

Risks of breast and endometrial cancer after estrogen and estrogen–progestin replacement

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Abstract

Objective: We studied the risk of breast and endometrial cancer in a cohort of 11,231 Swedish women prescribed different replacement hormone regimens.

Methods: All 10,472 women at risk of developing breast cancer and 8,438 women at risk of endometrial cancer were followed up from the time of the questionnaire in 1987–88 through 1993, by record-linkages to the National Swedish Cancer Registry. Using data from a questionnaire we analyzed the relationships between hormone exposures and cancer risk, with non-compliers and users of less than 1 year as a reference group.

Results: For breast cancer, women reporting use of estrogens combined with progestins had evidence of an increased risk relative to women denying intake or taking hormones for less than 1 year; relative risk (RR) = 1.4 (95% confidence interval 0.9–2.3) after 1–6 years of intake, and RR = 1.7 (95% CI 1.1–2.6) after more than 6 years. This excess risk seemed confined to recent exposure. We found no association with intake of estrogens alone using non-compliers and short-term takers as the reference group. The risk of invasive endometrial cancer was increased four-fold in women using medium-potency estrogens alone for 6 years or longer, RR = 4.2 (95% CI 2.5–8.4). Women on such long-term progestin-combined treatment had a lower, non-significant, excess risk (RR = 1.4; 95% CI 0.6–3.3).

Conclusions: We conclude that long-term recent use of estrogen–progestin combined replacement therapy may increase the risk of breast cancer. Exposure to estrogen alone substantially elevates the risk of endometrial cancer, an increase that can be reduced or perhaps avoided by adding progestins.

Introduction

The use of estrogen and estrogen–progestin combinations for hormone replacement therapy (HRT) is becoming increasingly popular for the alleviation of menopausal symptoms [1], prevention of osteoporosis [2], or of coronary heart diseases [3]. However, increased risks of cancer in the breast and the endometrium are feared adverse effects of long-term HRT. Data on these risk relationships are controversial, particularly with regard to combined estrogen–progestin regimens. For breast cancer, long-term intake of non-contraceptive estrogens has been associated with a slightly increased risk in several [4–12], but not all [13–15], studies; among

the studies reporting on the effect of combined treatment, some indicate a possibly enhanced [4, 10, 12, 16] or similar [6, 8] risk increase, or no change in risk [13, 14]. Regarding endometrial cancer, a substantial duration-dependent risk increase after treatment with estrogens alone is documented in numerous studies [17, 18], with the excess risk decreasing after cessation of treatment [17]; addition of progestin sequentially [18–24] or continuously [24] is reported to reduce [18, 20–23] or eliminate [24] the risk increase.

We have previously reported results from a cohort comprising over 23,000 Swedish women showing an increased risk of breast cancer after treatment with estrogens alone and in combinations with progestins

[4, 10]; we also reported an increase in the risk of endometrial cancer in association with estrogens unopposed by progestins, with a lesser risk increase with progestin-opposed treatment [10, 20].

Here, we studied the outcomes of breast and endometrial cancer in a selected subset of 11,231 women from the original cohort, who completed a questionnaire in 1987–88 and who were subsequently followed by linkage to the National Swedish Cancer Registry. Our aims were to study the risks of HRT for these two cancers in a late time window of observation when most women had reached an age of 60 years.

Material and methods

The cohort

The cohort under study is a subset of the original cohort formed in Sweden in 1977–80. The methodology used for establishment of this cohort has been described elsewhere [25]. In brief, during this 3-year period 23,246 women – residing in six counties in the central part of Sweden (the Uppsala Health Care Region) – who had received prescriptions for hormones were enrolled in the cohort by collecting, registering and computerizing information from their prescription forms concerning replacement estrogens.

Those women in the cohort who were included in the present study were examined in 1987/88 through a mailed questionnaire to obtain updated information on exposure to HRT and risk factors. We contacted only those women in the original cohort who were born after 1918 (to optimize response), and those who had ever been prescribed estradiol compounds or conjugated estrogens during the enrollment period. We excluded those receiving low-potency estrogens only (oral estriol or vaginally administered estriol or dienestrol) and those who had received a questionnaire as part of previous research (women selected on the basis of birth days 5 and 8 of the month). Altogether 13,925 of 23,246 women (60%) were eligible and alive.

We mailed the questionnaire to these cohort subjects during a 1-year period, 1987–88. The form covered details of life-time exposure to replacement estrogens and added progestins – providing a picture display of packages of all available brands to facilitate recall – and on relevant risk factors, *e.g.*, history of reproduction, previous or current medical events, gynecological surgery, smoking, body build and others. In all, 11,231 (81%) of the women returned the questionnaire, which needed supplementation through telephone calls in 20 percent of the cases.

