Published in final edited form as:
Cancer Res. 2014 December 1; 74(23): 6958–6967. doi:10.1158/0008-5472.CAN-14-2150.

Early Pregnancy Sex Steroids and Maternal Breast Cancer: A nested case-control study

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Abstract

Pregnancy, parity and circulating steroid hormone levels are associated with risk of breast cancer, but little is known about hormone concentrations during pregnancy and subsequent breast cancer risk. We evaluated early pregnancy (<140 days gestation) serum estradiol, estrone, progesterone, and testosterone and breast cancer risk in a nested case-control study in the Finnish Maternity Cohort. The cohort includes 98% of pregnancies registered in Finland since 1983. Individuals with samples collected in the first pregnancy leading to a live birth were eligible. Breast cancer cases (n=1,199) were identified through linkage with the Finnish Cancer Registry; 2,281 matched controls were selected using incidence density sampling. Odds ratios were calculated using conditional logistic regression. Hormone concentrations were not associated with breast cancer overall. Estradiol was positively associated with risk of breast cancer diagnosed age <40 (4^{th} vs. 1^{st} quartile OR 1.60 (1.07–2.39); p_{trend}=0.01), and inversely associated with breast cancer diagnosed at age ≥40 (4^{th} vs. 1^{st} quartile OR 0.71 (0.51–1.00); p_{trend}=0.02). Elevated concentrations of the steroid hormones were associated with increased risk of estrogen receptor (ER) and progesterone receptor (PR) negative tumors in women age <40 at diagnosis. We observed no association between steroid hormones and ER+/PR+ disease. These data suggest a positive association between high concentrations of early pregnancy steroid hormones and risk of ER−/PR− breast cancer in women diagnosed age <40, and an inverse association for overall breast

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cancer diagnosed age ≥40. Further research on pregnancy hormones and risk of steroid receptor negative cancers is needed to further characterize this association.

Keywords

pregnancy; endogenous hormones; breast cancer

The biological mechanisms relating pregnancy, parity and breast cancer are not fully understood. Breast cancer risk increases transiently following pregnancy, but parity is subsequently associated with a reduced risk, though this effect is dependent on age at first birth (reviewed in (1,2)). Animal models suggest a hormonal basis for the long-term protective effect conferred by pregnancy (3). Marked changes in endogenous hormone concentrations occur during pregnancy (4), and circulating endogenous hormones are associated with breast cancer risk (5–9). Therefore, pregnancy-associated changes in the hormonal milieu might influence the risk of breast cancer later in life. This hypothesis has remained largely unexplored.

Prior studies in non-pregnant premenopausal (5,7) and postmenopausal women (6,8,9) suggest a positive association between circulating endogenous estrogen and androgen concentrations and breast cancer, but data in pregnant women is sparse. During pregnancy, endogenous estradiol and progesterone are produced by the placenta; circulating concentrations increase several-fold across pregnancy (4). As in non-pregnant women, during pregnancy androgens are produced by the ovaries and the adrenal cortex; the adrenal glands and liver of the fetus are additional sources of androgens (10). Circulating androgen concentrations increase more gradually across gestation than those of estrogens and progesterone, increasing approximately two-fold between pre-conception and the third trimester (4). In experimental models, mimicking the hormonal effects of pregnancy on circulating estradiol and progesterone concentrations significantly reduced the risk of mammary tumors (3), suggesting that high concentrations of these hormones during pregnancy may provide improved protection.

There are only two prior studies on the association between endogenous hormones during pregnancy and breast cancer risk in the mother (11,12), one of which is a subset of our current study population (12). Peck et al. evaluated third trimester hormone levels and subsequent breast cancer risk, and observed an increased risk with high estrone, but not estradiol, concentrations (11). In our initial report from the Finnish Maternity Cohort (FMC; n=536 cases), high early pregnancy estradiol was associated with higher breast cancer risk among women diagnosed with breast cancer younger than age 40, and with lower risk among those were diagnosed at age 40 or older (12). However, statistical power was limited in subgroup analyses, and data on tumor steroid hormone receptor status were not available.

The relationships between pregnancy, parity, and breast cancer risk are complex and our understanding of the biological mechanisms underpinning these associations is still limited. Therefore, we conducted a nested case control study in the prospective FMC to evaluate early pregnancy steroid hormones in a primiparous pregnancy and subsequent breast cancer risk.

We hypothesized that higher early pregnancy sex steroids would be associated with decreased risk of breast cancer among women with older age at diagnosis, particularly ER +/PR+ breast cancer, given that the protective effect of parity is realized with increasing age (13,14), and is observed in hormone receptor-positive tumors (15). In addition, we hypothesized that the increased risk observed among women younger than age 40 in our previous analysis would be strongest in hormone receptor negative tumors, given the association between pregnancy and hormone receptor negative breast cancer and experimental data suggesting a role for estradiol in hormone receptor negative pregnancy-associated breast cancer (16). To our knowledge, the present report is the largest study on this topic and the only investigation by tumor hormone receptor status.

Methods

The FMC is a nationwide initiative in Finland, established in 1983 to preserve serum samples drawn from pregnant women for research use (12,17). The cohort includes 98% of all registered pregnancies with approximately 900,000 participants. Participants are recruited at the municipal maternity care units that provide free-of-charge pre- and post-natal care to all pregnant women. Clinical data enabling follow-up are available through linkages with the nationwide registries in Finland, including the Finnish Population Registry (includes emigration and vital status), Finnish Birth Registry, and Finnish Cancer Registry (data about cancer characteristics and patient outcome). After registration of each new pregnancy (usually during the latter part of the first trimester or early weeks of the second), a blood sample is drawn for routine screening tests; remaining serum specimens (usually 1 – 3 mL) are stored for research purposes. Samples are stored at −25°C at a central biorepository in Oulu, Finland. The study was approved by the ethical committee of the National Institute for Health and Welfare, Finland.

Selection of eligible case and control subjects

Cases and controls were selected from primiparous pregnancies (i.e. first pregnancy resulting in a live birth) in the FMC. To be eligible for selection as a case or control, participants had to meet the following criteria: available serum specimen, information about gestational age at the time of blood collection, age <40 at blood draw, blood sample provided within the first 140 days (20 weeks) of gestation, pregnancy led to full term birth (pregnancy duration of 37 to 43 weeks), and singleton pregnancy. Mother's age blood donation was used as a proxy for age at first birth.

