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Family history and risk of pregnancy-associated breast cancer (PABC)

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Abstract The risk of breast cancer is at least two-fold increased in young women with a family history of breast cancer. Pregnancy has a dual effect on breast cancer risk; a short-term increase followed by a long-term protection. We investigated if the risk of breast cancer during and within 10 years following pregnancy is affected by a family history of breast cancer. We followed a cohort of women aged 15–44 years between 1963 and 2009 identified in Swedish population-based registers. Family history was defined as having a mother or sister with breast cancer. We estimated incidence rate ratios of breast cancer during pregnancy and time intervals up to 10 years post-delivery, with a focus on pregnancy-associated breast cancer (PABC), defined as breast cancer during pregnancy or within 2 years post-delivery. In 3,452,506 women, there were 15,548 cases of breast cancer (1208 were PABC). Compared to nulliparous women, the risk of breast cancer was decreased during pregnancy, similar during first year and increased during second year post-delivery. The pattern was similar in women with or without family history of breast cancer. A peak in risk was observed 5–6 years following the first birth regardless of family history. After a second birth, this peak was only present in women with a family history. Our results indicate that women with a family history of breast cancer do not have a different breast cancer risk during and within 10 years following pregnancy compared to women without a family history.

Keywords Pregnancy · Family history · Breast cancer · Register-based cohort · Sweden · Case-cohort

Introduction

The risk of breast cancer is at least two-fold increased in young women with a family history of breast cancer, with an even stronger influence on risk in young women where a first-degree relative was diagnosed with breast cancer at an early age (below 50 years) [1, 2]. Women with a genetic predisposition for breast cancer may be more likely to harbor pre-malignant cells at younger ages and could be particularly susceptible to physiological changes during childbearing, especially during a first pregnancy [3].

The risk of breast cancer varies substantially close to childbirth, with a decreased risk during pregnancy and an increased risk around 1 year post-delivery, possibly reflecting diagnostic delays or pregnancy-related growth promotion of pre-clinical malignancies [4]. Thus, it cannot be excluded that a family history of breast cancer may influence this risk pattern. We are only aware of one study that has included the pregnancy period in the assessment of breast cancer risk in women with a family history [5]. This study found evidence of a three-fold increased risk associated with family history both during childbearing and within 2 years following delivery, a time window commonly used to denote pregnancy-associated breast cancer (PABC).

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The effects of a pregnancy on breast cancer risk are likely to persist beyond 2 years and several investigators have observed a transiently increased risk of breast cancer with a peak around 5–10 years following delivery [6–11]. It has been proposed that breast cancers occurring during pregnancy or lactation have different biological properties from those occurring 5–10 years post-delivery [12]. At least four studies have investigated the possible role of family history in relation to breast cancer risk more than 2 years after delivery [5, 13–15]. Although the overall findings from these studies indicate that family history does not alter the transient risk pattern following childbirth, there are subgroup findings of interest. In line with a suggested important role of the first pregnancy [3], Wohlfahrt et al. [13] found some, albeit weak, evidence that the transient risk increase was restricted to uniparous women with a family history of breast cancer. However, these studies have differed in methodological approach and two studies used broad 5-year intervals which precluded a detailed assessment of the risk pattern [13, 15].

We used information available in population-based Swedish registers to investigate if the effect of pregnancy on breast cancer risk is modified by a family history of breast cancer. We restricted the analysis to pre-menopausal women with a focus on PABC and breast cancer risk up to 10 years after childbirth.

Methods

In this population-based cohort study, we linked several Swedish national population registers using the personal identity number (PIN) assigned to all Swedish residents. Within the Swedish Multi-Generation Register (MGR), which links all persons born after 1932 and alive in 1961 to their parents, we established a cohort of women aged 15–44 years and residing in Sweden between 1963 and 2009. Data retrieved from the MGR provided information on dates of live childbirths for each woman, allowing assessment of risktime periods around a delivery. Information from the Swedish Cancer Register (SCR) was individually linked to each woman using the PIN. Since 1958, the SCR records all newly diagnosed tumors in Sweden, and includes date of diagnosis and tumor location based on the International Classification of Disease (ICD) versions 7 and later. In order to create a cohort free of cancer at start of follow-up, women with a cancer diagnosis prior to age 15 were excluded.

