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Pregnancy characteristics and maternal breast cancer risk: a review of the epidemiologic literature

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Abstract

The short- and long-term effects of pregnancy on breast cancer risk are well documented. Insight into potential biological mechanisms for these associations may be gained by studying breast cancer risk and pregnancy characteristics (e.g., preeclampsia, twining), which may reflect hormone levels during pregnancy. To date, no review has synthesized the published literature for pregnancy characteristics and maternal breast cancer using systematic search methods. We conducted a systematic search to identify all published studies. Using PUBMED (to 31 July 2009), 42 relevant articles were identified. Several studies suggest that multiple births may be associated with a lowered breast cancer risk of about 10–30%, but results were inconsistent across 18 studies. The majority of 13 studies suggest about a 20–30% reduction in risk with preeclampsia and/or gestational hypertension. Six of seven studies reported no association for infant sex and breast cancer risk. Data are sparse and conflicting for other pregnancy characteristics such as gestational age, fetal growth, pregnancy weight gain, gestational diabetes, and placental abnormalities. The most consistent findings in a generally sparse literature are that multiple births and preeclampsia may modestly reduce breast cancer risk. Additional research is needed to elucidate associations between pregnancy characteristics, related hormonal profiles, and breast cancer risk.

Keywords

Breast cancer; Pregnancy; Perinatal; Epidemiology

Introduction

Pregnancy is known to be a critically important time in relation to a woman's subsequent risk of breast cancer [1, 2]. Earlier age at first birth and increased parity have long been known to protect women from breast cancer [1, 3, 4]. Less established is the finding that pregnancy at any age is followed by a transient increase in breast cancer risk, with evidence for a stronger effect in women with a later age at first birth (i.e., >30 years) [5–10]. The biological mechanisms underlying the role of pregnancy in breast cancer etiology are not

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clear [11, 12], but several hypotheses have been proposed, all of which posit a role for pregnancy hormones (for reviews see: [2, 11–13]. It is difficult to directly investigate the maternal hormonal environment during pregnancy and subsequent breast cancer [14]. Insight into biological mechanisms may be gained by the study of breast cancer and certain pregnancy characteristics (e.g., preeclampsia, multiple births), which may be associated with specific pregnancy hormones, and may modify breast cancer risk among parous women [15–17].

Pregnancy characteristics known to influence hormonal profiles in pregnancy include multiple births (twins and higher order deliveries), preeclampsia, pregnancy-induced hypertension (PIH), infant sex, infant gestational age (GA) at delivery, fetal growth, pregnancy weight gain (PWG), and gestational diabetes (GDM). Hormones associated with one or more of these characteristics include estrogens [18–20], progesterone [19, 21], androgens [22–24], human chorionic gonadotropin (HCG) [25, 26], and insulin-like growth factor-I (IGF-I) [27, 28]. These hormonal factors have been implicated in breast cancer etiology and have been proposed to mediate the associations between pregnancy characteristics and maternal breast cancer risk [16, 17, 29–32]. For example, women who deliver twins appear to have increased levels of progesterone and HCG during pregnancy [25, 33, 34] compared to women who deliver singletons, while preeclamptic pregnancies are characterized by higher levels of progesterone [21, 31, 35], androgens [22, 23, 36, 37], and HCG [31, 38].

To date, few reviews have summarized epidemiologic findings for one or more pregnancy characteristics and subsequent breast cancer in mothers [31, 39–41]. No review has synthesized all the published literature on each characteristic and breast cancer using systematic search methods. We therefore conducted a review to summarize the epidemiologic evidence for the associations between pregnancy characteristics (multiple births, preeclampsia and/or PIH, placental characteristics, infant sex, infant gestational age, fetal growth, PWG, and GDM) and breast cancer and identify areas for future research.

Methods

Search strategy and study selection

The PUBMED interface of the electronic database Medline was searched systematically by one author (SN) for all articles published in peer-reviewed journals up to 31 July 2009. Searches included the medical subject heading “breast neoplasms” and the keyword “breast cancer” and terms for the pregnancy characteristics of interest (see “Appendix” for specific terms). We included peer-reviewed epidemiologic studies, which used population-based or hospital-based case–control or cohort study designs, to examine one or more pregnancy characteristics and breast cancer risk. The search strategy identified 1,566 possible articles. If the article title appeared relevant or relevance was unclear from the title, the abstract was reviewed (n = 218 abstracts). We excluded 1,500 articles based on title/abstract review. Full texts of articles were obtained for 66 potentially relevant studies; 37 met the inclusion criteria. In addition to the PUBMED search, the reference lists for each study and relevant review papers were hand searched. Further, citations of all relevant studies were searched in the citation index Web of Science (part of ISI Web of Knowledge [42]). These methods yielded an additional five reports for a total of 42 relevant studies identified.

Data from each study were abstracted directly from the published manuscript and tabulated by one author (SN) by study exposure (Tables 1, 2, 3, 4, 5, 6 and 7). Many breast cancer risk factors differ in their influence by menopausal status (or attained age, a proxy for menopausal status) [43–45] and hence we include results stratified by menopausal status/age, whenever available. Studies that did not report covariate-adjusted measures of

association with confidence intervals (CIs) were not tabulated or discussed in detail, but are listed in the text and in the Table footnotes as appropriate. Studies nested within a cohort with follow-up were considered cohort studies for brevity. The majority of case–control studies were population-based, only three were hospital-based [46–48], and we include a footnote in the Tables to indicate if the study was hospital-based. For each exposure, with the exception of placental characteristics for which there were only two studies, we first describe the epidemiologic findings for cohort and then case–control studies, followed by a commentary specific to each exposure, which includes a summary of the epidemiologic evidence to date, main methodologic issues (if applicable), and postulated biological mechanisms (focusing mainly on pregnancy-related hormonal mechanisms).

Methodologic issues

Two primary methodologic issues to be considered for interpretation of results, which are described in Tables 1, 2, 3, 4, 5, 6 and 7 include: (1) the data source for exposure measurement [maternal self-report (referred to as interview-based or mailed survey)], records-based (birth registry, medical records)); and (2) inclusion of established potential confounding factors [e.g., age at first birth, parity, breastfeeding history, adult body mass index (BMI)]. In addition, potential effect modifiers of the associations between pregnancy characteristics and breast cancer risk, in particular the established pregnancy-related factors age at first birth and parity, as well as time since index birth, are examined whenever available. However, it should be kept in mind that most studies, with the exception of large registry-based studies, may have lacked sufficient power to detect potential interactions.

Multiple births (Table 1)

Multiple births may be a marker of an altered hormonal environment during pregnancy, including elevated levels of estrogens, progesterone, and HCG, which may influence subsequent breast cancer risk [25, 34, 49]. The term “multiple births” indicates both twins only or twins and higher order births in the discussion (see Table 1 for exact exposures definitions) (for reviews of the etiology of multiple births see: [50–52]). The source of exposure data is not discussed, because maternal self-report for multiple births is not a concern.

Cohort studies

We identified nine cohort studies (all registry-based) of multiple births and breast cancer risk [30, 53–60]. Two studies, which did not report RRs or CIs, are not discussed further [53, 55]. Three studies, which examined exposure in *any birth*, a *last birth*, and a *birth prior to the last birth*, reported a decreased risk of breast cancer associated with multiple births [54, 58, 59] (see Table 1 for risk estimates by birth order). The largest of these (19, 368 cases), conducted in Sweden, found the protective effect was limited to women <55 years at diagnosis and was only significant for exposure in any birth, odds ratio (OR) = 0.85, 95% CI: 0.74–0.98 [59]; the other two studies were among women <57 [54] and <50 years of age [58]. Two additional Swedish studies using data partly overlapping with the above largest study (one among women<50 years [57]; the other with unknown age [60]), also reported some evidence for a reduction in breast cancer risk for women who ever had a multiple birth. In contrast, one large Danish cohort (9,495 cases) of latest births among women <58 years of age, reported a non-significant increase in breast cancer risk associated with a last multiple birth [30]. Finally, a US study did not find an association between multiple births and breast cancer risk [56].

