Family history is an important risk factor for breast cancer, a disease that accounts for approximately 25% of all cancers diagnosed in women.1 Approximately 15% of all breast cancers are diagnosed among women with a family history of the disease.2,4 Women with a family history of breast cancer are at a 2 to 4 times increased risk of breast cancer depending on the number of affected relatives and the age at which the relatives were diagnosed.5,6 Family history is a component of many available breast cancer risk assessment tools, the results of which are used by women and their clinicians when making decisions regarding using preventive services such as earlier mammography screening.7,9

Accurate and precise exposure assessment is a key factor for providing accurate risk estimates associated with an outcome. To the best of our knowledge, the majority of studies assessing the familial risk of cancers, including breast cancer, take family history as a marker of familial predisposition, and as constant during the lifetime of an individual. Common approaches that are used to assign family history status include having at least 1 affected first-degree relative (FDR), the number and type of affected FDRs, or a detailed combination of FDRs and second-degree relatives (SDRs).3,10-13 In register-based studies, family history often has been assessed and assigned (as a static variable) at a single point in time, typically at the end of follow-up, an approach that does not take into account the timing of events.

METHODS: The authors assessed the effect of incorporating the timing of cancer diagnosis events into the assessment of familial risks of breast cancer in first-degree and second-degree relatives in a nationwide cohort study of 5,099,172 women (follow-up was between 1958-2015). Family history was assessed using 3 approaches: 1) as a static variable (ever having a relative with breast cancer); 2) as accumulative history; and 3) as a dynamic variable (time-dependent variable).

RESULTS: For women aged <50 years, familial risk was mostly higher when family history was assessed as a dynamic variable compared with using a static or accumulative family history. For example, the cumulative risk of receiving a breast cancer diagnosis until age 50 years for women with a history of breast cancer in 1 first-degree relative was 2.6% (95% CI, 2.5%-2.7%) using the static method, 2.4% (95% CI, 2.3%-2.4%) using the accumulative method, and 3.1% (95% CI, 3.0%-3.2%) using the dynamic method. Relative risk in women aged <50 years with a breast cancer diagnosis in a sister was 1.40-fold (95% CI, 1.31-fold to 1.48-fold) using the static method, 1.66-fold (95% CI, 1.57-fold to 1.76-fold) using the accumulative method, and 2.28-fold (95% CI, 2.07-fold to 2.51-fold) using the dynamic method.

CONCLUSIONS: The results of the current study demonstrated that assessing family history as static, accumulative, or dynamic results in different familial risk estimates. The answer as to which method to use for family history assessment depends on the implications of the study, with the dynamic method appearing to be better suited for risk stratification studies, the accumulative method being the most convenient in practice and the least favored for risk prediction, and the static method being suitable for etiological impact and risk attribution studies. Cancer 2020;126:2837-2848. © 2020 The Authors. Cancer published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
approach, the time before the breast cancer diagnosis in the first affected relative of the woman still is considered as a period with a family history of breast cancer. Moreover, in studies that assess family history using the static approach, even when the family member is diagnosed with cancer after the cancer diagnosis is made in the index woman, the cancer in the index individual is considered familial. Assessing family history as a static variable also occurs in some prospective studies without repeat questionnaires to update exposure status, in which family history is merely assigned once at the start of follow-up. In this case, participants whose family history status changes during follow-up may be misclassified, which can lead to an underestimation of familial risks.

An alternative approach is to study family history as a dynamic (time-dependent or time-varying) variable, in which the person-years are appropriated to the corresponding family history status separately. Another possible approach is to assess family history as accumulated family history whereby a woman’s cumulative number of relatives with breast cancer is taken at a single point in time. Accumulated family history does not take into account the time at which cancer occurred in relatives and does not include “future family history” that occurs in the static method. To our knowledge, no study to date has compared the absolute familial risk derived from these 3 different methods of assessing family history in FDRs and SDRs of patients with breast cancer. Therefore, it is important to examine how differences in the definition of family history of breast cancer influence derived absolute risk estimates by age at diagnosis in women, which are more suitable than relative risk estimates for clinical counseling regarding screening and risk prediction tools. The objective of the current study was to evaluate the magnitude and direction of deviation between age-specific standardized incidence ratios (SIRs), lifetime cumulative risk, and 10-year cumulative risks calculated based on the 3 abovementioned approaches for assessing family history in FDRs and SDRs of patients with breast cancer.

