

Hormone Replacement Therapy Containing Progestins and Given Continuously Increases Breast Carcinoma Risk in Sweden

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BACKGROUND. The authors previously reported an increased risk of breast carcinoma with longer duration of hormone replacement therapy (HRT) use. It is unclear if different types of HRT confer different risks.

METHODS. In this study, a population-based cohort of 29,508 women were interviewed during 1990–1992 to determine whether there are any differences in breast carcinoma risk according to different types and duration of HRT use.

RESULTS. At the end of the follow-up period in December 2001, the cohort constituted 298,649 person-years. Slightly more breast carcinoma cases were seen ($n = 556$) than expected ($n = 508.37$; standardized morbidity ratio = 1.09, 95% confidence interval [CI] = 1.00–1.19). Approximately 3663 women had ever used HRT. In Cox regression models, time to breast carcinoma in relation to duration and type of HRT use was analyzed, adjusting for age at menarche, age at first full-term pregnancy, parity, age at menopause, family history of breast carcinoma, and age at interview. In women with a natural menopause, a significantly higher risk was observed for longer duration of combined continuous HRT use compared with never users (hazard ratio [HR] = 4.60, 95% CI = 2.39–8.84). Nonsignificant elevated risks also were observed for longer combined sequential (HR = 2.23, 95% CI = 0.90–5.56), gestagen only (HR = 3.74, 95% CI = 0.94–14.97), and estradiol only (HR = 1.89, 95% CI = 0.81–4.39). No increased risk was seen in women after 5 years of nonuse. When studying women who ever used only one type of HRT, even more elevated HRs for gestagen-containing preparations were seen. The highest risks were associated with the combined continuous and gestagen-only therapy in women with ≥ 48 months of use. Use of estradiol without progestins did not increase breast carcinoma risk significantly. The authors estimated the cumulative risk of breast carcinoma in a 50-year-old woman with gestagen-containing therapies for ≥ 48 months, with a follow-up of 10 years, to be 7% (95% CI = 5.4–11.4%) compared with 2% (95% CI = 1.6–2.9%) for never-users of HRT.

CONCLUSIONS. Longer use of HRT containing progestins significantly elevates breast carcinoma risk whereas estradiol use does not. Continued use of progestins rendered the highest risks. The yearly risk of breast carcinoma for long-term users of progestins is of the magnitude of 50% the risk of a BRCA1 mutation carrier.

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An increasing number of women will use hormone replacement therapy (HRT) at and after menopause. The overall long-term health consequences of HRT use are not fully known. Positive effects could be counterbalanced by more negative effects. One such nega-

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tive factor is the increased risk for breast carcinoma seen especially after longer HRT use. However, a metaanalysis and our previous study have indicated that the risk for breast carcinoma disappears after 5 years of nonuse.^{1,2}

There are indications that the tumor biology and prognosis of patients who develop breast carcinoma after HRT use are more favorable compared with other age-matched breast carcinoma patients.³⁻¹² However, it is unclear if certain preparations are more hazardous than others. Some studies have suggested that preparations containing estrogen alone do not increase the breast carcinoma risk substantially whereas preparations containing both estrogens and progestins do increase the risk.¹³⁻¹⁶ Because conflicting data are reported for the combined continuous and combined sequential HRT therapy, it is not known which is more strongly associated with breast carcinoma risk.^{13,14,16}

There is a need to further study the risk relationship through prospective studies. In the current cohort investigations, the risk for breast carcinoma has been studied in relation to the type of HRT, exposure time, and reproductive risk factors (i.e., age at menarche, parity, age at first full-term pregnancy, and family history of breast carcinoma). The difference between combined and continuous administration of estrogens and progestins compared with sequential administration could have a biologic significance.

MATERIALS AND METHODS

Forty thousand women ages 25-65 years were randomly selected from the general population of the South Swedish Health Care Region. They were invited to take part in a standardized written interview of risk factors of malignant melanoma and breast carcinoma. No woman had a past history of malignancy. The interviews were performed between 1990 and 1992. Approximately 74% of all women ($n = 29,508$) agreed to participate.

The questionnaire inquired about age at menarche, parity, age at first full-term pregnancy, age at menopause, type of menopause, oral contraceptive use (starting age, duration of use, brand use, and age at last use), HRT use (starting age, duration of use, brand use, and age at last use), family history of cancer/breast carcinoma, sun bathing habits, constitutional factors, and alcohol and smoking habits.

