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Maturitas 45 (2003) 29–38
MATURITAS
THE EUROPEAN MENOPAUSE JOURNAL
www.elsevier.com/locate/maturitas

Menopause after breast cancer: a survey on breast cancer survivors

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Received 4 April 2002; received in revised form 3 January 2003; accepted 27 January 2003

Abstract

Due to the younger age and the ever wider use of adjuvant chemotherapy and antiestrogens, menopausal symptoms are a frequent cause of concern for breast cancer patients. *Objectives:* To determine the prevalence of menopausal symptoms, and to explore the attitudes toward Hormone Replacement Therapy (HRT) or other treatments and the willingness to take oestrogen in breast cancer patients. *Methods:* A questionnaire-based survey on 250 breast cancer patients treated and followed-up at our department. Of them 144 (Group A) were in postmenopause and 106 (Group B) were in premenopause at time of diagnosis. *Results:* Adjuvant therapy with tamoxifen or tamoxifen plus chemotherapy is associated with a significant worsening of menopause-related symptoms of women belonging to Group A. These women are more concerned about risk of breast cancer recurrence than about risk of osteoporosis ($P = 0.05$) and heart disease ($P = 0.006$). Seventy-eight percent are against the use of HRT; only 22% would consider taking HRT mainly for vasomotor symptoms relief and osteoporosis prevention. The incidence of vasomotor and dystrophic symptoms is significantly higher in women belonging to Group B treated with chemotherapy and/or hormonotherapy as compared with postmenopausal women ($P < 0.000$ and $P = 0.02$, respectively). Premenopausal women are more concerned about risk of breast cancer recurrence than older women ($P = 0.09$) and at the same time are significantly more worried about the impairment of the quality of life due to adjuvant therapy ($P = 0.005$). Younger women are more prone to consider HRT than postmenopausal women ($P = 0.05$). Sixty-six percent are against HRT use, and 34% would consider taking HRT to alleviate vasomotor and dystrophic symptoms and to prevent osteoporosis. *Conclusions:* Breast cancer survivors are interested to treatments that may improve their quality of life, but fear of HRT persists among these women and their doctors, despite new evidence suggesting the low probability of detrimental effects.

Keywords: Hormone replacement therapy; Breast cancer; Adjuvant therapy

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doi:10.1016/S0378-5122(03)00087-2

1. Introduction

Breast cancer incidence is increasing steadily almost worldwide, whereas the National Center of Statistics of the United States has reported a 6% decrease of breast cancer mortality in the years from 1991 to 1995. Given these trends, the number of breast cancer survivors is notably going to grow in the next future.

In the United States, 195 000 women are diagnosed with breast cancer annually: 25% are in their reproductive years and 70% of them develop premature menopause following adjuvant chemotherapy. On the average, in a 40-year-old woman, standard adjuvant chemotherapy increases the chances of entering the menopause from less than 5 to more than 40%. [1] Cross-sectional surveys suggest that symptoms of oestrogen deficiency, which occur in up to 66% of women treated for breast cancer, are the most common side-effects of adjuvant therapy. Furthermore, they may be more bothersome and persist for longer time as compared with the same symptoms experienced by healthy women [2,3].

Breast cancer survivors may benefit from strategies alternative to Hormone Replacement Therapy (HRT) for the prevention of cardiovascular disease and osteoporosis, whose risks are both increased by early menopause [4,5], whereas the management of symptoms related to oestrogen deficiency is more problematic. It is well recognised that hot flushes, mood and sleep disturbances, memory impairment and sexual dysfunction can be really debilitating for these women [6]. In particular, it has been reported that hot flushes among tamoxifen users are significantly more severe in perimenopausal women with a previous history of severe symptoms [7–9].

