

Supplementary Material*

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Statistical methods supplement

Allocation of person-time

Only person-time observed during follow-up was analyzed; women entered the analysis at the age they enrolled in the cohort. For example, if a women enrolled in a study cohort at age 50 and reported having a first child at age 28, a second child at age 30, a third child at age 34, first breastfeeding at age 30, having a family history of breast cancer, and did not develop breast cancer and was censored at age 54.9, her exposure status would appear as:

Age interval	Parity indicator	Number of births	Time since most recent birth	Breastfeeding	Family history of breast cancer
50.0-<51	1	3	16.5	Parous-ever breastfed	Yes
51.0-<52	1	3	17.5	Parous-ever breastfed	Yes
52.0-<53	1	3	18.5	Parous-ever breastfed	Yes
53.0-<54	1	3	19.5	Parous-ever breastfed	Yes
54.0-<55	1	3	20.5	Parous-ever breastfed	Yes

Analysis of time-varying exposures:

Time since most recent birth (years), parity (continuous number of births, 0-10), and breastfeeding status (nulliparous, parous-never breastfed, parous-breastfed) were analyzed as time-varying exposures. When time since most recent birth was modeled as a continuous spline variable, nulliparous women were assigned the value of 0 for the time since most recent birth variable and models contained an indicator variable for parity to allow the risk at 0 years since most recent birth for parous women to differ from that for nulliparous women. Time since most recent birth was reset to 0 at each additional birth reported during follow-up. Breastfeeding was analyzed as an absorbing state (i.e. once a woman was defined as breastfeeding she did not return to a nulliparous or parous-never breastfeeding state). Family history was also an absorbing state—women transitions from no family history to having a family history at the age they first reported having a first-degree family history of breast cancer.

For example, if a nulliparous woman enrolled in a study cohort at age 25.2 and had a first child at age 28, a second child at age 30, a third child at age 34, reported first breastfeeding at age 30, reported having a family history of breast cancer at age 35, and developed breast cancer at 38 her exposure status would appear as:

Age interval	Parity indicator	Number of births	Time since most recent birth	Breastfeeding	Family history of breast cancer
25.2-<28	0	0	Nulliparous	Nulliparous	No
28.0-<29	1	1	0.5	Parous-never breastfed	No
29.0-<30	1	1	1.5	Parous-never breastfed	No
30.0-<31	1	2	0.5	Parous-ever breastfed	No
31.0-<32	1	2	1.5	Parous-ever breastfed	No
32.0-<33	1	2	2.5	Parous-ever breastfed	No
33.0-<34	1	2	3.5	Parous-ever breastfed	No
34.0-<35	1	3	0.5	Parous-ever breastfed	No
35.0-<36	1	3	1.5	Parous-ever breastfed	Yes
36.0-<37	1	3	2.5	Parous-ever breastfed	Yes
37.0-<38	1	3	3.5	Parous-ever breastfed	Yes

Frequency of updated exposure information

Each study contributed information from study enrollment and any available (at time of data delivery) follow-up rounds. The total number of questionnaires (including enrollment) with information available for each time-varying covariate is shown below:

Cohort	Births	Breastfeeding	Family history of breast cancer
Black Women's Health Study (21)	9	8	2
Campaign against Cancer and Heart Disease (25)	3	2	3
European Prospective Investigation into Cancer and Nutrition (30) †	2	1	Not available
Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (22)	1	2	2
Generations Study (33)	2	2	1
Helseundersøkelsen i Nord-Trøndelag (28)	1	Not available	Not available
Melbourne Collaborative Cohort Study (26)	2	2	2
Norwegian Women and Cancer Study (29)	2	2	2
Nurses' Health Study (27)	6	1	8
Nurses' Health Study II (23)	11	8	5
Sister Study (34)	3	3	1
Southern Community Cohort Study (32)	1	1	1
Sweden Women's Lifestyle and Health Study (31)	2	2	1
Swedish Mammography Cohort (35)	2	Not available	1
United States Radiologic Technologist Cohort (24)	2	Not available	2

Timing of updated exposure information

Adjustment factors (e.g. parity, breastfeeding) reflect status at study enrollment, and at the ages parity and breastfeeding status changed, as reported during study follow-up. We evaluated two strategies for the timing of changes to exposure status:

- a) Exposure status changes at the age of subsequent follow-up. This strategy has the advantage of minimizing the potential for immortal person-time bias based on the requirement for women to survive (i.e. not develop breast cancer) to the age when the follow-up occurred, and has the disadvantage of inaccurately assigning person-time retrospectively (but not differentially by survival status). In this setting, a woman who enrolled in the study at age 33 and said she had one child at age 30; and who later completed a follow-up questionnaire at age 40 and said she had 3 children age at ages 30, 34, and 36; and then developed breast cancer at age 44; would have her parity exposure status updated 1 time at age 40 as follows:

Age interval	Parity	Time since most recent birth
33-<34	1	3.5
34-<35	1	4.5
35-<36	1	5.5
36-<37	1	6.5
37-<38	1	7.5
38-<39	1	8.5
39-<40	1	9.5
40*-<41	3	4.5
41-<42	3	5.5
42-<43	3	6.5
43-<44	3	7.5
*Exposure status change at age 40 follow-up interview		

b) **Exposure status changes at the age of reported births (retrospectively).** This strategy has the advantage of more accurately assigning person time based on the information available, but the disadvantage of allowing for potential immortal person-time bias as person time will be more accurately assigned for women who survive during follow-up to provide additional information. Using the same example of a woman who enrolled in the study at age 33 and said she had one child at age 30; and who later completed a follow-up questionnaire at age 40 and said she had 3 children age at ages 30, 34, and 36; and then developed breast cancer at age 44; parity exposure status would be updated twice at ages 34 and 36 as follows:

Age interval	Parity	Time since most recent birth
33-<34	1	3.5
34*-<35	2	0.5
35-<36	2	1.5
36*-<37	3	0.5
37-<38	3	1.5
38-<39	3	2.5
39-<40	3	3.5
40-<41	3	4.5
41-<42	3	5.5
42-<43	3	6.5
43-<44	3	7.5
*Exposure status changes made at ages of births reported retrospectively at age 40 follow-up interview.		

Between these approaches, the overall pattern of the association was highly similar. The plot appeared to be shifted slightly upward when exposure time was assigned at the age of each birth. Therefore, we repeated analyses for cohorts with the most frequent follow-up as they would be the least sensitive to survival biases and/or inaccuracies in exposure information. The overall shape of the curve within these studies was most similar to the overall plot when exposure is assigned at the age of reported births. Therefore, our analysis prioritized the accuracy of exposure information by retrospectively assign exposure changes at each age an additional birth was reported during study follow-up, rather than the age the follow-up information was received.