Case–control studies

We found nine case–control studies of multiple births and breast cancer risk [16, 17, 29, 47, 48, 61–64]. One US study of women aged 20–54 with 3,918 cases, which examined exposure in first, last, and any births, reported a significant decrease in breast cancer risk only for a multiple last birth [61]. In contrast, both a US study of first births only [16] and an international multi-center study conducted in the 1960s [48] reported a non-significant elevation in risk of breast cancer for having a multiple birth. Other case–control studies of both younger and older women have found limited evidence for an association between multiple births and breast cancer [17, 29, 47, 62–64].

Several of the aforementioned studies examined potential effect modifiers of the association between multiple births and breast cancer risk. The large Danish cohort study of latest births reported an elevated risk only in the first 5 years after birth (relative risk (RR) = 1.8, 95% CI: 1.1–2.8) [30]. The US case–control study of first births only reported a significant increase in breast cancer risk associated with a multiple birth among women with a later age at first birth (>30 years) and also for shorter time since first birth (≤5 years) [16]. Other studies with smaller and larger sample sizes, which investigated time since a multiple birth [17, 54, 59, 61–63], or age at index birth [17, 54, 59, 61–63], however, have not found evidence for effect modification. Finally, some studies examined the infant sex distribution of multiples, with two studies finding a non-significant protective effect of a multiple birth only for women who delivered all females compared to all males [17, 54].

Commentary

Across 18 identified studies, findings for the association between multiple births and breast cancer risk are inconsistent. Based on five large Scandinavian cohort studies conducted among mainly younger women [54, 57–60], multiple births appear to decrease risk of breast cancer by about 10–30%. Three cohort studies of breast cancer risk and multiples in any birth, a last birth, or prior to the last birth suggest protection is found regardless of birth order [54, 58, 59]. Null findings in several large studies [62–64], however, and a possible elevation in short-term risk for women with a recent last multiple birth [30], demonstrate the need for additional studies. Future studies with information on type of multiple births (spontaneous, due to assisted-reproduction) and zygosity and chorionicity, may help clarify the association between multiples and breast cancer. Further, the role of different characteristics of women who have multiple births (e.g., maternal body size, being born a twin) [50–52, 65] or other factors associated with multiples (e.g., infertility drug use, length of gestation), which may also be associated with breast cancer, warrant further investigation [58, 59].

Elevated maternal levels of estrogens [26, 49, 66], progesterone [34], HCG [25, 26, 33], and alpha-fetal protein (AFP) [25, 26, 67], have been found in multiple compared to singleton pregnancies. Investigators have hypothesized that elevated estrogens during a multiple pregnancy may help explain the increased short-term breast cancer risk found in some studies [16, 30, 48]. Alternatively, elevated maternal HCG, progesterone, or AFP (a protein which may have “anti-estrogenic” effects in the breast tissue [68, 69]) may mediate the long-term protective effect of multiple births on breast cancer risk in parous women [17, 54, 59, 61].

Preeclampsia and pregnancy-induced hypertension (Table 2)

Preeclampsia is a complication of pregnancy and is defined by the presence of new onset hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) and proteinuria (≥300 mg per 24 h) after 20 weeks of gestation [70] (for reviews on hypertension during pregnancy/preeclampsia see [70–73]). Women with pre-eclampsia or

only PIH may have altered levels of hormonal factors, such as elevated androgens [22, 23, 36, 37], HCG [31, 38] or AFP [74–76], compared to women with uncomplicated pregnancies.

Cohort studies

Seven cohort studies have examined preeclampsia and/or PIH and breast cancer risk [15, 55, 77–81]. Four of these found limited evidence for an association [15, 55, 80, 81] (two were based on the Child Health and Development Studies (CHDS) follow-up cohort [80, 81]) and did not report RRs and/or were limited in sample size. The two largest studies, which used registry-based data in Norway and had overlapping populations [5,474 cases (2002) and 9,160 cases (2007)], reported that preeclampsia and/or PIH in a first birth was associated with a significantly reduced risk of breast cancer [77, 78] (RR in most recent report = 0.86, 95% CI: 0.78–0.94). RRs were not modified by age at diagnosis [77, 78]. In contrast, the Jerusalem Perinatal Cohort Study (1,624 cases), which used hospital records for women who had births during 1964–1976, reported a significantly increased risk of breast cancer for women with a history of preeclampsia in two reports (one was an update with additional follow-up), hazard ratio (HR) = 1.37, 95% CI: 1.06–1.78 [79, 82].

Case–control studies

Five case–control (two registry-based [16, 29] and three interview-based [17, 83, 84]) studies reported evidence for an inverse association between preeclampsia and/or PIH and breast cancer, though only two reported significant findings [83, 84]. The most recent of these, with information on both preeclampsia and PIH for a woman's entire pregnancy history and data on menopausal status, found that preeclampsia and PIH were inversely associated with breast cancer risk, adjusted for several potential confounders (e.g., BMI, age at menarche, lactation, family history) [83]. Results stratified by menopausal status revealed that the associations for preeclampsia/PIH with breast cancer were largely limited to postmenopausal women [83]. In contrast to the aforementioned five population-based studies, one hospital-based study reported that hypertension during pregnancy was associated with non-significant increased risks of both pre- and postmenopausal breast cancer [46].

Two of the aforementioned 13 cohort or case–control studies considered age at index birth and/or time since index birth as potential effect modifiers of the association between preeclampsia/PIH and breast cancer. One reported a stronger inverse association between preeclampsia and breast cancer for women>30 years at first birth and also in the first 3 years after the first birth [16]. Another reported no evidence for effect modification by time since last birth [17].

Some studies examined effect modification by length of gestation [77, 83], fetal growth [77], and offspring sex [78, 79, 83, 85]. In the largest cohort study from Norway, the protective effect of preeclampsia/PIH was largely limited to women who delivered a male infant [78]. A second study [85], using the case–control data originally used by Innes and Byers [16], revealed a stronger protective effect of preeclampsia for women who delivered a male (compared to female) infant, but only among women>30 years at first birth [85].

Commentary

Most studies based on both maternal self-report and registry data have reported that preeclampsia and/or PIH are associated with a decrease in breast cancer risk of approximately 20–30% [16, 17, 29, 77, 78, 83, 84]. Studies of preeclampsia and PIH separately have generally found a decreased risk of breast cancer for both [17, 83]. On the other hand, one large cohort study reported increased breast cancer risk among women with

a history of preeclampsia [79], while four cohort studies (two based on the same cohort) reported limited evidence for an association [15, 55, 80, 81], albeit with small sample size. These latter findings suggest that protection due to preeclampsia and/or PIH may be modified by unknown or unmeasured factors. High BMI, which is associated with decreased breast cancer risk prior to menopause and an increased risk after menopause [86], is a potential confounder of the association between preeclampsia/PIH and breast cancer risk. Only one study reported results by menopausal status and also adjusted for BMI. This study found an inverse association between preeclampsia/PIH and breast cancer risk largely limited to postmenopausal women, highlighting the need for future studies to present findings for pre- and postmenopausal women separately and adjust for potential confounders that may differ in their influence by menopausal status. Finally, few studies considered potential effect modifiers such as parity and age at index birth, or time since index birth, though some studies did find that infant sex may modify the association between pre-eclampsia and/or PIH and breast cancer.