Using a unique identification number, the vital status and the cancer incidence up to age 75 years of these referents then were followed from the time of interview onward in the population-based Census Registry, Cause of Death Registry, and the Swedish Cancer Registry (South Swedish Regional and National

Swedish Tumour Registry). Each individual could have had more than one tumor registered. The vital status was determined up to January 1, 2002. None of the subjects were lost to follow-up. The type and duration of HRT were studied within the cohort using the Cox regression model.¹⁷ Adjustments were made for age at interview, age at menarche, parity, age at first full-term pregnancy, and a first-degree relative with breast carcinoma. Women who did not have information concerning all studied variables were excluded from the analysis. The covariates were evaluated by likelihood ratio tests and the assumptions for the Cox model were investigated.¹⁷ A P value < 0.05 was considered significant.

When estimating cumulative risks for different exposure groups, we used the life table actuarial method.¹⁷ Using the Cox regression model, the risk for different HRTs was modeled while adjusting for possible confounding factors both for all women and for women with a natural menopause. Analyses were presented both for women using only one brand and for women using more than one brand. Individuals were followed from the time of interview to the first event of breast carcinoma, death, or the end of follow-up (January 1, 2002).

The HRT exposure was divided into combined exposures (combined and sequential) and single exposures with estradiol, estriol, and gestagens using the Swedish pharmacopoeia available. Individuals who did not know the brand name were grouped into a separate entity.

RESULTS

At the end of the follow-up in December 2001, the cohort constituted 298,649 person-years. A total of 556 malignant breast tumors developed (508.37 were expected; standardized morbidity ratio [SMR] = 1.09, 95% confidence interval [CI] = 1.00-1.19). Approximately 3600 women had ever used HRT.

Table 1 shows the number of women exposed for each category of HRT use and the number of each exposure group, as well as the number of diagnosed breast carcinoma cases. Table 2 presents a Cox regression analysis of the time to breast carcinoma in relation to the type of HRT use and ever-use of HRT among all women ($n = 28,378$) and among women with a natural menopause ($n = 8442$). Hazard ratios are adjusted simultaneously for the other types of HRT exposures and for year of interview. Among women with a natural menopause, significantly increased risks were associated with the combined continuous and combined sequential use of HRT. Of all the data gathered, combined continuous use of HRT showed the highest risks.

TABLE 1
Number of Women Exposed for Each Category of HRT Use and the Number of Women with Different Base Characteristics Used as Covariates (First-Degree Relatives with Breast Carcinoma, Age at First Full-Term Pregnancy, Nulliparity, Age at Menarche)^a

Characteristics	Women with a natural menopause (<i>n</i> = 8357)	All women (<i>n</i> = 28378)
HRT use (combined sequential therapy)		
1-48 mos	184 (13)	410 (16)
48+ mos	136 (6)	245 (11)
HRT use (combined continuous therapy)		
1-48 mos	272 (15)	377 (23)
48+ mos	173 (16)	245 (19)
HRT use (gestagens only)		
1-48 mos	178 (4)	429 (13)
48+ mos	86 (3)	136 (6)
HRT use (estradiol only)		
1-48 mos	245 (8)	526 (13)
48+ mos	137 (2)	300 (8)
HRT use (estriol)		
1-48 mos	290 (8)	409 (9)
48+ mos	185 (7)	256 (11)
HRT use (unknown)		
1-48 mos	211 (2)	328 (4)
48+ mos	65 (3)	110 (3)
Never users of HRT	6707 (153)	25,515 (429)
First-degree relative with breast carcinoma		
Yes	589 (26)	1574 (55)
No	7830 (196)	26,981 (483)
Age at first full-term pregnancy		
< 35 yrs	7139 (181)	22,939 (430)
≥ 35 yrs	241 (11)	615 (21)
Age at menarche		
< 14	1765 (46)	8410 (136)
≥ 14	6529 (171)	19,662 (394)
Nulliparous	963 (30)	4717 (83)

HRT: hormone replacement therapy.

^a The number of breast carcinomas that developed during the follow-up time is shown in parentheses.

The median age at interview was 45 years of age (range, 25-65) for all women and 56 years (range, 35-65 years) for women who underwent a natural menopause.

