Hormone Replacement Treatment and Breast Cancer Risk: An Age-specific Analysis[1]

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Abstract

The relationship between hormone replacement treatment (HRT) and breast cancer risk was considered in age-specific groups of women, combining data from two case-control studies conducted between 1983 and 1994 in six Italian centers. Cases were comprised of 5984 women, below age 75 years, with histologically confirmed breast cancer, and controls were comprised of 5504 women admitted to the hospital for a wide spectrum of acute, nonneoplastic, nonhormone-related diseases. Ever-use of HRT was reported by 6.1% of the cases and 5.5% of the controls, corresponding to a multivariate odds ratio (OR) of 1.2 [95% confidence interval (CI), 1.0–1.4]. A significant trend in risk with duration of use was observed. Separate analysis for women <55, 55–64, and 65–74 years old at diagnosis showed that the excess risk of breast cancer associated with ever-use of HRT was not observed in the youngest age group (OR, 0.9) and increased with age at diagnosis to 1.2 (95% CI, 0.9–1.5) for women 55–64 years old and 1.6 (95% CI, 1.2–2.3) for those 65–74 years old at diagnosis. A significant trend in risk with duration was observed only in the oldest group (65–74 years old), with ORs of 1.6 (95% CI, 1.1–2.3) and 2.2 (95% CI, 1.1–4.7), respectively, for <60 and ≥60 months of use. Thus, this study suggests that the relationship between HRT and breast cancer risk is influenced by age at diagnosis and that any risk-benefit assessment is particularly critical for women using HRT several years after menopause.

Introduction

The possible relationship between HRT[3] and the risk of breast cancer in women is a topic of major interest on an epidemiological and public health scale but, despite several studies, various questions remain unanswered (1–5). The risk associated with ever-use of HRT is generally close to unity, and there is some evidence of elevated risks with the long duration of use, but no evidence of any trend with recent or current use (1–11).

Both cohort and case-control studies have attempted to establish whether certain subgroups of users are more susceptible to the effect of estrogens, but only a few studies have evaluated age-specific effects of various measures of HRT (*e.g.*, duration of use, age at starting and stopping, dose, time since first and last use) (2). Ever-use of HRT by age group was considered in three case-control studies (12–14) and in the American Nurses' health studies (15–17), which found a stronger association with breast cancer risk with increasing age at diagnosis. The data, however, are not totally consistent (18–20).

In consideration of the scant epidemiological evidence and the importance of these issues for individual risk assessment and on a public health scale in different populations, we analyzed the age-specific patterns of the HRT breast cancer relationship using data from two large case-control studies conducted in Italy.

Subjects and Methods

The data were derived from two case-control studies of breast cancer. The first study was conducted between January 1983 and June 1991 in the greater Milan area (21, 22), and the second study was conducted between June 1991 and February 1994 (8) in six Italian areas: in greater Milan, the province of Pordenone, and Gorizia, the urban area of Genoa and the province of Forlì, in northern Italy; in the province of Latina, in central Italy; and in the urban area of Naples, in southern Italy. Structured questionnaires were used for the two studies and tested for reliability and reproducibility. All interviewers were centrally trained. The questionnaires of the two studies differed mainly with regard to information on diet and physical activity, which was more detailed in the more recent study. On average, in both studies, less than 4% of the cases and controls approached for interview refused to participate.

Cases. Cases were women with incident (*i.e.*, diagnosed within the year before interview), histologically confirmed breast cancer, admitted to the major teaching and general hospitals in the areas mentioned. A total of 5984 cases 22–74 years old (median age, 54 years) was included in the present analysis.

Controls. Controls were women residing in the same geographical areas and admitted for acute conditions to the same network of hospitals where cases had been identified. Women were not included if they had been admitted for gynecological, hormonal, or neoplastic diseases. A total of 5504 controls 15–74 years old (median age, 55 years) was interviewed. They were admitted to hospital for a wide spectrum of acute diseases unrelated to known or potential risk factors for breast cancer. Of these, 27% had traumatic conditions (mostly fractures and sprains), 32% had non-

Received 5/2/96; revised 9/30/96; accepted 10/11/96.

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[1] This work was conducted within the framework of the Consiglio Nazionale delle Ricerche (Italian National Research Council) "Risk Factors for Disease" (Contract 95.00952.PF41), Clinical Applications of Oncological Research (Contracts 95.00562.PF39 and 95.00504.PF39) and with the contribution of the Italian Association for Cancer Research.

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[3] The abbreviations used are: HRT, hormone replacement treatment; OR, odds ratio; CI, confidence interval.