Many agents have been evaluated as potentially useful for alleviating hot flushes in survivors of breast cancer as an alternative to HRT [10]. The efficacy of progestins has been well described. A significant reduction of hot flashes with the use of low doses of megestrol acetate as compared with placebo (ca. 80 vs. 20%) has been reported, while there are no convincing data to support that it has any substantial positive or negative effect on breast cancer morbidity or mortality [11–13]. Also tibolone appears to be an attractive alternative to HRT [14–16], but its safety and efficacy in breast cancer survivors still requires to be tested in the setting of a controlled clinical trial.

Prompted by the concern that any type of hormonal treatment may be detrimental in breast cancer survivors, investigators have tested non-hormonal methods to alleviate hot flushes; unfortunately, primrose oil, vitamin E, clonidine, phytoestrogens have all been shown to be no more effective than placebo [17–22]. Conversely, selective serotonine-uptake inhibitors (SSRIs), a new class of antidepressants such as venlafaxine, fluoxetine and paroxetine, are effective in reducing hot flushes, though the balance between their efficacy and side-effects needs consideration [23–25].

Raloxifene and other Selective Estrogen Receptor Modulators (SERMs) which are under development have no role in the treatment of vasomotor symptoms in breast cancer patients, although they may be useful for the prevention and treatment of osteoporosis and may decrease the incidence of breast cancer in postmenopausal women treated for osteoporosis [26,27].

Although all these drugs have some effect, only HRT has the potentiality of relieving the whole range of menopausal symptoms [28] while protecting against osteoporosis [4]. HRT is generally felt as contraindicated in patients with previous breast cancer [10]. Indeed, epidemiological studies in healthy menopausal women suggest a small increase of breast cancer risk for long-term oestrogen use (>5 years) [29–31]. A 26% risk increase after more than 4 years of HRT has been confirmed by the recently published prospective WHI trial, which casts doubt on the protective role of HRT on cardiovascular diseases [31]. Nonetheless, the interest shown by many breast cancer survivors on HRT [32,33], has recently reinforced the debate regarding its safety in these women [34,35].

The Consensus Statement of Charlottesville in 1997 stated that alternative therapies should be used whenever possible for the relief of menopausal symptoms in breast cancer survivors, and that "tailored treatment strategies" should be applied to individual patients [10]. Carefully designed trials should be undertaken to explore the effectiveness

and the safety of estrogens and/or progestins in women with a previous diagnosis of breast cancer, who are also receiving tamoxifen.

This survey was conducted to determine the prevalence and severity of vasomotor, gynaecologic and other menopausal symptoms and their impact on the quality of life among women with a history of early breast cancer, and also to explore the attitudes of these women and their physicians toward HRT or other treatments of menopause-related problems and the reasons that influence their willingness to take oestrogen.

2. Study design and subject recruitment

Participants were recruited from a group of breast cancer patients treated and followed-up at the Department of Gynaecological Oncology, University of Turin and at the Institute for Cancer Research and Treatment (IRCC) of Candiolo, Turin.

Eligibility criteria for inclusion were as follows: tumour registry classification of invasive loco-regional disease (Stage I–II), current disease-free status, and updated follow-up information. Women with other active cancers or serious disabling medical or psychiatric conditions were excluded.

250 women were interviewed and divided in two subgroups: Group A, consisting of 144 patients in postmenopause at the time of primary diagnosis (median age 59 years); Group B, consisting of 106 patients in premenopause at the time of primary diagnosis (median age 45 years).

2.1. Survey instrument

The survey was conducted by questionnaire-based interviews to all participants. The 35-items questionnaire has been formulated for this study; the average time for completion was 15 min (range 12–20).

Women were defined as postmenopausal at the time of diagnosis if their menstrual periods had ceased at least 6 month before the diagnosis. All subjects were interviewed by a trained interviewer who investigated on subject's treatments for breast carcinoma, past history of HRT use and symptoms potentially related to physiological menopause.

Women already postmenopausal at time of primary treatment were asked about any worsening of menopausal symptoms after chemotherapy or endocrine-therapy. Younger women, who were premenopausal at time of cancer diagnosis, were interviewed about the onset of ex novo symptoms potentially related to adjuvant therapies.

