

# Family history of breast cancer as a determinant of the risk of developing endometrial cancer: a nationwide cohort study

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Despite recent declines in its incidence, endometrial cancer remains the most common cancer of the female reproductive tract in the United States<sup>1</sup> and in the western world.<sup>2</sup> Well established risk factors include exposure to unopposed oestrogen, older age, nulliparity, obesity, and smoking.<sup>3</sup> There are inconsistent reports on the association between endometrial cancer risk and family history of any cancer. Most of the familial studies of endometrial cancer among younger (20–54 years old) women have indicated an association with a family history of endometrial cancer<sup>4–6</sup>; however, this association among older (55–69 years old) women has been inconsistent.<sup>7–10</sup> Olson *et al*<sup>7</sup> showed that neither family history of cancer (for example, endometrium, colon, or breast) overall nor at any specific site was a risk factor in postmenopausal women, whereas Nelson *et al*<sup>8</sup> reported a significantly higher risk of endometrial cancer among women with a family history of any of the selected sites (that is, uterine, breast, colon, or ovarian cancer).

Endometrial cancer and breast cancer share some of the same reproductive and hormonal risk factors, such as nulliparity and exposure to unopposed oestrogen.<sup>11–18</sup> Reports on double primary cancers in the same person provide further evidence for an aetiological association between breast cancer and endometrial cancer.<sup>19–21</sup>

In addition, it seems likely that there are shared genetic components involved in the aetiology of at least some endometrial and breast cancer cases. Cowden syndrome and hereditary non-polyposis colorectal cancer (HNPCC) are genetic disorders which are said to include a predisposition to both endometrial and breast cancer in genetically at risk family members.<sup>22–25</sup>

However, the familial association between breast and endometrial cancer is uncertain. Lynch *et al*<sup>26</sup> have identified families in which there are high frequencies of both breast and endometrial cancer. Anderson *et al*<sup>27</sup> showed a significant excess risk of breast cancer among study participants with a family history of endometrial cancer. On the other hand, Parazzini *et al*<sup>28</sup> found no association between family history of endometrial cancer in first degree relatives and the risk of breast cancer. In addition, Kelsey *et al*<sup>10</sup> found no indication of an increased frequency of breast cancer in the first degree female relatives of women with endometrial cancer.

To investigate further the hypothesis of an association between family history of breast cancer and the risk of developing endometrial cancer, we analysed data from a large prospective cohort of women with detailed information regarding the number and relationship of relatives affected with breast cancer, their age at breast cancer diagnosis, and breast cancer laterality.

## MATERIALS AND METHODS

### The NCI BCDDP follow up study

The Breast Cancer Detection Demonstration Project (BCDDP), sponsored by the American Cancer Society and the National

## Key points

- Although endometrial and breast cancers share some of the same reproductive, hormonal, and genetic risk factors, it is not well established if a family history of breast cancer is associated with endometrial cancer risk. We examined this association among 37 583 women, who were former participants in a national breast cancer screening programme and were then selected for additional follow up (average 13.8 years) after the screening study had been completed. There were 648 women with endometrial cancer identified during the follow up period (1979–1998).
- This prospective cohort study collected information on the breast cancer history of mothers, sisters, daughters, aunts, and grandmothers of the participants. Data on the number of affected relatives, their age, and breast cancer laterality were also collected during the last three phases of the study. Poisson regression analyses were used to derive rate ratios and 95% confidence intervals.
- Controlling for attained age, menopausal status, race, body mass index, breast cancer diagnosis, and family size, the presence of breast cancer in a first degree (RR=0.96, 95% CI 0.78 to 1.2) or a second degree (RR=1.0, 95% CI 0.81 to 1.2) relative did not influence the risk of developing endometrial cancer. In addition, the risk of endometrial cancer did not vary by age of the relative at breast cancer diagnosis or by the number of affected relatives with breast cancer. However, there was a non-significant increase in the risk of endometrial cancer among women with a first degree relative with bilateral breast cancer (RR=1.4, 95% CI 0.84 to .4) but not among women with a first degree relative with unilateral breast cancer (RR=0.83, 95% CI 0.62 to 1.1). Women with a personal history of previous breast cancer were more likely to develop endometrial cancer during the course of follow up (RR=1.3; 95%CI 1.1 to 1.7), but even in this subgroup family history of breast cancer did not confer additional risk of endometrial cancer.
- These results do not provide support for the hypothesis that a family history of breast cancer is an important determinant of the risk of developing endometrial cancer.

