Original Research

Breast Cancer Risk in Postmenopausal Women Using Estrogen-Only Therapy

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OBJECTIVE: To evaluate whether the risk of estrogen-only therapy on breast cancer varies by dose, constituent, and route of administration.

METHODS: All Finnish women older than age 50 years using oral or transdermal estradiol (n=84,729), oral estriol (n=7,941), or vaginal estrogens (n=18,314) for at least 6 months during 1994–2001 were identified from the national medical reimbursement register. They were followed for breast cancer with the aid of the Finnish Cancer Registry to the end of 2002.

RESULTS: Altogether, 2,171 women with breast cancer were identified. The standardized incidence ratio of breast cancer with systemic estradiol for less than 5 years was 0.93 (95% confidence interval 0.80–1.04), and for estradiol use for 5 years or more, 1.44 (1.29–1.59). Oral and transdermal estradiol was accompanied by a similar risk of breast cancer. The risk was most prominent with the dose greater than 1.9 mg/d orally; whereas the risk associated with transdermal route was not dose-dependent. The standardized incidence ratio for the lobular type of breast cancer (1.58) was slightly higher than that for the ductal type (1.36). The use of estradiol was associated with both localized breast cancer (1.45; 1.26–1.66) and cancer spread to regional nodes (1.35; 1.09–1.65). The incidence of carcinoma in situ (n=32) was increased (2.43; 1.66–3.42) among estradiol users.

CONCLUSION: Estradiol for 5 years or more, either orally or transdermally, means 2–3 extra cases of breast cancer per 1,000 women who are followed for 10 years. Oral estradiol use for less than 5 years, oral estriol, or vaginal estrogens were not associated with a risk of breast cancer.

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See related editorial on page 1352.

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Although hyperestrogenic states, such as early menarche, nulliparity, obesity, high levels of endogenous estrogens, and late menopause, are known to predispose women to an elevated risk of breast cancer,[1] data on the effect of estrogen-only therapy on the risk of breast cancer are inconclusive. A reanalysis of 51 epidemiologic studies demonstrated a relative risk (RR) of 1.35 (95% confidence interval [CI] 1.21–1.49) for 5 or more years of postmenopausal hormone therapy, but these women were not exclusively estrogen users; 12% had also used progestins,[2] which may promote breast pathology more than does estrogen.[3–12] A meta-analysis of 45 studies on the use of estrogen-only therapy revealed no association between this regimen and the risk of breast cancer.[13] After this meta-analysis, estrogen-only therapy (mostly involving conjugated equine estrogens), even for 25 years or longer, was shown to have no effect on the risk of breast cancer, although the associated odds ratios were not inconsistent with a possible small effect.[4] In Europe, estradiol-based regimens dominate, and the Million Women Study[5] reported that current use of estrogen-only therapy was accompanied by a risk of breast cancer (RR 1.30, 95% CI 1.21–1.40). In contrast, conjugated equine estrogens given for 6.8 years were associated with an almost significantly decreased risk of breast cancer (RR 0.77, 95% CI 0.59–1.01) in a placebo-controlled study.[14] Oral and transdermal routes of estrogen administration result in different estrogenic milieu, and therefore, the route of administration may be a determinant for the risk of breast cancer. Two studies

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comparing oral and transdermal regimens in this regard found no evidence to support this hypothesis, but they were both rather short in duration.[5,6] Altogether, data on the effect of oral or transdermal estrogen-only therapy on the risk of breast cancer are still far from being clear.

Epidemiologic studies are always open to criticism such as inaccurate documentation of use, recall bias, and national differences in postmenopausal hormone therapy. In Finland, the use of postmenopausal hormone therapy can be accurately traced from the medical reimbursement register of the National Social Insurance Institution, to which the details of postmenopausal hormone therapy purchases have been entered since 1994. Estrogen-only therapy is commonly used, because 20% of Finnish women undergo hysterectomy by the age of 60 years,[15] enabling them to use such a therapy if invalidating postmenopausal symptoms occur. Therefore, we studied the effect of different doses, constituents, and routes of administration of estrogen-only therapy on the risk of breast cancer in a cohort representing the entire Finnish postmenopausal population.

MATERIALS AND METHODS

With the permission from the National Research and Development Centre for Welfare and Health, all women older than 50 years of age (n=283,680) who had bought (at least once) an estrogen-only regimen (oral, transdermal, vaginal) in 1994–2001 were identified from the medical reimbursement register (Fig. 1). This register covers all use of postmenopausal hormone therapy in the whole country, because these regimens, available only by doctor's prescription, are financially reimbursed (except a few estriol-containing vaginal ointments and suppositories). From this group we excluded 172,309 women with estrogen-only use of less than 6 months and 387 women who had bought conjugated equine estrogens (available from 1997). Thus, our final cohort consisted of 110,984 women using estradiol and estriol-based regimens (Fig. 1, Table 1).