In Table 3, stratified Cox regression analyses of time to breast carcinoma in relation to the type of HRT use and duration of use among women with a natural menopause are shown both for women using only one type of HRT and for women using different types. Hazard ratios are adjusted for year of interview. Among women using only one brand and among women using different brands, the highest risks were seen for combined continuous and gestagen-only therapy. Significantly elevated risks were also associated with combined sequential therapy and there was a suggestion that the risk appeared earlier compared with other exposures. Although there were little data to indicate a risk with estradiol use, the risk was non-

TABLE 2
Cox Regression Analysis of Time to Breast Carcinoma in Relation to Type of HRT Use and Ever Use among All Women (*n* = 28,378) and among Women with a Natural Menopause (*n* = 8442)^a

Characteristics	Women with a natural menopause (<i>n</i> = 8357) Hazard ratio 95% CI	All women (<i>n</i> = 28,378) Hazard ratio 95% CI
HRT use (combined sequential therapy)	2.27 (1.26-4.10)	1.22 (0.74-2.00)
HRT use (combined continuous therapy)	2.33 (1.38-3.93)	2.45 (1.61-3.71)
HRT use (gestagens only)	1.05 (0.37-2.96)	1.41 (0.79-2.53)
HRT use (estradiol only)	0.81 (0.34-1.96)	0.71 (0.40-1.26)
HRT use (estriol)	1.45 (0.80-2.63)	1.29 (0.79-2.13)
HRT use (unknown type)	0.57 (0.18-1.80)	0.41 (0.15-1.10)

CI: confidence interval; HRT: hormone replacement therapy.

^a Hazard ratios are adjusted simultaneously for the other types of HRT exposures and for year of interview.

significantly elevated after estriol use. Use of HRT of unknown type was not associated with a significantly increased risk.

Table 4 presents a Cox regression analysis of time to breast carcinoma in relation to type and duration of HRT use, family history, age at first full-term pregnancy, nulliparity, and age at menarche among all women (*n* = 28,378). Adjusting for each factor simultaneously, hazard ratios also are adjusted for types of HRT and year of interview. Again, the highest risk is associated with the longer use of combined continuous HRT use and gestagen-only use. In addition, longer use of estriol is associated with a significantly increased risk.

Table 5 shows a Cox regression analysis of time to breast carcinoma in relation to type and duration of HRT use, family history, age at first full-term pregnancy, nulliparity, and age at menarche among women experiencing a natural menopause (*n* = 8357). Adjusting for each factor simultaneously, hazard ratios also are adjusted for types of HRT, menopausal age, and year of interview. The highest risk is associated with the longer use of combined continuous HRT use and gestagen-only use. Longer use of combined sequential therapy and estriol use are associated with a nonsignificantly increased risk. No increased risk was noted among women after 5 years of nonuse.

We estimated the cumulative risk of breast carcinoma in a 50-year-old woman with gestagen-containing therapies for 48 months or more, with a follow-up of 10 years, to be 7% (95% CI = 5.4-11.4%) compared with 2% (95% CI = 1.6%-2.9%) for never-users of HRT.

TABLE 3
Stratified Cox Regression Analyses of Time to Breast Carcinoma in Relation to Type of HRT Use and Duration of Use among Women with a Natural Menopause^a

Characteristics	Women who ever used only one type of HRT HR 95% CI	Women who used different types of HRT HR 95% CI
HRT use (combined sequential therapy)		
Never users of HRT	1.00	1.00
1-48 mos	2.98 (1.29-6.90)	2.94 (1.41-6.12)
48+ mos	3.11 (0.99-9.83)	2.97 (1.21-7.28)
HRT use (combined continuous therapy)		
Never users of HRT	1.00	1.00
1-48 mos	1.45 (0.52-3.99)	1.74 (0.80-3.78)
48+ mos	6.28 (3.17-12.41)	5.03 (2.63-9.62)
HRT use (gestagens only)		
Never users of HRT	1.00	1.00
1-48 mos	1.44 (0.20-10.38)	0.78 (0.19-3.19)
48+ mos	6.30 (0.88-45.29)	3.14 (1.00-9.94)
HRT use (estradiol only)		
Never users of HRT	1.00	1.00
1-48 mos	1.56 (0.38-6.38)	1.40 (0.56-3.48)
48+ mos	—	1.05 (0.25-4.26)
HRT use (estriol)		
Never users of HRT	1.00	1.00
1-48 mos	1.44 (0.63-3.28)	1.44 (0.59-3.53)
48+ mos	2.29 (0.93-5.68)	2.27 (0.99-5.20)
HRT use (unknown)		
Never users of HRT	1.00	1.00
1-48 mos	0.35 (0.05-2.52)	0.31 (0.04-2.22)
48+ mos	1.10 (0.15-7.95)	1.76 (0.43-7.18)

HRT: hormone replacement therapy; CI: confidence interval; HR: hazard ratio.