Incident cancers were identified through a linkage with the Finnish Cancer Registry. Reporting of cancer cases has been mandatory by legislation in Finland since 1961; the registry has close to 100% coverage of all diagnosed cancers (18). Eligible cases had histologically confirmed invasive breast cancer, donated a blood sample to the FMC prior to the diagnosis of breast cancer, and had no history of *in situ* breast cancer or any other invasive cancer (except non-melanoma skin cancer). Breast cancers included in this study were diagnosed from 1988 through 2007. Two randomly selected controls were matched to each case on age (±6 months) and date of blood collection (±3 months) from the eligible cohort subjects with no prior diagnosis of *in situ* or invasive breast cancer or any other

invasive cancer (except non-melanoma skin cancer) at the date of diagnosis of their matched case.

Laboratory Assays

Serum estradiol, estrone, progesterone and testosterone were measured using high performance liquid chromatography tandem mass spectrometry, performed with an Applied Biosystems API4000 triple stage quadrupole mass spectrometer. Laboratory assays were conducted at the Department of Clinical Chemistry, Umeå University, Sweden. Cases and control samples were analysed in the same batch alongside blinded quality control samples. The intra-batch coefficient of variation (CV) ranged from 7.2% (for estradiol) to 13.3% (for testosterone); the inter-batch CVs ranged from 7.2% (estradiol) to 18.7% (testosterone).

Statistical Analyses

We applied a $\log_2$ transformation to improve the normality of the hormone data distributions and to allow estimation of the effect of a doubling of the concentrations on breast cancer risk (a 1-unit increase in $\log_2$ transformed hormone concentration corresponds to a doubling). Outliers were defined as values exceeding three times the interquartile range; a single outlier for progesterone was identified. This outlier was excluded as it was identified as an influential data point in subsequent analyses investigating the linearity of the associations. However, exclusion of this single value did not meaningfully impact the effect estimates. We examined the possibility of a non-linear relation between the investigated hormones and breast cancer risk non-parametrically with restricted cubic splines (19). Tests for non-linearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms. Conditional logistic regression was used to estimate odds ratios and 95% confidence intervals. We defined quartiles using the hormone concentration distribution of the controls. Tests for trend were carried out by entering an ordered quartile exposure variable into the models.

Family history of breast cancer, number of pregnancies, parity at breast cancer diagnosis, use of assisted reproductive technology, and smoking during pregnancy were evaluated as potential confounders. With the exception of family history of breast cancer, adjusting for these factors caused negligible difference in the effect estimates (<10% change in the ORs). All models control for gestational age at blood collection given established associations between gestational age and circulating hormones. Therefore, gestational age and family history of breast cancer were retained in the final models.

We examined associations by hormone receptor status and conducted analyses stratified by age at first birth (categorized as <30 vs. ≥30 years), age at breast cancer diagnosis (<40 vs. ≥40 years), number of pregnancies at the time of blood sample collection (1 vs. >1), and the time interval between blood sampling and breast cancer diagnosis (<5 vs. ≥5 years; and <10 vs. ≥10 years). Matched sets were retained in stratified analyses. Heterogeneity between the effect estimates (p_{het}) was tested with the χ^2 test (20). All calculations were done using SAS 9.3 (Cary, NC, USA). Two-sided p-values < 0.05 were considered statistically significant.

Results

The study population included 1,199 cases and 2,281 matched controls. The median age at first birth was 30 years (range: 18–40; Table 1). The majority of cases and controls were multiparous at the time of breast cancer diagnosis. Cases and controls were largely similar with respect to pregnancy characteristics, except that cases were more likely to have a positive family history of breast cancer (11% of cases vs. 5% of controls; $p<0.001$) and cases were more likely to be multiparous than controls at diagnosis/selection as a control ($p=0.04$).

The median age at the time of breast cancer diagnosis was 41.2 years (range, 21.7–58.1), and a median of 10.9 years (range, 1.1–21.0) elapsed between the first birth and breast cancer diagnosis. A total of 687 cases (57%) had tumor estrogen receptor (ER) and progesterone receptor (PR) expression data available. Of tumors with ER and PR status available, 67% were classified ER and PR positive (ER+/PR+) and 25% were classified ER −/PR−, according to local pathology reports. As expected, a higher proportion of breast cancers diagnosed within 5 years of first birth were ER−/PR− as compared with tumors diagnosed 5 or more years since the first birth ($p=0.03$).

There were no significant associations between circulating steroid hormone concentrations and risk of breast cancer overall (Table 2). In subgroup analyses, age at first birth and age at breast cancer diagnosis modified the associations between circulating steroid hormone levels and breast cancer risk. High serum estradiol was associated with an increased risk of breast cancer among women diagnosed with breast cancer at a relatively young age (age at diagnosis <40, 4^{th} vs. 1^{st} quartile OR: 1.60 (95% CI: 1.07–2.39), $p_{trend}=0.01$), whereas we observed an inverse association in women diagnosed with breast cancer at age 40 or older (4^{th} vs. 1^{st} quartile OR: 0.71 (0.51–1.00), $p_{trend}=0.02$; $p_{het}<0.01$). High serum testosterone was only associated with an increased risk of breast cancer in the subset of women diagnosed younger than age 40 (4^{th} vs. 1^{st} quartile ORs, age <40: 1.39 (0.99–1.96), $p_{trend}=0.02$; age ≥40: 1.00 (0.75–1.34), $p_{trend}=0.68$; $p_{het}=0.15$). No significant associations emerged between circulating estrone or progesterone and breast cancer risk.

We next evaluated the effect of steroid hormone concentrations on risk of breast cancer by hormone receptor subtype in analyses stratified by age at first birth (age <30 vs. ≥30) and age at diagnosis (age <40 vs. ≥40; Table 3). Associations for ER+/PR+ tumors were similar regardless of age at first birth or age at diagnosis (e.g., estradiol: Age at diagnosis <40, OR: 0.96 (0.72–1.30); Age at diagnosis ≥40, OR: 0.93 (0.74–1.16); $p_{het}=0.83$). Higher concentrations of serum estradiol, progesterone, and testosterone were significantly associated with an increased risk of ER−/PR− cancer in women younger than 40 at diagnosis (e.g., estradiol: OR: 1.48 (1.00–2.17)), whereas we observed no significant associations between steroid hormones and ER−/PR− cancers in women older than 40 at diagnosis (e.g., estradiol: OR: 0.87 (0.55–1.39); $p_{het}=0.09$). Results stratified by age at first birth were similar to those stratified by age at diagnosis. All associations were linear after exclusion of the single progesterone outlier; exclusion of the outlier resulted in essentially no change in the observed associations (e.g., age at first birth >30 before exclusion of outlier: odds ratio (OR) 1.01 95% confidence interval (0.84–1.21); after exclusion: OR 1.01 (0.84–1.22)).

