Breast Cancer Res Treat (2008) 111:559–568
DOI 10.1007/s10549-007-9814-2

EPIDEMIOLOGY

Population attributable risks for breast cancer in Swedish women by morphological type

Charlotta Granström · Jan Sundquist · Kari Hemminki

Received: 31 October 2007 / Accepted: 31 October 2007 / Published online: 8 November 2007

Abstract The purpose of this population-based cohort study is to describe the etiology of invasive and in situ breast cancer, using the Swedish Family-Cancer Database. A total of 1,028,455 women, aged 40–61 years, were followed from 1993 through 2004. Invasive and in situ breast cancer was identified in 27,243 and 3,496 women, respectively, with data on family history, reproductive variables, residential region and socioeconomic status. Relative risks (RRs) and population attributable fractions (PAFs) were estimated by Poisson regression. The overall PAF of invasive breast cancer was 5.3% for family history and 17.9% for reproductive factors. Morphology-specific PAFs were calculated for ductal (family history: 5.2%, reproductive factors: 16.6%), lobular (family history: 6.2%, reproductive factors: 19.9%) and comedo types (family history: 5.2%, reproductive factors: 25.9%). The corresponding PAFs of in situ tumors were higher due to family history and reproductive factors. Family history, late age at first birth and high socioeconomic status were associated with elevated risks in all morphologies, whereas low parity did not have an impact on the invasive and in situ lobular and comedo tumors. The risks for women with a family history were the highest, but these women accounted for the smallest proportion of the cases, thus resulting in the lowest PAFs.

Keywords Family history · Morphological types · Parity · Population attributable fraction · Relative risk

Abbreviations

RR	relative risk
PAF	population attributable fraction
CI	confidence interval

Introduction

There are limited numbers of studies evaluating the association between well-established risk factors for breast cancer by morphological subtype. These studies suggest that the subtypes do not tend to share a common risk profile although some of the results are inconsistent [1–4]. Some well-known risk factors for breast cancer include family history [5–8], nulliparity [9], late age at first child birth [9], early menarche [10], late menopause [10], use of hormone replacement therapy [11] and high socioeconomic status [12]. Among women whose first child birth occurred after age 35 years, the risk is higher than those of nullipara [10]. There is evidence that an increasing number of births is a protective factor for ductal carcinoma, but the findings on the lobular subtype are inconsistent [1–4]. Late age at first birth seems to be associated with lobular carcinoma more strongly than with ductal carcinoma [1–4]. In one study early age at menarche and late age at menopause showed a higher risk for lobular than for ductal carcinoma [1], but in another study the findings were reversed [13]. Long

C. Granström (✉) · J. Sundquist · K. Hemminki
Center for Family and Community Medicine, Karolinska Institute, Alfred Nobels allé 12, 141 83 Huddinge, Sweden
e-mail: charlotta.granstrom@ki.se

J. Sundquist
Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA, USA

K. Hemminki
Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

duration of breastfeeding is observed to have a protective role [12], but this protective effect seems to be limited mostly to ductal carcinoma [1, 2, 13]. Current oral contraceptive use is linked to lobular carcinoma, but the association with ductal carcinoma is unclear [13, 14]. In a meta-analysis, the risk of breast cancer due to hormonal replacement therapy varied according to morphological types whereby the largest relative risks were seen for lobular and tubular carcinomas [15]. Additional risk factors include alcohol use and obesity in postmenopausal women [12]. A recent review found evidence for a reduced risk for physical activity, especially for postmenopausal breast cancer [16].

Data on risk factors for histology-specific breast carcinoma in situ are sparse. In one study, ductal carcinoma in situ was positively associated with a family history of breast cancer, mammographic examination, clinical breast examination, low gravidity, late age at first birth and late menopause [17]. Similar associations were observed for lobular carcinoma in situ although some of these did not reach statistical significance.

We use here the year 2006 update of the nation-wide Swedish Family-Cancer Database, covering 11.5 million individuals and some 1.2 million tumors retrieved from the Swedish Cancer Registry. The Database offers unique possibilities for many types of family studies, because complete data are available on family members and their cancers, supplemented by socio-economic and other background data from the national censuses. Our aim was to determine relative risks (RRs) and population attributable fractions (PAFs) of invasive and in situ breast cancer for reproductive, familial, socioeconomic and residential factors according to morphological subtype.

Materials and methods

Statistics Sweden created a family database, "Second Generation Register" in 1995. After a few expansions, it covered offspring born after 1931 with their parents, renamed to "Multigeneration Register" to indicate that the number of generations was more than two. We have linked this Register to the Swedish Cancer Registry (1958–2004) to make the Family-Cancer Database (MigMed2) in year 2006 for the seventh time. In the Database all data are organized in child–mother–father triplets; the parents have been registered at the time of birth of the child, allowing tracking of biological parents. The Database includes all persons resident in Sweden after 1931 with their biological parents, totalling over 11.5 million individuals. The present study included women born between years 1932 and 1953, i.e., those whose minimal age at the beginning of the follow-up ranged from 40 to 61 years.