The questionnaire included a menopausal symptom list comprehensive of a severity 4-points scale with (1) indicating no symptoms, (2) slight, (3) moderate, and (4) extremely severe symptoms. Participants were asked if they were: not at all, slightly, moderately, or extremely concerned about their risk of getting heart disease, osteoporosis, worsening of quality of life, or having a recurrence of breast cancer.

The attitude about HRT use after breast cancer was also investigated: patients were asked if they would be willing to take HRT under medical supervision, if they had any concern about taking HRT, and if so, to indicate, from a list of statements, the ones that applied to them.

Women were also interviewed on their awareness of alternative non-hormonal therapies for the relief of menopausal symptoms. The questionnaire also included sections addressing the issue of family history, and social-demographic characteristics.

3. Results

3.1. Group A (144 postmenopausal patients)

3.1.1. Symptoms related to adjuvant therapy

Eighteen percent of these patients had already used HRT in the past, although only 8% were on HRT at the time of breast cancer diagnosis. Medical adjuvant therapy had been used by 122 out of 144 patients: 49 patients received only tamoxifen, 59 chemotherapy followed by tamoxifen, 14 only chemotherapy; 22 received only radiotherapy. The prevalence of symptoms after chemotherapy and/or hormonotherapy (mainly tamoxifen) is listed in Table 1. Adjuvant therapy is associated with a worsening of menopause-

Table 1
Worsening of menopausal symptoms after hormonotherapy, chemotherapy or hormono plus chemotherapy in postmenopausal breast cancer patients

Symptoms	Prevalence of symptoms in postmenopausal women					
	Hormonotherapy		Chemotherapy		Hormono+chemotherapy	
	Number	%	Number	%	Number	%
Hot flashes	21/49	43	4/14	29	32/59	54
Night sweat	13/49	27	3/14	21	16/59	27
Insomnia	11/49	22	6/14	43	18/59	31
Tiredness	19/49	39	7/14	50	32/59	54
Anxiety	11/49	22	7/14	50	21/59	36
Depression	9/49	18	5/14	36	15/59	25
Irritability	7/49	14	3/14	21	14/59	24
Vaginal dryness	7/49	14	3/14	21	11/59	19
Dyspareunia	2/49	4	2/14	14	6/59	10
Libido reduction	2/49	4	3/14	21	7/59	12
Leuchorrea	7/49	14	0/14	0	7/59	12
Vaginal bleeding	3/49	6	0/14	0	2/59	3

related symptoms in all the three groups of older patients. Tamoxifen use was associated with higher frequency and severity of hot flashes . Forty-three to 54% of women on tamoxifen (respectively, with and without chemotherapy) reported a worsening of hot flashes, compared with 29% of those treated with chemotherapy alone ($P = 0.175$). Half of the women receiving chemotherapy comply of tiredness and anxiety; these symptoms are reported also by 39 and 22% of women treated with tamoxifen alone ($P = 0.160$ and 0.09, respectively). Each of these symptoms was rated as severe by approximately one half of the women who experienced them. Reduction of sexual activity and libido and dyspareunia were reported by 12–21% of the women who underwent

