**Distinct reproductive risk profiles for intrinsic-like breast cancer subtypes: pooled analysis of population-based studies**

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**ABSTRACT** (248 words; maximum 250 words)

**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) and by invasiveness.

**Results:** Compared to 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. In contrast, parous women had a higher risk of triple-negative breast cancer right after their last birth that was attenuated with time but persisted for decades. Older age at first birth and breastfeeding were associated with lower risk of triple-negative 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.

**Conclusion:** This large and comprehensive study demonstrates a distinct reproductive risk factor profile for triple-negative breast cancer compared to other subtypes, with implications for the understanding of disease etiology and risk prediction.

**INTRODUCTION** (3,646 words revised)

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), human epidermal growth factor receptor 2 (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 <10 years for ER-positive tumors [15] but persist even ≥25 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 S1**, 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 S1**. All individual studies were approved by their institutional review boards and/or medical ethical committees. Written informed consent was obtained from all study subjects.

### Breast cancer risk factors

Studies provided information on at least one reproductive risk factor, or exogenous hormone use and lifestyle risk factors that will be the focus for subsequent analyses. Data from studies was centrally quality-controlled and harmonized using a common data dictionary. The distributions of individual risk factors according to study are shown in **Supplementary Table S2**.

### Breast cancer tumor markers

The source of tumor marker data varied across studies and included clinical records and immunohistochemistry (IHC) involving full face tumor sections or tissue microarrays [51]. Breast tumors were classified according to ER status (ER-positive/ER-negative), and the following invasive intrinsic-like subtypes using histologic grade as proxy for proliferation [52]: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&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).

**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 12 5-year categories) in women with different numbers of births (nulliparous (ref.), 1, 2, ≥3 births), and the following additional variables: age at first birth (<20 years (ref.), 20-<25, 25-<30, ≥30), breastfeeding duration (0 months (ref.), >0-6, >6-12, >12-24, >24), age at menarche (≥15 years (ref.), 14, 13, ≤12), and age at menopause (<50 years (ref.), 50-54, ≥54, premenopausal). We fit two models with all the covariates – one for intrinsic-like subtypes and the other for ER-positive/ER-negative/*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/*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 / ER-positive as the comparison group.

As secondary analyses and for comparison to 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 >90% of cases or controls on time since last birth or breastfeeding duration.

All statistical tests were two-sided; statistical significance was considered with P values <0.05. 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 ~30 years after birth (**Figure 1**, **Table 2** for ORs (95%CIs)). Biparous and multiparous women had a higher risk of luminal A-like than nulliparous women within ~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)) than biparous women (OR 0.94 (95%CI 0.80 to 1.10)) ~20 years after their last birth. For triple-negative disease, all parous women were at higher risk than nulliparous women, particularly within 5 years after last birth. This relative increase in risk attenuated with time but persisted until 30-35 years after last birth with no crossover in risk. Even for multiparous women the increased risk of triple-negative disease associated with childbirth lasted until 15 years after last birth.

*Heterogeneity of associations between reproductive risk factors and invasive intrinsic-like subtypes: case-case analyses*

Tests for OR heterogeneity by subtypes based on case-case comparisons showed statistically significant differences in the ORs for time since last birth for triple-negative compared to luminal-A-like breast cancer among uniparous (P-heterogeneity=5.49E-06), biparous (P-heterogeneity=1.17E-04), and multiparous women (P-heterogeneity=1.21E-02). ORs for all the other subtypes were not significantly different from that for luminal-A-like tumors (**Supplementary Figure S2**, **Supplementary Table S3**). Increasing age at first birth was associated with decreasing risk of triple-negative breast cancer, but not other intrinsic-like subtypes (P-heterogeneity=5.94E-08 for triple-negative compared to luminal-A like). Breastfeeding for >6 months was associated with lower risk of triple-negative breast cancer compared to no breastfeeding in parous women, but not other disease subtypes (P-heterogeneity=3.77E-05 for triple-negative compared to luminal-A like). Older age at menarche was inversely associated with risk of all subtypes, with strongest associations for luminal-A-like (P-heterogeneity>1.68E-01). Older age at menopause was significantly associated with 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, test for OR heterogeneity by subtype was not statistically significant (P-heterogeneity>2.43E-01). These case-case analyses further demonstrate that evidence for etiological 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=8.89E-03) (**Figure 2**, **Supplementary Table S4**), age at first birth (P-interaction=6.55E-05) (**Supplementary Figure S3**, **Supplementary Table S5**) and breastfeeding duration (P-interaction=1.07E-02) (**Supplementary Figure S4**, **Supplementary Table S6**) with risk of luminal A-like disease. Risk associations were strongest for younger women in their 40's 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=1.59E-03) (**Supplementary Figure S5**, **Supplementary Table S7**). There was no evidence that other associations between reproductive risk factors including age at menopause (**Supplementary Figure S6**, **Supplementary Table S8**) and intrinsic-like subtypes were modified by age.

*Associations between reproductive risk factors and invasiveness (ER status and* in situ*)*

For comparability to previous reports, we also evaluated associations by ER status and *in situ* disease (for case-control comparisons: **Figure 3**, **Supplementary Table S9**; for case-case comparisons: **Supplementary Figure S7**, **Supplementary Table S10**). 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 were like those we reported for triple-negative tumors, while associations for invasive ER-positive were more similar to those for luminal-like tumors. A notable finding was that breastfeeding for >6 months was associated with a decreased risk for ER-negative disease while longer breastfeeding duration of >24 months was necessary for 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 (ER status and* in situ)

Parity was associated with decreased risk of all intrinsic subtypes except triple-negative, for which there was an increased risk becoming weaker with additional births (**Supplementary Figure S8**, **Supplementary Table S11**). 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 OR heterogeneity by subtypes based on case-case comparisons were like those from the model that included time since last birth (**Supplementary Figure S9**, **Supplementary Table S12**).

In case-control comparisons, associations between risk factors and risk of ER+/ER-/*in situ* tumors were in line with those from the model fit with time since last birth (**Supplementary Figure S10**, **Supplementary Table S13**). Tests for OR heterogeneity by invasiveness and *in situ* based on case-case comparisons (**Supplementary Figure S11**, **Supplementary Table S14**) were similar to those from the model fit with time since last birth in that there were differences in the ORs for number of births (P-heterogeneity=1.23E-14), age at first birth (P-heterogeneity=9.25E-03), and breastfeeding duration (P-heterogeneity=4.25E-04) for ER- compared to ER+ disease. ORs for age at menarche for *in situ* disease was also different to those for ER+ disease (P-heterogeneity=1.73E-03).

*Sensitivity analyses*

There was no evidence for heterogeneity by study design for associations between reproductive risk factors and intrinsic-like subtypes (P-heterogeneity >8.00E-02) except for age at menopause (P-heterogeneity=1.00E-03) (**Supplementary Figures S12-S19**). Excluding studies that had missing data on time since last birth or breastfeeding duration in

>90% of cases or controls yielded substantially unchanged results (**Supplementary Figure S20**).

## 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, ~3-5 times larger than previously published reports [8, 15, 16], and wide range of exposures that allowed us to expand considerably 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 has been consistently associated with a lower risk for ER-positive disease [5, 6, 8, 18, 53, 54]. The association with ER-negative disease has been less clear with studies suggesting no association [5, 18, 53, 54] or a higher risk [6, 8, 53]. 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, while 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 to nulliparous women, parous women are at transient increased risk of all intrinsic-like subtypes peaking between 5-15 years after last birth for luminal-like tumors, lasting ~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 <5 years after birth, lasted ~30-35 years for uniparous and biparous women and 10-15 years for multiparous women with no decrease in risk even >55 years 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 two case-case analyses [55, 56], 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/ethnicity.

Associations of breastfeeding and risk of ER-positive breast cancer has not been consistent and some studies suggest differences by race/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 or more 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/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 tumours that disproportionally affect women of African ancestry [57]. Given that breastfeeding initiation and duration is lower for African-American women compared to other races/ethnicities in the US [58], 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 had accounted for time since last childbirth. Our data adds 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 [59]. 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 those of a pooled analysis, where there was no protection from ER- breast cancers even ≥25 years after the last birth [8]. The authors then postulated that the mechanisms behind this long-term effect may be different 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 [60].

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, in that increasing parity and increasing breastfeeding duration were observed to be associated with a decreased risk of *in situ*, in line with some studies [61-64] but not others [64, 65]. Our observations that increasing age at first birth and younger age at menarche were associated with increased risk of *in situ* tumors likewise corroborates results from some studies [61-63, 66] but not others [65-67] that were likely limited by small sample sizes. Age at menopause was not associated with *in situ* in our much larger study sample, while younger menopausal age has been previously reported to decrease *in situ* breast cancer risk [61-63, 66].

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 and African-American women reported that in women $\geq 50$ years of age, breastfeeding duration was more strongly related to a decreased ER-positive risk [68] as well as decreased ER-negative risk [8], and older age at menarche to a decreased risk of ER-positive tumors [68].

From sensitivity analyses, associations between reproductive risk factors and intrinsic-like subtypes were similar across the two 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 IHC determinations of ER and PR may be inaccurate due to varying thresholds for positivity and interpretation criteria [69]. Another limitation is that we did not examine breastfeeding duration specific for each birth. There was 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 (83.6%; Hispanic American 0.3%; African 4.5%; Asian subcontinent 0.1%; South-East Asian 5.4%; Other 3.8%; 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 to 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.

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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* 71,072 | Luminal A-like† 12,405 (53.1%) | Luminal B-like 2,832 (12.1%) | Luminal B-HER2-like 3,088 (13.2%) | HER2-enriched-like 1,498 (6.4%) | Triple-negative 3,530 (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 | 11246 (15.8) | 2153 (17.4) | 504 (17.8) | 622 (20.1) | 367 (24.5) | 703 (19.9) |
| 2 | 26564 (37.4) | 4464 (36.0) | 1003 (35.4) | 1063 (34.4) | 495 (33.0) | 1288 (36.5) |
| ≥3 | 23966 (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-<5 years | 888 (1.3) | 92 (0.7) | 41 (1.5) | 68 (2.2) | 42 (2.8) | 104 (3.0) |
| 5-<10 years | 1279 (1.8) | 228 (1.8) | 71 (2.5) | 94 (3.0) | 45 (3.0) | 133 (3.8) |
| 10-<15 years | 2022 (2.9) | 409 (3.3) | 121 (4.2) | 129 (4.2) | 70 (4.7) | 175 (5.0) |
| 15-<20 years | 2987 (4.2) | 591 (4.8) | 134 (4.7) | 169 (5.5) | 91 (6.1) | 269 (7.6) |
| 20-<25 years | 4042 (5.7) | 723 (5.8) | 160 (5.7) | 199 (6.4) | 137 (9.2) | 329 (9.3) |
| 25-<30 years | 4441 (6.3) | 865 (7.0) | 183 (6.5) | 238 (7.7) | 138 (9.2) | 303 (8.6) |
| 30-<35 years | 4795 (6.8) | 1119 (9.0) | 231 (8.2) | 292 (9.5) | 142 (9.5) | 314 (8.9) |
| 35-<40 years | 4892 (6.9) | 1135 (9.2) | 250 (8.8) | 244 (7.9) | 114 (7.6) | 264 (7.5) |
| 40-<45 years | 2937 (4.1) | 793 (6.4) | 165 (5.8) | 158 (5.1) | 82 (5.5) | 189 (5.4) |
| 45-<50 years | 1361 (1.9) | 418 (3.4) | 83 (2.9) | 75 (2.4) | 33 (2.2) | 77 (2.2) |
| 50-<55 years | 408 (0.6) | 149 (1.2) | 34 (1.2) | 29 (0.9) | 10 (0.7) | 33 (0.9) |
| ≥55 years | 87 (0.1) | 65 (0.5) | 16 (0.6) | 8 (0.3) | 7 (0.5) | 8 (0.2) |
| Missing | 32303 (45.5) | 4068 (32.8) | 915 (32.3) | 906 (29.3) | 375 (25.0) | 938 (26.6) |
| Age at first full-term birth | | | | | | |
| <20 years | 6508 (9.2) | 1295 (10.4) | 311 (11.0) | 299 (9.7) | 178 (11.9) | 578 (16.4) |
| 20-<25 years | 23178 (32.6) | 4124 (33.2) | 910 (32.1) | 946 (30.6) | 469 (31.3) | 1231 (34.9) |
| 25-<30 years | 18563 (26.1) | 3144 (25.3) | 677 (23.9) | 806 (26.1) | 387 (25.8) | 816 (23.1) |
| ≥30 years | 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 months | 7031 (9.9) | 1826 (14.7) | 469 (16.6) | 469 (15.2) | 252 (16.8) | 839 (23.8) |
| >0-6 months | 10954 (15.4) | 2528 (20.4) | 559 (19.7) | 702 (22.7) | 311 (20.8) | 739 (20.9) |
| >6-12 months | 5625 (7.9) | 1150 (9.3) | 259 (9.2) | 274 (8.9) | 142 (9.5) | 291 (8.2) |
| >12-24 months | 4280 (6.0) | 1013 (8.2) | 219 (7.7) | 224 (7.3) | 91 (6.1) | 232 (6.6) |
| >24 months | 2374 (3.3) | 500 (4.0) | 101 (3.6) | 102 (3.3) | 46 (3.1) | 129 (3.7) |
| Missing | 32178 (45.3) | 3638 (29.3) | 796 (28.1) | 838 (27.1) | 444 (29.6) | 906 (25.7) |
| Age at menarche | | | | | | |
| ≤12 years | 23572 (33.2) | 4469 (36.0) | 1075 (38.0) | 1106 (35.8) | 510 (34.1) | 1427 (40.4) |
| 13 years | 18005 (25.3) | 3406 (27.5) | 742 (26.2) | 799 (25.9) | 385 (25.7) | 880 (24.9) |
| 14 years | 13151 (18.5) | 2093 (16.9) | 475 (16.8) | 518 (16.8) | 265 (17.7) | 549 (15.6) |
| ≥15 years | 12041 (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 | 19399 (27.3) | 4157 (33.5) | 941 (33.2) | 998 (32.3) | 491 (32.8) | 1144 (32.4) |
| 50-<54 | 13647 (19.2) | 3179 (25.6) | 617 (21.8) | 638 (20.7) | 342 (22.8) | 656 (18.6) |
| ≥54 | 5863 (8.3) | 1490 (12.0) | 276 (9.8) | 337 (10.9) | 147 (9.8) | 281 (8.0) |
| Missing | 10496 (14.8) | 989 (8.0) | 245 (8.65) | 219 (7.1) | 80 (5.3) | 256 (7.3) |

* Control subjects in population-based studies were randomly selected from the same source population as the case patients and recruited during the same period of time.

† Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&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).

**Table 2**. ORs and 95%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.

| Risk factor | | Intrinsic-like breast cancer subtype† | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Luminal A-like | | Luminal B-like | | Luminal B-HER2-like | | HER2-enriched-like | | Triple-negative | |
| | 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 (years) | | | | | | | | | | | |
| 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-<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-<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 | . | 1 | 0.88 (0.11 to 6.93) | 1 | 0.61 (0.08 to 4.69) |
| ≥3 births | | | | | | | | | | | |
| 0-<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 | 52 | 0.53 | 43 | 0.30 | 23 | 0.47 | 62 | 0.87 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | (0.41 to 0.59) | | (0.38 to 0.75) | | (0.21 to 0.43) | | (0.29 to 0.77) | | (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 | . | 1 | 0.94 (0.12 to 7.51) |
| | | | | | | | | | | | |
| Age at first birth‡ (years) | | | | | | | | | | | |
| <20 | 6508 | 1295 | 1.00 (Ref.) | 311 | 1.00 (Ref.) | 299 | 1.00 (Ref.) | 178 | 1.00 (Ref.) | 578 | 1.00 (Ref.) |
| 20-<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-<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‡ (months) | | | | | | | | | | | |
| 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 (years) | | | | | | | | | | | |
| ≥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 (years) | | | | | | | | | | | |
| <50 | 19 399 | 4157 | 1.00 (Ref.) | 941 | 1.00 (Ref.) | 998 | 1.00 (Ref.) | 491 | 1.00 (Ref.) | 1144 | 1.00 (Ref.) |
| 50-<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) |

* The multivariable model was additionally adjusted for reference age (age at diagnosis for cases, age at interview for controls) and study.

† Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&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).

‡ Among parous women.

## FIGURE LEGENDS

**Figure 1.** ORs (colored dots) and 95%CIs (colored horizontal lines) 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 model was also adjusted for reference age (age at diagnosis for cases, age at interview for controls) and study.

**Figure 2.** ORs (colored dots) and 95%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 model was also adjusted for study.

**Figure 3**. ORs (colored dots) and 95%CIs (colored horizontal lines) 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 ER subtypes and *in situ* tumors. The model was also adjusted for reference age (age at diagnosis for cases, age at interview for controls) and study.

## NOTES

### Role of the funder

The 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.

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## Authors' Contributions

**AYJ**: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing—original draft; Writing—review & editing. **TUA**: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing—review & editing. **SB**: Data curation; Formal Analysis; Resources; Writing – review & editing. **PM**: Resources; Writing—review & editing. **MKB**: Data curation; Resources; Writing – review & editing. **QW**: Data curation; Resources; Writing – review & editing. **VA**: Resources; Writing – review & editing. **KJA**: Resources; Writing – review & editing. **AA**: Resources; Writing – review & editing. **LEBF**: Resources; Writing – review & editing. **HB**: Resources; Writing – review & editing. **HB**: Resources; Writing – review & editing. **FC**: Resources; Writing – review & editing. **LAC**: Resources; Writing – review & editing. **CC**: Resources; Writing – review & editing. **KC**: Resources; Writing – review & editing. **AHE**: Resources; Writing – review & editing. **ME**: Resources; Writing – review & editing. **DGE**: Resources; Writing – review & editing. **JDF**: Resources; Writing – review & editing. **LF**: Resources; Writing – review & editing. **MG**: Resources; Writing – review & editing. **GGG**: Resources; Writing – review & editing. **PG**: Resources; Writing – review & editing. **AH**: Resources; Writing – review & editing. **CAH**: Resources; Writing – review & editing. **NH**: Resources; Writing – review & editing. **PH**: Resources; Writing – review & editing. **UH**: Resources; Writing – review & editing. **RH**: Resources; Writing – review & editing. **JLH**: Resources; Writing – review & editing. **AH**: Resources; Writing – review & editing. **DJH**: Resources; Writing – review & editing. **AH**: Resources; Writing – review & editing. **RK**: Resources; Writing – review & editing. **V-MK**: Resources; Writing – review & editing. **SK**: Resources; Writing – review & editing. **PK**: Resources; Writing – review & editing. **JVL**: Resources; Writing – review & editing. **LL**: Resources; Writing – review & editing. **JL**: Resources; Writing – review & editing. **MAL**: Resources; Writing – review & editing. **AM**: Resources; Writing –

review & editing. **TM**: Resources; Writing – review & editing. **RAM**: Resources; Writing – review & editing. **AFO**: Resources; Writing – review & editing. **HO**: Resources; Writing – review & editing. **AVP**: Resources; Writing – review & editing. **CMP**: Resources; Writing – review & editing. **GR**: Resources; Writing – review & editing. **RS**: Resources; Writing – review & editing. **X-OS**: Resources; Writing – review & editing. **MCS**: Resources; Writing – review & editing. **JS**: Resources; Writing – review & editing. **RMT**: Resources; Writing – review & editing. **LRT**: Resources; Writing – review & editing. **MAT**: Resources; Writing – review & editing. **TT**: Resources; Writing – review & editing. **CMV**: Resources; Writing – review & editing. **SSW**: Resources; Writing – review & editing. **AW**: Resources; Writing – review & editing. **AHW**: Resources; Writing – review & editing. **XRY**: Resources; Writing – review & editing. **WZ**: Resources; Writing – review & editing. **AMD**: Data curation; Funding acquisition; Project administration; Resources; Writing—review & editing. **PDPP**: Data curation; Funding acquisition; Project administration; Resources; Writing—review & editing. **DFE**: Data curation; Funding acquisition; Project administration; Resources; Writing—review & editing. **RLM**: Data curation; Funding acquisition; Project administration; Resources; Writing—review & editing. **NC**: Data curation; Funding acquisition; Methodology; Project administration; Resources; Writing—review & editing. **MKS**: Data curation; Funding acquisition; Project administration; Resources; Writing—review & editing. **MG-C**: Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing. **JC-C**: Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing.

**Data availability statement**: 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.

**SUPPLEMENTARY TABLES**

**Supplementary Table S1.** Description of studies included in the analysis.

| | | | | | | Breast cancer case patients with information on ER, PR, HER2 expression and grade in the tumors* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Study, first author, year (reference) | Country | Control subjects† (n = 71,072) | Case patients (n = 47,350) | Invasive tumors (n = 42,524) | *In situ* (n = 5,055) | Luminal A-like (n = 12,405) | Luminal B-like (n = 2,832) | Luminal B-HER2-like (n = 3,088) | HER2-enriched-like (n = 1,498) | Triple-negative (n = 3,530) |
| Prospective cohort | | | | | | | | | | |
| AHS, Koutros, 2010 [1] | USA | 1237 | 518 | 516 | 2 | 48 | 7 | 2 | 4 | 8 |
| CPSII, Calle, 2002 [2] | USA | 3368 | 2703 | 2088 | 615 | 620 | 124 | 121 | 10 | 31 |
| CTS, Bernstein, 2002 [3] | USA | 1621 | 1213 | 1213 | 0 | 0 | 0 | 0 | 0 | 101 |
| EPIC, Riboli, 2002 [4] | France, Germany, Greece, Italy, Spain, The Netherlands, UK | 3688 | 2672 | 2251 | 421 | 522 | 157 | 166 | 39 | 58 |
| KARMA, Li, 2016 [5] | Sweden | 15292 | 2345 | 2051 | 294 | 1044 | 302 | 169 | 67 | 122 |
| MCCS, Milne, 2017 [6] | Australia | 1365 | 1193 | 1184 | 9 | 578 | 147 | 99 | 55 | 139 |
| MEC, Kolonel, 2000 [7] | USA | 1944 | 1617 | 1612 | 5 | 82 | 19 | 17 | 5 | 6 |
| MISS, Olsson, 2003 [8] | Sweden | 1656 | 613 | 535 | 78 | 18 | 1 | 28 | 9 | 43 |
| MMHS, Olson, 2012 [9] | USA | 1716 | 384 | 535 | 78 | 175 | 26 | 16 | 5 | 19 |
| NHS, Hankinson, 1998 [10] | USA | 3568 | 2536 | 2018 | 518 | 456 | 108 | 136 | 41 | 118 |
| NHS2, Tworoger, 2006 [11] | USA | 2164 | 1714 | 1229 | 485 | 513 | 111 | 110 | 38 | 95 |
| PLCO, Pfeiffer, 2013 [12] | USA | 3070 | 3041 | 2355 | 686 | 1065 | 173 | 142 | 54 | 144 |
| SMC, Suzuki, 2005 [13] | Sweden | 685 | 1177 | 1177 | 0 | 221 | 61 | 36 | 19 | 27 |
| Population-based case-control study | | | | | | | | | | |
| ABCFS, Dite, 2003 [14] | Australia | 1398 | 1445 | 1443 | 2 | 0 | 0 | 6 | 3 | 4 |
| BCEES, Fritschi, 2013 [15] | Australia | 858 | 713 | 713 | 0 | 342 | 48 | 49 | 0 | 0 |
| BCINIS, Rennert, 2010 [16] | Israel | 900 | 1960 | 1857 | 103 | 966 | 204 | 144 | 84 | 232 |
| CBCS, Grundy, 2013 [17] | Canada | 1179 | 1151 | 931 | 220 | 381 | 120 | 239 | 69 | 76 |
| CECILE, Menegaux, 2013 [18] | France | 1315 | 1208 | 1072 | 136 | 0 | 0 | 95 | 41 | 106 |
| ESTHER, Widschwendter, 2008 [19] | Germany | 766 | 644 | 639 | 5 | 79 | 26 | 37 | 16 | 24 |
| GENICA, Pesch, 2005 [20] | Germany | 1015 | 999 | 979 | 20 | 303 | 111 | 138 | 61 | 74 |
| GESBC, Chang-Claude, 2000 [21] | Germany | 1381 | 600 | 555 | 45 | 0 | 0 | 0 | 0 | 0 |
| KBCP, Hartikainen, 2005 [22] | Finland | 536 | 574 | 531 | 43 | 276 | 49 | 78 | 30 | 52 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| LAABC, Wu, 2009 [23] | USA | 1047 | 686 | 682 | 4 | 0 | 0 | 0 | 0 | 0 |
| MARIE, Flesch-Janys, 2008 [24] | Germany | 7337 | 3797 | 3554 | 243 | 1864 | 371 | 455 | 212 | 392 |
| MASTOS, Hadjisavvas, 2010 [25] | Cyprus | 1174 | 568 | 516 | 52 | 291 | 56 | 55 | 22 | 61 |
| NBHS, Zheng, 2009 [26] | USA | 1075 | 1061 | 855 | 206 | 61 | 31 | 88 | 99 | 217 |
| NCBCS, Newman, 1995 [27] | USA | 2022 | 4980 | 4477 | 503 | 1478 | 429 | 390 | 230 | 965 |
| PBCS, Garcia-Closas, 2006 [28] | Poland | 2393 | 1973 | 1844 | 129 | 772 | 97 | 117 | 124 | 262 |
| PROCAS, Evans, 2016 [29] | UK | 1745 | 478 | 381 | 97 | 250 | 54 | 31 | 9 | 21 |
| SASBAC, Wedren, 2004 [30] | Sweden | 1515 | 860 | 860 | 0 | 0 | 0 | 0 | 0 | 0 |
| SBCGS, Zheng, 2009 [26] | China | 2042 | 1927 | 1871 | 56 | 0 | 0 | 124 | 152 | 133 |

* Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&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).

† Control subjects in population-based studies were randomly selected from the same source population as the case patients and recruited during the same period of time.