Purchases of estrogen formulations were classified into estradiol-containing regimens (tablets, patches, and gels), oral estriol, and vaginally administered estrogens. First, we analyzed subgroups of women who had exclusively used tablets, patches, or gels, and in this classification a deviation of up to 6 months from the index regimen was allowed. Then, users of patches and gels were combined to obtain a transdermal estrogen therapy group. Women using oral estriol were analyzed as a group on their own. This classification was not affected by a possible concomitant use of vaginal estrogens.

The register was opened in 1994, and a possibility existed that some women had used postmenopausal hormone therapy before this period. Therefore, to obtain the group of estrogen-only therapy users who had not definitely used any other form of postmenopausal hormone therapy, we analyzed women who bought their first estrogen regimen at least 1 year after the register opened and used it for at least 6 months. This group had been exposed to only estrogen therapy, and in them we analyzed the effect of the use of estrogen-only therapy for less than 5 years on the risk of breast cancer.

Cumulative doses of estrogens to which women had become exposed during use were calculated for each formulation, and these were divided by the numbers of days of exposure. In this calculation women using both patch and gel were classified according to patch use. Thus, we could calculate the

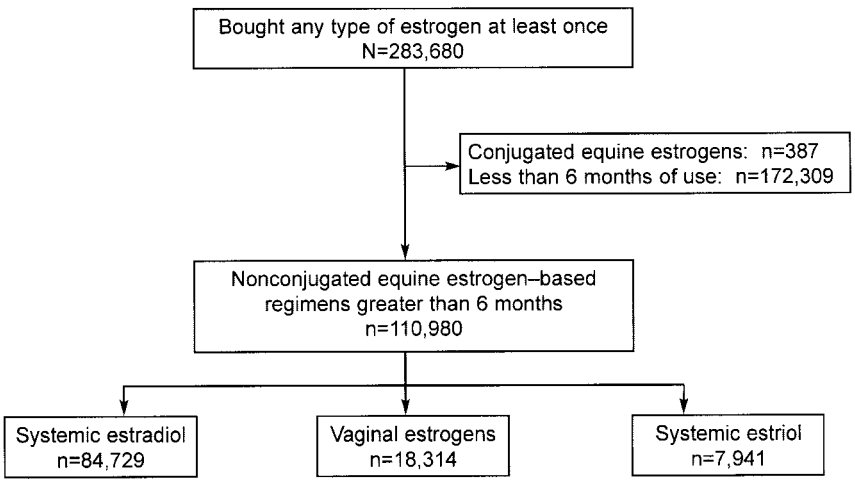

Fig. 1. Flow chart of the cohort of women using estrogen-only therapy.
Lyytinen. Breast Cancer Risk Among Estrogen Users. Obstet Gynecol 2006.

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Table 1. Cohort Using Oral or Transdermal Estradiol, Oral Estriol, and Vaginal Estrogens for at Least 6 Months Without Progestin*

Age (y)	n	Woman-Years	Breast Cancer Cases
50–54	30,277	67,049	185
55–59	24,533	164,589	512
60–64	18,289	152,169	509
65–69	14,740	109,422	432
70–74	10,860	75,587	240
75–79	6,873	44,805	166
80–84	3,572	22,287	74
85+	1,840	12,114	53
Total	110,984	648,022	2,171

* Number of women by age at the beginning of the follow-up, women-years by age at the follow-up, and breast cancer cases up to December 31, 2002, during 1994–2001.

accurate mean daily dose of estrogen to which each user had become exposed, and we did not need to rely on the doses marked on prescriptions.

We followed our subjects from the completion of the selected exposure to estrogen times in 1994–2001 to the end of 2002 or to death. In the analysis of breast cancer risk after at least 6 months of exposure, there were altogether 648,022 women-years at risk and 2,171 breast cancer cases (Table 1). Finnish Cancer Registry receives notifications on cancer from hospitals, from pathological and cytological laboratories, and also from physicians working outside hospitals, and its coverage is almost 100%.[16] The ductal type of breast cancer dominated (76%), followed by the lobular type (17%). Of all the cancers, 66% were localized, 26% were spread to regional nodes, and 2.5% showed distant metastases at the time of diagnosis. In situ cancers (n=141) were analyzed separately.