The completeness of cancer registration in the 1970s has been estimated to be over 95%, and is now considered to be close to 100%. The percentage of cytologically or histologically verified cases of breast cancer has been close to 100% [18]. The Swedish Cancer Registry is based on compulsory notification of cases [18]. A 4-digit diagnostic code according to the International Classification of Diseases, 7th revision was combined with morphology codes according to the International Classification of Diseases for Oncology, World Health Organization (WHO) and the Systematized Nomenclature of Medicine (SNOMED) used since 1993. The ICD-7 code 170 was used to identify breast cancer cases and a Swedish selection of SNOMED was used to classify the morphological subtypes.

Follow-up was started at immigration or January 1, 1993, whichever came latest. Follow-up was terminated on diagnosis of first cancer, death, emigration or the closing date of the study, December 31, 2004. A Poisson regression analysis was performed to model overall invasive and in situ breast cancer incidence using following variables: age at diagnosis (5-year bands), family history of invasive breast cancer (mother, sister, no history), parity (0, 1, 2, 3+), age at first child birth (13–20, 21–24, 25–29, 30+ years), socioeconomic status (manual worker, blue collar, professional, other) and residential area (big city, south, north) [19, 20]. Similar separate Poisson regression analyses were also performed for each of the morphologic-specific breast cancers: ductal, lobular and comedo invasive and in situ carcinomas. RRs and confidence intervals (95% CI) were calculated using the result of the Poisson regression. For simplicity we do not show results of age at diagnosis, although this variable was always included in the model.

The PAF is the proportion of disease cases in a population that is attributable to a particular exposure. Using the relevant variables from the Poisson regression models, individual PAFs due to each of the variables were calculated on the basis of RRs generated by new Poisson regression models with the variables classified dichotomously (exposed/unexposed). The population belonging to the lowest level of the variables in the initial Poisson regression models was defined as unexposed and the other levels were aggregated into the exposed group. PAF was calculated according to the formula $((RR - 1)/RR) \times$ the proportion of cases in the exposed population, where RR was the risk in the exposed population [21]. Joint PAFs were calculated by defining the unexposed population as those being unexposed to all risk factors simultaneously. For joint PAF we used the formula $((inc_{all} - inc_{ref})/inc_{all}) \times 100$, where inc_{all} denotes the overall population incidence and inc_{ref} denotes the incidence in the unexposed population. The incidence was age-standardized according to the Swedish census 2000. CIs for PAFs were estimated by bootstrapping with 1,000 simulations [22].

Results

Our study covered 1,028,455 women who were followed from 1993 through 2004 and who accumulated 11,066,977 person-years at risk. Invasive and in situ breast cancer was identified in 27,243 and 3,496 women, respectively, with data on family history, reproductive variables, socioeconomic status and residential region. Table 1 shows the distribution of cases and person-years by all categories in each of the morphologies. The majority of the invasive morphology-specific cases were ductal (62%) and lobular (14%), whereas only 7% were tubular and 3% comedo.

The variables included in the Poisson regression models were age at diagnosis (data not shown), family history, parity, age at first child birth, socioeconomic status and residential area, all of which had a significant or borderline significant effect on the risk of breast cancer (Table 2). A family history through a mother proband increased the risk of overall invasive breast cancer to 1.64 and a through a sister proband to 1.77 relative to women with no familial history. There was a clear trend for increasing RRs with increasing age at first child birth and low-gravidity showed significant elevated risks with uniparity showing the highest RR of 1.20. High socioeconomic status was associated with increased risk, as was living in big cities.

As for the overall invasive breast carcinoma, the morphology-specific types (Table 2) showed stronger positive associations with a family history through a sister proband than through a mother proband (ductal: 1.70 and 1.67, respectively, lobular: 2.09 and 1.66, respectively, tubular: 2.09 and 1.68, respectively); the exception was the comedo morphology, for which the risk was lower through a sister proband (1.23) than through a mother proband (1.89). There was a clear trend for increasing RRs with increasing age at first child birth for all the morphologies, with the strongest effect observed for lobular carcinoma. On the other hand, low parity had little or no effect on lobular and comedo carcinomas as opposed to the ductal and tubular subtypes, where the most elevated risks were observed for uniparity. Nulliparity was inversely associated with lobular and comedo carcinoma, but the reversed result was observed in the ductal and tubular subtypes with risks