In a subsequent step, we retrieved information on first emigration after age 15 from the Migration Register and date of death from the Cause of Death Register and the Total Population Register. Further, we obtained information on the highest achieved educational level from the Education Register.

Breast cancer and family history

Cases were defined as first occurrence of a malignant breast cancer during follow-up (ICD version 7: 170, patho-anatomical diagnosis (PAD) code: 096). By linking information in the MGR and the SCR, we were able to obtain information on family history of breast cancer in biological mothers and sisters to the women in the cohort. We defined family history as having a first-degree relative (mother or sister) with breast cancer at any age, and young familial onset as having a mother or a sister with breast cancer diagnosed before age 50 (old familial onset if both mother and sisters were diagnosed after age 50). Mean age at diagnosis was 60 years for mothers and 52 years for sisters.

Risktime and case-cohort design

Women were followed from entry to the cohort (at age 15 or in 1963) until first occurrence of breast cancer or censoring at date of diagnosis of another cancer, death, 45th birthday, first emigration, or at the end of follow-up in 2009, whichever came first. To simplify the analysis, only women who had four or fewer children were included (women with five or more children were censored 9 months prior to the fifth birth). More than 95 % of all breast cancers in the cohort occurred in women of parity less than 5. The final cohort for analysis comprised 3,452,506 women.

To enable fine adjustment for age, each woman's follow-up time was split on attained age in 1-year intervals. Similarly, calendar time was split into intervals 1963–1969, 1970–1979, 1980–1989, 1990–1999, and 2000–2009. Furthermore, the risktime of parous women was split by parity into uniparous, biparous, triparous, and quadriparous timebands. These timebands were further split by time-since-pregnancy, including the pregnancy period (defined as nine months prior to delivery date of a liveborn child) and 1-year periods following delivery (first year post-delivery, second year post-delivery, up to 10th year post-delivery, and 10+ years post-delivery). Time-since-latest-pregnancy was coded as a time-varying exposure variable: a woman who had her second pregnancy 2 years after her first delivery changed status to "pregnant" 9 months prior to her second birth, so that time-since-latest-pregnancy represented the time from the start of the second pregnancy. Parity was coded as a time-varying exposure variable in a similar way, i.e., parity status was increased by 1 at 9 months prior to delivery of an additional child (the pregnancy period contributed to the assigned parity status).

For reasons of computational efficiency due to the massive amount of time splitting, we generated a case-cohort sample from the full cohort. We randomly selected a

subcohort of 2 % of the women in the full cohort at start of follow-up, and also included all breast cancer cases occurring outside the subcohort. The total case-cohort sample included 83,800 women, of which 15,548 were cases (335 inside the subcohort, 15,213 outside the subcohort) and 68,252 were non-cases inside the subcohort. To account for the sampling in the statistical analysis, each woman's risktime was weighted according to her case-cohort sampling probability using inverse probability weighting [16]. For non-cases, the weights were calculated as one over the sampling fraction of non-cases. For cases, the weights were set to 1, since all women with breast cancer were sampled. The weighted analysis yielded inference for the full cohort which gave rise to all the cases.

Statistical methods

We estimated incidence rate ratios (IRR) with 95 % confidence intervals (CI) using weighted Poisson regression models, including the case-cohort weights in the likelihood of the model, with robust standard errors [17]. The models were adjusted for attained age (by applying a restricted cubic spline), and for attained period and education (both in categories). Since 8.7 % of the women lacked information on education, the adjusted models are based on fewer observations than the overall numbers reported in Table 1.

