Title

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Journal

Journal of the National Cancer Institute, 114(12)

ISSN

0027-8874

Authors

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Publication Date

2022-12-08

DOI

10.1093/jnci/djac117

Peer reviewed

OXFORD

JNCI J Natl Cancer Inst (2022) 114(12): djac117

https://doi.org/10.1093/jnci/djac117
First published online June 20, 2022
Article

Distinct Reproductive Risk Profiles for Intrinsic-Like Breast Cancer Subtypes: Pooled Analysis of Population-Based Studies

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Received: September 21, 2021; **Revised:** March 22, 2022; **Accepted:** May 3, 2022

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Abstract

Background: Reproductive factors have been shown to be differentially associated with risk of estrogen receptor (ER)-positive and ER-negative breast cancer. However, their associations with intrinsic-like subtypes are less clear. **Methods:** Analyses included up to 23 353 cases and 71 072 controls pooled from 31 population-based case-control or cohort studies in the Breast Cancer Association Consortium across 16 countries on 4 continents. Polytomous logistic regression was used to estimate the association between reproductive factors and risk of breast cancer by intrinsic-like subtypes (luminal A-like, luminal B-like, luminal B-HER2–like, HER2-enriched–like, and triple-negative breast cancer) and by invasiveness. All statistical tests were 2-sided. **Results:** Compared with nulliparous women, parous women had a lower risk of luminal A-like, luminal B-like, luminal B-HER2–like, and HER2-enriched–like disease. This association was apparent only after approximately 10 years since last birth and became stronger with increasing time (odds ratio [OR] = 0.59, 95% confidence interval [CI] = 0.49 to 0.71; and OR = 0.36, 95% CI = 0.28 to 0.46 for multiparous women with luminal A-like tumors 20 to less than 25 years after last birth and 45 to less than 50 years after last birth, respectively). In contrast, parous women had a higher risk of triple-negative breast cancer right after their last birth (for multiparous women: OR = 3.12, 95% CI = 2.02 to 4.83) that was attenuated with time but persisted for decades (OR = 1.03, 95% CI = 0.79 to 1.34, for multiparous women 25 to less than 30 years after last birth). Older age at first birth ($P_{heterogeneity} < .001$ for triple-negative compared with luminal A-like breast cancer) and breastfeeding ($P_{heterogeneity} < .001$ for triple-negative compared with luminal A-like breast cancer) were associated with lower risk of triple-negative breast cancer but not with other disease subtypes. Younger age at menarche was associated with higher risk of all subtypes; older age at menopause was associated with higher risk of luminal A-like but not triple-negative breast cancer. Associations for in situ tumors were similar to luminal A-like. **Conclusions:** This large and comprehensive study demonstrates a distinct reproductive risk factor profile for triple-negative breast cancer compared with other subtypes, with implications for the understanding of disease etiology and risk prediction.

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Reproductive factors such as parity, age at first birth, and breastfeeding are established breast cancer risk factors (1). Although there is strong evidence for differential associations by estrogen receptor (ER) status of the tumor (2,3), associations with risk of intrinsic-like breast cancer subtypes defined by the cross-classification of ER, progesterone receptor (PR), HER2 status, and grade are unclear (4,5).

Parity and younger age at first birth are associated with lower risk for developing ER-positive or luminal tumors (2,4-9), but this protection does not seem to extend to ER-negative or triple-negative tumors (2,4-7,10). Studies investigating time since last birth have shown a transient increase in breast cancer risk associated with childbirth followed by long-term protection (11-14). More recent studies evaluating subtypes suggest the transient increased risk to last less than 10 years for ER-positive tumors (15) but persist 25 or more years after last birth for ER-negative tumors (8,16). Breastfeeding seems to be most often associated with a decreased risk of breast cancer, although this is not entirely consistent, especially for ER-negative or triple-negative tumors (4,5,9,10,17). A lower breast cancer risk associated with older age at menarche and younger age at menopause is most consistent for ER-positive or luminal tumors (2,4,6,7,10,18). Effect modification by age of associations between reproductive risk factors and risk of breast cancer subtypes has been reported with conflicting results (6,8,19,20).

Elucidating these relationships between reproductive risk factors and breast cancer subtypes as well as invasiveness helps delineate the etiologic heterogeneity of breast cancer as well as informs the development of subtype-specific risk prediction. To this end, we pooled data from 31 population-based studies to evaluate primarily risk of invasive intrinsic-like subtypes and secondarily risk of invasiveness (ER-positive, ER-negative) and in situ tumors associated with reproductive history. We also aimed to assess whether associations differ by age.

Methods

Study Sample

Thirty-seven population-based case-control or cohort studies from the Breast Cancer Association Consortium were eligible for inclusion in the analysis. Following exclusions shown in Supplementary Figure 1 (available online), the final study sample included 47 350 cases with known invasiveness (including 23 353 with known intrinsic-like subtype), and 71 072 controls from 13 prospective cohort studies and 18 case-control studies. Studies included (21-50) are described in Supplementary Table 1 (available online). All individual studies were approved by their institutional review boards and/or medical ethical committees. Written informed consent was obtained from all study participants.

Information about breast cancer risk factors and breast cancer tumor markers is described in the Supplementary Methods (available online).

Statistical Analyses

Polytomous logistic regression was used to fit multivariable models to estimate case-control odds ratios (ORs) and 95% confidence intervals (CIs) for associations with breast cancer subtypes for time since last birth (in twelve 5-year categories) in women with different numbers of births (nulliparous [reference (ref.)], 1, 2, ≥3 births), and the following additional variables: age at first birth (<20 years [ref.], 20 to <25 years, 25 to <30 years, ≥30 years), breastfeeding duration (0 months [ref.], >0-6 months, >6-12 months, >12-24 months, >24 months), age at menarche (≥15 years [ref.], 14 years, 13 years, ≥12 years), and age at menopause (<50 years [ref.], 50-54 years, ≥54 years, premenopausal). We fit 2 models with all the covariates: one for intrinsic-like subtypes and the other for ER-positive, ER-negative, or in situ subtypes as the outcome variables. All analyses were further adjusted for age at reference date (date of diagnosis for cases, date of interview for controls) and study. A category for missing values was included for covariates as well as intrinsic-like subtypes.

Heterogeneity in breast cancer risk factor associations between subtypes was evaluated using polytomous logistic regression for case-case comparisons with luminal A-like as reference for intrinsic-like subtypes and ER-positive as reference for ER-positive, ER-negative, or in situ subtypes, including the same variables as the case-control models. Categorical variables were modelled as ordinal variables using the median value for each category. Both case-control and case-case models included the same covariates as described above and the same number of cases. Case-case analyses excluded controls and used luminal A-like or ER-positive as the comparison group.

As secondary analyses and for comparison with previous reports evaluating reproductive factors by subtypes, we also fit a series of multivariable polytomous logistic regression models similar to those described above excluding time since last birth. These simpler models were also used to evaluate potential effect modification by age on these associations between risk factors and intrinsic-like subtypes. Multivariable associations were stratified by 5-year age categories based on reference age. Heterogeneity in estimates across 5-year age categories was tested using the likelihood-ratio test comparing models with and without an interaction term between age and each reproductive risk factor of interest as ordinal variables using the median value for each category ($P_{interaction}$). Each subtype was tested separately in a case-control comparison in models fit excluding cases of the other subtypes.

We performed analyses to assess heterogeneity of risk estimates by study design using a likelihood-ratio test comparing models with and without an interaction term between study design and each reproductive risk factor of interest as ordinal variables using the median value for each category ($P_{interaction}$). To further test for heterogeneity by study, analyses were additionally performed by study and the results meta-analyzed using a random-effects model. To explore the robustness of our results, risk associations were assessed excluding studies with missing data in more than 90% of cases or controls on time since last birth or breastfeeding duration.

All statistical tests were 2-sided; statistical significance was considered with P values less than .05. Statistical analyses were performed using SAS, version 9.4 (SAS Institute). All figures were created using Wolfram Mathematica, version 12.1 (Wolfram Research).

Results

The distributions of risk factors according to intrinsic-like subtype are shown in Table 1.