Table 1 Cases and person-years in breast cancer

Variable	Invasive						In situ				
	All	Ductal	Lobular	Tubular[a]	Comedo	Person-years	All	Ductal	Lobular	Comedo	Person-years
Family history											
Mother	2,222	1,403	309	170	72	579,656	310	210	44	26	576,644
Sister	1,276	767	207	110	23	305,556	156	102	23	13	305,079
No history	23,745	14,848	3,259	1,753	642	10,181,766	3,030	2,118	322	292	9,990,515
Parity											
0	3,844	2,455	468	270	80	1,320,991	553	378	69	58	1,333,945
1	4,977	3,108	692	384	121	1,781,455	600	423	64	51	1,742,707
2	11,808	7,291	1,665	909	343	4,828,863	1,521	1,058	167	142	4,742,710
3+	6,614	4,164	950	470	193	3,135,668	822	571	89	80	3,052,876
Age at first birth											
13–20	4,731	3,026	602	335	130	2,270,522	554	389	52	51	2,149,698
21–24	7,501	4,705	996	576	217	3,337,686	938	653	110	86	3,270,113
25–29	7,454	4,579	1,113	587	207	2,910,313	987	683	107	92	2,896,633
30+	3,713	2,253	596	265	103	1,227,465	464	327	51	44	1,221,850
Socioeconomic status											
Blue collar	12,113	7,517	1,703	972	311	4,532,635	1,592	1,080	193	149	4,457,857
Professional	3,898	2,413	588	283	107	1,386,755	502	349	65	50	1,367,189
Other	2,699	1,683	359	182	80	1,153,307	298	203	25	35	1,146,419
Manual worker	8,533	5,405	1,125	596	239	3,994,280	1,104	798	106	97	3,900,773
Residential region											
Big city	10,641	6,415	1,558	825	287	3,906,859	1,333	893	188	130	3,807,653
South	11,191	7,082	1,548	916	344	4,768,550	1,470	1,014	142	170	4,710,451
North	5,411	3,521	669	292	106	2,391,569	693	523	59	31	2,354,134
Total	27,243	17,018	3,775	2,033	737	11,066,977	3,496	2,430	389	331	10,872,238

[a] Tubuloductal/tubular

Table 2 Relative risks in invasive breast cancer according to the Poisson model

Variable	All invasive			Ductal			Lobular			Tubuloductal/tubular			Comedo		
	Cases	RR	(95% CI)	Cases	RR	(95% CI)	Cases	RR	(95% CI)	Cases	RR	(95% CI)	Cases	RR	(95% CI)
Family history															
Mother	2,222	1.64	(1.57–1.72)	1,403	1.67	(1.58–1.76)	309	1.66	(1.48–1.87)	170	1.68	(1.43–1.96)	72	1.89	(1.48–2.41)
Sister	1,276	1.77	(1.67–1.87)	767	1.70	(1.58–1.83)	207	2.09	(1.81–2.40)	110	2.09	(1.72–2.53)	23	1.23	(0.81–1.87)
No history	23,745	1		14,848	1		3,259	1		1,753	1		642	1	
Parity															
0	3,844	1.10	(1.04–1.16)	2,455	1.16	(1.08–1.24)	468	0.77	(0.67–0.89)	270	1.17	(0.96–1.43)	80	0.76	(0.55–1.06)
1	4,977	1.20	(1.16–1.25)	3,108	1.22	(1.16–1.28)	692	1.07	(0.96–1.19)	384	1.32	(1.14–1.52)	121	1.00	(0.79–1.27)
2	11,808	1.11	(1.08–1.15)	7,291	1.11	(1.06–1.15)	1,665	1.05	(0.97–1.14)	909	1.18	(1.05–1.32)	343	1.08	(0.90–1.29)
3+	6,614	1		4,164	1		950	1		470	1		193	1	
Age at first birth															
13–20	4,731	0.78	(0.74–0.81)	3,026	0.81	(0.77–0.86)	602	0.60	(0.54–0.68)	335	0.83	(0.70–0.98)	130	0.74	(0.56–0.98)
21–24	7,501	0.80	(0.77–0.83)	4,705	0.82	(0.78–0.87)	996	0.65	(0.58–0.72)	576	0.90	(0.77–1.05)	217	0.83	(0.65–1.06)
25–29	7,454	0.86	(0.83–0.90)	4,579	0.87	(0.83–0.92)	1,113	0.78	(0.70–0.86)	587	0.97	(0.83–1.12)	207	0.88	(0.69–1.12)
30+	3,713	1		2,253	1		596	1		265	1		103	1	
Socioeconomic status															
Blue collar	12,113	1.21	(1.17–1.24)	7,517	1.20	(1.16–1.25)	1,703	1.27	(1.17–1.37)	972	1.36	(1.23–1.51)	311	1.04	(0.87–1.23)
Professional	3,898	1.23	(1.18–1.28)	2,413	1.23	(1.17–1.29)	588	1.36	(1.23–1.51)	283	1.26	(1.09–1.45)	107	1.15	(0.91–1.46)
Other	2,699	1.05	(1.01–1.10)	1,683	1.04	(0.98–1.10)	359	1.05	(0.93–1.18)	182	1.03	(0.87–1.21)	80	1.15	(0.89–1.48)
Manual worker	8,533	1		5,405	1		1,125	1		596	1		239	1	
Residential region															
Big city	10,641	1.14	(1.11–1.18)	6,415	1.06	(1.02–1.11)	1,558	1.34	(1.22–1.47)	825	1.62	(1.42–1.86)	287	1.58	(1.26–1.98)
South	11,191	1.04	(1.01–1.08)	7,082	1.01	(0.97–1.06)	1,548	1.16	(1.06–1.27)	916	1.58	(1.38–1.80)	344	1.60	(1.28–1.99)
North	5,411	1		3,521	1		669	1		292	1		106	1	
Total	27,243			17,018			3,775			2,033			737		