First, we modeled the interaction between family history and time-since-latest-pregnancy, while adjusting for age, period, and education (Tables 2, 3). The IRRs by time-since-latest-pregnancy are presented separately for women with or without family history. In addition, we also present the ratio between the IRR (with family history) and the IRR (without family history) in each interval corresponding to the log of the interaction parameter for that interval (which is a Wald test of the interaction). Second, to adjust for parity, we assessed the effect of time-since-latest-pregnancy in women having an additional birth compared to those not having that additional birth, separately for women with or without family history. This approach has been proposed previously [9, 13] and compares the risk between women of a given parity to other women with similar reproductive history except for the latest childbirth, i.e., the excess risk associated with having an additional child. Hence, we assessed the effect of family history by time-since-first-pregnancy compared to nulliparous, by time-since-second-pregnancy compared to uniparous, and by time-since-third-pregnancy compared to biparous women (Table 4). The model also included adjustment for age at first birth, which because of collinearity with time-since-latest-pregnancy and attained age was estimable only in women with two or more children. The significance level was 5 % and all tests were two-sided.

Data preparations were done in SAS (version 9.3) and the statistical modeling in Stata (version 12.1). The study was approved by the Ethical Review Board at Karolinska Institutet, Sweden.

Results

Among 3,452,506 women aged 15–44 years and residing in Sweden from 1963 to 2009, we identified 15,548 breast cancers in women with at most four children. As expected, the breast cancer incidence increased with age and calendar time (Table 1). Among women with breast cancer, the proportion with a family history of breast cancer was 14.5 %, and 4.8 % had a mother or sister with onset of disease below 50 years. Compared to women without a family history of breast cancer, women with a family history had a two-fold higher rate of breast cancer (adjusted IRR = 2.04, 95 % CI 1.92–2.16). If the woman had a relative with onset of breast cancer below 50 years, the rate was three times higher (IRR = 3.00, 95 % CI 2.70–3.34).

A total of 1208 women had PABC, while 5569 women were diagnosed with breast cancer between 2 and 10 years post-delivery. The proportion of PABC cases with a family history was 13.3 %, while 14.0 % of cases diagnosed between 2 and 10 years had a family history. Compared to nulliparous women, the rate of breast cancer was reduced during pregnancy following adjustment for age, period, and education. There was a modestly increased rate of breast cancer during the second year and 5–6 years following the most recent birth, compared to nulliparous women.

Risk during pregnancy and within 2 years post-delivery (PABC)

In women without a family history, the incidence rate of breast cancer was more than halved during pregnancy compared to nulliparous women (adjusted IRR = 0.36, 95 % CI 0.30–0.45) (Table 2). A similar pattern was observed in women with a family history (adjusted IRR = 0.39, 95 % CI 0.24–0.65; test of interaction: IRR ratio with vs without family history = 1.08; 95 % CI 0.63–1.85).

In women without a family history, there was some evidence of a lower incidence during the first year post-delivery compared to nulliparous women (IRR = 0.92, 95 % CI 0.82–1.03), while the rate was slightly increased during the second year after childbirth (IRR = 1.18, 95 % CI 1.07–1.30) (Table 2). In women with a family history, the pattern was similar (IRR = 0.78, 95 % CI 0.57–1.06 for the first year and IRR = 1.27; 0.99–1.62 for the second year, respectively). In each time window, there was no difference in IRR between women with or without family history (test of interaction: 0.85 (95 % CI

Table 1 Number of person-years and cases of breast cancer (BC) and adjusted incidence ratios (IRR) in the case-cohort sample of Swedish women aged 15–44 years between 1963 and 2009