In a sensitivity analysis, we classified cases into four groups based on both age at first birth and age at breast cancer diagnosis (age at first birth/age at diagnosis <30/<40 years, <30/≥40 years, ≥30/<40 years, and ≥30/≥40years) to evaluate the joint effects of these variables on the associations between serum hormone concentrations and breast cancer risk (Table 4). The associations between endogenous hormone concentrations and breast cancer risk stratified by age at diagnosis (<40 vs. ≥40) were similar regardless of age at first birth (<30 vs. ≥30) overall and for ER+/PR+ tumors (data not shown). All four hormones were significantly associated with an increased risk of ER−/PR− breast cancer among women with both age at first birth <30 and age at diagnosis <40 (estradiol, OR_{log2} 1.72, 95% CI 1.11–2.67; estrone, OR_{log2} 1.44, 95% CI 1.02–2.05; progesterone, OR_{log2} 1.99, 95% CI 1.04–3.82; testosterone, OR_{log2} 1.67, 95%CI 1.13–2.47).

We observed no significant heterogeneity in analyses stratified by the time between age at first birth and breast cancer diagnosis (<5 years vs. ≥5 years or <10 years vs. ≥10 years), and in analyses stratified by number of pregnancies (1 vs. >1). Progesterone and testosterone were suggestively more strongly associated with ER−/PR− tumors diagnosed < 10 vs. ≥10 years of first birth, however neither the heterogeneity nor the effect estimates were statistically significant (e.g., progesterone: <10 years OR 1.91 (0.99–3.70); ≥10 years OR: 1.04 (0.59–1.82); p_{het}=0.17) (Table 5). To investigate whether the observed associations among women <40 at diagnosis were due to shorter time between first birth and diagnosis, we examined risk based on both age at diagnosis and time between first pregnancy and diagnosis (age at diagnosis/years between first birth and diagnosis; <40/<10; <40/≥10; ≥40/<10; ≥40/≥10) (Supplemental Table). The association between estrone and ER−/PR− breast cancer among women ≥40 at diagnosis was significantly different comparing women with <10 vs. ≥10 years between first birth and diagnosis (p=0.03), however neither of the effect estimates were statistically significant (age at diagnosis/years between first birth and diagnosis: ≥40/<10 OR 1.49 (0.79–2.82); ≥40/≥10: OR 0.63 (0.40–1.02)) and this subgroup had relatively few cases (≥40/<10: n=17 cases; ≥40/≥10: n=48 cases).

Discussion

In the largest study on early pregnancy hormones and breast cancer, higher concentrations of steroid hormones were associated with breast cancer risk in women with first birth before age 30 or diagnosed with breast cancer before age 40. These associations were strongest for ER−/PR− tumors. Early pregnancy estradiol appeared to be associated with decreased risk in women age 40 or older at diagnosis. We observed no associations between the evaluated hormones and breast cancer overall or in ER+/PR+ tumors.

The relationship between pregnancy and breast cancer in humans is complex. An initial pregnancy-associated transient increase in risk shifts to a parity-associated reduction in risk more than a decade post-pregnancy. Further, these associations differ by age at first birth. Younger age at first birth (i.e., age <25) is associated with shorter time from pregnancy to parity-associated reduction in risk (1,21) and parity with older age at first birth (i.e., age ≥35) is associated with a persistent deleterious effect (22,23). Further, the transient increase in risk is more pronounced for hormone receptor negative tumors, whereas the protective effect of parity is restricted to hormone receptor positive tumors (13,24). Breastfeeding is

also associated with risk of breast cancer, with suggestively stronger protective effects for hormone receptor negative disease (15). While the mechanisms of parity-induced protection in humans are still under investigation, animal models provide strong, consistent evidence that the hormonal milieu of pregnancy protects against mammary tumors (reviewed in (3)). Tumorigenesis is substantially lower in parous vs. nulliparous rodents treated with carcinogen, with similar results for nulliparous rodents treated with estradiol and progesterone to mimic the effect of pregnancy (3).

Endogenous hormones and breast cancer have been extensively studied outside of pregnancy, but little is known about hormones in pregnancy and subsequent breast cancer risk. In the only study to date outside of the FMC, Peck et al. (case n=194) evaluated 3rd trimester hormone concentrations and breast cancer risk and reported an inverse association for progesterone (OR, extreme deciles: 0.49 (0.22–1.1); p_{trend}=0.08), a positive association for estrone (OR, extreme deciles: 2.5 (1.0–6.1); p_{trend}=0.12), and no association for estradiol or estriol (11). We found no association between estrone or progesterone and breast cancer overall. The discrepant findings between the two studies may be due to the difference in gestational age at blood collection (Peck et al: mean, 34.5 weeks (range, 26–42 weeks); FMC: mean, 11.6 weeks (range, 5.0–19.9 weeks) and differences in hormone concentrations and breast differentiation in early vs. late pregnancy.

Along with changes in the hormonal milieu, the breast undergoes differentiation during pregnancy, reaching full differentiation in the final trimester (25,26). The protective effect of parity is evident for full term pregnancies (27), but not interrupted pregnancies (28) or those ending in early preterm delivery (29), suggesting that the full differentiation achieved in the third trimester is necessary for the long-term protective effect of pregnancy. We quantified hormone exposure during the early stages of pregnancy-associated breast differentiation. There are limited data on correlations between consecutive trimesters of a single pregnancy for individual hormones (i.e. correlation between women's estradiol concentrations in the 1st vs. 2nd or 1st vs. 3rd trimesters). However, ongoing work in our group suggests significant correlations between 1st and 2nd trimester estradiol (r=0.60, p=0.004), estrone (r=0.76, p<0.01), and testosterone (r=0.74, p<0.01), and 1st and 3rd trimester estrone (r=0.67, p<0.01), and testosterone (r=0.67, p<0.01). Progesterone was not significantly correlated between the 1st and 2nd trimesters (0.07, p=0.76) and estradiol and progesterone were not significantly correlated between the 1st and 3rd trimesters (estradiol: r=0.42, p=0.06; progesterone: r=0.25, p=0.28) (personal communication, Helena Schock). Therefore, our early pregnancy hormone measures are likely a reasonable proxy for estrone and testosterone in late pregnancy, at the stage of full differentiation, while estradiol and progesterone in early pregnancy may not be reflective of late pregnancy concentrations.