Associations Between Reproductive Risk Factors and Invasive Intrinsic-Like Subtypes: Case-Control Analyses

Compared with nulliparous women, uniparous women were at decreased risk of breast cancer approximately 30 years after birth (Figure 1; Table 2 for odds ratios with 95% confidence intervals). Biparous and multiparous women had a higher risk of luminal A-like than nulliparous women within approximately 10 years since their last birth before crossing over to having lower risk. There was evidence of a stronger risk decrease for multiparous (OR = 0.59, 95% CI = 0.49 to 0.71; and OR = 0.36, 95% CI = 0.28 to 0.46 for 20 to <25 and 45 to <50 years after last birth, respectively) than biparous women. For triple-negative disease, parous women were at higher risk than nulliparous women, particularly within 5 years after last birth (OR = 3.12, 95% CI = 2.02 to 4.83) for multiparous women, with this relative increase in risk attenuating over time but persisting until 25 to less than 30 years after last birth (OR = 1.03, 95% CI = 0.79 to 1.34), with no crossover in risk.

Heterogeneity of Associations Between Reproductive Risk Factors and Invasive Intrinsic-Like Subtypes: Case-Case Analyses

Tests for odds ratio heterogeneity by subtypes based on case-case comparisons showed statistically significant differences in the odds ratios for time since last birth for triple-negative compared with luminal A-like breast cancer among uniparous ($P_{heterogeneity} < .001$), biparous ($P_{heterogeneity} < .001$), and multiparous women ($P_{heterogeneity} = .01$). Odds ratios for all the other subtypes were not statistically significantly different from that for luminal A-like tumors (Supplementary Figure 2 and Supplementary Table 3, available online). Increasing age at first birth was associated with decreasing risk of triple-negative breast cancer, but not other intrinsic-like subtypes ($P_{heterogeneity} < .001$ for triple-negative compared with luminal A-like). Breastfeeding for more than 6 months was associated with

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Table 1. Characteristics of risk factors among 23 353 breast cancer patients by intrinsic-like subtype and 71 072 controls from 31 population-based studies

Characteristics	Controls[a] No. (%)	Luminal A-like[b] No. (%)	Luminal B-like No. (%)	Luminal B-HER2–like No. (%)	HER2-enriched–like No. (%)	Triple-negative No. (%)
Total	71 072 (100)	12 405 (53.1)	2832 (12.1)	3088 (13.2)	1498 (6.4)	3530 (15.1)
Age at diagnosis, median (IQR)	58.0 (15.0)	62.0 (15.0)	60.0 (17.0)	59.0 (16.0)	57.0 (16.0)	56.0 (18.0)
Parity						
Nulliparous	8630 (12.1)	1750 (14.1)	429 (15.2)	479 (15.5)	212 (14.2)	394 (11.2)
1	11 246 (15.8)	2153 (17.4)	504 (17.8)	622 (20.1)	367 (24.5)	703 (19.9)
2	26 564 (37.4)	4464 (36.0)	1003 (35.4)	1063 (34.4)	495 (33.0)	1288 (36.5)
≥3	23 966 (33.7)	3933 (31.7)	867 (30.6)	890 (28.8)	408 (27.2)	1122 (31.8)
Missing	666 (0.9)	105 (0.9)	29 (1.0)	34 (1.1)	16 (1.1)	23 (0.7)
Time since last birth						
0 to <5 y	888 (1.3)	92 (0.7)	41 (1.5)	68 (2.2)	42 (2.8)	104 (3.0)
5 to <10 y	1279 (1.8)	228 (1.8)	71 (2.5)	94 (3.0)	45 (3.0)	133 (3.8)
10 to <15 y	2022 (2.9)	409 (3.3)	121 (4.2)	129 (4.2)	70 (4.7)	175 (5.0)
15 to <20 y	2987 (4.2)	591 (4.8)	134 (4.7)	169 (5.5)	91 (6.1)	269 (7.6)
20 to <25 y	4042 (5.7)	723 (5.8)	160 (5.7)	199 (6.4)	137 (9.2)	329 (9.3)
25 to <30 y	4441 (6.3)	865 (7.0)	183 (6.5)	238 (7.7)	138 (9.2)	303 (8.6)
30 to <35 y	4795 (6.8)	1119 (9.0)	231 (8.2)	292 (9.5)	142 (9.5)	314 (8.9)
35 to <40 y	4892 (6.9)	1135 (9.2)	250 (8.8)	244 (7.9)	114 (7.6)	264 (7.5)
40 to <45 y	2937 (4.1)	793 (6.4)	165 (5.8)	158 (5.1)	82 (5.5)	189 (5.4)
45 to <50 y	1361 (1.9)	418 (3.4)	83 (2.9)	75 (2.4)	33 (2.2)	77 (2.2)
50 to <55 y	408 (0.6)	149 (1.2)	34 (1.2)	29 (0.9)	10 (0.7)	33 (0.9)
≥55 y	87 (0.1)	65 (0.5)	16 (0.6)	8 (0.3)	7 (0.5)	8 (0.2)
Missing	32 303 (45.5)	4068 (32.8)	915 (32.3)	906 (29.3)	375 (25.0)	938 (26.6)
Age at first full-term birth						
<20 y	6508 (9.2)	1295 (10.4)	311 (11.0)	299 (9.7)	178 (11.9)	578 (16.4)
20 to <25 y	23 178 (32.6)	4124 (33.2)	910 (32.1)	946 (30.6)	469 (31.3)	1231 (34.9)
25 to <30 y	18 563 (26.1)	3144 (25.3)	677 (23.9)	806 (26.1)	387 (25.8)	816 (23.1)
≥30 y	9609 (13.5)	1678 (13.5)	394 (13.9)	409 (13.2)	199 (13.3)	361 (10.2)
Missing	4584 (6.5)	414 (3.3)	111 (3.9)	149 (4.8)	53 (3.5)	150 (4.3)
Breastfeeding duration						
0 mo	7031 (9.9)	1826 (14.7)	469 (16.6)	469 (15.2)	252 (16.8)	839 (23.8)
>0 to 6 m	10 954 (15.4)	2528 (20.4)	559 (19.7)	702 (22.7)	311 (20.8)	739 (20.9)
>6 to 12 m	5625 (7.9)	1150 (9.3)	259 (9.2)	274 (8.9)	142 (9.5)	291 (8.2)
>12 to 24 m	4280 (6.0)	1013 (8.2)	219 (7.7)	224 (7.3)	91 (6.1)	232 (6.6)
>24 m	2374 (3.3)	500 (4.0)	101 (3.6)	102 (3.3)	46 (3.1)	129 (3.7)
Missing	32 178 (45.3)	3638 (29.3)	796 (28.1)	838 (27.1)	444 (29.6)	906 (25.7)
Age at menarche						
≤12 y	23 572 (33.2)	4469 (36.0)	1075 (38.0)	1106 (35.8)	510 (34.1)	1427 (40.4)
13 y	18 005 (25.3)	3406 (27.5)	742 (26.2)	799 (25.9)	385 (25.7)	880 (24.9)
14 y	13 151 (18.5)	2093 (16.9)	475 (16.8)	518 (16.8)	265 (17.7)	549 (15.6)
≥15 y	12 041 (16.9)	1971 (15.9)	431 (15.2)	504 (16.3)	288 (19.2)	548 (15.5)
Missing	4303 (6.1)	466 (3.8)	109 (3.9)	161 (5.2)	50 (3.3)	126 (3.8)
Age at menopause						
<50	19 399 (27.3)	4157 (33.5)	941 (33.2)	998 (32.3)	491 (32.8)	1144 (32.4)
50 to <54 y	13 647 (19.2)	3179 (25.6)	617 (21.8)	638 (20.7)	342 (22.8)	656 (18.6)
≥54 y	5863 (8.3)	1490 (12.0)	276 (9.8)	337 (10.9)	147 (9.8)	281 (8.0)
Missing	10 496 (14.8)	989 (8.0)	245 (8.65)	219 (7.1)	80 (5.3)	256 (7.3)

[a]Control patients in population-based studies were randomly selected from the same source population as the case patients and recruited during the same period of time. ER = estrogen receptor; IQR = interquartile range; PR = progesterone receptor.

