Menopause: The Journal of The North American Menopause Society
Vol. 17, No. 3, pp. 524-528
DOI: 10.1097/gme.0b013e3181ca0c74

Estrogen therapy and risk of breast cancer in postmenopausal women: a case-control study and results of a multivariate analysis

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Abstract

Objective: Several randomized trials and observational studies show that the use of hormone therapy (HT) increases the risk of breast cancer (BC). The aim of this study was to assess the effects of exposure to both HT and oral contraceptives (OCs) on BC risk in postmenopausal women, all residing in the same metropolitan area.

Methods: Data regarding a series of 238 consecutive postmenopausal women with infiltrating ductal carcinoma (cases) and 255 randomly selected age-matched healthy women (controls) were reviewed. Odds ratios for no breast-feeding and HT and OC use were 1.82 (95% CI, 1.20-2.77), 2.49 (95% CI, 1.73-3.58), and 2.06 (95% CI 1.14-3.70), respectively.

Results: Four independent variables (years between menarche and menopause, breast-feeding, OC use, and HT use) were included in the final multivariate analysis using logistic regression. The cumulative odds ratio calculated from the observed versus predicted values, obtained using the logistic regression function, was 4.55 (95% CI, 2.13-9.71), whereas the cumulative risk of common exposure to both OCs and HT was 2.77 (95% CI, 1.44-5.32). The logistic model correctly classified 67.5% (95% CI, 63.2-71.5) of cases. The receiver operating characteristic (ROC) curve of the complete logistic function showed a fair area of accuracy (0.77; 95% CI, 0.72-0.81).

Conclusions: Our results show that the risk of common exposure to both OCs and HT increases in women with other risk factors. However, several parameters traditionally considered in epidemiological studies do not have the same weight in each local community, suggesting the need to create different models to correctly select the high-risk population.

Key Words: Breast cancer risk – Menopause – Hormone therapy – Oral contraceptives – Estrogen therapy – Risk factors.

Breast cancer (BC) is the most common cancer among women and is a significant global health problem, even though several advances in the diagnosis, staging, and therapeutic approach of BC have been achieved over the past few years.[1,2] The relationship between BC and various risk factors (RFs) has been investigated for almost half a century, and significant geographical variations in BC incidence have also been observed.[3-5] Several randomized trials and observational studies show that hormone therapy (HT) increases the risk of BC, especially when estrogen-progestin combinations are chosen,[6] whereas oral contraceptives (OCs) are usually considered as a weak RF.[7-9] Few studies consider HT and OCs together.[10-12] The aim of this study was to assess the effects of exposure to both HT and OCs on BC risk in postmenopausal women, all residing in the same metropolitan area, and the cumulative risk in the presence of other RFs.

Received September 9, 2009; revised and accepted November 9, 2009.

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This article was presented in part at The Endocrine Society 89th Annual Meeting, Toronto (Canada), June 2-5, 2007.

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector. Consent was obtained from each woman after full explanation of the purpose and nature of all procedures used. The investigation was approved by the local ethics committee.

Financial disclosure/conflicts of interest: None reported.

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METHODS

Overall population

We retrospectively reviewed data regarding a series of 404 consecutive women (median age, 56 y; range, 27-81 y) who underwent curative surgery for primary BC (cases). The preoperative diagnosis was obtained by fine-needle aspiration cytology, core biopsy, or open biopsy. In women with non-palpable lesions, the biopsy was performed using wire needle localization, under ultrasound or stereotactic guidance. Method

TABLE 1. *Method of diagnosis, histological type, and staging of the tumors*

Characteristics	No. of women	%
Method of preoperative diagnosis		
Fine-needle aspiration cytology	347	85.9
Core-needle biopsy	39	9.6
Excisional biopsy	18	4.5
Histological type		
Infiltrating ductal	335	82.9
Infiltrating lobular	43	10.6
Medullary	12	3.0
Other and mixed	14	3.5
Staging		
pT1a	15	3.7
pT1b	70	17.3
pT1c	143	35.4
pT2	148	36.7
pT3	28	6.9
pN0	272	67.3
pN1-3	104	25.8
pNx	28	6.9

of diagnosis, histological type, and staging of the tumors are reported in Table 1.