	Person-years (weighted[a]) $N = 83,800$		BC cases $N = 15,548$		IRR[b] (95 % CI)
	Person-years	%	*N*	%	
Overall	69,260,324	100	15,548	100	
Age					
15–19	12,857,060	18.6	5	0.0	0.01 (0.00–0.02)
20–24	12,722,203	18.4	80	0.5	0.12 (0.10–0.16)
25–29	12,490,780	18.0	612	3.9	1.00 (Ref)
30–34	11,835,795	17.1	2100	13.5	3.71 (3.38–4.08)
35–39	10,399,435	15.0	4507	29.0	8.83 (8.08–9.65)
40–44	8,955,052	12.9	8244	53.0	18.3 (16.8–20.0)
Period					
1963–1969	7,692,033	11.1	242	1.6	0.46 (0.39–0.54)
1970–1979	14,802,860	21.4	2389	15.4	0.84 (0.79–0.89)
1980–1989	16,359,094	23.6	4140	26.6	0.89 (0.85–0.93)
1990–1999	15,432,020	22.3	4288	27.6	1.00 (Ref)
2000–2009	14,974,317	21.6	4489	28.9	1.06 (1.01–1.11)
Educational level					
≤9 years	13,079,815	18.9	3374	21.7	1.03 (0.97–1.10)
10–13 years	31,331,739	45.2	6930	44.6	0.95 (0.90–1.00)
Undergraduate	9,609,653	13.9	2277	14.6	1.04 (0.97–1.11)
Postgraduate	12,790,682	18.5	2780	17.9	1.00 (Ref)
Missing	2,448,435	3.5	187	1.2	
Family history of BC[c]					
No	64,530,359	93.2	13,299	85.5	1.00 (Ref)
Yes	4,729,965	6.8	2249	14.5	2.04 (1.92–2.16)
Relative's age onset <50 years	1,191,977	1.7	744	4.8	3.00 (2.70–3.34)
Relative's age onset ≥50 years	3,537,988	5.1	1505	9.7	1.76 (1.64–1.88)
Parity[d]					
0 children (nulliparous)	32,963,787	47.6	2663	17.1	1.00 (Ref)
1 child (primiparous)	11,076,683	16.0	2779	17.9	1.03 (0.97–1.10)
2 children (biparous)	17,002,969	24.5	6651	42.8	0.95 (0.90–1.00)
3 children (triparous)	6,653,399	9.6	2867	18.4	0.85 (0.80–0.91)
4 children (quadriparous)	1,563,487	2.3	588	3.8	0.68 (0.61–0.75)
Age at first birth					
Nulliparous (ever)	15,034,230	21.7	2439	15.7	1.00 (Ref)
13–24	27,393,720	39.6	6245	40.2	0.75 (0.71–0.79)
25–29	16,798,070	24.3	4389	28.2	0.95 (0.89–1.01)
30–34	7,496,936	10.8	1905	12.3	1.03 (0.96–1.11)
35–39	2,164,975	3.1	494	3.2	0.84 (0.75–0.94)
40–44	372,392	0.5	76	0.5	0.67 (0.52–0.87)
Time-since-latest-pregnancy					
Nulliparous	32,963,787	47.6	2663	17.1	1.00 (Ref)
Pregnant	3,244,045	4.7	126	0.8	0.37 (0.30–0.44)
First year	4,120,146	5.9	451	2.9	0.90 (0.81–1.00)
Second year	3,541,904	5.1	631	4.1	1.19 (1.08–1.30)
3–4 years	5,429,311	7.8	1193	7.7	1.06 (0.98–1.14)

Table 1 continued

	Person-years (weighted[a]) $N = 83,800$		BC cases $N = 15,548$		IRR[b] (95 % CI)
	Person-years	%	*N*	%	
5–6 years	4,241,251	6.1	1416	9.1	1.09 (1.02–1.17)
7–8 years	3,587,860	5.2	1451	9.3	0.99 (0.93–1.07)
9–10 years	3,103,120	4.5	1509	9.7	0.94 (0.88–1.01)
>10 years	9,028,901	13.0	6108	39.3	0.86 (0.81–0.91)

[a] Weighted person-time is an estimate of person-time in full cohort (from which the case-cohort was sampled)

[b] Adjusted for attained age, attained period, and education

[c] Mother or sister with breast cancer

[d] Parity is a time-varying covariate which counts a child from conception (9 months prior to delivery). E.g., a woman who is pregnant with her second child has parity = 2

Table 2 Number of breast cancer cases (BC) and adjusted incidence rate ratios (IRR) of BC in relation to time-since-pregnancy and by family history of breast cancer