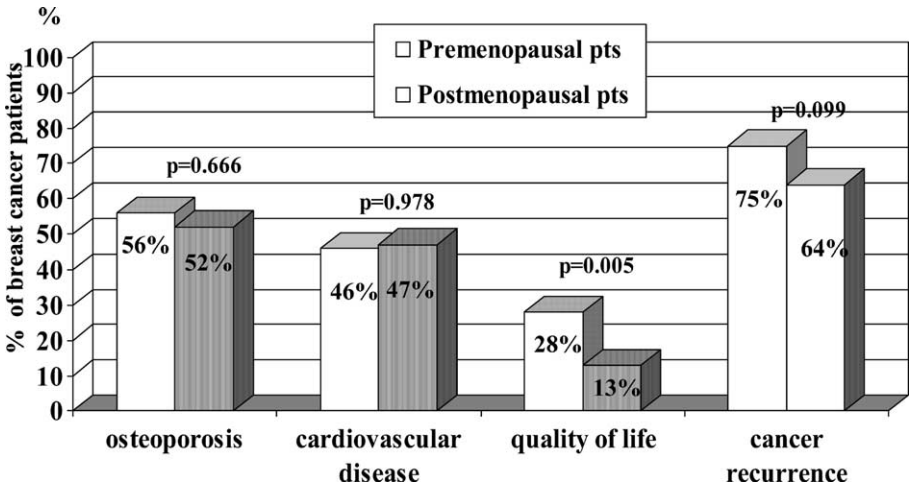

Fig. 1. Fear of cancer's recurrence, osteoporosis, cardiovascular disease, worsening of quality of life in breast cancer survivors.

chemotherapy and by 4% of those who did not, but the difference does not reach statistical significance.

3.1.2. Concern about personal health and about taking HRT

Postmenopausal women were more concerned about their risk of breast cancer recurrence (64%) than about the risk of osteoporosis (52%) and of heart diseases (47%) ($P = 0.05$ and 0.006, respectively). Conversely, only 13% of menopausal women had their quality of life impaired either by their condition of cancer patients or by the adjuvant therapies received (Fig. 1).

Thirty-one percent of patients had already requested physician's advice for menopausal symptoms. The specialist consulted was mainly a gynaecologist (62%) and in a lower percentage of cases an oncologist (22%) or a general practitioner (16%). The majority of women were advised not to take HRT (58%) or to wait for symptoms' regression (15%); only for the minority of them (21%) the physician suggested alternative remedies.

Among all postmenopausal women who filled the questionnaire, one half had heard or read about HRT. The majority of respondents had one or more concerns about taking HRT. Seventy-eight percent were against the use of HRT after breast cancer. The reasons for this attitude were: concern that the use of HRT may increase the risk of cancer relapse (33%), fear of HRT side effects (24%), the negative opinion of their physician (15%), or the mild discomfort caused by their menopausal symptoms (10%) (Fig. 2). Despite these concerns, when asked if they would be willing to take HRT under medical supervision, 22% of women responded positively, with the motivation of vasomotor symptoms relief (50%), osteoporosis prevention (45%), vaginal dryness reduction (19%) and, only marginally, cardiovascular disease prevention (13%) (Fig. 2).

The number of women who would consider taking oestrogen increases together with the increasing severity of vasomotor symptoms, feelings of depression, and sleeping disturbances.

3.2. Group B (premenopausal patients)

3.2.1. Symptoms related to adjuvant therapy

The unfavourable effects of chemotherapy and endocrine-therapy on menopausal symptoms were more evident in the group of women who were premenopausal at time of primary surgery for breast cancer as compared with older women (Table 2). Most of these patients received chemotherapy, alone (27 cases) or followed by anti-