**Supplementary Table S2**. Distribution of risk factors according to study.

| study | Recruitment period* | Reference age (controls) | Reference age (cases) | Number of births (controls) | Number of births (cases) | Time since last birth (controls) | Time since last birth (cases) | Age at first birth (controls) | Age at first birth (cases) | Breastfeeding duration (controls) | Breastfeeding duration (cases) | Age at menarche (controls) | Age at menarche (cases) | Age at menopause (controls) | Age at menopause (cases) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Prospective cohort studies | | 58 (16) | 64 (14) | 2 (1) | 2 (1) | 26 (16) | 29 (15) | 25 (6) | 24 (6) | 6 (14) | 6 (14) | 13 (2) | 13 (2) | 50 (6) | 50 (5) |
| AHS | 1993-1997 | 53 (14) | 61 (15) | 3 (2) | 3 (2) | 24 (16) | 35 (24) | 22 (5) | 23 (6) | . | . | 13 (2) | 13 (2) | 48 (10) | 49 (9) |
| CPSII | 1982 | 62 (9) | 71 (10) | 3 (2) | 3 (2) | 32 (9) | 46 (17) | 23 (5) | 24 (4) | . | . | 13 (2) | 13 (1) | 49 (7) | 50 (6) |
| CTS | 1998-2008 | 55 (14) | 62 (13) | 2 (2) | 2 (2) | 24 (16) | 29 (14) | 26 (5) | 26 (6) | . | . | 12 (1) | 12 (1) | . | . |
| EPIC | 1992-2000 | 53 (12) | 60 (11) | 2 (2) | 2 (1) | 24 (12) | 29 (11) | 25 (5) | 25 (5) | 4 (8) | 4 (8) | 13 (2) | 13 (2) | 50 (6) | 50 (5) |
| KARMA | 2010-2013 | 57 (17) | 60 (16) | 2 (2) | 2 (1) | 26 (20) | 28 (18) | 26 (7) | 26 (7) | . | . | 13 (2) | 13 (2) | 51 (5) | 51 (7) |
| MCCS | 1990-1994 | 63 (13) | 64 (14) | 2 (1) | 2 (2) | 31 (12) | 32 (12) | 24 (5) | 24 (6) | 9 (16) | 10 (16) | 13 (2) | 13 (2) | 49 (7) | 50 (6) |
| MEC | 1993-2002 | 60 (15) | 66 (14) | 2 (3) | 2 (2) | 31 (13) | 37 (20) | 23 (4) | 23 (9) | 2 (11) | 3 (11) | 12 (2) | 12 (2) | 47 (13) | 47 (13) |
| MISS | 1990-1992 | 49 (15) | 58 (18) | 2 (2) | 2 (2) | 18 (21) | 26 (18) | 25 (5) | 25 (6) | 11 (12) | 11 (12) | 13 (2) | 13 (2) | 50 (5) | 50 (5) |
| MMHS | 2003-2006 | 43 (11) | 65 (15) | 2 (2) | 2 (1) | 16 (13) | 32 (23) | 25 (8) | 23 (6) | . | . | 13 (1) | 13 (1) | 49 (7) | 50 (7) |
| NHS | 1989-1990 | 65 (12) | 64 (12) | 3 (2) | 3 (2) | 33 (12) | 32 (12) | 24 (3) | 24 (4) | 2 (9) | 2 (9) | 13 (1) | 13 (1) | 50 (4) | 51 (3) |
| NHS2 | 1996-1999 | 49 (8) | 50 (9) | 2 (2) | 2 (2) | 19 (11) | 19 (12) | 26 (6) | 26 (7) | 12 (21) | 12 (18) | 12 (1) | 12 (2) | 48 (8) | 50 (4) |
| PLCO | 1993-2001 | 62 (8) | 68 (9) | 3 (2) | 3 (2) | 35 (11) | 38 (17) | 22 (5) | 22 (5) | . | . | 13 (2) | 13 (0) | 47 (10) | 52 (10) |
| SMC | 1987-2011 | 59 (13) | 64 (12) | 2 (1) | 2 (2) | 30 (12) | 35 (16) | 24 (7) | 24 (6) | . | . | 13 (2) | 13 (2) | 51 (4) | 51 (4) |
| Population-based case-control studies | | 58 (15) | 56 (18) | 2 (2) | 2 (2) | 28 (15) | 25 (16) | 24 (6) | 24 (7) | 4 (10) | 3 (10) | 13 (2) | 13 (2) | 49 (7) | 49 (7) |
| ABCFS | 1992-1999, 1993-1998 | 44 (21) | 40 (14) | 2 (2) | 2 (2) | 17 (23) | 12 (17) | 25 (6) | 25 (7) | 9 (17) | 8 (16) | 13 (2) | 13 (2) | 48 (8) | 48 (9) |
| BCEES | 2009-2011 | 61 (14) | 58 (17) | 2 (1) | 2 (1) | 30 (16) | 26 (19) | 24 (6) | 24 (7) | 11 (19) | 12 (21) | 13 (2) | 13 (2) | 48 (9) | 49 (9) |
| BCINIS | 1990-2000 | 64 (18) | 63 (19) | 2 (1) | 2 (2) | 45 (24) | 37 (23) | 23 (4) | 23 (5) | 8 (13) | 8 (13) | 13 (2) | 13 (2) | 50 (5) | 50 (5) |
| CBCS | 2005-2009 | 55 (15) | 55 (17) | 2 (2) | 2 (2) | 24 (17) | 24 (18) | 26 (7) | 27 (7) | 6 (7) | 5 (6) | 13 (2) | 13 (2) | 50 (7) | 48 (7) |
| CECILE | 2005-2007 | 55 (17) | 55 (16) | 3 (2) | 2 (1) | 25 (18) | 24 (17) | 24 (5) | 24 (6) | 1 (4) | 1 (4) | 13 (2) | 13 (2) | 50 (6) | 50 (6) |
| ESTHER | 2001-2003 | 62 (14) | 61 (13) | 2 (2) | 2 (2) | . | . | . | . | 6 (7) | 5 (9) | 14 (3) | 14 (3) | 48 (8) | 49 (7) |
| GENICA | 2000-2004 | 59 (15) | 59 (16) | 2 (1) | 2 (1) | 30 (14) | 30 (14) | 25 (6) | 25 (6) | 2 (5) | 2 (4) | 14 (3) | 13 (2) | 48 (9) | 49 (8) |
| GESBC | 1992-1998 | 44 (8) | 43 (8) | 2 (1) | 1 (1) | 15 (11) | 16 (12) | 24 (6) | 24 (7) | 3 (8) | 2 (6) | 13 (2) | 13 (2) | 46 (7) | 44 (7) |
| KBCP | 1990-1995 | 52 (16) | 58 (22) | 2 (2) | 2 (2) | 23 (15) | 25 (17) | 24 (6) | 24 (6) | 0 (2) | 0 (0) | 13 (2) | 13 (2) | 50 (5) | 50 (6) |
| LAABC | 1995-2007 | 52 (14) | 53 (16) | 2 (1) | 2 (2) | . | . | . | . | . | . | 13 (2) | 13 (2) | . | . |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MARIE | 2001-2005 | 62 (10) | 62 (9) | 2 (1) | 2 (1) | 33 (9) | 33 (9) | 24 (6) | 24 (6) | 3 (6) | 2 (6) | 14 (3) | 14 (3) | 49 (8) | 49 (8) |
| MASTOS | 1999-2005 | 55 (10) | 51 (14) | 2 (1) | 2 (1) | 26 (12) | 21 (14) | 23 (5) | 24 (6) | 5 (11) | 3 (10) | 13 (2) | 13 (2) | 50 (7) | 49 (6) |
| NBHS | 2001-2011 | 52 (18) | 55 (18) | 2 (2) | 2 (2) | 22 (22) | 24 (19) | 23 (7) | 22 (8) | . | . | 12 (1) | 12 (1) | 46 (13) | 47 (12) |
| NCBCS | 1993-1996, 1996-2000, 2008-2013 | 51 (17) | 50 (17) | 2 (2) | 2 (2) | 24 (16) | 22 (18) | 21 (6) | 22 (8) | 0 (5) | 0 (6) | 13 (2) | 12 (1) | 45 (11) | 46 (10) |
| PBCS | 2000-2003 | 55 (16) | 55 (15) | 2 (1) | 1 (1) | 26 (15) | 25 (15) | 23 (5) | 24 (6) | 6 (11) | 4 (10) | 14 (2) | 13 (2) | 50 (5) | 50 (6) |
| PROCAS | 2009-2014 | 60 (11) | 61 (12) | 2 (2) | 2 (2) | 28 (14) | 30 (14) | 25 (7) | 25 (7) | . | . | 13 (2) | 13 (2) | 50 (7) | 50 (5) |
| SASBAC | 1993-1995 | 63 (11) | 63 (10) | 2 (2) | 2 (2) | 31 (9) | 31 (9) | 24 (6) | 25 (6) | 9 (11) | 9 (10) | 14 (1) | 14 (1) | 50 (4) | 50 (5) |
| SBCGS | 1996-2009 | 55 (13) | 53 (14) | 1 (1) | 1 (1) | 23 (11) | 21 (7) | 26 (5) | 27 (4) | 10 (16) | 7 (12) | 15 (2) | 14 (3) | 49 (4) | 50 (5) |

* In years.

Note: All values are median (IQR) unless stated otherwise.

**Supplementary Table S3**. ORs and 95%CIs for case-case* 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.

| Risk factor | | Intrinsic-like breast cancer subtype‡ | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Luminal B-like | | Luminal B-HER2-like | | HER2-enriched-like | | Triple negative | |
| | Luminal A-like cases | Cases | OR (95%CI) | Cases | OR (95%CI) | Cases | OR (95%CI) | Cases | OR (95%CI) |
| Time since last birth (years) | | | | | | | | | |
| Nulliparous | 1750 | 429 | 1.00 (Ref.) | 479 | 1.00 (Ref.) | 212 | 1.00 (Ref.) | 394 | 1.00 (Ref.) |
| 1 birth | | | | | | | | | |
| 0-<5 | 31 | 12 | 1.23 (0.60 to 2.52) | 21 | 1.65 (0.88 to 3.08) | 12 | 1.65 (0.77 to 3.57) | 31 | 2.65 (1.50 to 4.69) |
| 5<10 | 49 | 21 | 1.46 (0.82 to 2.60) | 24 | 1.12 (0.64 to 1.96) | 12 | 1.06 (0.51 to 2.18) | 28 | 1.72 (1.01 to 2.93) |
| 10<15 | 107 | 33 | 1.18 (0.74 to 1.86) | 41 | 0.89 (0.58 to 1.39) | 25 | 0.92 (0.53 to 1.59) | 44 | 1.42 (0.93 to 2.17) |
| 15<20 | 151 | 34 | 0.92 (0.60 to 1.43) | 66 | 0.89 (0.61 to 1.30) | 42 | 0.77 (0.48 to 1.24) | 83 | 1.70 (1.20 to 2.41) |
| 20<25 | 192 | 47 | 1.08 (0.73 to 1.58) | 77 | 0.94 (0.66 to 1.33) | 57 | 0.94 (0.61 to 1.44) | 105 | 1.89 (1.38 to 2.59) |
| 25<30 | 274 | 56 | 0.94 (0.67 to 1.34) | 72 | 0.80 (0.58 to 1.11) | 56 | 1.02 (0.69 to 1.52) | 92 | 1.51 (1.12 to 2.04) |
| 30<35 | 368 | 76 | 1.02 (0.75 to 1.40) | 84 | 0.81 (0.59 to 1.10) | 51 | 0.96 (0.65 to 1.42) | 94 | 1.62 (1.21 to 2.16) |
| 35<40 | 369 | 79 | 1.16 (0.85 to 1.58) | 81 | 0.89 (0.65 to 1.21) | 50 | 1.15 (0.78 to 1.69) | 88 | 1.73 (1.29 to 2.32) |
| 40<45 | 241 | 60 | 1.43 (1.01 to 2.02) | 62 | 1.19 (0.84 to 1.67) | 28 | 1.17 (0.73 to 1.87) | 60 | 2.13 (1.52 to 2.98) |
| 45<50 | 169 | 40 | 1.48 (0.99 to 2.21) | 41 | 1.28 (0.86 to 1.90) | 15 | 1.07 (0.59 to 1.94) | 29 | 1.73 (1.11 to 2.69) |
| 50<55 | 68 | 13 | 1.25 (0.67 to 2.35) | 16 | 1.37 (0.76 to 2.46) | 3 | 0.58 (0.18 to 1.92) | 17 | 2.74 (1.54 to 4.87) |
| ≥55 | 55 | 11 | 1.44 (0.72 to 2.87) | 7 | 1.12 (0.49 to 2.56) | 6 | 2.43 (0.98 to 6.02) | 6 | 1.99 (0.83 to 4.81) |
| | | | P-het = 1.84E-01 | | P-het = 1.48E-01 | | P-het = 1.07E-01 | | P-het = 5.49E-06 |
| 2 births | | | | | | | | | |
| 0-<5 | 37 | 18 | 1.66 (0.89 to 3.10) | 30 | 1.79 (1.03 to 3.11) | 12 | 1.72 (0.82 to 3.60) | 39 | 2.92 (1.74 to 4.91) |
| 5<10 | 90 | 32 | 1.31 (0.81 to 2.10) | 34 | 0.93 (0.58 to 1.48) | 19 | 1.27 (0.70 to 2.30) | 64 | 2.35 (1.58 to 3.50) |
| 10<15 | 164 | 50 | 1.23 (0.83 to 1.82) | 54 | 0.92 (0.62 to 1.35) | 23 | 0.94 (0.55 to 1.59) | 64 | 1.51 (1.06 to 2.17) |
| 15<20 | 271 | 57 | 0.90 (0.63 to 1.29) | 59 | 0.66 (0.46 to 0.93) | 24 | 0.64 (0.39 to 1.05) | 108 | 1.66 (1.24 to 2.24) |
| 20<25 | 340 | 64 | 0.85 (0.61 to 1.19) | 74 | 0.65 (0.47 to 0.89) | 45 | 0.91 (0.61 to 1.37) | 124 | 1.67 (1.27 to 2.20) |
| 25<30 | 341 | 75 | 1.07 (0.78 to 1.47) | 101 | 0.94 (0.70 to 1.27) | 49 | 1.07 (0.73 to 1.59) | 115 | 1.84 (1.40 to 2.42) |
| 30<35 | 420 | 77 | 0.93 (0.68 to 1.27) | 106 | 0.84 (0.63 to 1.12) | 58 | 1.12 (0.77 to 1.62) | 132 | 2.00 (1.54 to 2.61) |
| 35<40 | 397 | 98 | 1.36 (1.01 to 1.83) | 96 | 0.90 (0.67 to 1.21) | 34 | 0.79 (0.51 to 1.22) | 82 | 1.53 (1.14 to 2.07) |
| 40<45 | 279 | 53 | 1.15 (0.80 to 1.64) | 53 | 0.78 (0.55 to 1.11) | 31 | 1.15 (0.73 to 1.82) | 67 | 1.96 (1.42 to 2.72) |
| 45<50 | 127 | 20 | 0.99 (0.59 to 1.66) | 17 | 0.61 (0.35 to 1.06) | 12 | 1.14 (0.59 to 2.19) | 30 | 2.11 (1.35 to 3.30) |
| 50<55 | 41 | 12 | 1.78 (0.90 to 3.52) | 8 | 0.98 (0.45 to 2.17) | 3 | 1.03 (0.31 to 3.44) | 9 | 2.33 (1.09 to 4.96) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ≥55 | 6 | 3 | 3.00 (0.73 to 12.37) | 0 | . | 1 | 3.68 (0.42 to 32.09) | 1 | 2.56 (0.30 to 22.04) |
| | | | P-het = 4.68E-01 | | P-het = 7.30E-01 | | P-het = 3.38E-01 | | P-het = 1.17E-04 |
| ≥3 births | | | | | | | | | |
| 0-<5 | 24 | 11 | 1.61 (0.76 to 3.44) | 17 | 1.59 (0.81 to 3.12) | 18 | 4.33 (2.15 to 8.70) | 34 | 3.74 (2.09 to 6.67) |
| 5<10 | 89 | 18 | 0.79 (0.45 to 1.37) | 36 | 0.96 (0.61 to 1.50) | 14 | 0.95 (0.50 to 1.81) | 41 | 1.38 (0.89 to 2.21) |
| 10<15 | 138 | 37 | 1.09 (0.71 to 1.67) | 34 | 0.67 (0.43 to 1.03) | 22 | 1.11 (0.65 to 1.90) | 67 | 1.69 (1.18 to 2.42) |
| 15<20 | 169 | 43 | 1.10 (0.74 to 1.63) | 44 | 0.75 (0.51 to 1.11) | 25 | 1.11 (0.67 to 1.82) | 78 | 1.86 (1.34 to 2.58) |
| 20<25 | 191 | 49 | 1.15 (0.79 to 1.66) | 48 | 0.77 (0.53 to 1.11) | 35 | 1.45 (0.94 to 2.25) | 100 | 2.46 (1.82 to 3.32) |
| 25<30 | 250 | 52 | 1.00 (0.70 to 1.42) | 65 | 0.87 (0.63 to 1.22) | 33 | 1.15 (0.74 to 1.78) | 96 | 2.12 (1.58 to 2.84) |
| 30<35 | 331 | 78 | 1.19 (0.87 to 1.63) | 102 | 1.09 (0.81 to 1.46) | 33 | 0.94 (0.61 to 1.46) | 88 | 1.78 (1.32 to 2.38) |
| 35<40 | 369 | 73 | 1.07 (0.78 to 1.47) | 67 | 0.69 (0.50 to 0.96) | 30 | 0.87 (0.55 to 1.37) | 94 | 1.97 (1.47 to 2.64) |
| 40<45 | 273 | 52 | 1.08 (0.75 to 1.55) | 43 | 0.63 (0.43 to 0.92) | 23 | 1.00 (0.60 to 1.65) | 62 | 1.88 (1.35 to 2.64) |
| 45<50 | 122 | 23 | 1.15 (0.70 to 1.89) | 17 | 0.65 (0.38 to 1.14) | 6 | 0.76 (0.32 to 1.81) | 18 | 1.54 (0.90 to 2.65) |
| 50<55 | 40 | 9 | 1.35 (0.63 to 2.89) | 5 | 0.65 (0.25 to 1.70) | 4 | 1.83 (0.62 to 5.38) | 7 | 2.13 (0.91 to 4.94) |
| ≥55 | 4 | 2 | 3.17 (0.57 to 17.73) | 1 | 1.36 (0.15 to 12.56) | 0 | . | 1 | 4.40 (0.48 to 40.11) |
| | | | P-het = 6.24E-01 | | P-het = 5.93E-01 | | P-het = 6.54E-02 | | P-het = 1.21E-02 |
| Age at first birth§ (years) | | | | | | | | | |
| <20 | 1295 | 311 | 1.00 (Ref.) | 299 | 1.00 (Ref.) | 178 | 1.00 (Ref.) | 578 | 1.00 (Ref.) |
| 20-<25 | 4124 | 910 | 1.00 (0.86 to 1.16) | 946 | 1.04 (0.91 to 1.22) | 469 | 0.98 (0.81 to 1.19) | 1231 | 0.94 (0.83 to 1.07) |
| 25-<30 | 3144 | 677 | 0.93 (0.80 to 1.10) | 806 | 1.03 (0.88 to 1.21) | 387 | 0.91 (0.73 to 1.12) | 816 | 0.77 (0.67 to 0.88) |
| ≥30 | 1678 | 394 | 0.96 (0.80 to 1.16) | 409 | 0.91 (0.75 to 1.10) | 199 | 0.84 (0.66 to 1.09) | 361 | 0.60 (0.50 to 0.72) |
| | | | P-het = 3.21E-01 | | P-het = 3.90E-01 | | P-het = 8.62E-02 | | P-het = 5.94E-08 |
| Breastfeeding duration§ (months) | | | | | | | | | |
| 0 | 1826 | 469 | 1.00 (Ref.) | 469 | 1.00 (Ref.) | 252 | 1.00 (Ref.) | 839 | 1.00 (Ref.) |
| >0-6 | 2528 | 559 | 0.87 (0.75 to 1.00) | 702 | 0.98 (0.86 to 1.13) | 311 | 0.93 (0.77 to 1.12) | 739 | 0.84 (0.75 to 0.95) |
| >6-12 | 1150 | 259 | 0.91 (0.76 to 1.08) | 274 | 0.93 (0.78 to 1.10) | 142 | 0.99 (0.78 to 1.24) | 291 | 0.76 (0.64 to 0.89) |
| >12-24 | 1013 | 219 | 0.91 (0.75 to 1.10) | 224 | 1.01 (0.84 to 1.23) | 91 | 0.82 (0.63 to 1.07) | 232 | 0.71 (0.60 to 0.85) |
| >24 | 500 | 101 | 0.86 (0.67 to 1.11) | 102 | 1.02 (0.79 to 1.31) | 46 | 0.87 (0.61 to 1.24) | 129 | 0.78 (0.62 to 0.98) |
| | | | P-het = 9.38E-02 | | P-het = 8.33E-01 | | P-het = 3.52E-01 | | P-het = 3.77E-05 |
| Age at menarche (years) | | | | | | | | | |
| ≥15 | 1971 | 431 | 1.00 (Ref.) | 504 | 1.00 (Ref.) | 288 | 1.00 (Ref.) | 548 | 1.00 (Ref.) |
| 14 | 2093 | 475 | 0.98 (0.85 to 1.14) | 518 | 0.98 (0.85 to 1.13) | 265 | 0.96 (0.80 to 1.16) | 549 | 0.96 (0.83 to 1.10) |
| 13 | 3406 | 742 | 0.95 (0.83 to 1.09) | 799 | 0.97 (0.85 to 1.10) | 385 | 0.94 (0.79 to 1.12) | 880 | 0.93 (0.82 to 1.05) |
| ≤12 | 4469 | 1075 | 0.98 (0.87 to 1.12) | 1106 | 0.96 (0.85 to 1.09) | 510 | 0.89 (0.76 to 1.05) | 1427 | 0.96 (0.86 to 1.09) |
| | | | P-het = 7.97E-01 | | P-het = 1.68E-01 | | P-het = 2.04E-01 | | P-het = 7.09E-01 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Age at menopause (years) | | | | | | | | | |
| <50 | 4157 | 941 | 1.00 (Ref.) | 998 | 1.00 (Ref.) | 491 | 1.00 (Ref.) | 1144 | 1.00 (Ref.) |
| 50-<54 | 3179 | 617 | 0.91 (0.81 to 1.02) | 638 | 0.93 (0.83 to 1.04) | 342 | 1.07 (0.92 to 1.25) | 656 | 0.96 (0.86 to 1.08) |
| ≥54 | 1490 | 276 | 0.87 (0.75 to 1.01) | 337 | 1.06 (0.92 to 1.22) | 147 | 1.03 (0.85 to 1.26) | 281 | 0.92 (0.79 to 1.07) |
| | | | P-het = 2.43E-01 | | P-het = 4.92E-01 | | P-het = 5.42E-01 | | P-het = 9.50E-1 |

* Luminal A-like is the reference.

† The multivariable model was additionally adjusted for reference age (age at diagnosis for cases) and study.

‡ Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&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).

§ Among parous women.

**Supplementary Table S4**. ORs and 95%CIs for case-control* analyses† of associations between number of births and intrinsic-like subtypes‡ according to reference age in 5-year categories.

| | | | Intrinsic-like subtype | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Reference age** (years) | **Risk factor** | | **Luminal A-like** | | | | **Luminal B-like** | | | | **Luminal B-HER2-like** | | | | **HER2-enriched-like** | | | | **Triple negative** | | | |
| | **Number of births** | **Controls** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** |
| <40 | Nulliparous | 750 | 48 | 1.00 (Ref.) | | | 38 | 1.00 (Ref.) | | | 33 | 1.00 (Ref.) | | | 17 | 1.00 (Ref.) | | | 72 | 1.00 (Ref.) | | |
| | 1 | 592 | 68 | 1.34 | 0.70 | 2.56 | 28 | 0.99 | 0.44 | 2.23 | 33 | 1.15 | 0.50 | 2.64 | 20 | 1.36 | 0.51 | 3.64 | 71 | 1.37 | 0.78 | 2.40 |
| | 2 | 1082 | 85 | 0.81 | 0.43 | 1.51 | 47 | 0.87 | 0.41 | 1.86 | 55 | 1.13 | 0.51 | 2.50 | 28 | 1.47 | 0.59 | 3.69 | 114 | 1.37 | 0.81 | 2.31 |
| | ≥3 | 646 | 51 | 0.76 | 0.40 | 1.42 | 22 | 0.62 | 0.28 | 1.35 | 28 | 0.98 | 0.44 | 2.19 | 23 | 1.89 | 0.77 | 4.65 | 72 | 1.26 | 0.74 | 2.13 |
| 40-<45 | Nulliparous | 937 | 98 | 1.00 (Ref.) | | | 35 | 1.00 (Ref.) | | | 47 | 1.00 (Ref.) | | | 18 | 1.00 (Ref.) | | | 39 | 1.00 (Ref.) | | |
| | 1 | 1151 | 120 | 0.36 | 0.22 | 0.61 | 38 | 0.77 | 0.38 | 1.56 | 57 | 0.44 | 0.21 | 0.90 | 31 | 0.21 | 0.06 | 0.66 | 92 | 1.58 | 0.91 | 2.73 |
| | 2 | 2774 | 213 | 0.28 | 0.17 | 0.46 | 77 | 0.64 | 0.33 | 1.26 | 75 | 0.32 | 0.16 | 0.65 | 38 | 0.21 | 0.07 | 0.63 | 116 | 1.14 | 0.67 | 1.92 |
| | ≥3 | 1480 | 130 | 0.30 | 0.19 | 0.50 | 42 | 0.60 | 0.31 | 1.18 | 50 | 0.37 | 0.18 | 0.72 | 17 | 0.16 | 0.05 | 0.51 | 97 | 1.31 | 0.78 | 2.20 |
| 45-<50 | Nulliparous | 1047 | 181 | 1.00 (Ref.) | | | 45 | 1.00 (Ref.) | | | 67 | 1.00 (Ref.) | | | 33 | 1.00 (Ref.) | | | 53 | 1.00 (Ref.) | | |
| | 1 | 1479 | 199 | 0.45 | 0.31 | 0.65 | 53 | 0.62 | 0.33 | 1.15 | 100 | 0.46 | 0.25 | 0.84 | 60 | 0.37 | 0.18 | 0.79 | 101 | 0.95 | 0.59 | 1.54 |
| | 2 | 3195 | 441 | 0.42 | 0.30 | 0.59 | 107 | 0.54 | 0.30 | 0.96 | 116 | 0.37 | 0.21 | 0.66 | 50 | 0.30 | 0.15 | 0.61 | 181 | 1.10 | 0.71 | 1.71 |
| | ≥3 | 1932 | 250 | 0.38 | 0.27 | 0.53 | 66 | 0.55 | 0.31 | 0.97 | 52 | 0.25 | 0.14 | 0.45 | 41 | 0.38 | 0.19 | 0.76 | 109 | 0.94 | 0.60 | 1.46 |
| 50-<55 | Nulliparous | 1339 | 263 | 1.00 (Ref.) | | | 68 | 1.00 (Ref.) | | | 85 | 1.00 (Ref.) | | | 31 | 1.00 (Ref.) | | | 62 | 1.00 (Ref.) | | |
| | 1 | 1975 | 300 | 0.70 | 0.52 | 0.94 | 59 | 0.68 | 0.39 | 1.18 | 88 | 0.59 | 0.35 | 0.99 | 83 | 1.46 | 0.79 | 2.69 | 107 | 1.08 | 0.69 | 1.69 |
| | 2 | 4371 | 583 | 0.62 | 0.47 | 0.82 | 136 | 0.67 | 0.40 | 1.12 | 137 | 0.46 | 0.28 | 0.76 | 82 | 1.03 | 0.57 | 1.87 | 198 | 1.09 | 0.72 | 1.67 |
| | ≥3 | 2976 | 326 | 0.52 | 0.39 | 0.69 | 67 | 0.48 | 0.28 | 0.82 | 83 | 0.40 | 0.24 | 0.66 | 57 | 1.02 | 0.55 | 1.87 | 123 | 0.86 | 0.56 | 1.33 |
| 55-<60 | Nulliparous | 1405 | 276 | 1.00 (Ref.) | | | 58 | 1.00 (Ref.) | | | 69 | 1.00 (Ref.) | | | 41 | 1.00 (Ref.) | | | 55 | 1.00 (Ref.) | | |
| | 1 | 1807 | 376 | 0.92 | 0.70 | 1.21 | 83 | 1.53 | 0.91 | 2.57 | 104 | 0.79 | 0.49 | 1.29 | 61 | 0.92 | 0.50 | 1.71 | 123 | 1.56 | 1.00 | 2.43 |
| | 2 | 4413 | 626 | 0.71 | 0.55 | 0.93 | 142 | 1.12 | 0.68 | 1.84 | 193 | 0.70 | 0.44 | 1.12 | 82 | 0.74 | 0.41 | 1.34 | 210 | 1.28 | 0.84 | 1.95 |
| | ≥3 | 4144 | 370 | 0.47 | 0.36 | 0.62 | 99 | 0.88 | 0.53 | 1.46 | 132 | 0.58 | 0.36 | 0.92 | 58 | 0.67 | 0.37 | 1.23 | 166 | 1.06 | 0.69 | 1.62 |
| 60-<65 | Nulliparous | 1276 | 286 | 1.00 (Ref.) | | | 69 | 1.00 (Ref.) | | | 65 | 1.00 (Ref.) | | | 33 | 1.00 (Ref.) | | | 32 | 1.00 (Ref.) | | |

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 1771 | 396 | 0.96 | 0.74 | 1.26 | 90 | 1.19 | 0.71 | 1.99 | 103 | 1.17 | 0.72 | 1.89 | 53 | 0.64 | 0.31 | 1.34 | 92 | 2.41 | 1.39 | 4.17 |
| | 2 | 4465 | 878 | 0.91 | 0.70 | 1.17 | 169 | 0.92 | 0.56 | 1.50 | 191 | 0.93 | 0.59 | 1.47 | 86 | 0.46 | 0.22 | 0.93 | 183 | 2.11 | 1.25 | 3.55 |
| | ≥3 | 4711 | 615 | 0.60 | 0.47 | 0.78 | 137 | 0.69 | 0.42 | 1.12 | 166 | 0.73 | 0.46 | 1.14 | 63 | 0.34 | 0.17 | 0.70 | 140 | 1.34 | 0.80 | 2.26 |
| 65-<70 | Nulliparous | 1079 | 279 | 1.00 (Ref.) | | | 64 | 1.00 (Ref.) | | | 67 | 1.00 (Ref.) | | | 19 | 1.00 (Ref.) | | | 47 | 1.00 (Ref.) | | |
| | 1 | 1523 | 369 | 1.12 | 0.85 | 1.48 | 78 | 1.26 | 0.74 | 2.15 | 72 | 0.85 | 0.50 | 1.47 | 29 | 0.88 | 0.38 | 2.04 | 59 | 1.30 | 0.76 | 2.23 |
| | 2 | 3803 | 765 | 1.03 | 0.79 | 1.34 | 162 | 1.16 | 0.70 | 1.93 | 144 | 0.75 | 0.44 | 1.26 | 67 | 0.99 | 0.45 | 2.19 | 149 | 1.47 | 0.89 | 2.43 |
| | ≥3 | 4448 | 865 | 0.90 | 0.69 | 1.16 | 185 | 1.05 | 0.64 | 1.72 | 153 | 0.59 | 0.36 | 1.00 | 67 | 0.84 | 0.38 | 1.82 | 170 | 1.16 | 0.71 | 1.90 |
| ≥70 | Nulliparous | 797 | 319 | 1.00 (Ref.) | | | 52 | 1.00 (Ref.) | | | 46 | 1.00 (Ref.) | | | 20 | 1.00 (Ref.) | | | 34 | 1.00 (Ref.) | | |
| | 1 | 948 | 325 | 1.24 | 0.92 | 1.67 | 75 | 1.60 | 0.89 | 2.85 | 65 | 1.64 | 0.91 | 2.99 | 30 | 1.46 | 0.59 | 3.58 | 58 | 1.75 | 0.93 | 3.31 |
| | 2 | 2461 | 873 | 1.22 | 0.92 | 1.61 | 163 | 1.26 | 0.73 | 2.20 | 152 | 1.49 | 0.84 | 2.63 | 62 | 1.28 | 0.54 | 3.03 | 137 | 1.59 | 0.87 | 2.91 |
| | ≥3 | 3629 | 1326 | 1.08 | 0.82 | 1.42 | 249 | 1.18 | 0.69 | 2.03 | 226 | 1.32 | 0.76 | 2.30 | 82 | 1.01 | 0.43 | 2.36 | 245 | 1.63 | 0.90 | 2.95 |
| | | | | P for age interaction = 8.89E-03 | | | | P for age interaction = 8.01E-01 | | | | P for age interaction = 8.05E-01 | | | | P for age interaction = 6.35E-02 | | | | P for age interaction = 9.52E-01 | | |

* Controls is the reference.
† The model was also adjusted for reference age (age at diagnosis for cases, age at interview for controls) and study.
‡ Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&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).
Definitions: OR: odds ratio, Lower CL: lower confidence limit, Upper CL: upper confidence limit.