MATERIALS AND METHODS

Study Design and Linkage

We conducted a nationwide, open, population-based cohort study comprising all women who resided in Sweden and were born after 1931. Using the unique personal identity number assigned to each individual registered in Sweden, the Swedish Cancer Register (since 1958), the Swedish Multi-generation Register, and the Register of Causes of Death were linked. The Multi-generation Register is a record of all individuals residing in Sweden and born after 1931 with their registered biological parents, thereby providing a complete and unbiased record of genealogy. The Swedish Cancer Registry contains all incident, clinically confirmed cancers classified according to the International Classification of Diseases (ICD, Revision 7 and later revisions). The structure of the familial cancer data sets has been described previously elsewhere. Women were followed from their year of birth, 1958 (starting year of the Swedish Cancer Registry), or year of immigration, whichever occurred last. Follow-up ended at the year of death, year of emigration, year of invasive breast cancer diagnosis, or 2015 (end of the study), whichever came first.

Family History Assessment

The ICD, Revision 7 code 170 was used to identify breast cancer diagnoses. Only primary invasive breast cancers were included. We included only women who had at least 1 registered FDR. We identified FDRs and SDRs of all index women, including male relatives, and the year of diagnosis for relatives who were diagnosed with breast cancer during the follow-up period (1958-2015).

Family history was assessed using 3 approaches: 1) assessing ever having a family history of breast cancer as a static variable (the status at the end of study follow-up); 2) assessing ever having a family history of breast cancer as an accumulative family history (the status at the end of follow-up of the index woman [eg, by time of breast cancer diagnosis, emigration, or death in the index woman]); and 3) assessing family history as a dynamic variable (time-dependent variable) that was changing during follow-up of the index woman whenever a new relative was diagnosed with breast cancer (Fig. 1).

In the static approach, the person-years for each constellation of family history were assigned according to their latest available information (eg, a person with 2 affected FDRs during the study period was considered as having a family history of breast cancer in 2 FDRs even before the first or second relative was diagnosed or even when 1 or 2 of them were diagnosed after the death or the date of diagnosis of the index woman), whereas in the dynamic approach, the person-years were assigned exactly according to the sequence of cancer events in the family. In the dynamic approach, a woman would be considered as being without a family history until her first relative developed cancer, as having 1 affected FDR until the second relative developed cancer, and as having 2 affected FDRs from the year of diagnosis of the second relative. Diagnoses in relatives that occurred after the end of follow-up of the index woman (year of death, year of
emigration, or cancer diagnosis in the index woman) were not taken into account. The accumulative family history assessment imitates the clinical setting, whereby family history (number of affected relatives, type of relationships, and ages at the time of diagnosis) until the date of clinical assessment is taken, which does not include “future family history” (Fig. 1). In this case, we counted each woman’s number of FDRs and SDRs who were diagnosed with breast cancer until a cancer diagnosis was made in the index woman (or end of follow-up in women who did not develop breast cancer). The accumulative approach bears both similarities to and differences from the static and dynamic methods. Its difference compared with the static method is that it does not consider cancers occurring in relatives after a diagnosis is made in the index individual (or after his/her emigration or death). Its difference compared with the dynamic method is that it considers the time before diagnosis of the first affected relative as having a family history, which would be considered as without a family history under the dynamic method.

**Statistical Analysis**

The standardized incidence ratio (SIR), lifetime cumulative risk (ages birth to 79 years), and 10-year cumulative risk were used to compare cancer risks based on the 3 different definitions of family history (static, accumulative, and dynamic). The SIRs were calculated as the ratio of the observed to the expected number of cases. The expected rates were calculated based on strata-specific standard incidence rates in the reference group (eg, no family history) stratified by 5-year age groups (18 groups), sex, calendar period (1958-1964, 1965-1969, and onward to 2010-2015), region (3 groups: big city, small city in the North, and small city in the South), and socioeconomic status (6 groups: farmer, manual worker, low-income to middle-income office worker, high-income office worker/professional, company owner [except farmer], and other/unspecified). The expected number of cases was calculated by multiplying strata-specific incidence rates in the reference population by the corresponding numbers of available person-years from individuals with the exposure...
of interest (eg, 2 affected relatives). The analyses also were stratified by age at diagnosis of breast cancer in women (aged <50 years [ie, mostly premenopausal] or aged ≥50 years [ie, mostly postmenopausal]). The 95% CIs were calculated assuming a Poisson distribution. However, in family history constellations with small sample sizes, the basis for the inference regarding observed differences mainly was on the magnitude, direction, and consistency of differences across family history constellations. The reference group for the calculation of SIRs under the static method included women who never had a family history of breast cancer in our data sets, whereas under the dynamic method, in addition, women with a family history were contributing person-years to the reference group until their first relative received a breast cancer diagnosis.