We observed heterogeneity in the associations between pregnancy hormones and breast cancer risk by age at first birth and age at diagnosis. Estradiol was positively associated with tumors among women with age at first birth <30 or age at diagnosis <40 and inversely associated with risk in women diagnosed age ≥40. The increased risk in women with age at first birth <30 or age at diagnosis <40 was driven by positive associations with ER−/PR− tumors. ER−/PR− tumors are more common in women with young age at diagnosis (30) and with pregnancy-associated breast cancers (2). These results are in line with data from

experimental models of pregnancy-associated tumors (16), and the protective effect of bilateral oophorectomy against breast cancer in BRCA1 carriers, notable given the high proportion of ER− tumors in this population (31). Endogenous hormones increase risk of these tumors via paracrine mechanisms including the receptor activator of NF-kappa B ligand (RANKL) (32), epidermal growth factor receptor (EGFR), and Notch signaling pathways (33). ER data for this study, and most epidemiologic studies, reflects expression of ER-alpha (ER-α), the ER measured clinically. Expression of an additional ER, ER-beta (ER-β), may also be important in ER-α negative breast cancer (34–37). A proportion of the ER −/PR− tumors in the current study may be estrogen responsive due to expression of ER-β. The inverse associations observed in women diagnosed age ≥40 are in line with the expected parity-associated decrease in breast cancer risk. Data from experimental models suggest mimicking pregnancy with estradiol and progesterone affords protection against breast cancer similar to that of parity (3), with some suggestion of lower risk at higher hormone concentrations. Our findings of decreased risk of breast cancer after age 40 with higher early pregnancy estradiol are in agreement with these experimental studies.

Our study has important strengths and limitations. The FMC is uniquely positioned to investigate endogenous hormones in pregnancy and subsequent disease risk. This study is the largest to date, and the first to evaluate pregnancy hormones and breast cancer risk by hormone receptor subtype. A limitation of this study was the availability of a single measure of hormones in early pregnancy. Hence, we were unable to address changes in hormone concentrations across pregnancy and breast cancer risk. Coefficients of variation for evaluated hormones were as high as 18.7% (testosterone), introducing measurement error. Given that matched case-control sets were assayed in the same analytical batch, we do not expect this would result in bias, but rather would result in non-differential misclassification of exposure and a potential attenuation of results. An additional limitation of our study is lack of information on breastfeeding. Parity is positively associated with ER− breast cancer (38), with data suggesting this association is mediated by breastfeeding (39–41) and we were unable to account for this factor. Further, we did not have data on age at menarche or menopause, or subsequent postmenopausal hormone therapy use, and thus could not evaluate the effect of adjusting for these factors. Finally, we did not statistically adjust for multiple comparisons and we cannot exclude that some of our findings are due to chance.

This study provides novel data on the association between early pregnancy hormones and risk of breast cancer by age at first birth and age at diagnosis by hormone receptor status. Our data suggest that higher early pregnancy estradiol concentrations are positively associated with risk of breast cancer among women diagnosed before age 40. Further, we observed significant positive associations between early pregnancy hormones and ER−/PR− breast cancer in women with age at first birth before age 30 or diagnosed before age 40, and a protective effect for women diagnosed at age 40 or older. Future studies designed to evaluate pregnancy hormone concentrations and risk of breast cancer by age at first birth and diagnosis and time since pregnancy, as well as changes in hormone concentrations across pregnancy, are needed to increase our understanding of the mechanisms underlying the associations between pregnancy and breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This work was supported in part by the National Cancer Institute at the National Institutes of Health (CA114329).

References

1. Schedin P. Pregnancy-associated breast cancer and metastasis. Nat Rev Cancer. 2006; 6:281–291. [PubMed: 16557280]
2. Lyons TR, Schedin PJ, Borges VF. Pregnancy and Breast Cancer: when They Collide. J Mammary Gland Biol Neoplasia. 2009; 14:87–98. [PubMed: 19381788]
3. Sivaraman L, Medina D. Hormone-induced protection against breast cancer. J Mammary Gland Biol Neoplasia. 2002; 7:77–92. [PubMed: 12160088]
4. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. Obstet Gynecol. 2009; 114:1326–1331. [PubMed: 19935037]
5. Kaaks R, Tikk K, Sookthai D, Schock H, Johnson T, Tjønneland A, et al. Premenopausal serum sex hormone levels in relation to breast cancer risk, overall and by hormone receptor status-Results from the EPIC cohort. Int J Cancer. 2013 :n/a–n/a.
6. Kaaks R, Rinaldi S, Key TJ, Berrino F, Peeters PHM, Biessy C, et al. Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. Endocr Relat Cancer. 2005; 12:1071–1082. [PubMed: 16322344]
7. Endogenous Hormones and Breast Cancer Collaborative Group. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. Lancet Oncology. 2013; 14:009–019.
8. Key T, Appleby P, Barnes I, Reeves G. Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst. 2002; 94:606–616. [PubMed: 11959894]
9. Zhang X, Tworoger SS, Eliassen AH, Hankinson SE. Postmenopausal plasma sex hormone levels and breast cancer risk over 20 years of follow-up. Breast Cancer Res Treat. 2013; 137:883–892. [PubMed: 23283524]
10. Widmaier E, Raff H, Strang K. Vander's Human Physiology.
11. Peck JD, Hulka BS, Poole C, Savitz DA, Baird D, Richardson BE. Steroid hormone levels during pregnancy and incidence of maternal breast cancer. Cancer Epidemiol Biomarkers Prev. 2002; 11:361–368. [PubMed: 11927496]
12. Lukanova A, Surcel H-M, Lundin E, Kaasila M, Lakso H-A, Schock H, et al. Circulating estrogens and progesterone during primiparous pregnancies and risk of maternal breast cancer. Int J Cancer. 2012; 130:910–920. [PubMed: 21413009]
13. Colditz GA, Rosner BA, Chen WY, Holmes MD, Hankinson SE. Risk Factors for Breast Cancer According to Estrogen and Progesterone Receptor Status. J Natl Cancer Inst. 2004; 96:218–228. [PubMed: 14759989]
14. Clavel-Chapelon F, Gerber M. Reproductive factors and breast cancer risk. Do they differ according to age at diagnosis? Breast Cancer Res Treat. 2002; 72:107–115. [PubMed: 12038701]
15. Anderson KN, Schwab RB, Martinez ME. Reproductive risk factors and breast cancer subtypes: a review of the literature. Breast Cancer Res Treat. 2014; 144:1–10. [PubMed: 24477977]
16. Gupta PB, Proia D, Cingoz O, Weremowicz J, Naber SP, Weinberg RA, et al. Systemic Stromal Effects of Estrogen Promote the Growth of Estrogen Receptor-Negative Cancers. Cancer Res. 2007; 67:2062–2071. [PubMed: 17332335]