[b]Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1 and 2), luminal B-like (ER-positive or PR-positive, HER2-negative, grade 3), luminal B-HER2–like (ER-positive or PR-positive, HER2-positive, any grade), HER2-enriched–like (ER-negative, PR-negative, HER2-positive, any grade), and triple-negative (ER-negative, PR-negative, HER2-negative, any grade).

lower risk of triple-negative breast cancer compared with no breastfeeding in parous women, but not other disease subtypes ($P_{heterogeneity} < .001$ for triple-negative compared with luminal A-like). Older age at menarche was inversely associated with risk of all subtypes, with strongest associations for luminal A-like ($P_{heterogeneity} > .17$). Older age at menopause was statistically significantly associated with a modest increase in risk of luminal A-like, luminal B-HER2–like, and HER2-enriched–like breast cancer, but not luminal B-like or triple-negative breast cancer. However, the test for odds ratio heterogeneity by subtype was not statistically significant ($P_{heterogeneity} > .24$). These case-case analyses further demonstrate that evidence for etiological

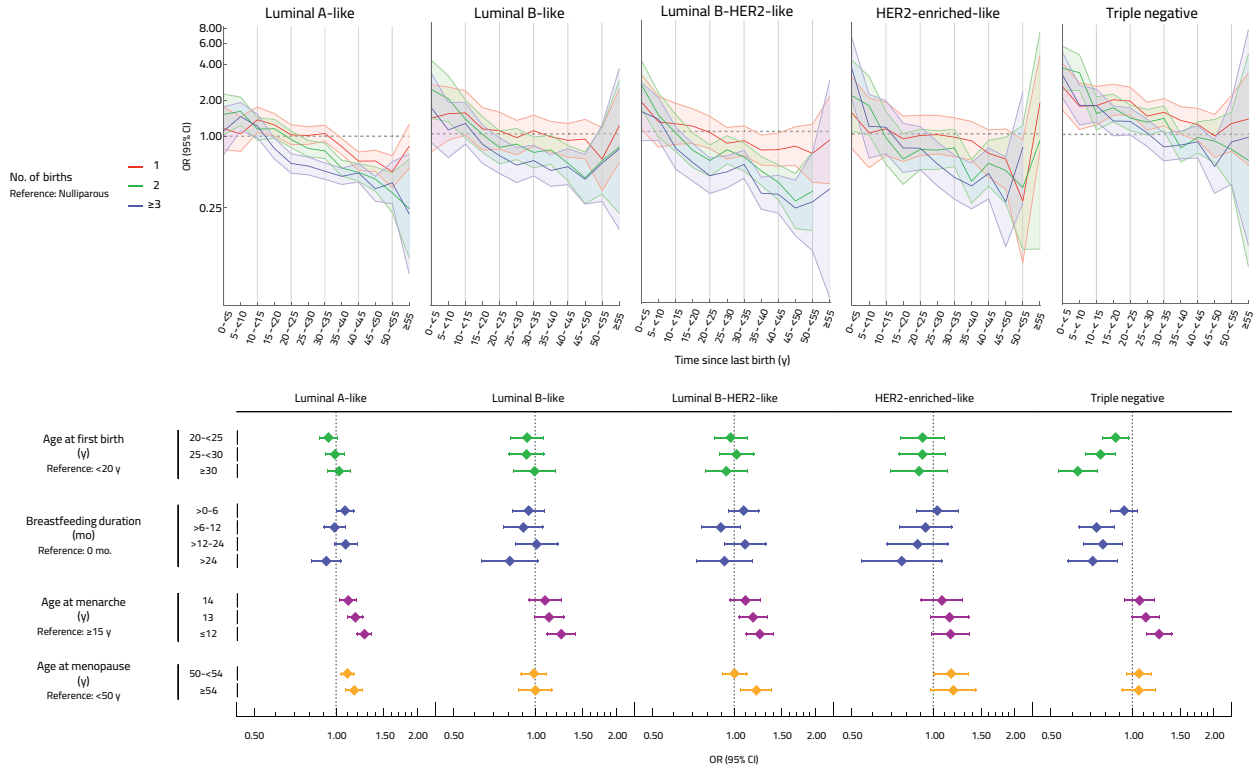

Figure 1. Odds ratios (ORs) and 95% confidence intervals (CIs) for case-control analyses of associations between reproductive factors (time since last birth by number of births, age at first birth, breastfeeding duration, age at menarche, and age at menopause) and intrinsic-like subtypes. The multivariable model was also adjusted for reference age (age at diagnosis for cases, age at interview for controls) and study. The **error bars** in the **bottom panel** represent the 95% confidence intervals.

heterogeneity was strongest for luminal A-like vs triple-negative tumors.

Associations Between Reproductive Risk Factors and Intrinsic-Like Subtypes Stratified by Age

Age modified the associations of number of births ($P_{interaction}$ = .009) (Figure 2; Supplementary Table 4, available online), age at first birth ($P_{interaction}$ < .001) (Supplementary Figure 3 and Supplementary Table 5, available online), and breastfeeding duration ($P_{interaction}$ = .01) (Supplementary Figure 4 and Supplementary Table 6, available online) with risk of luminal A-like disease. Risk associations were strongest for younger women in their 40s and attenuated with increasing age. In contrast, younger age at menarche was associated with higher risk of triple-negative breast cancer, particularly for younger women ($P_{interaction}$ = .002) (Supplementary Figure 5 and Supplementary Table 7, available online). There was no evidence that other associations between reproductive risk factors, including age at menopause (Supplementary Figure 6 and Supplementary Table 8, available online) and intrinsic-like subtypes, were modified by age.

Associations Between Reproductive Risk Factors and Invasiveness (ER Status and in Situ)

For comparability with previous reports, we also evaluated associations by ER status and in situ disease (for case-control comparisons: Figure 3, Supplementary Table 9, available online; for case-case comparisons: Supplementary Figure 7 and Supplementary Table 10, available online). Overall, reproductive risk factor associations with risk of in situ and invasive ER-positive breast cancer were like those observed for luminal-like subtypes. Associations for invasive ER-negative tumors were like those we reported for triple-negative tumors, whereas associations for invasive ER-positive were more similar to those for luminal-like tumors. A notable finding was that breastfeeding for more than 6 months was associated with a decreased risk for ER-negative disease, but a longer breastfeeding duration of more than 24 months was necessary for a similar decrease in risk for ER-positive and in situ disease.

Associations Between Reproductive Risk Factors Excluding Time Since Last Birth and Invasive Intrinsic-Like Subtypes as Well as Invasiveness

Parity was associated with decreased risk of all intrinsic subtypes except triple-negative breast cancer, for which there was an increased risk becoming weaker with additional births (Supplementary Figure 8 and Supplementary Table 11, available online). Increasing age at first birth also showed differential associations, with increasing risk of luminal A-like but decreasing risk of triple-negative breast cancer. Associations between other risk factors and intrinsic-like subtypes were like those from the model fit with time since last birth. Likewise, tests for odds ratio heterogeneity by subtypes based on case-case comparisons were like those from the model that included time since last birth (Supplementary Figure 9 and Supplementary Table 12, available online).

In case-control comparisons, associations between risk factors and risk of ER-positive, ER-negative, or in situ tumors were in line with those from the model fit with time since last birth (Supplementary Figure 10 and Supplementary Table 13,

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Table 2. Odds ratios and 95% confidence intervals for case-control analyses[a] of associations between reproductive factors (time since last birth by number of births, age at first birth, breastfeeding duration, age at menarche, and age at menopause) and intrinsic-like subtypes