**Supplementary Table S5**. ORs and 95%CIs for case-control* analyses† of associations between age at first birth and intrinsic-like subtypes‡ according to reference age in 5-year categories.

| | | | **Intrinsic-like subtype** | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Reference age** (years) | **Risk factor** | | **Luminal A-like** | | | | **Luminal B-like** | | | | **Luminal B-HER2-like** | | | | **HER2-enriched-like** | | | | **Triple negative** | | | |
| | **Age at first birth** (years) | **Controls** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** |
| <40 | <20 | 215 | 35 | 1.00 (Ref.) | | | 21 | 1.00 (Ref.) | | | 15 | 1.00 (Ref.) | | | 18 | 1.00 (Ref.) | | | 62 | 1.00 (Ref.) | | |
| | 20-<25 | 740 | 65 | 0.83 | 0.50 | 1.40 | 32 | 0.76 | 0.40 | 1.46 | 30 | 1.03 | 0.51 | 2.05 | 19 | 0.57 | 0.28 | 1.19 | 77 | 0.74 | 0.48 | 1.15 |
| | 25-<30 | 851 | 68 | 0.84 | 0.49 | 1.43 | 18 | 0.37 | 0.18 | 0.79 | 46 | 0.37 | 0.18 | 0.79 | 25 | 0.69 | 0.33 | 1.45 | 76 | 0.70 | 0.44 | 1.11 |
| | ≥30 | 484 | 33 | 0.55 | 0.29 | 1.03 | 24 | 0.72 | 0.33 | 1.56 | 23 | 1.19 | 0.53 | 2.67 | 8 | 0.53 | 0.20 | 1.44 | 37 | 0.65 | 0.37 | 1.13 |
| 40-<45 | <20 | 426 | 40 | 1.00 (Ref.) | | | 24 | 1.00 (Ref.) | | | 18 | 1.00 (Ref.) | | | 5 | 1.00 (Ref.) | | | 68 | 1.00 (Ref.) | | |
| | 20-<25 | 1442 | 143 | 1.50 | 0.99 | 2.26 | 45 | 0.98 | 0.56 | 1.72 | 46 | 1.20 | 0.66 | 2.19 | 30 | 2.37 | 0.88 | 6.40 | 103 | 0.81 | 0.56 | 1.19 |
| | 25-<30 | 1812 | 149 | 1.86 | 1.22 | 2.85 | 51 | 1.24 | 0.70 | 2.22 | 66 | 1.55 | 0.85 | 2.85 | 29 | 2.24 | 0.80 | 6.29 | 75 | 0.63 | 0.41 | 0.96 |
| | ≥30 | 1605 | 121 | 1.97 | 1.25 | 3.09 | 35 | 0.87 | 0.46 | 1.66 | 49 | 1.43 | 0.75 | 2.73 | 21 | 2.68 | 0.92 | 7.82 | 52 | 0.63 | 0.39 | 1.00 |
| 45-<50 | <20 | 669 | 98 | 1.00 (Ref.) | | | 31 | 1.00 (Ref.) | | | 23 | 1.00 (Ref.) | | | 19 | 1.00 (Ref.) | | | 76 | 1.00 (Ref.) | | |
| | 20-<25 | 2102 | 277 | 1.08 | 0.82 | 1.42 | 76 | 1.09 | 0.69 | 1.73 | 74 | 1.19 | 0.72 | 1.95 | 47 | 1.23 | 0.69 | 2.18 | 142 | 1.03 | 0.74 | 1.42 |
| | 25-<30 | 2139 | 293 | 1.37 | 1.03 | 1.82 | 54 | 0.91 | 0.55 | 1.50 | 97 | 1.45 | 0.88 | 2.41 | 45 | 1.04 | 0.56 | 1.94 | 109 | 0.99 | 0.69 | 1.41 |
| | ≥30 | 1457 | 205 | 1.51 | 1.11 | 2.06 | 61 | 1.48 | 0.88 | 2.49 | 69 | 1.72 | 1.00 | 2.93 | 38 | 1.72 | 0.90 | 3.30 | 55 | 0.91 | 0.59 | 1.38 |
| 50-<55 | <20 | 993 | 145 | 1.00 (Ref.) | | | 37 | 1.00 (Ref.) | | | 40 | 1.00 (Ref.) | | | 44 | 1.00 (Ref.) | | | 80 | 1.00 (Ref.) | | |
| | 20-<25 | 3135 | 393 | 0.96 | 0.77 | 1.19 | 78 | 0.79 | 0.52 | 1.20 | 105 | 1.00 | 0.68 | 1.48 | 67 | 0.61 | 0.40 | 0.92 | 158 | 0.97 | 0.72 | 1.31 |
| | 25-<30 | 2955 | 380 | 1.14 | 0.91 | 1.42 | 85 | 0.99 | 0.65 | 1.52 | 82 | 0.87 | 0.58 | 1.32 | 69 | 0.65 | 0.42 | 1.01 | 123 | 0.98 | 0.71 | 1.36 |
| | ≥30 | 1668 | 249 | 1.26 | 0.99 | 1.62 | 58 | 1.10 | 0.69 | 1.76 | 65 | 1.14 | 0.73 | 1.78 | 36 | 0.58 | 0.35 | 0.97 | 51 | 0.75 | 0.50 | 1.12 |

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 55-<60 | <20 | 1321 | 194 | 1.00 (Ref.) | | | 50 | 1.00 (Ref.) | | | 52 | 1.00 (Ref.) | | | 34 | 1.00 (Ref.) | | | 92 | 1.00 (Ref.) | | |
| | 20-<25 | 4250 | 520 | 0.92 | 0.76 | 1.12 | 111 | 0.74 | 0.52 | 1.06 | 151 | 1.03 | 0.74 | 1.45 | 64 | 0.71 | 0.46 | 1.10 | 194 | 0.93 | 0.71 | 1.23 |
| | 25-<30 | 2870 | 375 | 0.98 | 0.80 | 1.21 | 99 | 0.90 | 0.62 | 1.30 | 139 | 1.34 | 0.95 | 1.90 | 64 | 1.03 | 0.66 | 1.63 | 128 | 0.96 | 0.71 | 1.30 |
| | ≥30 | 1296 | 235 | 1.22 | 0.97 | 1.54 | 51 | 0.88 | 0.57 | 1.35 | 64 | 1.31 | 0.87 | 1.96 | 31 | 1.08 | 0.62 | 1.86 | 57 | 0.95 | 0.65 | 1.38 |
| 60-<65 | <20 | 1246 | 247 | 1.00 (Ref.) | | | 49 | 1.00 (Ref.) | | | 59 | 1.00 (Ref.) | | | 19 | 1.00 (Ref.) | | | 73 | 1.00 (Ref.) | | |
| | 20-<25 | 4719 | 759 | 0.85 | 0.72 | 1.01 | 175 | 0.93 | 0.67 | 1.31 | 203 | 0.93 | 0.68 | 1.27 | 99 | 1.43 | 0.86 | 2.38 | 178 | 0.80 | 0.60 | 1.09 |
| | 25-<30 | 3013 | 567 | 1.04 | 0.87 | 1.25 | 114 | 0.96 | 0.67 | 1.38 | 127 | 0.94 | 0.67 | 1.32 | 55 | 1.26 | 0.72 | 2.19 | 105 | 0.80 | 0.57 | 1.12 |
| | ≥30 | 1202 | 266 | 1.16 | 0.93 | 1.43 | 48 | 0.90 | 0.58 | 1.40 | 53 | 0.91 | 0.60 | 1.37 | 19 | 0.97 | 0.49 | 1.91 | 38 | 0.67 | 0.43 | 1.03 |
| 65-<70 | <20 | 1049 | 273 | 1.00 (Ref.) | | | 55 | 1.00 (Ref.) | | | 41 | 1.00 (Ref.) | | | 19 | 1.00 (Ref.) | | | 65 | 1.00 (Ref.) | | |
| | 20-<25 | 4015 | 860 | 0.84 | 0.72 | 1.00 | 171 | 0.83 | 0.60 | 1.15 | 164 | 0.93 | 0.65 | 1.34 | 72 | 1.20 | 0.70 | 2.04 | 169 | 0.81 | 0.59 | 1.12 |
| | 25-<30 | 2832 | 562 | 0.85 | 0.71 | 1.02 | 128 | 0.92 | 0.65 | 1.30 | 109 | 0.89 | 0.61 | 1.31 | 41 | 1.04 | 0.58 | 1.87 | 94 | 0.71 | 0.50 | 1.01 |
| | ≥30 | 1087 | 251 | 1.03 | 0.83 | 1.27 | 47 | 0.89 | 0.58 | 1.37 | 36 | 0.75 | 0.46 | 1.22 | 26 | 1.73 | 0.89 | 3.33 | 29 | 0.61 | 0.37 | 0.99 |
| ≥70 | <20 | 589 | 263 | 1.00 (Ref.) | | | 44 | 1.00 (Ref.) | | | 51 | 1.00 (Ref.) | | | 20 | 1.00 (Ref.) | | | 62 | 1.00 (Ref.) | | |
| | 20-<25 | 2775 | 1107 | 0.90 | 0.76 | 1.07 | 222 | 1.05 | 0.74 | 1.48 | 173 | 0.75 | 0.53 | 1.04 | 71 | 0.82 | 0.49 | 1.37 | 210 | 0.84 | 0.61 | 1.14 |
| | 25-<30 | 2091 | 750 | 0.83 | 0.69 | 1.00 | 128 | 0.81 | 0.56 | 1.18 | 140 | 0.80 | 0.56 | 1.14 | 59 | 0.95 | 0.55 | 1.63 | 106 | 0.59 | 0.41 | 0.83 |
| | ≥30 | 810 | 318 | 0.90 | 0.72 | 1.12 | 70 | 1.06 | 0.70 | 1.62 | 50 | 0.69 | 0.45 | 1.07 | 20 | 0.74 | 0.38 | 1.46 | 42 | 0.59 | 0.38 | 0.91 |
| | | | | P for age interaction = 6.55E-05 | | | | P for age interaction = 7.87E-01 | | | | P for age interaction = 9.29E-01 | | | | P for age interaction = 6.27E-01 | | | | P for age interaction = 8.15E-01 | | |

* Controls is the reference.
† The model was also adjusted for reference age (age at diagnosis for cases, age at interview for controls) and study.
‡ Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&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).
Definitions: OR: odds ratio, Lower CL: lower confidence limit, Upper CL: upper confidence limit.

**Supplementary Table S6**. ORs and 95%CIs for case-control* analyses† of associations between breastfeeding duration and intrinsic-like subtypes‡ according to reference age in 5-year categories.

| | | | Intrinsic-like subtype | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Reference age** (years) | **Risk factor** | | **Luminal A-like** | | | | **Luminal B-like** | | | | **Luminal B-HER2-like** | | | | **HER2-enriched-like** | | | | **Triple negative** | | | |
| | **Breastfeeding duration** (months) | **Controls** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** |
| <40 | 0 | 298 | 51 | 1.00 (Ref.) | | | 26 | 1.00 (Ref.) | | | 37 | 1.00 (Ref.) | | | 19 | 1.00 (Ref.) | | | 97 | 1.00 (Ref.) | | |
| | >0-6 | 506 | 65 | 1.75 | 1.11 | 2.76 | 27 | 1.51 | 0.81 | 2.80 | 27 | 0.68 | 0.38 | 1.20 | 16 | 1.09 | 0.53 | 2.25 | 72 | 1.01 | 0.68 | 1.49 |
| | >6-12 | 317 | 31 | 1.75 | 1.00 | 3.07 | 15 | 1.79 | 0.85 | 3.79 | 11 | 0.60 | 0.28 | 1.30 | 8 | 1.26 | 0.51 | 3.13 | 23 | 0.74 | 0.42 | 1.28 |
| | >12-24 | 293 | 21 | 1.35 | 0.72 | 2.53 | 14 | 2.19 | 1.00 | 4.79 | 11 | 0.83 | 0.38 | 1.81 | 6 | 1.17 | 0.43 | 3.22 | 13 | 0.50 | 0.25 | 0.99 |
| | >24 | 181 | 13 | 1.63 | 0.76 | 3.49 | 3 | 0.97 | 0.26 | 3.60 | 7 | 1.30 | 0.51 | 3.34 | 5 | 1.85 | 0.60 | 5.72 | 12 | 0.93 | 0.44 | 1.96 |
| 40-<45 | 0 | 493 | 99 | 1.00 (Ref.) | | | 48 | 1.00 (Ref.) | | | 37 | 1.00 (Ref.) | | | 18 | 1.00 (Ref.) | | | 105 | 1.00 (Ref.) | | |
| | >0-6 | 703 | 128 | 1.45 | 1.05 | 2.01 | 29 | 0.81 | 0.48 | 1.36 | 54 | 1.40 | 0.87 | 2.25 | 27 | 1.73 | 0.91 | 3.28 | 66 | 0.98 | 0.68 | 1.42 |
| | >6-12 | 486 | 72 | 1.18 | 0.81 | 1.73 | 15 | 0.65 | 0.34 | 1.25 | 27 | 1.07 | 0.60 | 1.89 | 8 | 0.73 | 0.30 | 1.77 | 24 | 0.60 | 0.36 | 1.00 |
| | >12-24 | 320 | 57 | 1.22 | 0.80 | 1.85 | 16 | 0.98 | 0.51 | 1.89 | 12 | 0.85 | 0.41 | 1.76 | 4 | 0.71 | 0.23 | 2.22 | 16 | 0.56 | 0.31 | 1.02 |
| | >24 | 203 | 38 | 1.22 | 0.75 | 2.00 | 8 | 0.82 | 0.35 | 1.92 | 14 | 1.69 | 0.82 | 3.49 | 5 | 1.39 | 0.47 | 4.14 | 22 | 1.25 | 0.70 | 2.22 |
| 45-<50 | 0 | 1002 | 189 | 1.00 (Ref.) | | | 59 | 1.00 (Ref.) | | | 62 | 1.00 (Ref.) | | | 37 | 1.00 (Ref.) | | | 157 | 1.00 (Ref.) | | |
| | >0-6 | 1138 | 241 | 1.59 | 1.25 | 2.01 | 54 | 1.25 | 0.83 | 1.90 | 67 | 1.06 | 0.72 | 1.55 | 28 | 1.02 | 0.60 | 1.74 | 78 | 0.86 | 0.63 | 1.18 |
| | >6-12 | 669 | 115 | 1.46 | 1.10 | 1.95 | 33 | 1.49 | 0.91 | 2.45 | 28 | 0.76 | 0.46 | 1.24 | 15 | 0.96 | 0.50 | 1.86 | 37 | 0.77 | 0.51 | 1.15 |
| | >12-24 | 404 | 110 | 1.94 | 1.43 | 2.63 | 22 | 1.43 | 0.82 | 2.52 | 23 | 1.23 | 0.72 | 2.10 | 11 | 1.44 | 0.69 | 2.99 | 25 | 0.82 | 0.51 | 1.32 |
| | >24 | 265 | 60 | 1.48 | 1.01 | 2.16 | 9 | 0.77 | 0.35 | 1.69 | 13 | 1.23 | 0.62 | 2.44 | 6 | 1.26 | 0.49 | 3.27 | 15 | 0.75 | 0.41 | 1.37 |
| 50-<55 | 0 | 1268 | 270 | 1.00 (Ref.) | | | 61 | 1.00 (Ref.) | | | 62 | 1.00 (Ref.) | | | 48 | 1.00 (Ref.) | | | 134 | 1.00 (Ref.) | | |
| | >0-6 | 1767 | 316 | 0.98 | 0.81 | 1.19 | 62 | 0.95 | 0.65 | 1.40 | 85 | 1.16 | 0.81 | 1.65 | 55 | 1.07 | 0.71 | 1.62 | 104 | 0.86 | 0.65 | 1.15 |
| | >6-12 | 1031 | 149 | 0.84 | 0.66 | 1.06 | 31 | 0.84 | 0.53 | 1.35 | 39 | 1.01 | 0.65 | 1.57 | 27 | 0.94 | 0.57 | 1.57 | 32 | 0.49 | 0.33 | 0.75 |
| | >12-24 | 691 | 139 | 1.14 | 0.88 | 1.46 | 29 | 1.11 | 0.68 | 1.82 | 36 | 1.55 | 0.98 | 2.47 | 19 | 1.26 | 0.70 | 2.26 | 35 | 0.91 | 0.60 | 1.38 |
| | >24 | 334 | 94 | 1.24 | 0.91 | 1.67 | 15 | 0.94 | 0.50 | 1.76 | 11 | 0.89 | 0.44 | 1.79 | 6 | 0.81 | 0.33 | 1.99 | 17 | 0.81 | 0.46 | 1.42 |

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 55-<60 | 0 | 1175 | 299 | 1.00 (Ref.) | | | 72 | 1.00 (Ref.) | | | 78 | 1.00 (Ref.) | | | 45 | 1.00 (Ref.) | | | 133 | 1.00 (Ref.) | | |
| | >0-6 | 1972 | 433 | 1.09 | 0.91 | 1.30 | 83 | 0.78 | 0.56 | 1.10 | 133 | 1.10 | 0.81 | 1.48 | 51 | 0.86 | 0.56 | 1.32 | 128 | 0.89 | 0.68 | 1.17 |
| | >6-12 | 892 | 141 | 0.89 | 0.71 | 1.13 | 42 | 1.06 | 0.70 | 1.60 | 50 | 1.05 | 0.71 | 1.55 | 22 | 0.84 | 0.49 | 1.45 | 54 | 0.93 | 0.66 | 1.33 |
| | >12-24 | 731 | 128 | 1.05 | 0.82 | 1.36 | 28 | 0.96 | 0.60 | 1.55 | 39 | 1.08 | 0.70 | 1.66 | 10 | 0.47 | 0.23 | 0.96 | 40 | 0.87 | 0.59 | 1.30 |
| | >24 | 310 | 66 | 1.16 | 0.83 | 1.61 | 18 | 1.41 | 0.79 | 2.53 | 17 | 1.10 | 0.61 | 1.97 | 6 | 0.64 | 0.26 | 1.58 | 17 | 0.82 | 0.47 | 1.43 |
| 60-<65 | 0 | 1165 | 342 | 1.00 (Ref.) | | | 77 | 1.00 (Ref.) | | | 90 | 1.00 (Ref.) | | | 33 | 1.00 (Ref.) | | | 92 | 1.00 (Ref.) | | |
| | >0-6 | 2046 | 519 | 1.06 | 0.90 | 1.25 | 119 | 1.00 | 0.73 | 1.36 | 137 | 1.01 | 0.76 | 1.35 | 60 | 1.13 | 0.72 | 1.77 | 116 | 1.08 | 0.79 | 1.47 |
| | >6-12 | 880 | 203 | 1.07 | 0.87 | 1.32 | 39 | 0.89 | 0.59 | 1.35 | 35 | 0.70 | 0.46 | 1.07 | 19 | 0.99 | 0.55 | 1.79 | 40 | 0.94 | 0.63 | 1.42 |
| | >12-24 | 676 | 145 | 1.11 | 0.88 | 1.41 | 30 | 1.04 | 0.66 | 1.65 | 42 | 1.37 | 0.91 | 2.05 | 17 | 1.38 | 0.73 | 2.61 | 27 | 0.92 | 0.57 | 1.48 |
| | >24 | 342 | 61 | 1.05 | 0.76 | 1.47 | 12 | 0.95 | 0.50 | 1.83 | 13 | 0.98 | 0.52 | 1.83 | 2 | 0.37 | 0.09 | 1.61 | 10 | 0.72 | 0.36 | 1.45 |
| 65-<70 | 0 | 937 | 320 | 1.00 (Ref.) | | | 72 | 1.00 (Ref.) | | | 60 | 1.00 (Ref.) | | | 34 | 1.00 (Ref.) | | | 84 | 1.00 (Ref.) | | |
| | >0-6 | 1604 | 437 | 0.92 | 0.77 | 1.10 | 106 | 0.98 | 0.71 | 1.36 | 108 | 1.13 | 0.80 | 1.58 | 36 | 0.72 | 0.43 | 1.18 | 91 | 0.86 | 0.62 | 1.19 |
| | >6-12 | 735 | 216 | 1.03 | 0.83 | 1.27 | 44 | 0.96 | 0.64 | 1.44 | 45 | 1.08 | 0.71 | 1.65 | 17 | 0.77 | 0.41 | 1.44 | 31 | 0.63 | 0.40 | 0.98 |
| | >12-24 | 591 | 139 | 0.86 | 0.67 | 1.10 | 27 | 0.78 | 0.48 | 1.26 | 21 | 0.67 | 0.39 | 1.14 | 15 | 0.86 | 0.44 | 1.67 | 35 | 0.89 | 0.57 | 1.38 |
| | >24 | 393 | 61 | 0.64 | 0.46 | 0.88 | 11 | 0.54 | 0.28 | 1.07 | 13 | 0.65 | 0.34 | 1.25 | 6 | 0.46 | 0.18 | 1.17 | 14 | 0.48 | 0.26 | 0.90 |
| ≥70 | 0 | 693 | 256 | 1.00 (Ref.) | | | 54 | 1.00 (Ref.) | | | 43 | 1.00 (Ref.) | | | 18 | 1.00 (Ref.) | | | 37 | 1.00 (Ref.) | | |
| | >0-6 | 1218 | 389 | 0.87 | 0.72 | 1.06 | 79 | 0.78 | 0.53 | 1.13 | 91 | 1.07 | 0.73 | 1.58 | 38 | 1.08 | 0.60 | 1.94 | 84 | 1.39 | 0.92 | 2.10 |
| | >6-12 | 615 | 223 | 0.87 | 0.70 | 1.10 | 40 | 0.66 | 0.42 | 1.02 | 39 | 0.87 | 0.55 | 1.39 | 26 | 1.41 | 0.74 | 2.66 | 50 | 1.40 | 0.88 | 2.22 |
| | >12-24 | 574 | 274 | 1.08 | 0.86 | 1.35 | 53 | 0.91 | 0.59 | 1.39 | 40 | 1.00 | 0.62 | 1.61 | 9 | 0.52 | 0.22 | 1.21 | 41 | 1.09 | 0.67 | 1.78 |
| | >24 | 346 | 107 | 0.71 | 0.54 | 0.95 | 25 | 0.73 | 0.43 | 1.24 | 14 | 0.59 | 0.31 | 1.12 | 10 | 0.81 | 0.35 | 1.89 | 22 | 0.78 | 0.44 | 1.40 |
| | | | | P for age interaction = 1.07E-02 | | | | P for age interaction = 9.910E-01 | | | | P for age interaction = 7.73E-01 | | | | P for age interaction = 4.21E-01 | | | | P for age interaction = 2.20E-01 | | |

* Controls is the reference.
† The model was also adjusted for reference age (age at diagnosis for cases, age at interview for controls) and study.
‡ Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&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).
Definitions: OR: odds ratio, Lower CL: lower confidence limit, Upper CL: upper confidence limit.

**Supplementary Table S7**. ORs and 95%CIs for case-control* analyses† of associations between age at menarche and intrinsic-like subtypes‡ according to reference age in 5-year categories.

| | | | **Intrinsic-like subtype** | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Reference age** (years) | **Risk factor** | | **Luminal A-like** | | | | **Luminal B-like** | | | | **Luminal B-HER2-like** | | | | **HER2-enriched-like** | | | | **Triple negative** | | | |
| | **Age at menarche** (years) | **Controls** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** |
| <40 | ≥15 | 362 | 25 | 1.00 (Ref.) | | | 12 | 1.00 (Ref.) | | | 16 | 1.00 (Ref.) | | | 10 | 1.00 (Ref.) | | | 25 | 1.00 (Ref.) | | |
| | 14 | 540 | 32 | 0.92 | 0.50 | 1.69 | 24 | 1.68 | 0.78 | 3.61 | 22 | 1.09 | 0.54 | 2.21 | 8 | 0.62 | 0.23 | 1.63 | 45 | 1.48 | 0.85 | 2.59 |
| | 13 | 894 | 67 | 1.13 | 0.66 | 1.93 | 33 | 1.17 | 0.57 | 2.39 | 35 | 0.99 | 0.51 | 1.89 | 19 | 0.87 | 0.38 | 1.94 | 74 | 1.34 | 0.80 | 2.25 |
| | ≤12 | 1279 | 128 | 1.33 | 0.81 | 2.20 | 66 | 1.44 | 0.73 | 2.81 | 76 | 1.32 | 0.72 | 2.39 | 50 | 1.30 | 0.63 | 2.70 | 184 | 1.88 | 1.16 | 3.03 |
| 40-<45 | ≥15 | 859 | 53 | 1.00 (Ref.) | | | 27 | 1.00 (Ref.) | | | 29 | 1.00 (Ref.) | | | 16 | 1.00 (Ref.) | | | 39 | 1.00 (Ref.) | | |
| | 14 | 1114 | 100 | 1.36 | 0.93 | 1.99 | 33 | 0.91 | 0.53 | 1.57 | 40 | 1.19 | 0.71 | 1.98 | 14 | 0.85 | 0.40 | 1.79 | 34 | 0.80 | 0.49 | 1.31 |
| | 13 | 1717 | 167 | 1.54 | 1.08 | 2.19 | 39 | 0.69 | 0.41 | 1.16 | 64 | 1.19 | 0.74 | 1.90 | 30 | 1.32 | 0.69 | 2.52 | 96 | 1.53 | 1.01 | 2.31 |
| | ≤12 | 2555 | 240 | 1.37 | 0.97 | 1.93 | 92 | 0.98 | 0.62 | 1.55 | 96 | 1.13 | 0.72 | 1.78 | 45 | 1.42 | 0.76 | 2.66 | 174 | 1.63 | 1.10 | 2.41 |
| 45-<50 | ≥15 | 1088 | 110 | 1.00 (Ref.) | | | 21 | 1.00 (Ref.) | | | 52 | 1.00 (Ref.) | | | 30 | 1.00 (Ref.) | | | 53 | 1.00 (Ref.) | | |
| | 14 | 1539 | 184 | 1.06 | 0.81 | 1.38 | 47 | 1.46 | 0.86 | 2.49 | 51 | 0.85 | 0.56 | 1.27 | 36 | 1.19 | 0.72 | 1.98 | 67 | 1.07 | 0.73 | 1.57 |
| | 13 | 1907 | 271 | 1.17 | 0.91 | 1.50 | 78 | 1.66 | 1.01 | 2.74 | 84 | 1.09 | 0.75 | 1.59 | 55 | 1.42 | 0.88 | 2.30 | 114 | 1.25 | 0.88 | 1.79 |
| | ≤12 | 3062 | 503 | 1.30 | 1.02 | 1.64 | 125 | 1.53 | 0.94 | 2.47 | 152 | 1.26 | 0.88 | 1.79 | 65 | 1.04 | 0.64 | 1.68 | 205 | 1.31 | 0.93 | 1.84 |
| 50-<55 | ≥15 | 1645 | 187 | 1.00 (Ref.) | | | 43 | 1.00 (Ref.) | | | 53 | 1.00 (Ref.) | | | 42 | 1.00 (Ref.) | | | 74 | 1.00 (Ref.) | | |
| | 14 | 2019 | 242 | 1.05 | 0.85 | 1.29 | 51 | 0.98 | 0.65 | 1.49 | 56 | 1.00 | 0.68 | 1.47 | 51 | 1.37 | 0.89 | 2.09 | 87 | 1.17 | 0.85 | 1.63 |
| | 13 | 2672 | 364 | 1.11 | 0.91 | 1.36 | 78 | 0.98 | 0.67 | 1.44 | 101 | 1.17 | 0.83 | 1.67 | 63 | 1.29 | 0.85 | 1.95 | 103 | 0.93 | 0.68 | 1.28 |
| | ≤12 | 3943 | 645 | 1.30 | 1.08 | 1.57 | 157 | 1.28 | 0.90 | 1.83 | 166 | 1.33 | 0.96 | 1.86 | 97 | 1.41 | 0.95 | 2.10 | 219 | 1.25 | 0.94 | 1.67 |
| 55-<60 | ≥15 | 1922 | 238 | 1.00 (Ref.) | | | 46 | 1.00 (Ref.) | | | 82 | 1.00 (Ref.) | | | 43 | 1.00 (Ref.) | | | 83 | 1.00 (Ref.) | | |
| | 14 | 2054 | 300 | 1.08 | 0.89 | 1.30 | 70 | 1.21 | 0.83 | 1.78 | 78 | 0.86 | 0.62 | 1.19 | 34 | 0.82 | 0.51 | 1.31 | 90 | 1.00 | 0.73 | 1.37 |
| | 13 | 3186 | 438 | 1.13 | 0.94 | 1.35 | 97 | 1.24 | 0.86 | 1.78 | 139 | 1.09 | 0.82 | 1.46 | 72 | 1.30 | 0.87 | 1.94 | 133 | 1.07 | 0.80 | 1.43 |
| | ≤12 | 3990 | 615 | 1.11 | 0.93 | 1.31 | 153 | 1.34 | 0.95 | 1.89 | 174 | 0.98 | 0.74 | 1.30 | 85 | 1.03 | 0.69 | 1.53 | 220 | 1.06 | 0.81 | 1.40 |
| 60-<65 | ≥15 | 2242 | 369 | 1.00 (Ref.) | | | 72 | 1.00 (Ref.) | | | 75 | 1.00 (Ref.) | | | 56 | 1.00 (Ref.) | | | 84 | 1.00 (Ref.) | | |
| | 14 | 2241 | 399 | 1.12 | 0.95 | 1.32 | 67 | 0.96 | 0.68 | 1.35 | 101 | 1.53 | 1.12 | 2.09 | 45 | 0.92 | 0.61 | 1.38 | 77 | 1.06 | 0.76 | 1.46 |
| | 13 | 3159 | 595 | 1.11 | 0.95 | 1.28 | 131 | 1.31 | 0.97 | 1.77 | 133 | 1.37 | 1.02 | 1.84 | 51 | 0.79 | 0.53 | 1.17 | 116 | 0.98 | 0.72 | 1.32 |