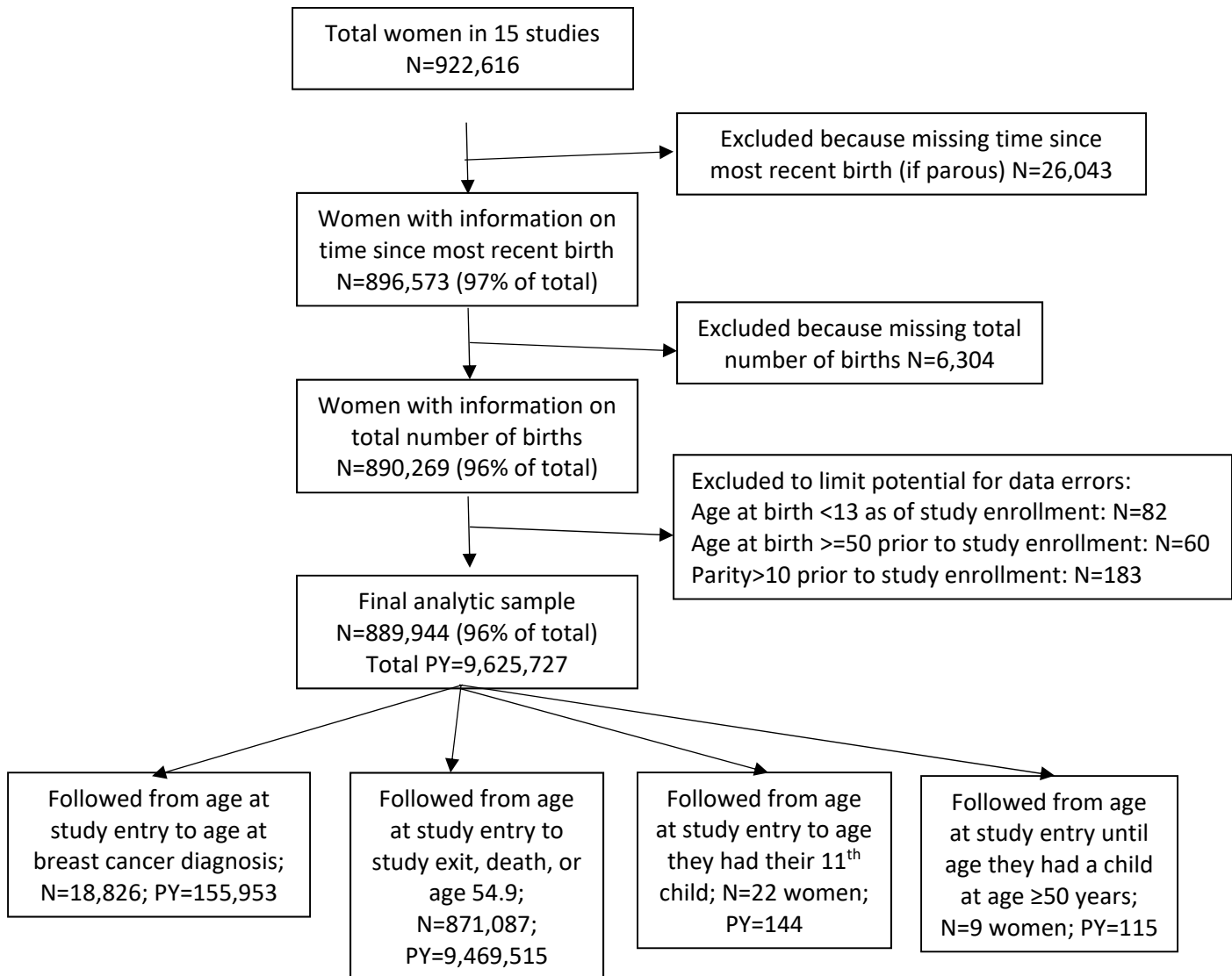
Adjusted cumulative incidence plot (Supplement Figure 4)

We used an inverse probability of exposure approach to calculate the adjusted cumulative incidence of breast cancer for the time since most recent childbirth categories (nulliparous; 0-2.9, 3-6.9, 7-14.9, 15-24.9, and 25+ years) (Cole and Hernán 2004). The time scale for the risk plots was attained age. We fit a multinomial logistic regression to estimate the probability of being in a time since most recent childbirth category given the total number of births (0-10). Stabilized weights were calculated as the inverse of the conditional probabilities of exposure, rescaled by the overall proportion of participants in each time since most recent childbirth category to reduce variability of weights across groups (49). The adjusted cumulative incidence was calculated as $1-S(t)$, where $S(t)$ is the weighted Kaplan-Meier estimator for each time since most recent birth category.

Adjusted cumulative incidence standardized to a common age interval (Supplement Figure 5)