Table 1 Distribution of 5984 breast cancer cases and 5504 controls according to selected covariates (Italy, 1983–1994)

	Breast cancer		Controls	
	No.	%	No.	%
Age (yr)				
<35	226	3.8	385	7.0
35–44	1039	17.4	824	15.0
45–54	1808	30.2	1484	27.0
55–64	1750	29.2	1614	29.3
65–74	1161	19.4	1197	21.7
Education (yr)[a]				
<7	2982	49.8	3253	59.1
7–11	1671	27.9	1369	24.9
>11	1313	21.9	855	15.5
Body mass index (kg/m^2)[a]				
<25	3526	58.9	3135	57.0
≥25	2440	40.8	2356	42.8
No. of children[a]				
0	1042	17.4	1003	18.2
1–2	3633	60.7	3003	54.6
>2	1306	21.8	1490	27.1
Age at menopause[a] (yr)				
Pre-/perimenopause	2405	40.2	1926	35.0
<50	1575	26.3	1829	33.2
≥50	1989	33.2	1741	31.6
Family history of breast cancer				
No	5303	88.6	5239	95.2
Yes	681	11.4	265	4.8

[a] The sum and percentages do not add up to the total because of some missing values.

traumatic orthopedic disorders (mostly low back pain and disc disorders), 17% were admitted for acute surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia), and 24% were admitted for other miscellaneous illnesses such as eye, ear, nose and throat, and dental disorders.

Both structured questionnaires included information on personal characteristics and habits, education and other socioeconomic factors, general lifetime habits, such as smoking, alcohol and coffee consumption, gynecological and obstetric data, related medical history, and history of lifetime use of oral contraceptives, HRT in menopause, and female hormone preparations for other indications, including time and duration of each episode of use and brand name, whenever available. All interviews for cases and controls were conducted in the hos-pital.

Data Analysis. The ORs of breast cancer and the corresponding 95% CIs for various measures of HRT were derived using unconditional multiple logistic regression, fitted using the method of maximum likelihood (23, 24), including terms for geographic area, quinquennia of age (10 levels), education (<7/7–11/>11 years), body mass index (<25/≥25 kg/m^2), number of children (nulliparous/1–2/>2), age at menopause (pre- and peri-, <50/≥50 years), benign breast disease, and family history of breast cancer in a first-degree relative (no/yes).

Results

Table 1 gives the distribution of breast cancer cases and the comparison group according to age and other major identified covariates. Cases were more educated, had comparable body mass index, were less frequently multiparous and in premenopause, had later menopause, and reported a family history of breast cancer more frequently than controls. All of these factors were considered potential confounders for the HRT-breast cancer analysis and were included in multiple logistic regression equations.

Table 2 considers the distribution of cases and controls in three strata of age at diagnosis according to various measures of HRT. Ever-use of HRT was reported by 3.1% of the cases and 3.6% of the controls among women <55 years old, by 9.5% of the cases and 8.2% of the controls among women 55–64 years old, and by 9.0% of the cases and 6.0% of the controls among women 65–74 years old. Few women <55 years old had a duration of use of 60 months or longer (9 cases and 9 controls) or had started HRT 15 or more years before (6 cases and 12 controls). Conversely, among women 65–74 years old, only a few had started HRT <15 years before (20 cases and 9 controls) and had stopped use <10 years before (7 cases and 5 controls).

The ORs (and 95% CIs) for ever-use of HRT, after allowance for study/center and age, were 0.8 (0.6–1.1) for women <55 years old, 1.2 (0.9–1.5) for women 55–64 years old, and 1.6 (1.2–2.3) for those ≥65 years old.

The multivariate OR according to various measures of HRT are reported in Table 3. When women of all ages were considered together, the OR for ever-use was 1.2 (95% CI, 1.0–1.4). The risk was higher for women starting use when 50 years or older (OR, 1.1) compared to those starting use when younger than 50 years (OR, 1.1) and for those with more recent use (OR, 1.3).

In the analysis of strata of age at diagnosis (Table 3), among women <55 years old, we found no association between risk of breast cancer and any measure of HRT (OR, 0.9 for ever use). In the 55–64-year-old group, the OR was 1.2 (95% CI, 1.0–1.6) for ever-use of HRT, in the absence, however, of a duration-risk relationship; the risk increased with age at starting HRT, with an OR of 1.0 and 1.6, respectively, for women starting when <50 years old and ≥50 years old. In these age groups, shorter latency and recent use were associated with elevated risk: the OR for having started use <15 years before was 1.4 compared to 1.0 for having started use 15 or more years before, and the OR for having stopped use <10 years earlier was 1.5 compared to 1.0 for longer time. In women 65–74 years old at diagnosis, risk estimates were all above unity. For ever-use of HRT, the OR was 1.6 (95% CI, 1.2–2.3), and 1.6 (95% CI, 1.1–2.3), and 2.2 (95% CI, 1.0–4.7), respectively, for <60 and ≥60 months of use, with a significant trend in risk with duration of use (χ^2 trend, 10.32; P = 0.001). In the oldest group, the OR rose with age at starting use: the OR was 2.0 for women ≥50 years old at starting use and 1.3 for those <50 years old. The OR was higher for women who had started use <15 years before (OR, 2.1) than for those who had started HRT earlier (OR, 1.5).

