ELSEVIER

Maturitas 39 (2001) 217–225

MATURITAS
THE EUROPEAN MENOPAUSE JOURNAL

www.elsevier.com/locate/maturitas

A prospective study on women with a history of breast cancer and with or without estrogen replacement therapy

Merja B. Marttunen [a], Päivi Hietanen [b], Seppo Pyrhönen [b], Aila Tiitinen [a], Olavi Ylikorkala [a,*]

[a] *Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, PO Box 140, Helsinki, FIN-00029 HUS, Finland*

[b] *Department of Oncology, Helsinki University Central Hospital, Helsinki, FIN-00029 HUS, Finland*

Received 29 September 2000; received in revised form 21 March 2001; accepted 30 March 2001

Abstract

Objective: Because a categorical refusal of estrogen replacement therapy (ERT) from postmenopausal patients with a history of breast cancer is not based on any research evidence and may be more harmful than beneficial, we evaluated the safety and efficacy of ERT in these women. *Methods:* We recruited 131 patients who had been treated for breast cancer for a mean of 4.2 years (range 1 month to 20 years) before. Eighty-eight decided to use ERT, whereas 43 refused or had no need for ERT. At recruitment, the patients were carefully examined for breast and gynaecologic findings. Non-hysterectomized patients wishing to receive ERT ($n = 54$) then started using estradiol as oral tablets (2 mg/day) ($n = 44$) or as transdermal gel (1.5 mg/day) ($n = 10$) in combination with 10-day courses of oral medroxyprogesterone acetate at 4-week intervals, whereas hysterectomized patients ($n = 34$) used only estradiol, orally (2 mg/day) ($n = 31$) or transdermally (1.5 mg/day) ($n = 3$). The patients using ERT were carefully examined 6 and 12 months later, and then annually at a specific outpatient department, and the mean follow-up time is now 2.5 years (range from 1 month to 5.2 years, 216 woman-years). The 43 patients not wishing to receive ERT were followed annually at the oncologic department for a mean of 2.6 years (range from 1 month to 4.7 years), and served as a control group. *Results:* ERT significantly reduced climacteric symptoms, and the Kupperman score fell by 63%, from 26.9 ± 8.6 to 9.9 ± 6.7 (mean $\pm$ SD). In non-hysterectomized women, medroxyprogesterone acetate triggered withdrawal bleeding in all except seven women. Seven patients (13%) experienced spotting during ERT. In 27 women, endometrial thickness exceeded 10 mm, and two of the total of 54 patients (3.7%) had simple hyperplasia. This vanished spontaneously in 3–6 months. Ten patients terminated the use of ERT within the first 12 to 39 months due to the lack of severe vasomotor symptoms ($n = 4$) or due to the recurrence of breast cancer or to cancer of the contralateral breast ($n = 6$). Eighty-one of the 88 patients (92%) using ERT showed no evidence of recurrence, whereas five patients (5.7%) had recurrence in 12–36 months and two patients (2.3%) developed a cancer of the contralateral breast in 14–24 months; another one of those wanted to continue with ERT. Thus the combined risk of recurrence or a new cancer of the contralateral breast in ERT users was 7/216 woman-years (3% per year). In the control group, 38 of 43 patients (88.4%) showed no evidence of recurrence or contralateral cancer, whereas four

* Corresponding author. Tel: +358-9-47172900; fax: +358-9-2412192.
E-mail address: olavi.ylikorkala@huch.fi (O. Ylikorkala).

PII: S0378-5122(01)00211-0

patients had recurrence and one developed a contralateral breast cancer (5/112 woman-years, 4% per year). *Conclusions:* Symptomatic climacteric patients with a history of breast cancer benefited from ERT without increasing their risk of recurrence, but the short follow-up and the small number of patients limit any definitive recommendations.