Control subjects (controls) were 408 randomly selected age-matched healthy women who have undergone screening mammography twice and were followed up for at least 2 years. In both groups, the analysis was restricted to women who gave complete information.

Both cases and controls resided in the same region (Veneto) in the northeast of Italy, in which there is an estimated yearly BC incidence of 150 cases per 100,000 women, one of the highest in Italy.[13] Overall, 274 (33.7%) and 232 (28.6%) of 812 women were current or former users of OCs and/or HT, respectively. Women with a history of previous cancer or BC onset during follow-up, as well as those who have used estrogen + progestin therapy and/or were non–OC users, were excluded from the study.

Written informed consent was obtained from all participants in accordance with institutional review board approval.

Study population

With the aim of excluding further confounding data, we considered suitable for the study only postmenopausal women and cases of women with infiltrating ductal carcinoma. Thus, in the final study population, there were 238 cases and 255 controls, with a median age of 61 years.

Hormone therapy use was calculated to 1 year before current age because such a short exposure was unlikely to be causal.[12,14] Ever use of OCs was defined as at least 3 months of use, whereas current use of either OCs or HT was defined as use within 2 years of the reference date.[8]

Statistical analysis

The reported data are expressed as mean ± SD. Two-tailed Student's *t* test for unpaired data and the Mann-Whitney *U* test were used to compare means of grouped data of continuous or ordinal variables (ie, age of the women, years between menarche and menopause, and months of OC and HT use), whereas the χ^2 test and the Fisher exact probability test, when required, were used to compare categorical variables. The parameters found to be significantly related to BC in univariate analysis were assessed for the multivariate analysis using an unconditional multiple logistic regression model, fitted by the method of maximum likelihood.[15] Odds ratio (OR) estimates and the associated 95% CI were also obtained. Finally, the receiver operating characteristic (ROC) curve was used for representing the diagnostic accuracy. The significance level was set at $P < 0.01$.

RESULTS

The main characteristics of cases versus controls and the relative *P* value estimation are reported in Table 2, whereas Table 3 shows the distribution of cases and controls according to different potential RFs and the relative ORs at 95% CI in the study population (n = 493).

As expected, the risk was increased in women with family history of BC (OR, 2.38-4.40; 95% CI, 0.92-20.93), but the *P* value was not significant. OR for no breast-feeding was 1.82 (95% CI, 1.20-2.77) and for HT was 2.49 (95% CI, 1.73-3.58). An increased but nonsignificant (*P* = NS) incidence of BC was associated with OC use (OR, 2.06; 95% CI, 1.14-3.70), first childbearing after 30 years (OR, 1.93; 95% CI, 1.02-3.68), and body mass index greater than 24 kg/m^2 (OR, 1.30; 95% CI, 0.87-1.94).

The analysis showed also that BC onset was not significantly related to nulliparity and history of benign breast diseases. Controls were more probable than cases to report a history of spontaneous abortions and have surgical menopause.

Four independent variables (years between menarche and menopause, breast-feeding, OC use, and HT use) were included in the final multivariate analysis using the logistic regression. The cumulative OR calculated from the observed versus predicted values, obtained using the logistic regression function, was 4.55 (95% CI, 2.13-9.71), whereas the cumulative risk of common exposure to both OC and HT was 2.77 (95% CI, 1.44-5.32). The logistic model correctly classified 67.5% (95% CI, 63.2-71.5) of cases.

The areas under the ROC curves calculated for the single variables considered in the logistic model ranged from 0.57 (95% CI, 0.52-0.62) to 0.61 (95% CI, 0.57-0.66), whereas the

TABLE 2. *Main characteristics of cases versus controls (mean ± SD)*

Characteristics	Cases	Controls	*P*
Age at diagnosis, y	62.4 ± 9.6	61.2 ± 8.4	0.140
Age at first pregnancy, y[a]	25.3 ± 4.4	24.2 ± 3.8	0.009
Parity (children per woman)	1.4 ± 1.1	1.4 ± 1.0	0.999
Months of breast-feeding	10.2 ± 8.6	13.9 ± 10.0	<0.001
Age at menopause, y	49.1 ± 4.6	48.3 ± 3.6	0.031
Years between menarche and menopause	36.8 ± 4.8	35.1 ± 3.9	<0.001
Oral contraceptive use, mo[b]	28.4 ± 21.2	33.8 ± 33.5	0.470
Hormone therapy use, mo[c]	43.7 ± 30.2	30.9 ± 23.5	<0.001

[a]In childbearing women.
[b]In those who used oral contraceptives.
[c]In those who used hormone therapy.