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≤12 | 3672 | 716 | 1.14 | 0.99 | 1.32 | 177 | 1.48 | 1.11 | 1.97 | 184 | 1.62 | 1.22 | 2.16 | 72 | 0.94 | 0.65 | 1.36 | 147 | 1.01 | 0.75 | 1.34 |
| 65-<70 | ≥15 | 2300 | 433 | 1.00 (Ref.) | | | 92 | 1.00 (Ref.) | | | 92 | 1.00 (Ref.) | | | 42 | 1.00 (Ref.) | | | 73 | 1.00 (Ref.) | | |
| | 14 | 2153 | 389 | 1.05 | 0.90 | 1.23 | 86 | 1.14 | 0.84 | 1.55 | 99 | 1.36 | 1.01 | 1.84 | 40 | 1.30 | 0.83 | 2.04 | 65 | 1.15 | 0.81 | 1.64 |
| | 13 | 2598 | 629 | 1.15 | 0.99 | 1.32 | 130 | 1.18 | 0.89 | 1.57 | 105 | 1.10 | 0.81 | 1.48 | 42 | 1.03 | 0.65 | 1.61 | 122 | 1.56 | 1.14 | 2.13 |
| | ≤12 | 2891 | 731 | 1.28 | 1.11 | 1.48 | 152 | 1.30 | 0.98 | 1.71 | 117 | 1.10 | 0.81 | 1.47 | 49 | 1.09 | 0.70 | 1.70 | 145 | 1.60 | 1.18 | 2.18 |
| ≥70 | ≥15 | 1623 | 556 | 1.00 (Ref.) | | | 118 | 1.00 (Ref.) | | | 105 | 1.00 (Ref.) | | | 49 | 1.00 (Ref.) | | | 117 | 1.00 (Ref.) | | |
| | 14 | 1491 | 447 | 1.12 | 0.96 | 1.31 | 97 | 1.02 | 0.76 | 1.36 | 71 | 0.96 | 0.69 | 1.32 | 37 | 1.23 | 0.78 | 1.93 | 84 | 1.03 | 0.76 | 1.40 |
| | 13 | 1872 | 875 | 1.15 | 1.00 | 1.32 | 156 | 0.96 | 0.74 | 1.24 | 138 | 1.15 | 0.87 | 1.51 | 53 | 1.13 | 0.74 | 1.72 | 122 | 0.87 | 0.66 | 1.15 |
| | ≤12 | 2180 | 891 | 1.19 | 1.04 | 1.36 | 153 | 0.89 | 0.69 | 1.16 | 141 | 1.10 | 0.83 | 1.46 | 47 | 1.04 | 0.67 | 1.61 | 133 | 0.91 | 0.69 | 1.21 |
| | | | | P for age interaction = 8.80E-01 | | | | P for age interaction = 7.13E-01 | | | | P for age interaction = 5.10E-01 | | | | P for age interaction = 1.63E-01 | | | | P for age interaction = 1.59E-03 | | |

* Controls is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases, age at interview for controls) and study.

‡ Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&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).

Definitions: OR: odds ratio, Lower CL: lower confidence limit, Upper CL: upper confidence limit.

**Supplementary Table S8**. ORs and 95%CIs for case-control* analyses† of associations between age at menopause and intrinsic-like subtypes‡ according to reference age in 5-year categories.

| | | | **Intrinsic-like subtype** | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Reference age** (years) | **Risk factor** | | **Luminal A-like** | | | | **Luminal B-like** | | | | **Luminal B-HER2-like** | | | | **HER2-enriched-like** | | | | **Triple negative** | | | |
| | **Age at menopause** (years) | **Controls** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** |
| <40 | <50 | 73 | 17 | 1.00 (Ref.) | | | 12 | 1.00 (Ref.) | | | 11 | 1.00 (Ref.) | | | 4 | 1.00 (Ref.) | | | 21 | 1.00 (Ref.) | | |
| | 50-<54 | 0 | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . |
| | ≥54 | 0 | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . |
| 40-<45 | <50 | 228 | 61 | 1.00 (Ref.) | | | 25 | 1.00 (Ref.) | | | 24 | 1.00 (Ref.) | | | 8 | 1.00 (Ref.) | | | 41 | 1.00 (Ref.) | | |
| | 50-<54 | 0 | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . |
| | ≥54 | 0 | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . |
| 45-<50 | <50 | 1124 | 257 | 1.00 (Ref.) | | | 66 | 1.00 (Ref.) | | | 72 | 1.00 (Ref.) | | | 63 | 1.00 (Ref.) | | | 131 | 1.00 (Ref.) | | |
| | 50-<54 | 0 | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . |
| | ≥54 | 0 | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . | 0 | . | . | . |
| 50-<55 | <50 | 2820 | 384 | 1.00 (Ref.) | | | 88 | 1.00 (Ref.) | | | 108 | 1.00 (Ref.) | | | 93 | 1.00 (Ref.) | | | 180 | 1.00 (Ref.) | | |
| | 50-<54 | 1626 | 274 | 1.28 | 1.07 | 1.53 | 54 | 1.15 | 0.80 | 1.65 | 68 | 1.31 | 0.95 | 1.81 | 58 | 1.08 | 0.76 | 1.54 | 93 | 1.09 | 0.82 | 1.44 |
| | ≥54 | 26 | 6 | 2.02 | 0.76 | 5.39 | 1 | 1.46 | 0.19 | 11.54 | 3 | 4.69 | 1.30 | 16.92 | 2 | 2.20 | 0.48 | 10.23 | 3 | 2.62 | 0.72 | 9.48 |
| 55-<60 | <50 | 4088 | 626 | 1.00 (Ref.) | | | 127 | 1.00 (Ref.) | | | 198 | 1.00 (Ref.) | | | 89 | 1.00 (Ref.) | | | 222 | 1.00 (Ref.) | | |
| | 50-<54 | 3534 | 489 | 0.92 | 0.81 | 1.06 | 110 | 1.03 | 0.79 | 1.35 | 139 | 0.87 | 0.69 | 1.09 | 84 | 1.16 | 0.85 | 1.58 | 157 | 0.90 | 0.72 | 1.12 |
| | ≥54 | 1359 | 197 | 0.92 | 0.76 | 1.10 | 50 | 1.17 | 0.83 | 1.65 | 62 | 0.97 | 0.72 | 1.31 | 35 | 1.24 | 0.82 | 1.87 | 65 | 0.93 | 0.69 | 1.26 |
| 60-<65 | <50 | 4429 | 824 | 1.00 (Ref.) | | | 189 | 1.00 (Ref.) | | | 202 | 1.00 (Ref.) | | | 85 | 1.00 (Ref.) | | | 191 | 1.00 (Ref.) | | |
| | 50-<54 | 3434 | 671 | 1.16 | 1.03 | 1.31 | 144 | 1.09 | 0.87 | 1.37 | 136 | 0.97 | 0.77 | 1.21 | 71 | 1.17 | 0.85 | 1.63 | 127 | 1.03 | 0.81 | 1.31 |
| | ≥54 | 1990 | 394 | 1.14 | 1.00 | 1.31 | 65 | 0.82 | 0.61 | 1.09 | 117 | 1.42 | 1.12 | 1.80 | 50 | 1.37 | 0.95 | 1.96 | 63 | 0.85 | 0.63 | 1.14 |
| 65-<70 | <50 | 3991 | 887 | 1.00 (Ref.) | | | 200 | 1.00 (Ref.) | | | 172 | 1.00 (Ref.) | | | 72 | 1.00 (Ref.) | | | 180 | 1.00 (Ref.) | | |
| | 50-<54 | 2789 | 743 | 1.34 | 1.19 | 1.50 | 124 | 1.00 | 0.79 | 1.27 | 134 | 1.25 | 0.99 | 1.59 | 53 | 1.24 | 0.86 | 1.79 | 122 | 1.16 | 0.91 | 1.49 |

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≥54 | 1469 | 411 | 1.47 | 1.28 | 1.68 | 90 | 1.46 | 1.13 | 1.90 | 82 | 1.54 | 1.17 | 2.03 | 35 | 1.56 | 1.03 | 2.37 | 72 | 1.32 | 0.99 | 1.76 |
| ≥70 | <50 | 2646 | 1101 | 1.00 (Ref.) | | | 234 | 1.00 (Ref.) | | | 211 | 1.00 (Ref.) | | | 77 | 1.00 (Ref.) | | | 178 | 1.00 (Ref.) | | |
| | 50-<54 | 2264 | 1003 | 1.07 | 0.96 | 1.19 | 185 | 0.90 | 0.73 | 1.11 | 161 | 0.93 | 0.75 | 1.16 | 76 | 1.22 | 0.87 | 1.70 | 157 | 1.13 | 0.89 | 1.42 |
| | ≥54 | 1019 | 482 | 1.27 | 1.11 | 1.46 | 70 | 0.82 | 0.62 | 1.09 | 73 | 1.01 | 0.76 | 1.33 | 25 | 0.92 | 0.58 | 1.47 | 78 | 1.31 | 0.99 | 1.75 |
| | | | | P for age interaction = 4.77E-01 | | | | P for age interaction = 3.86E-01 | | | | P for age interaction = 7.44E-01 | | | | P for age interaction = 7.18E-01 | | | | P for age interaction = 4.58E-02 | | |

* Controls is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases, age at interview for controls) and study.

‡ Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&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).

Definitions: OR: odds ratio, Lower CL: lower confidence limit, Upper CL: upper confidence limit.

**Supplementary Table S9**. ORs and 95%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 ER subtypes and *in situ* tumors.

| | | **ER subtype and *in situ*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **ER+** | | | | **ER-** | | | | ***in situ*** | | | |
| | **Controls** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** |
| **Time since last birth** (years) | | | | | | | | | | | | | |
| Nulliparous | 8630 | 4701 | 1.00 (Ref.) | | | 1089 | 1.00 (Ref.) | | | 697 | 1.00 (Ref.) | | |
| 1 birth | | | | | | | | | | | | | |
| 0-<5 | 381 | 123 | 1.05 | 0.83 | 1.33 | 106 | 2.33 | 1.76 | 3.06 | 15 | 1.08 | 0.61 | 1.89 |
| 5<10 | 474 | 171 | 1.00 | 0.82 | 1.24 | 80 | 1.53 | 1.15 | 2.03 | 30 | 1.16 | 0.76 | 1.77 |
| 10<15 | 755 | 348 | 1.12 | 1.12 | 1.12 | 133 | 1.44 | 1.14 | 1.82 | 40 | 0.93 | 0.64 | 1.36 |
| 15<20 | 1125 | 607 | 1.11 | 0.97 | 1.27 | 244 | 1.45 | 1.19 | 1.76 | 66 | 1.00 | 0.73 | 1.36 |
| 20<25 | 1387 | 730 | 0.97 | 0.86 | 1.09 | 337 | 1.63 | 1.37 | 1.94 | 97 | 1.12 | 0.86 | 1.46 |
| 25<30 | 1427 | 729 | 0.81 | 0.72 | 0.92 | 277 | 1.39 | 1.17 | 1.65 | 108 | 1.00 | 0.77 | 1.28 |
| 30<35 | 1504 | 786 | 0.80 | 0.72 | 0.90 | 225 | 1.27 | 1.06 | 1.52 | 86 | 0.77 | 0.59 | 1.01 |
| 35<40 | 1564 | 769 | 0.69 | 0.61 | 0.77 | 206 | 1.16 | 0.96 | 1.40 | 105 | 0.81 | 0.63 | 1.05 |
| 40<45 | 1073 | 585 | 0.59 | 0.52 | 0.67 | 118 | 0.92 | 0.73 | 1.15 | 68 | 0.57 | 0.43 | 0.77 |
| 45<50 | 615 | 360 | 0.53 | 0.45 | 0.62 | 64 | 0.81 | 0.61 | 1.09 | 36 | 0.41 | 0.28 | 0.60 |
| 50<55 | 203 | 176 | 0.52 | 0.41 | 0.65 | 27 | 0.79 | 0.51 | 1.21 | 34 | 0.79 | 0.53 | 1.20 |
| ≥55 | 54 | 122 | 0.78 | 0.55 | 1.11 | 20 | 1.82 | 1.05 | 3.15 | 9 | 0.43 | 0.21 | 0.91 |
| 2 births | | | | | | | | | | | | | |
| 0-<5 | 264 | 196 | 1.63 | 1.32 | 2.02 | 130 | 2.79 | 2.15 | 3.62 | 21 | 1.75 | 1.07 | 2.88 |
| 5<10 | 393 | 304 | 1.46 | 1.22 | 1.75 | 170 | 2.46 | 1.96 | 3.09 | 41 | 1.45 | 0.99 | 2.11 |
| 10<15 | 697 | 431 | 1.00 | 0.86 | 1.17 | 179 | 1.40 | 1.14 | 1.73 | 79 | 1.22 | 0.91 | 1.65 |
| 15<20 | 967 | 580 | 0.91 | 0.80 | 1.04 | 238 | 1.36 | 1.12 | 1.63 | 110 | 1.11 | 0.86 | 1.45 |
| 20<25 | 1461 | 712 | 0.72 | 0.64 | 0.81 | 300 | 1.21 | 1.02 | 1.43 | 134 | 0.95 | 0.74 | 1.21 |
| 25<30 | 1610 | 758 | 0.65 | 0.58 | 0.73 | 274 | 1.06 | 0.90 | 1.26 | 125 | 0.89 | 0.70 | 1.13 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 30<35 | 1680 | 846 | 0.61 | 0.55 | 0.69 | 261 | 1.01 | 0.85 | 1.20 | 120 | 0.85 | 0.67 | 1.09 |
| 35<40 | 1725 | 812 | 0.48 | 0.43 | 0.54 | 171 | 0.62 | 0.51 | 0.76 | 99 | 0.59 | 0.46 | 0.77 |
| 40<45 | 997 | 478 | 0.37 | 0.32 | 0.43 | 147 | 0.81 | 0.66 | 1.00 | 57 | 0.38 | 0.28 | 0.53 |
| 45<50 | 379 | 217 | 0.33 | 0.27 | 0.40 | 59 | 0.71 | 0.53 | 0.97 | 24 | 0.30 | 0.19 | 0.47 |
| 50<55 | 117 | 74 | 0.26 | 0.19 | 0.36 | 15 | 0.50 | 0.28 | 0.87 | 8 | 0.21 | 0.10 | 0.45 |
| ≥55 | 20 | 11 | 0.16 | 0.08 | 0.35 | 2 | 0.41 | 0.09 | 1.77 | . | 0.00 | 0.00 | |
| ≥3 births | | | | | | | | | | | | | |
| 0-<5 | 243 | 135 | 1.15 | 0.91 | 1.46 | 111 | 2.47 | 1.88 | 3.24 | 16 | 1.33 | 0.77 | 2.31 |
| 5<10 | 412 | 275 | 1.16 | 0.97 | 1.39 | 107 | 1.46 | 1.13 | 1.88 | 31 | 0.93 | 0.62 | 1.41 |
| 10<15 | 570 | 319 | 0.87 | 0.74 | 1.02 | 146 | 1.43 | 1.14 | 1.78 | 60 | 0.98 | 0.71 | 1.35 |
| 15<20 | 895 | 437 | 0.69 | 0.60 | 0.79 | 186 | 1.20 | 0.98 | 1.46 | 66 | 0.64 | 0.47 | 0.87 |
| 20<25 | 1194 | 544 | 0.59 | 0.52 | 0.67 | 213 | 1.06 | 0.88 | 1.27 | 115 | 0.85 | 0.66 | 1.09 |
| 25<30 | 1404 | 630 | 0.49 | 0.44 | 0.56 | 214 | 0.87 | 0.73 | 1.05 | 105 | 0.65 | 0.50 | 0.84 |
| 30<35 | 1611 | 783 | 0.45 | 0.40 | 0.50 | 207 | 0.72 | 0.60 | 0.87 | 120 | 0.57 | 0.44 | 0.73 |
| 35<40 | 1603 | 740 | 0.36 | 0.32 | 0.40 | 178 | 0.61 | 0.50 | 0.74 | 115 | 0.45 | 0.35 | 0.57 |
| 40<45 | 867 | 508 | 0.35 | 0.30 | 0.40 | 111 | 0.62 | 0.49 | 0.78 | 60 | 0.28 | 0.20 | 0.38 |
| 45<50 | 367 | 192 | 0.24 | 0.19 | 0.29 | 44 | 0.52 | 0.37 | 0.73 | 27 | 0.20 | 0.13 | 0.31 |
| 50<55 | 88 | 58 | 0.23 | 0.16 | 0.32 | 13 | 0.58 | 0.32 | 1.07 | 9 | 0.19 | 0.09 | 0.40 |
| ≥55 | 13 | 7 | 0.16 | 0.06 | 0.40 | 1 | 0.32 | 0.04 | 2.51 | 1 | 0.13 | 0.02 | 1.03 |
| | | | | | | | | | | | | | |
| **Age at first birth‡** (years) | | | | | | | | | | | | | |
| <20 | 6508 | 3013 | 1.00 (Ref.) | | | 1151 | 1.00 (Ref.) | | | 498 | 1.00 (Ref.) | | |
| 20-<25 | 23178 | 10150 | 0.99 | 0.94 | 1.05 | 2719 | 0.86 | 0.80 | 0.94 | 1743 | 0.98 | 0.88 | 1.09 |
| 25-<30 | 18563 | 8463 | 1.07 | 1.01 | 1.13 | 2183 | 0.83 | 0.76 | 0.91 | 1299 | 0.96 | 0.86 | 1.08 |
| ≥30 | 9609 | 4323 | 1.08 | 1.01 | 1.15 | 1021 | 0.72 | 0.65 | 0.81 | 643 | 1.00 | 0.87 | 1.15 |
| | | | | | | | | | | | | | |
| **Breastfeeding duration‡** (months) | | | | | | | | | | | | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 7031 | 4283 | 1.00 (Ref.) | | | 1645 | 1.00 (Ref.) | | | 649 | 1.00 (Ref.) | | |
| >0-6 | 10954 | 5854 | 1.06 | 1.01 | 1.12 | 1755 | 0.96 | 0.89 | 1.04 | 818 | 1.10 | 0.99 | 1.24 |
| >6-12 | 5625 | 2816 | 0.96 | 0.90 | 1.02 | 799 | 0.80 | 0.73 | 0.88 | 364 | 0.92 | 0.80 | 1.06 |
| >12-24 | 4280 | 2383 | 1.03 | 0.96 | 1.11 | 613 | 0.80 | 0.72 | 0.90 | 316 | 0.98 | 0.85 | 1.14 |
| >24 | 2374 | 1092 | 0.82 | 0.75 | 0.90 | 354 | 0.73 | 0.64 | 0.84 | 152 | 0.74 | 0.61 | 0.90 |
| | | | | | | | | | | | | | |
| **Age at menarche** (years) | | | | | | | | | | | | | |
| ≥15 | 12041 | 5076 | 1.00 (Ref.) | | | 1482 | 1.00 (Ref.) | | | 747 | 1.00 (Ref.) | | |
| 14 | 13151 | 5677 | 1.12 | 1.06 | 1.17 | 1467 | 1.04 | 0.96 | 1.12 | 702 | 1.07 | 0.95 | 1.19 |
| 13 | 18005 | 8575 | 1.17 | 1.12 | 1.23 | 2162 | 1.11 | 1.03 | 1.19 | 1516 | 1.08 | 0.98 | 1.19 |
| ≤12 | 23572 | 11715 | 1.25 | 1.20 | 1.31 | 3200 | 1.19 | 1.11 | 1.28 | 1922 | 1.13 | 1.03 | 1.24 |
| | | | | | | | | | | | | | |
| **Age at menopause** (years) | | | | | | | | | | | | | |
| <50 | 19399 | 9709 | 1.00 (Ref.) | | | 2521 | 1.00 (Ref.) | | | 1623 | 1.00 (Ref.) | | |
| 50-<54 | 13647 | 7461 | 1.08 | 1.04 | 1.13 | 1599 | 1.09 | 1.02 | 1.17 | 1246 | 1.04 | 0.96 | 1.12 |
| ≥54 | 5863 | 3353 | 1.17 | 1.11 | 1.23 | 671 | 1.14 | 1.04 | 1.26 | 484 | 1.06 | 0.95 | 1.18 |

* Controls is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases, age at interview for controls) and study.

Definitions: OR: odds ratio, Lower CL: lower confidence limit, Upper CL: upper confidence limit.

‡ Among parous women.

**Supplementary Table S10**. ORs and 95%CIs for case-case* 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 ER subtypes and *in situ* tumors.

| | | **ER subtype and *in situ*** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **ER-** | | | | ***in situ*** | | | |
| | **ER+ cases** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** |
| **Time since last birth** (years) | | | | | | | | | |
| Nulliparous | 4701 | 1089 | 1.00 (Ref.) | | | 697 | 1.00 (Ref.) | | |
| 1 birth | | | | | | | | | |
| 0-<5 | 123 | 106 | 2.56 | 1.88 | 3.49 | 15 | 0.87 | 0.48 | 1.58 |
| 5<10 | 171 | 80 | 1.62 | 1.19 | 2.20 | 30 | 1.02 | 0.65 | 1.59 |
| 10<15 | 348 | 133 | 1.38 | 1.08 | 1.77 | 40 | 0.77 | 0.52 | 1.13 |
| 15<20 | 607 | 244 | 1.38 | 1.12 | 1.69 | 66 | 0.83 | 0.61 | 1.14 |
| 20<25 | 730 | 337 | 1.71 | 1.42 | 2.06 | 97 | 1.15 | 0.87 | 1.52 |
| 25<30 | 729 | 277 | 1.78 | 1.48 | 2.14 | 108 | 1.16 | 0.89 | 1.51 |
| 30<35 | 786 | 225 | 1.71 | 1.41 | 2.07 | 86 | 0.93 | 0.71 | 1.23 |
| 35<40 | 769 | 206 | 1.81 | 1.49 | 2.20 | 105 | 1.13 | 0.87 | 1.47 |
| 40<45 | 585 | 118 | 1.59 | 1.26 | 2.01 | 68 | 0.97 | 0.72 | 1.32 |
| 45<50 | 360 | 64 | 1.58 | 1.17 | 2.12 | 36 | 0.78 | 0.53 | 1.16 |
| 50<55 | 176 | 27 | 1.54 | 1.00 | 2.38 | 34 | 1.58 | 1.03 | 2.40 |
| ≥55 | 122 | 20 | 2.41 | 1.46 | 3.99 | 9 | 0.58 | 0.28 | 1.18 |
| | | | P-het = 1.65E-5 | | | | P-het = 9.07E-01 | | |
| 2 births | | | | | | | | | |
| 0-<5 | 196 | 130 | 2.10 | 1.60 | 2.75 | 21 | 0.85 | 0.51 | 1.41 |
| 5<10 | 304 | 170 | 1.98 | 1.56 | 2.52 | 41 | 0.86 | 0.58 | 1.27 |
| 10<15 | 431 | 179 | 1.59 | 1.27 | 1.98 | 79 | 1.11 | 0.82 | 1.52 |
| 15<20 | 580 | 238 | 1.67 | 1.37 | 2.03 | 110 | 1.14 | 0.87 | 1.49 |
| 20<25 | 712 | 300 | 1.89 | 1.58 | 2.26 | 134 | 1.22 | 0.95 | 1.56 |
| 25<30 | 758 | 274 | 1.83 | 1.53 | 2.19 | 125 | 1.28 | 0.99 | 1.64 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 30<35 | 846 | 261 | 1.80 | 1.50 | 2.16 | 120 | 1.28 | 0.99 | 1.65 |
| 35<40 | 812 | 171 | 1.35 | 1.10 | 1.66 | 99 | 1.22 | 0.93 | 1.59 |
| 40<45 | 478 | 147 | 2.14 | 1.71 | 2.68 | 57 | 1.12 | 0.81 | 1.55 |
| 45<50 | 217 | 59 | 2.06 | 1.50 | 2.83 | 24 | 1.05 | 0.66 | 1.67 |
| 50<55 | 74 | 15 | 1.72 | 0.97 | 3.05 | 8 | 1.19 | 0.55 | 2.61 |
| ≥55 | 11 | 2 | 1.98 | 0.43 | 9.14 | 0 | 0.00 | 0.00 | |
| | | | P-het = 2.59E-04 | | | | P-het = 6.92E-01 | | |
| ≥3 births | | | | | | | | | |
| 0-<5 | 135 | 111 | 2.59 | 1.93 | 3.48 | 16 | 0.99 | 0.56 | 1.75 |
| 5<10 | 275 | 107 | 1.42 | 1.09 | 1.85 | 31 | 0.72 | 0.47 | 1.10 |
| 10<15 | 319 | 146 | 1.85 | 1.46 | 2.34 | 60 | 1.03 | 0.74 | 1.44 |
| 15<20 | 437 | 186 | 1.93 | 1.56 | 2.38 | 66 | 0.85 | 0.62 | 1.16 |
| 20<25 | 544 | 213 | 1.97 | 1.62 | 2.40 | 115 | 1.36 | 1.04 | 1.77 |
| 25<30 | 630 | 214 | 1.94 | 1.60 | 2.35 | 105 | 1.21 | 0.93 | 1.59 |
| 30<35 | 783 | 207 | 1.74 | 1.43 | 2.11 | 120 | 1.23 | 0.95 | 1.59 |
| 35<40 | 740 | 178 | 1.77 | 1.44 | 2.17 | 115 | 1.30 | 0.99 | 1.69 |
| 40<45 | 508 | 111 | 1.76 | 1.38 | 2.24 | 60 | 0.92 | 0.66 | 1.27 |
| 45<50 | 192 | 44 | 2.12 | 1.48 | 3.03 | 27 | 1.11 | 0.71 | 1.76 |
| 50<55 | 58 | 13 | 2.26 | 1.21 | 4.21 | 9 | 1.06 | 0.50 | 2.27 |
| ≥55 | 7 | 1 | 1.88 | 0.23 | 15.40 | 1 | 0.90 | 0.10 | 7.94 |
| | | | P-het = 5.09E-03 | | | | P-het = 5.99E-01 | | |
| **Age at first birth**‡ (years) | | | | | | | | | |
| <20 | 3013 | 1151 | 1.00 (Ref.) | | | 498 | 1.00 (Ref.) | | |
| 20-<25 | 10150 | 2719 | 0.87 | 0.80 | 0.95 | 1743 | 1.02 | 0.91 | 1.14 |
| 25-<30 | 8463 | 2183 | 0.77 | 0.70 | 0.84 | 1299 | 0.94 | 0.83 | 1.06 |
| ≥30 | 4323 | 1021 | 0.67 | 0.59 | 0.75 | 643 | 0.97 | 0.84 | 1.13 |
| | | | P-het = 1.25E-10 | | | | P-het = 3.48E-01 | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Breastfeeding duration**‡ (months) | | | | | | | | | |
| 0 | 4283 | 1645 | 1.00 (Ref.) | | | 649 | 1.00 (Ref.) | | |
| >0-6 | 5854 | 1755 | 0.90 | 0.83 | 0.98 | 818 | 1.03 | 0.92 | 1.16 |
| >6-12 | 2816 | 799 | 0.85 | 0.76 | 0.94 | 364 | 0.94 | 0.81 | 1.09 |
| >12-24 | 2383 | 613 | 0.78 | 0.70 | 0.88 | 316 | 0.95 | 0.81 | 1.11 |
| >24 | 1092 | 354 | 0.88 | 0.76 | 1.02 | 152 | 0.89 | 0.72 | 1.10 |
| | | | P-het = 1.72E-03 | | | | P-het = 3.97E-02 | | |
| **Age at menarche** (years) | | | | | | | | | |
| ≥15 | 5076 | 1482 | 1.00 (Ref.) | | | 747 | 1.00 (Ref.) | | |
| 14 | 5677 | 1467 | 0.93 | 0.86 | 1.02 | 702 | 0.96 | 0.86 | 1.08 |
| 13 | 8575 | 2162 | 0.95 | 0.87 | 1.02 | 1516 | 0.92 | 0.83 | 1.01 |
| ≤12 | 11715 | 3200 | 0.95 | 0.88 | 1.03 | 1922 | 0.89 | 0.81 | 0.99 |
| | | | P-het = 8.04E-01 | | | | P-het = 4.34E-03 | | |
| **Age at menopause** (years) | | | | | | | | | |
| <50 | 9709 | 2521 | 1.00 (Ref.) | | | 1623 | 1.00 (Ref.) | | |
| 50-<54 | 7461 | 1599 | 1.01 | 0.94 | 1.08 | 1246 | 0.96 | 0.88 | 1.04 |
| ≥54 | 3353 | 671 | 0.98 | 0.89 | 1.08 | 484 | 0.91 | 0.81 | 1.02 |
| | | | P-het = 6.55E-01 | | | | P-het = 5.57E-01 | | |

* ER+ is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases) and study.

