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Risk Factors for Breast Cancer in Women Biopsied for Benign Breast Disease: A Nested Case-Control Study

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Abstract

Aim—Women with a history of benign breast disease are at increased risk of subsequent breast cancer. However, few studies have examined whether established breast cancer risk factors other than histology are associated with an altered risk of breast cancer in women with benign breast disease. We used a nested case-control design within a large, multi-center cohort of women biopsied for benign breast disease (BBD) to estimate odds ratios for breast cancer in association with exposure to a range of personal and lifestyle factors.

Methods—Cases were women biopsied for BBD who subsequently developed breast cancer; controls were individually matched to cases on center and age at diagnosis and were women biopsied for BBD who did not develop breast cancer in the same follow-up interval as that for the cases. After excluding women with prevalent breast cancer, 1357 records (661 case records and 696 records) were available for analysis. We used conditional logistic regression to obtain crude and multivariable-adjusted estimates of the association between specific factors and risk of breast cancer.

Results—In multivariable analyses age at first live birth, number of pregnancies, and postmenopausal status were inversely associated with risk of breast cancer. The odds ratio for women with age at first birth <25 years and >3 pregnancies, relative to nulliparous women, was

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Conflict of Interest
All authors declare that they have no conflict of interest, financial or otherwise.

0.49, 95% confidence interval 0.13-0.79, and that for postmenopausal women relative to premenopausal women was 0.60, 95% 0.37-0.99.

Conclusions—Further study of personal factors influencing the risk of breast cancer in women with BBD may help to identify subgroups of the population at increased risk of invasive disease.

Keywords

benign breast disease; breast cancer; reproductive factors; hormone therapy

Introduction

Benign breast disease (BBD) encompasses a spectrum of histologic changes, some of which are associated with increased risk of breast cancer (1, 2). Specifically, proliferative disease without atypia and atypical hyperplasia, are believed to represent steps in the progression from normal cellular architecture to invasive cancer (2, 3). Although risk factors for invasive breast cancer have been studied extensively amongst women in the general population, little is known about factors that are associated with risk of breast cancer among the subgroup of women with benign breast disease. Factors that promote cell proliferation, such as those associated with increased exposure to estrogen, might act to increase risk (4, 5), whereas factors that inhibit cell proliferation, including the effects of a first full-term pregnancy or of multiple births, may reduce risk (4, 5). Several studies have examined the associations of age at diagnosis of BBD, menopausal status, and family history of breast cancer with risk of breast cancer among women with BBD (6-12). However, only a few studies to date have examined the range of exposures that may influence risk of breast cancer in this population at increased risk (13-16). Such exposures include menstrual and reproductive factors, anthropometric factors, exogenous hormone use, and cigarette smoking. Study of personal factors influencing the risk of breast cancer in women with BBD may lead to the identification of subgroups of the population at increased risk of invasive disease.

We used a nested case-control design within a large, multi-center cohort of women biopsied for benign breast disease to estimate the odds ratio for the association of reproductive, hormonal, and other risk factors with risk of subsequent breast cancer.

Methods

Study Population

The study was conducted within a cohort of 20,697 women biopsied for benign breast disease and enrolled in 3 centers (Toronto, Canada; Portland, OR, USA; and London, UK). The three cohorts have been described in detail previously (17). Here we provide a brief description of the study populations and methods. In Toronto, women biopsied for benign breast disease were ascertained through the National Breast Screening Study (NBSS), a multi-center randomized controlled trial of screening for breast cancer in 89,835 Canadian women aged 40-59 who were recruited between 1980 and 1985. NBSS participants completed lifestyle questionnaires at the time of their enrollment. The variables of interest (in Toronto and the other centers) were: demographic characteristics, family history of breast cancer, menstrual and reproductive history, smoking history, and use of oral contraceptives and replacement estrogens). During the active follow-up phase of the NBSS, outcomes were ascertained by means of reports of diagnostic procedures and annual questionnaires sent to study participants. Thereafter, follow-up was obtained by linkage to provincial cancer registries and the Canadian National Mortality Database. The London (U.K.) cohort was created by enrolling women who were biopsied for BBD at Guy's Hospital, London between 1946 and 1984. Risk factor data were collected from the patient