17. Toriola AT, Vääräsmäki M, Lehtinen M, Zeleniuch-Jacquotte A, Lundin E, Rodgers K-G, et al. Determinants of Maternal Sex Steroids During the First Half of Pregnancy. Obstet Gynecol. 2011; 118:1029–1036. [PubMed: 22015870]
18. Teppo L, Pukkala E, Lehtonen M. Data quality and quality control of a population-based cancer registry. Experience in Finland. Acta Oncol. 1994; 33:365–369. [PubMed: 8018367]
19. Durrleman S, Simon R. Flexible regression models with cubic splines. Statist Med. 1989; 8:551–561.
20. Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. Statist Med. 1991; 10:1665–1677.
21. Albrektsen G, Heuch I, Hansen S, Kvåle G. Breast cancer risk by age at birth, time since birth and time intervals between births: exploring interaction effects. British J Cancer. 2005; 92:167–175.
22. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. Am J Epidemiol. 2000; 152:950–964. [PubMed: 11092437]
23. Rosner B, Colditz GA, Willett WC. Reproductive risk factors in a prospective study of breast cancer: the Nurses' Health Study. Am J Epidemiol. 1994; 139:819–835. [PubMed: 8178795]
24. Phipps AI, Chlebowski RT, Prentice R, McTiernan A, Wactawski-Wende J, Kuller LH, et al. Reproductive History and Oral Contraceptive Use in Relation to Risk of Triple-Negative Breast Cancer. J Natl Cancer Inst. 2011; 103:470–477. [PubMed: 21346227]
25. Russo J, Mailo D, Hu Y-F, Balogh G, Sheriff F, Russo IH. Breast differentiation and its implication in cancer prevention. Clin Cancer Res. 2005; 11:931s–936s. [PubMed: 15701889]
26. Ferguson DJ, Anderson TJ. A morphological study of the changes which occur during pregnancy in the human breast. Virchows Arch A Pathol Anat Histopathol. 1983; 401:163–175. [PubMed: 6415901]
27. Britt K, Ashworth A, Smalley M. Pregnancy and the risk of breast cancer. Endocr Relat Cancer. 2007; 14:907–933. [PubMed: 18045947]
28. Beral V, Bull D, Doll R, Peto R, Reeves G. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and abortion: collaborative reanalysis of data from 53 epidemiological studies, including 83,000 women with breast cancer from 16 countries. Lancet. 2004; 363:1007–1016. [PubMed: 15051280]
29. Nechuta S, Paneth N, Velie EM. Pregnancy characteristics and maternal breast cancer risk: a review of the epidemiologic literature. Cancer Causes Control. 2010; 21:967–989. [PubMed: 20224871]
30. Dunnwald LK, Rossing MA, Li CI. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. Breast Cancer Res. 2007; 9:R6. [PubMed: 17239243]
31. Foulkes WD, Metcalfe K, Sun P, Hanna WM, Lynch HT, Ghadirian P, et al. Estrogen receptor status in BRCA1- and BRCA2-related breast cancer: the influence of age, grade, and histological type. Clin Cancer Res. 2004; 10:2029–2034. [PubMed: 15041722]
32. Fernandez-Valdivia R, Lydon JP. From the ranks of mammary progesterone mediators, RANKL takes the spotlight. Molecular and cellular endocrinology. 2012; 357:91–100. [PubMed: 21964466]
33. Harrison H, Simões BM, Rogerson L, Howell SJ, Landberg G, Clarke RB. Oestrogen increases the activity of oestrogenreceptor negative breast cancer stem cellsthrough paracrine EGFR and Notch signalling. Breast Cancer Res. BioMed Central Ltd;. 2013; 15:R21.
34. Marotti JD, Collins LC, Hu R, Tamimi RM. Estrogen receptor-beta expression in invasive breast cancer in relation to molecular phenotype: results from the Nurses' Health Study. Mod Pathol. 2010; 23:197–204. [PubMed: 19898422]
35. Chantzi NI, Tiniakos DG, Palaiologou M, Goutas N, Filippidis T, Vassilaros SD, et al. Estrogen receptor beta 2 is associated with poor prognosis in estrogen receptor alpha-negative breast carcinoma. J Cancer Res Clin Oncol. 2013; 139:1489–1498. [PubMed: 23817696]
36. Higa GM, Fell RG. Sex Hormone Receptor Repertoire in Breast Cancer. Int J Breast Cancer. 2013; 2013:284036. [PubMed: 24324894]

37. Gruvberger-Saal SK, Bendahl PO, Saal LH, Laakso M, Hegardt C, Eden P, et al. Estrogen Receptor β Expression Is Associated with Tamoxifen Response in ER-α Negative Breast Carcinoma. Clin Cancer Res. 2007; 13:1987–1994. [PubMed: 17404078]

38. Yang XR, Chang-Claude J, Goode EL, Couch FJ, Nevanlinna H, Milne RL, et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. J Natl Cancer Inst. 2011; 103:250–263. [PubMed: 21191117]

39. Millikan RC, Newman B, Tse C-K, Moorman PG, Conway K, Smith LV, et al. Epidemiology of basal-like breast cancer. Breast Cancer Res Treat. 2007; 109:123–139. [PubMed: 17578664]