Definitions: OR: odds ratio, Lower CL: lower confidence limit, Upper CL: upper confidence limit.

‡ Among parous women.

**Supplementary Table S11**. ORs and 95%CIs for case-control* analyses† of associations between reproductive factors (number of births, age at first birth, breastfeeding duration, age at menarche, and age at menopause) and intrinsic-like subtypes‡.

| Risk factor | | Intrinsic-like subtype | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Luminal A-like | | | | Luminal B-like | | | | Luminal B-HER2-like | | | | HER2-enriched-like | | | | Triple negative | | | |
| | Controls | Cases | OR | Lower CL | Upper CL | Cases | OR | Lower CL | Upper CL | Cases | OR | Lower CL | Upper CL | Cases | OR | Lower CL | Upper CL | Cases | OR | Lower CL | Upper CL |
| **Number of births** | | | | | | | | | | | | | | | | | | | | | |
| Nulliparous | 8630 | 1750 | 1.00 (Ref.) | | | 429 | 1.00 (Ref.) | | | 479 | 1.00 (Ref.) | | | 212 | 1.00 (Ref.) | | | 394 | 1.00 (Ref.) | | |
| 1 | 11246 | 2153 | 0.83 | 0.74 | 0.93 | 504 | 0.95 | 0.77 | 1.16 | 622 | 0.76 | 0.62 | 0.92 | 367 | 0.82 | 0.63 | 1.07 | 703 | 1.37 | 1.15 | 1.63 |
| 2 | 26564 | 4464 | 0.72 | 0.65 | 0.80 | 1003 | 0.78 | 0.65 | 0.95 | 1063 | 0.62 | 0.52 | 0.75 | 495 | 0.67 | 0.52 | 0.86 | 1288 | 1.26 | 1.07 | 1.49 |
| ≥3 | 23966 | 3933 | 0.60 | 0.54 | 0.67 | 867 | 0.67 | 0.56 | 0.82 | 890 | 0.52 | 0.43 | 0.63 | 408 | 0.61 | 0.48 | 0.79 | 1122 | 1.10 | 0.94 | 1.30 |
| **Age at first birth**§ (years) | | | | | | | | | | | | | | | | | | | | | |
| <20 | 6508 | 1295 | 1.00 (Ref.) | | | 311 | 1.00 (Ref.) | | | 299 | 1.00 (Ref.) | | | 178 | 1.00 (Ref.) | | | 578 | 1.00 (Ref.) | | |
| 20-<25 | 23178 | 4124 | 0.97 | 0.90 | 1.05 | 910 | 0.96 | 0.84 | 1.10 | 946 | 1.01 | 0.88 | 1.16 | 469 | 0.94 | 0.78 | 1.13 | 1231 | 0.90 | 0.81 | 1.01 |
| 25-<30 | 18563 | 3144 | 1.10 | 1.02 | 1.19 | 677 | 1.00 | 0.87 | 1.16 | 806 | 1.14 | 0.99 | 1.31 | 387 | 1.00 | 0.82 | 1.21 | 816 | 0.84 | 0.74 | 0.95 |
| ≥30 | 9609 | 1678 | 1.25 | 1.14 | 1.36 | 394 | 1.15 | 0.98 | 1.36 | 409 | 1.16 | 0.98 | 1.36 | 199 | 1.04 | 0.83 | 1.30 | 361 | 0.75 | 0.65 | 0.88 |
| **Breastfeeding duration**§ (months) | | | | | | | | | | | | | | | | | | | | | |
| 0 | 7031 | 1826 | 1.00 (Ref.) | | | 469 | 1.00 (Ref.) | | | 469 | 1.00 (Ref.) | | | 252 | 1.00 (Ref.) | | | 839 | 1.00 (Ref.) | | |
| >0-6 | 10954 | 2528 | 1.06 | 0.99 | 1.14 | 559 | 0.95 | 0.83 | 1.09 | 702 | 1.09 | 0.96 | 1.23 | 311 | 1.03 | 0.86 | 1.23 | 739 | 0.93 | 0.83 | 1.04 |
| >6-12 | 5625 | 1150 | 0.98 | 0.90 | 1.07 | 259 | 0.93 | 0.79 | 1.09 | 274 | 0.90 | 0.77 | 1.06 | 142 | 0.95 | 0.76 | 1.18 | 291 | 0.75 | 0.64 | 0.86 |
| >12-24 | 4280 | 1013 | 1.08 | 0.99 | 1.19 | 219 | 1.03 | 0.87 | 1.23 | 224 | 1.10 | 0.93 | 1.31 | 91 | 0.90 | 0.70 | 1.17 | 232 | 0.80 | 0.68 | 0.94 |
| >24 | 2374 | 500 | 0.96 | 0.85 | 1.08 | 101 | 0.85 | 0.67 | 1.07 | 102 | 0.94 | 0.75 | 1.19 | 46 | 0.82 | 0.59 | 1.15 | 129 | 0.75 | 0.61 | 0.92 |
| **Age at menarche** (years) | | | | | | | | | | | | | | | | | | | | | |
| ≥15 | 12041 | 1971 | 1.00 (Ref.) | | | 431 | 1.00 (Ref.) | | | 504 | 1.00 (Ref.) | | | 288 | 1.00 (Ref.) | | | 548 | 1.00 (Ref.) | | |
| 14 | 13151 | 2093 | 1.12 | 1.04 | 1.20 | 475 | 1.10 | 0.96 | 1.26 | 518 | 1.11 | 0.98 | 1.26 | 265 | 1.09 | 0.91 | 1.29 | 549 | 1.07 | 0.95 | 1.22 |
| 13 | 18005 | 3406 | 1.19 | 1.11 | 1.27 | 742 | 1.13 | 1.00 | 1.28 | 799 | 1.18 | 1.05 | 1.33 | 385 | 1.16 | 0.99 | 1.36 | 880 | 1.13 | 1.01 | 1.26 |
| ≤12 | 23572 | 4469 | 1.28 | 1.20 | 1.36 | 1075 | 1.25 | 1.11 | 1.41 | 1106 | 1.25 | 1.11 | 1.40 | 510 | 1.17 | 1.00 | 1.37 | 1427 | 1.26 | 1.13 | 1.40 |

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age at menopause** (years) | | | | | | | | | | | | | | | | | | | | | |
| <50 | 19399 | 4157 | 1.00 (Ref.) | | | 941 | 1.00 (Ref.) | | | 998 | 1.00 (Ref.) | | | 491 | 1.00 (Ref.) | | | 1144 | 1.00 (Ref.) | | |
| 50-<54 | 13647 | 3179 | 1.10 | 1.04 | 1.16 | 617 | 0.99 | 0.89 | 1.10 | 638 | 1.01 | 0.91 | 1.12 | 342 | 1.17 | 1.02 | 1.35 | 656 | 1.06 | 0.96 | 1.17 |
| ≥54 | 5863 | 1490 | 1.16 | 1.08 | 1.24 | 276 | 1.00 | 0.87 | 1.16 | 337 | 1.22 | 1.07 | 1.39 | 147 | 1.19 | 0.98 | 1.44 | 281 | 1.05 | 0.92 | 1.21 |

* Controls is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases, age at interview for controls) and study.

‡ Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&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).

Definitions: OR: odds ratio, Lower CL: lower confidence limit, Upper CL: upper confidence limit.

§ Among parous women.

**Supplementary Table S12**. ORs and 95%CIs for case-case* analyses† of associations between reproductive factors (number of births, age at first full-term birth, breastfeeding duration, age at menarche, and age at menopause) and intrinsic-like subtypes‡.

| **Risk factor** | | **Intrinsic-like subtype** | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Luminal B-like** | | | | **Luminal B-HER2-like** | | | | **HER2-enriched-like** | | | | **Triple negative** | | | |
| | **Luminal A-like cases** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** |
| **Number of births** | | | | | | | | | | | | | | | | | |
| Nulliparous | 1750 | 429 | 1.00 (Ref.) | | | 479 | 1.00 (Ref.) | | | 212 | 1.00 (Ref.) | | | 394 | 1.00 (Ref.) | | |
| 1 | 2153 | 504 | 1.14 | 0.92 | 1.42 | 622 | 0.92 | 0.74 | 1.14 | 367 | 1.03 | 0.78 | 1.36 | 703 | 1.74 | 1.43 | 2.11 |
| 2 | 4464 | 1003 | 1.08 | 0.88 | 1.33 | 1063 | 0.89 | 0.72 | 1.09 | 495 | 0.99 | 0.76 | 1.29 | 1288 | 1.88 | 1.56 | 2.26 |
| ≥3 | 3933 | 867 | 1.12 | 0.91 | 1.37 | 890 | 0.89 | 0.73 | 1.09 | 408 | 1.08 | 0.83 | 1.40 | 1122 | 1.97 | 1.65 | 2.37 |
| | | | P-het = 5.24E-01 | | | | P-het = 8.50E-01 | | | | P-het = 7.16E-02 | | | | P-het = 1.94E-12 | | |
| **Age at first birth**§ (years) | | | | | | | | | | | | | | | | | |
| <20 | 1295 | 311 | 1.00 (Ref.) | | | 299 | 1.00 (Ref.) | | | 178 | 1.00 (Ref.) | | | 578 | 1.00 (Ref.) | | |
| 20-<25 | 4124 | 910 | 0.99 | 0.86 | 1.15 | 946 | 1.05 | 0.91 | 1.22 | 469 | 0.98 | 0.81 | 1.19 | 1231 | 0.94 | 0.83 | 1.06 |
| 25-<30 | 3144 | 677 | 0.91 | 0.78 | 1.07 | 806 | 1.03 | 0.88 | 1.20 | 387 | 0.90 | 0.73 | 1.10 | 816 | 0.76 | 0.66 | 0.87 |
| ≥30 | 1678 | 394 | 0.93 | 0.78 | 1.11 | 409 | 0.92 | 0.77 | 1.10 | 199 | 0.83 | 0.66 | 1.05 | 361 | 0.59 | 0.50 | 0.70 |
| | | | P-het = 3.05E-01 | | | | P-het = 4.57E-01 | | | | P-het = 3.98E-02 | | | | P-het = 2.15E-02 | | |
| **Breastfeeding duration**§ (months) | | | | | | | | | | | | | | | | | |
| 0 | 1826 | 469 | 1.00 (Ref.) | | | 469 | 1.00 (Ref.) | | | 252 | 1.00 (Ref.) | | | 839 | 1.00 (Ref.) | | |
| >0-6 | 2528 | 559 | 0.88 | 0.77 | 1.02 | 702 | 1.00 | 0.87 | 1.15 | 311 | 0.94 | 0.78 | 1.13 | 739 | 0.85 | 0.75 | 0.96 |
| >6-12 | 1150 | 259 | 0.93 | 0.78 | 1.11 | 274 | 0.93 | 0.78 | 1.11 | 142 | 1.01 | 0.80 | 1.27 | 291 | 0.76 | 0.65 | 0.90 |
| >12-24 | 1013 | 219 | 0.93 | 0.77 | 1.12 | 224 | 1.02 | 0.84 | 1.23 | 91 | 0.86 | 0.66 | 1.12 | 232 | 0.73 | 0.61 | 0.87 |
| >24 | 500 | 101 | 0.87 | 0.68 | 1.12 | 102 | 1.01 | 0.79 | 1.30 | 46 | 0.93 | 0.66 | 1.32 | 129 | 0.79 | 0.63 | 0.99 |
| | | | P-het = 3.15E-01 | | | | P-het = 9.58E-01 | | | | P-het = 5.33E-01 | | | | P-het = 5.91E-05 | | |
| **Age at menarche** (years) | | | | | | | | | | | | | | | | | |
| ≥15 | 1971 | 431 | 1.00 (Ref.) | | | 504 | 1.00 (Ref.) | | | 288 | 1.00 (Ref.) | | | 548 | 1.00 (Ref.) | | |
| 14 | 2093 | 475 | 0.98 | 0.85 | 1.14 | 518 | 0.98 | 0.85 | 1.13 | 265 | 0.96 | 0.80 | 1.15 | 549 | 0.96 | 0.83 | 1.10 |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 13 | 3406 | 742 | 0.95 | 0.83 | 1.08 | 799 | 0.97 | 0.85 | 1.10 | 385 | 0.94 | 0.80 | 1.12 | 880 | 0.93 | 0.82 | 1.05 |
| ≤12 | 4469 | 1075 | 0.98 | 0.86 | 1.12 | 1106 | 0.96 | 0.85 | 1.09 | 510 | 0.89 | 0.76 | 1.05 | 1427 | 0.96 | 0.85 | 1.09 |
| | | | P-het = 6.41E-01 | | | | P-het = 1.59E-01 | | | | P-het = 1.22E-01 | | | | P-het = 8.28E-01 | | |
| **Age at menopause** (years) | | | | | | | | | | | | | | | | | |
| <50 | 4157 | 941 | 1.00 (Ref.) | | | 998 | 1.00 (Ref.) | | | 491 | 1.00 (Ref.) | | | 1144 | 1.00 (Ref.) | | |
| 50-<54 | 3179 | 617 | 0.91 | 0.81 | 1.02 | 638 | 0.94 | 0.84 | 1.05 | 342 | 1.09 | 0.93 | 1.26 | 656 | 0.97 | 0.87 | 1.08 |
| ≥54 | 1490 | 276 | 0.87 | 0.75 | 1.01 | 337 | 1.08 | 0.93 | 1.24 | 147 | 1.05 | 0.86 | 1.28 | 281 | 0.93 | 0.80 | 1.08 |
| | | | P-het = 1.19E-01 | | | | P-het = 1.65E-01 | | | | P-het = 4.82E-01 | | | | P-het = 8.85E-01 | | |

* Luminal A-like is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases) and study.

‡ Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&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).

Definitions: OR: odds ratio, Lower CL: lower confidence limit, Upper CL: upper confidence limit.

§ Among parous women.

**Supplementary Table S13.** ORs and 95%CIs for case-control* analyses† of associations between reproductive factors (number of births, age at first full-term birth, breastfeeding duration, age at menarche, and age at menopause) and ER subtypes and *in situ* tumors.

| | | **ER subtype and *in situ*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **ER+** | | | | **ER-** | | | | ***In situ*** | | | |
| | **Controls** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** |
| **Number of births** | | | | | | | | | | | | | |
| Nulliparous | 8630 | 4701 | 1.00 (Ref.) | | | 1089 | 1.00 (Ref.) | | | 697 | 1.00 (Ref.) | | |
| 1 | 11246 | 5900 | 0.71 | 0.66 | 0.77 | 1954 | 1.20 | 1.06 | 1.35 | 721 | 0.77 | 0.65 | 0.92 |
| 2 | 26564 | 11249 | 0.61 | 0.57 | 0.66 | 3032 | 1.04 | 0.93 | 1.17 | 1757 | 0.73 | 0.63 | 0.86 |
| ≥3 | 23966 | 10686 | 0.52 | 0.48 | 0.56 | 2614 | 0.93 | 0.83 | 1.04 | 1864 | 0.59 | 0.51 | 0.70 |
| | | | | | | | | | | | | | |
| **Age at first birth‡** (years) | | | | | | | | | | | | | |
| <20 | 6508 | 3013 | 1.00 (Ref.) | | | 1151 | 1.00 (Ref.) | | | 498 | 1.00 (Ref.) | | |
| 20-<25 | 23178 | 10150 | 1.03 | 0.98 | 1.09 | 2719 | 0.90 | 0.83 | 0.97 | 1743 | 1.02 | 0.91 | 1.13 |
| 25-<30 | 18563 | 8463 | 1.19 | 1.13 | 1.26 | 2183 | 0.92 | 0.85 | 1.01 | 1299 | 1.07 | 0.95 | 1.20 |
| ≥30 | 9609 | 4323 | 1.32 | 1.24 | 1.40 | 1021 | 0.88 | 0.80 | 0.97 | 643 | 1.19 | 1.04 | 1.36 |
| | | | | | | | | | | | | | |
| **Breastfeeding duration‡** (months) | | | | | | | | | | | | | |
| 0 | 7031 | 4283 | 1.00 (Ref.) | | | 1645 | 1.00 (Ref.) | | | 649 | 1.00 (Ref.) | | |
| >0-6 | 10954 | 5854 | 1.05 | 1.00 | 1.11 | 1755 | 0.96 | 0.89 | 1.04 | 818 | 1.08 | 0.96 | 1.21 |
| >6-12 | 5625 | 2816 | 0.96 | 0.90 | 1.03 | 799 | 0.81 | 0.74 | 0.90 | 364 | 0.92 | 0.80 | 1.06 |
| >12-24 | 4280 | 2383 | 1.04 | 0.97 | 1.12 | 613 | 0.83 | 0.74 | 0.92 | 316 | 0.99 | 0.85 | 1.15 |
| >24 | 2374 | 1092 | 0.85 | 0.78 | 0.93 | 354 | 0.78 | 0.68 | 0.89 | 152 | 0.77 | 0.63 | 0.94 |
| | | | | | | | | | | | | | |
| **Age at menarche** | | | | | | | | | | | | | |
| ≥15 | 12041 | 5076 | 1.00 (Ref.) | | | 1482 | 1.00 (Ref.) | | | 747 | 1.00 (Ref.) | | |
| 14 | 13151 | 5677 | 1.13 | 1.08 | 1.19 | 1467 | 1.05 | 0.96 | 1.13 | 702 | 1.08 | 0.96 | 1.20 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 13 | 18005 | 8575 | 1.18 | 1.13 | 1.24 | 2162 | 1.11 | 1.03 | 1.20 | 1516 | 1.09 | 0.99 | 1.20 |
| ≤12 | 23572 | 11715 | 1.26 | 1.20 | 1.31 | 3200 | 1.19 | 1.11 | 1.28 | 1922 | 1.13 | 1.03 | 1.24 |
| | | | | | | | | | | | | | |
| **Age at menopause** | | | | | | | | | | | | | |
| <50 | 19399 | 9709 | 1.00 (Ref.) | | | 2521 | 1.00 (Ref.) | | | 1623 | 1.00 (Ref.) | | |
| 50-<54 | 13647 | 7461 | 1.08 | 1.04 | 1.12 | 1599 | 1.09 | 1.02 | 1.17 | 1246 | 1.04 | 0.96 | 1.12 |
| ≥54 | 5863 | 3353 | 1.16 | 1.10 | 1.22 | 671 | 1.13 | 1.03 | 1.25 | 484 | 1.06 | 0.95 | 1.18 |

* Controls is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases, age at interview for controls) and study.

Definitions: OR: odds ratio, Lower CL: lower confidence limit, Upper CL: upper confidence limit.

‡ Among parous women.

**Supplementary Table S14**. ORs and 95%CIs for case-case* analyses† of associations between reproductive factors (number of births, age at first full-term birth, breastfeeding duration, age at menarche, and age at menopause) and ER subtypes and *in situ* tumors.

| | | **ER subtype and *in situ*** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **ER-** | | | | ***in situ*** | | | |
| | **ER+ cases** | **Cases** | **OR** | **Lower CL** | **Upper CL** | **Cases** | **OR** | **Lower CL** | **Upper CL** |
| **Number of births** | | | | | | | | | |
| Nulliparous | 4701 | 1089 | 1.00 (Ref.) | | | 697 | 1.00 (Ref.) | | |
| 1 | 5900 | 1954 | 1.69 | 1.49 | 1.92 | 721 | 1.05 | 0.88 | 1.26 |
| 2 | 11249 | 3032 | 1.76 | 1.56 | 1.98 | 1757 | 1.15 | 0.97 | 1.35 |
| ≥3 | 10686 | 2614 | 1.83 | 1.62 | 2.06 | 1864 | 1.09 | 0.93 | 1.29 |
| | | | P-het = 1.23E-14 | | | | P-het = 3.95E-01 | | |
| **Age at first birth**‡ (years) | | | | | | | | | |
| <20 | 3013 | 1151 | 1.00 (Ref.) | | | 498 | 1.00 (Ref.) | | |
| 20-<25 | 10150 | 2719 | 0.87 | 0.80 | 0.95 | 1743 | 1.01 | 0.90 | 1.13 |
| 25-<30 | 8463 | 2183 | 0.77 | 0.70 | 0.84 | 1299 | 0.93 | 0.82 | 1.05 |
| ≥30 | 4323 | 1021 | 0.67 | 0.60 | 0.74 | 643 | 0.93 | 0.81 | 1.07 |
| | | | P-het = 9.25E-03 | | | | P-het = 9.34E-01 | | |
| **Breastfeeding duration**‡ (months) | | | | | | | | | |
| 0 | 4283 | 1645 | 1.00 (Ref.) | | | 649 | 1.00 (Ref.) | | |
| >0-6 | 5854 | 1755 | 0.90 | 0.83 | 0.98 | 818 | 1.02 | 0.91 | 1.15 |
| >6-12 | 2816 | 799 | 0.86 | 0.77 | 0.95 | 364 | 0.93 | 0.80 | 1.07 |
| >12-24 | 2383 | 613 | 0.79 | 0.71 | 0.89 | 316 | 0.93 | 0.80 | 1.09 |
| >24 | 1092 | 354 | 0.90 | 0.78 | 1.04 | 152 | 0.87 | 0.71 | 1.07 |
| | | | P-het = 4.25E-04 | | | | P-het = 1.09E-01 | | |
| **Age at menarche** (years) | | | | | | | | | |
| ≥15 | 5076 | 1482 | 1.00 (Ref.) | | | 747 | 1.00 (Ref.) | | |
| 14 | 5677 | 1467 | 0.93 | 0.85 | 1.01 | 702 | 0.96 | 0.86 | 1.08 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 13 | 8575 | 2162 | 0.95 | 0.87 | 1.02 | 1516 | 0.92 | 0.83 | 1.01 |
| ≤12 | 11715 | 3200 | 0.95 | 0.88 | 1.03 | 1922 | 0.89 | 0.81 | 0.99 |
| | | | P-het = 8.97E-01 | | | | P-het = 1.73E-03 | | |
| **Age at menopause** (years) | | | | | | | | | |
| <50 | 9709 | 2521 | 1.00 (Ref.) | | | 1623 | 1.00 (Ref.) | | |
| 50-<54 | 7461 | 1599 | 1.01 | 0.94 | 1.09 | 1246 | 0.97 | 0.89 | 1.05 |
| ≥54 | 3353 | 671 | 0.98 | 0.89 | 1.08 | 484 | 0.92 | 0.82 | 1.03 |
| | | | P-het = 9.45E-01 | | | | P-het = 4.71E-01 | | |

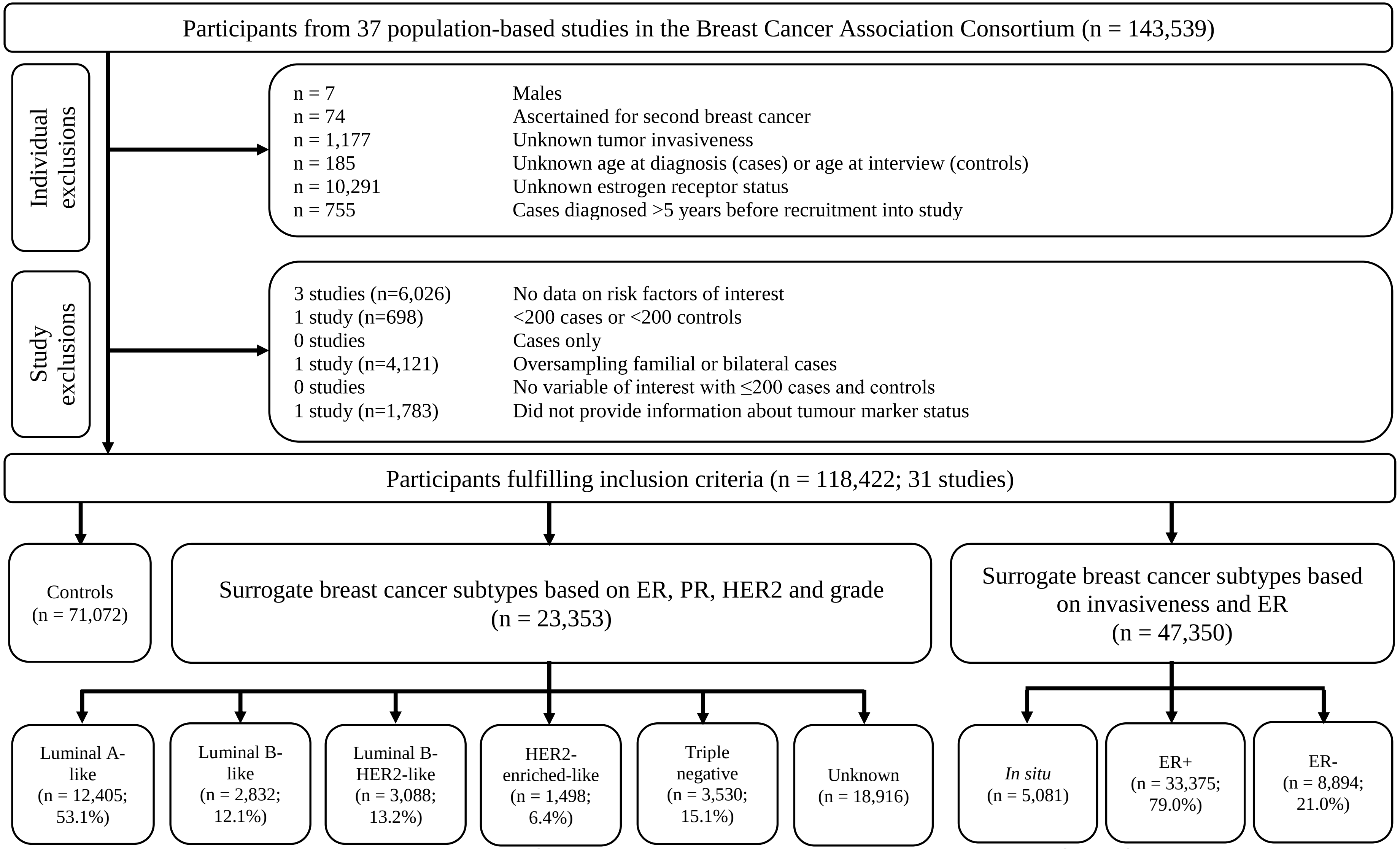
* ER+ is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases) and study.