The 10-year cumulative risks for the different family history groups were calculated as follows. The age-specific incidence rate at a certain age X was calculated as the number of cases at age X divided by person-years of follow-up at that age. The 10-year cumulative incidence rate at age X was calculated as the sum of 10 consecutive 1-year age-specific incidence rates from age X until age X+9. The 10-year cumulative rate then was converted into a 10-year cumulative risk using the following formula:

\[ \text{10-year cumulative risk} = 100 \times \left[ 1 - e^{-\text{(10-year cumulative rate)}} \right] \]

Similarly, the lifetime cumulative rate was calculated as a sum of age-specific incidence rates from birth to age 79 years. The lifetime risk was derived from the lifetime cumulative risk using the following formula:

\[ \text{Lifetime cumulative risk} = 100 \times \left[ 1 - e^{-\text{(lifetime cumulative rate)}} \right] \]

Cumulative risks were expressed as percentages. All analyses were conducted using SAS software (version 9.4; SAS Institute Inc, Cary, North Carolina). The study was approved by the Lund Regional Ethics Committee (2012/795). Patient consent was not obtained because the presented secondary data were pseudonymized and there was no risk of identification.

**RESULTS**

**Cohort Description**

In total, 5,099,172 women were eligible (those with genealogical information, residing in Sweden, and who were born after 1931) and were included in the study. The mean follow-up was 33.4 years (median, 35 years; interquartile range, 16-54 years). During follow-up, a total of 118,953 women received a breast cancer diagnosis. Of these, 15,045 patients (12.65%) had 1 update in their family history prior to their diagnosis, 1539 patients (1.29%) had 2 updates, and 191 patients (0.002%) had their family history updated >2 times during follow-up.

**Familial Risk by Family History Constellation**

When age at the time of diagnosis of breast cancer in the index woman was not considered, familial risk in terms of relative risk (SIR) estimates calculated using different methods of family history assessment were found to be rather similar, except for accumulative history, which yielded lower estimates (Table 1). However, for women at younger ages, using the static family history assessment approach resulted in pronounced differences in familial risk (Table 2). For women aged <50 years, the associated
### TABLE 2. Relative Risk of Breast Cancer by Age at Breast Cancer Diagnosis Among Index Women, Number of Affected FDRs and SDRs, and Method of Family History Assessment