40. Palmer JR, Boggs DA, Wise LA, Ambrosone CB, Adams-Campbell LL, Rosenberg L. Parity and Lactation in Relation to Estrogen Receptor Negative Breast Cancer in African American Women. Cancer Epidemiol Biomarkers Prev. 2011; 20:1883–1891. [PubMed: 21846820]

41. Ambrosone CB, Zirpoli G, Ruszczyk M, Shankar J, Hong C-C, McIlwain D, et al. Parity and breastfeeding among African-American women: differential effects on breast cancer risk by estrogen receptor status in the Women's Circle of Health Study. Cancer Causes Control. 2013; 25:259–265. [PubMed: 24249438]

Table 1

Baseline characteristics of breast cancer cases and controls: Finnish Maternity Cohort

Characteristic*	Cases n=1199 *n* (%)	Controls n=2281 *n* (%)	*P***
Age at blood collection, years	30.3 (18.4–40.0)	30.2 (18.0–40.0)	†
Gestational age at blood collection, days	73 (38–136)	73 (35–139)	0.06
No. of pregnancies at diagnosis/selection as control			
1	290 (25%)	610 (27%)	0.06
>1	890 (75%)	1619 (73%)	
No. of births at diagnosis/selection as control			
1	434 (36%)	757 (33%)	0.04
2	537 (45%)	1055 (46%)	
> 3	228 (19%)	469 (21%)	
Time between the first and the second birth, years	2.4 (0.8–13.8)	2.4 (0.9–14.6)	0.99
Use of assisted reproductive technology, index pregnancy			
No	1162 (98%)	2212 (98%)	0.90
Yes	27 (2%)	52 (2%)	
Hospitalization during pregnancy			
No	1034 (87%)	1943 (86%)	0.36
Yes	155 (13%)	321 (14%)	
Smoking			
No	974 (84%)	1916 (87%)	0.06
Yes	183 (16%)	299 (13%)	
Family history of breast cancer			
No	1075 (90%)	2157 (95%)	<0.001
Yes	124 (11%)	124 (5%)	
Endogenous Hormone Concentrations§			
Estradiol (ng/mL)	1.81 (1.74–1.87)	1.73 (1.68–1.78)	0.04
Estrone (ng/mL)	0.78 (0.75–0.81)	0.74 (0.72–0.77)	0.06
Progesterone (ng/mL)	26.2(25.5–26.8)	25.3 (24.9–25.8)	0.03
Testosterone (ng/mL)	0.90 (0.87–0.92)	0.87 (0.85–0.89)	0.09
Case Characteristics			
Median age at breast cancer diagnosis (range)	41.2 (21.7–58.1)	-	
Median time between blood donation and cancer diagnosis, years (range)	10.9 (1.1–21.0)	-	
Histology			
Ductal	958 (80%)	-	
Lobular	167 (14%)	-	
Medullary	29 (2%)	-	
Other	43 (4%)	-	
Stage			
Stage 1	455 (38%)		

Characteristic*	Cases n=1199 *n* (%)	Controls n=2281 *n* (%)	*P***
Stage 2–4	562 (47%)	-	
unknown	182 (15%)	-	
Hormone Receptor Status			
ER−/PR−	162 (25%)	-	
ER+/PR−	57 (9%)	-	
ER+/PR+	437 (67%)	-	

*Values are n (%) or median (range)

**Conditional logistic regression models were used to compare differences between cases and matched controls

†Matching factor

§Hormones are geometric mean (range); adjusted for gestational age

Table 2

First Trimester Circulating Endogenous Hormone Concentrations and Breast Cancer Risk: Finnish Maternity Cohort

Hormone	Cases/ Controls	Quartile 1 OR (95% CI)	Quartile 2 OR (95% CI)	Quartile 3 OR (95% CI)	Quartile 4 OR (95% CI)	p_{trend}	p_{het}*
Estradiol							
Overall	1192/2261	ref.	0.92 (0.74–1.14)	0.87 (0.70–1.09)	1.00 (0.77–1.29)	0.86	
ER+/PR+	434/813	ref.	0.97 (0.68–1.36)	0.76 (0.52–1.11)	0.96 (0.63–1.47)	0.57	0.78
ER−/PR−	162/311	ref.	1.69 (0.92–3.11)	1.29 (0.70–2.35)	1.08 (0.53–2.20)	0.93	
Age at First Birth <30	565/1079	ref.	1.05 (0.76–1.44)	1.13 (0.82–1.57)	1.35 (0.93–1.95)	0.11	0.02
Age at First Birth ≥30	627/1182	ref.	0.80 (0.60–1.08)	0.67 (0.49–0.92)	0.74 (0.51–1.06)	0.06	
Age at Diagnosis <40	510/979	ref.	1.05 (0.75–1.48)	1.26 (0.89–1.79)	1.60 (1.07–2.39)	0.01	<0.01
Age at Diagnosis ≥40	682/1282	ref.	0.85 (0.64–1.12)	0.68 (0.51–0.91)	0.71 (0.51–1.00)	0.02	
Estrone							
Overall	1192/2262	ref.	0.99 (0.80–1.21)	0.95 (0.76–1.17)	1.07 (0.85–1.36)	0.68	
ER+/PR+	434/814	ref.	1.01 (0.71–1.43)	0.83 (0.59–1.17)	1.06 (0.72–1.56)	0.88	0.51
ER−/PR−	162/311	ref.	1.40 (0.75–2.61)	1.59 (0.89–2.84)	1.36 (0.71–2.60)	0.32	
Age at First Birth <30	565/1079	ref.	1.03 (0.76–1.40)	1.19 (0.87–1.61)	1.20 (0.85–1.69)	0.21	0.36
Age at First Birth ≥30	627/1183	ref.	0.94 (0.71–1.26)	0.76 (0.57–1.03)	0.97 (0.70–1.33)	0.52	
Age at Diagnosis <40	510/979	ref.	1.01 (0.72–1.41)	1.18 (0.84–1.64)	1.38 (0.96–2.00)	0.06	0.07
Age at Diagnosis ≥40	682/1283	ref.	0.97 (0.74–1.27)	0.81 (0.61–1.08)	0.89 (0.65–1.21)	0.27	
Progesterone							
Overall	1192/2262	ref.	1.01 (0.82–1.25)	1.06 (0.85–1.31)	1.14 (0.90–1.45)	0.24	
ER+/PR+	434/813	ref.	1.06 (0.75–1.51)	1.09 (0.76–1.57)	0.96 (0.64–1.43)	0.86	0.17
ER−/PR−	162/311	ref.	1.21 (0.66–2.20)	1.19 (0.64–2.23)	1.64 (0.86–3.15)	0.16	
Age at First Birth <30	565/1080	ref.	1.11 (0.83–1.49)	1.16 (0.85–1.58)	1.33 (0.95–1.88)	0.11	0.22
Age at First Birth ≥30	627/1182	ref.	0.90 (0.67–1.22)	0.95 (0.69–1.29)	0.99 (0.71–1.37)	0.92	
Age at Diagnosis <40	510/980	ref.	1.07 (0.78–1.46)	1.09 (0.78–1.52)	1.13 (0.78–1.64)	0.52	0.97
Age at Diagnosis ≥40	682/1282	ref.	0.96 (0.72–1.28)	1.02 (0.77–1.37)	1.14 (0.84–1.55)	0.33	
Testosterone							
Overall	1190/2260	ref.	1.03 (0.84–1.27)	1.29 (1.06–1.59)	1.14 (0.92–1.43)	0.07	