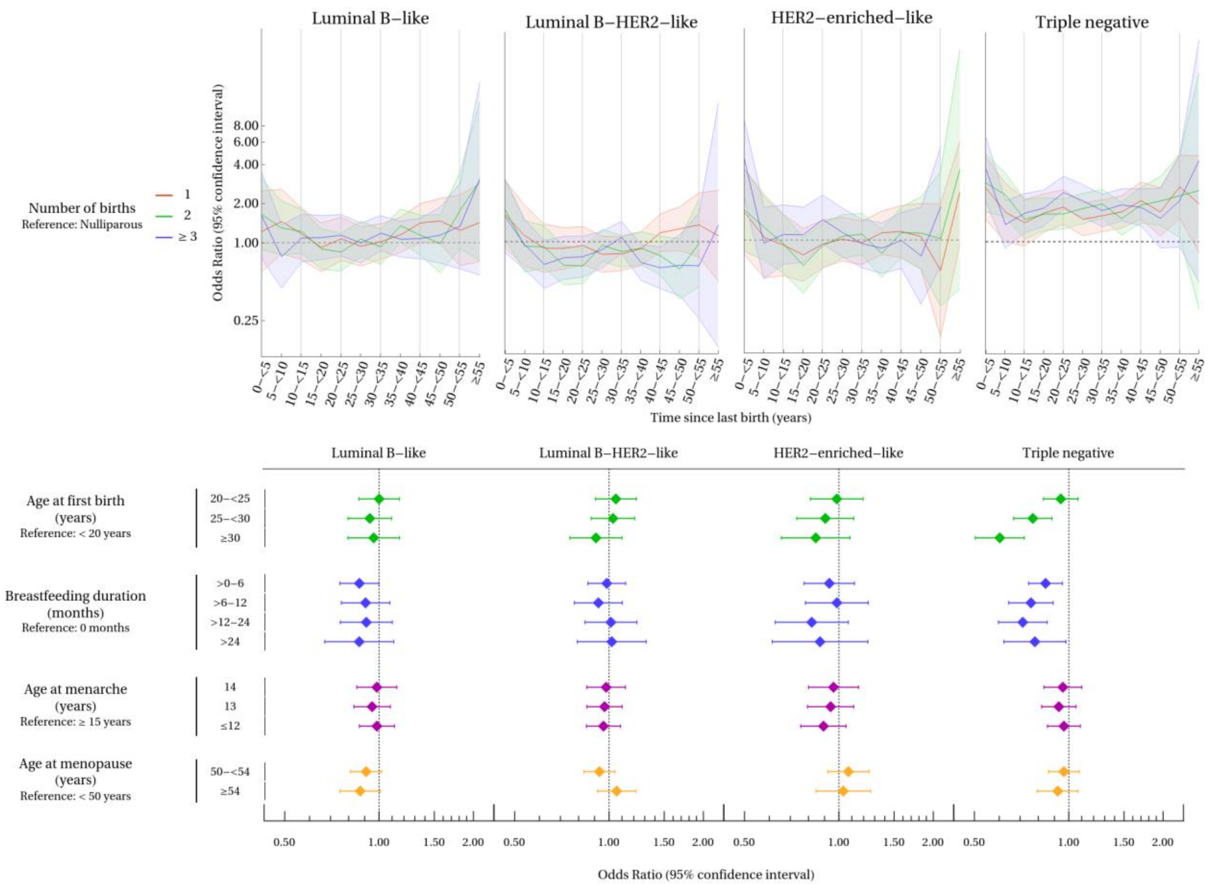
Definitions: OR: odds ratio, Lower CL: lower confidence limit, Upper CL: upper confidence limit.

‡ Among parous women.

## SUPPLEMENTARY FIGURES




**Supplementary Figure S1**. Consolidated Standards of Reporting Trials (CONSORT) diagram showing the flow of participants through the study.

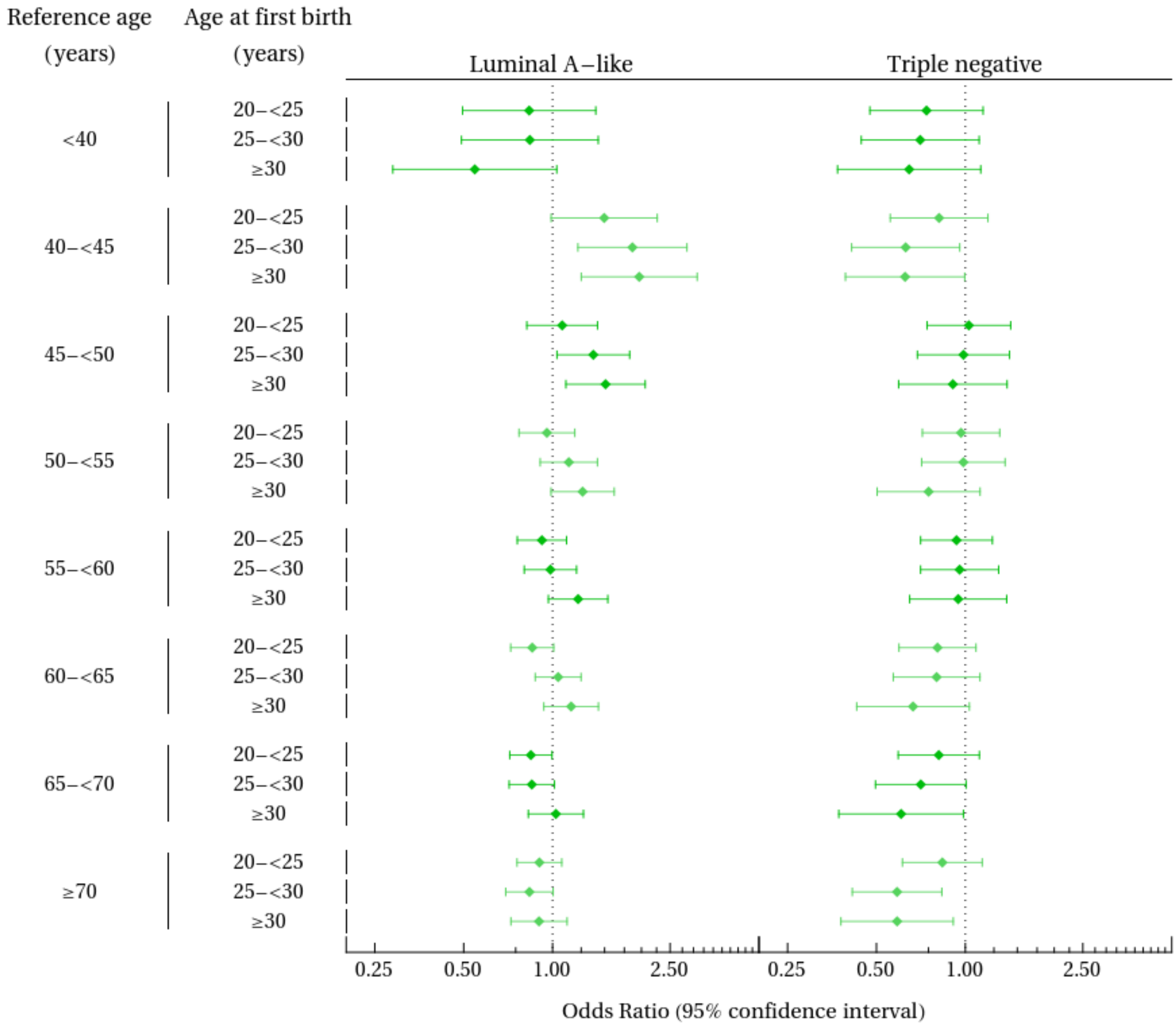



**Supplementary Figure S2**. ORs (colored dots) and 95%CIs (colored horizontal lines) for case-case* analyses† of associations between reproductive factors (time since last birth by number of births, age at first birth, breastfeeding duration, age at menarche, and age at menopause) and intrinsic-like subtypes‡.

* Luminal A-like is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases) and study.

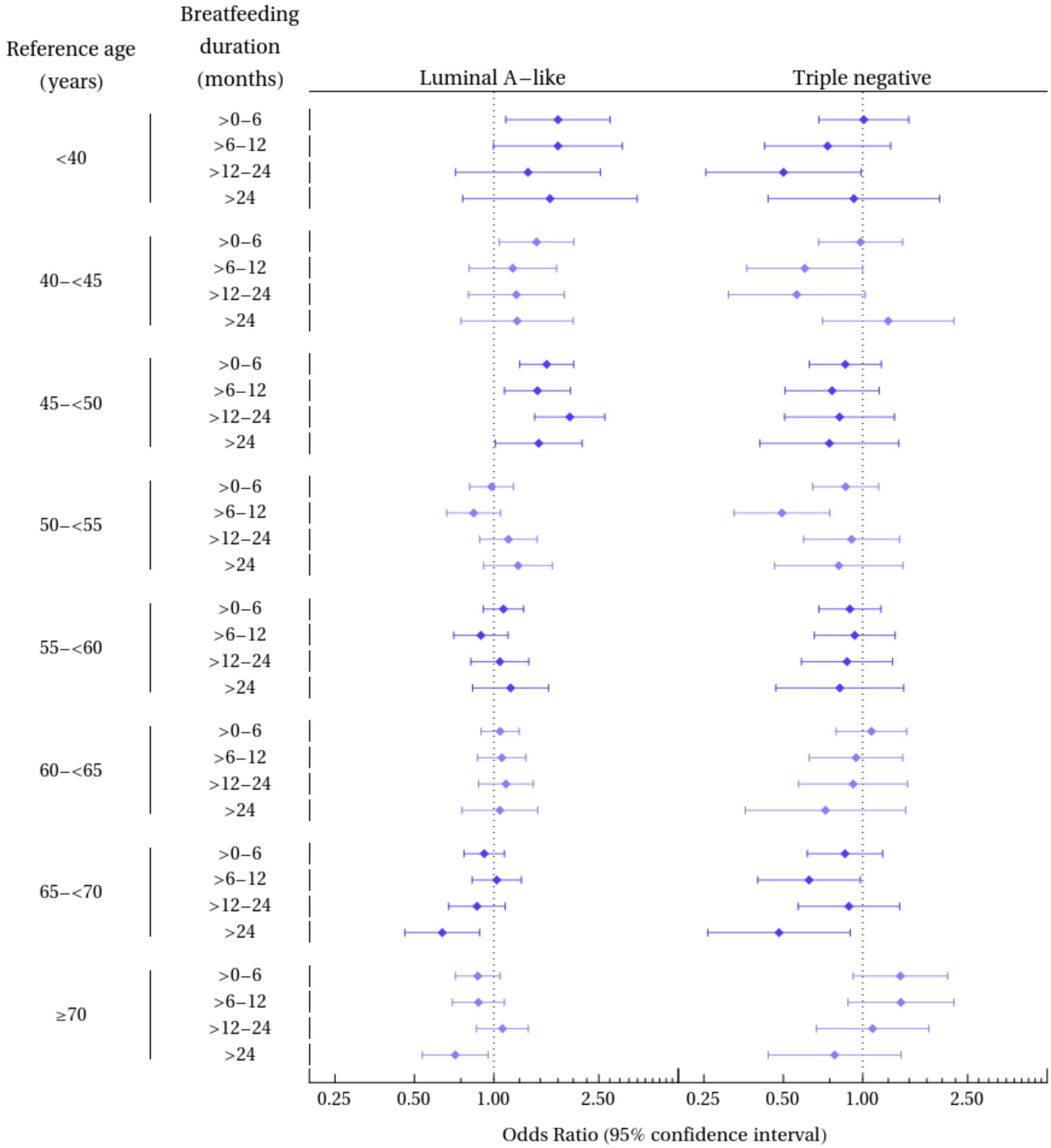
‡ Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&2), luminal B-like (ER-positive or PR-positive, HER2-negative, grade 3), luminal B-HER2-like (ER-positive or PR-positive, HER2-positive, any grade), HER2-enriched-like (ER-negative, PR-negative, HER2-positive,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




**Supplementary Figure S3**. ORs (colored dots) and 95%CIs for case-control* analyses† of the association between age at first full-term birth 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).

* Controls is the reference.

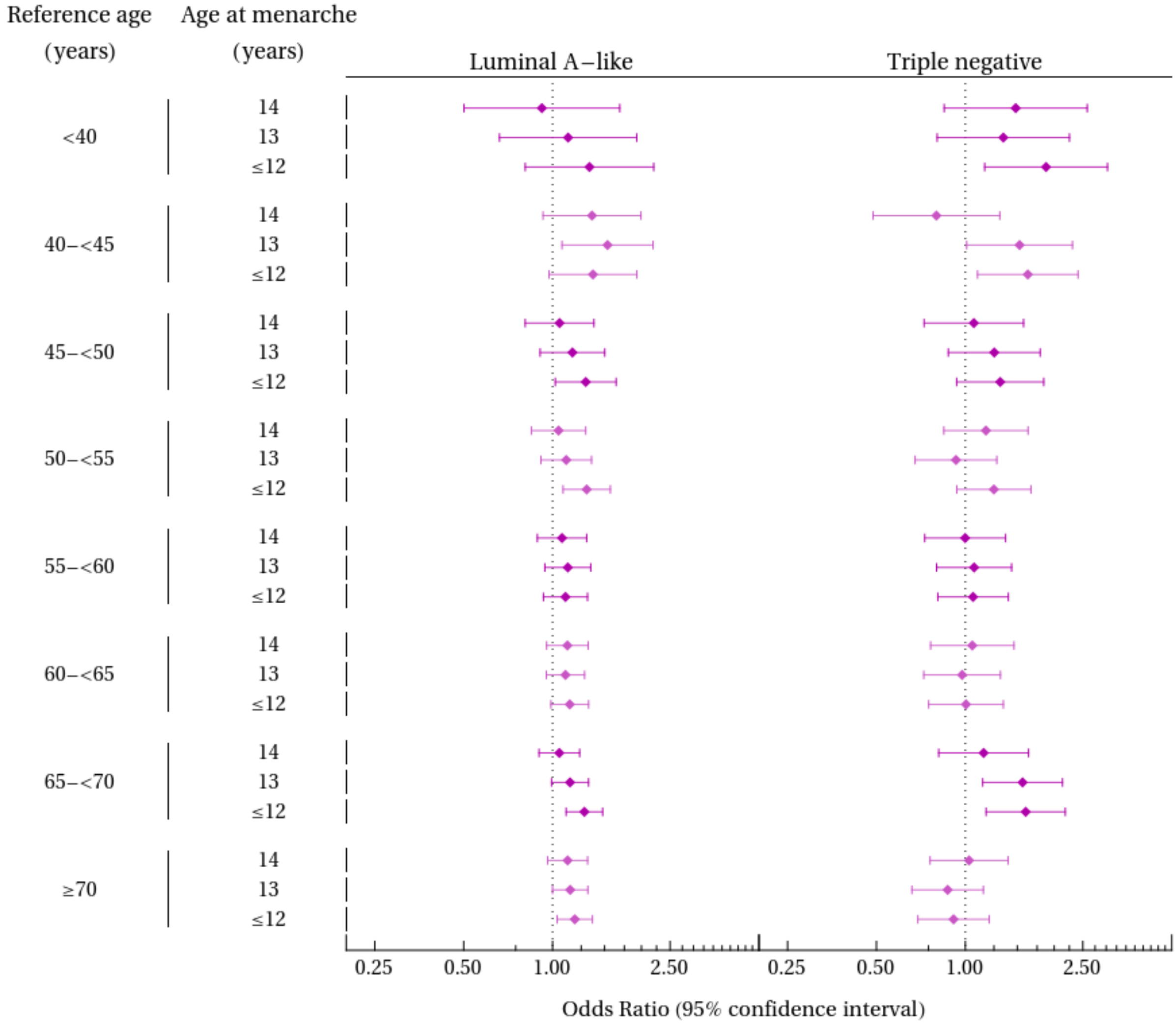
† The model was also adjusted for study.




**Supplementary Figure S4**. ORs (colored dots) and 95%CIs for case-control* analyses† of the association between breastfeeding duration 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).

* Controls is the reference.

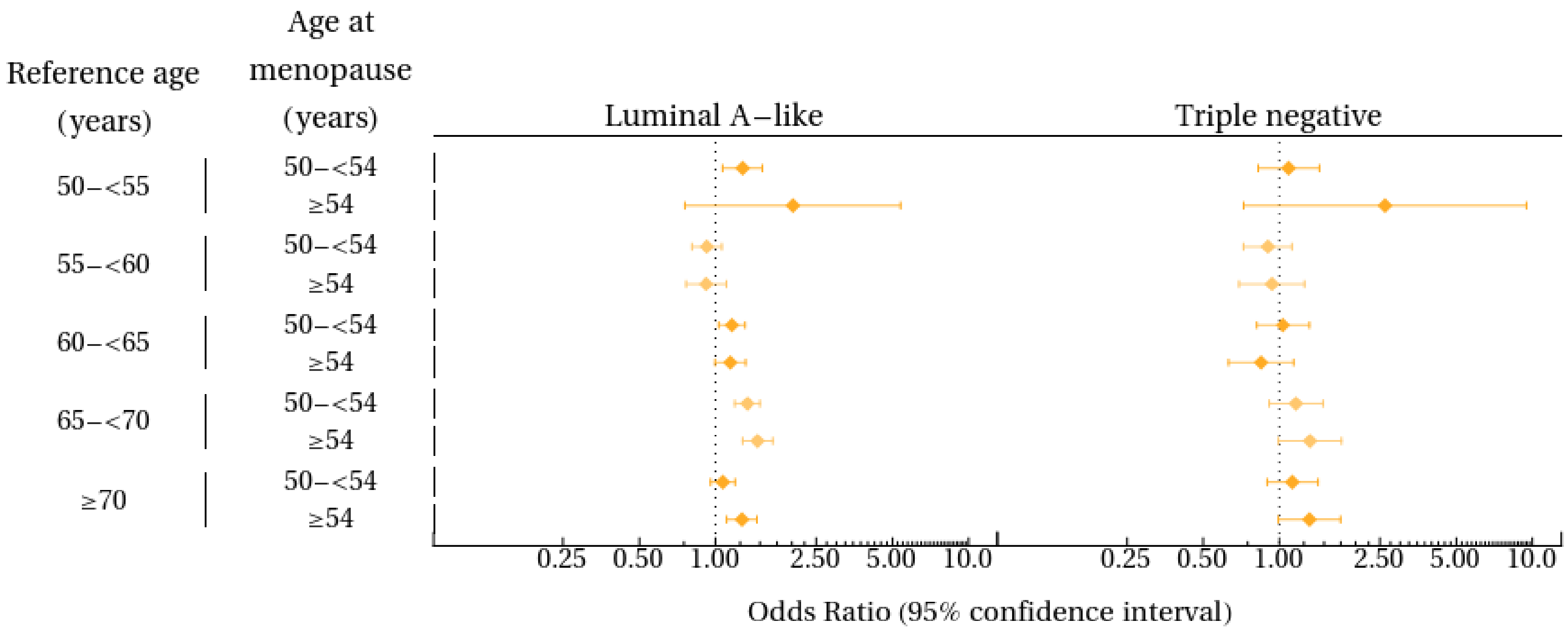
† The model was also adjusted for study.




**Supplementary Figure S5**. ORs (colored dots) and 95%CIs case-control* analyses† of the association between age at menarche 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).

* Controls is the reference.

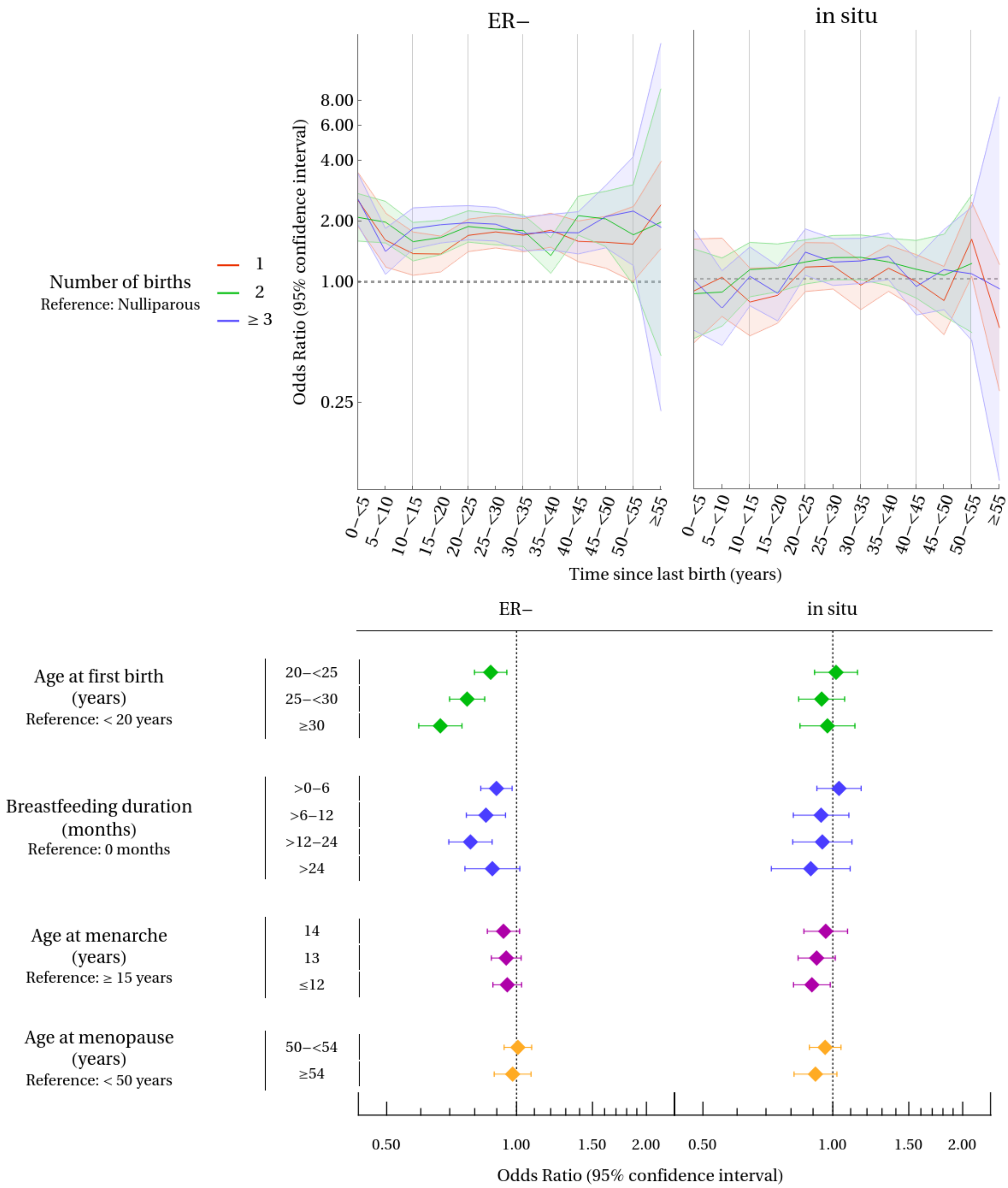
† The model was also adjusted for study.




**Supplementary Figure S6**. ORs (colored dots) and 95%CIs for case-control* analyses† of the association between age at menopause 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).

* Controls is the reference.

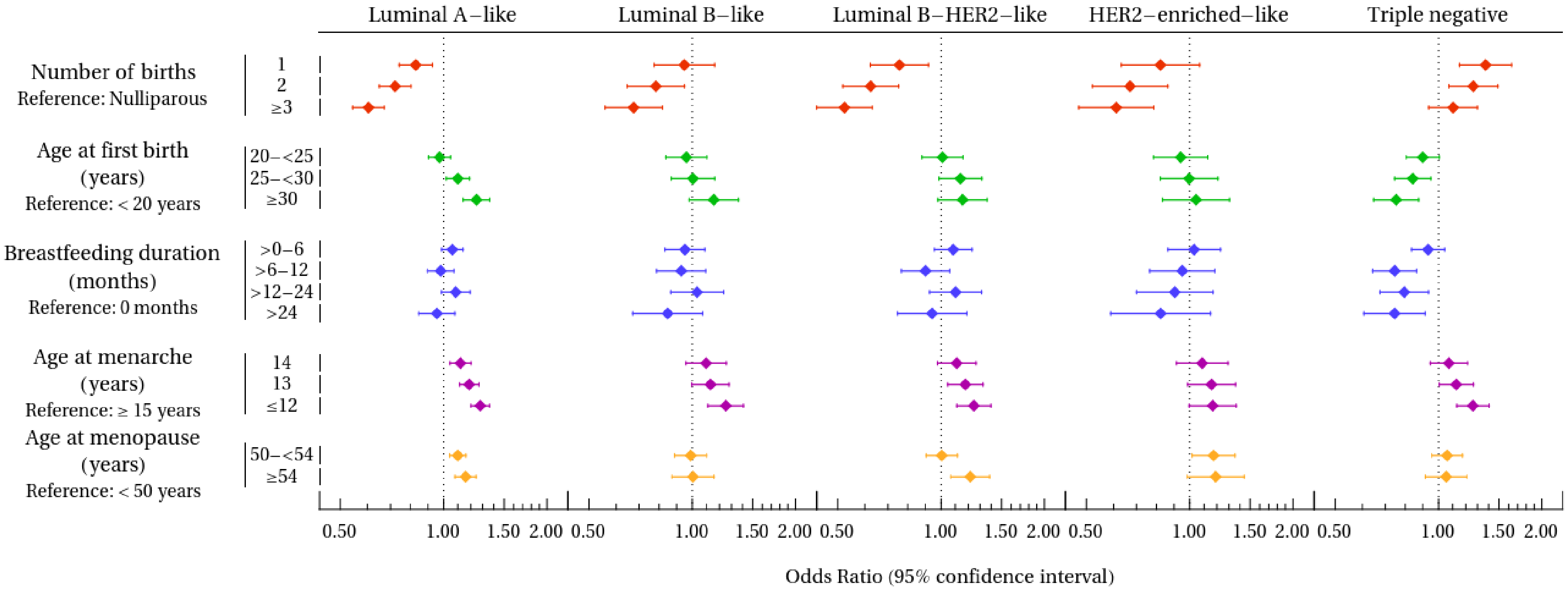
† The model was also adjusted for study.




**Supplementary Figure S7**. ORs (colored dots) and 95%CIs (colored horizontal lines) for case-case* 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 ER- and *in situ* tumors.

* ER+ is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases) and study.

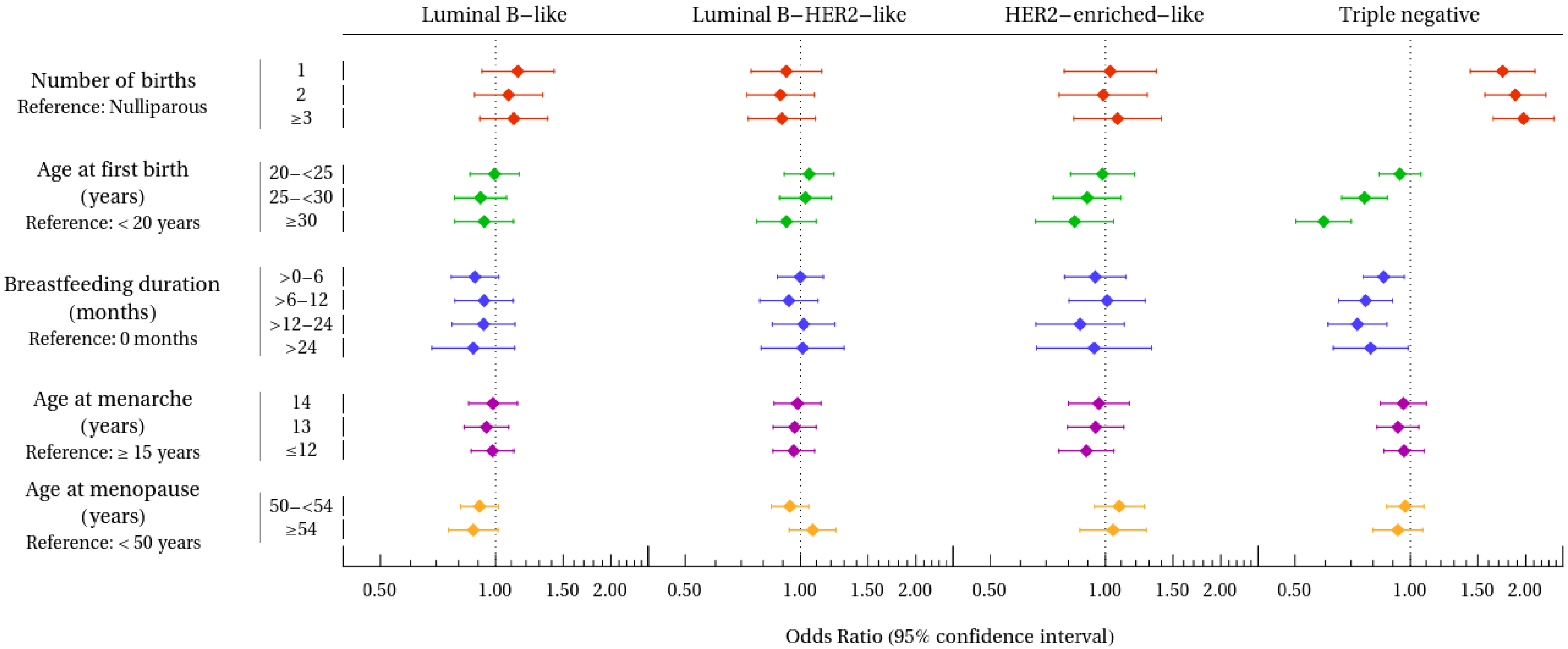



**Supplementary Figure S8**. ORs (colored dots) and 95%CIs (colored horizontal lines) for case-control* analyses† of associations between reproductive factors (number of births, age at first full-term birth, breastfeeding duration, age at menarche, and age at menopause) and intrinsic-like subtypes‡.

* Controls are the reference.