	Without family history		With family history		IRR_{fh}/IRR_{nofh} (95 % CI)[a,b]
	BC *N*	IRR[a] (95 % CI)	BC *N*	IRR[a] (95 % CI)	
Time-since-latest-pregnancy					
Nulliparous	2218	1.00 (Ref)	380	1.00 (Ref)	1.99 (1.73–2.28)[c]
Pregnant	101	0.36 (0.30–0.45)	17	0.39 (0.24–0.65)	1.08 (0.63–1.85)
First year	383	0.92 (0.82–1.03)	51	0.78 (0.57–1.06)	0.85 (0.61–1.18)
Second year	523	1.18 (1.07–1.30)	90	1.27 (0.99–1.62)	1.07 (0.82–1.40)
3–4 years	1021	1.07 (0.99–1.16)	155	0.99 (0.80–1.22)	0.92 (0.74–1.15)
5–6 years	1193	1.09 (1.01–1.18)	204	1.11 (0.91–1.35)	1.02 (0.83–1.25)
7–8 years	1249	1.01 (0.93–1.09)	195	0.93 (0.76–1.13)	0.92 (0.75–1.13)
9–10 years	1278	0.94 (0.87–1.01)	221	0.98 (0.81–1.19)	1.05 (0.85–1.28)
>10 years	5160	0.86 (0.80–0.91)	922	0.92 (0.79–1.07)	1.08 (0.92–1.27)

fh family history, *nofh* no family history

[a] Adjusted for attained age, attained period, and education

[b] Ratio of IRR (with family history) and IRR (without family history) in each interval of time-since-pregnancy, which equals the interaction term associated with family history. CIs are Wald tests of the interaction

[c] The effect of family history among nulliparous women

0.61–1.18) during the first year; 1.07 (0.82–1.40) during the second year).

Early age at onset of the relative's breast cancer did not influence the incidence during pregnancy or the first year post-delivery differently compared to women without family history (Table 3). However, during the second year post-delivery, the increase in incidence compared to nulliparous was most pronounced among women with a familial onset below age 50 (IRR = 1.53; 95 % CI 1.02–2.28); the incidence was not increased in women with a familial onset above 50 years (IRR = 1.08, 95 % CI 0.78–1.49); and only modestly increased in women without family history (IRR = 1.18; 95 % CI 1.07–1.30).

Following stratification by parity, a reduced incidence rate during pregnancy was present after the first, second, and third pregnancy regardless of family history status (Table 4). An increased incidence rate within the second year post-delivery was present after first and second childbirth for women without a family history (IRR = 1.28, 95 % CI 1.07–1.53; IRR = 1.25, 95 % CI 1.09–1.43, respectively). For women with a family history, an increased incidence rate was only present after the second childbirth (IRR = 1.52, 95 % CI 1.08–2.12), although point estimates were slightly, but not statistically significantly, increased also after the first and third pregnancy. The IRRs for each time window were not

Table 3 Number of breast cancer cases (BC) and adjusted incidence rate ratios (IRR) of BC in relation to time-since-pregnancy and by young or old age onset of familial breast cancer

	Without family history		With family history			
			Relative's age onset <50 years		Relative's age onset ≥50 years	
	BC *N*	IRR[a] (95 % CI)	BC *N*	IRR[a] (95 % CI)	BC *N*	IRR[a] (95 % CI)
Time-since-latest-pregnancy						
Nulliparous	2218	1.00 (Ref)	127	1.00 (Ref)	253	1.00 (Ref)
Pregnant	101	0.36 (0.30–0.45)	10	0.58 (0.30–1.14)	7	0.26 (0.12–0.55)
First year	383	0.92 (0.82–1.03)	26	1.01 (0.63–1.60)	25	0.61 (0.40–0.93)
Second year	523	1.18 (1.07–1.30)	41	1.53 (1.02–2.28)	49	1.08 (0.78–1.49)
3–4 years	1021	1.07 (0.99–1.16)	61	1.05 (0.73–1.50)	94	0.93 (0.72–1.20)
5–6 years	1193	1.09 (1.01–1.18)	76	1.13 (0.80–1.60)	128	1.07 (0.85–1.36)
7–8 years	1249	1.01 (0.93–1.08)	69	0.92 (0.65–1.31)	126	0.91 (0.72–1.16)
9–10 years	1278	0.94 (0.87–1.01)	65	0.83 (0.58–1.19)	156	1.05 (0.84–1.31)
>10 years	5160	0.85 (0.80–0.91)	264	0.81 (0.60–1.08)	658	0.98 (0.82–1.17)