Keywords: Estrogen replacement therapy; Breast cancer; Contralateral

1. Introduction

At present, approximately 80–90% of breast cancer patients survive for at least 5 years [1–3]. Due to earlier diagnosis of breast cancer by effective screening programs, and also to improved treatments, the number of women surviving breast cancer will drastically increase [4,5]. Thus, an increasing number of patients with a history of breast cancer will enter the menopause, which may even start earlier in these patients due to adjuvant chemotherapy [6,7]. In vitro [8] and epidemiological evidence [9] linking estrogens to the development of breast cancer has led to rather uniform denial of, or at least strong reservations about, the use of estrogen replacement therapy (ERT) in these patients, because of the fear that ERT could increase the risk of cancer recurrence or cancer in the contralateral breast [10–12]. This policy can be a double-edged sword, because it also denies these patients all the immediate and long-term health benefits of ERT [13,14]. Therefore, the wisdom of the categoric denial of ERT to breast cancer patients has been seriously questioned [15–17] and, indeed, some retrospective surveys on breast cancer patients using ERT may lend support for this criticism [18–25]. We felt it imperative to study the issue of ERT in breast cancer patients in a carefully controlled prospective research setting.

2. Patients and methods

We started this project, with the permission of the local ethics committee, in 1993, when a specific outpatient department for breast cancer patients was opened at our university hospital, serving a female population of approximately 0.8 million. We encouraged oncologists, surgeons, general practitioners and gynaecologists seeing patients with a history of breast cancer who complained of incapacitating climacteric symptoms to admit them freely to our clinic. One gynaecologist (M.M.) interviewed these patients, whose breasts were then carefully examined (mammography, tumour markers such as Ca 15-3) to exclude any recurrence or a cancer in the contralateral breast. Their postmenopausal status was confirmed by serum follicle stimulating hormone (FSH) exceeding 30 IU/l. In addition, because of increased risk of endometrial cancer in these patients [26], each patient underwent a careful pelvic examination, including vaginal sonography (endometrial thickness, and uterine and ovarian morphology). An endometrial biopsy was taken if endometrial thickness (a double layer) exceeded 5 mm at entry or 10 mm on a follow-up visit, or if there had been abnormal uterine bleeding before recruitment or such bleeding appeared during the trial. A Pap smear test was taken. The patients were also carefully interviewed to determine risk factors of cardiovascular diseases (i.e. ischemic heart disease at < 55 years of age in a first-degree relative) or osteoporosis (i.e. family history of osteoporotic fractures; systemic use of corticosteroids). The benefits and risks of ERT in postmenopausal women were explained thoroughly, both orally and in written form, and all patients gave written informed consent.

After the first visit, the patients started recording climacteric symptoms on Kupperman's scale, and they were seen again 2–3 weeks later. At this visit, the patients who were judged to have invalidating climacteric symptoms (Kupperman score ≥ 10) ($n = 95$), and/or had a family tendency to cardiovascular disease ($n = 10$) or risk factors of osteoporosis ($n = 12$), were offered ERT, whereas patients having only mild symptoms (Kupperman score < 10) or having no risk factors were advised

not to start ERT. ERT consisted of either 2 mg of estradiol valerate daily (Progynova®, Schering, Berlin, Germany), or 1.5 mg of estradiol daily as a transdermal gel (Estrogel®, Leiras, Turku, Finland); the selection between oral and transdermal routes was primarily made by the patient herself. For non-hysterectomized patients, ERT was combined with 10-day courses of 10 mg/day medroxyprogesterone acetate (Provera®, Pharmacia & Upjohn, Kalamazoo, Michigan) at 4-week intervals. Patients starting ERT were seen 6 and 12 months later, and then annually, and the baseline breast and gynaecological examinations were repeated. In addition, the patients were encouraged to contact the research centre whenever they so wished. The patients who decided not to start ERT were seen annually at the oncological department only.

All data are expressed as the mean $\pm$ SD. Paired and unpaired Student's t-test and the chi-square test were used for statistical analysis.

3. Results

From August 1, 1993 to the end of 1998, 131 breast cancer patients had been admitted to the clinic. They had been operated upon for ductal carcinoma (ca) in situ ($n = 4$), stage I ($n = 87$), stage II ($n = 37$), or stage III ($n = 3$) breast cancer a mean of 4.2 years (range 1 month to 20 years) before. Sixty-two patients (47%) had experienced mastectomy, 100 patients (76%) had received postoperative radiotherapy and 19 patients (14%), adjuvant chemotherapy (Table 1). Five patients had used antiestrogens before the initiation of the trial, but none used them during the trial.