lower than for uniparity. Residential region had very small or moderately elevated risks with the reference group 'North' in all morphologies and with the lowest RRs found in the ductal morphology. There was also a moderately positive association with high socioeconomic status in all morphologies, where the strongest effect was observed for lobular and tubular carcinoma and the weakest for the comedo subtype.

The corresponding results for in situ carcinoma are shown in Table 3 with the ductal morphology constituting 70% of all cases. Here, family history refers to the family history of invasive breast cancer. The association with a mother history was stronger in comparison with the corresponding invasive analyses, with the exception for the comedo morphology; by contrast, the sister history association was weaker for overall and ductal carcinoma in situ. The strongest associations with family history were observed for lobular carcinoma in situ, for which the RRs were 2.24 (mother) and 2.43 (sister). A clear trend for increasing RRs with increasing age at first child birth in all the in situ models were observed, with equal effects on ductal and comedo carcinomas in situ. Unlike the invasive models, the effect on lobular carcinoma in situ was the smallest and it was less pronounced than for the invasive lobular subtype. On the other hand, the effect of age at first birth on ductal carcinoma in situ was found to be more pronounced than the corresponding invasive model. Clear trends for decreasing RRs with increasing parity were observed for the overall and ductal in situ carcinoma. As for the invasive models, low parity had little or no effect on the lobular and comedo in situ subtypes, but nulliparity was associated with insignificant elevated risks. Residential region had small to moderately elevated risks with the lowest RRs in the ductal in situ morphology and the highest RRs in comedo carcinoma in situ. Lobular and especially comedo carcinoma in situ was more strongly associated with living in the more densely populated south and big cities compared with the corresponding invasive subtypes. There was a positive association with high socioeconomic status in all the in situ models and the associations for the lobular and comedo subtypes were stronger than the corresponding invasive analyses. The most pronounced effect of high socioeconomic status was observed for lobular carcinoma in situ.

Table 3 Relative risks in in situ breast cancer according to the Poisson model

Variable	All in situ			Ductal			Lobular			Comedo		
	Cases	RR	(95% CI)	Cases	RR	(95% CI)	Cases	RR	(95% CI)	Cases	RR	(95% CI)
Family history												
Mother	310	1.75	(1.56–1.97)	210	1.71	(1.49–1.97)	44	2.24	(1.63–3.07)	26	1.48	(0.99–2.21)
Sister	156	1.68	(1.43–1.98)	102	1.56	(1.28–1.90)	23	2.43	(1.59–3.70)	13	1.48	(0.85–2.58)
No history	3,030	1		2,118	1		322	1		292	1	
Parity												
0	553	1.23	(1.06–1.43)	378	1.20	(1.01–1.43)	69	1.38	(0.90–2.13)	58	1.25	(0.79–2.00)
1	600	1.14	(1.02–1.28)	423	1.16	(1.02–1.33)	64	1.07	(0.77–1.50)	51	1.00	(0.69–1.44)
2	1,521	1.11	(1.02–1.21)	1,058	1.12	(1.01–1.25)	167	1.06	(0.82–1.38)	142	1.06	(0.80–1.40)
3+	822	1		571	1		89	1		80	1	
Age at first birth												
13–20	554	0.75	(0.66–0.86)	389	0.73	(0.63–0.86)	52	0.72	(0.48–1.09)	51	0.72	(0.47–1.11)
21–24	938	0.80	(0.71–0.90)	653	0.78	(0.68–0.90)	110	0.94	(0.66–1.33)	86	0.77	(0.52–1.12)
25–29	987	0.91	(0.81–1.02)	683	0.88	(0.77–1.01)	107	0.94	(0.67–1.33)	92	0.88	(0.61–1.28)
30+	464	1		327	1		51	1		44	1	
Socioeconomic status												
Blue collar	1,592	1.36	(1.20–1.54)	1,080	1.37	(1.18–1.59)	193	1.86	(1.23–2.83)	149	1.23	(0.94–1.60)
Professional	502	1.35	(1.17–1.56)	349	1.40	(1.17–1.66)	65	1.96	(1.23–3.12)	50	1.29	(0.91–1.83)
Other	298	1		203	1		25	1		35	1.15	(0.78–1.70)
Manual worker	1,104	1.14	(1.00–1.30)	798	1.21	(1.03–1.41)	106	1.36	(0.88–2.11)	97	1	
Residential region												
Big city	1,333	1.11	(1.02–1.22)	893	1.03	(0.94–1.13)	188	1.77	(1.32–2.38)	130	2.39	(1.61–3.55)
South	1,470	1.06	(0.97–1.16)	1,014	1		142	1.19	(0.88–1.61)	170	2.71	(1.85–3.98)
North	693	1		523	1.03	(0.93–1.15)	59	1		31	1	
Total	3,496			2,430			389			331		