Cancer Institute (NCI), was a breast cancer screening programme conducted between 1973 and 1980. The BCDDP provided up to five annual breast examinations to 283 222 women at 29 screening centres in 27 cities throughout the United States.<sup>29</sup> Over 99% of the participants were between the ages of 35 and 74 when they entered the screening

programme, with a median age of 50 years. The NCI began a follow up study of a subset ( $n=64\ 182$ ) of the BCDDP participants in 1979, which included (1) all women who were diagnosed with breast cancer during the BCDDP ( $n=4275$ ); (2) all women who had breast surgery performed during the screening programme with no evidence of malignant breast disease ( $n=25\ 114$ ); (3) all women who had received a recommendation by the project for a surgical consultation, but who did not have either a biopsy or aspiration performed ( $n=9628$ ); and (4) a sample of women who were not recommended for surgical consultation and did not undergo a biopsy ( $n=25\ 165$ ).

The follow up study was conducted in four phases. Phase I, carried out between 1979 and 1986, involved the administration of a baseline and up to six annual telephone interviews by the personnel at the BCDDP screening centres. Between 1987 and 1998, phase II (1987-1989), III (1993-1995), and IV (1995-1998) data collection was conducted through self-administered mailed questionnaires to all participants not known to be dead. In addition, attempts were made to conduct follow up interviews by telephone for all non-respondents to the mailed questionnaires.

Data on race and education were available from screening visits between 1973 and 1979. Information collected from phase I of the study included age at menarche, number of live births, age at first live birth, use of oral contraceptives (if yes, years taken and age at first use), age at menopause, use of female hormones other than birth control pills (if yes, reasons for use, number of years taken, and age at first use), family history of breast cancer in specific blood relatives (mother, sister, daughter, grandmother, aunt) including the number in each category affected with breast cancer, menopausal status (including date and reason for periods stopping; menopause was defined as no period having occurred within the three months before interview), removal of the uterus and/or ovaries (if yes, year of surgery), and breast biopsy resulting in either benign or malignant diagnosis. Information on all these factors, except for the first four variables, was also collected in phases II-IV.

The following information, not collected during phase I, was collected during phases II, III, and IV: a more detailed family history of breast cancer, including an enumeration of all first and second degree relatives (including half sisters and both maternal and paternal lineage grandmothers and aunts), the relative's age at breast cancer diagnosis and information regarding whether the breast cancer was unilateral or bilateral; use of oestrogen and progestin pills in the same month (if yes, age at first use, total duration of use, and number of days in the month progestin pills were taken); medical history, including diabetes, osteoporosis, bone fractures, new cancers (including date of diagnosis); date of first diagnosis of endometrial cancer; tobacco and alcohol use; physical parameters, including both "usual" and current adult height, weight, and body shape. Finally, data regarding recent blood pressure and age at last childbirth were available from phase III.

During each phase, pathology reports were sought to confirm objectively self-reported cancers. In addition, the cohort was linked periodically to the National Death Index (NDI), and to selected population based cancer registries, with the last known address of each participant used as her state of residence. Death certificates were retrieved and coded for cause of death during the first three phases of the study. During phase IV, cause of death was obtained from coding done by the NDI.

### Analytical cohort Study population

Of the 64 182 women selected for participation in the follow up study, 61 431 (95.7%) completed a baseline interview.

Women with a diagnosis of endometrial cancer or who had had a hysterectomy before the baseline interview were excluded from the analytical cohort. This yielded 37 583 women who were eligible for inclusion in the current analysis. Of the 37 583 eligible women at baseline, 31 568 (84%), 27 526 (73%), and 26 225 (70%) completed the phase II, III, and IV interviews. Missing phase II questionnaires were the result of death (4.9%), illness (0.8%), refusal (3.8%), and inability to contact before the end of the questionnaire period (6.5%). The corresponding proportions for missing phase III and IV questionnaires were 11.1%, 0.9%, 4.5%, and 10.5%, and 14.9%, 1.1%, 1.5%, and 12.6%. In addition, 71% ( $n=26\ 780$ ) of those who answered the baseline interview ( $n=37\ 583$ ) and 74% ( $n=23\ 324$ ) of those who answered the phase II interview ( $n=31\ 569$ ) in the endometrial cancer follow up study were linked to state cancer registries. Most study participants were white (87%), with small percentages of black (4%), Asian-American (5%), and Hispanic (2%) participants.