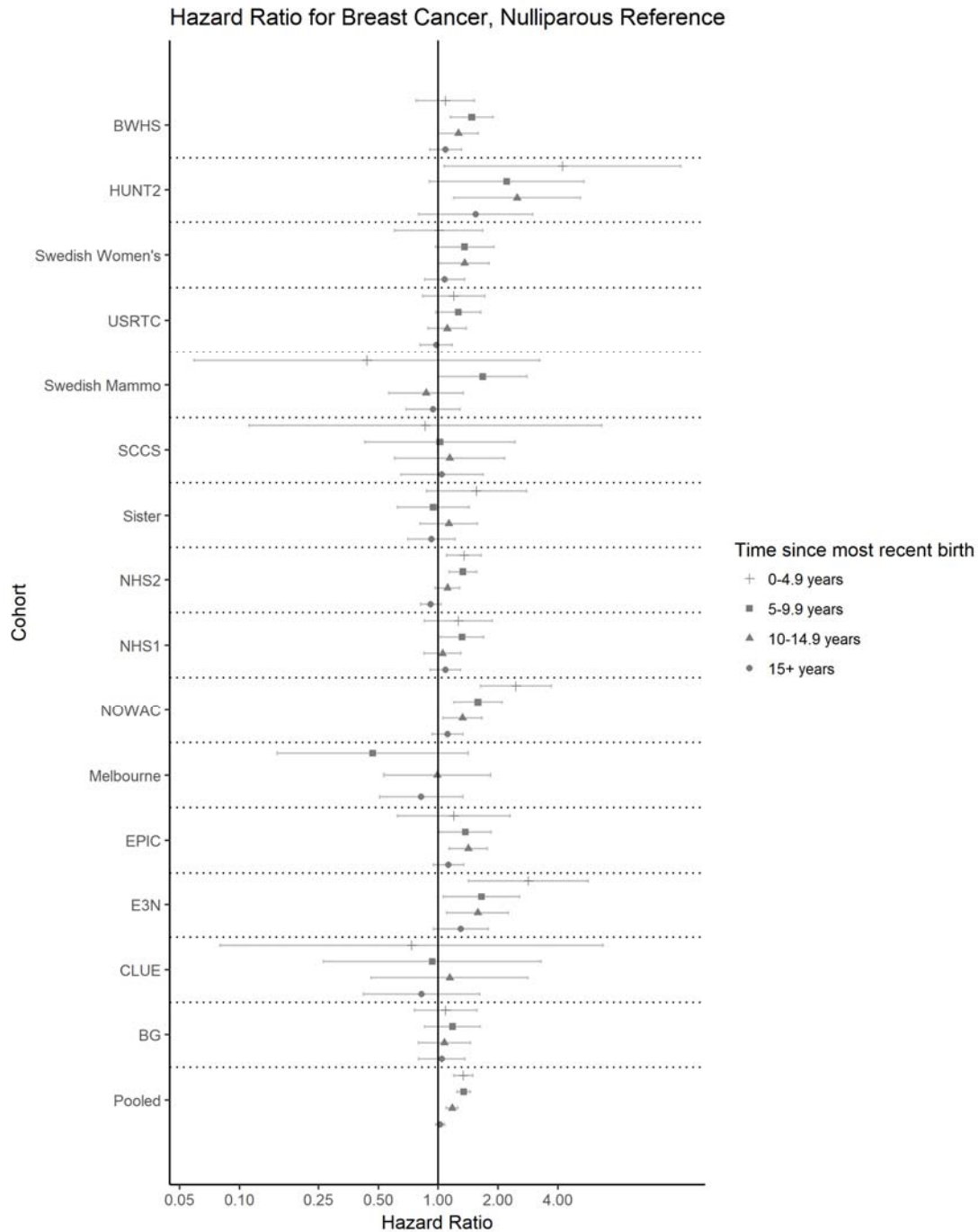
The adjusted cumulative incidence plot shown in Supplement Figure 4 provides the cumulative incidence for each exposure category by attained age. This does not allow for the direct comparison of risk between exposure groups at a given age because the cumulative incidence is additive across a longer time period for risk estimates for exposure categories that start at younger ages (e.g. 0-2.9 years since most recent birth), than for exposure categories that have initial events at older ages (e.g. 25+ years since most recent birth). Therefore, we standardized the survival probability to a common age interval where events occurred among all time since most recent birth categories. The common interval starts at age 41.5 at which age the survival probability was set to 1. The standardized survival probability was achieved by dividing the survival probability at all ages between 41.5 and 50 by the survival probability at 41.5. The standardized incidence is calculated as $1 - \text{the standardized survival probability}$. The resulting plot allows comparison of cumulative incidence across time since most recent birth categories.

Supplement Figure 1. Flowchart of exclusions from analysis based on analysis eligibility criteria and censoring during follow-up.

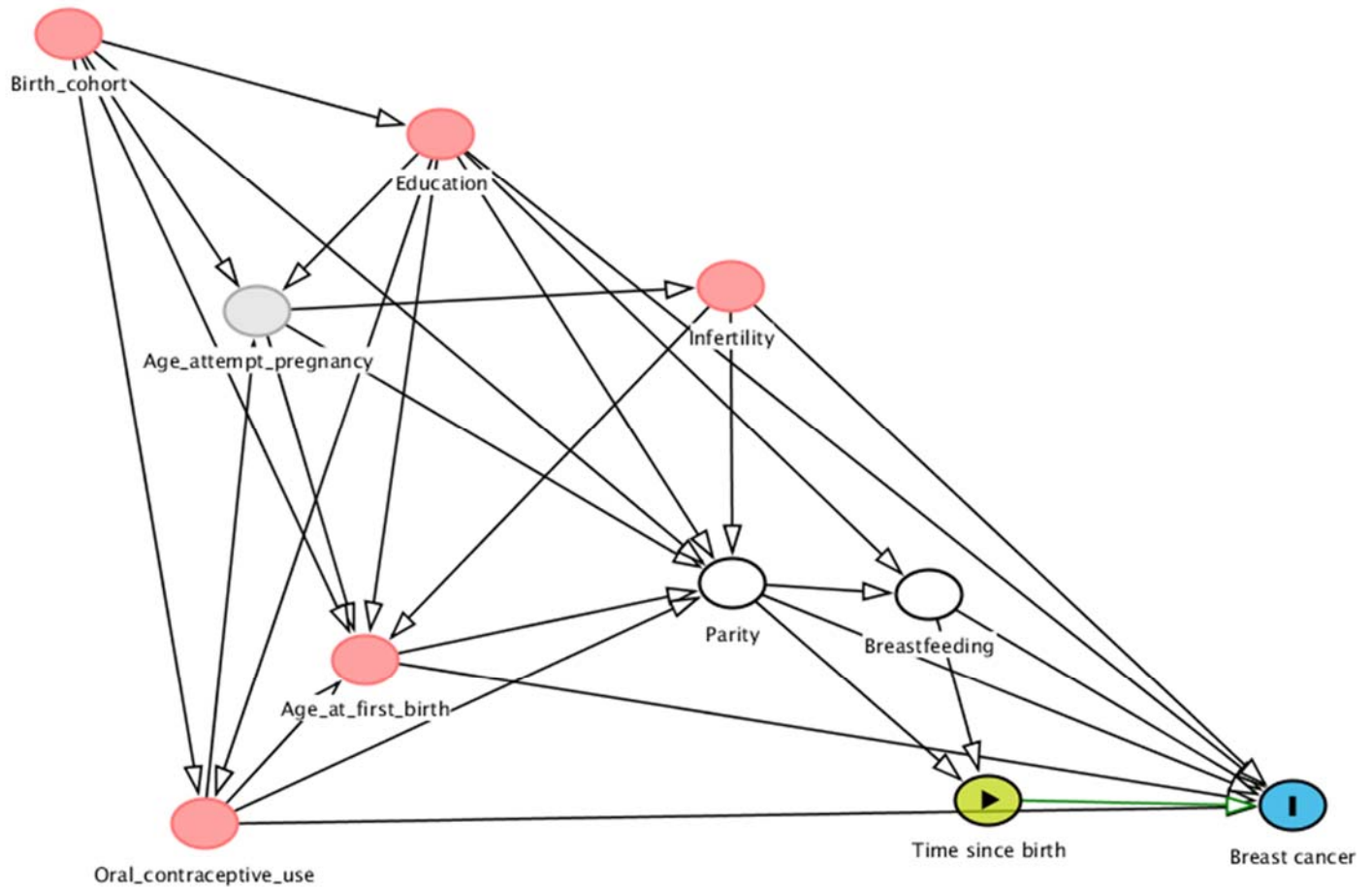


Supplement Figure 2. Forest plot of the association between time since most recent birth and breast cancer risk by study, adjusted for parity (continuous). Cochran's Q , degrees of freedom (df), p , and I^2 for each category shown below (43).