† The model was also adjusted for reference age (age at diagnosis for cases, age at interview for controls) and study.

‡ Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&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).

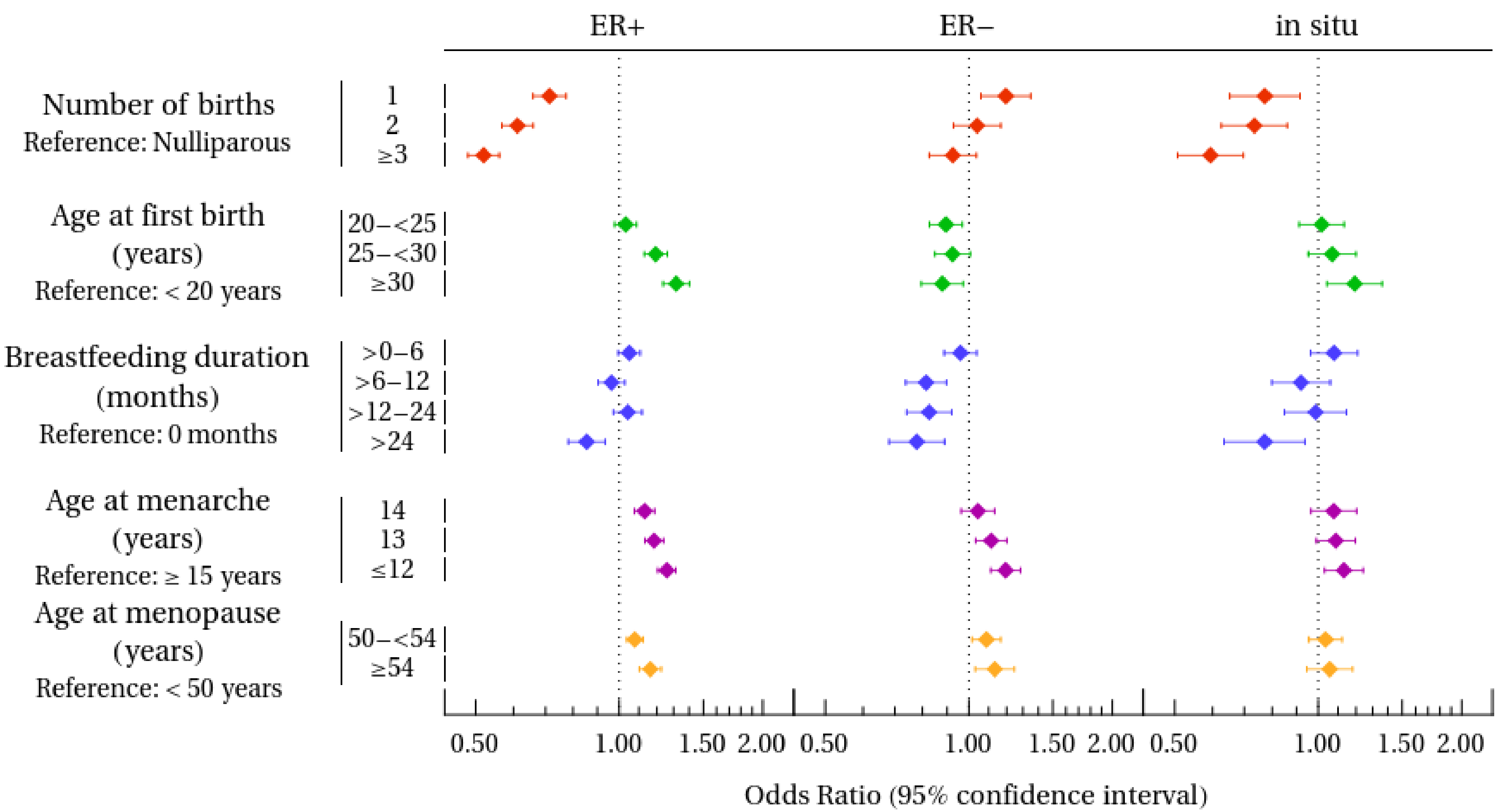



**Supplementary Figure S9**. ORs (colored dots) and 95%CIs (colored horizontal lines) for case-case* analyses† of associations between reproductive factors (number of births, age at first full-term birth, breastfeeding duration, age at menarche, and age at menopause) and intrinsic-like subtypes‡.

* Luminal A-like is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases) and study.

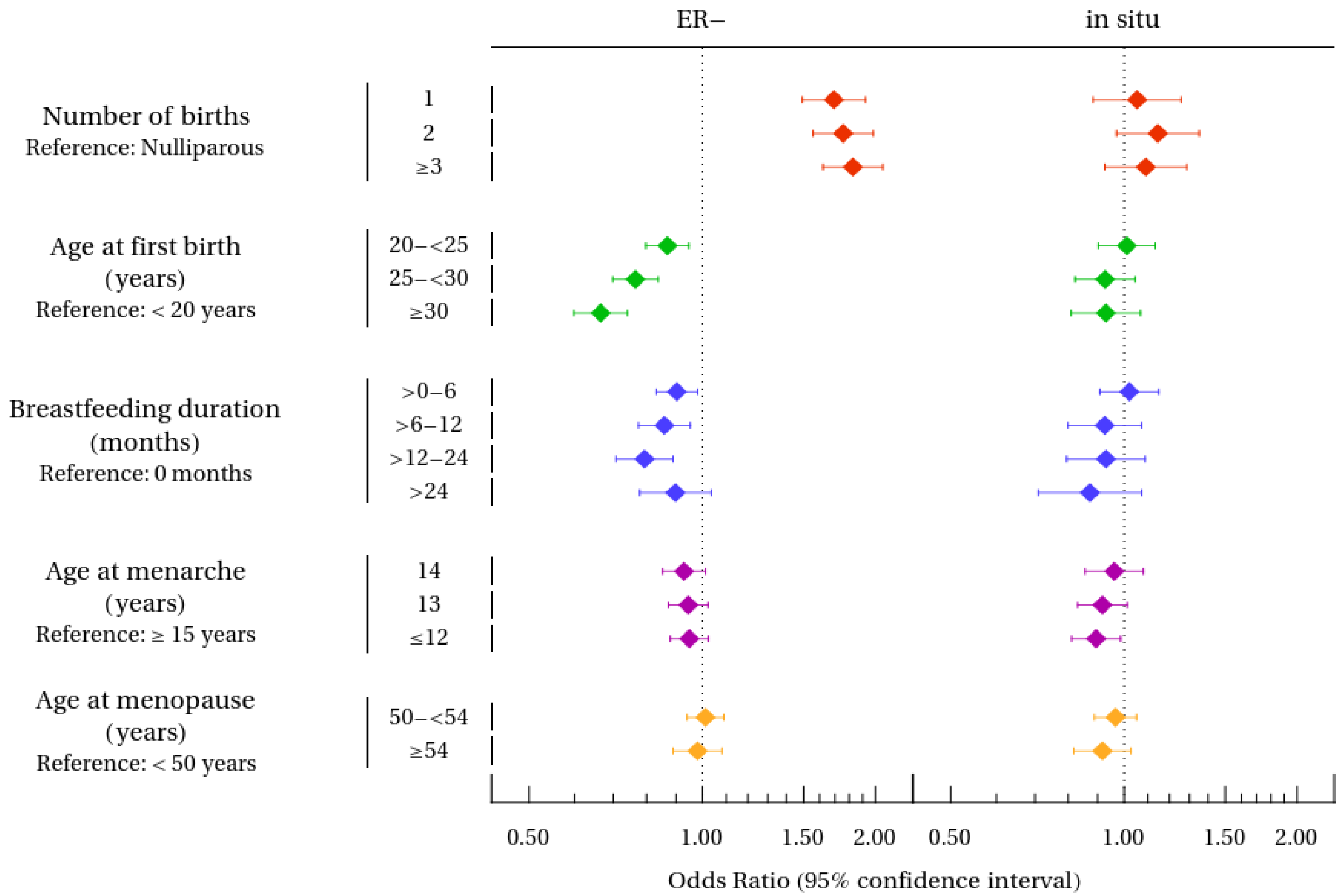
‡ Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&2), luminal B-like (ER-positive or PR-positive, HER2-negative, grade 3), luminal B-HER2-like (ER-positive or PR-positive, HER2-positive, any grade), HER2-enriched-like (ER-negative, PR-negative, HER2-positive,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




**Supplementary Figure S10**. ORs (colored dots) and 95%CIs (colored horizontal lines) for case-control* analyses† of associations between reproductive factors (number of births, age at first full-term birth, breastfeeding duration, age at menarche, and age at menopause) and *in situ* and ER+/- tumors.

* Controls is the reference.

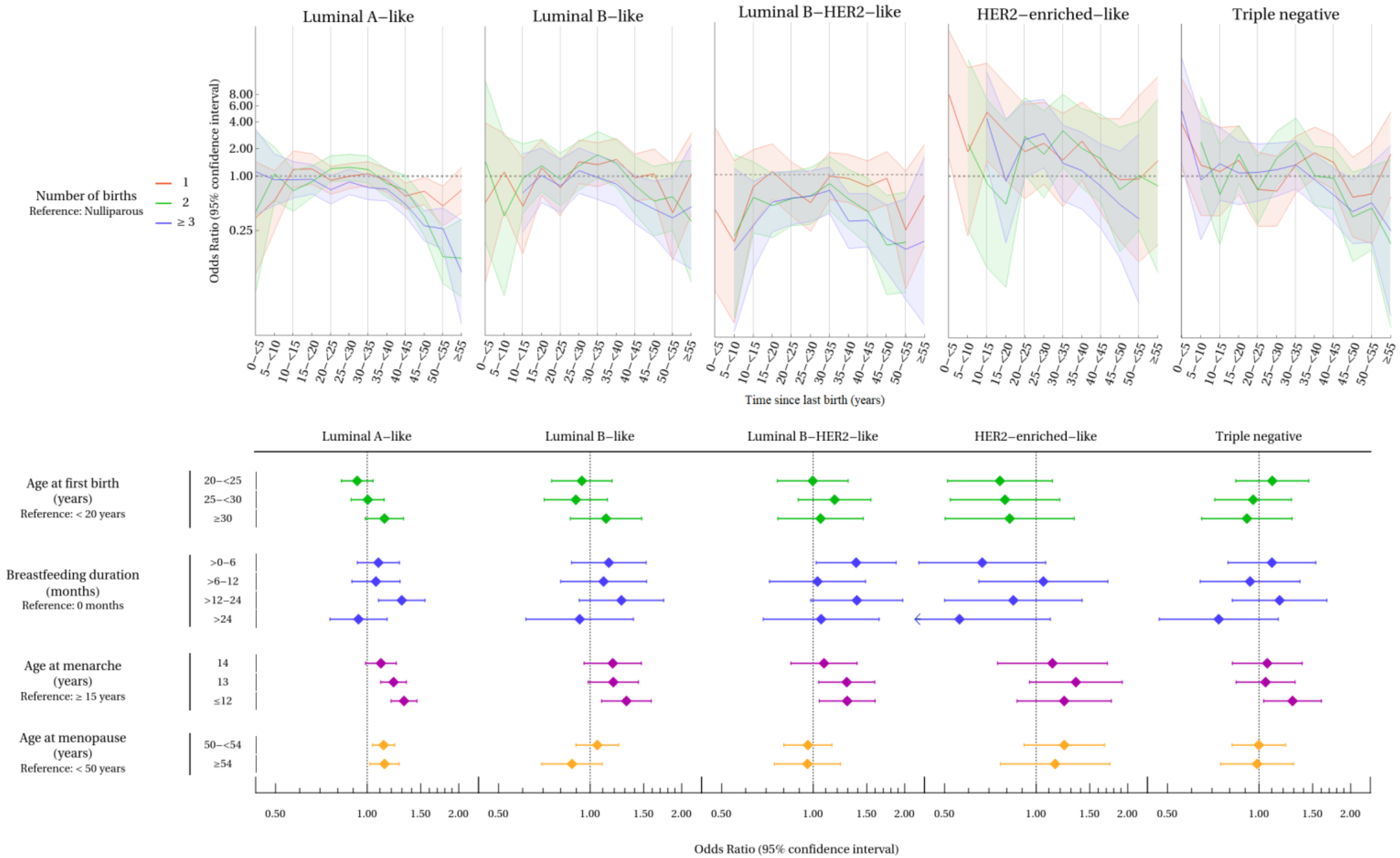
† The model was also adjusted for reference age (age at diagnosis for cases, age at interview for controls) and study.




**Supplementary Figure S11**. ORs (colored dots) and 95%CIs (colored horizontal lines) for case-case* analyses† of associations between reproductive factors (number of births, age at first full-term birth, breastfeeding duration, age at menarche, and age at menopause) and ER- and *in situ* tumors.

* ER+ is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases) and study

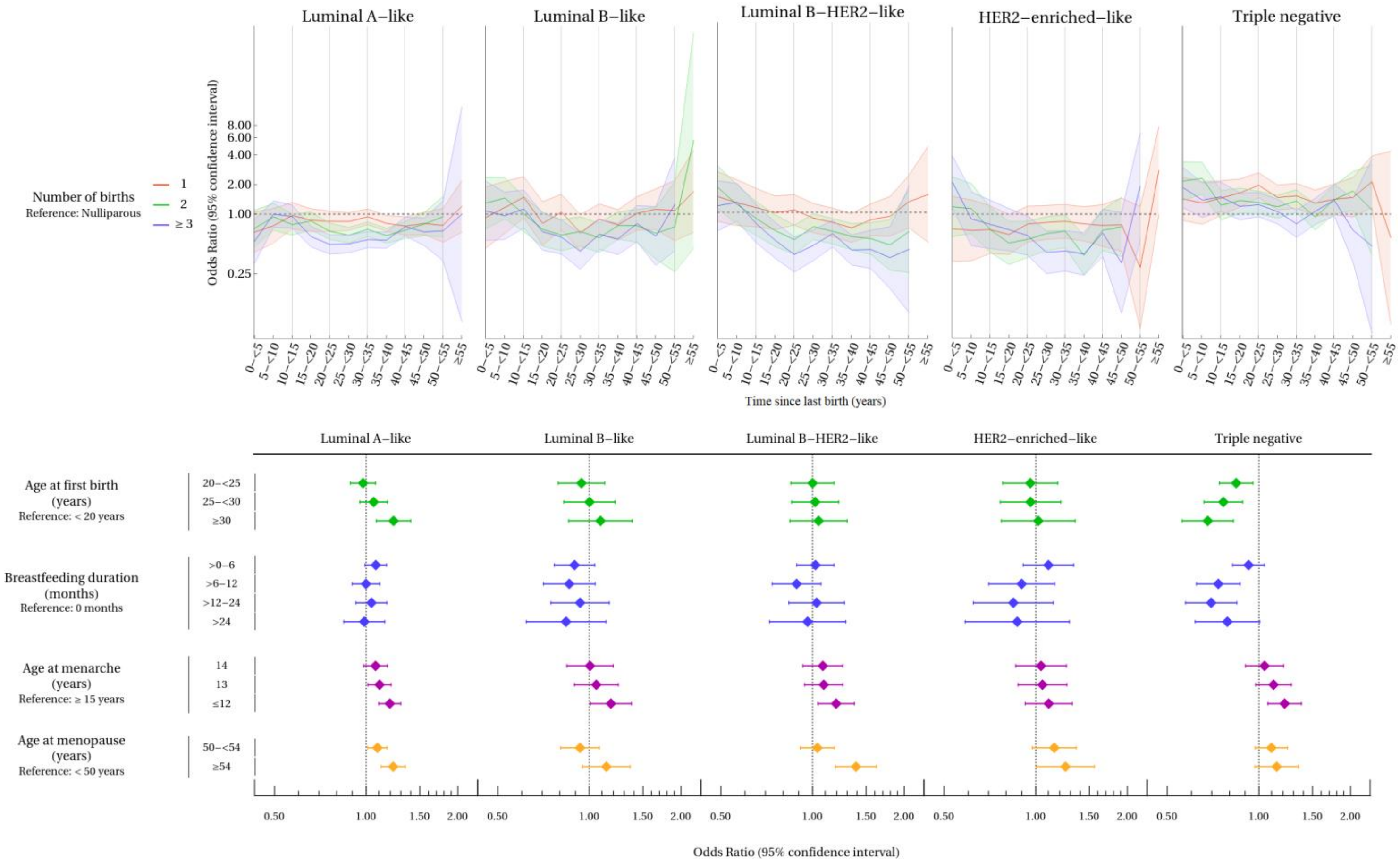



**Supplementary Figure S12**. ORs (colored dots) and 95%CIs (colored horizontal lines) for case-control* analyses† of associations between reproductive factors (time since last birth by number of births, age at first birth, breastfeeding duration, age at menarche, and age at menopause) and intrinsic-like subtypes‡ in prospective cohort studies.

* Controls is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases) and study.

‡ Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&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).

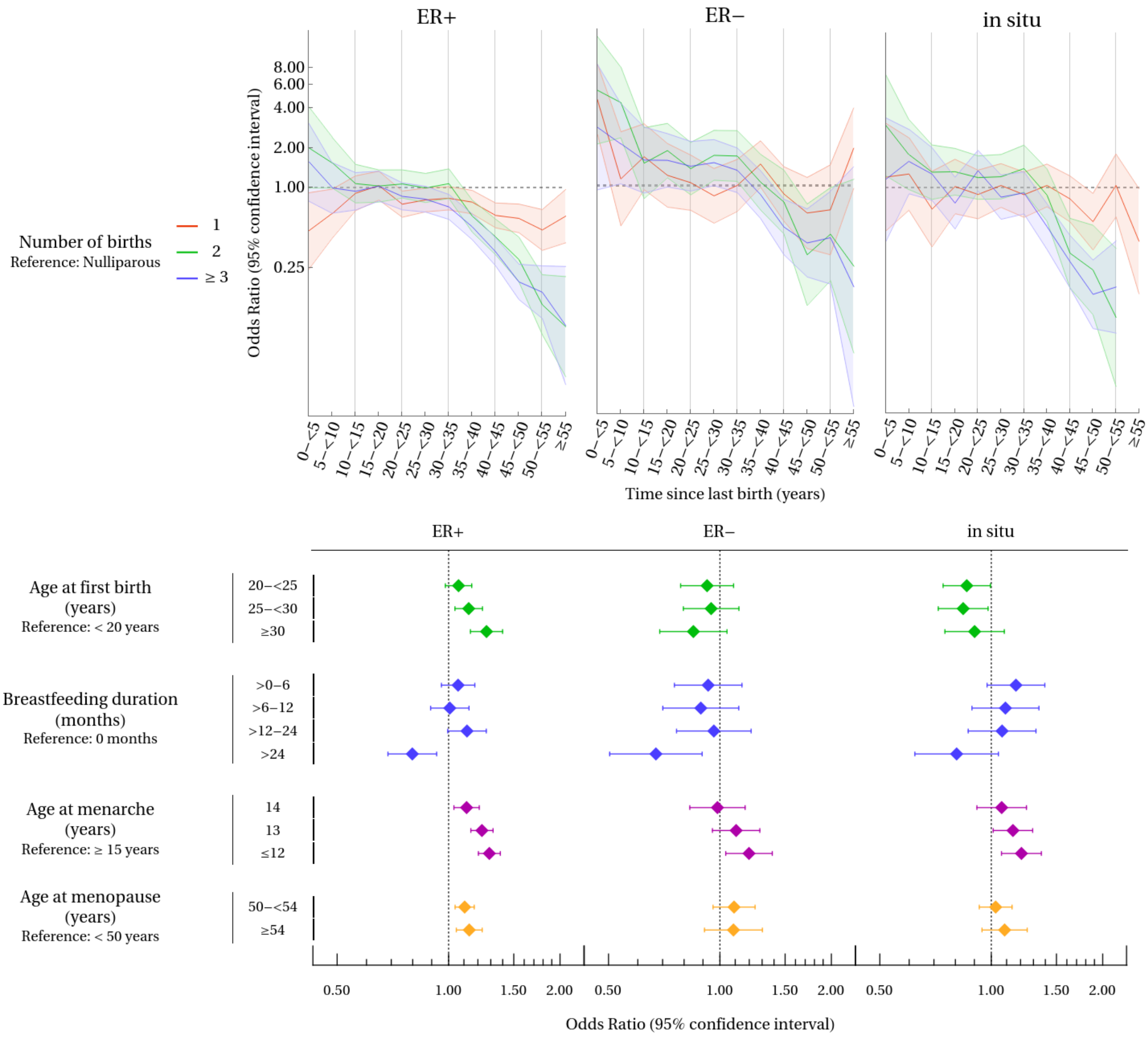



**Supplementary Figure S13**. ORs (colored dots) and 95%CIs (colored horizontal lines) for case-control* analyses† of associations between reproductive factors (time since last birth by number of births, age at first birth, breastfeeding duration, age at menarche, and age at menopause) and intrinsic-like subtypes‡ in population-based case-control studies.

* Controls is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases) and study.

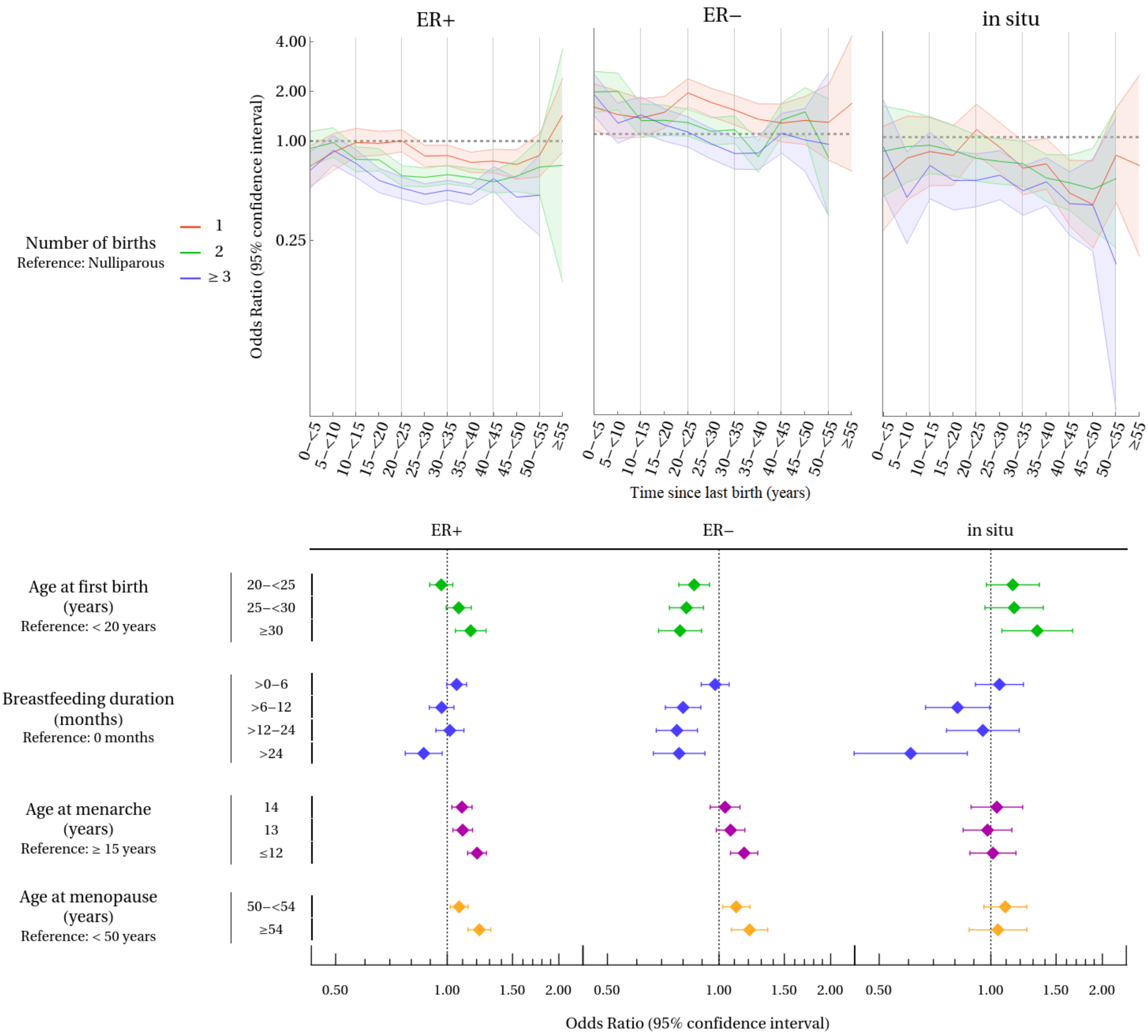
‡ Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&2), luminal B-like (ER-positive or PR-positive, HER2-negative, grade 3), luminal B-HER2-like (ER-positive or PR-positive, HER2-positive, any grade), HER2-enriched-like (ER-negative, PR-negative, HER2-positive,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




**Supplementary Figure S14**. ORs (colored dots) and 95%CIs (colored horizontal lines) 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 ER subtypes and *in situ* in prospective cohort studies.

* Controls is the reference.

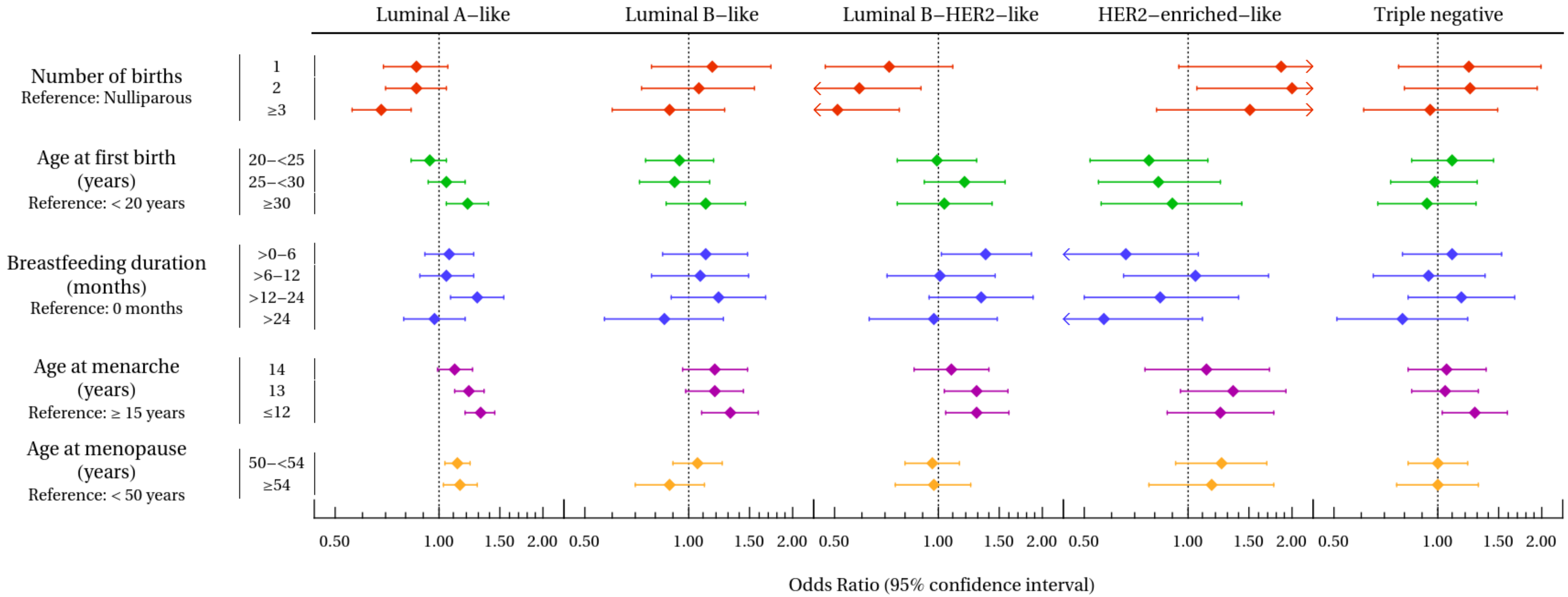
† The model was also adjusted for reference age (age at diagnosis for cases) and study.




**Supplementary Figure S15**. ORs (colored dots) and 95%CIs (colored horizontal lines) 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 ER subtypes and *in situ* in population-based case-control studies.

* Controls is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases) and study.