charts held in the Guy's Hospital Breast Unit. Breast cancer diagnoses were ascertained through the National Health Service Central Register (NHSCR). Any cancer registrations prior to the inception of the NHSCR (which took place in 1962) were identified through the Guy's Hospital Cancer Registry and the Thames Cancer Registry. The Portland cohort was created by identifying women who were biopsied for BBD within the Kaiser Permanente Northwest (KPNW) health care system between 1970 and 1994. Risk factor information was obtained by abstracting data from the KPNW medical records. The occurrence of breast cancer was ascertained by linking records from the cohort to the KPNW Tumor Registry. Median follow-up for all centers was 14.7 years (20.8 years in London, 15.1 years in Toronto, and 12.7 years in Portland).

Cases were women who had a biopsy for benign breast disease between 1946 and 1994 with a subsequent diagnosis of *in situ* or invasive breast cancer. In each cohort, controls were women with a biopsy for benign breast disease who were still at risk of developing breast cancer at the time the index case was diagnosed/identified. Thus, controls were matched to the index case with respect to sampling time. In each cohort, controls were individually matched to cases on age and on age at diagnosis of benign breast disease (with additional matching in the Portland cohort on duration of membership in Kaiser Permanente health plan). Controls were selected with replacement, and were eligible to be selected again or to become cases subsequently. For this reason, although there were 1325 women in the nested case-control study, there were a total of 1362 records in the analysis, 665 case records and 697 control records. Of the 1362 records in the original study, we excluded 5 records in which a diagnosis of breast cancer occurred prior to baseline (N = 3) or at the time of biopsy (N = 2), leaving 1357 records with information on breast cancer risk factors (661 case and 696 controls).

The study protocol was approved by the institutional review boards at all four sites (Toronto, London, Portland, and the New York coordinating center).

Histologic review

At each center, slides were reviewed by a designated pathologist, and histologic sections were classified according to the criteria developed by Page and Anderson (18) and the subsequent consensus conference of the College of American Pathologists (19) without knowledge of the case-control status of the study subjects. In addition, pathologists from Portland and London, but not Toronto, had a joint session to standardize criteria.

Available risk factor data

Data were available on a range of established and hypothesized breast cancer risk factors, including age at menarche, at age first live birth, number of pregnancies, menopausal status, history of bilateral oophorectomy, family history of breast cancer, height and weight, oral contraceptive use, hormone therapy, and cigarette smoking. The main variables with a substantial proportion of missing data were oral contraceptive use, hormone therapy, cigarette smoking, and height and weight. In London data were not available on hormone therapy, cigarette smoking, or height and weight, and were partially missing on age at menarche (36% missing) and oral contraceptive use (39% missing). In Portland, 75% of women had missing data on oral contraceptive use and 51% were missing data on hormone therapy. The proportions of missing data for each variable are given in Table 1.

Statistical Analysis

We used conditional logistic regression to estimate odds ratios and 95% confidence intervals for each risk factor with risk of subsequent breast cancer. Risk factors were included in the multivariable conditional logistic model if they showed a significant univariate association

with breast cancer (at the 5% significance level) or if their addition to the model altered the point estimate for variables that showed a significant univariate association by >10%. Because a substantial number of subjects were missing information on certain variables in some cohorts (body mass index, oral contraceptive use, hormone therapy use, and cigarette smoking), multivariable analyses were carried out in two stages in order to maximize statistical power. The first stage focused on those variables with a low proportion (<20%) of missing data (age at menarche, age at first live birth, number of pregnancies, menopausal status, histology, and family history of breast cancer in first degree relative). This made it possible to estimate the effects of these variables with maximum precision in this "core" model. The core model included age at first live birth/number of pregnancies, menopausal status, family history of breast cancer in a first degree relative, and histology. Although family history of breast cancer in a first degree relative did not satisfy either of our criteria, it was included based on its known strong association with breast cancer risk. The second stage extended the model to include variables for which there was substantial missing data (greater than 35%: body mass index, oral contraceptive use, hormone therapy use, and cigarette smoking). The analysis was restricted to those not missing information on these variables. Second stage models included age at first live birth/number of pregnancies, menopausal status, and histology as covariates because of their significant associations with breast cancer. Continuous variables were categorized, and we performed tests for linear trend on the resulting ordered categorical variables based on the median value of each interval. In order to avoid collinearity between age at first live birth and number of pregnancies, we created a compound variable (nulliparous; age at first live birth ≥ 25 years and number of pregnancies <3; age at first live birth ≥ 25 years and number of pregnancies ≥3; age at first live birth <25 years and number of pregnancies <3; age at first live birth <25 years and number of pregnancies ≥3). All analyses were performed in SAS 9.1 (SAS Institute, Cary, NC).