[a] Adjusted for attained age, attained period, and education

statistically different when comparing women with versus without family history (test of interaction).

Risk after 2 and before 10 years post-delivery

In women without a family history, the breast cancer risk was modestly and transiently increased with a peak in incidence rate 5–6 years following delivery compared to nulliparous (IRR = 1.09, 95 % CI 1.01–1.18) (Table 2). A similar transient increase in risk was observed in women with a family history (IRR = 1.11, 95 % CI 0.91–1.35 at 5–6 years post-delivery). Age at onset of familial breast cancer did not affect the shape or size of the transient risk within 10 years post-delivery (Table 3).

Stratifying by parity, the transient risk beyond 2 years post-delivery was most pronounced following the first birth with around 40 % increased incidence at 5–6 years after delivery (IRR = 1.44, 95 % CI 1.25–1.66 without family history; IRR = 1.43 (1.00–2.05) with family history) (Table 4). In women with a family history, the risk was also increased at 5–6 years following the second birth (IRR = 1.36, 95 % CI 1.07–1.72), but no transient risk increase was detected after the third birth. For women without a family history, the transient risk was much less pronounced and not significant after the second or third birth (with the possible exception of an increase at 3–4 years post-delivery following third birth). The IRRs in each time window were not significantly different in women with or without family history (test of interaction).

In a sensitivity analysis, the analysis was restricted to women at risk after 1990 or later (including 56 % of the breast cancer cases) and yielded results similar to those for the full period.

Discussion

Taken together our findings indicate that a family history of breast cancer neither modifies the risk of PABC, nor the pattern of risk up to 10 years post-delivery. The risk of breast cancer was much lower than expected during pregnancy, a finding that was consistent over family history and parity status. Further, while no increased risk of breast cancer during the first year post-delivery was observed, there was evidence of an increased risk of breast cancer during the second year post-delivery. This finding was also consistent when assessed by family history, with the possible exception of a stronger effect during the second year post-delivery in women with a family history of early age onset breast cancer.

Beyond 2 years post-delivery there was a peak in the risk around 5–6 years, which was most pronounced following the first birth with a more than 40 % increase in breast cancer incidence both in women with or without a family history. The transient risk increase was less pronounced after the second and not detectable after the third birth in women without a family history, while there was some evidence of a transient risk after the second birth in women with a family history, but not following a third birth.

This is the first study that has examined breast cancer risk by family history in narrow time windows around delivery, separating the pregnancy period from the first and second years post-delivery. In contrast to our finding of similar risk pattern for women with and without family history around delivery, Hou et al. [5] found some evidence of a risk-modifying influence of family history in women diagnosed during pregnancy and within 2 years following

Table 4 Number of breast cancer cases (BC) and adjusted incidence rate ratios (IRR) of BC in relation to time-since-pregnancy, parity, and by family history of breast cancer