The expected numbers of cases of breast cancer were calculated by multiplying the number of person-years in each 5-year age group by the corresponding average breast cancer incidence among all Finnish women during the same period of observation.[17] To calculate standardized incidence ratios, the observed numbers of cases were divided by the numbers expected. Ninety-five percent confidence intervals (CIs) were estimated on the presumption that the number of observed cases followed a Poisson distribution.[18] The risk of breast cancer was compared between different estradiol doses and analyzed by the Wald test.[19]

RESULTS

The use of estradiol was associated with an increased risk of breast cancer after 5 years of use (Table 2). Neither an oral estriol regimen nor vaginal use of any estrogen formulations were accompanied by a significantly increased risk of breast cancer (Table 2). Among women who had used estradiol for less than 5 years during the observation time and were users when the register was opened, the risk of breast cancer was increased (standardized incidence ratio 1.30, 95% CI 1.23–1.38), but preregister use of postmenopausal hormone therapy was possible among these women (Table 2).

The standardized incidence ratio of breast cancer increased along with the increasing daily dose of oral estradiol, and the risk was significantly elevated if the

Table 2. Standardized Incidence Ratios of Breast Cancers among Women Using Oral or Transdermal Estradiol, Oral Estriol, and Vaginal Estrogens by Duration of Use*

Duration	n	Obs	Exp	SIR	95% CI
Estradiol					
6 mo or more to less than 5 y†	28,380	340	363	0.93	0.80–1.04
6 mo or more to less than 5 y‡	29,445	1,166	895	1.30	1.23–1.38
5 y or more	26,904	345	239	1.44	1.29–1.59
Estriol					
6 mo or more to less than 5 y†	2,857	34	35	0.98	0.68–1.37
6 mo or more to less than 5 y‡	3,717	88	82	1.07	0.86–1.32
5 y or more	1,367	16	11	1.41	0.80–2.28
Vaginal estrogens					
6 mo or more to less than 5 y†	7,303	43	64	0.67	0.48–0.90
6 mo or more to less than 5 y‡	10,879	138	130	1.06	0.89–1.25
5 y or more	132	1	0.71	1.41	0.04–7.86

Obs, observed number of breast cancer cases; Exp, expected number of cases; SIR, standardized incidence ratio; CI, confidence interval.
* Use in ages older than 50 years during 1994–2001, observed and expected number of breast cases up to December 31, 2002, and standardized incidence ratios with their 95% confidence intervals.
† Only users from 1995 to 2001 (with completely known exposure history) were included.
‡ Users from 1994 (with possible preregister use) were included.

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mean calculated dose of estradiol had been higher than 1.9 mg/d in users of 5 years or more (Table 3). However, the trend by dose was not statistically significant (*P* for trend=.27).

Use of patches of all doses for 5 years or more was accompanied by an elevated standardized incidence ratio of breast cancer: 1.74 (0.79–3.29, n=599) for less than 30 mcg/d, 1.30 (1.07–1.66, n=6845) for 30–60 mcg/d, and 1.62 (0.74–3.07, n=611) for more than 60 mcg/d. Most of gel users had used more than 0.9 mg/d (90%, n=867) for 5 years or more, and the standardized incidence ratio was 1.52 (0.73–2.78). In a joint analysis of transdermal estradiol use, doses of less than 30 mcg from patches and less than 0.6 mg from gel were regarded as equivalent and grouped together ("low dose"), as were 30–60 mcg from a patch and 0.6–0.9 mg from gel ("medium dose") and more than 60 mcg from a patch and more than 0.9 mg from gel ("high dose"). Transdermal use of estradiol for 5 years or more at any dose was associated with an elevated standardized incidence ratio of breast cancer (Table 3).

The standardized incidence ratio for the lobular type of breast cancer among estradiol users for 5 years or more was slightly higher than that for ductal cancer, and the standardized incidence ratio was highest for the small category of breast cancer not classified as the ductal or lobular type (Table 4). The use of estradiol for 5 years or more was associated with an increased incidence of both localized cancer and cancer spread to regional nodes, whereas breast cancer with unknown stage seemed to be more common among estradiol users for any length of time than in the general population (Table 4). The standardized incidence ratio for carcinoma in situ was 2.43 (1.66–3.42) among estradiol users for 5 years or more (Table 4).

Because postmenopausal hormone therapy use before 1994 was not known, we estimated the duration of estradiol use in women using estradiol since 1994 by assuming that they had started use at the age of 52 years, which is the case generally in Finland. The standardized incidence ratio related to estimated estradiol use of 5–10 years was 1.34 (95% CI 1.16–1.54; 193 observed cases of breast cancer), for use of 10–20 years 1.57 (1.31–1.86; 125 cases), and for use of more than 20 years, 1.75 (1.16–2.55; 27 cases).