Results

In univariate analyses, relative to nulliparous women, women who had a relatively early age at first live birth had a significantly decreased risk of subsequent breast cancer (Table 1). A relatively high number of pregnancies, being postmenopausal (vs. premenopausal), ever use of oral contraceptives, and greater duration of oral contraceptive use all showed significant inverse associations with risk (Table 1).

In the first stage of the multivariable analyses, age at first live birth, number of pregnancies, family history, and menopausal status, earlier age at first live birth, and a relatively high number of pregnancies were each associated with reduced risk when entered into separate models with menopausal status, family history of breast cancer in a first degree relative, and histology as covariates (data not shown). When age at first live birth and number of pregnancies were combined, the compound variable age at first live birth/number of pregnancies showed a significant inverse association with risk (Table 2) Relative to nulliparous women, women with 3 or more pregnancies and women who had a first live birth before age 25 years had roughly half the risk of breast cancer. For women with age at first birth <25 years and 3+ pregnancies the odds ratio was 0.49 (95% CI 0.13-0.79). Postmenopausal women were at decreased risk relative to premenopausal women: OR 0.60, 95% CI 0.37-0.99. A positive family history of breast cancer was not associated with altered risk. Odds ratios for proliferative disease without atypia and for atypical hyperplasia relative to no BBD/non-proliferative disease were similar to those previously reported (and therefore not reported here) (17). Because of the difference in data collection methods in Toronto, where risk factor information was obtained using a structured questionnaire, on the one hand, and London and Portland, where information was abstracted from the medical chart, on the other, we repeated the analysis restricted to London and Portland. The results were

very similar. The odds ratio for women with age at first birth <25 years and >3 pregnancies, relative to nulliparous women, was 0.51, 95% CI 0.30-0.87, and that for postmenopausal status, relative to premenopausal status was 0.63, 95% CI 0.37-1.05. When the analysis was repeated excluding women who were missing histology data (N = 82), the results were unchanged (data not shown).

The associations of age at first live birth/number of pregnancies and of postmenopausal status with risk persisted in separate analyses of women with nonproliferative disease and women with proliferative disease (including atypical hyperplasia). The inverse association of postmenopausal status with breast cancer was stronger in women with non-proliferative benign breast disease than in women with proliferative disease, and the interaction between menopausal status and histologic grouping was significant (p = 0.025). The effect of age at first live birth/number of pregnancies did not differ by histologic category (p for interaction = 0.9 (data not shown).

In the second stage of multivariable modeling we included each of the variables not included in the first stage (i.e., those with a relatively high proportion of missing values) in a separate model with age at first live birth/parity, menopausal status, and histology as covariates (Table 3). After adjustment for covariates, ever use of oral contraceptives was no longer associated with breast cancer risk and there was no trend with increasing duration of use. None of the other variables in Table 3 was associated with risk.

Discussion

In this large case-control study nested within a cohort of women biopsied for benign breast disease, several reproductive and hormonal factors were associated with subsequent risk of breast cancer. After adjustment for covariates, postmenopausal status and the compound variable for age at first live birth and number of pregnancies were significantly inversely associated with breast cancer risk, whereas oral contraceptive use was no longer statistically significant.