Table 4 Population attributable fractions (PAFs) in breast cancer

Morphology/Variable	Cases	RR	(95% CI)	Prop (%)	PAF (%)	(95% CI)	Morphology/Variable	Cases	RR	(95% CI)	Prop (%)	PAF (%)	(95% CI)
All invasive							*All in situ*						
Family history							Family history						
Family history	3,498	1.69	(1.63–1.75)	12.8	5.3	(5.1–5.4)	Family history	466	1.74	(1.57–1.91)	13.3	5.7	(5.3–6.0)
No history	23,745	1		87.2			No history	3,030	1		86.7		
Parity & age at first birth							Parity & age at first birth						
Other	25,062	1.24	(1.19–1.30)	92.0	17.9	(17.1–19.0)	Other	3,260	1.48	(1.30–1.69)	93.2	30.4	(28.1–32.9)
3+: 13–20	2,181	1		8.0			3+: 13–20	236	1		6.8		
Socioeconomic status							Residential region						
Other	18,710	1.24	(1.21–1.27)	68.7	13.2	(12.7–13.6)	Other	2,803	1.11	(1.02–1.21)	80.2	7.9	(6.4–9.7)
Manual worker	8,533	1		31.3			North	693	1		19.8		
Residential region							All						
Other	21,832	1.10	(1.06–1.13)	80.1	7.1	(6.4–7.7)	Other	3,446			98.6	45.2	(41.3–49.7)
North	5,411	1		19.9			All combined	50			1.4		
All													
Other	26,984			99.1	26.9	(23.2–32.6)							
All combined	259			1.0									
Ductal invasive							*Ductal in situ*						
Family history							Family history						
Family history	2,170	1.68	(1.61–1.76)	12.8	5.2	(5.0–5.3)	Family history	312	1.67	(1.48–1.88)	12.8	5.1	(4.7–5.6)
No history	14,848	1		87.2			No history	2,118	1		87.2		
Parity & age at first birth							Parity & age at first birth						
Other	15,626	1.22	(1.15–1.29)	91.8	16.6	(15.6–17.9)	Other	2,259	1.43	(1.22–1.67)	93.0	27.9	(25.1–31.0)
3+: 13–20	1,392	1		8.2			3+: 13–20	171	1		7.0		
Socioeconomic status							Residential region						
Other	11,613	1.22	(1.18–1.26)	68.2	12.3	(11.7–12.8)	Other	1,416	1.06	(0.98–1.15)	58.3	3.3	(2.0–4.6)
Manual worker	5,405	1		31.8			South	1,014	1		41.7		
Residential region							All						
Other	13,497	1.04	(1.01–1.08)	79.3	3.4	(2.6–4.2)	Other	2,357			97.0	36.1	(31.9–40.7)
North	3,521	1		20.7			All combined	73			3.0		
All													
Other	16,849			99.0	26.6	(22.7–32.8)							
All combined	169			1.0									
Lobular invasive							*Lobular in situ*						
Family history							Family history						
Family history	516	1.82	(1.66–2.00)	13.7	6.2	(5.8–6.5)	Family history	67	2.33	(1.79–3.04)	17.2	9.8	(8.6–11.0)
No history	3,259	1		86.3			No history	322	1		82.8		

Table 4 continued

Morphology/Variable	Cases	RR	(95% CI)	Prop (%)	PAF (%)	(95% CI)	Morphology/Variable	Cases	RR	(95% CI)	Prop (%)	PAF (%)	(95% CI)
Parity & age at first birth							Parity & age at first birth						
Other	3,548	1.27	(1.11–1.45)	94.0	19.9	(17.5–23.0)	Other	365	1.58	(1.05–2.39)	93.8	34.4	(27.9–42.5)
2: 13–20	227	1		6.0			3+: 13–20	24	1		6.2		
Socioeconomic status							Residential region						
Other	2,650	1.34	(1.25–1.44)	70.2	18.0	(16.8–19.1)	Other	330	1.52	(1.15–2.00)	84.8	28.8	(24.3–33.7)
Manual worker	1,125	1		29.8			North	59	1		15.2		
Residential region							All						
Other	3,106	1.26	(1.16–1.37)	82.3	17.0	(15.4–18.6)	Other	385			99.0	61.5	(56.1–77.9)
North	669	1		17.7			All combined	4			1.0		
All													
Other	3,755			99.5	56.5	(51.4–63.4)							
All combined	20			0.5									
Comedo invasive							*Comedo in situ*						
Family history							Family history						
Family history	95	1.68	(1.35–2.08)	12.9	5.2	(4.4–5.9)	Family history	39	1.49	(1.06–2.07)	11.8	3.8	(2.8–4.9)
No history	642	1		87.1			No history	292	1		88.2		
Parity & age at first birth							Parity & age at first birth						
Other	724	1.36	(0.78–2.35)	98.2	25.9	(17.2–37.6)	Other	315	2.04	(1.24–3.38)	95.2	48.6	(42.6–56.8)
1: 13–20	13	1		1.8			3+: 13–20	16	1		4.8		
Socioeconomic status							Residential region						
Other	498	1.11	(0.95–1.30)	67.6	6.9	(4.4–9.5)	Other	300	2.63	(1.82–3.81)	90.6	56.2	(52.6–60.6)
Manual worker	239	1		32.4			North	31	1		9.4		
Residential region							All						
Other	631	1.60	(1.30–1.97)	85.6	32.2	(29.1–35.4)	Other	330			99.7	89.9	(88.2–100)
North	106	1		14.4			All combined	1			0.3		
All													
Other	736			99.9	62.2	(56.8–100)							
All combined	1			0.1									