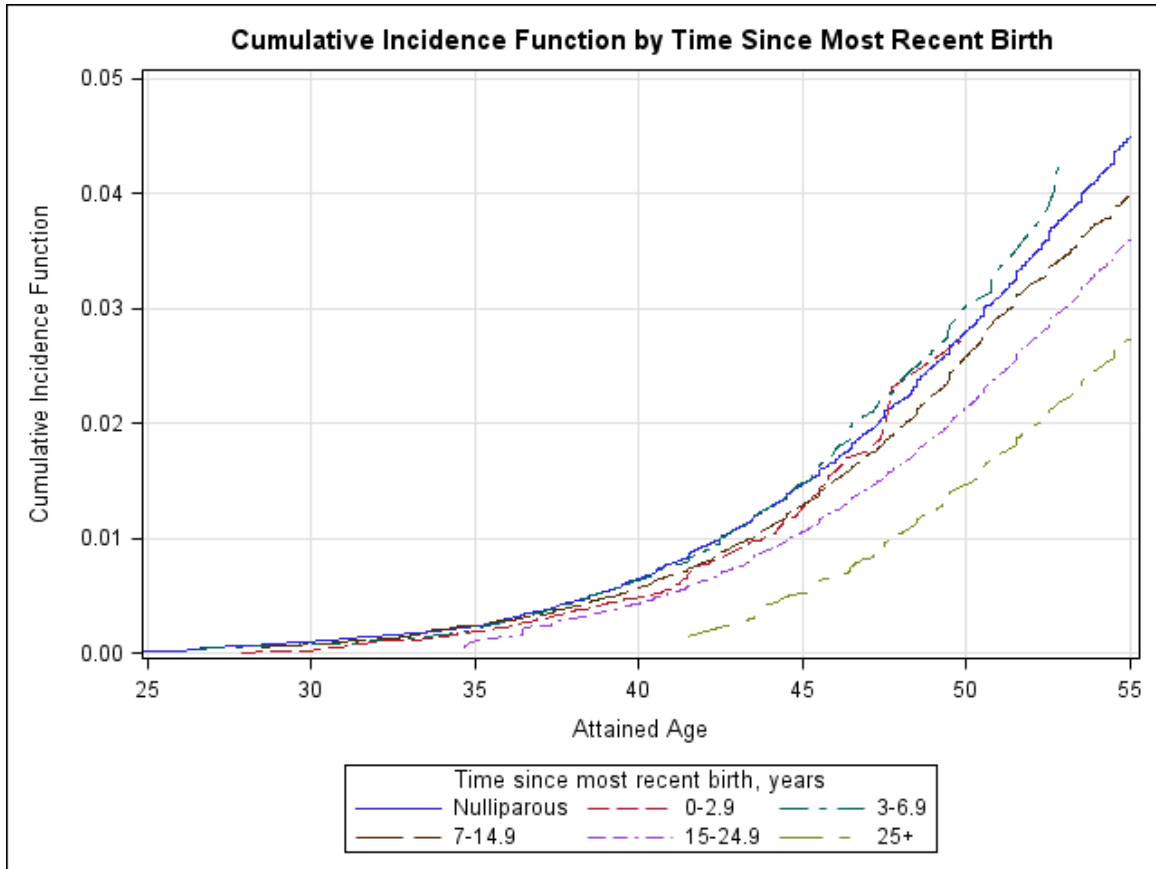
Time since birth	HR (95% CI)	Q statistic	df	P-value	I^2 (%)
0-4.9	1.36 (1.11, 1.67)	22.14	14	0.08	41.29%
5-9.9	1.34 (1.23, 1.46)	12.49	15	0.64	<0%
10-14.9	1.20 (1.10, 1.31)	16.22	15	0.37	13.68%
15+	1.03 (0.97, 1.09)	12.33	15	0.65	<0%