Of the 131 breast cancer patients, 88 patients (67.2%) finally started ERT (Table 1). The main reason for starting ERT was severe climacteric symptoms (in 85 women); only two patients started ERT primarily for cardiovascular prevention and one for fear of osteoporosis. Twenty-three patients were judged not to be candidates for ERT, six (4.5%) because they were not menopausal (FSH < 30 IU/L), and 17 (13.0%) who had only modest climacteric symptoms (Kupperman score < 10) and no family tendency to cardiovascular diseases or osteoporosis. In addition, 20 patients (15.3%) who were judged to be candidates for ERT refused it for fear of relapse. Thus, 43 patients came to serve as controls. The patient groups with and without ERT were comparable (e.g. in regard to the estrogen receptor status) except for the fact that the women starting ERT were slightly more often node negative (81.8%) than the controls (69.8%) (Table 1). The proliferative activity of tumour cells had been measured by flow cytometry in 40 patients (25 ERT users and 15 controls), and the nuclear protein Ki67 had been determined in 38 patients (22 ERT users and 16 controls); there were no differences in these prognostic factors between the groups.

Seventy-five patients (44 non-hysterectomized, 31 hysterectomized) elected to use oral ERT, whereas 13 patients (ten non-hysterectomized, three hysterectomized) preferred transdermal ERT. All patients offered ERT alone or in combination with medroxyprogesterone acetate could use it as instructed. ERT reduced the Kupperman score significantly; in this regard the oral and transdermal regimens were equally effective (Fig. 1). The Kupperman score was reduced by 63% at the first 6-month follow-up visit and no further improvement was seen in this score at later visits. Five patients increased the dose of oral estradiol to 3 mg between 6 and 12 months to control symptoms, and three women reduced the dose of estradiol to 1 mg between 1 and 4 months because of breast tenderness. Three non-hysterectomized patients experienced PMS-like symptoms (depression, fatigue, oedema) during the progestin phase, and in these women progestin was given for 14 days at 2-month intervals. Four patients decided to discontinue ERT within 1.4–3.3 years because of the lack of climacteric symptoms.

Of the 54 patients with an intact uterus, the endometrial thickness (double layer) was less than 5 mm at entry in all except one patient, who had a benign endometrial polyp; the polyp was removed through hysteroscopy before the start of ERT. Regular withdrawal bleeds after the progestin phase ensued in all women except for seven who did not bleed at all. During ERT,

seven patients (13%) experienced spotting, four of them after 1 year's use and three patients after 2 years' use. In these cases, endometrial biopsies showed normal proliferation ($n = 4$) or secretion ($n = 3$). No hyperplasia was seen. Endometrial thickness exceeded 10 mm after 2 ($n = 20$) or 3 ($n = 7$) years use of ERT in 27 patients, and endometrial biopsy showed proliferative ($n = 18$) or secretory ($n = 10$) changes in all except for two patients (endometrial thickness 12 and 18 mm, respectively) whose endometrium showed simple hyperplasia. In these two women, repeat biopsies were collected 3 and 6 months later, and then the endometrium was proliferative. There were no

Table 1
Clinical characteristics (mean ± SD or %) (range) of postmenopausal women with a history of breast cancer ($n = 131$) who either started estrogen replacement therapy (ERT) ($n = 88$) or who were followed without it ($n = 43$)

	Women with ERT ($n = 88$)	Women without ERT ($n = 43$)	P-value
Parity			
Nulliparous	14 (16%)	10 (23%)	NS
Parous	74 (84%)	33 (77%)	
Hysterectomised	34 (38.6%)	9 (20.9%)	NS
At diagnosis of breast cancer			
Age (years) (range)	49.2 ± 6.8 (30–68)	48.6 ± 7.4 (33–76)	NS
Postmenopausal	33 (37%)	21 (49%)	NS
Treatment of breast cancer			
Mastectomy	37 (42.0%)	25 (58.1%)	NS
Conservative surgery	51 (58.0%)	18 (41.9%)	NS
Postoperative radiotherapy	64 (72.7%)	36 (83.7)	NS
Adjuvant chemotherapy	10 (11.4%)	9 (20.9%)	NS
Adjuvant hormonal therapy	3 (3.4%)	2 (4.6%)	NS
Classification of tumour spread			
Size			
Ductal ca in situ	3 (3.4%)	1 (2.3%)	NS
T1	67 (76.1%)	29 (67.4%)	NS
T2	17 (19.3%)	11 (25.6%)	NS
T3	1 (1.1%)	2 (4.7%)	NS
Axillary nodes			<0.05
N0	72 (81.8%)	30 (69.8%)	
N1	10 (11.4%)	13 (30.2%)	
1–3 positive nodes	9 (10.0%)	10 (23.3%)	
≥4 positive nodes	1 (1.1%)	3 (7.0%)	
Not analysed	6 (6.8%)	0 (0%)	
Estrogen receptors			NS
Positive	57 (64.8%)	29 (67.4%)	
Negative	15 (17.0%)	9 (20.9%)	
Not analysed	16 (18.2%)	5 (11.6%)	
Positive receptors	54 (61.4%)	30 (69.8%)	NS
	13 (14.8%)	7 (16.3%)	
	21 (23.9)	6 (13.9%)	
Histological grade			NS
Ductal ca in situ	3 (3.4%)	1 (2.3%)	
Gr I	37 (42.0%)	1 (27.9%)	
Gr II	28 (31.8%)	15 (27.9%)	
GrIII	12 (13.6%)	7 (16.3%)	
Not known	8 (9.1%)	8 (18.6%)	