| Family History of Breast Cancer | Age at Breast Cancer Diagnosis Among Index Women, Years |  |  |  |  |  |  |  |  |  |  |  |  |
|---------------------------------|-------------------------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|
|                                 | <50                                                   | 50 |  |  |  |  |  |  |  |  |  |  |  |
|                                 | Accumulative SIR 95% CI                              | Static SIR 95% CI | Dynamic SIR 95% CI | Accumulative SIR 95% CI | Static SIR 95% CI | Dynamic SIR 95% CI | Accumulative SIR 95% CI | Static SIR 95% CI | Dynamic SIR 95% CI | Accumulative SIR 95% CI | Static SIR 95% CI | Dynamic SIR 95% CI | Accumulative SIR 95% CI | Static SIR 95% CI | Dynamic SIR 95% CI |
| No family history               | 29,366 Reference 1.55-1.65                           | 28,576 Reference 1.76-1.86 | 31,751 Reference 1.94-2.09 | 67,586 Reference 1.58-1.64 | 66,986 Reference 1.62-1.68 | 71,000 Reference 1.58-1.65 | 11,244 Reference 1.65-1.68 | 11,623 Reference 1.62-1.68 | 9191 Reference 1.62-1.68 |
| 1 FDR + 0 SDR                  | 4418 1.60 1.55-1.65                                  | 4855 1.81 1.76-1.86 | 2884 2.01 1.94-2.09 | 6137 1.64 1.60-1.68 | 6159 1.65 1.61-1.69 | 5871 1.60 1.56-1.64 |
| Mother                          | 3085 1.70 1.65-1.77                                  | 3217 1.81 1.74-1.87 | 2426 1.97 1.89-2.05 | 39 1.51 1.08-2.07 | 40 1.56 1.11-2.12 | 37 1.43 1.00-1.97 |
| Father                         | 23 2.07 1.31-3.11                                   | 23 2.10 1.33-3.15 | 21 2.90 1.79-4.43 | 393 1.59 1.54-1.64 | 3953 1.64 1.59-1.69 | 2715 1.63 1.57-1.70 |
| Sister                          | 1071 1.40 1.31-1.48                                  | 1276 1.66 1.57-1.76 | 416 2.28 2.07-2.51 | 6137 1.64 1.60-1.68 | 6159 1.65 1.61-1.69 | 5871 1.60 1.56-1.64 |
| Brother                         | 9 2.65 1.21-5.03                                    | 10 2.91 1.4-5.36 | 1 1.54 0.04-8.58 | 25 2.43 1.57-3.58 | 26 2.49 1.63-3.65 | 20 3.07 1.88-4.74 |
| Daughter                        | 205 1.32 1.15-1.51                                  | 404 2.39 2.16-2.64 | 14 3.17 1.73-5.32 | 1175 1.51 1.42-1.60 | 1366 1.66 1.58-1.75 | 499 1.67 1.53-1.83 |
| Twin sister$^a$                 | 24 1.99 1.28-2.97                                   | 24 1.99 1.28-2.96 | 6 2.62 0.96-5.70 | 73 1.88 1.48-2.37 | 76 1.94 1.53-2.43 | 58 2.12 1.61-2.74 |
| 1 FDR + ≥1 SDR                 | 516 2.36 2.16-2.57                                  | 574 2.58 2.38-2.80 | 314 2.88 2.57-3.22 | 451 1.88 1.71-2.06 | 503 2.00 1.83-2.18 | 230 2.00 1.75-2.27 |
| 0 FDR + 1 SDR                  | 1895 1.23 1.17-1.28                                  | 2001 1.29 1.24-1.35 | 1656 1.38 1.31-1.45 | 1453 1.24 1.17-1.30 | 1547 1.28 1.22-1.35 | 856 1.25 1.17-1.34 |
| 0 FDR + ≥2 SDRs                | 296 1.70 1.52-1.91                                  | 296 1.76 1.56-1.97 | 225 1.84 1.61-2.10 | 77 1.24 0.88-1.55 | 84 1.35 1.08-1.68 | 51 1.23 0.92-1.62 |
| 2 FDRs + 0 SDR                 | 376 2.55 2.3-2.82                                   | 453 3.13 2.85-3.43 | 100 3.95 3.21-4.80 | 1020 2.22 2.09-2.37 | 1071 2.33 2.19-2.47 | 621 2.33 2.15-2.52 |
| ≥2 FDRs+≥1 SDR                 | 50 3.97 2.95-5.24                                   | 60 5.06 3.86-6.51 | 8 3.87 1.67-7.63 | 92 2.97 2.49-3.65 | 104 3.30 2.70-4.00 | 23 2.20 1.39-3.29 |

Abbreviations: FDR, first-degree relative; Obs, observed number of patients; SDR, second-degree relative; SIR, standardized incidence ratio.

Bold type indicates statistical significance.

$^a$Unknown whether monozygotic twin or not.
familial risks were mostly higher when family history was assessed using dynamic compared with static family history. For example, the risk associated with having only 1 affected FDR was 1.81 (95% CI, 1.76-1.86) using static and was 2.01 (95% CI, 1.94-2.09) using dynamic family history. Likewise, for women aged <50 years with only 1 affected SDR, the associated familial risk was 1.29 (95% CI, 1.24-1.35) when using a static family history and was 1.38 (95% CI, 1.31-1.45) when using a dynamic one. This increase in familial risks for younger women when switching from a static to a dynamic exposure definition was consistent across all constellations of family history except for those with multiple affected FDRs and SDRs (Fig. 2) (Tables 1 and 2). For example, in young women (those aged <50 years) with a family history of breast cancer in a sister, the associated risk was 1.40 (95% CI, 1.31-1.48) times higher than the risk in women with no family history and it was 2.28 (95% CI, 2.07-2.51) times higher when using the dynamic method.

In older women (those aged ≥50 years), using a static family history inconsistently resulted in slightly lower familial risks (Table 2). For example, women aged ≥50 years with ≥2 affected FDRs and at least 1 affected SDR had an associated familial risk of 3.30 (95% CI, 2.70-4.00) using the static family history compared with 2.20 (95% CI, 1.39-3.29) using the dynamic family history (only 1 affected FDR: 1.65 [95% CI, 1.62-1.68] using the static family history and 1.62 [95% CI, 1.58-1.65] using the...
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The risk of developing breast cancer until age 50 years was 1.57% (95% CI, 1.56%-1.59%) and the lifetime risk (ages birth-

Dynamic family history). However, the associated familial risks over the entire life course were found to be very close for static and dynamic approaches. For example, women with only 1 relative with breast cancer had a 69% increased risk of breast cancer compared with women with no family history in analyses assuming a static family history and a 70% increased risk when family history was analyzed as a dynamic variable.