### Analytical data set

#### Case definition

Endometrial cancer cases (ICD\_O codes 179.0, 179.9, 182.0, and ICD\_9 codes 179X, 179.9, 182.0, 183.8, 183.9, 233.2) were identified through self-report on the follow up questionnaires (phases II, III, and IV), pathology reports, death certificates, and state cancer registries.

Of the 648 persons with endometrial cancer identified, 468 (72%) were identified by self-report on the follow up questionnaires; 90% of these were confirmed by pathology reports ( $n=404$ ), state cancer registries ( $n=16$ ), or death certificates ( $n=1$ ). Independent confirmation was unavailable for 47 self-reports. Thirty-nine cases were ascertained by pathology reports only, 46 cases were identified by death certificates obtained from the NDI (of these, state cancer registry information provided additional confirmation for 16 cases), and 95 cases were found only by matching study participants to various state cancer registries data files.

#### Statistical analyses

The follow up study began upon completion of the baseline interview. Person years accrued until the earliest of the following dates: (1) hysterectomy, (2) endometrial cancer diagnosis, (3) study end date, which was either the date of completion of the phase IV questionnaire or for non-respondents to phase IV, the estimated date that they would have completed the phase IV questionnaire (1995-1998) if still alive (that is, depending on when they completed the phase III questionnaire, 1993-1995), and (4) date of death or date of state cancer registry diagnosis of endometrial cancer if both of these dates were before the study end date. To assign dates of cancer diagnosis for cases identified by death certificates only, we used time since onset of disease from the death certificate, medical information from earlier interviews, date of hysterectomy if done, or date of death if no other information was available.

All of the family history variables were analysed as time dependent variables in the analyses. Women who reported breast cancer in a sister, mother, and/or daughter were classified as having a "first degree family history" and those who reported breast cancer in a grandmother, and/or aunt were classified as having a "second degree family history". Study participants were defined to have a family history at their age at the midpoint between first report of exposure and the previous interview or questionnaire.

Rate ratios (RR) and 95% confidence intervals (CI) were estimated by Poisson regression. The reference category for all the analyses comprised women who did not have relatives with breast cancer in that category. Time dependent variables (attained age, body mass index (BMI: weight divided by height squared,  $\text{kg}/\text{m}^2$ ), menopausal status, breast cancer

**Table 1** Prevalence of first degree family history according to selected factors in BCDDP endometrial cancer follow up study, 1979–1998

Risk factor	No 1st degree family history of breast cancer (%)	1st degree family history of breast cancer (%)	Unsure 1st degree family history of breast cancer (%)	Total person years
Attained age (y)				
<50	85.0	14.0	1.0	47 881
50–54	83.1	15.4	1.6	72 040
55–59	81.6	16.5	1.9	100 680
60–64	80.3	17.7	2.0	101 318
65–69	78.9	19.0	2.1	82 058
70–74	77.7	20.1	2.2	55 842
75+	75.7	21.8	2.5	58 927
Race				
White	79.7	18.3	1.9	451 128
Hispanic	85.2	12.5	2.3	11 692
Black	83.7	14.5	1.7	19 998
Other	84.6	13.8	1.6	35 930
Body mass index (kg/m <sup>2</sup> )				
<22.05	81.1	17.3	1.6	185 058
22.05–25.07	80.3	17.6	2.1	154 982
25.08–27.85	79.8	18.2	2.0	80 203
27.86–32.06	79.6	18.1	2.3	53 369
32.07+	78.8	19.0	2.2	26 508
Unknown	79.6	18.6	1.8	18 625
Personal history of breast cancer				
No	81.3	16.8	1.9	468 590
Yes	71.4	26.3	2.3	50 157
Menopausal status				
Premenopausal	83.5	15.1	1.4	65 740
Menopausal	79.9	18.1	2.0	437 138
Unknown	79.9	17.3	2.8	15 869
1st degree family size				
<4	82.6	15.4	2.0	237 784
4–5	78.1	20.3	1.6	134 371
6–7	74.9	23.5	1.6	50 616
8+	71.3	26.7	2.0	20 526
Unknown	83.5	14.2	2.3	75 451

diagnosis, duration of oral contraceptive use, hormone replacement therapy use (ever), duration of oestrogen only use, hypertension, diabetes, smoking status (never, current, former), and time independent variables (education, race, parity, age at menarche, age at first live birth, age at last birth, and age at natural menopause) were each considered as potential confounders for the family history variables. Although there was no evidence of confounding by variables other than attained age, final models included adjustment for a combination of time dependent (attained age, menopausal status, a personal history of breast cancer, and BMI) and time independent (race and family size) variables that were associated with either endometrial cancer or family history. Further adjustment for other risk factors did not alter the risk estimates.