One biological hypothesis originally proposed to explain the protective effect of preeclampsia/PIH on breast cancer risk was that lower levels of estrogen during complicated pregnancies may mediate the inverse association [22, 31]. However, studies of the associations between maternal estriol and/or estradiol with preeclampsia/PIH have been inconsistent, with several studies reporting no association [21–23, 35, 37, 87–90]. Other hormonal factors found to be altered in preeclamptic pregnancies include higher levels of progesterone [21, 31, 35], androgens [22, 23, 36, 37], and HCG [31, 38]. Lower levels of maternal IGF-I may also play a role [31], but studies of maternal serum IGF-I and preeclampsia/PIH are also inconsistent and associations may depend on severity and/or length of gestation [27, 28, 91–95]. AFP may be elevated in women with preeclamp-sia/PIH, though findings again are inconsistent [38, 74–76]. Finally, given the role of angiogenesis in tumor growth and metastasis [96], a novel biological hypothesis recently proposed [39, 97, 98], is that the antiangiogenic profile [high levels of antiangiogenic factors (e.g., soluble fms-like tyrosine kinase-1 and soluble endoglin) and low levels of proangiogenic factors (e.g., placental growth factor)], which characterizes preeclampsia [99, 100], may help explain the protective effect on later breast cancer.

Infant sex (Table 3)

Cohort and case–control studies

Maternal hormonal profiles during pregnancy may vary by infant gender (e.g., higher HCG levels for women carrying female fetuses) [101], which could influence subsequent breast cancer risk. We identified four cohort [15, 30, 54, 102] and three case–control [16, 17, 64] studies of infant sex and breast cancer, as well as two reports of additional analyses on the same cohorts [103, 104]. Almost all studies reported no association for infant sex and breast cancer [15–17, 54, 64], including studies that examined the role of infant sex in both the short- and long-term effects of a last birth on breast cancer risk [30, 103, 104]. The one exception, a cohort study of 2,328 cases in Sweden, reported reduced breast risk associated with having male offspring, in particular among women with two or more births who reported all males (compared to all females) [102]. This finding was limited to women <40 years of age at diagnosis (Table 3).

Commentary

In summary, the epidemiologic evidence to date based on seven studies provides limited support for an association between infant sex and breast cancer risk. Infant sex, however, has been shown to be a potential effect modifier of associations of other pregnancy characteristics (e.g., preeclampsia [78, 85] and multiple births [17, 54]) and breast cancer

risk. With regard to hypothesized biological mechanisms, briefly, third trimester HCG levels may be higher for women carrying female fetuses [101], while levels of progesterone may be lower [19]. Higher levels of AFP have also been reported for women carrying male fetuses, though results have been inconsistent [105–107].

Infant gestational age at delivery (Table 4)

Induced and spontaneous abortion, which reflect pregnancy interruption in early gestation (primarily first trimester), and breast cancer have been well studied [108, 109], but few studies have examined breast cancer and variation in gestational length for live births. Pregnancies that are shorter in duration during the third trimester have been hypothesized to increase breast cancer risk, due to a possible lack of full terminal differentiation of the mammary gland after elevated pregnancy hormonal levels [16, 110]. GA at delivery has been examined using the well-studied categories of very preterm delivery (VTPD), defined as <32 weeks of gestation, and preterm delivery (PTD), defined as<37 weeks of gestation, or other arbitrary categorical cut points (for reviews on the etiology of preterm delivery, see [111–113]).

Cohort studies

Three of the four cohort studies identified (all registry-based) [15, 114–116] reported evidence for an increased risk of breast cancer with delivery of an infant at earlier GAs. Two reported a significant trend for increasing breast cancer risk with decreasing GA in a last birth [114] and a first birth [115]. Both studies reported increased risk for a VPTD; the estimate for the smaller cohort (1,363 cases), but not the larger (5,474 cases) was significant (RR = 1.72, 95% CI: 1.14–2.59). A third study reported a significant increase in breast cancer risk for a PTD in a first birth among women ≥40 years of age, but not <40 years of age [116]. The fourth study did not report an effect estimate and found no association for GA and breast cancer [15].

Case–control studies

We found three case–control studies of GA and breast cancer risk [16, 17, 29]. One small (275 cases) US registry-based study of first births reported a non-significant reduction in risk for a PTD and delivery at<30 weeks [29]. Alternatively, a recent larger US registry-based study of first births reported a non-significant increased risk for a VPTD after adjusting for several covariates, but not delivery at 32–36 weeks of gestation [16]. In this later study, however, findings are difficult to interpret because adjustment was made for birthweight, which is problematic given birthweight is determined by both fetal growth and GA. The third study, which used self-reported GA, did not find any association with breast cancer risk using varying definitions and for exposure in a first birth or ever [17].

Few studies have reported findings for the relation between breast cancer risk and GA by potential effect modifiers such as age or parity at index birth [114, 116]. Findings are inconclusive for stratified analyses reported by two cohort studies, due to small sample sizes [114, 116]. Most studies were among younger women (<57 years) [15–17, 29, 114], and only one study was able to report results stratified by age [116] with an adequate sample size.

Commentary

In summary, only seven studies have examined the association between GA and breast cancer risk, with conflicting findings. Based on results from three cohort studies [114–116], earlier GA appears to be associated with about a 20–70% increase in breast cancer risk. However, one small case–control study found a non-significant decreased risk for earlier

GAs [29], and two studies (one cohort [15] and one case–control [17]) have reported null findings. Limited data exist on whether the association is modified by menopausal status, birth order, age at index birth, or time since index birth. Finally, it should be noted that accurate measurement of GA is difficult, and birth registry data, especially from older databases, may include errors, some of them systematic [117–119]. Despite this, most registry-based studies did not provide information on the accuracy of GA, or if any data cleaning methods were employed to reduce misclassification.

Levels of hormonal factors (e.g., estrogens, progesterone, IGF-I) increase fairly steadily from the first trimester or early second trimester until delivery, with the exception of HCG, which peaks during the first trimester and declines to about 10 IU/ml [120]. The elevated hormone levels, coupled with a possible lack of complete terminal differentiation of the mammary gland, could increase the susceptibility of the breast to the proliferating effects of the hormones, and is one hypothesis to explain the increased breast cancer risk following a PTD and VPTD [16, 121]. Further, in prospective studies, shorter length of gestation at delivery (in continuous weeks) [19] and a PTD [122] have been found to be positively associated with maternal estrogen levels measured earlier in the index pregnancy.

Fetal growth (Table 5)

An association between high estimated fetal growth and increased breast cancer risk is biologically plausible, given that high rates of estimated fetal growth may be associated with elevated maternal estrogens and IGF-I levels during pregnancy [20, 123–125], but few studies have examined fetal growth and maternal breast cancer. Infant birthweight is influenced by both duration of gestation and rate of fetal growth [126]. To estimate fetal growth, studies have examined birthweight adjusted for GA as a covariate or used birthweight alone.

Cohort studies

We found four cohort studies of fetal growth and breast cancer risk [15, 30, 55, 81]; two did not report effect estimates [55, 81]. The remaining two studies, both registry-based, adjusted for GA, and found some evidence for increased breast cancer risk with elevated fetal growth (HR per 500 g increase in birthweight = 1.11, 95% 1.04–1.18 [15]; RR for>3,750 g vs. ≤3,000 g = 1.1 95% CI: 1.0–1.2 [30]).

Case–control studies

Two registry-based case–control studies have examined fetal growth and breast cancer risk, with conflicting findings. One study of first births reported a non-significant reduction in breast cancer associated with very low (<1,500 g) and very high (≥4,500 g) birthweight [16], adjusted for GA. A second study reported non-significant increased risks of breast cancer for lower or higher birth-weight in any birth and did not adjust for GA [64].