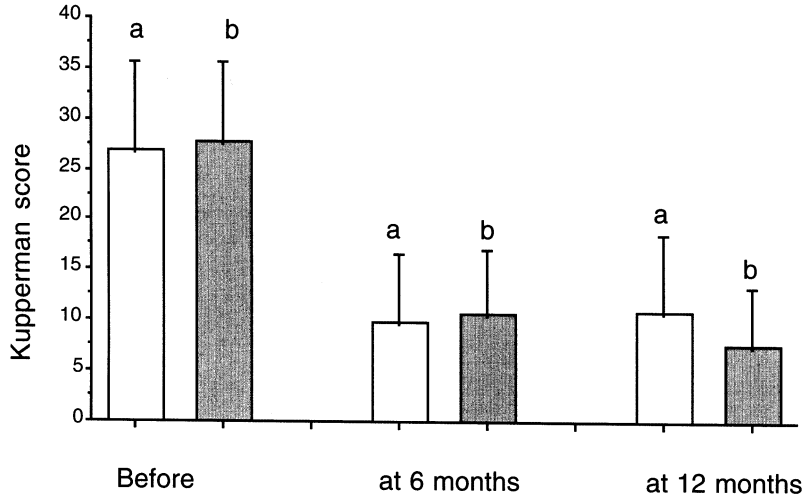

Fig. 1. The Kupperman score before and during a one-year course of oral ($n = 75$, white bar) or transdermal ($n = 13$, gray bar) estrogen replacement therapy. (a and $b = p < 0.0001$).

abnormal findings in the ultrasound examinations of the ovaries during the study.

Before the initiation of ERT, 49 of the 54 non-hysterectomized women had normal Pap smears, atypical squamous cells of undetermined significance were detected in three women and benign reactive changes in two women. All these changes had vanished in the control Pap smear 3 to 6 months later. During the follow-up time, 13 patients had atypical squamous cells and two patients reactive changes; ten of these improved spontaneously. Colposcopy was performed in five women with repeated atypia, and no precancerous cervical lesions were detected.

So far, 36 women have used ERT for more than 3 years, 20 women for 2–3 years, 20 women for 1–2 years, and 12 women for less than 1 year. The mean ($\pm$ SD) duration of ERT is 2.5 ± 1.5 years (range 1 month to 5.2 years), which corresponds to 216 woman-years. In careful oncological examinations, 81 of the 88 patients (92%) have shown entirely normal findings and no signs of relapse. Seven women (7.9%) (four with estrogen receptor positive cancer) have experienced either recurrence ($n = 5$) or a new cancer of the contralateral breast ($n = 2$); two patients have died of breast cancer (Table 2). The incidence of recurrence or new cancer per woman-year with ERT was 3%. Another of the patients with contralateral breast cancer wanted to continue ERT. Of 43 patients not using ERT, four had relapses and one had a contralateral breast cancer (three with estrogen receptor positive cancer) in 10–14 months' time. Thus the recurrence rate was 4% per follow-up year. Three of the controls have died of the breast cancer.