DISCUSSION

Because genes, diets, lifestyles, and mammography screening programs, which all are factors in the development and detection of breast cancer, show large national differences,[20–22] possible associations between postmenopausal hormone therapy and breast cancer should be studied nationally. We wanted to focus on estrogen-only therapy first, because estrogen is the key hormone in treatment of menopausal complaints, and–because of the liberal attitude toward hysterectomy in Finland, approximately 20% of women undergo hysterectomy by age 60 (60% of these before 50 and 75% before 60 years of age[23])–only these women can use unopposed estro-

Table 3. Standardized Incidence Ratios of Breast Cancers Among Women Using Oral or Transdermal Estradiol by Average Daily Dose and Duration of Use*

	Oral					Transdermal†				
Dose and Duration	n	Obs	Exp	SIR	95% CI	n	Obs	Exp	SIR	95% CI
Low dose‡										
6 mo or more to less than 5 y§	3,067	28	37	0.75	0.50–1.09	1,844	24	26	0.94	0.60–1.39
5 y or more	2,133	21	18	1.15‖	0.71–1.75	739	10	6	1.60	0.77–2.95
Medium dose‡										
6 mo or more to less than 5 y	408	2	1	1.60	0.19–5.78	7,006	102	104	0.99	0.80–1.19
5 y or more	1,738	20	15	1.38‖	0.84–2.12	8,445	104	76	1.32	1.12–1.64
High dose‡										
6 mo or more to less than 5 y	6,837	88	90	0.98	0.79–1.21	6,583	98	89	1.10	0.90–1.35
5 y or more	9,532	130	87	1.49‖	1.25–1.75	1,677	20	14	1.44	0.88–2.22

Obs, observed number of breast cancer cases; Exp, expected number of cases; SIR, standardized incidence ratio; CI, confidence interval.

* Use in ages older than 50 years during 1994–2001, observed and expected numbers of breast cancer cases up to December 31, 2002, and standardized incidence ratios with their 95% confidence intervals. Only women with accurate use are included.

† Includes both patch and gel users.

‡ Low dose includes oral less than 1.1 mg, patch less than 30 mcg, and gel less than 0.6 mg medium daily doses. Medium dose includes oral 1.1–1.9 mg, patch 30–60 mcg, and gel 0.6–0.9 mg medium daily doses. High dose includes oral more than 1.9 mg, patch more than 60 mcg, and gel more than 0.9 mg medium daily doses.

§ Only users from 1995 to 2001 (with completely known exposure history) were included.

‖ Trend by dose for at least 5 years of use (*P* for trend=.27).

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Table 4. Standardized Incidence Ratios of Breast Cancers Among Women Using Oral or Transdermal Estradiol, by Duration of Use, Stage Including Cancer In Situ, and Histologic Type*

	6 Months or More to Less Than 5 Years†				5 Years or More			
	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI
Histology								
Ductal	271	280	0.97	0.86–1.09	248	183	1.36	1.19–1.53
Lobular	53	60	0.89	0.66–1.16	66	42	1.58	1.22–2.01
Other	16	23	0.70	0.40–1.13	31	15	2.08	1.42–2.96
Stage								
Localized	195	213	0.92	0.79–1.05	198	136	1.45	1.26–1.66
Regional	97	106	0.92	0.73–1.12	92	68	1.35	1.09–1.65
Distant	4	12	0.34	0.09–0.87	9	9	1.03	0.47–1.95
Unknown stage	46	32	1.43	1.04–1.90	46	26	1.76	1.29–2.35
In situ‡	26	22	1.20	0.78–1.76	32	13	2.43	1.66–3.42

Obs, observed number of breast cancer cases; Exp, expected number of cases; SIR, standardized incidence ratio; CI, confidence interval.
* Use in ages older than 50 years during 1994–2001, observed and expected number of breast cancer cases up to December 31, 2002, and standardized incidence ratios with their 95% confidence intervals.
† Only users from 1995–2001 (with completely known exposure history) were included.
‡ Not included in other tables.

gens according to our national guidelines. In our country, only estradiol and estriol-based regimens are used, as generally also in many other European countries. Therefore, in contrast to previous studies[4,7,9–11,24] where conjugated equine estrogens have been most often used, we analyzed the effect of estradiol and estriol-based regimens on the risk of breast cancer.

One of the most important sources of error in most epidemiological studies on the risk of breast cancer in postmenopausal hormone therapy users[2,5,7,8,13,24] is inaccurate documentation of the use of postmenopausal hormone therapy; women diagnosed with breast cancer are much more likely to recall the use of postmenopausal hormone therapy than women without breast cancer.[25,26] We could accurately trace the type, dose, and duration of estrogen-only therapy for the study period, but we readily admit that some women could have used progestin-containing hormone therapy before hysterectomy and before the register was opened.