**Familial Risk by Type of Affected Relative and Age at Diagnosis**

Using static family history resulted in lower familial risk estimates for women aged <50 years across nearly all types of affected relatives compared with using dynamic family history (Table 2). For example, having an affected mother was associated with a relative risk of 1.81 (95% CI, 1.74-1.87) when using static history, whereas it was 1.97 (95% CI, 1.89-2.05) when using dynamic family history. The differences in familial risk estimates were most pronounced for young women (those aged <50 years) with an affected sister, father, or daughter. For these women, the familial risk associated with an affected sister was 1.66 (95% CI, 1.57-1.76) when using static family history and 2.28 (95% CI, 2.07-2.51) when using dynamic family history. The familial risk associated with an affected father was 2.10 (95% CI, 1.33-3.15) when using static family history and 2.90 (95% CI, 1.79-4.43) when using dynamic family history, and that associated with an affected daughter was 2.39 (95% CI, 2.16-2.64) when using static family history and 3.17 (95% CI, 1.73-5.32) when using dynamic family history.

**Familial Risk by Age at Diagnosis of Relatives**

The attenuating effect of using static family history on risk of breast cancer in older women and lower familial risk estimates in younger women were persistent even after stratification by age at diagnosis of the affected relative (Table 3). For example, in women aged <50 years, having 1 affected FDR diagnosed after age 50 years was associated with a relative risk of 1.73 (95% CI, 1.66-1.80) when using static family history, which was less than the relative risk of 2.27 (95% CI, 2.16-2.64) when using dynamic family history. A similar trend was observed for women with 2 affected FDRs. For example, having 1 affected FDR diagnosed after age 50 years was associated with a relative risk of 1.59 (95% CI, 1.55-1.63) when using static family history, while it was 1.64 (95% CI, 1.59-1.66) when using dynamic family history. A similar trend was observed for women with 2 affected FDRs.

Using static family history resulted in lower familial risk estimates for women aged <50 years across nearly all types of affected relatives compared with using dynamic family history (Table 3). For example, in women aged <50 years, having 1 affected FDR diagnosed after age 50 years was associated with a relative risk of 1.73 (95% CI, 1.66-1.80) when using static family history, which was less than the relative risk of 2.27 (95% CI, 2.16-2.64) when using dynamic family history. A similar trend was observed for women with 2 affected FDRs.

**Premenopausal Status and Lifetime Cumulative Risks**

The risk of women in the general population to develop breast cancer until age 50 years was 1.57% (95% CI, 1.56%-1.59%) and the lifetime risk (ages birth-

**TABLE 3. Relative Risk of Breast Cancer Among Women With 1 or 2 Affected FDRs by Age at the Time of Diagnosis of Index Women and Relatives and Method of Family History Assessment**

| Family History of Breast Cancer | Youngest Age at Diagnosis of Relatives, Years | Age at Breast Cancer Diagnosis Among Index Women, Years | Static | Dynamic | Static | Dynamic | Static | Dynamic | Static | Dynamic |
|---------------------------------|---------------------------------------------|-----------------------------------------------------|--------|---------|--------|---------|--------|---------|--------|---------|
|                                 |                                             | <50                                                 | Obs    | SIR     | 95% CI | Obs    | SIR     | 95% CI | Obs    | SIR     | 95% CI |
| No family history               |                                             | All ages                                            | 28,576 | Reference | 31,751 | Reference | 66,986 | Reference | 71,000 | Reference | 95,562 | Reference |
| 1 FDR + 0 SDR                  |                                             | All ages                                            | 4955   | 1.81 | 1.76-1.86 | 2884   | 2.01 | 1.94-2.09 | 11,623 | 1.65 | 1.62-1.68 | 9191   | 1.62 | 1.58-1.65 | 16,578 | 1.69 | 1.67-1.72 | 12,075 | 1.70 | 1.67-1.73 |
| Age <50 y                       |                                             | All ages                                            | 1422   | 2.40 | 2.27-2.52 | 1003   | 2.56 | 2.41-2.73 | 2548   | 1.76 | 1.69-1.83 | 2030   | 1.72 | 1.65-1.80 | 3970   | 1.94 | 1.88-2.00 | 3033   | 1.93 | 1.86-2.00 |
| Age ≥50 y                       |                                             | All ages                                            | 3533   | 1.64 | 1.59-1.70 | 1881   | 1.81 | 1.73-1.89 | 9075   | 1.62 | 1.59-1.66 | 7161   | 1.59 | 1.55-1.63 | 12,608 | 1.69 | 1.60-1.66 | 9042   | 1.63 | 1.6-1.66 |
| 2 FDRs + 0 SDR                 |                                             | All ages                                            | 453    | 3.13 | 2.85-3.43 | 100    | 3.95 | 3.21-4.81 | 1071   | 2.33 | 2.19-2.47 | 621    | 2.39 | 2.15-2.62 | 1524   | 2.52 | 2.39-2.65 | 721    | 2.47 | 2.29-2.66 |
| Age <50 y                       |                                             | All ages                                            | 2846   | 2.80 | 2.60-3.00 | 72     | 4.26 | 3.22-5.44 | 506    | 2.93 | 2.33-2.76 | 331    | 2.51 | 2.25-2.80 | 772    | 2.86 | 2.66-3.07 | 403    | 2.71 | 2.45-2.99 |
| Age ≥50 y                       |                                             | All ages                                            | 187    | 2.50 | 2.15-2.88 | 28     | 3.34 | 2.22-4.82 | 565    | 2.17 | 1.99-2.35 | 290    | 2.15 | 1.91-2.41 | 752    | 2.24 | 2.08-2.41 | 318    | 2.22 | 1.98-2.47 |