4. Discussion

It can be calculated from the Finnish Cancer Registry databases that approximately 11 000 postmenopausal women with a history of breast cancer were living in the area served by our outpatient department in the period 1993–1998 (Finnish Cancer Register), yet only 131 of them (1%) were admitted to our department. The low rate can be explained by several factors and insufficient spread of information on our policy could be one explanation. However, we feel that the most important cause of refusal to register at our clinic is the severe fear of ERT among these patients. Further, it is likely that such reservations about the use of ERT concern not only patients, but also their physicians. Nevertheless we managed to recruit a representative number of pa-

Table 2
Clinical data on patients who had relapses or a new cancer in the contralateral breast during the ERT or follow-up (f-u)

	AGE AT DIAGNOSIS	TNM	PRIMARY TREATMENT	Interval between diagnosis and start of ERT/f-u	Interval between start of ERT/f-u and relapse	Actual situation
With ERT						
Patient 1	50 yrs	T1N0M0	conservative surgery, radiation	53 mths	20 mths	local recurrence, alive, no signs of disease
Patient 2	43 yrs	T1N0M0	conservative surgery, radiation	46 mths	14 mths	systemic recurrence, death
Patient 3	47 yrs	T1N1M0	mastectomy, radiation and chemotherapy	10 mths	14 mths	systemic recurrence, death
Patient 4	49 yrs	T1N1M0	mastectomy, radiation and chemotherapy	24 mths	36 mths	systemic recurrence,alive, on aromatase inhibitor treatment
Patient 5	50 yrs	T1N0M0	conservative surgery, radiation	12 mths	24 mths	contralateralbreast cancer, alive, on tamoxifen
Patient 6	39 yrs	T2N0M0	mastectomy, radiation and chemotherapy	10 mths	12 mths	systemic recurrence, alive, on tamoxifen
Patient 7	42 yrs	T2N1M0	mastectomy, radiation	153 mths	14 mths	contralateral breast cancer, alive, on ERT
Without ERT						
Patient 1	48 yrs	T1N1M0	mastectomy, radiation and chemotherapy	24 mths	10 mths	systemic recurrence, death
Patient 2	47 yrs	T1N0M0	Conservative surgery, radiation	38 mths	12 mths	systemic recurrence, death
Patient 3	50 yrs	Ductal CIS	mastectomy	10 mths	13 mths	contralateral breast cancer T1N0
Patient 4	65 yrs	T2N1M0	mastectomy, radiation and chemotherapy	10 mths	14 mths	systemic recurrence, death
Patient 5	40 yrs	T1N1M0	mastectomy, radiation and chemotherapy	96 mths	12 mths	systemic recurrence, alive

tients, but out of the 131 patients registered only 108 (82.4%) turned out to have solid indications for using ERT. Even of this population, 20 (18.5%) refused to start using ERT, which left 88 patients to start ERT. We studied our patients carefully at recruitment to ensure that none of them had any recurrence before being included in our study. In addition, the patients starting ERT were also thoroughly examined during the ERT to detect any recurrence as soon as possible. Because a history of breast cancer denotes an increased risk of endometrial cancer [26], we also carefully monitored endometrial health. ERT was given either orally or transdermally, at doses commonly used in otherwise healthy women, and, as expected, all climacteric symptoms were alleviated and their quality of life improved. As regards protection against cardiovascular diseases and osteoporosis by ERT, we acknowledge that the follow-up time was far too short and the number of patients too limited to provide any reliable data; however, it was conspicuous that none of these postmenopausal patients using ERT developed ischemic heart disease or became hypertensive during the trial.

Large prospective, preferably placebo-controlled trials would be necessary to assess the final safety of ERT in healthy women, not to mention patients with a history of breast cancer. In practice such a study would be difficult to perform, and perhaps even unethical, because one cannot offer a placebo for a symptomatic climacteric patient wishing to receive ERT. Moreover, due to the good present prognosis of breast cancer patients [1–3], thousands of such patients would be needed if the end point of the trial were to be a recurrence of the cancer. Nevertheless, we feel that our trial, although limited in patient number and duration, is valuable. The strength of our study was increased because we carefully excluded any recurrence in our patients before and during ERT, which has not been the case in some previous surveys dealing with the same topic [18–25].

The overall risk of recurrence or contralateral breast cancer was similar in patients with ERT (3%) or without ERT (4%). Thus our data may indicate that ERT as given for 2–3 years did not increase the risk of recurrence, or a new cancer of the contralateral breast. Moreover, our data obtained in a prospective set-up are in harmony with the published recurrence rate (1–5%) of breast cancer in women using ERT (Table 3). We admit all the limitations, such as a lack of randomisation or potential differences between study group and controls in our study, but even smaller, non-randomised series on this controversial topic are valuable.