Overall, consideration of effect modification by birth order, time since birth, or age at index birth has not been reported. The exception, the cohort study conducted in Denmark [30], reported some evidence for a stronger increase in risk for the first 5 years following delivery. No studies reported results by menopausal status, though populations were primarily among younger women.

Commentary

Only six studies have examined fetal growth and breast cancer, and two did not report effect estimates. Evidence from two registry-based cohort studies that adjusted for GA suggest high fetal growth in a first or last birth may be associated with about a 10% increase in

breast cancer risk. Two case–control studies reported inconsistent findings, though one study did not adjust for GA, which could contribute to the observed differences. Birthweight alone or adjusting for GA as a covariate are not optimal approaches for estimation of fetal growth [127], but no study to date has estimated fetal growth using approaches that are more appropriate (e.g., using reference birthweight percentiles for each gestational week [118]). Finally, the etiology of fetal growth is complex (for reviews see [111, 128]) and residual confounding cannot be ruled out, given few studies were able to consider non-pregnancy related factors (e.g., family history, lifestyle factors).

Most studies have reported that fetal growth is positively associated with maternal estriol levels (primarily of fetal origin), mainly in the third trimester [18, 19, 123, 124, 129]. The evidence has been less consistent for an association with maternal estradiol [20, 123–125], which is clearly implicated in breast cancer risk [130]. Alternatively, higher maternal serum IGF-1, inconsistently associated with fetal growth/birthweight (particularly during late gestation) [131–134] may mediate a positive association between fetal growth and breast cancer.

Pregnancy weight gain (Table 6)

Researchers have hypothesized that weight gain during periods of hormonal change over the life course, including weight gain during pregnancy (PWG), may be of particular importance in relation to subsequent breast cancer risk [135–137]. However, few studies have examined PWG and later breast cancer risk. Higher PWG may reflect increased exposure to maternal hormonal factors during pregnancy (e.g., estrogens), which could potentially increase breast cancer risk [138, 139].

Cohort studies

We identified three cohort studies of the association between PWG and breast cancer [81, 138, 139]. One of these did not report effect estimates and is not discussed further [81]. The other two had limited sample sizes (<150 cases) and did not report information on birth order (e.g., first, last pregnancy) [138, 139]. One used hospital records, with about 50% follow-up of the original cohort, and found a positive association between estimated weight gain during pregnancy >15 kg (reference: 11–15 kg) and post-menopausal breast cancer risk (RR = 1.80, 95% CI: 1.05–3.07). No association was found for premenopausal breast cancer risk (RR = 1.00, 95% CI: 0.40–2.48), but only 25 premenopausal breast cancer cases were included in the analysis [139]. The other cohort study, which used a mailed survey, found no association among predominantly pre-menopausal women [138].

Case–control studies

Three US case–control studies, of women aged 35–79 [140], 20–44 [17], and <50 [141] have reported limited evidence for an association between breast cancer risk and PWG in the first pregnancy [17, 140], or most recent pregnancy [141], or for maximum weight gain in all pregnancies [17].

Commentary

In summary, there is limited evidence for an association between PWG and subsequent breast cancer risk based on the six studies identified. One cohort study did report a positive association only among postmenopausal women, but it is not clear if this is due to the known relation between high current adiposity, adult weight gain, and postmenopausal breast cancer [137], given that women who gain more weight during pregnancy have been shown to retain more weight both postpartum [142] and into the menopausal years [143, 144]. Further, if the measure of interest is increased adipose tissue during pregnancy, increased

body fat may be a better measure than PWG, which reflects several components (fetus, placenta, edema, amniotic fluid, and adipose tissue) [145].

With regard to hypothesized biological mechanisms, investigations of maternal serum estrogens and elevated PWG have been inconsistent. One early study reported a positive association for weight gain up to the 31st week of gestation and maternal estriol and total estrogens [146]. Subsequent studies have reported null results [19, 147, 148], including a recent study that found no evidence for an association between PWG and maternal estrogens or androgens measured at delivery [149]. Other hormonal factors found to be associated with high PWG include lower levels of SHBG [19, 148] or progesterone [19].

Gestational diabetes (Table 7)

In the US, GDM is usually screened for at 24–28 weeks of pregnancy [150], though the American Diabetes Association (ADA) recommends that women with a high risk of GDM (e.g., women who are obese or have a personal history of GDM) are screened earlier and some women with very low risk do not need to be screened [150]. A diagnosis of GDM is based on an oral glucose tolerance test, with either a 100 or 75-g glucose load (for specific screening and diagnostic criteria see [150]). The association between type II diabetes and breast cancer risk has been investigated in many epidemiologic studies [151, 152], but few studies have examined the association between GDM and breast cancer.

Cohort studies

We found three cohort studies, two of women with a diagnosis of GDM [15, 153] and one of measures of glucose intolerance during pregnancy [154], and later breast cancer risk. One of the studies of GDM and breast cancer, based on Swedish registry-data, reported no association, though the sample size was small (ten exposed cases) [15]. In contrast, authors from the Jerusalem perinatal cohort study [153], where all women are screened prenatally for GDM, reported an elevated RR for breast cancer for history of GDM among women ≥50 years (1.7, 95% CI: 1.1–2.5), but not among women <50 years (1.0, 95% CI: 0.5–2.1). The third cohort study (only 18 cases) reported that elevated fasting glucose during pregnancy was associated with increased breast cancer risk [154].

Case–control studies

Two US case–control studies of self-reported GDM [17, 155] reported inconsistent findings. One study of women aged 20–44 with 1,235 cases did not find an association [17], though when examined by years since last birth (<5 years and ≥5 years), a non-significant protective effect of GDM in the first 5 years and a non-significant elevated long-term risk was found [17]. The other study with 2,319 cases conducted in the Southwestern states among Hispanic and Non-Hispanic women reported an inverse association between self-reported GDM and breast cancer; results were only significant among postmenopausal women [155]. In analyses further stratified by age at onset (<35 years and ≥35 years), the inverse association was limited to women aged <35 at onset [155].

Commentary

To date, studies of the association between GDM and breast cancer are few. Findings from the three largest studies include a significant protective effect in a US interview-based case–control study conducted in the Southwestern states that appears to be limited to women <35 years at onset, a significantly increased risk for women in the Jerusalem Perinatal Cohort registry-study aged 50 or older, and no association in a US interview-based case–control study. Both current BMI and pre-pregnancy BMI are potential confounders of the association between GDM and breast cancer risk, which varies by menopausal status/age.

Results from the US case–control study in the Southwestern states were adjusted for BMI at age 15 [155], but the cohort study conducted in Israel did not adjust for BMI at any age [153] (Table 7). Given the discrepant findings to date, additional studies are needed; in particular, studies that may help elucidate if GDM is an independent risk factor for breast cancer (i.e., with information on postpregnancy diabetes, current body size, body size before and after pregnancy, and biomarkers associated with diabetes development).

The potential biological mechanisms underlying a possible association between GDM and breast cancer risk have been little described [153, 155]. However, given women with GDM are at increased risk for the development of Type II diabetes (a review of 28 studies found 2.6 to>70% developed type II diabetes, depending on length of follow-up [156]), mechanisms proposed for the positive association between Type II diabetes and breast cancer risk can be considered [151, 152, 157]. Hyperinsulinemia and hyperglycemia are associated with both GDM and type II diabetes (at least initially with type II diabetes) [150] and fasting insulin and glucose have been associated with elevated breast cancer risk, though studies have been inconsistent [157]. Insulin may play a role in tumorigenesis and promotes growth in both normal cells [158] and breast cancer cells [159], and glucose may also play a role in tumor growth promotion [160]. Alternatively, hyperglycemia has been linked to increased oxidative stress [161], which can result in DNA cell damage and increased cellular proliferation [162].