For calculation of PAF, the individual variables in Tables 2 and 3 were classified dichotomously into two groups, the exposed group and the reference or unexposed group (Table 4). As nulliparous women have no age at first birth, parity and age at first birth were merged into one variable. In order to calculate a joint PAF, all the unexposed groups of the individual variables, were combined simultaneously to form the joint reference group. Socioeconomic status was excluded in the in situ analyses due to the limited number of cases in the joint reference groups, but this did not alter the remaining individual PAFs. The joint PAFs in all invasive breast carcinoma and ductal carcinoma were equal, 26.9% and 26.6% respectively, which was higher than the individual PAFs due to reproductive factors (17.9% and 16.6% respectively). The lobular and comedo morphologies had notably large joint PAFs of 56.5% and 62.2% respectively, explaining more than half of all cases. These PAFs were, however, based on very few cases in the joint reference groups. In the all in situ and the ductal in situ models, the sum of the individual PAFs were equal to the joint PAF whereas in all the other models the sum of the individual PAFs exceeded the joint PAF. The reason for the latter could be that some of the individual risk factors may cancel out. With a few exceptions, the joint PAFs and individual PAFs due to family history and reproductive factors in the in situ models exceeded those in the corresponding invasive models.

Discussion

The major strength of this study is the large number of women from the nation-wide Swedish Family-Cancer Database and the registered and unbiased information on all variables. One limitation of the data source is the lack of information on known or potential risk/protective factors such as oral contraceptive use, hormone replacement therapy, breastfeeding, menstrual history, alcohol use, obesity and mammographic screening.

In this study family history, low parity, late age at first birth and high socioeconomic status increased the risk of both invasive and in situ overall breast cancer. As the ductal morphology constitutes the majority of all cases, it is not surprising that this subtype generated similar results as the overall model. The role of low parity or nulliparity was, however, different in the invasive lobular and comedo morphologies. For these morphologies, nulliparity had RRs below unity and there were no or small insignificant elevated risks for low parous women. These findings were also observed for lobular and comedo carcinoma in situ, but the result for nulliparity was reversed. Lobular carcinoma deviated from the other morphologies regarding family history and age at first birth; having a family history was most strongly associated with in situ tumors while age at first birth had the largest impact on the invasive type.

High socioeconomic status is a well-known risk factor [12], in which education is an important component. One recent study, based on the Family-Cancer Database, showed that university graduates were more likely to be diagnosed with in situ and invasive ductal cancer as well as in situ and invasive lobular cancer compared with women completing less than 9 years of education [23]. Furthermore, the association with invasive lobular cancer was stronger than with ductal cancer [23]. These findings are in line with our present study, although the correlation between education and socioeconomic status in Sweden is moderate [24]. High socioeconomic status was, in our study, found to have the largest impact on lobular carcinoma in situ.

The PAF is a summary measure for characterizing the public health impact of an exposure on population patterns of disease. PAF is the proportion of disease cases in a population that is attributable to a particular exposure or "the fraction of all cases (exposed and unexposed) that would not have occurred if exposure had not occurred [21, 25, 26]". Assuming exposure to be causal and removable, PAF could be used to estimate the potential impact of public health interventions. In this study however, exposures are not removable, and PAF is used as an etiological measure. The joint PAF of more than one exposure can analogously be defined as the fraction of cases that would not have occurred if all the exposures were avoided. Large PAFs indicate that a large proportion of the etiology is understood at the level of the defined variable. Since PAF here is defined as the product of the expression $((RR - 1)/RR)$ and the proportion of cases in the exposed population, large PAFs can only result from a high RR and relatively common exposure or from a moderate RR and common exposure.