^a Hazard ratios are shown both for women using only one type of HRT and for women using different types. Hazard ratios are adjusted for year of interview.

DISCUSSION

Using the same cohort of women in South Sweden, we reported previously that the risk of breast carcinoma in relation to HRT use after > 4 years of exposure was approximately doubled (SMR = 1.92) compared with never-users.² In the previous publication, we did not analyze the impact of different types of HRT. In the current study, we added another year of follow-up and analyzed whether the risk differed according to the different brands of HRT used. We divided the exposures into combined exposures (combined and sequential) and single exposures with estradiol, estriol, and gestagens.

The current results support the hypothesis that progestin-containing brands are associated with the highest risks. After > 4 years of exposure, hazard ratios more than doubled for combined exposures (combined and sequential) and for gestagen-only therapy whereas exposure to estriol and estradiol provided

TABLE 4
Cox Regression Analysis of Time to Breast Carcinoma in Relation to Type and Duration of HRT Use, Family History, Age at First Full-Term Pregnancy, Nulliparity, and Age at Menarche among All Women (n = 28,378)^a

Characteristics	HR	95% CI	P value
HRT use (combined sequential therapy)			
Never use	1.00		
1-48 mos	1.18	0.62-2.23	0.606
48+ mos	1.44	0.67-3.08	0.347
HRT use (combined continuous therapy)			
Never use	1.00		
1-48 mos	2.01	1.14-3.55	0.015
48+ mos	3.13	1.70-5.75	0.000
HRT use (gestagens only)			
Never use	1.00		
1-48 mos	1.14	0.56-2.32	0.724
48+ mos	2.53	0.94-6.80	0.065
HRT use (estradiol only)			
Never use	1.00		
1-48 mos	0.77	0.38-1.57	0.478
48+ mos	0.58	0.22-1.55	0.280
HRT use (estriol)			
Never use	1.00		
1-48 mos	0.87	0.41-1.85	0.723
48+ mos	1.98	1.04-3.79	0.038
HRT use (unknown)			
Never use	1.00		
1-48 mos	0.30	0.07-1.20	0.09
48+ mos	0.73	0.18-2.93	0.654
Family history of breast carcinoma	1.76	1.34-2.38	0.000
Age at first full-term pregnancy			
> 35 yrs	1.60	1.03-2.48	0.036
Nulliparity	1.36	1.07-1.73	0.012
Age at menarche			
> 13 yrs of age	1.02	0.85-1.25	0.781

CI: confidence interval; HRT: hormone replacement therapy; HR: hazard ratio.

^a Hazard ratios are adjusted for each factor simultaneously, year of interview menopause age.

lower hazard ratios and insignificant for estradiol. The data suggest that continuous administration of progestins is more hazardous than sequential administration, supporting the findings in a previous published Swedish case-control study.¹³ This interpretation is supported in our study both by findings among women using only one brand and among women using different HRT types. A smaller risk may be associated with sequential therapy, which mimics the natural cycle, compared with combined continuous therapy. Reports in the literature are inconsistent regarding the use of sequential versus continuous administration of HRT.^{13,14} Therefore, there is a need for more information, especially from prospective cohort investigations and randomized trials. We estimated

TABLE 5
Cox Regression Analysis of Time to Breast Carcinoma in Relation to Type and Duration of HRT Use, Family History, Age at First Full-Term Pregnancy, Nulliparity, and Age at Menarche among Women Experiencing a Natural Menopause ($n = 8357$)^a

Characteristics	HR	95% CI	P value
HRT use (combined sequential therapy)			
Never use of	1.00		
1-48 mos	2.53	1.21-5.28	0.013
48+ mos	2.23	0.90-5.56	0.084
HRT use (combined continuous therapy)			
Never use of	1.00		
1-48 mos	1.37	0.63-3.01	0.43
48+ mos	4.60	2.39-8.84	0.000
HRT use (gestagens only)			
Never use of	1.00		
1-48 mos	0.52	0.11-2.39	0.403
48+ mos	3.74	0.94-14.97	0.062
HRT use (estradiol only)			
Never use of	1.00		
1-48 mos	1.11	0.41-2.98	0.834
48+ mos	0.35	0.07-1.86	0.219
HRT use (estriol)			
Never use of	1.00		
1-48 mos	1.26	0.56-2.86	0.58
48+ mos	1.89	0.81-4.39	0.14
HRT use (unknown)			
Never use of	1.00		
1-48 mos	0.29	0.04-2.07	0.22
48+ mos	1.31	0.32-5.34	0.702
Family history of breast carcinoma	1.68	1.10-2.55	0.016
Age at first full-term pregnancy > 35 yrs	1.92	1.04-3.54	0.04
Nulliparity	1.20	0.81-1.79	0.36
Age at menarche > 13 yrs of age	0.99	0.72-1.37	0.96

HRT: hormone replacement therapy; CI: confidence interval; HR: hazard ratio.