Placental characteristics (not tabulated)

Two studies have examined placental characteristics and breast cancer risk [15, 81]. The biological rationale is that placental characteristics (e.g., lower placental weight) may represent reduced placental functionality, which in turn could reflect altered exposure to hormonal factors produced by the placenta during pregnancy [15]. A small (146 cases) cohort study that followed-up participants of the CHDS [81] examined placental characteristics (e.g., placental weight and diameter) and found some evidence for a decrease in breast cancer risk associated with smaller placentas. Similarly, a Swedish registry-based cohort study reported an increased risk of breast cancer per 100 g increase in placenta weight, (HR = 1.07 95% CI: 1.02–1.13), adjusted for several other pregnancy characteristics, including birthweight [15].

Conclusions

Though data have accumulated over the past 30 years on the associations between pregnancy characteristics and maternal breast cancer risk, the epidemiologic evidence remains largely inconclusive. The association between *multiple births* and breast cancer risk has been investigated in 18 studies, with some evidence that multiple births may protect against breast cancer by about 10–30%, in particular among younger women, but it is not clear if the association is modified by time since delivery. *Pre-eclampsia and/or PIH* was associated with about a 20–30% reduction in breast cancer risk in seven out of 13 studies, and some studies suggest results may be stronger for women with male when compared to female preeclamptic pregnancies. Epidemiologic evidence from seven studies suggests *infant sex* is not associated with breast cancer overall. Findings for other pregnancy characteristics and maternal breast cancer risk are inconclusive, with few studies conducted (seven studies of *infant GA at delivery*, six studies each for *fetal growth* and *PWG*, and five studies of *GDM*).

Several limitations of the current body of literature on pregnancy characteristics and breast cancer should be addressed in future studies. First, many studies are registry-based and lack information on confounding factors besides pregnancy-related variables (e.g., family history,

lifestyle factors); hence, residual confounding cannot be ruled out for many reported associations. Second, many studies have not considered potential effect modifiers (e.g., age and parity at index birth, time since index birth) or have been underpowered to detect potential interactions. Studies with adequate sample size to consider both potential effect modifiers and confounders are needed. Overall, few studies have been conducted among older or postmenopausal women, or results were not examined separately by age/menopausal status, which is critically important given breast cancer risk varies for several key confounders by menopausal status. Finally, the interrelationships among pregnancy characteristics must be carefully considered in multivariable models, including concerns regarding adjustment for mediators or highly correlated variables (e.g., gestational age and birthweight).

In addition to the aforementioned methodologic considerations, further work is needed to understand the biological mechanisms underlying the relations between pregnancy characteristics and breast cancer risk. One research area that has largely been unexplored is whether the associations for pregnancy characteristics and breast cancer risk vary by tumor characteristics. Differences by hormone-receptor status or histology can provide further insight into potential biological mechanisms. Large prospective studies with multiple biological measurements during pregnancy are needed to examine the maternal biological factors associated with the pregnancy characteristics, and can improve our understanding of the biological mechanisms underlying the role of pregnancy in breast cancer etiology.

In conclusion, few adequately powered studies able to consider key potential confounders and effect modifiers have investigated associations between maternal breast cancer risk and pregnancy characteristics, and results remain inconclusive for most pregnancy exposures. Additional epidemiologic research that addresses previous limitations, as well as research able to shed light on biological mechanisms underlying associations between pregnancy characteristics and breast cancer, would be particularly valuable.

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Appendix: Additional details on search strategy

Search terms and limits used for PUBMED searches

Search terms (keywords and medical subject headings)

1. Outcome:
    a. Breast cancer: breast neoplasms [Mesh] OR ("breast cancer")
2. Exposures:
    a. Fetal growth and birthweight: birthweight OR birthweights OR "birth weight" OR "fetal growth"
    b. Preterm delivery/length of gestation: premature OR preterm OR "preterm birth" OR "preterm delivery" OR "length of gestation" OR "gestational length" OR "pregnancy weeks" OR "pregnancy length" OR "weeks gestation" OR "gestation" OR "gestation length" OR "gestational age"
    c. Multiple births: twinning OR "multiple births" OR "multiple birth" OR "twins" OR "twin" OR "multiple pregnancy" OR "multiple pregnancies" OR "multiple fetuses" OR "twin pregnancy" OR "twin pregnancies" or "twin birth" OR "multifetal gestation"
    d. Preeclampsia: preeclampsia OR preeclampsia OR eclampsia OR toxemia OR preeclamptic OR preeclamptic
    e. Pregnancy-induced hypertension: "pregnancy-induced hypertension" OR (pregnancy and hypertension) OR (pregnancy and "high blood pressure") OR "pregnancy-related hypertension"
    f. Placental characteristics: placenta OR placental OR "placental characteristics"
    g. Gestational diabetes: "gestational diabetes" OR (gestational and diabetes) or (diabetes and pregnancy) OR ("insulin resistance" and pregnancy) OR ("glucose intolerance" and pregnancy) OR "diabetes during pregnancy"
    h. Pregnancy weight gain: (weight and pregnancy) OR ("weight gain" and pregnancy) OR "pregnancy weight gain"
    i. Offspring sex: [(offspring and sex) or (offspring and sex)]

j. Overall terms: “perinatal” OR “pregnancy factors” or “pregnancy characteristics” OR “prenatal” OR (“birth characteristics” and offspring) OR “pregnancy conditions” OR “pregnancy-related factors”

Search limits

Articles published in English, studies of humans, the fields title/abstract.

Table 1

Multiple births and maternal breast cancer risk[a]

First author and year	Study location	Cases/Controls	Attained age (years)	Comparison	OR/RR/IRR (95% CI)	Comments
Case–control, registry-based						
Polednak 1983 [29]	United States	313/623	<45	First birth: Twins vs. singleton	1.33 (0.46–1.83)[b]	Matched on location and time of first delivery. No adjustment for covariates
Olsen 1998 [64]	Denmark	5,213/20,025	NR	Any birth: Twins vs. all singletons	1.07 (0.88–1.29)	Matched on parity, attained age, date of delivery, and hospital of delivery. No adjustment for covariates
Innes 2004 [16]	United States	2,522/10,052	22–55	First birth: Multiple vs. singleton	1.43 (0.75–2.73)	Matched on county of residence and date of delivery. Adjusted for attained age, maternal age at first birth, race, education, infant birthweight, gestational age at delivery, infant sex, preeclampsia, and abruptio placentae
Case–control, interview-based						
Jacobson 1989 [61]	United States	3,918/4,047	20–54	Last birth: Multiple vs. all singletons Prior to last birth: Multiple vs. all singletons	0.60 (0.43–0.85) 1.11 (0.79–1.57)	Matched on attained age and geographic area. Adjusted for age at first birth and parity
Nasca 1992 [62]	United States	2,561/2,616	20–79	Any birth: ≥1 multiple birth vs. all singletons	By attained age: 20–55 years: 1.10 (0.67–1.81) 55–79 years: 1.01 (0.66–1.53)	Adjusted for attained age, county of residence, age at first live birth and number of live births
				Last birth: Multiple vs. all singletons	20–55 years: 0.97 (0.50–1.86) 55–79 years: 1.00 (0.55–1.80)	
				Prior to last birth: Multiple vs. all singletons	20–55 years: 1.31 (0.62–2.77) 55–79 years: 1.02 (0.57–1.81)	
Hsieh 1993 [48][c]	Seven international sites[d]	2,821/8,882	NR	Any birth: ≥1 multiple birth vs. all singletons	All participants: 1.21 (0.94–1.55) By attained age: <55 years: 1.29 (0.92–1.82) ≥55 years: 1.08 (0.74–1.57)	Adjusted for study center, parity, age at first birth, age at interview, menopausal status, and BMI. The results presented by age are from a subsequent analysis reported in a letter to the editor [163]
				Last birth: Multiple vs. all singletons	<55 years: 1.29 (0.80–2.11) ≥55 years: 0.86 (0.47–1.58)	
				Prior to last birth: Multiple vs. all singletons	<55 years: 1.29 (0.80–2.06) ≥55 years: 1.26 (0.78–2.01)	
Dietz 1995 [63]	United States	5,880/8,217	<75	Any birth: ≥1 multiple vs. all singletons Last birth: Multiple vs. all singletons	0.94 (0.75–1.17) 1.14 (0.80–1.62) 0.83 (0.63–1.11)	Conditioned on attained age and state. Adjusted for parity, age at first full-term pregnancy, menopausal status, BMI, age at menarche, and age at menopause