## RESULTS

The mean duration of follow up was 13.8 years, with a median of 15.8 years, a maximum of 19.8 years, and a minimum of less than one year. During prospective follow up of the cohort, 518 747 person years of observation were accumulated for the 37 583 participants. The average age at the start of follow up was 55 years.

Fifty-six percent of person years were associated with no breast cancer family history of any type, 29% occurred in women with some family history of breast cancer (first degree, second degree, or both), and 15% were associated with an uncertain or unascertained family history. Eighty-one percent of accumulated person years were associated with no first degree family history of breast cancer, 17% occurred in women with a first degree family history, and 2% were associated with an uncertain or unascertained first degree family history; the corresponding figures for a second degree family history were 64%, 17%, and 19%.

Table 1 summarises the distribution of person time by first degree family history of breast cancer, stratified by risk factors for endometrial cancer. Person years associated with a first degree family history did not vary meaningfully by most factors. A greater percentage of person years associated with a first degree family history was evident for older attained age and a personal history of breast cancer. Moreover, slightly greater percentages of person years associated with race, higher BMI, and menopausal status were also associated with a first degree family history.

Rate ratios of endometrial cancer associated with different categories of breast cancer family history are shown in table 2. All the analyses for second degree family history categories also included adjustments for a first degree family history. In general, there were no associations between each category of breast cancer family history and the risk of endometrial cancer.

- The number of family members with breast cancer did not alter the risk of endometrial cancer.
- The same analyses excluding unconfirmed cases or cases diagnosed after the last questionnaire showed no associations.
- Similar associations between family history of breast cancer and the risk of endometrial cancer were found among women with and without a personal history of breast cancer.
- The rate ratio for women with both a first and a second degree relative with breast cancer was neither increased nor significant.

In all these analyses, the women who did not have relatives with breast cancer in the category under analysis formed the reference group for each group, as has been done in previously published studies of this kind; however, choosing women with

**Table 2** Rate ratios (RR) of endometrial cancer associated with family history of breast cancer in BCDDP endometrial cancer follow up study, 1979–1998

Relative	No of person years	No of cases	Adjusted* RR (95% CI)
Any family history			
No history	283 382	352	1.0 (reference)
1 affected	111 368	138	0.9 (0.7 to 1.1)
2 or more affected	45 652	59	0.9 (0.7 to 1.2)
Any affected	157 020	197	0.9 (0.8 to 1.1)
Unknown	78 345	99	0.8 (0.6 to 1.0)
Any 1st degree			
No history	416 839	521	1.0 (reference)
1 affected	78 650	104	1.0 (0.8 to 1.2)
2 or more affected	13 331	15	0.8 (0.5 to 1.3)
Any affected	91 981	119	1.0 (0.8 to 1.2)
Unknown	9927	8	0.6 (0.3 to 1.1)
Mother			
No history	458 967	577	1.0 (reference)
Mother affected	50 579	64	1.0 (0.8 to 1.3)
Unknown	9201	7	0.5 (0.3 to 1.2)
Sister			
No history	467 353	583	1.0 (reference)
1 affected	38 600	50	0.9 (0.7 to 1.2)
2 or more affected	6412	9	0.9 (0.5 to 1.8)
Any affected	45 012	59	0.9 (0.7 to 1.2)
Unknown	6381	6	0.7 (0.3 to 1.6)
Daughter			
No history	509 734	638	1.0 (reference)
1 affected	3307	4	0.7 (0.3 to 2.0)
2 or more affected	452	1	0.8 (0.1 to 7.8)
Any affected	3759	5	0.8 (0.3 to 1.9)
Unknown	5255	5	0.7 (0.3 to 1.6)
Any 2nd degree			
No history	333 569	404	1.0 (reference)
1 affected	68 458	84	1.0 (0.7 to 1.2)
2 or more affected	20 309	30	1.1 (0.8 to 1.7)
Any affected	88 767	114	1.0 (0.8 to 1.2)
Unknown	96 411	130	0.9 (0.8 to 1.2)
Grandmother			
No history	410 817	508	1.0 (reference)
1 affected	21 126	21	0.8 (0.5 to 1.3)
2 affected	1196	2	1.2 (0.3 to 4.9)
Any affected	22 322	23	0.9 (0.6 to 1.3)
Unknown	85 609	117	1.0 (0.8 to 1.2)
Aunt			
No history	376 329	449	1.0 (reference)
1 affected	59 104	72	1.0 (0.7 to 1.3)
2 or more affected	13 754	25	1.5 (1.0 to 2.3)
Any affected	72 858	97	1.1 (0.8 to 1.3)
Unknown	69 560	102	1.1 (0.9 to 1.4)