Hormone	Cases/ Controls	Quartile 1 OR (95% CI)	Quartile 2 OR (95% CI)	Quartile 3 OR (95% CI)	Quartile 4 OR (95% CI)	P_{trend}	P_{het}*
ER+/PR+	433/813	ref.	1.01 (0.71–1.44)	1.43 (1.03–1.99)	0.98 (0.68–1.43)	0.48	0.78
ER−/PR−	162/311	ref.	1.08 (0.62–1.87)	1.28 (0.73–2.24)	1.08 (0.61–1.93)	0.66	
Age at First Birth <30	564/1078	ref.	1.07 (0.77–1.49)	1.45 (1.06–1.99)	1.26 (0.91–1.76)	0.07	0.44
Age at First Birth ≥30	626/1182	ref.	1.02 (0.78–1.34)	1.19 (0.91–1.56)	1.06 (0.78–1.43)	0.44	
Age at Diagnosis <40	509/978	ref.	1.14 (0.81–1.61)	1.53 (1.10–2.13)	1.39 (0.99–1.96)	0.02	0.15
Age at Diagnosis ≥40	681/1282	ref.	0.99 (0.76–1.29)	1.16 (0.89–1.52)	1.00 (0.75–1.34)	0.68	

Conditional logistic regression models adjusted for gestational age at blood donation and family history of breast cancer.

*p for heterogeneity comparing ER+/PR+ vs. ER−/PR−, age at first birth <30 vs. ≥30, or age at diagnosis <40 vs. ≥ 40

Table 3

Doubling of the Endogenous Circulating Steroid Hormone Concentrations and Breast Cancer Risk: Finnish Maternity Cohort

	cases/ controls	OR (95% CI)	cases/ controls	OR (95% CI)	p_{het}*
	Age at First Birth <30		**Age at First Birth ≥30**		
Estradiol					
Overall	565/1079	1.12 (0.97 – 1.31)	627/1182	0.91 (0.79 – 1.05)	0.05
ER+/PR+	175/333	1.02 (0.77 – 1.33)	259/480	0.91 (0.72 – 1.15)	0.54
ER−/PR−	100/193	1.53 (1.05 – 2.23)	62/118	0.71 (0.43 – 1.19)	0.02
Estrone					
Overall	565/1079	1.08 (0.96 – 1.22)	627/1183	0.96 (0.86 – 1.07)	0.13
ER+/PR+	175/333	0.99 (0.81 – 1.21)	259/481	0.99 (0.83 – 1.18)	0.99
ER−/PR−	100/193	1.27 (0.95 – 1.70)	62/118	0.87 (0.62 – 1.21)	0.09
Progesterone					
Overall	565/1080	1.22 (0.98 – 1.51)	627/1183	1.01 (0.84 – 1.21)	0.19
ER+/PR+	175/333	0.97 (0.66 – 1.44)	259/480	0.89 (0.66 – 1.22)	0.74
ER−/PR−	100/193	1.82 (1.02 – 3.23)	62/118	0.82 (0.41 – 1.65)	0.09
Testosterone					
Overall	564/1078	1.15 (0.98 – 1.35)	626/1182	1.04 (0.90 – 1.20)	0.36
ER+/PR+	175/333	1.08 (0.81 – 1.44)	258/480	1.08 (0.86 – 1.34)	0.98
ER−/PR−	100/193	1.49 (1.04 – 2.14)	62/118	0.73 (0.44 – 1.23)	0.03
	Age at Diagnosis <40		**Age at Diagnosis ≥40**		
Estradiol					
Overall	510/979	1.22 (1.04 – 1.44)	682/1282	0.87 (0.76–1.00)	0.002
ER+/PR+	149/284	0.96 (0.72 – 1.30)	285/529	0.93 (0.74 – 1.16)	0.83
ER−/PR−	97/188	1.48 (1.00 – 2.17)	65/123	0.87 (0.55 – 1.39)	0.09
Estrone					
Overall	510/979	1.15 (1.01 – 1.30)	682/1283	0.92 (0.83 – 1.02)	0.01
ER+/PR+	149/284	0.98 (0.78 – 1.23)	285/530	0.98 (0.83 – 1.15)	0.99
ER−/PR−	97/188	1.27 (0.95 – 1.71)	65/123	0.87 (0.62 – 1.23)	0.10
Progesterone					
Overall	510/980	1.11 (0.88 – 1.39)	682/1282	1.09 (0.91 – 1.30)	0.91

	cases/ controls	OR (95% CI)	cases/ controls	OR (95% CI)	p_{het}*
ER+/PR+	149/284	0.79 (0.52 – 1.21)	285/529	0.99 (0.73 – 1.33)	0.41
ER−/PR−	97/188	2.05 (1.13–3.71)	65/123	0.80 (0.41 – 1.55)	0.04
Testosterone					
Overall	509/978	1.16 (0.98 – 1.36)	681/1282	1.05 (0.91 – 1.20)	0.35
ER+/PR+	149/284	1.07 (0.79 – 1.45)	284/529	1.08 (0.87 – 1.33)	0.98
ER−/PR−	97/188	1.62 (1.13 – 2.33)	65/123	0.62 (0.36 – 1.05)	0.004

Conditional logistic regression models adjusted for gestational age at blood donation and family history of breast cancer.