		Intrinsic-like breast cancer subtype[b]									
		Luminal A-like		Luminal B-like		Luminal B-HER2–like		HER2-enriched–like		Triple-negative	
Risk factor	Controls	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
Time since last birth, y											
Nulliparous	8630	1750	1.00 (Ref.)	429	1.00 (Ref.)	479	1.00 (Ref.)	212	1.00 (Ref.)	394	1.00 (Ref.)
1 birth											
0 to <5	381	31	1.16 (0.77 to 1.75)	12	1.34 (0.71 to 2.55)	21	1.75 (1.04 to 2.95)	12	1.49 (0.75 to 2.94)	31	2.50 (1.59 to 3.92)
5 < 10	474	49	1.04 (0.75 to 1.46)	21	1.47 (0.88 to 2.44)	24	1.20 (0.74 to 1.94)	12	1.02 (0.52 to 1.98)	28	1.72 (1.10 to 2.70)
10 < 15	755	107	1.37 (1.07 to 1.76)	33	1.49 (0.98 to 2.27)	41	1.16 (0.78 to 1.71)	25	1.10 (0.66 to 1.82)	44	1.74 (1.20 to 2.52)
15 < 20	1125	151	1.25 (1.01 to 1.55)	34	1.10 (0.73 to 1.65)	66	1.10 (0.79 to 1.54)	42	0.91 (0.59 to 1.40)	83	1.95 (1.45 to 2.63)
20 < 25	1387	192	1.03 (0.85 to 1.25)	47	1.06 (0.74 to 1.51)	77	0.98 (0.72 to 1.33)	57	0.97 (0.66 to 1.43)	105	1.90 (1.45 to 2.49)
25 < 30	1427	274	1.01 (0.86 to 1.20)	56	0.93 (0.67 to 1.29)	72	0.80 (0.59 to 1.08)	56	0.98 (0.68 to 1.42)	92	1.42 (1.09 to 1.86)
30 < 35	1504	368	1.06 (0.90 to 1.23)	76	1.06 (0.79 to 1.43)	84	0.84 (0.63 to 1.11)	51	0.94 (0.65 to 1.36)	94	1.53 (1.18 to 1.99)
35 < 40	1564	369	0.82 (0.70 to 0.96)	79	0.95 (0.71 to 1.27)	81	0.70 (0.53 to 0.93)	50	0.87 (0.60 to 1.26)	88	1.31 (1.00 to 1.71)
40 < 45	1073	241	0.63 (0.52 to 0.74)	60	0.88 (0.64 to 1.22)	62	0.71 (0.52 to 0.97)	28	0.69 (0.44 to 1.08)	60	1.21 (0.89 to 1.65)
45 < 50	615	169	0.62 (0.50 to 0.76)	40	0.91 (0.62 to 1.32)	41	0.76 (0.52 to 1.09)	15	0.62 (0.35 to 1.10)	29	0.97 (0.64 to 1.47)
50 < 55	203	68	0.50 (0.37 to 0.69)	13	0.62 (0.34 to 1.13)	16	0.66 (0.38 to 1.14)	3	0.28 (0.09 to 0.89)	17	1.23 (0.72 to 2.11)
≥55	54	55	0.82 (0.54 to 1.26)	11	1.16 (0.58 to 2.34)	7	0.85 (0.37 to 1.94)	6	1.79 (0.72 to 4.44)	6	1.34 (0.55 to 3.26)
2 births											
0 to <5	264	37	1.53 (1.03 to 2.26)	18	2.33 (1.34 to 4.06)	30	2.43 (1.53 to 3.85)	12	2.07 (1.05 to 4.06)	39	3.59 (2.35 to 5.47)
5 < 10	393	90	1.62 (1.23 to 2.13)	32	1.95 (1.26 to 3.02)	34	1.36 (0.89 to 2.08)	19	1.71 (0.98 to 2.99)	64	3.28 (2.33 to 4.63)
10 < 15	697	164	1.15 (0.93 to 1.42)	50	1.32 (0.92 to 1.91)	54	0.97 (0.68 to 1.38)	23	0.92 (0.56 to 1.53)	64	1.50 (1.09 to 2.07)
15 < 20	967	271	1.16 (0.97 to 1.38)	57	0.99 (0.70 to 1.39)	59	0.70 (0.50 to 0.97)	24	0.62 (0.38 to 1.01)	108	1.67 (1.28 to 2.18)
20 < 25	1461	340	0.94 (0.80 to 1.10)	64	0.77 (0.56 to 1.06)	74	0.57 (0.43 to 0.77)	45	0.74 (0.50 to 1.09)	124	1.37 (1.07 to 1.76)
25 < 30	1610	341	0.79 (0.67 to 0.92)	75	0.82 (0.61 to 1.11)	101	0.70 (0.54 to 0.92)	49	0.73 (0.51 to 1.06)	115	1.27 (0.99 to 1.62)
30 < 35	1680	420	0.75 (0.65 to 0.88)	77	0.70 (0.52 to 0.94)	106	0.61 (0.47 to 0.80)	58	0.76 (0.54 to 1.09)	132	1.36 (1.07 to 1.73)
35 < 40	1725	397	0.54 (0.46 to 0.63)	98	0.74 (0.56 to 0.97)	96	0.47 (0.36 to 0.62)	34	0.40 (0.27 to 0.61)	82	0.77 (0.59 to 1.02)
40 < 45	997	279	0.50 (0.42 to 0.59)	53	0.57 (0.41 to 0.80)	53	0.38 (0.27 to 0.53)	31	0.57 (0.37 to 0.88)	67	0.94 (0.70 to 1.27)
45 < 50	379	127	0.44 (0.35 to 0.55)	20	0.43 (0.26 to 0.71)	17	0.27 (0.16 to 0.45)	12	0.50 (0.26 to 0.94)	30	0.88 (0.58 to 1.33)
50 < 55	117	41	0.34 (0.23 to 0.49)	12	0.60 (0.32 to 1.13)	8	0.32 (0.15 to 0.68)	3	0.36 (0.11 to 1.17)	9	0.75 (0.37 to 1.53)
≥55	20	6	0.25 (0.10 to 0.64)	3	0.78 (0.22 to 2.74)	0	Not calculated	1	0.88 (0.11 to 6.93)	1	0.61 (0.08 to 4.69)
≥3 births											
0 to <5	243	24	1.11 (0.70 to 1.76)	11	1.65 (0.85 to 3.19)	17	1.46 (0.84 to 2.53)	18	3.45 (1.93 to 6.18)	34	3.12 (2.02 to 4.83)
5 < 10	412	89	1.46 (1.11 to 1.92)	18	1.08 (0.64 to 1.82)	36	1.26 (0.84 to 1.90)	14	1.15 (0.63 to 2.12)	41	1.75 (1.20 to 2.57)
10 < 15	570	138	1.21 (0.97 to 1.52)	37	1.22 (0.82 to 1.81)	34	0.73 (0.49 to 1.09)	22	1.13 (0.68 to 1.87)	67	1.74 (1.27 to 2.39)
15 < 20	895	169	0.79 (0.65 to 0.96)	43	0.82 (0.57 to 1.18)	44	0.55 (0.39 to 0.79)	25	0.76 (0.48 to 1.22)	78	1.30 (0.97 to 1.73)
20 < 25	1194	191	0.59 (0.49 to 0.71)	49	0.66 (0.47 to 0.93)	48	0.43 (0.31 to 0.60)	35	0.76 (0.50 to 1.15)	100	1.29 (0.99 to 1.67)
25 < 30	1404	250	0.56 (0.47 to 0.67)	52	0.55 (0.40 to 0.77)	65	0.46 (0.34 to 0.63)	33	0.56 (0.37 to 0.86)	96	1.03 (0.79 to 1.34)
30 < 35	1611	331	0.51 (0.43 to 0.60)	78	0.60 (0.45 to 0.80)	102	0.53 (0.41 to 0.70)	33	0.44 (0.29 to 0.66)	88	0.78 (0.60 to 1.03)
35 < 40	1603	369	0.46 (0.39 to 0.54)	73	0.50 (0.37 to 0.67)	67	0.31 (0.23 to 0.42)	30	0.37 (0.24 to 0.57)	94	0.82 (0.62 to 1.07)
40 < 45	867	273	0.49 (0.41 to 0.59)	52	0.53 (0.38 to 0.75)	43	0.30 (0.21 to 0.43)	23	0.47 (0.29 to 0.77)	62	0.87 (0.63 to 1.18)
45 < 50	367	122	0.36 (0.28 to 0.46)	23	0.42 (0.26 to 0.67)	17	0.23 (0.14 to 0.39)	6	0.27 (0.12 to 0.64)	18	0.54 (0.32 to 0.90)
50 < 55	88	40	0.41 (0.27 to 0.61)	9	0.57 (0.28 to 1.18)	5	0.26 (0.10 to 0.67)	4	0.77 (0.27 to 2.21)	7	0.86 (0.38 to 1.95)
≥55	13	4	0.22 (0.07 to 0.71)	2	0.75 (0.16 to 3.45)	1	0.33 (0.04 to 2.63)	0	Not calculated	1	0.94 (0.12 to 7.51)

(continued)

Table 2. (continued)