It is known that hysterectomy as such should not affect the incidence of breast cancer.[27] We included in our cohort only women who were older than 50 years of age to confirm that we studied truly postmenopausal women who had had vasomotor symptoms before the initiation of estrogen-only therapy. We do not know if ovaries were removed at the time of hysterectomy, but this may not be a major weakness; all women had suffered from hot flushes and other clinical symptoms that led to the initiation of estrogen-only therapy. We could not control confounders such as parity, age at the birth of the first child, and weight of the woman, but it is noteworthy that there are no socioeconomic differences between postmenopausal hormone therapy users and the general population in Finland.[28] Therefore, because important confounders are relative to socioeconomic status, it seems unlikely that there would have been major differences in the confounders between estrogen-only therapy users and the national average in our study. Furthermore, not all data support the effect of the confounders mentioned above on the risk of breast cancer.[29] It is also known that the rate of *BRCA1/2* mutations in unselected Finnish breast cancer patients is only 1.8%,[30] and therefore, it appears unlikely that these women could have appeared in our cohort.

To get prescriptions, the estrogen-only therapy users must have paid regular visits to their general practitioners or gynecologists, during which the breasts would have been palpated and examined by mammogram, if needed. This may have resulted in a breast cancer detection bias, and this is supported by a significantly increased incidence of carcinoma in situ in our cohort. Since 1987, 90% of Finnish women have taken part in mass mammogram screening programs that offer a free-of-charge mammogram every second year to all women between 50 and 60 years of age (in many communities up to 65 years of age).[31] This policy should reduce the effect of a possible detection bias in our cohort. Estrogen-only therapy slightly increases breast density,[32,33] which in turn reduces the diagnostic accuracy of mammograms.[34] This might explain, at least in part, the increased incidence of cancers spread to regional nodes after 5 years of use, particularly in that it is not customary to discontinue estrogen-only therapy before performing mammograms in our country.

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We compared the incidence of breast cancer in estrogen-only therapy users with that in the whole age-matched population (including those using any postmenopausal hormone therapy) and found a slightly elevated risk of breast cancer in users of estrogen-only therapy. It is known that up to 40% of Finnish women around 55 years of age have initiated postmenopausal hormone therapy,[35] but according to our data, only 7% of women use such a therapy for more than 5 years, a situation that is considered to increase the risk of breast cancer in previous studies.[2] Such a proportion of moderate-risk women in the reference population dilutes the observed relative risk estimate only marginally toward unity and should not affect the conclusions.[36]

It has been discussed that transdermal use of estradiol may be safer than oral dosage with regard to the risk of breast cancer, but in our study a transdermal route did not vary from the oral one in this regard. Thus, our data are in line with the British[5] and French data.[6] Likewise, it has been speculated that "low-dose" regimens might be safer.[37] Although our data did not confirm any significant trend between increasing dose and the risk of breast cancer, higher doses of oral estradiol were accompanied by a slightly higher risk of breast cancer than the lower doses. Thus, a modern shift toward smaller doses of estrogen[37] may be beneficial in reducing the risk of breast cancer.

Oral estriol is used mainly for improving vaginal health. It does not increase the risk of breast cancer, as is evident in our study, and this is in line with previous data.[12,38] Moreover, our data show that women can use various estrogenic formulations vaginally without any measurable risk of breast cancer.

The use of progestin-containing postmenopausal hormone therapy favors the occurrence of a lobular rather than a ductal type of breast cancer,[4,7,9,10,24] whereas the effect of estrogen-only therapy on the type of breast cancer is less clear.[4,7,10,24] Our data show that the use of estradiol is associated with an increased risk of both the ductal and lobular types of breast cancer, and this risk appears rather similar. Breast cancer can be more benign in users of postmenopausal hormone therapy,[2,11,39–41] but in our cohort breast cancer was equally often localized or spread to regional nodes. This may argue against the benign character of breast cancer in Finnish estrogen-only therapy users. Clearly, follow-up mortality data on estrogen-only therapy users with breast cancer are needed.

In summary, our nationwide study shows that the use of oral or transdermal estradiol for less than 5 years does not increase the risk of breast cancer, but such a risk appears with increasing duration of use. The higher rate of carcinoma in situ in estradiol users hints at a detection bias. The standardized incidence ratio 1.34 (1.16–1.54) found in our study for use of estradiol for 5–10 years would result in two to three extra cases of breast cancer per 1,000 women in 10 years of follow-up.

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