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First author and year	Study location	Cases/Controls	Attained age (years)	Comparison	OR/RR/IRR (95% CI)	Comments
				Prior to last birth: Multiple vs. all singletons		
La Vecchia 1996 [47][c]	Italy	2,569/2,588	20–74	Any birth: ≥1 multiple vs. all singletons Last birth: Multiple vs. all singletons	0.74 (0.51–1.06) 0.79 (0.37–1.67)	Adjusted for age, center, parity, age at menarche, age at first birth, menopausal status, age at menopause, history of benign breast disease, family history of breast cancer, oral contraceptive use, and BMI
Troisi 1998 [17]	United States	1,233/1,162	20–44	Any birth: ≥1 twin vs. all singletons Last birth: Twins vs. all singletons Prior to last birth: Twins vs. all singletons	0.94 (0.58–1.5) 0.80 (0.44–1.5) 1.2 (0.56–2.6)	Matched on attained age and geographic area. Adjusted for age, site, race, and parity/ age at first birth
Cohort, registry-based						
Lambe 1996 [59]	Sweden	19,368/100,459	≤65	Any birth: ≥1 multiple birth vs. all singletons	By attained age: <55 years: 0.85 (0.74–0.98) ≥55 years: 0.97 (0.76–1.24)	Matched on year and month of birth. Adjusted for parity and age at first-full term birth
				Last birth: Multiple vs. all singletons	<55 years: 0.88 (0.74–1.03) ≥55 years: 0.94 (0.66–1.33)	
				Prior to last birth: Multiple vs. all singletons	<55 years: 0.80 (0.62–1.03) ≥55 years: 0.97 (0.61–1.54)	
Murphy 1997 [58]	Sweden	4,790/46,751	<50	Any birth: ≥1 twin vs. all singletons Last birth: Twins vs. all singletons Prior to last birth: Twins vs. all singletons	0.71 (0.55–0.91) 0.67 (0.49–0.91) 0.81 (0.52–1.27)	Matched on maternal year of birth. Adjusted for parity and age at first-full term birth
Albrektsen 1995 [54]	Norway	4,782/797,487	20–56	Any birth: Multiple vs. all singletons Last birth: Multiple vs. all singletons Prior to last birth: Multiple vs. all singletons	0.89 (0.73–1.09) 0.85 (0.66–1.09) 0.96 (0.69–1.34)	Adjusted for attained age, birth cohort, and number of full term pregnancies
Wohlfahrt 1999 [30]	Denmark	9,495/989,004	<58	Last birth: Multiple vs. singleton	1.1 (1.0–1.3)	Adjusted for attained age, calendar period, age at first birth, number of births, and extremely preterm birth
Neale 2004 [56]	United States	536/15,261	15–71 (baseline)	Any birth: Multiple vs. all singletons	By attained age: ≤50 years: 1.02 (0.69–1.51) >50 years: 1.03 (0.84–1.26)	Twin mothers matched to singleton mothers on year and year of index delivery. Adjusted for number of pregnancies and age at first and last birth
Neale 2005 [57]	Sweden	6,309/NR	<50	Any birth: Multiple vs. all singletons	0.91 (0.75–1.09)	Adjusted for number of births, age at first birth, and date of birth of mother. Study

First author and year	Study location	Cases/Controls	Attained age (years)	Comparison	OR/RR/IRR (95% CI)	Comments
						used data that partly overlaps with Lambe et al. [59], but due to differences in study design and exclusions is included here as a separate study
Ji 2007 [60]	Sweden	1,010[e]/NR	NR	Any birth: Twin vs. all singletons	0.85 (0.74–0.98)	Adjusted for attained age, period, age at first childbirth, and number of pregnancies. Used data that overlaps with Lambe et al. [59] and Neale et al. [57], but due to differences in study design, exclusions, and analyses is included here as a separate study

CI confidence interval, *OR* odds ratio, *RR* relative risk or rate ratio, *IRR* incidence rate ratio, *NR* not reported, *BMI* body mass index

[a] Studies that did not report covariate-adjusted measures of association are not summarized in the Table [55]. Table also excludes one US record-based cohort because a confidence interval was not reported for the non-significant RR (1.1 for dizygotic twins vs. singletons and breast cancer) [53]

[b] 90% confidence interval

[c] This was a hospital-based case–control study

[d] Study was conducted in Taiwan, Japan, Greece, Brazil, Slovenia, United States, and Wales

[e] Number of breast cancer cases among women with a twin birth

Table 2

Preeclampsia, pregnancy-induced hypertension, and maternal breast cancer risk[a]

First author and year	Study location	Cases/Controls	Attained age (years)	Comparison	OR/RR/HR (95% CI)	Comments
Case–control, registry-based						
Polednak 1983 [29]	United States	314/628	<45	First birth: Preeclampsia/ toxemia (yes vs. no)	0.28 (0.08–1.00)[b]	Matched on location and time of first delivery. Adjusted for maternal age at first birth
Innes 2004 [16]	United States	2,522/10,052	22–55	First birth: Preeclampsia (yes vs. no)	0.85 (0.65–1.12)	Matched on county of residence and date of delivery. Adjusted for attained age, maternal age at first birth, race, education, infant birthweight, gestational age at delivery, infant sex, abruptio placentae, and multifetal gestation
Case–control, interview-based						
Thompson 1989 [84]	United States	4,668/4,635	20–54	Before the end of the most recent term birth: Hypertension (yes vs. no)	0.73 (0.59–0.92)	Matched on attained age and geographic area. Adjusted for attained age, geographic region, parity, age at first birth, and duration of breastfeeding
Talamini 1997 [46][c]	Italy	2,569/2,588	20–74	Any birth: First diagnosis of hypertension during pregnancy	By menopausal status: Premenopausal: 1.4 (0.6–3.4) Postmenopausal: 2.3 (1.0–5.4)	Adjusted for study area, attained age, education, parity, and BMI
Troisi 1998 [17]	United States	1,236/1,162	20–44	Any birth: Toxemia vs. never PIH vs. never	0.81 (0.61–1.1) 0.94 (0.73–1.4)	Matched on attained age and geographic area. Adjusted for attained age, site, race, parity/age at first birth, BMI, and menopausal status
Terry 2007 [83]	United States	1,310/1,385	20–98	Any birth: Preeclampsia vs. never	By menopausal status: Premenopausal: 0.99 (0.52–1.88) Postmenopausal: 0.63 (0.41–0.98)	Matched on attained age. Adjusted for attained age, age at first birth, BMI at age 20 and reference date, parity, smoking status, age at menarche, lactation, family history of breast cancer, ethnicity, education, preeclampsia, and PIH. Found stronger protective effects for multiple occurrences of preeclampsia alone or both conditions, but not PIH alone
				PIH vs. never	Premenopausal: 0.89 (0.51–1.56) Postmenopausal: 0.78 (0.51–1.19)	
Cohort, registry-based						
Richardson 2000 [80][d]	United States	205/337	17–44 (baseline)	Index birth: Preeclampsia alone PIH alone Both preeclampsia/ PIH	1.57 (0.63–3.88) 0.79 (0.40–1.57) 1.07 (0.60–1.90)	Matched on maternal birth date. Adjusted for age at index pregnancy, age at first full-term pregnancy, and race. Unknown reference group for ORs (assume never). It was not indicated if the index birth was first/last etc.
Vatten 2002 [77]	Norway	5,474/689,183	<30–80	First birth: Preeclampsia and/or PIH vs. neither	By attained age <50 years: 0.81 (0.7–0.9) ≥50 years: 0.81 (0.6–1.1)	Adjusted for attained age, calendar period of diagnosis, age at first birth, and parity