	Without family history		With family history		IRR_{fh}/IRR_{nofh} (95 % CI)[a,b]
	BC *N*	IRR[a] (95 % CI)	BC *N*	IRR[a] (95 % CI)	
Time-since-first-pregnancy					
Nulliparous	2218	1.00 (Ref)	380	1.00 (Ref)	1.97 (1.72–2.27)[c]
Pregnant first child	33	0.45 (0.32–0.64)	2	0.17 (0.04–0.70)	0.38 (0.09–1.61)
First year after first child	100	0.91 (0.74–1.11)	17	0.98 (0.60–1.62)	1.08 (0.63–1.85)
Second year	133	1.28 (1.07–1.53)	19	1.13 (0.70–1.81)	0.88 (0.53–1.46)
3–4 years	180	1.06 (0.90–1.24)	27	0.95 (0.63–1.43)	0.90 (0.58–1.40)
5–6 years	231	1.44 (1.25–1.66)	39	1.43 (1.00–2.05)	1.00 (0.68–1.46)
7–8 years	227	1.31 (1.13–1.51)	38	1.26 (0.88–1.82)	0.97 (0.66–1.43)
9–10 years	196	1.04 (0.89–1.21)	32	0.99 (0.67–1.45)	0.95 (0.63–1.44)
>10 years	1276	0.97 (0.89–1.05)	191	0.81 (0.65–1.01)	0.84 (0.67–1.06)
Time-since-second-pregnancy					
Uniparous	2376	1.00 (Ref)	365	1.00 (Ref)	1.76 (1.54–2.02)[c]
Pregnant second child	37	0.31 (0.22–0.43)	10	0.63 (0.33–1.19)	2.03 (0.99–4.15)
First year after second child	171	0.95 (0.81–1.12)	20	0.82 (0.52–1.30)	0.86 (0.53–1.40)
Second year	249	1.25 (1.09–1.43)	42	1.52 (1.08–2.12)	1.21 (0.84–1.73)
3–4 years	483	1.06 (0.95–1.17)	80	1.23 (0.94–1.59)	1.16 (0.88–1.53)
5–6 years	576	1.07 (0.97–1.18)	109	1.36 (1.07–1.72)	1.27 (0.99–1.64)
7–8 years	606	0.97 (0.88–1.07)	102	1.07 (0.84–1.37)	1.11 (0.85–1.43)
9–10 years	672	0.95 (0.86–1.04)	123	1.16 (0.92–1.46)	1.22 (0.96–1.56)
>10 years	2792	0.86 (0.80–0.93)	527	1.11 (0.94–1.32)	1.29 (1.08–1.54)
Time-since-third-pregnancy					
Biparous	5586	1.00 (Ref)	1013	1.00 (Ref)	2.18 (2.00–2.38)[c]
Pregnant third child	27	0.39 (0.27–0.57)	4	0.33 (0.12–0.88)	0.84 (0.29–2.43)
First year after third child	85	0.83 (0.67–1.03)	12	0.66 (0.37–1.18)	0.80 (0.43–1.48)
Second year	117	1.04 (0.86–1.25)	25	1.25 (0.83–1.89)	1.20 (0.77–1.89)
3–4 years	294	1.14 (1.01–1.29)	42	0.89 (0.64–1.23)	0.78 (0.55–1.10)
5–6 years	311	1.03 (0.91–1.16)	38	0.69 (0.49–0.97)	0.67 (0.47–0.96)
7–8 years	344	1.02 (0.91–1.14)	44	0.73 (0.53–1.00)	0.71 (0.51–1.00)
9–10 years	334	0.95 (0.85–1.07)	55	0.92 (0.69–1.23)	0.96 (0.70–1.32)
>10 years	929	0.93 (0.85–1.01)	180	1.06 (0.87–1.29)	1.14 (0.93–1.41)

fh family history, *nofh* no family history

[a] Adjusted for attained age, attained period, education, parity, and age at first birth (time-since-first-pregnancy not adjusted for age at first birth due to collinearity)

[b] Ratio of IRR (with family history) and IRR (without family history) in each interval of time-since-pregnancy, which equals the interaction term associated with family history. CIs are Wald tests of the interaction

[c] The effect of family history among nulliparous, uniparous, and biparous women, respectively

delivery. Hou et al. also reported a higher proportion of BRCA1/BRCA2 carriers (25 %) among women with PABC, compared to women diagnosed more than 5 years post-delivery (11.5 %). The parameterization used by Hou et al. precluded detailed assessment of the shape of the transient risk increase following pregnancy.