Few studies have reported on the classical risk factors for breast cancer other than family history of breast cancer and menopausal status among women biopsied for BBD (6-16). Thus, our findings require confirmation in other studies. The strongest and most consistent finding was that the combination of an early age at first birth and greater parity was associated with reduced risk. Relative to nulliparous women, women who had had a first live birth before age 25 and had had 3 or more pregnancies had an odds ratio for breast cancer of 0.49, 95% CI 0.31-0.79. The protective effects of an early age at first birth and of greater parity are well-established for invasive breast cancer in the general population (5), but no previous study has reported on the association of age at first live birth or parity and risk breast cancer among women with BBD.

Similar to our univariate finding regarding oral contraceptive use, Worsham et al. (12) observed a significant inverse association of ever use of oral contraceptives with risk in univariate analyses (odds ratio 0.57, 95% CI 0.36-0.90); however, they did not provide adjusted results. After adjustment for covariates in our study, the inverse associations of ever use of oral contraceptives and duration of use were no longer statistically significant. Our results concerning postmenopausal hormone therapy are in agreement with those of several cohort studies showing no effect of hormone use on risk of breast cancer in women with benign breast disease (13-16). In the study by Thomas et al. (13), although exogenous estrogens taken prior to the initial benign lesion did not alter the risk of breast cancer, subsequent use, primarily of conjugated estrogens, abolished the protective effect of an

artificial menopause. No previous studies have examined the association of body mass index or cigarette smoking with risk of breast cancer among women with BBD.

The difference in data collection methods between Toronto, where the data were collected using a structured questionnaire, and London and Portland, where risk factor data were abstracted from medical recordst, might have affected the accuracy of our data. Furthermore, the fact that certain centers did not obtain data on some variables might have affected the representativeness of our results. We addressed these issues in our analysis. First, we repeated the first-phase analysis for Toronto and London + Portland, separately, and observed similar inverse associations with age at first live birth/number of pregnancies and postmenopausal status. Second, we analyzed each of the second-stage variables, which had a substantial proportion of missing data, separately in the presence of the variables from the first stage. No significant associations or trends were observed; however, we had reduced power to assess associations with these other variables (body mass index, hormone use, and cigarette smoking).

As demonstrated in numerous studies (6-12, 17), women biopsied for benign breast disease are a heterogeneous group with respect to their risk for breast cancer, ranging from no increased risk among women with no evidence of pathology, minimally increased risk among women with non-proliferative disease, slightly increased risk among women with proliferative disease without atypia, and substantially increased risk among women with atypical hyperplasia. Therefore, it is of interest to assess the effect of the different risk factors within different categories of BBD. In stratified analyses, age at first live birth/ number of pregnancies and postmenopausal status were both inversely associated with risk among both women with non-proliferative disease and women with proliferative disease without atypia. However, missing data on several variables (body mass index, oral contraceptive use, hormone therapy, and cigarette smoking) precluded a full analysis of all relevant variables. Furthermore, the small number of cases of atypical hyperplasia precluded analysis of risk factors in this group at highest risk of breast cancer.

Strengths of the present study include the large cohort of women biopsied for BBD, from which cases and controls were selected, and information available on menstrual and reproductive variables which have received little attention previously. However, the fact that information on a number of other risk factors or potential risk factors was not available from all collaborating centers imposed limitations on our analysis, and we had reduced power to detect an effect on these factors. Furthermore, we had limited power to carry out analyses stratified by menopausal status, histology, and other variables. Finally, we did not have information on the type of postmenopausal hormone therapy (estrogen alone or estrogen plus progestin), or on several other factors that have been studied in detail in relation to breast cancer risk in the general population (e.g., alcohol consumption, history of breastfeeding).

In conclusion, few studies have examined risk factors for breast cancer in women with BBD other than histology, family history of breast cancer, and menopausal status. We found that early age at first live birth and a relatively high number of pregnancies were associated with reduced risk of breast cancer among women biopsied for benign breast disease. In addition, postmenopausal women were at reduced risk compared to premenopausal women. Further study of personal factors influencing the risk of breast cancer in women with BBD may help to identify subgroups of the population at increased risk of invasive disease.

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Table 1

Univariate associations of background variables and breast cancer risk factors with subsequent risk of breast cancer among women biopsied for benign breast disease.