A number of previous studies have been conducted to examine the impact of modifiable risk factors on breast cancer. One study estimated a PAF of 9% due to hormone replacement therapy for Australian women aged 40–79 years [27] and in a meta-analysis PAF due to alcohol use in the UK was 6% [28]. Another study estimated that low β-carotene intake, high alcohol intake and low levels of physical activity together explained 33% of the cases of breast cancer in Italian women [29]. Regarding unmodifiable risk factors, previous studies have estimated general invasive PAFs due to family history in different populations with varying results from 2.5% to 17% [30–34]. To our knowledge only one study has previously estimated morphology-specific invasive and in situ PAFs due to family history [35]. However this study, which was based on an older version of the Swedish Family-Cancer Database including women 0–66 years, did not include any

other risk factors. Our findings showed similar PAFs throughout all invasive morphologies, regarding family history and reproductive factors. In these morphologies, family history accounted for the smallest PAFs (between 5.2% and 6.2%) due to the small proportion (13%) of exposed women although these women had the highest relative risks. These findings are in line with our previous study although the women belonged to another age group [35]. The broad definition of exposure due to parity and age at first child birth resulted in very large (more than 90%) exposed groups, with resulting PAFs between 16.6% and 25.9% although the corresponding RRs were moderate. In the study of Tavani et al. [31], PAF due to nulliparity and late age at first birth was estimated to 38.2% for 23–74-year old women compared with 29.5% for equally old women in the study of Madigan et al. [32]. These results are, however, not fully comparable with ours as the women belonged to another age group and the definition of late age at first birth included women of all parities. High socio-economic status held similar RRs as the reproductive factors, with the exception of comedo carcinoma, but the exposed groups were smaller (70%) giving smaller PAFs between 12.3% to 18.0% for the major morphologies and 6.9% for comedo carcinoma. These estimations are a possible result of potential risk factors correlating with socioeconomic status, such as low level of education, alcohol consumption, hormone replacement therapy, obesity, dietary habits and physical inactivity [27–29]. Higher PAFs due to high education (20.3%) and high income (18.9%) were reported in the studies of Tavani et al. [31] and Madigan et al. [32] respectively. The small to moderate PAFs due to being resident in big cities or in the more densely populated south are likewise a possible result of the potential risk factors correlating with socio-economic status stated above. These results could also be explained by different pathology classification criteria across medical regions and different access to hospital care. In the lobular morphology, the joint PAF of 56.5% suggests that the four variables explain more than a half of all cases. This figure should however, be interpreted with care as it was based on few cases in the joint reference group.

Also in the in situ models, family history accounted for the smallest individual PAFs and reproductive factors for the highest PAFs, except for comedo carcinoma in situ. The in situ PAFs were larger than or equal to the corresponding invasive ones due to family history and reproductive factors, with the exception of comedo carcinoma in situ. These results show some discrepancy with the PAFs due to family history in our previous study [35], but we would like to point out again that the women belong to another age group. Moderate and high PAFs due to residential area were observed in the specific lobular and comedo in situ morphologies with larger results in the in situ models. These two in situ morphologies also had the largest joint PAFs, but as they were based on very few cases, a meaningful interpretation is hard to make.

Acknowledgements The Family-Cancer Database was created by linking registers maintained at Statistics Sweden and the Swedish Cancer Registry and is supported by Deutsche Krebshilfe, the Swedish Cancer Society, the Swedish Council for Working Life and Social Research and EU LSHC-CT-2004-503465.

References

1. Li CI, Daling JR, Malone KE, Bernstein L, Marchbanks PA, Liff JM, Strom BL, Simon MS, Press MF, McDonald JA et al (2006) Relationship between established breast cancer risk factors and risk of seven different histologic types of invasive breast cancer. Cancer Epidemiol Biomarkers Prev 15(5):946–954
2. Ursin G, Bernstein L, Lord SJ, Karim R, Deapen D, Press MF, Daling JR, Norman SA, Liff JM, Marchbanks PA et al (2005) Reproductive factors and subtypes of breast cancer defined by hormone receptor and histology. Br J Cancer 93(3):364–371
3. Wohlfahrt J, Mouridsen H, Andersen PK, Melbye M (1999) Reproductive risk factors for breast cancer by receptor status, histology, laterality and location. Int J Cancer 81(1):49–55
4. Rosenberg LU, Magnusson C, Lindstrom E, Wedren S, Hall P, Dickman PW (2006) Menopausal hormone therapy and other breast cancer risk factors in relation to the risk of different histological subtypes of breast cancer: a case–control study. Breast Cancer Res 8(1):R11
5. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease (2001) Lancet 358(9291):1389–1399
6. Pharoah PDP, Day NE, Duffy S, Easton DF, Ponder BAJ (1997) Family history and the risk of breast cancer: a systematic review and meta-analysis. Int J Cancer 71(5):800–809
7. Negri E, Braga C, La Vecchia C, Franceschi S, Parazzini F (1997) Family history of cancer and risk of breast cancer. Int J Cancer 72(5):735–738
8. Hemminki K, Granstrom C (2002) Familial breast carcinoma risks by morphology: a nationwide epidemiologic study from Sweden. Cancer 94(11):3063–3070
9. Lambe M, Hsieh CC, Chan HW, Ekbom A, Trichopoulos D, Adami HO (1996) Parity, age at first and last birth, and risk of breast cancer: a population-based study in Sweden. Breast Cancer Res Treat 38(3):305–311
10. MacMahon B (2006) Epidemiology and the causes of breast cancer. Int J Cancer 118(10):2373–2378
11. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer (1997) Lancet 350(9084):1047–1059
12. Zografos GC, Panou M, Panou N (2004) Common risk factors of breast and ovarian cancer: recent view. Int J Gynecol Cancer 14(5):721–740
13. Li CI, Malone KE, Porter PL, Weiss NS, Tang MT, Daling JR (2003) Reproductive and anthropometric factors in relation to the risk of lobular and ductal breast carcinoma among women 65–79 years of age. Int J Cancer 107(4):647–651
14. Newcomer LM, Newcomb PA, Trentham-Dietz A, Longnecker MP, Greenberg ER (2003) Oral contraceptive use and risk of breast cancer by histologic type. Int J Cancer 106(6):961–964