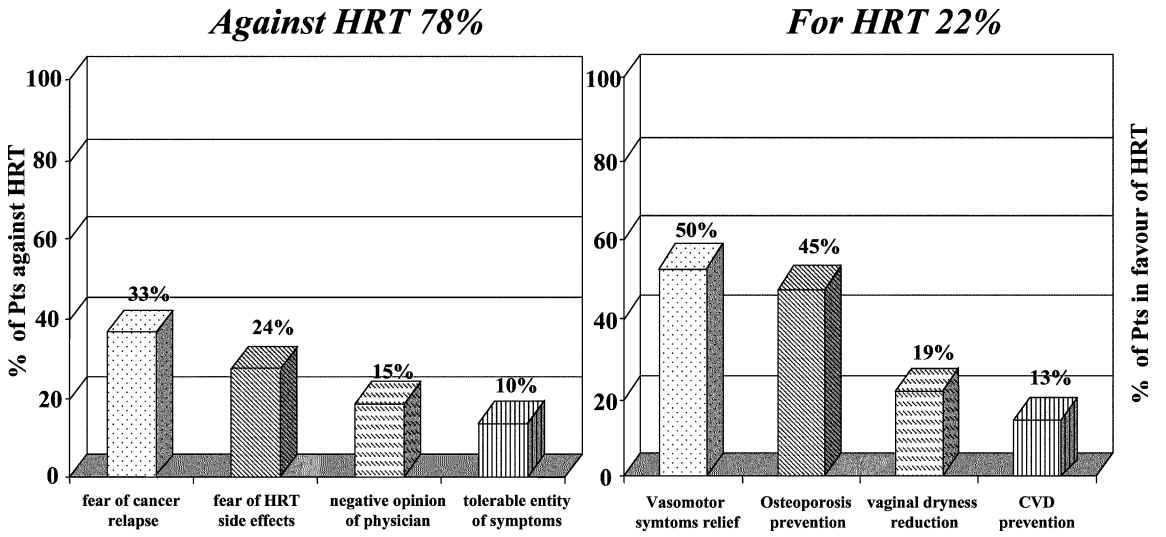

Fig. 2. Attitude of postmenopausal patients toward HRT after breast cancer and reasons for treating.

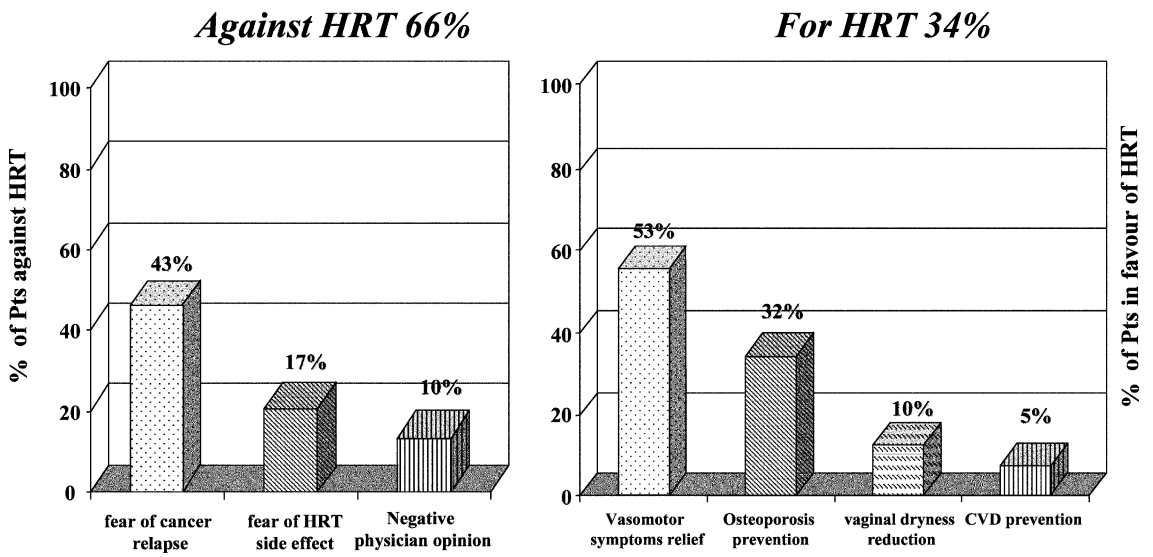

Fig. 3. Attitude of premenopausal patients toward HRT after breast cancer and reasons for treating.

estrogens (associated to LHRH analogues if not yet amenorrhoic) (41 cases); 29 patients received tamoxifen and LHRH analogues as the only treatment.

The incidence of menopausal symptoms is listed in Table 3. Seventy-eight percent of premenopausal women in whom chemotherapy had caused early ovarian failure reported the outbreak of hot flashes; this percentage increases to 90% in women receiving tamoxifen plus chemotherapy. Overall, one third of these women reported also insomnia, anxiety and irritability and a percentage ranging from 41 to 48% complaints of tiredness. Vaginal dryness and loss of sexual desire are reported more frequently in premenopausal women (42 and 32% of the cases), compared with postmenopausal women ($P = 0.023$ and 0.000, respectively) (Table 2). Each of these symptoms was classified as severe by more than two third of the younger women. The frequency and the severity of symptoms do not differ significantly in women treated with chemotherapy (with or without tamoxifen) compared with those treated with tamoxifen alone (Table 3).