Follow-up and cohorts at risk

To ascertain new cases of breast and endometrial cancers we linked the cohort to the National Swedish Cancer Registry. The Registry is virtually complete as to registration of new cancer cases in all of Sweden [26]. It also provides information on causes and time of deaths. Therefore, linkage through the national registration number – a unique personal identifier assigned to all residents in Sweden – secured a complete ascertainment of cancer events during this follow-up period, *i.e.*, from response date in 1987/88 until 31 December 1993. Only cancers registered as invasive tumors of the breast and the endometrium were included.

We excluded from the cohort women who had a cancer diagnosed before the start of this follow-up (except non-melanoma skin cancer), in all 759 women. For analyses of endometrial cancer, we also excluded those who had undergone a hysterectomy before the response date (2,034 women). The resulting cohort at risk of breast cancer included 10,472 women and that for endometrial cancer, 8,438 women (Table 1). At the start of follow-up, the women had a median age of 65 years; their average observation time was 5.7 years.

All women in the respective cohorts were followed from time of questionnaire until a first cancer event, death or end of the follow-up period, whichever came first.

Classification of exposure and covariables

For each treatment episode the women reported information on dates of initiation and termination (or current intake), compound type and dose, and possible combinations with a progestin (compound, dose and regimen). We classified the women into categories of treatment according to type of the estrogen (potency), duration and recency of intake and use of progestins. The 1,684 (15%) of the responding women who denied intake of a prescribed estrogen and those 1,360 (12%) who reported any estrogen use for less than 1 year constituted the reference group in all analyses performed within the cohort (Table 1).

We defined the exposure categories such that:

- (1) Women who had used estradiol compounds or conjugated estrogens for more than a year (denoted as medium-potency estrogens) without progestins, or combined with progestins for less than one-third of the treatment period, were classified in the “estrogens-only” group. These women may also have used other (weak) estrogens. The duration was calculated only for intake of the medium-potency compounds, *i.e.*, weak estrogens were disregarded.

Table 1. Description of the two cohorts at risk of breast and endometrial cancer. Number of accumulated person-years (pyears) of observation (O) and expected (E) numbers of cases, by categories of exposure and covariates

Characteristics	Cohorts at risk					
	Breast cancer ^a (n = 10,472)			Endometrial cancer ^b (n = 8,438)		
	Pyears	O	E	Pyears	O	E
Whole cohort	60,298	198	167.9	48,887	66	34.8
Exposure groups						
Reference group ^c	17,794	48	49.2	15,192	12	10.7
Medium-potency estrogens ^d						
1–6 years, estrogens only ^e	8,132	23	23.4	6,399	5	4.8
1–6 years, estrogens + progestins ^f	7,044	28	18.8	6,472	6	4.4
6+ years, estrogens only	11,596	35	33.2	7,103	27	5.3
6+ years, estrogens + progestins	9,021	44	24.4	8,136	11	5.6
Other estrogens, 1+ years ^g	6,711	20	19.1	5,581	5	4.1
Parity						
Nulliparous	7,174	27	20.0	5,688	15	4.0
Parous	53,085	170	147.8	43,171	51	30.8
AFFTP ^h						
Nulliparous	7,168	27	20.0			
≤20	7,024	25	18.8			
21–29	39,454	120	110.2			
≥30	6,451	24	18.4			
BMI (quartiles)						
Q1	1,055	5	2.9	883	1	0.6
Q2	24,352	81	67.5	20,229	22	14.3
Q3	26,769	90	75.0	21,428	32	15.4
Q4	7,584	20	21.1	5,871	11	4.2
Education						
Elementary school	36,200	98	101.3	28,714	31	20.6
Higher level	23,732	99	65.5	19,888	35	14.0
Menopausal age/status						
< 50	25,391	52	68.9	16,821	20	11.6
50–54	22,366	91	64.2	20,171	26	14.9
55+	5,164	24	15.1	4,742	10	3.6
Premenopausal	808	4	1.7	793	1	0.3
Ongoing HRT	2,503	12	6.5	2,519	5	1.6
Missing	4,066	15	11.5	3,842	4	2.8
Smoking						
Never		–		26,070	34	19.0
Previous		–		9,983	18	7.1
Current		–		12,835	14	8.8
Oral contraceptive use						
Never/< 12 months		–		39,614	56	28.6
≥12 months		–		9,274	10	6.2
Diabetes						
No		–		47,585	62	33.9
Yes		–		1,302	4	1.0

Table 1. Continued

Characteristics	Cohorts at risk					
	Breast cancer ^a (n = 10,472)			Endometrial cancer ^b (n = 8,438)		
	Pyears	O	E	Pyears	O	E
Hypertension						
No		–		37,990	55	26.9
Yes		–		10,897	11	7.9

^a Excluding 759 women with a cancer diagnosed before questionnaire response.