^a Hazard ratios are adjusted for each factor simultaneously, year of interview, and menopausal age.

that the cumulative risk for a 50-year-old women in the highest risk group (combined continuous therapy and duration of ≥ 48 months) was 7% and that the corresponding risk for never users was 2%. Although studies have suggested a better survival rate for HRT users who develop breast carcinoma,³⁻¹² we believe that the increased incidence is remarkably high. For example, the risk associated with a first-degree relative with breast carcinoma is about 1.5-2.0. A first-degree relative with breast carcinoma is one of the strongest risk factors for breast carcinoma.

A percentage (12.5%) of the respondents could not name the type of HRT given. The analyses in that group suggest that the majority were estrogen preparations or were not HRT at all. Because the women

selected for interview had no previous cancer history, there should be no recall bias between the type of HRT and outcome (breast carcinoma).

A recent trial found a high incidence of breast carcinoma, stroke, and cardiovascular events among women followed up to 5 years, which led to the termination of the trial.¹⁶ Therefore, there is a need for further prospective studies with longer follow-up to investigate the various modes of therapy.

Progestin-containing preparations used continuously are the most hazardous to women. We cannot yet address whether ≥ 10 years of HRT use confers an even higher breast carcinoma risk for women taking progestin-containing brands because too few women in this cohort have been exposed to HRT for such a duration.

There is a possibility that the effect of HRT is underestimated because during the follow-up, women assigned as unexposed may have started to use HRT. The cohort is currently being reinterviewed and future studies will be able to look at this potential bias.

Compared with another Swedish cohort investigation of HRT use, the current investigation has the advantage of retrieving the HRT information by direct interviews and not by prescriptions filled at pharmacies.¹⁸ The recall of the exposure was further aided by time calendar and charts of brands prescribed in Sweden. Furthermore, the current cohort is population based and is not limited to the use of certain pharmacies, hospitals, or attending mammography units.

A small percentage of the women (12.5%) could not name the brand of HRT that they had been given. The hazard ratios in this group of women who were exposed to an unknown type of HRT did not reveal a very high risk, suggesting that the majority of the exposure in the unknown group was due to estradiol-only brands or to drugs that were not part of HRT. A possible shortcoming in the design of our investigation is that we did not confirm the HRT exposure by comparing it with the prescribing physicians' records. However, not all records would be available due to clearing of records after 5 years by some physicians. In addition, prescriptions are not always taken by the patients. By relying on information provided by the patient, such bias is reduced. Conversely, previous studies have confirmed a satisfactory agreement between patient recall and records regarding brand and type of HRT exposure.^{19,20}

All risk and prognostic studies concerning HRT so far have had limited follow-up time. There is a need to follow women with HRT exposure for a longer period of time as a recent U.S. investigation has suggested that survival after > 10 years is worse for HRT-exposed women compared with never-users.²¹

These data suggest that estrogen-only therapy is a rather safe therapy with little breast carcinoma risk. If there is a need for HRT containing progestins, as in women with intact uterine tissue, an attractive alternative would be to use a more androgenic progestin combination (e.g., tibolone). This type of therapy would not render the breast tissue as dense as most other progestin-containing preparations would. It is not known if this would transfer to a lower breast carcinoma risk. Therefore, risk studies should be initiated.

The results of the current investigation confirm a high risk for breast carcinoma after at least 4 years of HRT use, especially for progestin-containing preparations. We found a 7% cumulative risk for breast carcinoma patients after ≥ 48 months of combined estrogen and progestin use with a follow-up of 10 years compared with a 2% risk among never users.

The greatest hazard appears to be for continuous combined therapy, whereas combined sequential therapy shows an intermediate risk and estradiol-only preparations are not associated with a significantly increased risk. These results may help physicians to better tailor therapy to avoid breast carcinoma.

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