TABLE 3. *Distribution of potential risk factors for breast cancer (infiltrating ductal carcinoma) in cases and controls (χ^2 test corrected by Yates and Fisher exact probability test[a]) P-value, and relative odds ratios (OR) at 95% CI*

Characteristics	Cases	%	Controls	%	*P*	OR	95% CI
No. of women	238	100	255	100	–	–	–
Mother with breast cancer	15	6.3	7	2.7	0.09	2.38	0.95-5.95
Sister(s) with breast cancer	8	3.4	2	0.9	0.04[a]	4.40	0.92-20.93
No pregnancies	56	23.5	49	19.2	0.29	1.29	0.84-1.99
First childbearing after 30 y	27[a]	11.6	17[a]	6.4	0.06	1.93	1.02-3.68
Spontaneous abortions	35	14.7	40	15.7	0.76	0.93	0.56-1.52
No breast-feeding	79[b]	43.4	61[b]	29.6	0.006	1.82	1.20-2.77
No bilateral oophorectomy	218	91.6	240	94.1	0.36	0.68	0.34-1.36
Body mass index >24 kg/m^2	69	29.0	61	23.9	0.24	1.30	0.87-1.94
Alcohol abuse	25	10.5	24	9.4	0.80	1.13	0.63-2.04
History of benign breast diseases	25	10.5	22	8.6	0.58	1.24	0.68-2.27
Smoking past	15	6.3	20	7.8	0.62	0.79	0.39-1.58
Smoking present	28	11.8	26	10.2	0.68	1.17	0.66-2.07
Oral contraceptive use	34	19.3	19	7.5	0.02	2.06	1.14-3.70
Hormone therapy use	138	57.9	91	35.7	<0.001	2.49	1.73-3.58

[b]Out of 182 and 206 childbearing women: cases versus controls, respectively.

ROC curve of the complete logistic function (Fig. 1) showed a fair area of accuracy (0.77; 95% CI, 0.72-0.81).

DISCUSSION

BC remains a major public health problem in developed countries. Unfortunately, epidemiological studies mainly identify uncorrectable RFs (ie, family history and reproductive, hormonal, and medical factors), and, in addition, large geographical differences in both BC incidence and mortality have been observed.[3,5,16,17] Increased risk of BC is correlated with the use of several drugs, including drugs acting on the female reproductive system, and in Western countries, HT has long been considered as an RF, as in reanalyzed studies.[6,14,18,19] However, a recent Japanese survey showed a significant negative correlation (OR, 0.43; 95% CI, 0.35-0.53) between HT use and BC.[20] Moreover, it has also been found that HT may be associated with more favorable tumor characteristics (ie, low tumor grade, high S phase, and positive receptor status) and survival.[21-26] In our study, the risk of BC was relatively low when OCs and HT were considered as single variables (OR, 2.06 and 2.49, respectively), but an increased risk (OR, 2.77) of common exposure to both OCs and HT was found, as reported by others.[12,27] In our study, the ROC curve, typically used to evaluate clinical utility for both diagnostic and prognostic models, showed a fair area (>0.75) under the curve of the complete function. Thus, our predictive model showed that women with concomitant RFs, such as no breast-feeding, long interval between menarche and menopause, and OCs and HT use, should be considered as having a significantly increased risk of BC.

Several studies have also provided strong evidence for increased risk of BC, especially invasive lobular carcinomas, in women using estrogen-progestin combinations than in those using estrogen alone, whether the progestin component was taken in a continuous or in a sequential manner.[6,28-30] In 1999, about 22% of US women were dispensed prescriptions for unopposed estrogen or estrogen + progestin, whereas dispensing was 29% and 59% lower in 2003 and 69% and 79% lower in 2006, respectively, in conjunction with dropped incidence rates of BC for women 45 years or older in 2003-2006.[31] In addition, in Australia, prescribing of HT dropped by 40% from 2001 to 2003, and age-standardized BC incidence rates in women 50 years or older were lower compared with those in the 1996-2001 period.[32] Table 4 shows the results of studies reporting data on risk of BC using OCs and HT.