15. Reeves GK, Beral V, Green J, Gathani T, Bull D (2006) Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. Lancet Oncol 7(11):910–918
16. Monninkhof EM, Elias SG, Vlems FA, van der Tweel I, Schuit AJ, Voskuil DW, van Leeuwen FE (2007) Physical activity and breast cancer: a systematic review. Epidemiology 18(1):137–157
17. Claus EB, Stowe M, Carter D (2001) Breast carcinoma in situ: risk factors and screening patterns. J Natl Cancer Inst 93(23):1811–1817
18. Center for Epidemiology. Cancer incidence in Sweden 2005 (2007) National Board of Health and Welfare, Stockholm
19. Clayton D, Schifflers E (1987a) Models for temporal variation in cancer rates. I: Age-period and age-cohort models. Stat Med 6(4):449–467
20. Clayton D, Schifflers E (1987b) Models for temporal variation in cancer rates. II: Age-period-cohort models. Stat Med 6(4):469–481
21. Miettinen OS (1974) Proportion of disease caused or prevented by a given exposure, trait or intervention. Am J Epidemiol 99(5):325–332
22. Greenland S (2004) Interval estimation by simulation as an alternative to and extension of confidence intervals. Int J Epidemiol 33(6):1389–1397
23. Hussain SK, Altieri A, Sundquist J, Hemminki K (2007) Influence of education level on breast cancer risk, survival in Sweden between 1990 and 2004. Int J Cancer
24. Geyer S, Hemstrom O, Peter R, Vagero D (2006) Education, income, and occupational class cannot be used interchangeably in social epidemiology. Empirical evidence against a common practice. J Epidemiol Community Health 60(9):804–810
25. dos Santos Silva I (1999) Cancer epidemiology: principles and methods. IARC, Lyon
26. Rothman K, Greenland S (1998) Modern epidemiology, 2nd edn. Lippincott-Raven, Philadelphia
27. Coombs NJ, Taylor R, Wilcken N, Boyages J (2005) HRT and breast cancer: impact on population risk and incidence. Eur J Cancer 41(12):1775–1781
28. Key J, Hodgson S, Omar RZ, Jensen TK, Thompson SG, Boobis AR, Davies DS, Elliott P (2006) Meta-analysis of studies of alcohol and breast cancer with consideration of the methodological issues. Cancer Causes Control 17(6):759–770
29. Mezzetti M, La Vecchia C, Decarli A, Boyle P, Talamini R, Franceschi S (1998) Population attributable risk for breast cancer: diet, nutrition, and physical exercise. J Natl Cancer Inst 90(5):389–394
30. Hemminki K, Czene K (2002) Attributable risks of familial cancer from the Family-Cancer Database. Cancer Epidemiol Biomarkers Prev 11(12):1638–1644
31. Tavani A, Braga C, La Vecchia C, Negri E, Russo A, Franceschi S (1997) Attributable risks for breast cancer in Italy: education, family history and reproductive and hormonal factors. Int J Cancer 70(2):159–163
32. Madigan MP, Ziegler RG, Benichou J, Byrne C, Hoover RN (1995) Proportion of breast cancer cases in the United States explained by well-established risk factors. J Natl Cancer Inst 87(22):1681–1685
33. Colditz GA, Willett WC, Hunter DJ, Stampfer MJ, Manson JE, Hennekens CH, Rosner BA (1993) Family history, age, and risk of breast cancer. Prospective data from the Nurses' Health Study. Jama 270(3):338–343
34. Slattery ML, Kerber RA (1993) A comprehensive evaluation of family history and breast cancer risk. The Utah Population Database. Jama 270(13):1563–1568
35. Hemminki K, Granstrom C, Czene K (2002) Attributable risks for familial breast cancer by proband status and morphology: a nationwide epidemiologic study from Sweden. Int J Cancer 100(2):214–219