The role of progestin on the development of breast cancer is still unclear. The data from Sweden and United States have shown that adding progestin to estrogen replacement increases the risk of breast cancer by 14–40% in healthy women [27–29], whereas a progestin addition does not affect the risk of cancer recurrence in women with a history of breast cancer who are using estrogen replacement [21,23,25]. Progestins are also of importance for endometrial protection, because breast cancer per se indicates an increased risk of endometrial cancer [26]. In our study, ERT did not lead to endometrial cancer, although our progestin regimen was not so rigorous as sometimes recommended [30]. However, a word of caution is needed. The duration of exposure to ERT may need to exceed 5–10 years in healthy women before the risks of breast and endometrial cancer become evident [9], and therefore we will continue the follow-up of our patients.

Previous retrospective reports on ERT in breast cancer patients are based on study populations of 25–90 patients who have used ERT for a mean of 1.5–2.5 years (Table 3). We treated our patients in a prospective setting. The recurrence rate during ERT was rather similar to that in previous surveys [18–24] (Table 3). This finding may suggest that previous retrospective data [18–24] is rather accurate. Yet we readily admit that a much larger number of patients with breast cancer using or not using ERT must be followed before ERT can be routinely prescribed to breast cancer patients. In addition, the need for ERT in these patients can be questionable, because selective estrogen receptor modulators, such as raloxifene, decrease the risk of breast cancer and provide several health benefits, but unfortunately increase vasomotor symptoms [31].

Table 3
Previous, non-comparative data on the use of ERT following breast cancer as compared with the present data on patients using (ERT+) or not using (ERT-) ERT

Variable	First author							Present study	
	Wile, 1993	Powles, 1993	DiSaia, 1993	Eden, 1995	V-Sellin, 1995	Natrajan, 1999	U-Vrscaj, 1999	ERT +	ERT −
No. of patients	25	35	77	90	43	50	21	88	43
STAGE, NO. OF PATIENTS							NA		
Ca in situ	2		6		2	1		3	1
I	13		43		22	46		59	25
II	7		17		19	3		22	15
III	1		5					1	2
NA	2		6					3	
Size of tumour, no. of patients									
T1		12						70	30
T2		14						17	11
T3		9						1	2
Axillary nodes, no. of patients									
Negative		12	58	72	28	46	14	72	30
Positive		10	13	18	8	3	7	10	13
NA		13	6		7	1		6	
Estrogen receptors, no. of patients									
Positive	NA	NA	28	12	7	12	5	57	29
Negative			12	10	20	7	16	15	9
NA			37	68	16	31		16	5
Mean interval between surgery and start of ERT / follow-up	26	31	24	60	84	17	62	49	55
(mean, range)	(0–180)	(0–215)	(0–324)	(0–300)	(0–286)	(6–300)	(1–180)	(1–204)	(3–230)
Mean duration of ERT / follow-up	35	15	27	18	31	66	28	29	31
(months, range)	(6–78)	(1–44)	(1–233)	(4–144)	(24–142)	(6–384)	(3–72)	(1–62)	(1–55)
No. of recurrences	3/25	2/35	7/77	6/90	1/43	3/50	4/21	7/88	5/43
Recurrence (% / woman-year)	4%	5%	4%	4%	1%	1%	8%	3%	4%

NA = Data not available.

References

[1] Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. Lancet 1992;339:1-15, 71-85.

[2] Carter CL, Allen C, Henson DE. Relation of tumour size, lymph node status, and survival in 24740 breast cancer cases. Cancer 1989;63:181–7.

[3] Joensuu H, Pylkkänen L, Toikkanen S. Late mortality from pT1N0M0 breast cancer. Cancer 1999;85:2183–9.

[4] Garne JP, Aspegren K, Balldin G, Ranstam J. Increasing incidence of and declining mortality from breast carcinoma: trends in Malmö, Sweden, 1961-1992. Cancer 1997;79:69–74.

[5] UK Trial of Early Detection of Breast Cancer Group. 16-year mortality from breast cancer in UK Trial of Early Detection of Breast Cancer. Lancet 1999;353:1909–2014.