Characteristic	Cases (N = 661)	Non-cases (N = 696)	Crude odds ratio	95% CI
Age at menarche				
<12	109	107	1.00	Reference
12	127	123	1.09	0.72-1.66
13	150	173	0.85	0.58-1.27
≥14	145	175	0.88	0.59-1.31
P for trend			*0.29*	
Missing	130	118		
Age at first live birth				
Nulliparous	132	99	1.00	Reference
≥30	71	61	0.73	0.45-1.18
25-<30	125	136	0.54	0.36-0.83
20-<25	210	278	0.46	0.31-0.68
<20	53	62	0.49	0.29-0.81
P for trend			*0.01*	
Missing	70	60		
Age at first live birth among parous women				
≥30	71	61	1.00	Reference
25-<30	125	136	1.09	0.78-1.51
20-<25	210	278	0.66	0.43-1.03
<20	53	62	0.74	0.54-1.01
P for trend			*0.14*	
Missing (includes nulliparous)	202	159		
Nulliparous	132	99	1.00	Reference
Parous	522	588	0.62	0.44-0.87
Missing	7	9		
Number of pregnancies				
None	132	99	1.00	Reference
1	107	98	0.77	0.51-1.16
2	189	213	0.60	0.41-0.87
3	115	138	0.59	0.39-0.88
4	65	74	0.56	0.35-0.93
≥5	46	65	0.46	0.27-0.78
P for trend			*0.002*	
Missing	7	9		
Age at first birth and number of pregnancies combined				
Nulliparous	132	99	1.00	Reference
Aflb ≥25 y/ <3 pregnancies	145	121	0.68	0.44-1.04
Aflb ≥25 y/ ≥3 pregnancies	50	74	0.40	0.23-0.68

Characterististic	Cases (N = 661)	Non-cases (N = 696)	Crude odds ratio	95% CI
Aflb <25 y/ <3 pregnancies	113	154	0.45	0.29-0.69
Aflb <25 y/ ≥3 pregnancies	149	184	0.46	0.30-0.712
Missing	72	64		
Menopausal status				
Premenopausal	364	352	1.00	Reference
Perimenopausal	63	82	0.72	0.47-1.09
Postmenopausal	234	262	0.66	0.44-0.99
History of bilateral oophorectomy				
No	570	598	1.00	Reference
Yes	54	55	1.19	0.77-1.84
Missing	37	43		
Family history of breast cancer in a first degree relative				
No	528	583	1.00	Reference
Yes	107	93	1.25	0.90-1.73
Missing	26	20		
Body mass index (kg/m)				
<22	97	123	1.00	Reference
22-<24	103	90	1.26	0.82-1.93
24-<28	121	129	1.24	0.82-1.85
>28	95	107	1.13	0.72-1.78
P for trend			*0.80*	
Missing	245	247		
Oral contraceptive use				
Never	145	151	1.00	Reference
Ever	178	230	0.65	0.41-1.01
Missing	338	315		
Duration of oral contraceptive use:				
Never	145	151	1.00	Reference
<12 mo	26	35	0.50	0.21-1.19
12-<36	30	38	0.79	0.33-1.87
36-<72	24	41	0.39	0.16-0.95
72-<108	22	26	0.84	0.31-2.30
≥108	19	25	0.34	0.13-0.92
P for trend			*0.09*	
Missing	395	380		
Hormone therapy				
Never	97	113	1.00	Reference
Ever	171	198	0.95	0.52-1.75
Missing	393	385		
Duration of hormone therapy use:				
Never	97	113	1.00	Reference
<12 mo	26	31	0.84	0.36-1.99