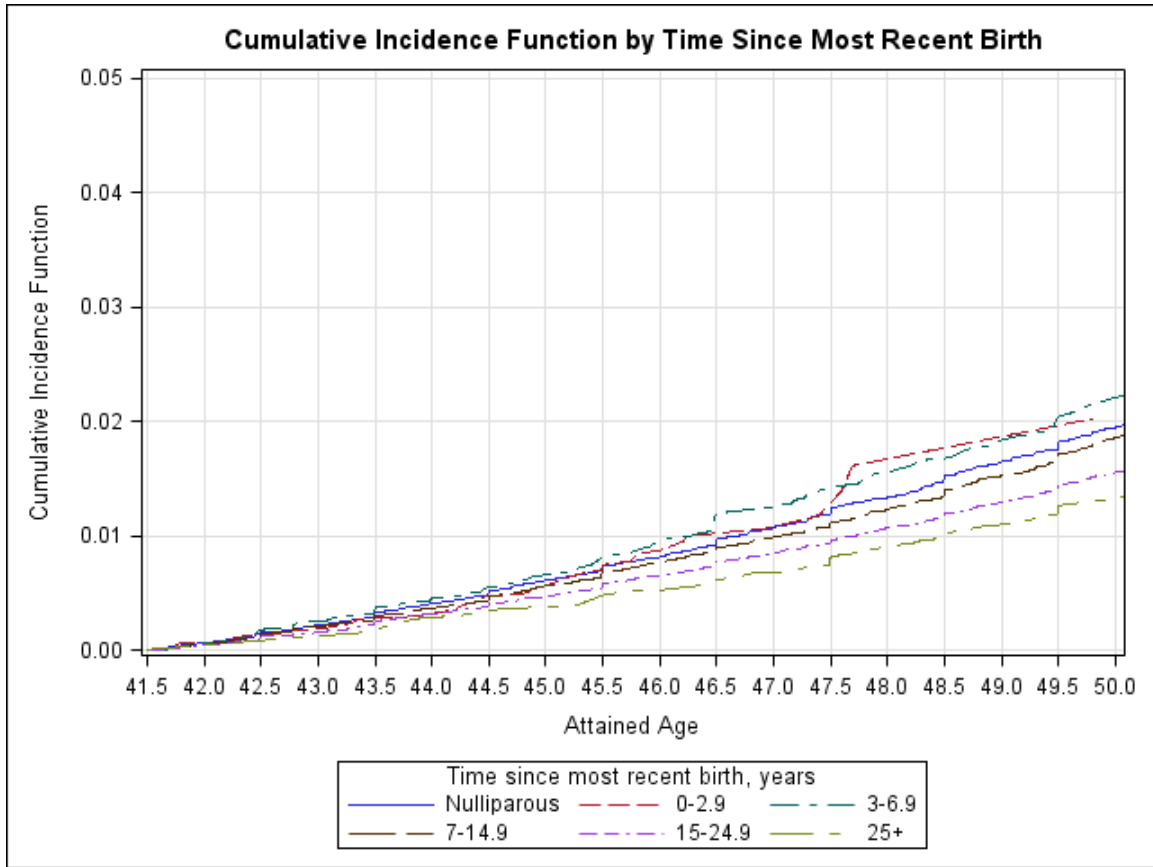
Supplement Figure 3. Directed acyclic graph drawn using DAGitty (<http://dagitty.net/>). The minimal sufficient adjustment set to estimate the total or direct effect of time since most recent birth on breast cancer risk includes adjustment for breastfeeding and parity. Pink circles indicate ancestors of exposure *and* outcome, grey circles indicate unobserved (latent) variables, white circles indicate adjusted variables, the green circle is the primary exposure, and the blue circle is the outcome. Any biasing paths would be shown in red.



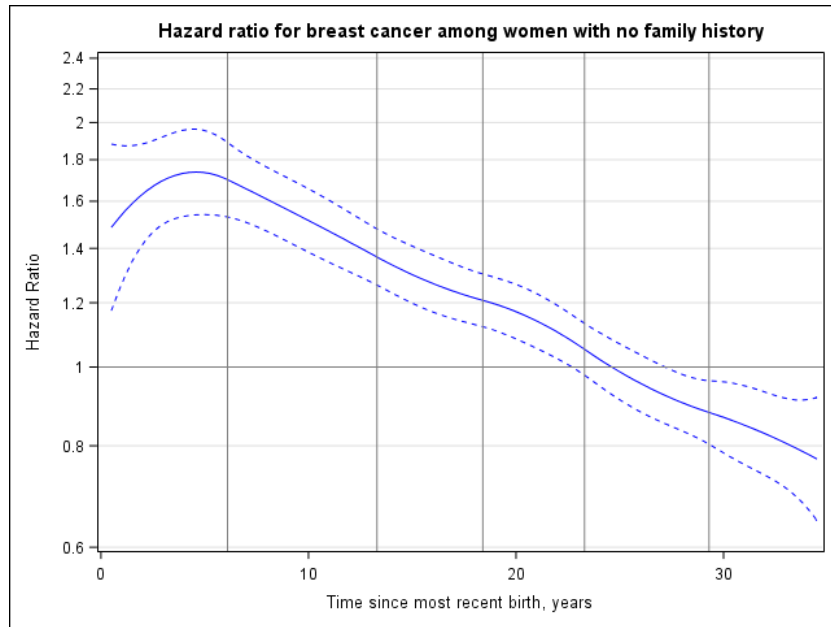
Supplement Figure 4. Cumulative incidence for breast cancer according to time since most recent birth, weighted by parity.



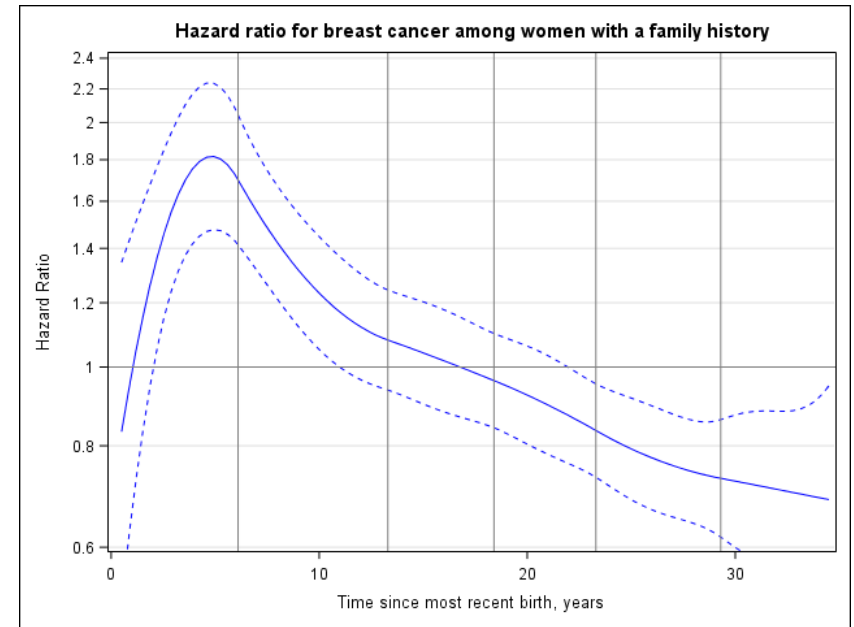
Supplement Figure 5. Cumulative incidence for breast cancer according to time since most recent birth, weighted by parity and standardized to a common age interval.



Supplement Figure 6. Hazard ratio (HR) for breast cancer risk according to years since most recent birth and stratified according to family history of breast cancer (Panels A and B). HRs are adjusted for attained age, study, and parity and nulliparous women are the reference group. The dashed curves correspond to 95% confidence intervals. The vertical lines represent the quadratic spline knots at 6.1, 13.3, 18.4, 23.3, 29.3 years after birth. Likelihood ratio tests for models with and without interaction terms for time since most recent birth and family history indicated a statistically significant interaction ($P=0.044$).

