005).

Eleven of 20 studies analysed the proportion of women who used HT before the onset of BC (Wile et al., 1993; Vassilopoulou-Sellin et al., 1997; Brewster et al., 1999; Guidozzi, 1999; Beckmann et al., 2001; O'Meara et al., 2001; Durna et al., 2002; Natrajan and Gambrell, 2002; Decker et al., 2003; Holmberg and Anderson, 2004; von Schoultz et al., 2005). Seven of these were controlled studies (Beckmann et al., 2001; O'Meara et al., 2001; Durna et al., 2002; Natrajan and Gambrell, 2002; Decker et al., 2003; Holmberg and Anderson, 2004; von Schoultz et al., 2005), and two were randomized trials (Holmberg and Anderson, 2004; von Schoultz et al., 2005). In the study of Natrajan and Gambrell (2002), the proportion of HT users before the onset of BC was provided only for the women exposed to HT. Two studies reported that BC survivors using HT were more likely to have used it before the onset of disease (Durna et al., 2002; Decker et al., 2003).

HT data (Supplementary Table III)

Nine of the 20 studies did not provide the indication for HT in the BC patients (DiSaia et al., 1996; Vassilopoulou-Sellin et al., 1997; Bluming et al., 1999; Brewster et al., 1999; DiSaia et al., 2000; O'Meara et al., 2001; Natrajan and Gambrell, 2002; Vassilopoulou-Sellin et al., 2002; von Schoultz et al., 2005). Only three studies provided detailed indication criteria. These were mostly climacteric symptoms, risk factors for osteoporosis but also for cardiovascular disease (Marttunen et al., 2000; O'Meara et al., 1996; Vassilopoulou-Sellin et al., 1999; Brewster et al., 1999; DiSaia et al., 2000; Peters et al., 2001; Natrajan and Gambrell, 2002; Vassilopoulou-Sellin et al., 2002).
2001; Decker et al., 2003; Holmberg and Anderson, 2004). On the contrary, in the study of Holmberg and Anderson (2004), increased risk of cardiovascular disease was considered to be a contraindication for participating in their study, after 2001.

All but one study described the HT regimen used (Bluming et al., 1999). But these were extremely varied between studies as well as in relation to drugs used. One should also note that in the HABITS study (Holmberg and Anderson, 2004), 18% of the patients in the control group were using HT and 10% were in the Stockholm trial (von Schoultz et al., 2005).

Only two studies analysed the effect of different HT regimens (Brewster et al., 1999; Durna et al., 2002).

**Patients’ outcome (Supplementary Table IV, Figure 1)**

**Recurrence and contralateral BC**

No difference in local or distant recurrence was reported in the Stockholm trial (von Schoultz et al., 2005), whereas Holmberg and Anderson (2004) reported an increased risk of ‘recurrence of events’ (including local recurrences, contralateral new BCs or metastases) using HT [recurrence rate (RR) = 3.5 (95% CI 1.5–8.1)], but these events were not analysed separately. Furthermore, one should note that two of seven patients from the control group who developed a new cancer event were also HT users.

Some of the patients followed in the study by Vassilopoulou-Sellin et al. (2002) were either randomized to the use of HT or not (n = 34 using 0.625 mg conjugated equine estrogens (CEE) and 43 controls). In this study, where women exposed to HT and controls were comparable for tumour size, receptor status, node invasion and menopause status at the time of diagnosis, no difference in BC events (details not provided) was observed. Some studies considered the number of relapses (including both locoregional BC recurrence and contralateral BC) rather than the number of recurrences (Bluming et al., 1999; Durna et al., 2002). Only Durna et al. (2002) reported a reduction of relapses among HT users [RR = 0.62 (95% CI 0.43–0.87)].

Only one study (O’Meara et al., 2001) of the seven controlled studies that evaluated RRs found a reduced rate of recurrence among HT users [RR = 0.5 (95% CI 0.3–0.85)] (Supplementary Table IV). Gorins et al. (2003) provided no information about the control group. There was no report of a significantly increased risk of recurrence in the six uncontrolled studies (Powles et al., 1993; Wile et al., 1993; Vassilopoulou-Sellin et al., 1997; Brewster et al., 1999; Guidozzi, 1999; Peters et al., 2001).