There are several possible explanations for our finding of a lower incidence of breast cancer during pregnancy and the rebound observed shortly after delivery [4]. These include factors related to detection, such as patient's and doctor's delay, and a lower diagnostic intensity during childbearing. Other possible contributing factors are true lower (during pregnancy) or higher (post-delivery) risks, due to physiological changes associated with childbearing. Such changes include exposure to increased levels of pregnancy hormones, immunological changes, and alterations in the tissue microenvironment of the breast following post-lactation involution that may promote the

growth of pre-clinical malignant cells [18]. A lower incidence during pregnancy may also reflect under-ascertainment of cases during pregnancy due to spontaneous or induced abortions.

Our finding that family history does not modify the transient risk between 2 and 10 years post-delivery (including among uniparous women) is not in line with findings by Wohlfahrt et al. who observed a weak transient risk within 5 years post-delivery restricted to uniparous women with a family history [13]. While Wohlfahrt et al. found no increased risk following the second or higher order births, we found a possible increase after the second birth in women with family history. Albrektsen et al. reported an increased transient risk among women with a family history, but the comparison group was nulliparous women without family history [14]. Hence, the time-since-birth effect reported was a mix of time-since-birth and family history, and is likely to be primarily driven by family history which is the stronger effect of the two.

Based on a similar Swedish dataset, Hemminki et al. found no apparent effect of family history on the pattern of short-term risk following delivery [15]. However, the authors made comparisons between women of same parity and used broad 5 years post-delivery intervals limiting the possibility to examine time-since-pregnancy in detail.

Strengths of the present study included the use of one of the largest databases to date where the effect of family history on breast cancer risk around pregnancy can be investigated. The population-based setting using information from nationwide registers provided high quality data on reproductive history and family history, and a virtually complete follow-up.

Unlike earlier studies, we included the pregnancy window in the analysis since risks during pregnancy may be driven by mechanisms different than those further away from delivery. Similar to Wohlfahrt et al. [13], we compared women with the same parity and age at first birth with or without an additional childbirth. This approach is likely to better capture the effect of time-since-pregnancy than a comparison to nulliparous women which rather reflects the combined effect of time-since-pregnancy and parity [14]. Also, a comparison between women of same parity would make the comparison group too similar and precludes assessment of any risk increase attributable to an additional pregnancy [15]. In contrast to previous studies, we assessed the pregnancy window separately and thus excluded it from being counted as risktime in a previous pregnancy, which could alter estimates when comparing different parities. Also, a comparison of women with and without an additional birth, allowed for adjustment of possible carry-over effects between subsequent pregnancies.

Several limitations of the present study need to be acknowledged. Firstly, despite the large dataset at hand, the lack of power in some of the analyses hampered the possibilities to draw firm conclusions. Only about 8 % of all pre-menopausal breast cancers occurred during pregnancy or within 2 years following delivery. Corroborating earlier estimates, the proportion of breast cancer cases with a family history was 14.5 % in our cohort [1, 19]. Since no data were available on induced abortions, miscarriages, or stillbirths, only pregnancies resulting in a live birth were included in the analyses. While we were able to identify first-degree relatives using register information, we cannot exclude that some breast cancers in relatives were not captured since information in the SCR was restricted to cases identified from the start of the SCR (1958). However, adjustment for period and age should minimize cohort and period effects. A sensitivity analysis showed that the overall results were similar to those in women diagnosed after 1990.

No information was available as to whether a breast cancer case was detected by screening or not. While invitational mammography screening was broadly introduced in Sweden in the 1990s, it was not until recently all Swedish regions included women from 40 years of age in outreach screening programmes [20, 21]. Also, the data at hand did not include information on TNM stage at presentation, or BRCA1/BRCA2 status.

In conclusion, our results indicate that the risk of breast cancer during and within 10 years following pregnancy appears to be unrelated to family history of breast cancer, i.e., genetic factors or shared familial factors. Hence, this study does not support the hypothesis that a recent pregnancy increases the risk of breast cancer to a higher extent in women with family history of breast cancer.

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Ethical Review Board at Karolinska Institutet, Sweden. For this type of study formal consent is not required.

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