First author and year	Study location	Cases/Controls	Attained age (years)	Comparison	OR/RR/HR (95% CI)	Comments
Vatten 2007 [78]	Norway	9,160/691,846	NR	First birth: Preeclampsia and/or PIH vs. neither	Overall: 0.86 (0.78–0.94) By offspring gender Male: 0.79 (0.60–0.90) Female: 0.94 (0.82–1.06)	Adjusted for attained age, age at first birth, length of gestation, parity, marital status and offspring gender. This study includes overlapping data with Vatten et al. [77], but is not an update and different exclusion criteria and modeling approaches were used
Calderon- Margalit 2009 [79][e]	Israel	1,624/NR	<20 to ≥40 (baseline)	Any birth: Preeclampsia vs. never	1.37 (1.06–1.78)	Adjusted for age at first birth, and parity

CI confidence interval, *OR* odds ratio, *HR* hazard ratio, *RR* relative risk or rate ratio, *PIH* pregnancy-induced hypertension, *NR* not reported, *BMI* body mass index

[a] Studies that did not report covariate-adjusted measures of association are not summarized in the Table {[55] (preeclampsia only), [15] (hypertensive disorders of pregnancy), [81] (preeclampsia only; used the same initial pregnancy cohort as Richardson et al. [80])}

[b] This is a 90% confidence interval

[c] Hospital-based case–control study

[d] This study was based on linking data from the Child Health and Development cohort to cancer registry data. Exposure assessment was based on medical records

[e] Update of [82]

Table 3

Infant sex and maternal breast cancer risk[a]

First author and year	Study location	Cases/Controls	Attained age (years)	Comparison	OR/RR/IRR (95% CI)	Comments
Case–control, registry-based						
Olsen 1998 [64]	Denmark	5,213/20,025	NR	All births: Sex ratio (male to female)	1.01 (0.95–1.08)	Matched on parity, attained age, date of delivery, and hospital of delivery. No adjustment for covariates
Innes 2004 [16]	United States	2,522/10,052	22–55	First birth: Female vs. male[b]	1.03 (0.93–1.15)	Matched on county of residence and date of delivery. Adjusted for attained age, maternal age at first birth, race, education, infant birthweight, gestational age at delivery, preeclampsia, abruptio placentae, and multifetal gestation
Cohort, registry-based						
Wohlfahrt 1999 [30]	Denmark	9,495/989,004	<58	Last birth: Female vs. male[b]	1.0 (1.0–1.0)	Adjusted for attained age, calendar period, age at first birth, number of births, and extremely preterm birth In a subsequent report, the authors examined the long-term effect of infant sex on maternal breast cancer (starting five years after the last birth) and also found no association [103]
Hsieh 1999 [102]	Sweden	2,328/10,250	16–64	Infant sex distribution among biparous women vs. all females[b]	By age at diagnosis <40 years: all males: 0.63 (0.49–0.81); mixed sex: 0.85 (0.69–1.04) ≥40 years: all males: 1.13 (0.81–1.57); mixed: 1.09 (0.82–1.46)	Matched on maternal birth year. Adjusted for attained age and age at first birth
Albrektsen 1995 [54]	Norway	4,782/797,487	20–56	First birth: Male vs. female[b] Last birth: Male vs. female[b]	0.99 (0.93–1.05) 1.03 (0.96–1.09)	Adjusted for attained age, birth- cohort, and parity. In a subsequent report, the authors examined potential effect modification by infant sex of the time-related effects of pregnancy on breast cancer risk and found no evidence for modification by infant sex [104]

CI confidence interval, *OR* odds ratio, *RR* relative risk or rate ratio, *IRR* incidence rate ratio

[a] Studies that did not report covariate-adjusted measures of association are not summarized in the Table ([15, 17] [both reported no association between infant sex and maternal breast cancer])

[b] Singleton births only

Table 4

Infant gestational age at delivery and maternal breast cancer risk[a]

First author and year	Study location	Cases/Controls	Attained age (years)	Gestational age (weeks)	OR/RR (95% CI)	Comments
Case–control, registry-based						
Polednak 1983 [29]	United States	275/550	<45	First birth:		Matched on location and time of first delivery. No adjustment for covariates
				<30 vs. ≥ 37	0.33 (0.06–1.00)[b]	
				<37 vs. ≥ 37	0.81 (0.45–1.38)[b]	
Innes 2004 [16]	United States	2,522/10,052	22–55	First birth:		Matched on county of residence and date of delivery. Adjusted for attained age, maternal age at first birth, race, education, infant birthweight, infant sex, preeclampsia, abruptio placentae, and multifetal gestation
				<32	2.14 (1.16–3.94)	
				32–36	0.93 (0.73–1.14)	
				≥37	1.00 (REF)	
Cohort, registry-based						
Melbye 1999 [114]	Denmark	1,363/472,793	15–57	Last birth:		Adjusted for attained age, calendar period, parity, and age at first birth
				<29	2.11 (1.00–4.45)	
				29–31	2.08 (1.20–3.60)	
				32–33	1.12 (0.62–2.04)	
				34–35	1.08 (0.71–1.66)	
				36–37	1.04 (0.83–1.32)	
				38–39	1.02 (0.89–1.17)	
				40	1.00 (REF)	
				≥41	1.03 (0.90–1.18)	
				Ever <32 vs. never	1.72 (1.14–2.59)	
Hsieh 1999 [116]	Sweden	2,318/10,199	NR	First birth:	By attained age	Matched on maternal birth year and adjusted for age at first birth
				<37 vs. ≥37 weeks	<40 years: 1.03 (0.79–1.35); ≥ 40 years: 1.30 (1.02–1.65)	
Vatten 2002 [115]	Norway	5,474/689,183	<30–80	First birth:		Adjusted for attained age, calendar period of diagnosis, age at first birth, and total number of births
				<32	1.22 (0.97–1.53)	
				32–36	1.11 (0.97–1.19)	
				37–39	1.03 (0.98–1.05)	
				≥40	1.00 (REF)	

CI confidence interval, *OR* odds ratio, *RR* relative risk or rate ratio, *NR* not reported

[a] Studies that did not report covariate-adjusted measures of associations are not summarized in the Table [15, 17] and both reported null results for infant gestational age at delivery and maternal breast cancer

[b] 90% confidence interval

Table 5

Fetal growth and maternal breast cancer risk[a]