\*Adjusted for number of relatives, attained age, BMI, personal breast cancer diagnosis, race, and menopausal status. The second degree variables were also adjusted for a first degree family history. Women who did not have relatives with breast cancer in that category formed the reference group for each group.

no first or second degree family history as the comparison groups made no difference to the results (data not shown).

Because both the diagnosis of breast cancer at an earlier than usual age and the development of cancer in both breasts (bilateral breast cancer) are considered harbingers of a genetic predisposition to breast cancer, we analysed the risk of endometrial cancer taking this information into account. As shown in table 3, women reporting bilateral breast cancer in any first degree relative (RR=1.4, 95% CI 0.8 to 2.4) or mothers (RR=1.5, 95% CI 0.7 to 3.1) or sisters (RR=1.4, 95% CI 0.7 to 2.7) all had non-significantly increased rates compared to women without a family history of breast cancer in that category. With regard to age at breast cancer diagnosis among family members, there were no associations with endometrial cancer when women with early and later onset breast cancer were compared to women without a family history of breast cancer.

As has been previously reported, women in this cohort with a previous personal history of breast cancer were at significantly increased risk of developing endometrial cancer during prospective follow up (RR=1.3, 95% CI 1.1 to 1.7). This was a subgroup in which we had a previous hypothesis that the influence of family history of breast cancer on the risk of endometrial cancer might be more readily detected, but that proved not to be the case, either overall (data not shown), or when considering early age at breast cancer diagnosis among first degree family members. However, in this group of women, subjects reporting a bilateral breast cancer in any first degree relative (n=4) had a non-significantly raised rate (RR=1.8, 95% CI 0.6 to 5.2) of endometrial cancer as compared with women without a first degree family history of breast cancer.

## DISCUSSION

In this nationwide prospective study of 37 583 women, reported family history of breast cancer was not associated with an increased risk of endometrial cancer. This null result was found despite our having detailed information on breast cancer family history, including age at diagnosis and bilaterality in the affected relatives. Furthermore, the cohort was large, as was the number of women who developed endometrial cancer during follow up, which averaged 13.8 years per participant.

Our results are consistent with the reports of two other large cohort studies,<sup>7,9</sup> but inconsistent with a family study.<sup>26</sup> The study by Lynch *et al*<sup>26</sup> included highly selected families with two or more members affected with breast cancer and who therefore had a relatively strong predisposition for cancer. On the other hand, two reports have been published from the Iowa Women's Health Study (IWHS), a cohort whose participants are similar to those in the BCDDP, but who were recruited via different methods (for example, use of Iowa Department of Transportation driver's licence list). The IWHS collected family history information at one point in time, that is, baseline, and there was no information about family size or age at onset of cancer in family members. However, the nested case-control analysis<sup>7</sup> showed a slight, non-significant increase in endometrial cancer risk among women with a first degree family history of breast cancer (OR=1.2, 95% CI 0.6 to 2.5).

A major strength of our study was the evaluation of endometrial cancer risk in relation to a family history of bilateral breast cancer, the number of affected relatives, and their age at breast cancer diagnosis. These features of breast cancer are of great potential interest in assessing whether a family history might increase endometrial cancer risk through a genetic mechanism.<sup>30–36</sup> In that regard, it was of interest to note that endometrial cancer risk among women reporting a bilateral breast cancer in a first degree relative (mother/sister and/or daughter) was increased by 40%, an increase that was not statistically significant. However, there were no associations between endometrial cancer risk and age at breast cancer diagnosis among family members and the number of affected relatives. Our data do not permit us to distinguish between this “increase” being false, a consequence of intensive data analysis with multiple comparisons having been made, and its being a true finding compromised by low statistical power in this subgroup.