^b Excluding in addition 2,793 women with a hysterectomy performed before questionnaire response.

^c Reference group: women denying intake (1,684) or having intake of any estrogen for < 1 year (1,360).

^d Medium-potency estrogens: estradiol compounds or conjugated estrogens taken for at least 1 year.

^e Medium-potency estrogens without added progestins or combined with a progestin for less than one-third of the intake duration.

^f Combined with a progestin for at least one-third of the duration of the estrogen intake.

^g Other estrogens: use of low-potency estrogens orally (estriol) or vaginally (estriol or dienestrol) only.

^h AFFTP: age at first full-term pregnancy.

Forty-four percent of the women had used both medium-potency and weak estrogens, of whom 39% had weak estrogens during less than half of their intake time. Thirteen percent had an additional progestin for less than one-third of the estrogen intake.

- (2) Those who combined their intake of medium-potency estrogens (exceeding 1 year) with a progestin for all or during more than one-third of the estrogen cycles were categorized into the “estrogens + progestins” group. In this group, 71% of the women had progestins added to more than 90% of their cycles and 29% from one-third up to 90%. Duration of use was calculated for intake of medium-potency estrogens, without regard to whether a particular episode was combined with a progestin.
- (3) Women reporting exclusive use 1 year or longer of the low-potency brands – estriol taken orally or estriol/dienestrol used vaginally – were grouped in the “other estrogen” category. These women were initially included in the cohort because they had a prescription for a medium-potency estrogen registered. However, in the questionnaire they reported only use of low-potency estrogens, meaning that they did not comply with the prescription but actually used these other brands.

We used the time between last intake and response date (*i.e.*, start of observation) as a surrogate variable for recency; “recent” being exposure on-going or stopped within 1 year of the questionnaire response, and “distant” that which ended still longer ago.

Analyses of risk relationships in more detailed exposure strata were not meaningful due to small numbers. Further description of some characteristics of our exposure groups is given in Table 2.

Table 2. Detailed characteristics of hormonal exposures; proportions (%) of cohort women reporting intake

Estrogen compounds (medium-potency)	
Estradiol	48.0
Conjugated estrogens	15.2
Mixed	36.8
Estrogen–progestin use	
Regimen	
Cyclic (7–10 days)	56.2
Continuous	1.3
Mixed	42.5
Type of compound	
Testosterone derived ^a	45.0
Progesterone derived ^b	55.0
Recency of use ^c	
“Recent” users	
Current	88.9
≤ 1 year	11.1
“Distant” users	
1–5 years	25.4
> 5 years	74.6

^a Levonorgestrel 250 µg or Norethisterone acetate 1 mg.

^b Medroxyprogesterone acetate 5 or 10 mg.

^c Time for discontinued use in relation to questionnaire response.

Analyses

The expected numbers of breast and endometrial cancer cases in the cohorts at risk were calculated on the basis of the incidence of cancer in the Swedish population at large with adjustment for age and calendar year. The standardized incidence ratio (SIR) – the ratio of the observed to the expected number of cases – was used as the measure of risk. In the statistical analyses, the number of observed cases was assumed to be Poisson distributed. To obtain estimates of the effects of the

explanatory variables after adjustment for the other variables, multivariate models were formulated assuming that the SIR depended multiplicatively on the explanatory variables. The models were estimated by the maximum-likelihood method using the generalized linear model approach [27]. Data in grouped form were used with the categorization shown in Table 1. The deviance was used in testing the effect of different variables in addition to direct inference based on parameter estimates and standard errors.

There was no indication of overdispersion. On the contrary, the deviances of all the models considered were smaller than the number of degrees of freedom. This is not surprising as the number of explanatory variable combinations was very large and the number of observed cases quite small. We report the results obtained by a direct application of the standard Poisson model, without any adjustment for overdispersion.

After univariate modeling, covariates were added stepwise to a multivariate model with little change in the risk estimates. We chose to show results for a model that adjusted for basically all variables available (Table 1).