Abbreviations: FDR, first-degree relative; Obs, observed number of patients; SDR, second-degree relative; SIR, standardized incidence ratio. Bold values indicate statistical significance.
to 79 years) was 10.5% (95% CI, 10.4%-10.5%) (Table 4). The lifetime risks of developing breast cancer for women with different constellations of family history were comparable using both the static and dynamic methods of family history assessment. However, using static family history rather consistently resulted in a lower risk of premenopausal breast cancer (diagnosis at age <50 years) compared with risks obtained using a dynamic family history. For example, using a static family history, the risk of developing premenopausal breast cancer for women with 1 affected FDR was 2.6% (95% CI, 2.5%-2.7%) and was 3.1% (95% CI, 3.0%-3.2%) when using a dynamic family history. Using a static family history also resulted in lower familial risks for women, even when only SDRs were affected. Overall, the choice of the static method of family history assessment resulted in lower familial risks for younger women, but the lifetime familial risks estimates were rather comparable for both the static and dynamic methods.

### Ten-Year Cumulative Risk Estimates

The 3 methods of family history assessment also resulted in differences in the 10-year cumulative risk estimates across a woman's life course (Fig. 2). For example, using a static family history, a woman aged 35 years with 2 FDRs diagnosed with breast cancer had a 10-year cumulative risk of 1.5%; this risk was 1.2% using an accumulative family history and was 2.3% using a dynamic family history. At age 50 years, the 10-year cumulative risk of developing breast cancer for women in the general population was 2.2%. Using a static family history, women with 2 FDRs diagnosed with breast cancer reached a 10-year cumulative risk of 2.2% at age 38 years, whereas the same risk was attained at an earlier age (age 35 years) when a dynamic family history was used. A similar trend was observed for women with 1 affected FDR.

### DISCUSSION

Using what to the best of our knowledge is the world's largest nationwide family cancer data set, we have...
provided relative and absolute familial risks of breast cancer among FDRs and SDRs of patients with breast cancer using 3 different approaches for defining family history of the disease. We found that assessing family history as a static variable (ie, as a constant trait over the time a woman was included in the follow-up), without taking into account the timing of the diagnosis of affected relatives, resulted in lower relative and absolute breast cancer risks across most common constellations of family history, particularly among younger women (those aged <50 years), compared with when family history was assessed as a dynamic variable. Familial risks derived using all methods did not appear to differ substantially among older women. Familial risk estimates that were derived using accumulative family history were the lowest.

The current study benefited from the register-based, nationwide family cancer data sets, and their structures allowed for the accurate assessment of family history of breast cancer using all 3 methods, including the accurate timing of diagnosis in index individuals and their relatives, and mitigated the selection and recall biases that often occur in case-control studies. The large sample size accorded by our nationwide data sets allowed for precise estimates of familial breast cancer risk, including subgroups with fewer incident cases, such as breast cancer in younger women. In the current study, regional differences in risk estimates most likely were reconciled by the adjustment for area of residence. Further adjustment for socioeconomic factors helped to control for factors related to lifestyle. We did not have data available regarding participation in mammography screening, but the effect of this factor would be nondifferential with regard to the 3 methods of family history assessment. Furthermore, a Swedish study found no association between family history of breast cancer and both past and planned future participation in screening.16 Although this analysis was based on Swedish data sets, the major conclusions are likely to be generalizable to other populations because familial relative risks (SIRs) are less likely to demonstrate major variations between populations compared with absolute levels of incidence.