Table 4 considers the relationship between breast cancer and HRT use at different ages in the strata of selected covariates. No important differences were found in the strata of period at diagnosis. With reference to type of menopause, a stronger association with advancing age was evident for women with natural, but not for those with artificial, menopause. Women with a family history of breast cancer were not analyzed, since too few had used HRT to allow meaningful analyses.

Data on use and duration of use of HRT in Table 3 are plotted in Fig. 1. The strength of the association between breast cancer risk and HRT rose with age at diagnosis.

Discussion

The results of this study indicate that the relationship between HRT and breast cancer risk is influenced by age at diagnosis and that the risk of breast cancer associated with various measures of HRT use in this Italian population is restricted to women 55 years or older, the OR rising with age at diagnosis.

Although some studies (2, 13–20), one of which is part of this dataset (22), have attempted to identify whether subgroups

Table 2 Distribution of 5984 cases of breast cancer and 5504 controls according to several measures of HRT (Italy, 1983–1994)

	<55 yr				55–64 yr				≥65 yr			
	Cases		Controls		Cases		Controls		Cases		Controls	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Use of HRT												
Never	2979	96.9	2596	96.4	1584	90.5	1482	91.8	1056	91.0	1125	94.0
Ever	94	3.1	97	3.6	166	9.5	132	8.2	105	9.0	72	6.0
Duration[a] (mo)												
<60	84	2.8	85	3.2	142	8.1	110	6.8	83	7.2	58	4.9
≥60	9	0.3	9	0.3	20	1.2	21	1.3	21	1.8	11	0.9
Age at starting[a] (yr)												
<50	69	2.3	74	2.8	74	4.2	83	5.2	46	4.0	43	3.6
≥50	25	0.8	22	0.8	92	5.3	49	3.0	57	4.9	29	2.4
Time since starting[a] (yr)												
<15	88	2.9	84	3.1	120	6.9	80	5.0	20	1.7	9	0.7
≥15	6	0.2	12	0.5	46	2.6	52	3.2	83	7.2	63	5.3
Time since stopping[a] (yr)												
<10	83	2.7	71	2.6	91	5.2	55	3.4	7	0.6	5	0.4
≥10	9	0.3	21	0.8	70	4.0	75	4.7	95	8.2	64	5.4

[a] The sum does not add up to the total because of missing values.

Table 3 ORs and their 95% CIs of 5984 cases of breast cancer and 5504 controls according to several measures of HRT (Italy, 1983–1994)

	OR (95% CI)[a]			
	<55 yr	55–64 yr	≥65 yr	All ages
Use of HRT				
Never	1[b]	1[b]	1[b]	1[b]
Ever	0.9 (0.7–1.2)	1.2 (1.0–1.6)	1.6 (1.2–2.3)	1.2 (1.0–1.4)
Duration (mo)				
<60	0.9 (0.6–1.2)	1.3 (1.0–1.7)	1.6 (1.1–2.3)	1.2 (1.0–1.5)
≥60	1.2 (0.5–3.1)	0.9 (0.5–1.7)	2.2 (1.0–4.7)	1.3 (0.8–2.0)
χ^2, trend	0.11 (P = 0.75)	1.37 (P = 0.24)	10.32 (P = 0.001)	5.68 (P = 0.02)
Age at starting (yr)				
<50	1.0 (0.7–1.4)	1.0 (0.7–1.4)	1.3 (0.9–2.1)	1.1 (0.8–1.3)
≥50	0.8 (0.4–1.5)	1.6 (1.1–2.3)	2.0 (1.2–3.2)	1.5 (1.2–2.0)
Time since starting (yr)				
<15	1.0 (0.7–1.3)	1.4 (1.0–1.8)	2.1 (0.9–4.7)	1.2 (1.0–1.5)
≥15	0.6 (0.2–1.6)	1.0 (0.7–1.6)	1.5 (1.1–2.2)	1.2 (0.9–1.6)
Time since stopping (yr)				
<10	1.1 (0.7–1.5)	1.5 (1.0–2.1)	1.5 (0.4–4.7)	1.3 (1.0–1.6)
≥10	0.5 (0.2–1.1)	1.0 (0.7–1.4)	1.7 (1.2–2.4)	1.2 (0.9–1.5)

[a] Estimates from multiple logistic regression equations including terms for age, study center, education, body mass index, number of children, age at menopause, history of benign breast disease, and family history of breast cancer.
[b] Reference category.

of users are more susceptible to the effect of estrogens, only limited data are available on the effects of various measures of HRT in the strata of age at diagnosis. The overall evidence supports a tendency to an increased breast cancer risk in relation to ever-use (2, 15–17) and duration (13–17) of use with age at diagnosis. Thus, our findings are consistent with the overall epidemiological evidence and with the biological decline of endogenous hormones with age (25, 26).