CONCLUSIONS

Most RFs, such as familial, personal, and reproductive history, are useful only for passive prevention, to find women at high risk requiring a careful mammographic surveillance, whereas other RFs (ie, Western diet and lifestyle, alcohol abuse, and inadequate body mass index), as well as prolonged HT administration, represent RFs suitable for active prevention, leading to a reduction in BC incidence.

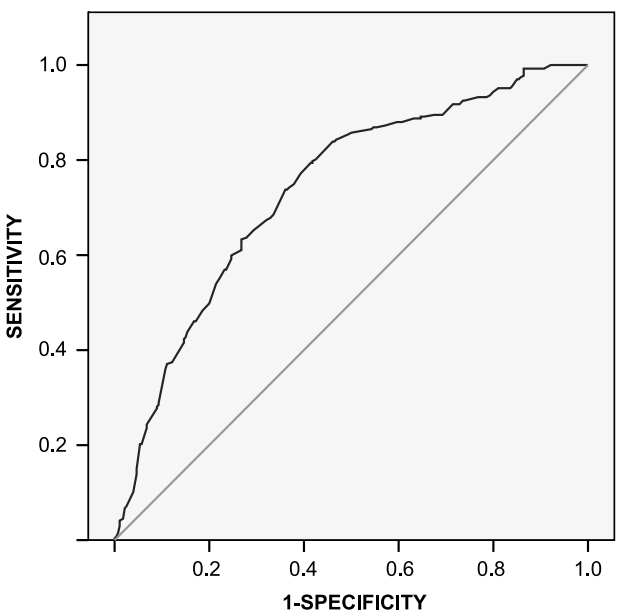

FIG. 1. Receiver operating characteristic curve of the complete logistic function.

TABLE 4. *Results of studies reporting data on risk of breast cancer using OCs and estrogen therapy*

Type of HT	Author and year	RR, OR, HR	95% CI
OCs	Nyante et al (2008)[33]	OR, 1.10 (ILC)	0.68-1.78
		OR, 1.21 (IDC)	1.01-1.45
	Kahlenborn et al (2006)[34]	OR, 1.19	1.09-1.29
	Collaborative Group on Hormonal Factors in Breast Cancer (1996)[35]	RR, 1.24 (current users)	1.15-1.33
		RR, 1.16 (between 1 and 4 y after use)	1.08-1.23
		RR, 1.01 (>10 y after use)	0.96-1.05
	Present study	OR, 2.06	1.14-3.70
HT	Lyytinen et al (2009)[36]	RR, 2.07 (>10 y after use)	1.84-2.30
	Lund et al (2007)[11]	HT alone: RR, 1.67	1.32-2.12
		OCs + HT: RR, 2.45	1.92-3.12
	Reeves et al (2006)[37]	RR, 2.25 (ILC)	2.0-2.52
		RR, 2.13 (IDLC)	1.68-2.70
	Li et al (2003)[28]	RR, 1.7	1.3-2.2
	Beral (2003)[6]	RR, 1.66	1.58-1.75
	Rossouw et al (2002)[38]	RR, 1.26	1.00-1.59
Estrogen + progestin	Beral (2003)[6]	RR, 2.00	1.88-2.12
	Rossouw et al (2002)[38]	HR, 1.26	1.00-1.59
Estrogens alone	Beral (2003)[6]	RR, 1.30	1.21-1.40
	Kirsh and Kreiger (2002)[16]	OR, 1.74 (>10 y of use)	0.93-3.24
	Present study	OR, 2.49	1.73-3.58

OC, oral contraceptive; HT, hormone therapy; RR, relative risk; OR, odds ratio: HR, hazard ratio; ILC, infiltrating lobular carcinoma; IDC, infiltrating ductal carcinoma; IDLC, infiltrating ductal and lobular carcinoma.

In addition, our results show that several parameters traditionally considered in epidemiological studies do not have the same weight in each local community, suggesting the need of creating different models to correctly select the high-risk population.

Acknowledgments: We thank Ms. Francesca Bissolotti for her help in writing the manuscript and reviewing the English.

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