		Intrinsic-like breast cancer subtype[b]									
		Luminal A-like		Luminal B-like		Luminal B-HER2–like		HER2-enriched–like		Triple-negative	
Risk factor	Controls	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
Age at first birth,[c] y											
<20	6508	1295	1.00 (Ref.)	311	1.00 (Ref.)	299	1.00 (Ref.)	178	1.00 (Ref.)	578	1.00 (Ref.)
20 to <25	23 178	4124	0.94 (0.87 to 1.01)	910	0.93 (0.81 to 1.07)	946	0.97 (0.85 to 1.12)	469	0.91 (0.76 to 1.10)	1231	0.87 (0.78 to 0.97)
25 to <30	18 563	3144	0.99 (0.92 to 1.07)	677	0.93 (0.80 to 1.08)	806	1.02 (0.88 to 1.18)	387	0.91 (0.75 to 1.11)	816	0.76 (0.67 to 0.87)
≥30	9609	1678	1.03 (0.93 to 1.13)	394	1.00 (0.83 to 1.19)	409	0.94 (0.78 to 1.12)	199	0.89 (0.70 to 1.13)	361	0.63 (0.54 to 0.74)
Breastfeeding duration,[c] mo											
0	7031	1826	1.00 (Ref.)	469	1.00 (Ref.)	469	1.00 (Ref.)	252	1.00 (Ref.)	839	1.00 (Ref.)
>0-6	10 954	2528	1.08 (1.00 to 1.16)	559	0.95 (0.83 to 1.08)	702	1.08 (0.95 to 1.23)	311	1.04 (0.87 to 1.24)	739	0.93 (0.83 to 1.04)
>6-12	5625	1150	0.99 (0.90 to 1.08)	259	0.91 (0.77 to 1.07)	274	0.89 (0.76 to 1.05)	142	0.94 (0.75 to 1.17)	291	0.74 (0.64 to 0.86)
>12-24	4280	1013	1.08 (0.98 to 1.19)	219	1.01 (0.85 to 1.21)	224	1.10 (0.92 to 1.31)	91	0.88 (0.68 to 1.13)	232	0.78 (0.66 to 0.92)
>24	2374	500	0.92 (0.81 to 1.04)	101	0.81 (0.64 to 1.02)	102	0.92 (0.73 to 1.17)	46	0.77 (0.55 to 1.08)	129	0.72 (0.58 to 0.88)
Age at menarche, y											
≥15	12 041	1971	1.00 (Ref.)	431	1.00 (Ref.)	504	1.00 (Ref.)	288	1.00 (Ref.)	548	1.00 (Ref.)
14	13 151	2093	1.11 (1.03 to 1.19)	475	1.09 (0.95 to 1.25)	518	1.10 (0.97 to 1.25)	265	1.08 (0.91 to 1.28)	549	1.06 (0.94 to 1.21)
13	18 005	3406	1.18 (1.10 to 1.26)	742	1.13 (0.99 to 1.27)	799	1.17 (1.04 to 1.32)	385	1.15 (0.98 to 1.35)	880	1.12 (1.00 to 1.26)
≤12	23 572	4469	1.27 (1.20 to 1.35)	1075	1.25 (1.11 to 1.41)	1106	1.24 (1.11 to 1.39)	510	1.16 (0.99 to 1.36)	1427	1.26 (1.13 to 1.40)
Age at menopause, y											
<50	19 399	4157	1.00 (Ref.)	941	1.00 (Ref.)	998	1.00 (Ref.)	491	1.00 (Ref.)	1144	1.00 (Ref.)
50 to <54	13 647	3179	1.10 (1.04 to 1.16)	617	0.99 (0.89 to 1.10)	638	1.00 (0.90 to 1.11)	342	1.16 (1.01 to 1.34)	656	1.06 (0.96 to 1.17)
≥54	5863	1490	1.17 (1.09 to 1.25)	276	1.00 (0.87 to 1.15)	337	1.21 (1.06 to 1.38)	147	1.19 (0.98 to 1.44)	281	1.06 (0.92 to 1.21)

[a]The multivariable model was additionally adjusted for reference age (age at diagnosis for cases, age at interview for controls) and study. CI = confidence interval; ER = estrogen receptor; OR = odds ratio; PR = progesterone receptor.

[b]Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1 and 2), luminal B-like (ER-positive or PR-positive, HER2-negative, grade 3), luminal B-HER2–like (ER-positive or PR-positive, HER2-positive, any grade), HER2-enriched-like (ER-negative, PR-negative, HER2-positive, any grade), and triple-negative (ER-negative, PR-negative, HER2-negative, any grade).

[c]Among parous women.

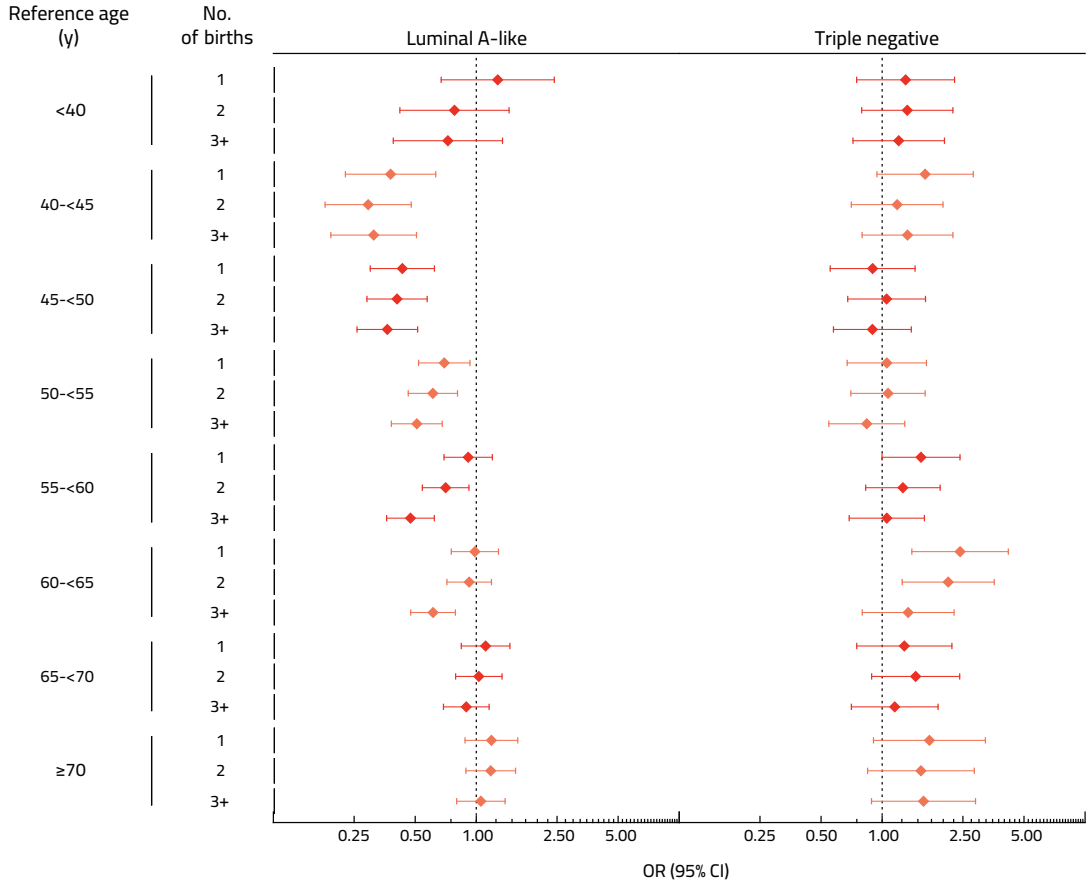

Figure 2. Odds ratios (ORs) and 95% confidence intervals (CIs) for case-control analyses of association between number of births and luminal A-like and triple-negative tumors according to reference age in 5-year categories (age at diagnosis for cases, age at interview for controls). The multivariable model was also adjusted for study. The **error bars** represent the 95% confidence intervals.

available online). Tests for odds ratio heterogeneity by invasiveness and in situ based on case-case comparisons (Supplementary Figure 11 and Supplementary Table 14, available online) were similar to those from the model fit with time since last birth in that there were differences in the odds ratios for number of births ($P_{heterogeneity} < .001$), age at first birth ($P_{heterogeneity} = .009$), and breastfeeding duration ($P_{heterogeneity} < .001$) for ER-negative compared with ER-positive disease. Odds ratios for age at menarche for in situ disease were also different from those for ER-positive disease ($P_{heterogeneity} = .002$).

Sensitivity Analyses

There was no evidence for heterogeneity by study design for associations between reproductive risk factors and intrinsic-like subtypes ($P_{heterogeneity} > .08$) except for age at menopause ($P_{heterogeneity} = .001$) (Supplementary Figures 12-19, available online). Excluding studies that had missing data on time since last birth or breastfeeding duration in more than 90% of cases or controls yielded substantially unchanged results (Supplementary Figure 20, available online).

Discussion

This report provides the strongest evidence to date for differential associations between reproductive risk factors and breast cancer subtypes as well as precise relative risk estimates for subtype-specific associations. Risk factor associations for triple-negative tumors were most distinct from other tumor subtypes. A key strength of this report is the large sample size, approximately 3-5 times larger than previously published reports (8,15,16), and wide range of exposures that allowed us to considerably expand on previous reports. Most notably, we investigated associations of time since last birth for women with different numbers of births on risk of breast cancer subtypes while accounting for other reproductive risk factors.