Results

Breast cancer

We found a slight excess of observed cases (198) vs. expected from the background population (167.9), SIR = 1.2 (95% CI 1.0–1.4), with indications of an elevated risk among short-term (1–6 years) and long-term (6+ years) takers of progestin-combined treatment (Table 1). In the cohort at risk for breast cancer, the reference group had as many observed cases as expected, *i.e.*, showing no alteration in risk as compared with the background population.

In the multivariate modeling of data from subjects within the cohort, we found no evidence of a risk increase with intake of estrogens only relative to the reference group, based on 58 observed cases (Table 2). However, for those women taking medium-potency estrogens combined with progestins for 1–6 years, there was evidence of a 40% non-significant, increase in the relative risk (RR = 1.4; 95% CI 0.9–2.3), and a further 70% increase after more than 6 years of exposure (RR = 1.7; 95% CI 1.1–2.6). We also performed analyses after stratifying for recency of HRT use (Table 3). The relative risk estimates were markedly, but non-significantly, elevated in association with “recent” use only, with RR values of 2.8 (95% CI 0.8–10.0) and 1.9 (95% CI 0.6–6.1) for progestin combined intake of 1–6 and 6+ years, respectively. For “distant” use, we found no alterations in risk.

Table 3. Breast cancer risk after hormone replacement therapy, based on all 198 incident cases. Relative risk estimates (RR) and 95% confidence intervals (95% CI), by duration and regimens

Exposure category ^a	No. of cases	RR (95% CI) ^b	RR (95% CI) ^c
Reference	48	1.0	1.0
Medium-potency estrogens			
1–6 years, estrogens only	23	1.0 (0.6–1.6)	1.0 (0.6–1.7)
1–6 years, estrogens + progestins	28	1.6 (1.0–2.5)	1.4 (0.9–2.3)
6+ years, estrogens only	35	1.1 (0.6–1.6)	1.1 (0.7–1.7)
6+ years, estrogens + progestins	44	1.9 (1.3–2.8)	1.7 (1.1–2.6)
Other estrogens			
1+ year	20	1.1 (0.6–1.8)	1.1 (0.6–1.8)

^a See footnotes to Table 1.

^b Age-adjusted.

^c Adjusted for age, follow-up time, age at first full-term pregnancy, body mass index, education, menopausal age/status.

Among the 2,694 non-responders to the questionnaire, 34 cases were observed vs. 42.9 expected, yielding a SIR of 0.8 (95% CI 0.6–1.1).

Endometrial cancer

In the cohort, 66 cases of endometrial cancer were observed vs. 34.8 expected from population rates (that had not been corrected for hysterectomies).

The internal multivariate analyses revealed relative risk estimates close to baseline for women taking estrogens for 1–6 years, regardless of whether progestins had been added or not (Table 5). However, for women using the medium-potency estrogens for 6 years or more without progestins we found a four-fold increased risk, RR = 4.2 (95% CI 2.1–8.4). When such long-term treatment had been combined with a progestin there was little evidence of an adverse effect, RR = 1.4 (95% CI 0.6–3.3).

In non-responding women, 22 cases were ascertained as compared with 11.0 expected, yielding an SIR of 2.0 (95% CI 1.3–3.0).

Discussion

At this late follow-up of the cohort – starting more than 10 years after its establishment and when the women had a median age of about 65 years – we found some risk relationships between HRT and incident cancers of both the breast and the endometrium.

Our results support an adverse effect of estrogen–progestin combined use on the breast, as suggested in results from the previous follow-up of this cohort [4, 10]

Table 4. The risk of breast cancer after hormone replacement therapy. RR and 95% CI; by duration and regimens, stratified by recency. Adjusted for covariates as in Table 2, footnote C

Exposure category ^a	Recent use ^b			Distant use		
	No. of cases	RR	(95% CI)	No. of cases	RR	(95% CI)
Reference	3	1.0	–	45	1.0	–
Medium-potency estrogens						
1–6 years, estrogens only	2	1.0	(0.2–5.9)	21	1.0	(0.6–1.7)
1–6 years, estrogens + progestins	14	2.8	(0.8–10.0)	14	0.9	(0.5–1.7)
6+ years, estrogens only	18	1.0	(0.3–3.4)	17	1.1	(0.6–2.0)
6+ years, estrogens + progestins	35	1.9	(0.6–6.1)	9	1.0	(0.5–2.1)
Other estrogens:						
1+ years	7	0.9	(0.2–3.5)	13	1.1	(0.6–2.0)

^a See footnotes to Table 1.