Risk estimates generated from Swedish family cancer data sets are relatively precise. However, bias in estimates of familial cancer can occur if population-based registers fail to identify cancer diagnoses in relatives when disease has occurred before the start of registration (“left truncation” of family history). A previous study demonstrated that for breast cancer, risk estimates from the Swedish multigenerational cohort do not generally appear to be biased by left truncation.17 Women in the current study with likely missing information were in their 20s, with many having parents aged <50 years at the start of the cancer registry (1958). Although familial cases in these age groups are not substantial in general, they might be slightly underestimated due to the structure of our data sets. In addition, the static approach is not completely “static” because some relatives still will develop breast cancer in the future, especially those who still are young at the end of follow-up (daughter vs mother), but such a right truncation, which exists in all familial studies, similarly affects the accumulative and dynamic approaches. In conclusion, any such condition would similarly affect estimates from all 3 methods and the inference on the difference between them most likely would remain valid.

A study conducted in 2010 assessed the familial risk for the siblings and offspring of patients with breast cancer up to age 74 years using static and dynamic approaches for defining family history without considering the age at onset of breast cancer in patients and reported that hazard ratios were equal using both methods.18 The results of the current study, based on all ages combined, are in line with the conclusion of that study, so that for all ages combined, the familial risks associated with having affected FDRs were similar using static and dynamic family history. However, in the current analyses, which stratified by age at the time of diagnosis of breast cancer in index women, the 2 methods were found to result in different familial risk estimates in younger women. In women aged >50 years, who constituted the majority of breast cancer cases and therefore had the largest effect on the overall results, the family history was more likely in the final status and therefore less subject to further major changes. Providing results using the accumulative approach and the comparison with estimates using 2 other methods are other novel aspects of the current study.

Using the dynamic method, some of the person-years (and their corresponding cancer cases) before diagnosis of the first or subsequent relative were allocated to no family history or lower family history constellations. For example, a significant proportion of person-years for women with 1 affected FDR are allocated to the “no family history” group and a proportion of person-years for women with 2 affected FDRs are allocated to women with 1 affected FDR. The minimal difference noted in most risk estimates for all ages combined indicates that the allocation of person-years to a lower family history constellation is somehow compensated by a shift in person-years from constellations with a higher number of affected family members and an increase in the baseline risk of the reference group due to the addition of person-years from women whose relative(s) later would develop breast cancer.
The absolute risk among those with no family history at a certain age was slightly higher using the dynamic definition of family history compared with the static definition because in this group there were individuals who in the future would have ≥1 family members diagnosed with cancer. Women who have no family history are a group comprised of those who will never have a family member with cancer and those who will have ≥1 relatives with cancer in the future. Under the static definition, especially in register-based studies, in which the cancer status of family members at any age is known, only individuals who will not have an affected family member by the end of follow-up are considered as the reference group without a family history. The observed number of cases in Tables 1 and 2 are different between the dynamic, accumulative, and static methods, which was to be expected. This is because, for example, with use of the static method, some cases would be included in the group of individuals with a family history, whereas when using the dynamic method they would be included in the group with no family history (e.g., when the cancer diagnosis in the index woman precedes the diagnosis in the relative).

A woman’s risk of breast cancer may vary over time due to aging and lifestyle factors. Of course, the inherited risk of breast cancer due to a genetic predisposition does not change by every cancer diagnosis in the family. However, this information can be used for better breast cancer risk predictions in real life without genetic testing or after a negative genetic test. The difference between the static and dynamic methods of risk estimation lies in the magnitude of risk that each method ascribes to a particular family history constellation. Although the static and dynamic methods yield different familial risk estimates, both have their specific indications and merits depending on the purpose of the analysis. For example, when familial risk estimates are intended for risk stratification to identify women at higher risk for participation in preventive interventions such as early initiation of screening, the dynamic method may be preferred because it better reflects the real-life situation, in which it always is unknown whether a woman’s relatives will develop breast cancer in the future. For example, using the static and accumulative methods resulted in lower risk estimates in younger women with family history. The fact that breast tumors in these women tend to be diagnosed at a late stage, are more aggressive, and have worse outcomes makes accurate risk estimation of paramount importance. Thus, using the dynamic method, which resulted in less conservative familial risk estimates and within this context had lower potential for missing high-risk women, would be preferred.