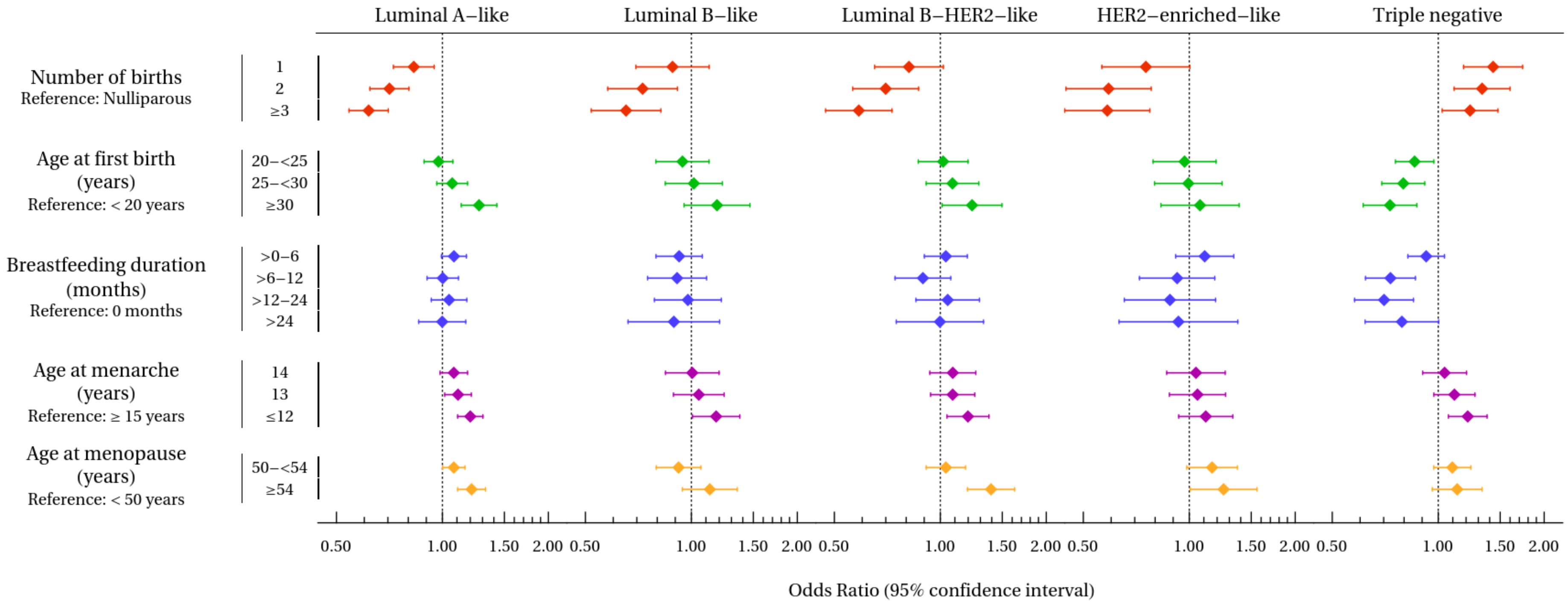



**Supplementary Figure S16**. ORs (colored dots) and 95%CIs (colored horizontal lines) for case-control* analyses† of associations between reproductive factors (number of births, age at first birth, breastfeeding duration, age at menarche, and age at menopause) and intrinsic-like subtypes‡ in prospective cohort studies.

* Controls is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases) and study.

‡ Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&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).

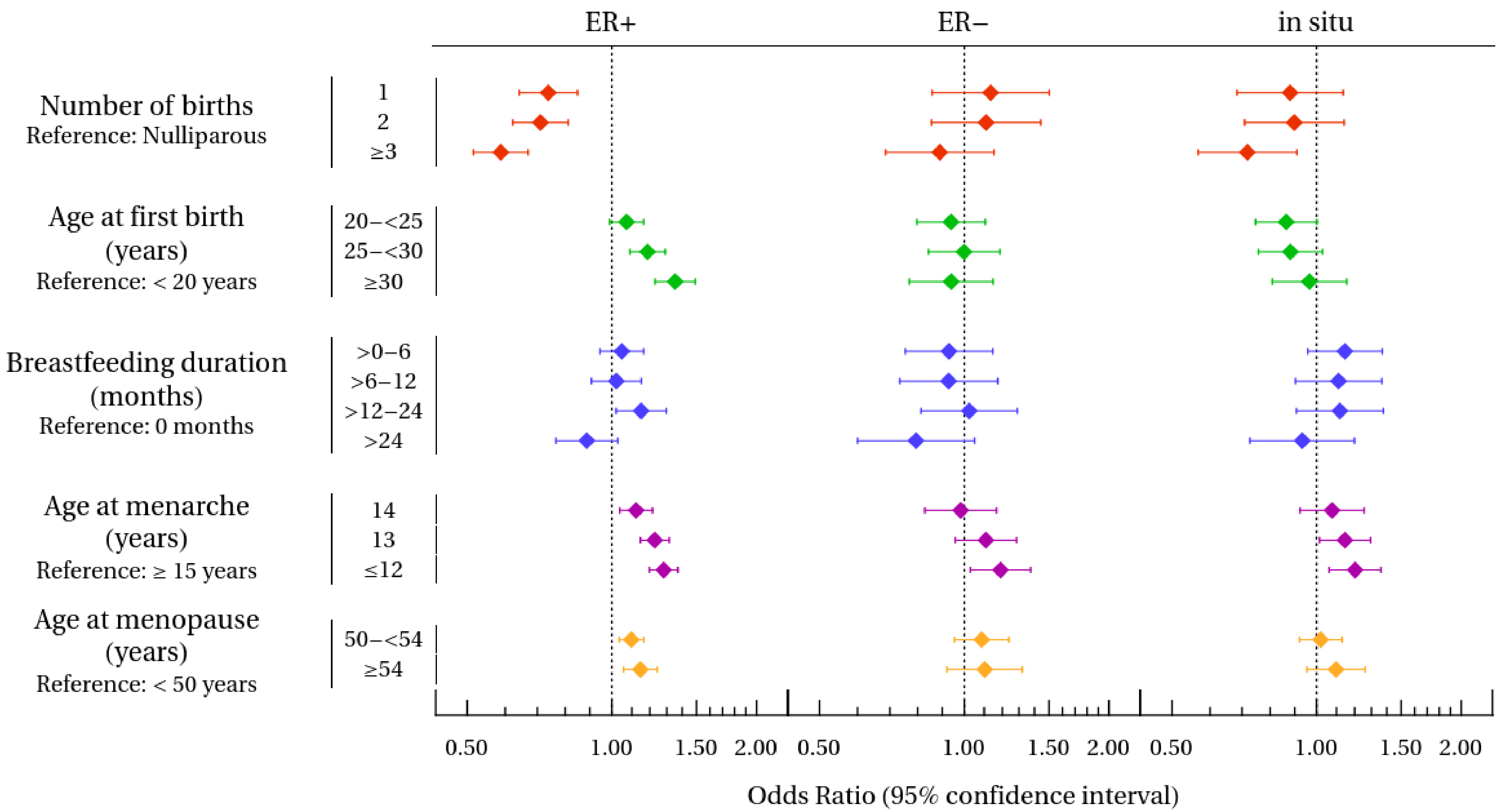



**Supplementary Figure S17**. ORs (colored dots) and 95%CIs (colored horizontal lines) for case-control* analyses† of associations between reproductive factors (number of births, age at first birth, breastfeeding duration, age at menarche, and age at menopause) and intrinsic-like subtypes‡ in population-based case-control studies.

* Controls is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases) and study.

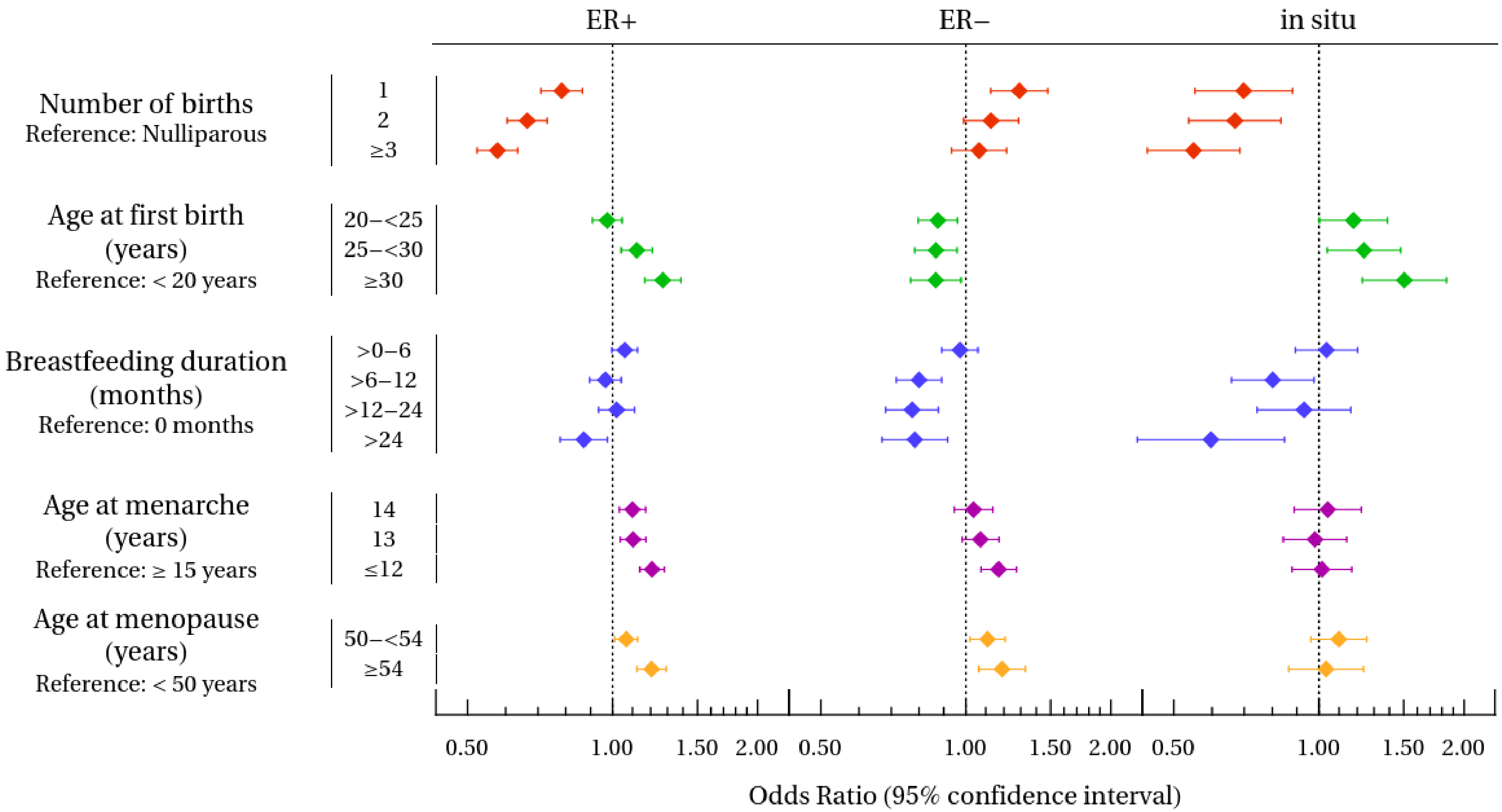
‡ Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&2), luminal B-like (ER-positive or PR-positive, HER2-negative, grade 3), luminal B-HER2-like (ER-positive or PR-positive, HER2-positive, any grade), HER2-enriched-like (ER-negative, PR-negative, HER2-positive,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




**Supplementary Figure S18**. ORs (colored dots) and 95%CIs (colored horizontal lines) for case-control* analyses† of associations between reproductive factors (number of births, age at first birth, breastfeeding duration, age at menarche, and age at menopause) and ER subtypes and *in situ* in prospective cohort studies.

* Controls is the reference.

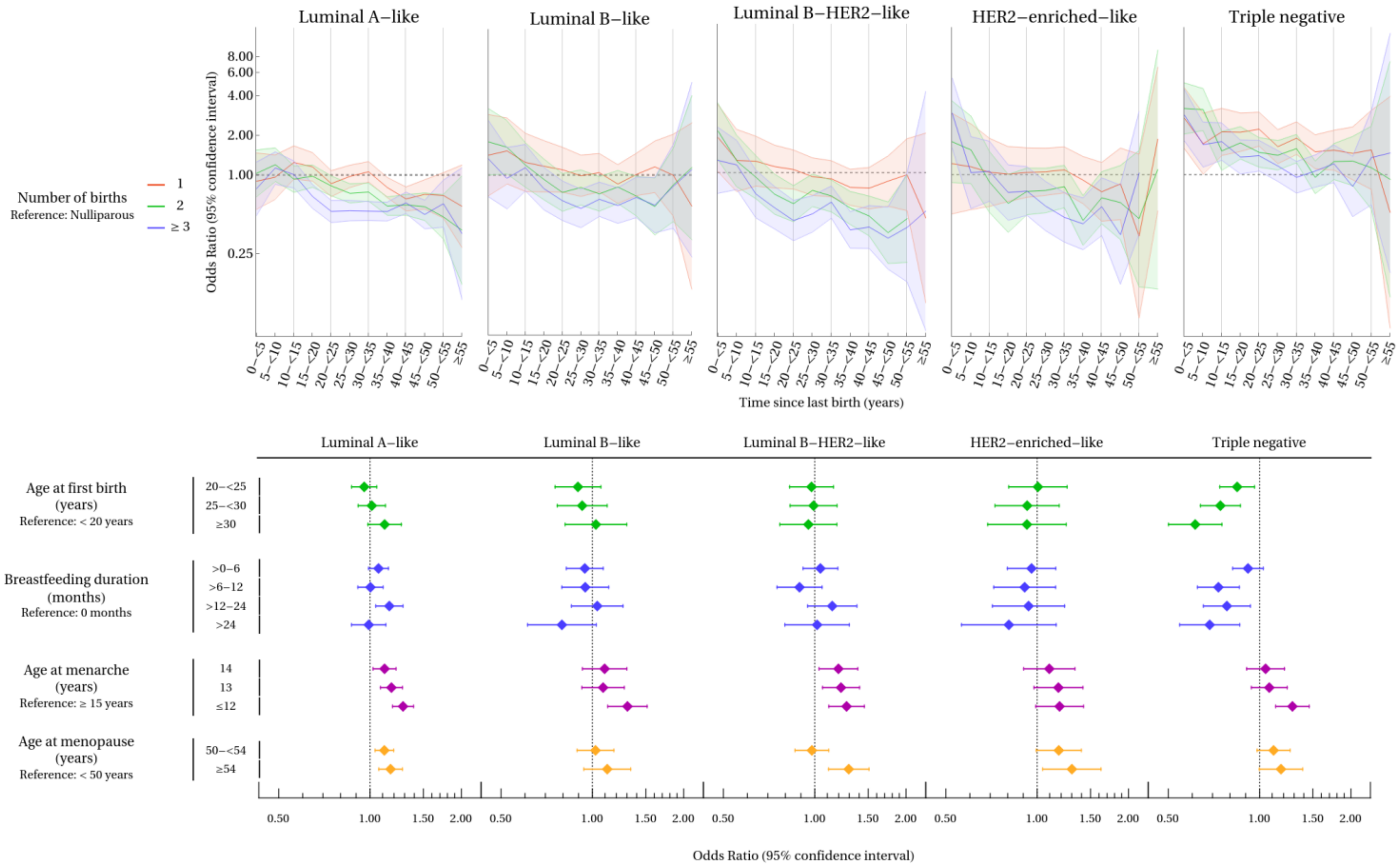
† The model was also adjusted for reference age (age at diagnosis for cases) and study.




**Supplementary Figure S19**. ORs (colored dots) and 95%CIs (colored horizontal lines) for case-control* analyses† of associations between reproductive factors (number of births, age at first birth, breastfeeding duration, age at menarche, and age at menopause) and ER subtypes and *in situ* in population-based case-control studies.

* Controls is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases) and study.



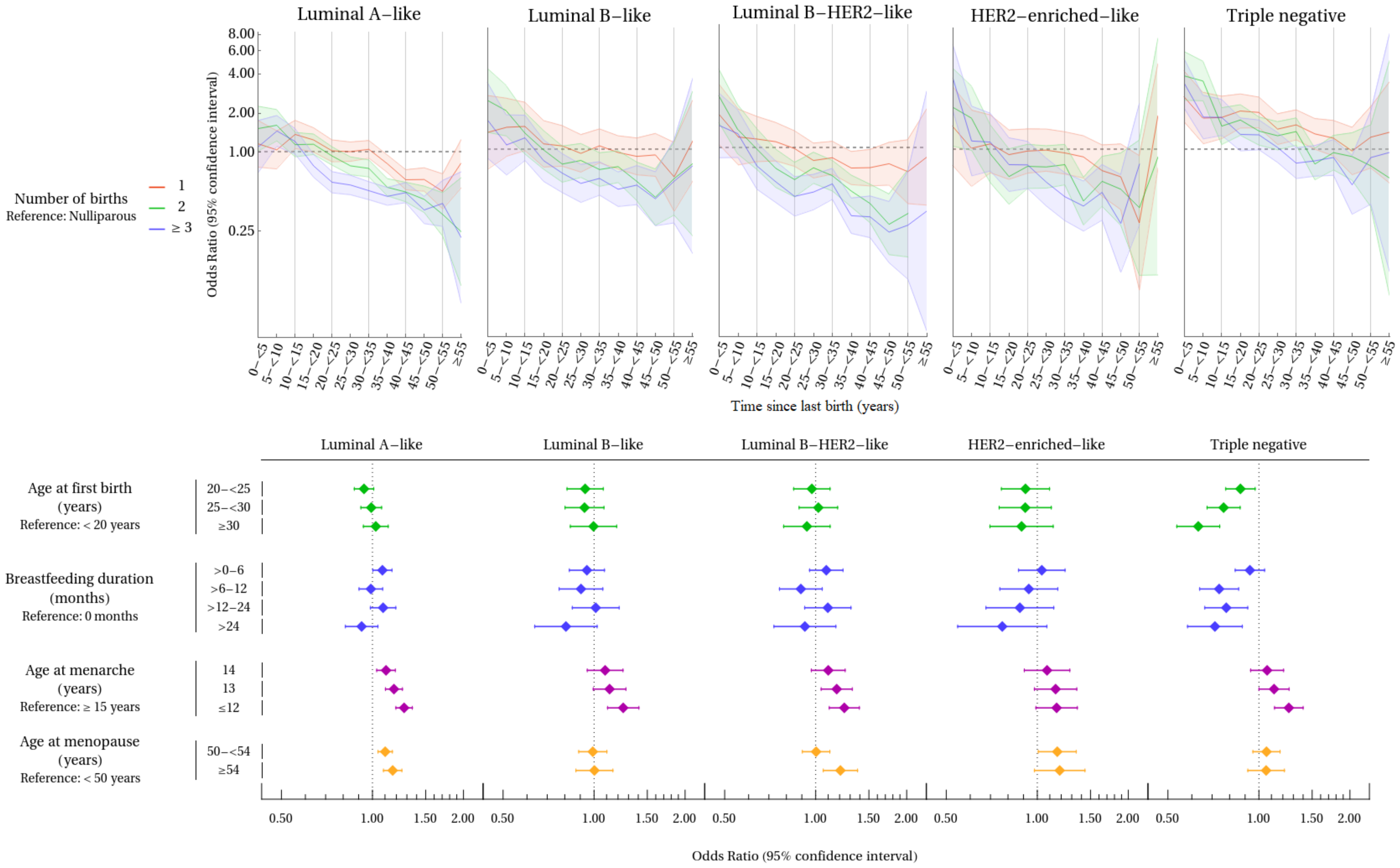

**Supplementary Figure S20**. Sensitivity analyses showing ORs (colored dots) and 95%CIs (colored horizontal lines) for case-control* analyses† of associations between reproductive factors (time since last birth by number of births, age at first birth, breastfeeding duration, age at menarche, and age at menopause) and intrinsic-like subtypes‡, after excluding studies with missing data on time since last birth or breastfeeding duration for >90% of cases or controls.

* Controls is the reference.

† The model was also adjusted for reference age (age at diagnosis for cases) and study.

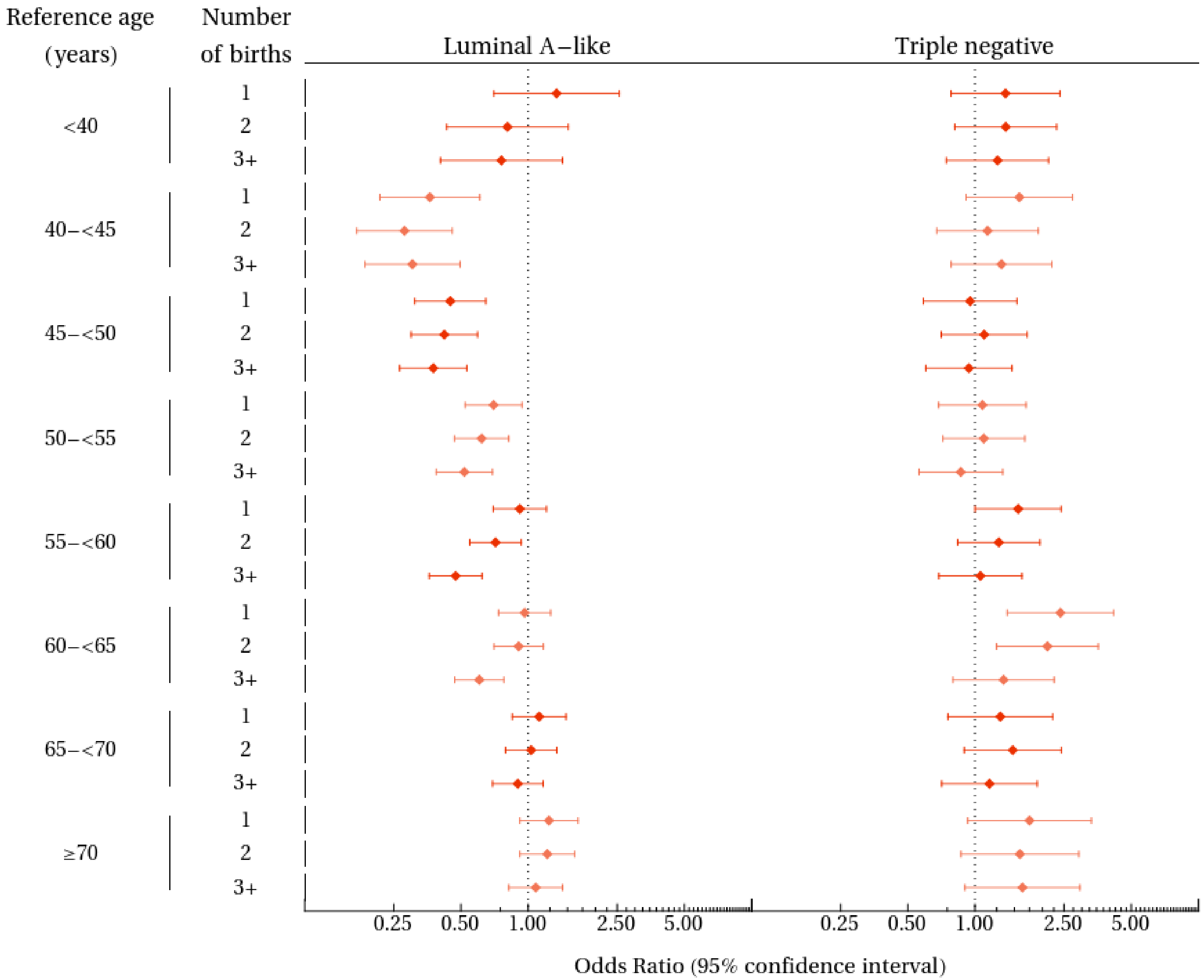
‡ Intrinsic-like subtype definitions: luminal A-like (ER-positive or PR-positive, HER2-negative, grade 1&2), luminal B-like (ER-positive or PR-positive, HER2-negative, grade 3), luminal B-HER2-like (ER-positive or PR-positive, HER2-positive, any grade), HER2-enriched-like (ER-negative, PR-negative, HER2-positive,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

Figure 1



Luminal A−like
Luminal B−like
Luminal B−HER2−like
HER2−enriched−like
Triple negative
Odds Ratio (95% confidence interval)
8.00
6.00
4.00
2.00
1.00
0.25
Number of births
Reference: Nulliparous
1
2
≥ 3
0−<5
5−<10
10−<15
15−<20
20−<25
25−<30
30−<35
35−<40
40−<45
45−<50
50−<55
≥55
Time since last birth (years)
Age at first birth
(years)
Reference: < 20 years
20−<25
25−<30
≥30
Breastfeeding duration
(months)
Reference: 0 months
>0−6
>6−12
>12−24
>24
Age at menarche
(years)
Reference: ≥ 15 years
14
13
≤12
Age at menopause
(years)
Reference: < 50 years
50−<54
≥54
0.50
1.00
1.50
2.00
Odds Ratio (95% confidence interval)

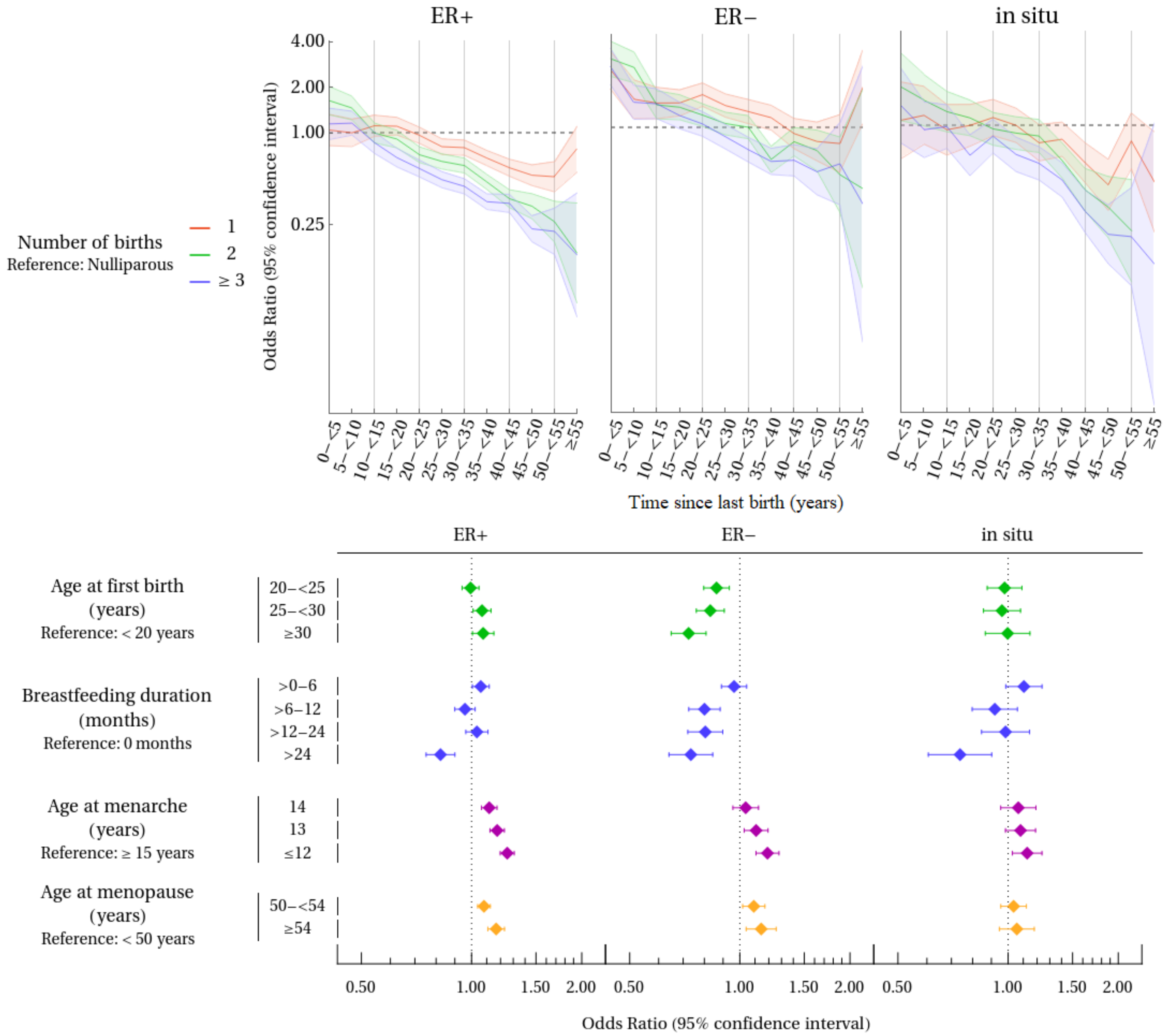
Figure 2



Reference age (years)
Number of births
Luminal A–like
Triple negative
<40
40–<45
45–<50
50–<55
55–<60
60–<65
65–<70
≥70
1
2
3+
0.25
0.50
1.00
2.50
5.00
Odds Ratio (95% confidence interval)


1

Figure 3



ER+
ER−
in situ
4.00
2.00
1.00
0.25
Odds Ratio (95% confidence interval)
Number of births
Reference: Nulliparous
1
2
≥ 3
0−<5
5−<10
10−<15
15−<20
20−<25
25−<30
30−<35
35−<40
40−<45
45−<50
50−<55
≥55
Time since last birth (years)
Age at first birth (years)
Reference: < 20 years
20−<25
25−<30
≥30
Breastfeeding duration (months)
Reference: 0 months
>0−6
>6−12
>12−24
>24
Age at menarche (years)
Reference: ≥ 15 years
14
13
≤12
Age at menopause (years)
Reference: < 50 years
50−<54
≥54
0.50
1.00
1.50
2.00
Odds Ratio (95% confidence interval)


1