We linked four nationwide Swedish population-based registries to identify first-degree family history of breast and ovarian cancer among breast cancer cases diagnosed between 1991 and 1998 and followed them until death, emigration or end of follow-up in December 1998. The median follow-up was 36 months. Using Cox proportional hazards models, the hazard ratio of death (HR) due to breast cancer was estimated. Women with a family history of breast or ovarian cancer (n = 2175, 12.7%) had a nonsignificantly better prognosis than women without any family history, HR 0.86 (95% CI 0.71 – 1.05); this appeared unrelated to age at diagnosis either in the index case or in relative(s) with breast and/or ovarian cancer. Our study shows that prognostic outlook is not worse among breast cancer patients with family history.

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Keywords: breast neoplasms; prognosis; family; registries

PATIENTS AND METHODS

Data sources

All Swedish residents are assigned an individually unique 10-digit national registration number. This number enables crosslinkage of various nationwide health data registries. Our study links four such registries: The Swedish Cancer Register, The Cause of Death Register, The Multi-Generation Register and The Total Population Register. The Swedish Cancer Register contains information about all cancers diagnosed in Sweden since 1958. It maintains a high degree of completeness due to mandatory reporting by both clinicians and pathologists/cytologists (Mattsson and Wallgren, 1984; National Board of Health and Welfare, 1996). The register does not include information about disease stage or treatment. Established in 1952, the Cause of Death Register provides the date of death, as well as the underlying and contributory causes of death of all deceased Swedish residents. The causes of death are classified according to the International Statistical Classification of Diseases and Related Health Problems (ICD), version 6 – 10. The completeness of the classification of the cause of death in the registry is estimated to exceed 99% (National Board of Health and Welfare, 2001).

The Multi-Generation Register includes all Swedish residents born after 1931, who were alive in 1960, and all those born thereafter. It contains links between children and parents through their national registration numbers. Adoptions and nonbiological relations are flagged. The register is updated yearly. We used the 31 December 2000 version for the present study (Statistics Sweden, 2001:5). The Total Population Register includes information about births and deaths in the entire Swedish population since 1968. The register is updated yearly and kept by the Swedish tax authorities.

The Karolinska Institutet Ethics Committee has reviewed and approved this study.

Study cohort and family history

In the Swedish Cancer Register, we identified 20 468 women born after 1931, alive in 1960, and diagnosed with primary breast cancer between 1991 and 1998. Our rationale for the choice of this recent study period was that for individuals who died between 1991 and 1998, notification of mothers in the Multi-Generation Register has reached 90% completeness (Statistics Sweden, 2001:5). To obtain follow-up information, we linked the study cohort to the Cause of Death Register and the Total Population Register. The breast cancer cases were followed from the date of breast cancer diagnosis until the end of the study, 31 December 1998, or the date of death.
or emigration, whichever occurred first. Breast cancer deaths only included those where breast cancer was coded as the underlying cause of death. Linkage of our cohort to the Multi-Generation Register provided us with information about any first-degree relatives (parents, siblings or children) of index cases. We excluded 2729 index patients who were registered as immigrants, and 158 who had been diagnosed with other cancers prior to their breast cancer. We could not identify any relatives for 486 index patients and therefore excluded them. Our cohort thus consisted of 17,095 index breast cancer cases. We identified incident cancers among the relatives of the index cases though rematching with the Swedish Cancer Register. Our inclusion criteria resulted in a maximum attained age at diagnosis that was 59 years in 1991 and 66 years in 1998.

**Statistical methods**

We used Cox proportional hazards models to estimate the hazard ratio of death due to breast cancer (HR) and 95% confidence intervals (95% CI) associated with family history. We only considered family history that was apparent at the time of index case diagnosis. Analyses were stratified by age at diagnosis (in 5-year age groups), calendar year (in 5-year intervals) and number of female first-degree relatives in order to control the interdependent effects of treatment time trends, age and varying potential of having a manifested family history of breast and/or ovarian cancer. We estimated survival during the entire follow-up and separately during the first 5 and the following years after diagnosis in order to check the assumption of proportional hazards during follow-up. By introducing interaction terms in the Cox model, we tested if there were differences in the effects of family history on prognosis according to age at diagnosis or follow-up time. All analyses were performed using SAS procedure PROC PHREG (Version 8.2, SAS Institute, NC, USA).