Conversely, from an etiological point of view, the static method may be better suited for estimation of the impact of a risk factor (in this case, family history) on disease burden. From this viewpoint, the dynamic definition can be considered subject to misclassification. Results obtained using the dynamic definition are subject to temporary underestimation of exposure due to cancers occurring among family members at older ages. Because underestimation selectively affects family history becoming known with cancers diagnosed at older ages only, which are associated with lower risk than those occurring at younger ages, using the dynamic approach would result in higher risk estimates. In etiological studies, the static method provides an opportunity to capture family history more completely and thus determine the impact of family history on breast cancer burden more precisely. Using the dynamic approach in these studies would result in biased results because exposure would be misclassified in mostly younger women, some of whom would later have a positive family history.

For breast cancer risk assessment, it may appear reasonable to use the accumulative family history approach because it does not include future risk and partly takes into consideration the timing of cancer events (only diagnoses of breast cancer in relatives occurring before diagnosis in the index woman are counted). However, the accumulative approach resulted in the lowest risk estimates noted among the 3 methods because it lacks the completeness of family history accorded by the static approach and also considers the time before a woman’s first relative was diagnosed with breast cancer as being with a family history, and thus may be suboptimal for the purposes of risk prediction. An optimal approach would be to further incorporate the timing of breast cancer diagnoses among a woman’s relatives (i.e., the person-years that a woman has lived with particular family histories of breast cancer) into their breast cancer risk calculation, and to recalculate the risk at the time of a new breast cancer diagnosis among the woman’s relatives (dynamic approach).

In general, a specific aim of the current study was to determine which of these 3 approaches of family history assessment is more appropriate for use in the development of risk prediction tools. Because each of these methods required a different set of variables in the data collection phase, the results of the current study can help clinicians and investigators know which information should be collected from study patients, on the basis of which a valid risk prediction tool can be developed. For example, for the accumulative method, which appears to be the most common approach in practice, only information regarding the number and type of affected relatives and their ages at the
time of diagnosis are recorded, but the date of diagnosis of cancer in a relative is not needed, whereas for the dynamic method, information regarding all of these variables is needed. Because the accumulative method yielded underestimated risks in most common familial scenarios, one can conclude that risk prediction tools that include family history assessed based on the most common method of assessment, the accumulative method, are most likely to be prone to underestimation of the risk associated with family history for the majority of those with a family history of cancer, especially in younger women. On the basis of the current study findings, family history as assessed by the dynamic approach appears to be the most appropriate method for risk prediction purposes and the data collection for such studies also should include the date of diagnosis of cancers in relatives to enable the analysis of family history as a time-dependent variable. However, in clinical practice without any intention for future research, the accumulative approach remains the most convenient method for family history assessment. Nevertheless, when possible, the collection of easy-to-obtain and free information regarding the date of diagnosis of cancer in relatives is recommended along with the number and type of affected relatives and their age at the time of diagnosis because of the increasing use of real world data in science.

The results of the current study have demonstrated that the 10-year cumulative risk determined using static family history was consistently lower than that estimated using the dynamic method. This underestimation of risk may represent missed opportunities for the early detection of breast cancer when familial risk estimates derived using the static or accumulative methods are used in risk prediction tools. For example, women usually are recommended to initiate screening at the age of 50 years.22,23

In the current study, the 10-year cumulative risk for the general population at age 50 years was 2.2%. Using static family history, women with a family history of breast cancer in 1 FDR reached this risk threshold at age 42 years, and it was reached at age 40 years using the dynamic method. Thus, under a risk-adapted screening program, using the familial risk estimates derived using static family history would result in a delayed screening recommendation by approximately 2 years for this group of women.

Conclusions
The results of the current study provide evidence that using the accumulative, static, and dynamic (time-dependent) approaches for defining a family history of breast cancer resulted in different familial risk estimates, particularly among younger women. The choice of method should depend on the purpose of the study, with the accumulative method being the most convenient in practice and the least favored for risk prediction, the static method being suitable for etiological impact and risk attribution studies, and the dynamic method being better suited for risk stratification studies. Studies aiming at risk stratification and the identification of high-risk women for early preventive interventions, such as personalized cancer prevention and risk-adapted screening strategies, should take into consideration the timing of breast cancer events in family members, especially if they are dealing with early-onset or premenopausal breast cancer.

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The authors made no disclosures.

AUTHOR CONTRIBUTIONS
Trasias Mukama, Elham Kharazmi, and Mahdi Fallah analyzed the data, interpreted the results, and drafted the article. Elham Kharazmi, Hermann Brenner, and Mahdi Fallah conceptualized and designed the study. Kristina Sundquist and Jan Sundquist provided the study material. All authors reviewed the article for important intellectual content and approved the final version.

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