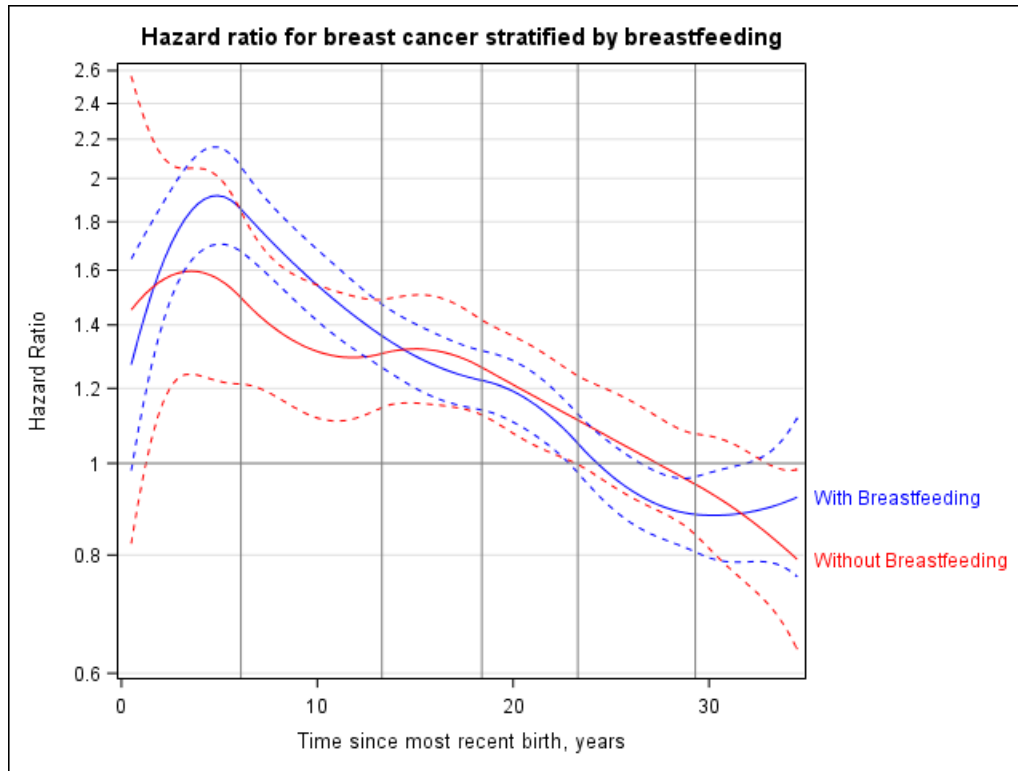


S6A. For women who did not have a family history of breast cancer, the peak HR of 1.74 (CI: 1.54, 1.96) occurred 4.6 years after last birth and the crossover occurred at 24.6 (22.9, 27.4) years before reaching a HR of 0.77 (CI: 0.65, 0.92) at 34.5 years compared with nulliparous women without a family history.

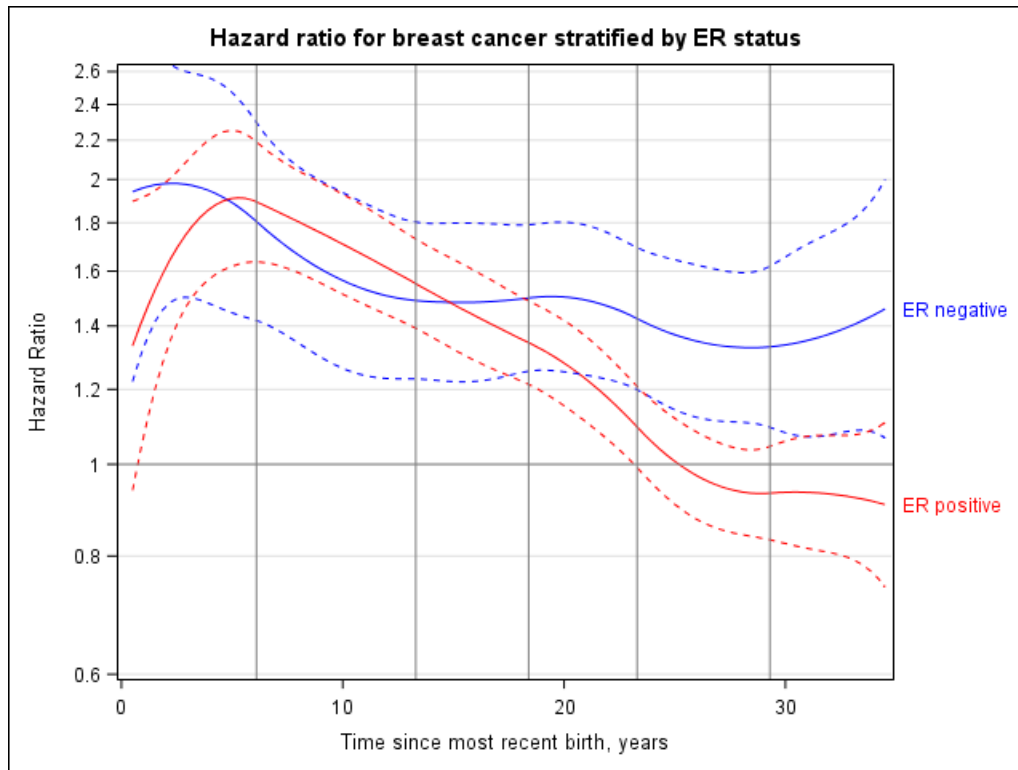


S6B. In women with a family history of breast cancer, breast cancer risk peaked at a HR of 1.82 (CI: 1.48, 2.24) at 4.9 years, crossed over 1 at 16.8 (11.0, 22.3) years, and reached its lowest observed point (HR=0.69; 95% CI: 0.50, 0.95) at 34.5 years after birth compared with nulliparous women with a family history of breast cancer.

Supplement Figure 7. Hazard ratio (HR) for breast cancer risk according to years since most recent birth and stratified by breastfeeding history. Nulliparous women are the reference group and HRs are adjusted for attained age, study, and parity. The dashed curves correspond to 95% confidence intervals. The vertical lines represent the quadratic spline knots at 6.1, 13.3, 18.4, 23.3, 29.3 years after birth. Likelihood ratio tests did not indicate a statistically significant interaction with breastfeeding ($P=0.38$). Women who breastfed had a peak HR of 1.92 (1.70, 2.16) for breast cancer at 4.9 years after last birth with a gradual cross-over to an inverse association at 24.3 years after last birth. For those who did not breastfeed, the peak HR of 1.60 (1.24, 2.05) occurred 3.6 years after last birth and the cross-over occurred at 27.4 years after last birth. As an approximation of the 95% CI for the crossover point, for women who breastfed, the lower bound crosses at 22.9 years and the upper bound crosses at 26.7 years since most recent birth. For women who did not breastfeed, the lower bound crosses at 23.3 and the upper bound crosses at 33.1 years since most recent birth.