**RESULTS**

Out of the 17,095 breast cancer cases we studied, 2175 (about 13%) had at least one first-degree relative with breast and/or ovarian cancer (Table 1). In all, 1238 women diagnosed with breast cancer between 1991 and 1998 died of breast cancer, 112 of who had a family history of breast and/or ovarian cancer (Table 2). The mean and median follow-up was 39.6 and 36 months, respectively. Familial cases had a nonsignificantly better prognosis than nonfamilial cases (HR = 0.87; 95% CI 0.71–1.05) without any appreciable difference related to duration of follow-up (Table 2, Figure 1). Among women who had more than one first-degree relative with breast or ovarian cancer, the association seemed particularly pronounced (HR = 0.21; 95% CI 0.03–1.53), although this estimate was based on small numbers. The age at diagnosis of the index case or the first-degree relative did not influence the association between family history and breast cancer prognosis (Table 2).

**DISCUSSION**

We show that there is no significant difference in the prognosis of breast cancer among women with a first-degree relative of breast or ovarian cancer to cases without family history. The relation was not convincingly modified by duration of follow-up or age at diagnosis in the index case or the relative.

This is one of the largest population-based studies of the relation between family history and breast cancer prognosis published to date. Through linkage of the Multi-Generation and Cancer registries by the national registration numbers instead of relying on reports from the study subjects, we have minimized misclassification of the factor of main interest, family history.

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**Table 1** Various aspects of family history of breast and ovarian cancer among women born after 1931, diagnosed with first breast cancer cases between 1991 and 1998 (n = 17,095)

| Family history of breast and/or ovarian cancer | Number (%) |
|-----------------------------------------------|------------|
| No                                            | 14,920 (87.2%) |
| Yes                                           | 2,175 (12.7%) |

**Table 2** Hazard ratios (HRs) for breast cancer death comparing women with and without first-degree family history of breast or ovarian cancer.

| Family history | Deaths | Person-years | HR | 95% CI |
|----------------|--------|--------------|----|--------|
| Overall        | No 1126 | 50,549       | 0.86 | 0.71–1.05 |
|                | Yes 112 | 6,039        | 1   |        |

**FDR age at diagnosis**

| Age at diagnosis | Number | HR | 95% CI |
|------------------|--------|----|--------|
| < 50 years       | Yes 43 | 2299 | 0.82 | 0.60–1.12 |
|                  | Yes 69 | 3740 | 0.89 | 0.70–1.14 |

**Number of FDR with breast or ovarian cancer**

| Number of FDR | Number | HR | 95% CI |
|---------------|--------|----|--------|
| One           | Yes 111 | 5821 | 0.89 | 0.73–1.08 |
| Two or more   | Yes 1 | 218 | 0.21 | 0.03–1.49 |

**Stratified by time period after diagnosis**

| Time period | Number | Person-years | HR | 95% CI |
|-------------|--------|--------------|----|--------|
| First 5 years | No 1061 | 45,115       | 0.86 | 0.70–1.05 |
|              | Yes 106 | 5418        | 1   |        |

**Stratified by index case age at diagnosis**

| Age at diagnosis | Number | Person-years | HR | 95% CI |
|------------------|--------|--------------|----|--------|
| < 50 years       | No 575 | 23,116       | 0.87 | 0.67–1.13 |
|                  | Yes 64 | 3054        | 1   |        |

Ascertainment of family history was based on the number of first-degree relatives with breast and/or ovarian cancer in the Swedish Cancer Registry. However, due to chance and the high incidence of breast cancer, there may be clustering of sporadic breast cancer in families, giving a spurious impression of familial disease. Indeed, in our data, frequency of family history does not vary substantially over age groups (data not shown). Such clustering would have

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In conclusion, our study shows that prognosis is not worse among familial breast cancer cases overall.

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