Characterististic	**Cases (N = 661)**	**Non-cases (N = 696)**	**Crude odds ratio**	**95% CI**
12-<48	40	46	1.44	0.64-3.22
48-<96	36	54	0.68	0.30-1.53
≥96	41	48	0.99	0.45-2.15
P for trend			*0.56*	
Missing	421	404		
Cigarette smoking				
Never	141	157	1.00	Reference
Ever	185	207	1.01	0.71-1.43
Missing	335	332		
Cigarettes per day				
Never smoked	141	157	1.00	Reference
1-<10	26	22	1.22	0.57-2.65
10-<20	36	45	0.97	0.52-1.82
20-<30	63	74	1.14	0.70-1.87
≥30	28	28	1.21	0.58-2.55
Ptrend			*0.54*	
Missing	367	370		
Duration of smoking				
Never smoked	141	157	1.00	Reference
1-<10 yrs	39	36	1.29	0.63-2.65
10-<20	35	46	0.69	0.37-1.26
20-<30	48	49	1.19	0.68-2.09
≥30	41	41	1.22	0.71-2.12
Ptrend			*0.35*	
Missing	357	367		

Table 2

Multivariate associations of breast cancer risk factors with subsequent risk of breast cancer among women biopsied for benign breast disease.

	Cases (N=661)	Controls (N=696)	Multivariate odds ratio*	95% CI
Age at first live birth/number of pregnancies				
Nulliparous	132	99	1.00	Reference
≥25 yrs/ <3	145	121	0.81	0.51-1.28
≥25 yrs/ ≥3	50	74	0.44	0.25-0.78
<25 yrs/ <3	113	154	0.53	0.33-0.86
<25 yrs/ ≥3	149	184	0.49	0.13-0.79
Missing	72	64		
Family history of breast cancer				
No	528	583	1.00	Reference
Yes	107	93	1.24	0.85-1.80
Missing	26	20		
Menopausal status				
Premenopausal	364	352	1.00	Reference
Perimenopausal	63	82	0.76	0.44-1.32
Postmenopausal	234	262	0.60	0.37-0.99

*Adjusted for the other variables in the table, as well as histology (no BBD/non-proliferative disease, proliferative disease without atypia, atypical hyperplasia).

Table 3

Multivariate associations of additional breast cancer risk factors with subsequent risk of breast cancer among women biopsied for benign breast disease.

	Cases (N=661)	Controls (N=696)	Multivariate odds ratio*	95% CI
Body mass index (kg/m)				
<22	97	123	1.00	Reference
22-<24	103	90	1.15	0.71-1.87
24-<28	121	129	1.22	0.78-1.92
>28	95	107	1.21	0.73-1.99
P for trend		*0.50*		
Missing	245	247		
Oral contraceptive use				
Never	145	151	1.00	Reference
Ever	178	230	0.86	0.51-1.45
Missing	338	315		
Duration of oral contraceptive use				
Never	145	151	1.00	Reference
<72 months	80	114	0.56	0.27-1.18
≥72 months	41	51	0.56	0.23-1.37
P for trend		*0.35*		
Missing	395	380		
Hormone therapy				
Never	97	113	1.00	Reference
Ever	171	198	0.91	0.44-1.88
Missing	393	385		
Duration of hormone therapy use				
Never	97	113	1.00	Reference
<48 months	66	77	1.31	0.59-2.92
≥48 months	77	102	0.70	0.30-1.62
P for trend		*0.10*		
Missing	421	292		
Cigarette smoking				
Never	141	157	1.00	Reference
Ever	186	207	0.98	0.66-1.45
Missing	334	332		
Cigarettes per day*				
Never smoked	141	157	1.00	Reference
1-<10	26	22	1.24	0.54-2.84
10-<20	36	45	0.83	0.41-1.65
20-<30	63	74	1.21	0.69-2.13
≥30	28	28	1.16	0.53-2.56
P for trend		*0.57*		

	Cases (N=661)	Controls (N=696)	Multivariate odds ratio*	95% CI
Missing	367	370		
Duration of smoking				
Never smoked	141	157	1.00	Reference
1-<10 yrs	39	36	1.21	0.53-2.73
10-<20	35	46	0.57	0.29-1.13
20-<30	48	49	1.20	0.65-2.21
≥30	41	41	1.16	0.64-2.11
P for trend		*0.61*		
Missing	357	367		

*Each variable in the table was included in a separate model with age at first live birth/number of pregnancies, menopausal status, and benign breast disease histology as covariates in matched analyses.