We provide confirmatory evidence and additional insights for several subtype-specific risk factor associations. Earlier age at first birth and increasing number of births have been consistently associated with a lower risk for ER-positive disease (5,6,8,18,51,52). The association with ER-negative disease has been less clear, with studies suggesting no association (5,18,51,52) or a higher risk (6,8,51). Additionally, reports have shown a transient increase in breast cancer risk after a recent childbirth that reverts to a long-term protection (8,11,13-16). A pooled analysis of premenopausal women of European descent showed that this transient increase was limited to ER-positive tumors, whereas the increased risk persisted for ER-negative tumors up to 35 years after birth (16). We confirmed these patterns of risk associations with data that spanned beyond 55 years after last birth. Compared with nulliparous women, parous women are at transient increased risk of all intrinsic-like subtypes, peaking between 5 and 15 years after last birth for

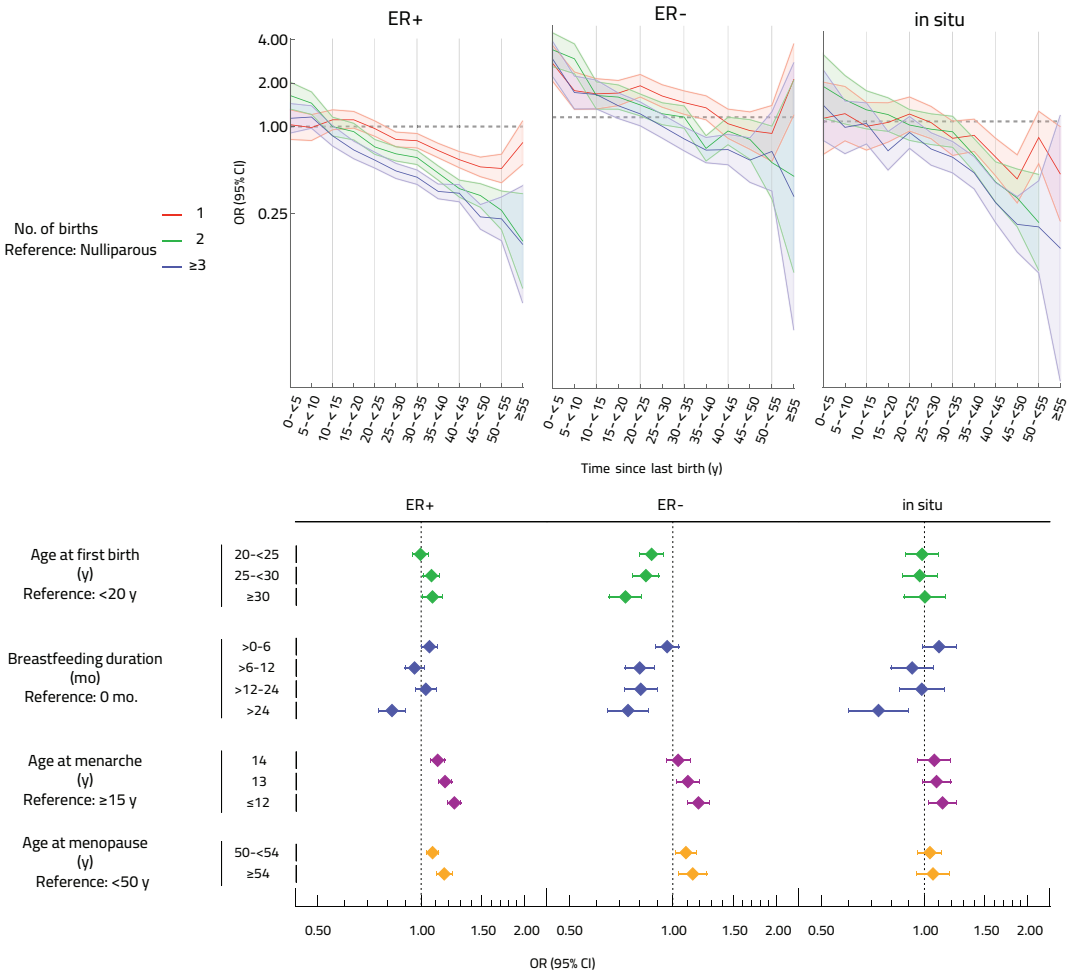

Figure 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for case-control analyses of associations between reproductive factors (time since last birth by number of births, age at first full-term birth, breastfeeding duration, age at menarche, and age at menopause) and estrogen receptor subtypes and in situ tumors. The multivariable model was also adjusted for reference age (age at diagnosis for cases, age at interview for controls) and study. The **error bars** in the **bottom panel** represent the 95% confidence intervals.

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luminal-like tumors and lasting approximately 10 years for biparous and multiparous women and 20 years for uniparous women before risk decrease. Risk of triple-negative breast cancer after childbirth peaked immediately until less than 5 years after birth and lasted approximately 30-35 years for uniparous and biparous women and 10-15 years for multiparous women, with no decrease in risk even 55 years and longer after most recent birth. We confirm that there is little protection from ER-negative tumors even decades after most recent birth (8,16). Together with 2 case-case analyses (53,54), these studies provide evidence of heterogeneous associations between time since last birth and hormone receptor subtypes. Our results further reveal that it is primarily triple-negative and not HER2-enriched–like tumors that differ in these risk factor associations from other breast cancer subtypes. Additional studies in diverse populations are needed to clarify possible differences of these associations by race or ethnicity.

Associations of breastfeeding and risk of ER-positive breast cancer have not been consistent, and some studies suggest differences by race or ethnic groups (3,8,9,17,18). Our study of women mostly of European descent showed no protection of ER-positive disease from breastfeeding, with a possible inverse association only for women with long breastfeeding duration (≥24 months). In contrast, breastfeeding for at least 6 months was associated with a lower risk of triple-negative disease. These findings are generally consistent with studies across race or ethnicity groups (3,8,9,17,18) and further support promotion of breastfeeding for at least 6 months to reduce breast cancer risk, particularly triple-negative tumors that disproportionally affect women of African ancestry (55). Given that breastfeeding initiation and duration is lower for African American women compared with other races or ethnicities in the United States (56), promotion of breastfeeding could help address breast cancer health disparities.

Younger age at menarche was associated with increased risk of all subtypes in the current analysis, corroborating results from previous reports (2,4,6,7,10,18). Our results further indicate that older age at menopause was associated with increased risk of ER-positive, ER-negative, luminal-like, and HER2-enriched–like but not triple-negative tumors. Older age at menopause has been previously reported to increase luminal-like (4,6) and hormone receptor–positive tumors (7,18).

Older age at first birth has been shown to increase risk of luminal A-like, luminal B-like, ER-positive, and hormone receptor–positive tumors and not to be associated with triple-negative, ER-negative, or hormone receptor–negative tumors

(2,4-7,9). However, none of these previous studies accounted for time since last childbirth. Our data add to the literature by providing clear evidence that older age at first birth is associated with decreased risk of triple-negative disease and ER-negative tumors after additionally accounting for time since last birth. The inclusion of time since last birth to the model attenuates the associations between age at first birth and luminal-like and ER-positive tumors while strengthening the inverse association with triple-negative disease and ER-negative tumors.

The possible biological mechanisms underpinning associations between reproductive history and breast cancer subtypes are unclear. Long-term protection of breast cells from carcinogenic transformation is partly hypothesized to be from terminal differentiation of the terminal ductal lobular unit in the final trimester of pregnancy, as proposed (57). That we do not see long-term protection from childbirth even decades after the last birth in women who develop triple-negative breast cancer mirrors the results of a pooled analysis, where there was no protection from ER-negative breast cancers even 25 years and longer after the last birth (8). The authors then postulated that the mechanisms behind this long-term effect may differ from mechanisms operating for pregnancy-associated breast cancers.

The potential biological mechanisms underlying the etiology of ER-negative breast cancer were recently described in a narrative review. These mechanisms include effects on progenitor cells in the mammary gland, involution following pregnancy, epigenetic reprogramming in the mammary gland following pregnancy hormone-induced differentiation and tissue remodeling, and aberrant DNA methylation of luminal progenitor genes (58).