There are very few indications in the literature on a relationship between HRT time-related factors and breast cancer risk in the strata of age at diagnosis. Overall, the present data point to a tendency to an increase in risk of breast cancer with more recent HRT use.

Most limitations and strengths of this study are common to other hospital-based case-control studies (8, 27). Although this study was not population-based, cases were identified in the major teaching and general hospitals of the area under surveillance; only acute conditions, unrelated to known or potential risk factors for breast cancer or to correlates of HRT in this population (28), were included in the comparison group. The participation of cases and controls was almost complete (about 3% refusal in both groups), and the hospital-based design may improve the comparability of drug recall by cases and controls. The results were similar in the two studies (8, 22), confirming their consistency. One weakness is the low prevalence of use of HRT in this Italian population, which hampered more detailed analysis and might have concealed some residual selection mechanisms. Still, the major determinants of HRT use in Italy were education level, body mass index, parity, and age at menopause (28). As in several other areas of the world, these factors had no appreciable impact on any of the OR estimates. Moreover, allowance for these and several other covariates did not materially change the risk estimates, suggesting that it is unlikely that any selection, information, or confounding bias would have led to systematic and substantial underestimation of the association between HRT and breast cancer risk.

Table 4 ORs and their 95% CIs of 5984 cases of breast cancer and 5504 controls according to ever-use of HRT in separate strata of selected covariates (Italy, 1983–1994)

	OR (95% CI)[a]			
	<55 yr	55–64 yr	≥65 yr	All ages
Period at diagnosis				
1983–1989	1.1(0.7–1.9)	1.3(0.9–2.0)	2.5(1.2–5.1)	1.4(1.1–1.9)
1990–1994	0.8(0.5–1.2)	1.2(0.9–1.7)	1.5(1.0–2.2)	1.2(0.9–1.4)
Type of menopause				
Natural	1.1(0.7–1.9)	1.3(1.0–1.8)	1.8(1.2–2.6)	1.4(1.1–1.7)
Artificial	1.3(0.8–2.4)	1.2(0.7–1.9)	1.4(0.7–2.9)	1.3(1.0–1.8)
Family history of breast cancer[b]				
No	0.8(0.6–1.2)	1.3(1.0–1.6)	1.6(1.2–2.3)	1.2(1.0–1.4)

[a] OR for ever-use; the reference category was never-use in each stratum. Estimates from multiple logistic regression equations, including terms for age, study center, education, body mass index, number of children, age at menopause, history of benign breast disease, and family history of breast cancer.
[b] Too few subjects with a family history of breast cancer had used HRT to allow meaningful analyses.

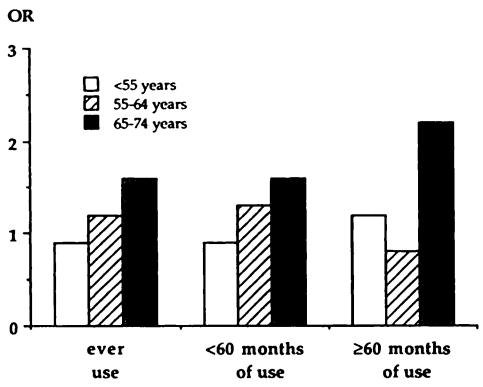

Fig. 1. ORs of 5984 cases of breast cancer and 5504 controls according to ever-use and duration of use of HRT in the strata of age at diagnosis (from data in Table 3).

This study supports a positive association between HRT and breast cancer risk with increasing age at diagnosis, which is stronger for more recent HRT use. Furthermore, several years after menopause, when the incidence of breast cancer is high, a greater excess risk in terms of OR means an even greater excess in terms of absolute risk. Thus, the prolonged use of HRT for long periods beyond the time needed for relief of perimenopausal symptoms might considerably increase the risk of breast cancer. However, to maintain protection against cardiovascular disease and osteoporosis, HRT (29, 30) should be taken for long periods beyond menopause. Thus, in elderly women the risk-benefit ratio must be carefully and individually assessed (29, 30).

Acknowledgments

We thank Judy Baggott, M. Paola Bonifacino, and the G. A. Pfeiffer Memorial Library for editorial assistance.

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