The occurrence of multiple persons with cancer in the members of a family could reflect a shared genetic predisposition, a common environmental exposure, a more complex interaction between genes and environment, or chance. Because we did not collect information on environmental risk factors from relatives of the participants and because we had a relatively small number of participants in subgroups of particular interest, we could not distinguish among these possibilities in evaluating the modest association between

**Table 3** Rate ratios for endometrial cancer, 95% confidence intervals, number of cases, and total person years by age of diagnosis and disease laterality of relative with breast cancer

Reference group	1st degree relative					
	Age at diagnosis*			Laterality status		
	<50	≥50	Unknown	Unilateral	Bilateral	Unknown
1.0	0.8 (0.5 to 1.2)	1.0 (0.8 to 1.3)	0.9 (0.6 to 1.3)	0.8 (0.6 to 1.1)	1.4 (0.8 to 2.4)	1.0 (0.8 to 1.3)
CA/PY	24/23 292	69/46 193	25/22 280	49/42 948	15/8349	55/41 562
<i>Women with a personal history of breast cancer</i>						
1.0	0.5 (0.2 to 1.7)	0.8 (0.4 to 1.5)	1.2 (0.5 to 2.8)	0.6 (0.2 to 1.3)	1.8 (0.6 to 5.2)	0.8 (0.4 to 1.7)
CA/PY	3/3187	10/6862	6/3053	6/5924	4/1351	9/5932
<i>Mother with breast cancer</i>						
<i>Mother's age at diagnosis*</i>						
Reference group	<50	≥50	Unknown	<i>Mother's laterality status</i>		
1.0	0.9 (0.4 to 1.7)	1.0 (0.8 to 1.4)	0.8 (0.5 to 1.4)	Unilateral	Bilateral	Unknown
CA/PY	8/7622	42/29 301	14/13 814	0.9 (0.6 to 1.3)	1.5 (0.7 to 3.1)	1.0 (0.7 to 1.5)
<i>Sister with breast cancer</i>						
<i>Sister's age at diagnosis*</i>						
Reference group	<50	≥50	Unknown	<i>Sister's laterality status</i>		
1.0	0.8 (0.5 to 1.4)	1.0 (0.7 to 1.4)	1.1 (0.6 to 1.8)	Unilateral	Bilateral	Unknown
CA/PY	14/13 707	30/20 349	15/11 015	0.8 (0.5 to 1.2)	1.4 (0.7 to 2.7)	0.9 (0.6 to 1.4)
<i>Daughter with breast cancer</i>						
<i>Daughter's age at diagnosis*</i>						
Reference group	<50	≥50	Unknown	<i>Daughter's laterality status</i>		
1.0	0.7 (0.2 to 2.2)	–	1.3 (0.3 to 5.4)	Unilateral	Bilateral	Unknown
CA/PY	3/2474	0	2/890	0.5 (0.1 to 2.1)	1.1 (0.1 to 9.0)	1.2 (0.3 to 5.1)

\*Age at diagnosis is the age of youngest relative in that category with breast cancer.

All analyses are adjusted for attained age, race, menopausal status, BMI, number of relatives in each category (except mother's category), and personal breast cancer diagnosis (except the category of women with a personal history of breast cancer).

Women who did not have relatives with breast cancer in that category formed the reference group for each group.

endometrial cancer risk and history of bilateral breast cancer in a first degree relative. It is notable, however, that this increased risk was consistently observed across categories of women with any first degree relative, mother, or sister with bilateral breast cancer.

There are two genetic syndromes, Cowden's disease and HNPCC, which some (but not all) investigators have suggested may include a predisposition to both endometrial and breast cancers among members of the same family.<sup>24–27 39–41</sup> However, despite the suggestion that breast cancer may be part of the HNPCC syndrome in at least a subset of families,<sup>24 25 37–39</sup> other reports do not support the hypothesis that HNPCC family members are at an increased risk of breast cancer.<sup>9 40 41</sup> The most recent study of this question provided evidence that at least some of the breast cancer that arises in women with HNPCC appears to be sporadic in nature, rather than caused by mutations in one of the mismatch repair genes.<sup>42</sup> Because we collected information related to family history of cancers other than breast cancer only during phase IV of this study, we were unable to assess whether any of the endometrial cancer cases in our study occurred in families likely to be affected by Cowden syndrome, HNPCC, or by other familial cancer syndromes.