We are unaware of other studies evaluating associations between time since last birth and risk of in situ breast cancer. Overall, we found evidence that patterns of association between other reproductive factors and in situ disease are similar to those for invasive ER-positive tumors; increasing parity and increasing breastfeeding duration were observed to be associated with a decreased risk of in situ, in line with some studies (59-62) but not others (62,63). Our observations that increasing age at first birth and younger age at menarche were associated with increased risk of in situ tumors likewise corroborate results from some studies (59-61,64) but not others (63-65) that were likely limited by small sample sizes. Age at menopause was not associated with in situ breast cancer risk in our much larger study sample, whereas younger menopausal age has been previously reported to decrease in situ breast cancer risk (59-61,64).

Our results further demonstrate that relationships between some reproductive risk factors and breast cancer subtype risk are modified by age. At younger ages, parity, age at first birth, and breastfeeding duration were more strongly associated with luminal A-like tumors, with associations weakening with increasing age, whereas age at menarche was more likely to be strongly associated with triple-negative disease. That age modifies the association between parity and hormone receptor status-based and intrinsic-like subtypes has been previously suggested (8,19), although not confirmed when using a less granular parameterization for age (6). Age at first birth has been reported to be more strongly associated with ER-positive disease for younger women (aged <50 years) than older women (20). Unlike our results, studies in African women and African American women reported that in those 50 years of age and older, breastfeeding duration was more strongly related to a decreased ER-positive risk (66) as well as decreased ER-negative risk (8) and older age at menarche to a decreased risk of ER-positive tumors (66).

From sensitivity analyses, associations between reproductive risk factors and intrinsic-like subtypes were similar across the 2 study designs except for age at menopause.

Our study is limited by the categorization of tumor subtypes based on ER, PR, HER2, and grade. Up to 20% of immunohistochemistry determinations of ER and PR may be inaccurate due to varying thresholds for positivity and interpretation criteria (67). Another limitation is that we did not examine breastfeeding duration specific for each birth. There were also missing data on the reproductive factors (time since last birth = 42.2%; parity = 1.5%; age at first birth = 7.0%; breastfeeding duration = 41.5%; age at menarche = 6.2%; age at menopause = 13.5%), although a sensitivity analysis demonstrated that the effects of missing data on these associations was likely to be minimal. Our study sample predominantly included women of European ancestry (African = 4.5%; Asian subcontinent = 0.1%; European = 83.6%; Hispanic American = 0.3%; Other = 3.8%; Southeast Asian = 5.4%; Unknown = 2.2%), so generalizing our findings to women of other ethnicities should be done with prudence.

In conclusion, this large and comprehensive analysis using population-based data demonstrates marked differences in associations of reproductive history with triple-negative breast cancer compared with the other intrinsic-like subtypes or in situ disease. These results are valuable in providing further evidence for the understanding of etiologic heterogeneity in breast carcinogenesis and could inform risk prediction and prevention strategies.

Funding

This work was supported by the following funding agencies. The Breast Cancer Association Consortium (BCAC) is funded by the European Union's Horizon 2020 Research and Innovation Programme (grant numbers 634935 and 633784 for BRIDGES and B-CAST respectively), and the PERSPECTIVE I&I project, funded by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research, the Ministère de l'Économie et de l'Innovation du Québec through Genome Québec, the Quebec Breast Cancer Foundation. Additional funding for BCAC is provided via the Confluence project which is funded with intramural funds from the National Cancer Institute Intramural Research Program, National Institutes of Health.

The Australian Breast Cancer Family Study (ABCFS) was supported by grant UM1 CA164920 from the National Cancer Institute (USA).

The ABCFS was also supported by the National Health and Medical Research Council of Australia, the New South Wales Cancer Council, the Victorian Health Promotion Foundation (Australia) and the Victorian Breast Cancer Research Consortium.

The AHS study is supported by the intramural research program of the National Institutes of Health, the National Cancer Institute (grant number Z01-CP010119), and the National Institute of Environmental Health Sciences (grant number Z01-ES049030).

The BCEES was funded by the National Health and Medical Research Council, Australia and the Cancer Council Western Australia and acknowledges funding from the National Breast Cancer Foundation.

The BCINIS study is supported in part by the Breast Cancer Research Foundation (BCRF).

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CBCS is funded by the Canadian Cancer Society (grant # 313404) and the Canadian Institutes of Health Research.

The CECILE study was supported by Fondation de France, Institut National du Cancer (INCa), Ligue Nationale contre le Cancer, Agence Nationale de Sécurité Sanitaire, de l'Alimentation, de l'Environnement et du Travail (ANSES), Agence Nationale de la Recherche (ANR).

The American Cancer Society funds the creation, maintenance, and updating of the CPS-II cohort.

The California Teachers Study (CTS) and the research reported in this publication were supported by the National Cancer Institute of the National Institutes of Health under award number U01-CA199277; P30-CA033572; P30-CA023100; UM1-CA164917; and R01-CA077398. The collection of cancer incidence data used in the California Teachers Study was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; Centers for Disease Control and Prevention's National Program of Cancer Registries, under cooperative agreement 5NU58DP006344; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201800032I awarded to the University of California, San Francisco, contract HHSN261201800015I awarded to the University of Southern California, and contract HHSN261201800009I awarded to the Public Health Institute.

The coordination of EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by: Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Center (DKFZ), Federal Ministry of Education and Research (BMBF) (Germany); the Hellenic Health Foundation, the Stavros Niarchos Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (the Netherlands); Health Research Fund (FIS), PI13/00061 to Granada, PI13/01162 to EPIC-Murcia, Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, ISCIII RETIC (RD06/0020) (Spain); Cancer Research UK (14136 to EPIC-Norfolk; C570/A16491 and C8221/A19170 to EPIC-Oxford), Medical Research Council (1000143 to EPIC-Norfolk, MR/M012190/1 to EPIC-Oxford) (United Kingdom).

The ESTHER study was supported by a grant from the Baden Württemberg Ministry of Science, Research and Arts. Additional cases were recruited in the context of the VERDI study, which was supported by a grant from the German Cancer Aid (Deutsche Krebshilfe).

The GENICA was funded by the Federal Ministry of Education and Research (BMBF) Germany grants 01KW9975/5, 01KW9976/8, 01KW9977/0 and 01KW0114, the Robert Bosch Foundation, Stuttgart, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, as well as the Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany.

The GESBC was supported by the Deutsche Krebshilfe e. V. [70492] and the German Cancer Research Center (DKFZ).

The KARMA study was supported by Märit and Hans Rausings Initiative Against Breast Cancer.

The KBCP was financially supported by the special Government Funding (VTR) of Kuopio University Hospital grants, Cancer Fund of North Savo, the Finnish Cancer Organizations, and by the strategic funding of the University of Eastern Finland.

LAABC is supported by grants (1RB-0287, 3PB-0102, 5PB-0018, 10PB-0098) from the California Breast Cancer Research Program. Incident breast cancer cases were collected by the USC Cancer Surveillance Program (CSP) which is supported under subcontract by the California Department of Health. The CSP is also part of the National Cancer Institute's Division of Cancer Prevention and Control Surveillance, Epidemiology, and End Results Program, under contract number N01CN25403.

The MARIE study was supported by the Deutsche Krebshilfe e. V. [70–2892-BR I, 106332, 108253, 108419, 110826, 110828], the Hamburg Cancer Society, the German Cancer Research Center (DKFZ) and the Federal Ministry of Education and Research (BMBF) Germany [01KH0402].

The MASTOS study was supported by "Cyprus Research Promotion Foundation" grants 0104/13 and 0104/17, and the Cyprus Institute of Neurology and Genetics.

The Melbourne Collaborative Cohort Study (MCCS) cohort recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further augmented by Australian National Health and Medical Research Council grants 209057, 396414 and 1074383 and by infrastructure provided by Cancer Council Victoria. Cases and their vital status were ascertained through the Victorian Cancer Registry and the Australian Institute of Health and Welfare, including the National Death Index and the Australian Cancer Database.

The MEC was supported by NIH grants CA63464, CA54281, CA098758, CA132839 and CA164973.

The MISS study is supported by funding from ERC-2011–294576 Advanced grant, Swedish Cancer Society, Swedish Research Council, Local hospital funds, Berta Kamprad Foundation, Gunnar Nilsson.

The MMHS study was supported by NIH grants CA97396, CA128931, CA116201, CA140286 and CA177150.

The NBHS was supported by NIH grant R01CA100374. Biological sample preparation was conducted the Survey and Biospecimen Shared Resource, which is supported by P30 CA68485.

The Carolina Breast Cancer Study (NCBCS) was funded by Komen Foundation, the National Cancer Institute (P50 CA058223, U54 CA156733, U01 CA179715), and the North Carolina University Cancer Research Fund.