^b Recent use: intake current at or terminated within 1 year of the response date; distant use: treatment ended 1 year or longer before response.

and from a few other studies [12, 16]. However, estrogen-only use was not associated with a noticeable risk increase for breast cancer, perhaps because we did not have sufficient numbers to evaluate very long-term use. In a previous analysis of this cohort [4], an increase in breast cancer risk with estrogens-only was seen only after 9 or more years of use. Our findings on endometrial cancer corroborate those from earlier follow-ups of the cohort [20] and from a number of other epidemiologic studies [17, 18]. To what extent progestins can reduce or prevent any increase in the risk of endometrial cancer could not be measured with precision in our study. Risk

estimates above baseline for long-term combined treatment have been reported in a few other studies that provide data on this type of exposure [18, 21–23].

The strengths of our design included the complete case ascertainment through record-linkages during a 6-year period of follow-up, detailed prospective characterization of exposure and risk factors of the cohort subjects, and the simultaneous examination of two major adverse effects of HRT.

The main limitation of our study is lack of power, precluding more detailed analyses of relationships with the specific regimens or timing of exposures, especially when studying endometrial cancer. Further, ascertainment of duration and recency of exposures was truncated at the time of questionnaire response, *i.e.*, at the start of the observation period. Therefore, true duration of intake is likely to have been underestimated and recency misclassified in those women who resumed intake after that date. Due to the restricted number of cases, some exposure groups had to contain subjects with mixed exposures. For instance, among women in the “estrogens + progestins” category, about one-third had progestins for only part of their period of estrogen intake. However, these misclassifications were likely to be independent of the outcome and therefore able only to bias associations towards the null.

We used women reporting non-compliance to their prescription for an estrogen or those using estrogens for less than 1 year as the reference group, when analyzing the effect of intake exceeding 1 year. The rationale for this was to reduce the potential for selection bias, since all study participants had sought medical advice and been prescribed an estrogen. However, non-compliance may be associated with some unmeasured risk factor [28], possibly leading to residual confounding even after multivariate adjustment.

Table 5. The risk of endometrial cancer after hormone replacement therapy. In all, 66 incident cases. RR and 95% CI, by duration and regimens

Exposure category ^a	No. of cases	RR	(95% CI) ^b	RR	(95% CI) ^c
Reference	12	1.0		1.0	
Medium-potency estrogens					
1–6 years, estrogens only	5	0.9	(0.3–2.6)	0.9	(0.3–2.5)
1–6 years, estrogens + progestins	6	1.3	(0.5–3.4)	1.1	(0.4–3.1)
6+ years, estrogens only	27	4.3	(2.2–8.5)	4.2	(2.1–8.4)
6+ years, estrogens + progestins	11	1.8	(0.8–4.1)	1.4	(0.6–3.3)
Other estrogens					
1+ years	5	1.1	(0.4–3.0)	1.0	(0.4–2.9)

^a See footnotes to Table 1.

^b Age-adjusted.

^c Adjustment for age, follow-up time, parity, body mass index, education, menopause age/status, smoking, use of combined oral contraceptives, prevalence of diabetes mellitus or at hypertension (see Table 1).

Detection bias due to more frequent use of mammography among users of HRT might exaggerate risk relationships. Population-based mammography screening was implemented in Sweden, and thus in the region from which cohort subjects were recruited, in the mid-1980s, with attendance rates among women below 70 years of age being close to 80% [29]. Since the present follow-up commenced in 1987, we believe that the majority of cohort subjects had screening surveillance with regular 1.5–2-year intervals. It is still possible, however, that women using long-term HRT could be examined more frequently and with shorter intervals.

Our results highlight major controversies surrounding HRT and its effects in postmenopausal women. Whereas progestins are deemed necessary to prevent development of hyperplasia and neoplasia of the endometrium during estrogen replacement therapy [24], it is not clear that available combined regimens, whether sequential or continuous, can fully prevent an increased risk of endometrial cancer in association with estrogen supplementation [17]. On the other hand, progestin combined treatments have been reported to enhance mammographic density [30, 31] and to increase breast cancer risk to a similar [6, 8] or possibly greater [4, 10, 12, 15] magnitude as compared with the intake of estrogens only. In clinical studies of normal breast tissue, progestins enhance the proliferation of epithelial cells after priming by estrogens [32], as opposed to a marked reduction of mitoses in the endometrium [33]. In experimental studies of Macaque monkeys, continuous addition of a progestin (medroxyprogesterone acetate) to conjugated estrogens led to a more pronounced hyperplasia of the breast epithelium as compared with estrogens alone [34].

Clearly, the effects of exogenous estrogens and added progestins on the breast and endometrium are complex and incompletely understood with regard to cancer transformation. It is a challenge for future research – basic, clinical and epidemiologic – to define efficient and safe hormone treatment modalities.

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