[6] Rose DP, Davis TE. Ovarian function in patients receiving adjuvant chemotherapy for breast cancer. Lancet 1977;1:1174–6.

[7] Bianco AR, Del Mastro L, Gallo C, Perrone F, Matano E, Pagliarulo C, et al. Prognostic role of amenorrhea induced by adjuvant chemotherapy in premenopausal patients with early breast cancer. Br J Cancer 1991;63:799–803.

[8] Lippman M, Bolan G, Huff K. The effects of estrogens and antiestrogens on hormone responsive human breast cancer in long-term tissue culture. Cancer Res 1976;36:4595–601.

[9] Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. Lancet 1997;350:1047–59.

[10] Fitzgerald CT, Elstein M, Mansel RE. Hormone replacement therapy and malignancy. Br J Obst Gynecol 1993;100:408–10.

[11] Marchant DJ. Supplemental estrogen replacement. Cancer 1994;74:512–7.

[12] Colditz GA. Oestrogen replacement therapy for breast cancer patients. Oncology 1997;11:1491–7.

[13] Ettinger B, Friedman GD, Bush T, Quesenberry CP. Reduced mortality associated with long-term postmenopausal oestrogen therapy. Obstet Gynecol 1996;87:6–12.

[14] Daly E, Vessey MP, Barlow D, Gray A, McPherson K, Roche M. Hormone replacement therapy in a risk-benefit perspective. Maturitas 1996;23:247–59.

[15] Cobleigh MA, Berris RF, Bush T, Davidson NE, Robert NJ, Sparano JA, et al. Oestrogen replacement therapy in breast cancer survivors. JAMA 1994;272:540–5.

[16] Roy JA, Sawka CA, Pritchard KI. Hormone replacement therapy in women with breast cancer: do the risks outweigh the benefits? J Clin Oncol 1996;14:997–1006.

[17] Braendle W. Hormone replacement therapy in women with breast cancer. Anticancer Res 1998;18:2253–6.

[18] Wile AG, Opfell RW, Margileth DA. Hormone replacement therapy in previously treated breast cancer patients. Am J Surg 1993;165:372–5.

[19] Powles TJ, Hickish T, Casey S, O'Brien M. Hormone replacement after breast cancer. Lancet 1993;342:60–1.

[20] DiSaia PJ, Odicino F, Grosen E, Cowan B, Pecorelli S, Wile AG. Hormone replacement therapy in breast cancer. Lancet 1993;342:1232.

[21] Eden JA, Bush T, Nand S, Wren BG. A case-control study of combined continuous oestrogen-progestin replacement therapy among women with a personal history of breast cancer. Menopause 1995;2:67–72.

[22] Vassilopoulou-Sellin R, Theriault R, Klein MJ. Oestrogen replacement therapy in women with prior diagnosis and treatment for breast cancer. Gyn Oncol 1997;65:89–93.

[23] Natrajan PK, Soumakis K, Gambrell RD. Estrogen replacement therapy in women with previous breast cancer. Am J Obstet Gynecol 1999;181:288–95.

[24] Ursic-Vrscaj M, Bebar S. A case-control study of hormone replacement therapy after primary surgical breast cancer treatment. Eur J Surg Oncol 1999;25:146–51.

[25] Dew J, Eden J, Beller E, Magarey C, Schwartz P, Crea P, Wren B. A cohort study of hormone replacement therapy given to women previously treated for breast cancer. Climactric 1998;1:137–42.

[26] Adami H-O, Bergström R, Weiderpass E, Persson I, Barlow L, McLaughlin JK. Risk for endometrial cancer following breast cancer: a prospective study in Sweden. Cancer Causes Control 1997;8:821–7.

[27] Persson I, Weiderpass E, Bergström R, Schairer C. Risks of breast and endometrial cancer after estrogen and estrogen-progestin replacement therapy. Cancer Causes Control 1999;10:253–60.

[28] Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and beast cancer risk. JAMA 2000;283:485–91.

[29] Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen-progestin. J Natl Cancer Inst 2000;92:328–32.

[30] Gambrell RD Jr. Strategies to reduce the incidence of endometrial cancer in postmenopausal women. Am J Obstet Gynecol 1997;177:1196–207.

[31] Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women. Results from the MORE randomized trial. JAMA 1999;281:2189–97.