*p for heterogeneity comparing age at first birth <30 vs. ≥30 or age at diagnosis <40 vs. ≥ 40

Table 4

Doubling of Circulating Endogenous Hormones and Breast Cancer Risk, by Age at First Birth and Age at Diagnosis; Finnish Maternity Cohort (n=3,480)

	Age at Diagnosis <40			Age at Diagnosis ≥40		
	cases/ controls	OR (95% CI)	p_{het}*	cases/ controls	OR (95% CI)	p_{het}*
Age at First Birth <30						
Estradiol						
Overall	384/738	1.20 (1.00 – 1.45)		181/341	0.96 (0.73 – 1.26)	
ER+/PR+	108/206	0.92 (0.65 – 1.31)	0.03	67/127	1.12 (0.72 – 1.75)	0.75
ER−/PR−	77/150	1.72 (1.11 – 2.67)		23/43	0.95 (0.38 – 2.41)	
Estrone						
Overall	384/738	1.17 (1.01 – 1.35)		181/341	0.91 (0.75 – 1.12)	
ER+/PR+	108/206	0.97 (0.74 – 1.27)	0.08	67/127	0.98 (0.71 – 1.35)	0.46
ER−/PR−	77/150	1.44 (1.02 – 2.05)		23/43	0.71 (0.33 – 1.56)	
Progesterone						
Overall	384/739	1.16 (0.89 – 1.51)		181/341	1.33 (0.90 – 1.95)	
ER+/PR+	108/206	0.84 (0.52 – 1.38)	0.04	67/127	1.18 (0.61 – 2.29)	0.92
ER−/PR−	77/150	1.99 (1.04 – 3.82)		23/43	1.10 (0.31 – 3.89)	
Testosterone						
Overall	383/737	1.17 (0.96 – 1.41)		181/341	1.11 (0.84 – 1.49)	
ER+/PR+	108/206	1.03 (0.72 – 1.49)	0.08	67/127	1.16 (0.71 – 1.88)	0.24
ER−/PR−	77/150	1.67 (1.13 – 2.47)		23/43	0.55 (0.17 – 1.74)	
Age at First Birth ≥30						
Estradiol						
Overall	126/241	1.31 (0.93 – 1.84)†		501/941	0.84 (0.71 – 0.99)†	
ER+/PR+	41/78	1.11 (0.63 – 1.97)	0.33	218/402	0.87 (0.68 – 1.13)	0.71
ER−/PR−	20/38	0.61 (0.21 – 1.78)		42/80	0.77 (0.43 – 1.40)	
Estrone						
Overall	126/241	1.09 (0.86 – 1.39)		501/942	0.93 (0.82 – 1.05)	
ER+/PR+	41/78	1.03 (0.66 – 1.61)	0.60	218/403	0.98 (0.81 – 1.19)	0.76
ER−/PR−	20/38	0.84 (0.45 – 1.55)		42/80	0.92 (0.61 – 1.37)	
Progesterone						

	Age at Diagnosis <40			Age at Diagnosis ≥40		
	cases/ controls	OR (95% CI)	p_{het}*	cases/ controls	OR (95% CI)	p_{het}*
Overall	126/241	0.97 (0.62 – 1.53)		501/941	1.03 (0.84 – 1.26)	
ER+/PR+	41/78	0.64 (0.26 – 1.56)	0.10	218/402	0.94 (0.67 – 1.31)	0.32
ER−/PR−	20/38	2.62 (0.61 – 11.20)		42/80	0.59 (0.25 – 1.38)	
Testosterone						
Overall	126/241	1.14 (0.83 – 1.58)		500/941	1.02 (0.87 – 1.20)	
ER+/PR+	41/78	1.19 (0.67 – 2.09)	0.90	217/402	1.06 (0.83 – 1.35)	0.10
ER−/PR−	20/38	1.28 (0.47 – 3.46)		42/80	0.61 (0.33 – 1.13)	

Conditional logistic regression models adjusted for gestational age at blood donation and family history of breast cancer.

*heterogeneity between ER+/PR+ and ER−/PR−

†p difference <0.05 comparing age at diagnosis <40 to ≥40; no significant heterogeneity by age at first birth

Table 5

Doubling of Circulating Endogenous Hormones and Breast Cancer Risk, by Time between First Birth and Diagnosis: Finnish Maternity Cohort(n=3,480)

	Years between first birth and diagnosis				
	<10		≥10		
	cases/ controls	OR (95% CI)	cases/ controls	OR (95% CI)	P_{het}*
Estradiol					
Overall	514/984	1.00 (0.85 – 1.17)	678/1277	1.02 (0.88 – 1.17)	0.89
ER+/PR+	173/326	0.87 (0.66 – 1.16)	261/487	1.01 (0.80 – 1.27)	0.43
ER−/PR−	83/161	1.32 (0.87 – 2.00)	79/150	1.07 (0.72 – 1.59)	0.47
Estrone					
Overall	514/985	1.03 (0.91 – 1.16)	678/1277	1.00 (0.90 – 1.11)	0.72
ER+/PR+	173/327	1.00 (0.82 – 1.23)	261/487	0.98 (0.82 – 1.16)	0.84
ER−/PR−	83/161	1.13 (0.84 – 1.52)	79/150	1.02 (0.75 – 1.40)	0.66
Progesterone					
Overall	514/986	0.98 (0.79 – 1.21)	678/1276	1.21 (1.00 – 1.46)	0.15
ER+/PR+	173/327	0.88 (0.60 – 1.27)	261/486	0.97 (0.70 – 1.34)	0.69
ER−/PR−	83/161	1.91 (0.99 – 3.70)	79/150	1.04 (0.59 – 1.82)	0.17
Testosterone					
Overall	514/986	1.06 (0.91 – 1.24)	676/1274	1.13 (0.97 – 1.30)	0.58
ER+/PR+	173/327	1.11 (0.85 – 1.44)	260/486	1.07 (0.84 – 1.35)	0.84
ER−/PR−	83/161	1.47 (0.95 – 2.27)	79/150	0.98 (0.66 – 1.46)	0.18

Conditional logistic regression models adjusted for gestational age at blood donation and family history of breast cancer.

*p heterogeneity between <10 and ≥10 years between first pregnancy and diagnosis