Supplement Figure 8. Hazard ratio (HR) for risk of ER-positive and ER-negative breast cancer risk according to years since most recent birth. Nulliparous women are the reference group and HRs are adjusted for attained age, study, parity (continuous), and breastfeeding (ever/never). The dashed curves correspond to 95% confidence intervals. The vertical lines represent the quadratic spline knots at 6.1, 13.3, 18.4, 23.3, 29.3 years after birth. Interaction terms for time since most recent birth and ER status indicated a statistically significant interaction ($P < 0.001$). ER-negative breast cancer risk peaked at HR=1.98 (1.48, 2.65) and did not crossover to an inverse association during follow-up. ER-positive breast cancer risk peaked at HR=1.91 (1.63, 2.25) at 5.3 years and crossed over to an inverse association at 25.3 years after birth (lower bound of the CI crossed over null at 23.3 years).



Supplement Table 1. Cohort-specific participant characteristics at study enrollment.

<i>Cohort study</i>	<i>Cohort acronym</i>	<i>Country</i>	<i>No women <55 years</i>	<i>Enrollment years</i>	<i>Years of follow-up, Mean (SD)</i>	<i>No. incident breast cancers</i>	<i>Age at enrollment, years Mean (SD)</i>	<i>No. of Follow-up rounds including baseline</i>	<i>% Nulliparous</i>	<i>Age at first birth, years Mean (SD)</i>	<i>Age at last birth, years Mean (SD)</i>	<i>Number of births, Mean (SD)</i>
Black Women's Health Study (21)	BWHS	United States (U.S.)	51,068	1995	12.6 (5.6)	1,270	37.1(8.6)	9	37.1%	22.4 (5.1)	28.0 (6.0)	1.3 (1.3)
Campaign against Cancer and Heart Disease (25)	CLUEII	U.S.A.	4,039	1989	11.2 (5.6)	93	39.7(9.6)	6	27.5%	22.7 (4.3)	27.0 (5.1)	1.6 (1.4)
European Prospective Investigation into Cancer and Nutrition (30)*	EPIC	Europe	126,043	1991-2000	7.4 (4.1)	1,758	44.2(8.2)	1	22.8%	24.8 (4.4)	29.0 (4.9)	1.7 (1.2)
Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (22)	E3N	France	59,126	1989-1991	8.1 (4.2)	1,538	46.4(4.2)	8	3.1%	24.9 (4.0)	29.0 (4.6)	2.1 (0.9)
Generations Study (33)	GS	United Kingdom	72,050	2003-2012	6.8 (2.7)	924	39.8(9.5)	2	35.1%	27.5 (4.8)	31.3 (4.7)	1.3 (1.2)
Helseundersøkelsen i Nord-Trøndelag (28)	HUNT2	Norway	20,533	1995-1997	10.1 (4.1)	208	39.0(9.6)	1	16.4%	22.8 (3.9)	28.0 (4.8)	2.0 (1.2)
Melbourne Collaborative Cohort Study (26)	MCCS	Australia	12,020	1990-1994	7.3 (4.4)	227	47.5(4.4)	3	16.6%	24.9 (4.8)	30.1 (4.9)	2.2 (1.4)
Norwegian Women and Cancer Study (29)	NOWAC	Norway	117,607	1991-2007	9.0 (5.8)	2,123	45.7(6.0)	3	10.0%	24.0 (4.5)	29.5 (5.2)	2.1 (1.1)
Nurses' Health Study (27)	NHS	U.S.A.	114,860	1976	12.2 (7.1)	2,680	42.6(7.1)	16	6.4%	25.1 (3.3)	30.7 (4.7)	2.7 (1.6)

Nurses' Health Study II (23)	NHS II	U.S.A.	115,908	1989	18.7 (3.7)	3,758	34.8(4.7)	12	28.8%	25.5 (4.1)	30.4 (4.6)	1.5 (1.2)
Sister Study (34)	SIS	U.S.A.	24,022	2003-2009	4.7 (2.5)	678	47.9(4.9)	3	21.6%	25.9 (5.6)	30.4 (5.6)	1.7 (1.2)
Southern Community Cohort Study (32)	SCCS	U.S.A.	29,934	2002-2009	5.1 (2.4)	230	47.3(4.2)	2	11.3%	20.4 (4.8)	27.5 (6.2)	2.4 (1.6)
Sweden Women's Lifestyle and Health Study (31)	WLHS	Sweden	49,003	1991-1992	14.4 (5.3)	1,192	39.7(5.8)	2	12.4%	23.8 (4.5)	29.4 (5.2)	2.0 (1.1)
Swedish Mammography Cohort (35)	SMC	Sweden	34,049	1987-1990	8.3 (4.3)	649	46.6(4.3)	2	9.3%	23.7 (4.5)	29.0 (5.1)	2.1 (1.1)
United States Radiologic Technologist Cohort (24)	USRTC	U.S.A.	59,682	1983-1998	14.5 (5.6)	1,498	36.7(7.3)	3	30.0%	25.2 (3.7)	29.6 (4.3)	1.4 (1.3)
<i>Total</i>			<i>889,944</i>		<i>10.8 (6.4)</i>	<i>18,826</i>	<i>41.8(8.0)</i>		<i>19.0%</i>	<i>24.6 (4.5)</i>	<i>29.6 (5.1)</i>	<i>1.9 (1.3)</i>
* Data from EPIC Sweden are excluded from this analysis due to data governance rules and data from EPIC-Norway and EPIC-France because they joined the collaboration as individual studies.												

Supplement Table 2. Multivariable hazard ratio (HR) and 95% confidence intervals (CI) for the association between time since most recent birth and ER-negative breast cancer risk according to breastfeeding history .