Another possible explanation for our null results was the absence of younger women from the cohort. Only 9% of the accumulated woman years of observation in this cohort were accrued by women aged less than 50 years. As noted previously, a younger than usual age at cancer diagnosis is one of the cardinal features of most hereditary cancer syndromes. The small contribution of such women to the events observed in this study may have compromised our ability to detect a breast cancer pattern suggestive of a genetic disorder. However, Schildkraut *et al*<sup>6</sup> found no increased relative risk for breast cancer among mothers and sisters of endometrial cancer cases younger than 55 years of age (RR=1.2, 95% CI 0.7 to 2.2).

The endometrial cancer risk factors identified in this study are consistent with those identified in previous studies.<sup>10 13 14 17 43–46</sup> The finding that women with a personal

history of breast cancer had a significant, 30% excess risk for endometrial cancer is interesting and consistent with earlier studies.<sup>21 47 48</sup> This could suggest that shared environmental, hormonal and/or genetic risk factors may be involved in the pathogenesis of these cancers. Because we adjusted for attained age, duration of menopausal oestrogen use, menopausal status, BMI, and parity in assessing the risk of endometrial cancer associated with a personal history of breast cancer, it is unlikely that these shared risk factors account for the association.

It is also possible that the increased risk of double primaries of the breast and endometrium could be the result of medications that increase the risk of endometrial cancer, such as hormone replacement therapy with unopposed oestrogen<sup>49</sup> and adjuvant therapy with tamoxifen.<sup>50–53</sup> An increased incidence of endometrial cancer in women with breast cancer has been reported.<sup>54 55</sup> Since the early 1970s, tamoxifen has been widely used for the treatment of advanced breast cancer and in the 1980s adjuvant tamoxifen therapy became the standard of care for women with stage II breast cancer. Cancer treatment trials using tamoxifen have shown an excess risk of up to two-fold for endometrial cancer among breast cancer patients treated with adjuvant tamoxifen.<sup>52 53 56 57</sup> Because we did not collect information on tamoxifen use or other hormonal therapies for breast cancer treatment, we were unable to evaluate whether the excess risk of endometrial cancer among participants with breast cancer is the result of tamoxifen use or shared genetic or environmental factors that we did not adjust for. However, the bulk of the person years of observation in the current study were accrued in an era when the adjuvant use of tamoxifen in the treatment of the earliest stages of breast cancer was not yet widespread.

Several methodological issues need to be considered in interpreting our results. Although most data were obtained prospectively, some of the information on family history of breast cancer was reported by cases on questionnaires that were completed after their diagnosis of endometrial cancer. Thus, it is possible that cases differentially recalled their family

history of breast cancer compared with non-cases. However, a methodological study found no difference in the reporting of breast cancer in family members between patients with and without breast cancer.<sup>58</sup> It is likely that these results would also pertain to reporting of family history of breast cancer by patients with and without endometrial cancer. In addition, we did not have complete information on a family history of breast cancer and other risk factors for some participants who did not complete all questionnaires. However, there was no difference in loss to follow up according to the family history of breast cancer data. Finally, no attempt was made to obtain objective verification of the breast cancers that were reported by study participants to have occurred among their relatives. However, previous studies have shown that the accuracy of reported occurrences of breast cancer in family studies is very high, in the range of 83-95%<sup>58-62</sup>; reporting of a family history of breast cancer in a second degree relative is less accurate.<sup>62-65</sup> We are therefore reasonably confident regarding the reliability of the reported family history information, particularly among first degree relatives.

In summary, our cohort study showed no overall association between a family history of breast cancer and endometrial cancer risk. Although we found a non-significant increased risk for women with a first degree (mother and/or sisters) family member with bilateral breast cancer, we did not see any associations with other features of various hereditary cancer syndromes, such as early age of onset and high incidence of multiple persons with breast cancer among family members. Thus, a family history of breast cancer does not seem to be an important endometrial cancer risk factor, although a personal history of breast cancer does increase the risk of developing endometrial cancer by approximately 30%.

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