None of the seven controlled studies (of the eleven) that did analyse the risk of contralateral BC reported an increased risk in HT users compared with non-users (Ursic-Vrscaj and Bebar, 1999; Marttunen et al., 2001; O’Meara et al., 2001; Natrajan and Gambrell, 2002; Vassilopoulou-Sellin et al., 2002; Decker et al., 2003). Gorins et al. (2003) mentioned only the data concerning HT users. Only one uncontrolled study mentioned the occurrence of one case of contralateral BC (Peters et al., 2001).

No difference in the occurrence of metastases was found in the five controlled trials that analysed this outcome (Beckmann et al., 2001; Natrajan and Gambrell, 2002; Vassilopoulou-Sellin et al., 2002; Decker et al., 2003; Gorins et al., 2003) or the two uncontrolled trials (Powles et al., 1993; Peters et al., 2001). One of the controlled studies did not provide data about the control group regarding metastases (Gorins et al., 2003).

Two studies analysed, separately, the effect of different HT regimens that were used. Durna et al. (2002) reported a reduced relative risk of BC recurrence in women using vaginal estrogens [RR = 0.18 (95% CI 0.04–0.75)] even after adjustment for the initial stage of BC. In the study of Brewster et al. (1999), no difference of RR was reported in relation to the treatment used whether given as an estrogen-only regimen or an estrogen–progestin combined regimen, but the number of women with recurrences was small (n = 6).

Holmberg and Anderson (2004) reported no difference between various HT regimens (results not shown) but added that this should be interpreted with caution because of the small number of women exposed to HT.

Few studies explicitly provided data about the time interval between the first occurrence of a BC and the BC recurrence. This information was not available for the two randomized trials and only available in one controlled study for patients using HT and for control patients (Marttunen et al., 2001). In this study, the time interval between the primary cancer and the recurrence ranged between 22 and 167 months for patients using ET and between 23 and 108 months for control patients (Marttunen et al., 2001).

**Mortality**

No difference in mortality was reported in the Stockholm trial (von Schoultz et al., 2005). All the controlled trials reported mortality data: four studies found reduced mortality among HT
users (DiSaia et al., 2000; O’Meara et al., 2001; Durna et al., 2002; Decker et al., 2003). Decker et al. (2003) found a reduced global mortality (P = 0.03) but not reduced BC-associated mortality. DiSaia et al. (2000) reported an increased survival rate among HT users versus non-users (88 versus 63%, p = 0.003), but they did not specify the causes of death. O’Meara et al. (2001) and Durna et al. (2002) reported reduced global mortality [RR = 0.34 (95% CI 0.19–0.59) and RR = 0.48 (95% CI 0.29–0.78), respectively] and BC-related mortality [RR = 0.4 (95% CI 0.22–0.72) and RR = 0.34 (95% CI 0.13–0.91)]. No difference in mortality was reported by Gorins et al. (1997), but they did not specify the causes of death. O’Meara et al. (2000) found an increased survival rate among HT users versus non-users (88 versus 63%, p = 0.003), but they did not specify the causes of death. O’Meara et al. (2000) and Durna et al. (2002) reported reduced global mortality [RR = 0.34 (95% CI 0.19–0.59) and RR = 0.48 (95% CI 0.29–0.78), respectively] and BC-related mortality [RR = 0.4 (95% CI 0.22–0.72) and RR = 0.34 (95% CI 0.13–0.91)]. No difference in mortality was reported by Gorins et al. (2003). Mortality appears to be low in five uncontrolled studies. (Wile et al., 1993; Vassilopoulou-Sellin et al., 1997; Brewster et al., 1999; GuidoZZi, 1999; Peters et al., 2001).