Time since most recent birth, years	BREASTFED				NEVER BREASTFED			
	Person-years	% PY	Total cases N	All Cases HR (95% CI)*	Person-years	% PY	Total cases N	All Cases HR (95% CI)*
Nulliparous	1,402,240	21.9	381	1	1,402,240	51.2	381	1
0-2.9	261,321	4.1	43	1.55 (1.07, 2.26)	39,555	1.4	4	0.93 (0.34, 2.57)
3-4.9	204,994	3.2	38	1.47 (1.01, 2.15)	33,566	1.2	14	2.95 (1.65, 5.30)
5-9.9	701,759	11.0	159	1.41 (1.11, 1.79)	130,666	4.8	24	0.94 (0.59, 1.51)
10-14.9	1,009,851	15.8	268	1.26 (1.02, 1.55)	221,199	8.1	80	1.37 (0.99, 1.89)
15-19.9	1,180,668	18.4	369	1.23 (1.01, 1.50)	309,477	11.3	147	1.50 (1.14, 1.98)
20-24.9	1,005,833	15.7	360	1.26 (1.04, 1.52)	321,436	11.7	170	1.46 (1.13, 1.88)
25-29.9	512,452	8.0	192	1.26 (1.02, 1.56)	205,858	7.5	116	1.42 (1.09, 1.85)
30+	122,644	1.9	62	1.68 (1.25, 2.25)	74,008	2.7	40	1.26 (0.88, 1.81)
Parity								
Per birth	6,401,762	100	1,872	0.89 (0.84, 0.94)	2,738,007	100	976	0.92 (0.85, 1.00)

* Women in 12 studies with available information on breastfeeding status, adjusted for age as the time-scale, study and parity.

Supplement Table 3. Multivariable hazard ratios (HR) and 95% confidence intervals (CI) for the association between time since last birth and breast cancer risk overall, and according to estrogen receptor (ER) status, among parous women.

Time since most recent birth, years	Person-years (PY)	Total cases	HR (95% CI)*	HR (95% CI) [†]	ER+ cases	HR (95% CI) [‡]	ER-cases	HR (95% CI) [‡]
0-2.9	300,939	166	0.94 (0.79,1.12)	0.94 (0.79, 1.13)	76	0.90 (0.69, 1.17)	47	1.02 (0.71, 1.46)
3-4.9	238,650	254	1.34 (1.17,1.54)	1.35 (1.17,1.55)	115	1.26 (1.03,1.55)	52	1.25 (0.91, 1.72)
5-9.9	833,363	1,126	1.14 (1.05,1.23)	1.14 (1.06, 1.23)	532	1.09 (0.98, 1.22)	183	1.02 (0.85, 1.24)
10-14.9	1,232,769	2,264	1	1	1,150	1	348	1
15-19.9	1,492,803	3,425	0.92 (0.87,0.98)	0.92 (0.87, 0.97)	1,746	0.90 (0.83, 0.97)	516	1.00 (0.86, 1.15)
20-24.9	1,329,779	3,401	0.84 (0.79,0.89)	0.83 (0.79, 0.88)	1,681	0.77 (0.71, 0.84)	530	0.99 (0.85, 1.15)
25-29.9	719,517	1,845	0.74 (0.69,0.79)	0.73 (0.68, 0.79)	909	0.66 (0.60, 0.73)	308	0.97 (0.81, 1.16)
30+	196,923	539	0.71 (0.64,0.79)	0.71 (0.64, 0.79)	271	0.64 (0.55, 0.75)	102	1.03 (0.80, 1.33)
Parity								
Per birth	6,344,743	13,020	0.87 (0.86, 0.89)	0.88 (0.86, 0.89)	6,480	0.85 (0.83, 0.87)	2,086	0.90 (0.86, 0.94)
Breastfeeding								
Never	1,337,537	2,924	---	1		1		1
Ever	5,007,206	10,096	---	0.96 (0.92, 1.00)	6,480	1.00 (0.93, 1.06)	2,086	0.89 (0.80, 0.99)
* Parous women in 12 studies with available information on breastfeeding status; HRs are adjusted for age as the time-scale, study, and parity.								
† Parous women in 12 studies with available information on breastfeeding status; HRs adjusted for age as the time-scale, study, parity and breast-feeding status.								
‡ ER status was available for 8,566 parous women in the 12 studies with available information on breastfeeding status. HRs are adjusted for age as the time-scale, study, parity and breast-feeding status.								

Supplement Table 4. Multivariable hazard ratio (HR) and 95% confidence intervals (CI) for the association between time since most recent birth and breast cancer risk according to stage at diagnosis.

Time since most recent birth, years	Person-years	% PY	Total cases N	All Cases HR (95% CI)*	All Cases HR (95% CI)†	Stage 1-3 cases‡	HR (95% CI)‡
Nulliparous	1,408,542	18.2%	2,572	1	1	1,428	1
0-2.9	300,939	3.9%	166	1.19 (1.00, 1.41)	1.23 (1.03, 1.47)	110	1.29 (1.03,1.62)
3-4.9	238,650	3.1%	254	1.71 (1.48, 1.97)	1.77 (1.53, 2.05)	157	1.78 (1.47,2.16)
5-9.9	833,363	10.7%	1,126	1.46 (1.33, 1.59)	1.51 (1.37, 1.66)	655	1.47 (1.29,1.66)
10-14.9	1,232,769	15.9%	2,264	1.30 (1.21, 1.40)	1.35 (1.24, 1.46)	1,323	1.38 (1.24,1.53)
15-19.9	1,492,803	19.2%	3,425	1.21 (1.13, 1.30)	1.26 (1.17, 1.35)	1,958	1.31 (1.19,1.45)
20-24.9	1,329,779	17.1%	3,401	1.11 (1.04, 1.19)	1.15 (1.07, 1.23)	1,805	1.18 (1.07,1.29)
25-29.9	719,517	9.3%	1,845	0.98 (0.91, 1.05)	1.01 (0.94, 1.09)	951	1.05 (0.95,1.16)
30+	196,923	2.5%	539	0.96 (0.87, 1.06)	0.98 (0.89, 1.09)	284	1.01 (0.88,1.17)
Parity							
Per birth	7,753,322	100%	15,592	0.88 (0.86, 0.89)	0.88 (0.86, 0.90)	8,671	0.89 (0.87, 0.91)
Breastfeeding							
Never	5,007,240	64.6	10,096	---	1	5,582	1
Ever	2,746,081	35.4	5,496	---	0.95 (0.91, 1.00)	3,089	0.95 (0.90, 1.01)

* Records from 12 studies with available information on breastfeeding status; HRs are adjusted for age as the time-scale, study and parity.

† Records from 12 studies with available information on breastfeeding status; HRs are adjusted for age as the time-scale, study, parity and breast-feeding status.

‡ Stage information was available for 11,078 women in the 12 studies with available information on breastfeeding status. HRs are adjusted for age as the time-scale, study, parity and breast-feeding status.