First author and year	Study location	Cases/Controls	Attained age (years)	Birthweight (g)	OR/RR/HR (95% CI)	Comments
Case–control, registry-based						
Olsen 1998 [64]	Denmark	5,213/20,025	NR	Any birth:		Matched on parity, attained age, date of delivery, and hospital of delivery. No adjustment for covariates. Reference group and parity at index birth not stated, assume results are for any birth and reference group is 2,500–4,000 g
				(<2,500) vs. (2,500–4,000)	1.27 (0.77–2.08)	
				(>4,000) vs. (2,500–4,000)	1.09 (0.80–1.49)	
Innes 2004 [16]	United States	2,522/10,052	22–55	First birth:		Matched on county of residence and date of delivery. Adjusted for attained age, maternal age at first birth, race, education, gestational age in weeks (<32, 32–36, ≥37), infant sex, preeclampsia, abruptio placentae, and multifetal gestation
				<1,500	0.82 (0.39–1.74)	
				1,500–1,999	0.96 (0.55–1.68)	
				2,000–2,499	0.96 (0.72–1.28)	
				2,500–3,499	1.00 (REF)	
				3,500–3,999	0.99 (0.88–1.12)	
				4,000–4,499	0.94 (0.77–1.14)	
				≥4,500	0.64 (0.38–1.06)	
Cohort, registry-based						
Wohlfahrt 1999 [30]	Denmark	3,874/NR	<58	Last birth:[b]		Adjusted for attained age, calendar period, age at first birth, number of births, and extremely preterm birth (<32 weeks, ≥32 weeks, unknown)
				≤3,000	1.0 (REF)	
				3,000–3,250	1.0 (0.9–1.1)	
				3,250–3,500	1.0 (0.9–1.1)	
				3,500–3,750	1.0 (0.9–1.1)	
				>3,750	1.1 (1.0–1.2)	
Cnattingius 2005 [15]	Sweden	2,216/311,803	95% <50	First birth:[b]		Adjusted for maternal age at first birth, gestational age in weeks (<37, 37, 38, 39, 40, 41, ≥42), infant sex, maternal height, maternal BMI, smoking, family situation, country of birth, pregnancy- induced hypertensive diseases, diabetes mellitus, vaginal bleeding in late pregnancy, and parity
				per 500 g increase	1.11 (1.04–1.18)	
				≥ 4,500 vs. 2,500–3,499	1.22 (0.86–1.73)	

CI confidence interval, *OR* odds ratio, *RR* relative risk or rate ratio, *HR* hazard ratio, *NR* not reported, *BMI* body mass index, *g* grams

[a] Results by menopausal status/attained age were not reported for any of the studies, though studies included predominantly premenopausal or younger women. Studies that did not report covariate-adjusted measures of association are not summarized in the Table [55, 81]

[b] Limited to singleton births

Table 6

Pregnancy weight gain and maternal breast cancer risk[a]

First author and year	Study location	Cases/Controls	Attained age (years)	Weight gain during pregnancy (kilograms)	OR/RR (95% CI)	Comments
Case–control, interview-based						
Troisi 1998 [17]	United States	954/889	20–44	First birth:		Matched on attained age and geographic area. Adjusted for attained age, site, race, parity/age at first birth, current BMI, age at menarche, recent alcohol intake, and oral contraceptive use
				≤10.21	1.0 (0.78–1.4)	
				10.22–12.5	1.0 (REF)	
				12.6–14.7	0.93 (0.68–1.3)	
				14.8–17.0	1.1 (0.74–1.6)	
				17.1–19.3	0.75 (0.52–1.1)	
				>19.4	1.1 (0.79–1.5)	
Peterson 2008 [141]	United States	1,706/1,756	<50	Last birth: Percent weight change[b]		Matched on attained age. Adjusted for attained age, state, parity, age at first birth, education, mammogram in the last 5 years, family history of breast cancer, BMI, and BDD
				<20	1.00 (REF)	
				20–28	0.92 (0.76–1.11)	
				≥29	0.87 (0.72–1.07)	
Cohort, mailed survey						
Hilakivi-Clarke 2005 [138]	Finland	98/392	32–58	Any birth:		Matched on attained age and use of the intrauterine device Mirena. Adjusted for education, age at menarche, age at first birth, family history of breast cancer, and change in BMI during adult life
				<10	1.0 (REF)	
				10–15	0.8 (0.44–1.47)	
				16–20	1.0 (0.47–2.04)	
				20?	0.8 (0.27–2.13)	
Cohort, registry-based						
Kinnunen 2004 [139]	Finland	123/1,966	35–74	Any birth:	By menopausal status	Adjusted for age at menarche, age at first birth, age at index pregnancy, parity, and pre-pregnancy BMI
				>15 vs. 11–15	Premenopausal: 1.0 (0.40–2.48)	
					Postmenopausal: 1.80 (1.05–3.07)	

CI confidence interval, *OR* odds ratio, *RR* relative risk or rate ratio, *BMI* body mass index, *BDD* benign breast disease

[a] Studies that did not report covariate-adjusted measures of association are not summarized in the Table ([81] [Reported a trend of increasing age-adjusted incidence of breast cancer across quartiles of weight change per week, but did not examine this exposure further), [140] (reported no association for weight gain in first pregnancy and pre-or postmenopausal breast cancer risk)]

[b] Defined as weight gain in final pregnancy relative to the most recent BMI

Table 7

Gestational diabetes and maternal breast cancer risk[a]

First author and year	Study location	Cases/Controls	Attained age (years)	Comparison	OR/RR/HR (95% CI)	Comments
Case–control, interview-based						
Troisi 1998 [17]	United States	1,235/1,163	20–44	Any birth: GDM vs. never	1.1 (0.73–1.5)	Matched on attained age and geographic area. Adjusted for attained age, site, race, parity/age at first birth, current BMI, age at menarche, mammography, and alcohol intake
Rollison 2007 [155]	United States	2,319/2,518	<25–79	Any birth: GDM vs. no history of any diabetes	By menopausal status and age at onset Pre or perimenopausal: all ages: 0.79 (0.52–1.21); <35 years: 0.61 (0.36–1.02); ≥35 years: 1.41 (0.67–2.98) Postmenopausal: all ages: 0.60 (0.37–0.97); <35 years: 0.47 (0.27–0.82); ≥35 years: 1.33 (0.44–4.02)	Matched on attained age. Adjusted for attained age, BMI at 15 years, and number of full-term pregnancies
Cohort, registry-based						
Cnattingius 2005 [15]	Sweden	2,216/311,803	95% <50	First birth: Diabetes during pregnancy vs. no[a]	1.07 (0.51–2.25)	Adjusted for maternal age at first birth, gestational age, infant sex, height, maternal BMI, smoking, family situation, country of birth, pregnancy-induced hypertensive diseases, vaginal bleeding in late pregnancy, parity, birthweight, and placenta weight
Dawson 2004 [154]	Scotland	18/753	NR	Log of fasting glucose during pregnancy at ~32 weeks (quartiles):		Adjusted for age, maternal BMI, and smoking at time of index pregnancy. Study did not report parity at index pregnancy (e.g., first birth, last birth)
				4.06–4.28	1.0 (REF)	
				4.29–4.32	2.59 (0.23–28.75)	
				4.33–4.38	7.18 (0.85–60.43)	
				4.39–4.67	10.66 (1.34–85.01)	
Perrin 2008 [153]	Israel	1,626/36,300	43–94	Ever GDM vs. never	By age at diagnosis	Adjusted age and birth order at first observed birth, social class, ethnic origin, education, and immigration status
					<50 years: 1.0 (0.5–2.1)	
					≥50 years: 1.7 (1.1–2.5)	

CI confidence interval, *OR* odds ratio, *RR* relative risk or rate ratio, *HR* hazard ratio, *NR* not reported, *BMI* body mass index, *GDM* gestational diabetes mellitus

[a] Any type of diabetes during pregnancy (gestational or pregestational (type I, type II))