Two studies analysed, separately, the effect of different HT regimens that were used. Durna et al. (2002) reported reduced mortality from all causes with combined HT (RR = 0.27 (95% CI 0.1–0.73)) and with progestin alone [RR = 0.34 (95% CI 0.12–0.93)] and reduced mortality from BC with combined HT [RR = 0.32 (95% CI 0.12–0.88)] and progestin alone [RR = 0.33 (95% CI 0.12–0.91)] even after adjustment for the initial stage of BC.

Only one study explicitly provided data about the time interval between the first occurrence of a BC and the death due to BC, respectively, in two patients using HT (1 year and 8 years after diagnosis) and in six control patients (ranging between one and eleven years) (Natraj and Gambrell, 2002).

Discussion

More than half of the studies evaluating the innocuousness of HT in BC patients are retrospective studies, with the associated bias: incomplete and unreliable data, data collected in charts or using questionnaires, selection of women with a better prognosis when starting HT, inadequate or incomplete matching between women exposed to HT and controls for all confounding factors. This is even more true because, in many of these studies, difference in prognostic factors, such as tumour characteristics, exists between HT users and controls. Finally, about half of the studies were uncontrolled trials.

Whereas the total number of included patients may seem high, only a small number of patients were actually using HT in many of these trials, rendering most of them underpowered to assess the primary question, that is the safety of the treatment. Furthermore, no quantitative meta-analysis of the data is possible because a huge heterogeneity in methodology and selection criteria characterizes these trials (histology and stage of cancer, delay between diagnosis and treatment, regimen used and length of follow-up). Although most studies reporting data about tumour characteristics did not show any differences, an important heterogeneity exists in the quality of the reporting and in at least two studies, HT users had less advanced stages of disease than did control patients. In some studies, HT users had more often tumours with negative estrogen receptors, than controls.

The oncological management seems to be similar in HT users and control patients, with the exception of tamoxifen use, which is reported in only about a third of the studies and which seems to be variable between studies.

Most studies report the HT used, but the regimens vary between studies or even within the same study. The results of these studies can therefore not be compared and certainly not be pooled.

Finally, most observational studies concluded that HT had no negative influence on BC prognosis. Only two studies reported a reduced RR, and four observed lowered mortality rates in HT users, but among these, the mortality reduction was attributable to BC in only two studies.

Most of the observational studies as well as one randomized trial, the Stockholm trial, are in opposition to the results of the other randomized study, the HABITS trial which reported an increased rate of new BC events (including recurrence, contralateral new cancers or metastases) in HT users. These two studies have a higher level of evidence and need to be analysed in more detail. Some criticism has been made regarding both randomized trials, such as the absence of a placebo control group, the non-blinding of the analysis, lack of data about the climacteric symptoms and the rather short follow-up period. The difference in results may be because of heterogeneity in the assessed patients (for instance a higher number of involved nodes and a lower proportion of tamoxifen treated patients) or in the regimens used (more often combined regimens) in the HABITS trial. Therefore, we did not pool their results.

Furthermore, the conclusions of the HABITS trial are in line with a plausible carcinogenic role of estrogens and progestins, which has been supported by many experimental and clinical data (Rossouw et al., 2002; Collins et al., 2005; Yager and Davidson, 2006). We therefore believe that, currently, guidelines should advise against using HT in patients with a history of BC, although it is possible that some regimens entail a lower risk than others. Our conclusions are therefore similar to those published recently by Col et al. (2005), although this review had not taken into consideration the randomized Stockholm trial. Our results are in opposition to those of Batur et al. (2006), who had not considered randomized trials at all.

In conclusion, we currently have, unfortunately, no reassuring data indicating the absence of harmful effect of HT in BC patients. One of the two randomized trials (using HT), on the contrary, indicated the opposite. Further studies should also analyse whether some regimens are safer than others. We believe that there is a need for randomized trials assessing the safety of different HT regimens in these patients. In the meantime, physicians should inform patients about the absence of safety data.

Supplementary materials

Supplementary data are available at http://humrep.oxfordjournals.org/.

References


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