3.2.2. *Concerns about personal health and about taking HRT*

The risk of breast cancer recurrence (75%) is the major concern among premenopausal patients, whereas also the risk of osteoporosis (56%) and cardiovascular diseases (46%) is frequently reported. The younger women were more frequently worried about the impact that both their cancer and the chemotherapy-induced early menopause

Table 2
Prevalence of menopausal symptoms in pre and postmenopausal women after chemotherapy plus hormonotherapy

Symptoms	Premenopausal		Postmenopausal		*P*
	Number	%	Number	%	
Hot flashes	37/41	90	32/59	54	0.000
Night sweat	27/41	66	16/59	27	0.000
Vaginal dryness	17/41	42	11/59	19	0.023
Libido reduction	13/41	32	7/59	12	0.000

Table 3
Incidence of menopausal symptoms after hormonotherapy, chemotherapy or hormono plus chemotherapy in premenopausal breast cancer

Symptoms	Incidence of symptoms in premenopausal women					
	Hormonotherapy		Chemotherapy		Hormono+chemotherapy	
	Number	%	Number	%	Number	%
Hot flashes	22/29	76	21/27	78	37/41	90
Insomnia	10/29	35	11/27	41	18/41	44
Night sweat	17/29	59	13/27	48	27/41	66
Tiredness	14/29	48	11/27	41	19/41	46
Anxiety	11/29	38	8/27	30	12/41	29
Depression	6/29	21	3/27	11	6/41	15
Irritability	9/29	31	7/27	26	8/41	20
Vaginal dryness	9/29	31	11/27	41	17/41	42
Dyspareunia	6/29	21	8/27	30	11/41	27
Libido reduction	6/29	21	8/27	30	13/41	32
Leucorrhea	4/29	14	1/27	4	3/41	7
Vaginal bleeding	1/29	3	2/27	7	3/41	7

could have on their quality of life (28%) than women of group A (13%) ($P = 0.005$) (Fig. 1).

As a consequence, more than 50% of these women consulted with a physician about these issues. The majority of the specialists consulted were gynaecologists (61%), and less frequently oncologists (16%) or general practitioners (23%). Doctors discouraged women from taking HRT in 38% of cases, deemed as irrelevant their complaints in 21% of cases and suggested alternative remedies in 18% of cases.

Among all women who filled the questionnaire, two third had heard or read about HRT. The majority of respondents (85%) had one or more concerns about taking HRT. Sixty-six percent were against the use of HRT, mainly because they feared it could increase their risk of cancer relapse (43%); 17% were worried of side-effects and 10% were discouraged by their physician's opinion (Fig. 3).

Despite these concerns, when asked if they would be willing to take HRT under medical supervision, 34% of these young women answered they would, mainly to alleviate vasomotor symptoms (53%), prevent osteoporosis (32%), reduce vaginal dryness (10%) and only marginally to decrease their cardiovascular risk (5%) (Fig. 3). The difference as compared with women included in group A is statistically significant (34 vs. 22%; $P = 0.05$).

4. Discussion

Menopausal symptoms are a frequent problem for breast cancer survivors [2,3,6–9,36]. Tamoxifen, the most widely prescribed drug for the adjuvant treatment of breast cancer, often exacerbates hot flushes [36]. In younger women, adjuvant chemotherapy and LHRH analogues cause premature ovarian failure and a high incidence of menopausal symptoms, which are frequently unexpected and particularly severe. These women might also have long-term problems like osteoporosis and an increased risk of cardiovascular diseases due to oestrogen deficiency.