The NHS was supported by NIH grants P01 CA87969, UM1 CA186107, and U19 CA148065.

The NHS2 was supported by NIH grants UM1 CA176726 and U19 CA148065.

The PBCS was funded by Intramural Research Funds of the National Cancer Institute, Department of Health and Human Services, USA.

Genotyping for PLCO was supported by the Intramural Research Program of the National Institutes of Health, NCI, Division of Cancer Epidemiology and Genetics. The PLCO is supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics and supported by contracts from the Division of Cancer Prevention, National Cancer Institute, National Institutes of Health.

The SASBAC study was supported by funding from the Agency for Science, Technology and Research of Singapore (A*STAR), the US National Institute of Health (NIH) and the Susan G. Komen Breast Cancer Foundation.

The SBCGS was supported primarily by NIH grants R01CA64277, R01CA148667, UMCA182910, and R37CA70867. Biological sample preparation was conducted the Survey and Biospecimen Shared Resource, which is supported by P30 CA68485. The scientific development and funding of this project were, in part, supported by the Genetic Associations and Mechanisms in Oncology (GAME-ON) Network U19 CA148065.

The SMC is funded by the Swedish Cancer Foundation and the Swedish Research Council (VR 2017–00644) grant for the Swedish Infrastructure for Medical Population-based Life-course Environmental Research (SIMPLER).

Notes

Role of the funder: The EU Horizon 2020 Research and Innovation Programme funding source had no role in study design, data collection, data analysis, data interpretation or writing of the report. Other funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript.

Disclosures: The authors declare no conflicts of interest. CMV and AHE, who are *JNCI* Associate Editors and co-authors on this article, were not involved in the editorial review or decision to publish this manuscript.

Author contributions: **AYJ**: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing—original draft; Writing—review and editing. **TUA**: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing—review and editing. **SB**: Data curation; Formal Analysis; Resources; Writing—review and editing. **PM**: Resources; Writing—review and editing. **MKB**: Data curation; Resources; Writing—review and editing. **QW**: Data curation; Resources; Writing—review and editing. **VA**: Resources; Writing—review and editing. **KJA**: Resources; Writing—review and editing. **AA**: Resources; Writing—review and editing. **LEBF**: Resources; Writing—review and editing. **HB**: Resources; Writing—review and editing. **HB**: Resources; Writing—review and editing. **FC**: Resources; Writing—review and editing. **LAC**: Resources; Writing—review and editing. **CC**: Resources; Writing—review and editing. **KC**: Resources; Writing—review and editing. **AHE**: Resources; Writing—review and editing. **ME**: Resources; Writing—review and editing. **DGE**: Resources; Writing—review and editing. **JDF**: Resources; Writing—review and editing. **LF**: Resources; Writing—review and editing. **MG**: Resources; Writing—review and editing. **GGG**: Resources; Writing—review and editing. **PG**: Resources; Writing—review and editing. **AH**: Resources; Writing—review and editing. **CAH**: Resources; Writing—review and editing. **NH**: Resources; Writing—review and editing. **PH**: Resources; Writing—review and editing. **UH**: Resources; Writing—review and editing. **RH**: Resources; Writing—review and editing. **JLH**: Resources; Writing—review and editing. **AH**: Resources; Writing—review and editing. **DJH**: Resources; Writing—review and editing. **AH**: Resources; Writing—review and editing. **RK**: Resources; Writing—review and editing. **V-MK**: Resources; Writing—review and editing. **SK**: Resources; Writing—review and editing. **PK**: Resources; Writing—review and editing. **JVL**: Resources; Writing—review and editing. **LL**: Resources; Writing—review and editing. **JL**: Resources; Writing—review and editing. **MAL**: Resources; Writing—review and editing. **AM**: Resources; Writing—review and editing. **TM**: Resources; Writing—review and editing. **RAM**: Resources; Writing—review and editing. **AFO**: Resources; Writing—review and editing. **HO**: Resources; Writing—review and editing. **AVP**: Resources; Writing—review and editing. **CMP**: Resources; Writing—review and editing. **GR**: Resources; Writing—review and editing. **RS**: Resources; Writing—review and editing. **X-OS**: Resources; Writing—review and editing. **MCS**: Resources; Writing—review and editing. **JS**: Resources; Writing—review and editing. **RMT**: Resources; Writing—review and editing. **LRT**: Resources; Writing—review and editing. **MAT**: Resources; Writing—review and editing. **TT**: Resources; Writing—review and editing. **CMV**: Resources; Writing—review and editing. **SSW**: Resources; Writing—review and editing. **AW**: Resources; Writing—review and editing. **AHW**: Resources; Writing—review and editing. **XRY**: Resources; Writing—review and editing. **WZ**: Resources; Writing—review and editing. **AMD**: Data curation; Funding acquisition; Project administration; Resources; Writing—review and editing. **PDPP**: Data curation; Funding acquisition; Project administration; Resources; Writing—review and editing. **DFE**: Data curation; Funding acquisition; Project administration; Resources; Writing—review and editing. **RLM**: Data curation; Funding acquisition; Project administration; Resources; Writing—review and editing. **NC**: Data curation; Funding acquisition; Methodology; Project administration; Resources; Writing—review and editing. **MKS**: Data curation; Funding acquisition; Project administration; Resources; Writing—review and editing. **MG-C**: Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing—original draft; Writing—review and editing. **JC-C**: Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing—original draft; Writing—review and editing.

Acknowledgements: We pay special tribute to the contribution of Håkan Olsson who passed away on 30 June 2021. He led the MISS cohort and was a very active collaborator in the BCAC. He will be much missed for his generosity, enthusiasm, and insights.

The authors thank all the researchers, clinicians, technicians, and administrative staff involved in the BCAC. The authors would also like to thank all study participants, researchers, clinicians, technicians and administrative staff who participated in the parent studies (ABCFS, AHS, BCEES, BCINIS, CBCS, CECILE, CPSII, CTS, EPIC, ESTHER, GENICA, GESBC, KARMA, KBCP, LAABC, MARIE, MASTOS, MCCS, MEC, MISS,

MMHS, NBHS, NCBCS, NHS, NHS2, PBCS, PLCO, PROCAS, SASBAC, SBCGS, SMC) and have enabled this work to be carried out. BCEES thanks BreastScreen Western Australia. The BCINIS study would not have been possible without the contributions of the NICCC in Haifa, and all the contributing family medicine, surgery, pathology, and oncology teams in all medical institutes in Northern Israel. Investigators from the CPS-II cohort thank the participants and Study Management Group for their invaluable contributions to this research. They also acknowledge the contribution to this study from central cancer registries supported through the Centers for Disease Control and Prevention National Program of Cancer Registries, as well as cancer registries supported by the National Cancer Institute Surveillance Epidemiology and End Results program. The authors would like to thank the California Teachers Study Steering Committee that is responsible for the formation and maintenance of the Study within which this research was conducted. A full list of California Teachers Study (CTS) team members is available at https://www.calteachersstudy.org/team. The GENICA Network consists of Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, and University of Tübingen, Germany, German Cancer Consortium (DKTK) and German Cancer Research Center (DKFZ), Partner Site Tübingen, 72074 Tübingen, Germany, gefördert durch die Deutsche Forschungsgemeinschaft (DFG) im Rahmen der Exzellenzstrategie des Bundes und der Länder—EXC 2180 – 390900677, Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany, Institute of Pathology, University of Bonn, Germany, Molecular Genetics of Breast Cancer, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany, Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, Germany; and Institute of Occupational Medicine and Maritime Medicine, University Medical Center Hamburg-Eppendorf, Germany. KARMA and SASBAC thank the Swedish Medical Research Counsel. For NHS and NHS2 the study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. The authors thank the participants and staff of the NHS and NHS2 for their valuable contributions as well as the following state cancer registries for their help. PROCAS thank NIHR for funding.

Disclaimers: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. The opinions, findings, and conclusions expressed herein are those of the author(s) and do not necessarily reflect the official views of the State of California, Department of Public Health, the National Cancer Institute, the National Institutes of Health, the Centers for Disease Control and Prevention or their Contractors and Subcontractors, or the Regents of the University of California, or any of its programs.

Data Availability

The data underlying this article cannot be shared publicly due to ethical guidelines, aiming to protect the privacy of individuals that participated in the study. The data may be shared on reasonable request to the corresponding author, after permission from the Institutional Review Board.

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