HRT is the first choice in healthy women with menopausal symptoms, but is generally felt as contraindicated in breast cancer survivors for the concern that it can stimulate or hasten the growth of occult micrometastases. In spite of this, published data from a few observational trials of HRT in breast cancer survivors, both in early or advanced stage of the disease, have not demonstrated any increase of disease progression rates or cause-specific mortality [37–40].

Also the few, unfortunately small, studies including an untreated control group seem to be reassuring. Dew followed 167 cases treated with HRT for up to 22 years with both decreased recurrences and improved survival when compared with 1305 non users [41]. Di Saia in a report of 125 HRT users up to 30 years compared with 362 controls observed lower mortality (12%) among the users than non users (37%) [42]. O'Meara compared 147 HRT users to 656 non users and observed both a lower recurrence (17/1000 vs. 30/1000 person/years) and decreased mortality (5/1000 vs. 15/1000 person/years) in the HRT groups [43].

Some authors have explored the acceptability of HRT among breast cancer survivors. Couzi et al. [6] reported the occurrence of hot flushes (65%), night sweats (44%), vaginal dryness (48%), and dyspareunia (26%) among 222 breast cancer survivors, of whom 190 were menopausal. Thirty-one percent of these women declared that they would consider taking oestrogen; those who experienced menopause-related problems were more likely to consider oestrogen than those who did not (42 vs. 22%). Surprisingly, women's awareness regarding the potential benefits of estrogens in reducing the risk of heart disease and osteoporosis was not associated with an increased willingness to take them.

Ganz et al. performed a decision-analysis interview, in which visual aids were used to describe different hypothetical risks of breast cancer. Subjects were presented with a series of scenarios, in which a hypothetical woman might be experiencing one of several menopausal symptoms or might have a risk reduction of serious heart disease or osteoporotic hip fracture. This study reaffirms the reluctance of breast cancer survivors to take oestrogen after breast cancer diagnosis since there was an increasing willingness to consider therapy only if multiple symptoms coexisted and the possible risk of recurrence was small [33].

Our survey confirms that postmenopausal women with a history of breast cancer frequently report a worsening or the outbreak of vasomotor symptoms, feeling of depression and sleep disturbances as a consequence of adjuvant therapy for breast cancer. The overall percentage of women willing to take HRT is consistent with other reports and is higher in pre than in postmenopausal women. Patients' opinion concerning the protective effects of HRT against heart disease or osteoporosis did not influence the decision making process, whereas relief of menopausal symptoms was the predominant motivation for seeking information.

We also found that a significant proportion of breast cancer patients in Italy might be receptive to the idea of taking HRT. However, there is a diffuse sceptical attitude in the lay public and also in the medical community about the safety of this treatment for breast cancer survivors. Indeed, the majority of women had been advised against HRT by their physicians, who also very rarely did inform the patients about the existence of alternative non-hormonal remedies. We believe that at least part of the reluctance to prescribe HRT in patients with previous breast or endometrial cancers may be attributed to the fact that national health guidelines usually state that estrogens are contraindicated in these patients.

5. Conclusions

Women who become menopausal after receiving treatment for breast carcinoma have been advised to avoid HRT, but this practice is now being questioned. Most of these women have a favourable prognosis, so careful management of other existing conditions that may impair quality of life and mortality is necessary.

This survey shows that awareness of health issues is high among breast cancer survivors, who also show legitimate interest to treatments that may make them feel better and perhaps live longer. Nevertheless, a sort of unease regarding HRT persists among breast cancer patients and their doctors, despite the growing body of evidence suggesting the lack of any detrimental effect, yet in small series of patients and with a short follow up.

Therefore, the most prudent course may be to conduct short-term trials, with low-dose of HRT, in highly symptomatic and well-informed women, so that patients are likely to realise a tangible benefit from therapy. For those women who are

not willing to consider enrolment in HRT trials, effective non-hormonal means are now available to treat or improve symptoms associated with menopause or to prevent heart disease and osteoporosis. As currently most of these women do not receive adequate information, a better understanding is necessary if doctors want to improve the quality of care that they provide.

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