A POPULATION-BASED CASE-CONTROL STUDY OF PREGNANCY-RELATED FACTORS AND MATERNAL BREAST CANCER RISK AMONG YOUNGER WOMEN

by

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ABSTRACT

A POPULATION-BASED CASE-CONTROL STUDY OF PREGNANCY-RELATED FACTORS AND MATERNAL BREAST CANCER RISK AMONG YOUNGER WOMEN

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Though the etiology of breast cancer among younger women (≤ 50 years of age) remains largely unknown, pregnancy is known to be a critically important time in relation to a women's subsequent risk of breast cancer. The biological mechanisms underlying the observed short-term increase and long-term decrease in breast cancer risk following childbirth, which depend on age at pregnancy, are not clear. Variation in fetal growth (FG) or gestational age (GA) in a woman's own pregnancies may serve as indirect markers of the hormonal environment during pregnancy. The overall goal of this dissertation research is to investigate the associations between two under-investigated perinatal exposures—FG and GA, as well as age at first and last delivery, number of live births, and maternal breast cancer risk (overall and for ductal and lobular histologic types) among parous Black and White Michigan (MI) women ≤ 50 years of age. We conducted a population-based case-control study using linked MI Cancer Registry (1985-2004) and MI Live Birth records (1978-2004). Cases were matched to controls 1:4 on maternal birth year and race (original sample: 8,251 cases and 33,004 controls). Using conditional logistic regression, we examined the associations for breast cancer and age at first and last birth, number of live births, GA and FG (defined using BW percentiles both as a

continuous variable and categorized ((SGA) < 10th, (AGA) 10-90th (referent), (LGA) > 90th)). Later age at first and last birth and multiparity were independently associated with increased risks for both ductal and lobular breast cancer, with odds ratios (ORs) of similar magnitude. Some differences were found by race (White, Black), including an increased risk of lobular tumors for age at last birth ≥ 30 years (vs. < 30 years) among White women only (OR=1.70, 95% CI: 1.21-2.40). Delivery of an SGA or an LGA infant in a first or last birth was not significantly associated with breast cancer risk, but among women with a last birth at age ≥ 30 years, delivery of an SGA infant in a last birth was associated with a reduced risk of breast cancer (OR=0.82, 95% CI: 0.68-0.98). A first delivery at < 32 weeks or at > 41 weeks (reference: 37-41 week) was associated with reduced risks (ORs: 0.80, 95% CI: 0.62-1.04 and 0.92, 95% CI: 0.85-0.99, respectively). In this large, population-based case-control study of parous women ≤ 50 years of age, we found limited evidence for an association between low or high FG and overall breast cancer risk. Delivery of an infant < 32 weeks in a first birth may reduce breast cancer risk, but this finding was in contrast to our hypothesis and the underlying biological mechanisms are not clear. Our results for GA and breast cancer risk, as well as the inconsistent findings to date in this area warrant future research to characterize these associations, including studies with information on both biologic measures during pregnancy and other potential confounding factors (e.g., maternal body size).

This dissertation is dedicated to Nate, thank you for your unfailing kindness, love, and support.

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ABBREVIATIONS

Alpha-feto protein (AFP)

Appropriate for gestational age (AGA)

Benign breast disease (BDD)

Body mass index (BMI)

Confidence intervals (CIs)

Grams (g)

Gestational age (GA)

Gestational diabetes mellitus (GDM)

Hazard ratios (HR)

Human chorionic gonadotropin (HCG)

International Classification of Diseases for Oncology (ICD-O-3)

Incidence rate ratio (IRR)

Insulin-like-growth-factor-I (IGF-I)

Large for gestational age (LGA)

Medical subject heading (MeSH)

Michigan Department of Community Health (MDCH)

Not reported (NR)

Odds ratio (OR

Pregnancy-induced hypertension (PIH)

Preterm delivery (PTD)

Relative risk (RR)

Small for gestational age (SGA)

Surveillance, Epidemiology, & End Results (SEER)

Sex-hormone binding globulin (SHBG)

Socioeconomic status (SES)

Standard deviation (SD)

Very preterm delivery (VTPD)

CHAPTER 1: INTRODUCTION AND AIMS

1. Introduction

Premenopausal breast cancer (< 50 years of age at diagnosis), is less common than postmenopausal breast cancer (1, 2), but breast tumors in younger women (particularly < 40 years of age) are associated with characteristics related to poorer prognosis including later stage at diagnosis, estrogen receptor negativity, higher tumor grade, and positive lymph node status(2-6). Five-year survival rates are lower in women with breast cancer before age 40 (2, 4, 7, 8) and studies have reported that younger women diagnosed with breast cancer have lower overall quality of life than older women, as well as higher psychological morbidity (9, 10). Despite this, the etiology of premenopausal breast cancer remains largely unknown.

In the United States, the age-specific incidence of breast cancer differs by race/ethnicity and socioeconomic status (SES) (1, 2, 11-14). Overall, White women have higher age-adjusted rates of breast cancer compared to other racial/ethnic groups (1, 13, 14) and women of higher SES have elevated rates of breast cancer compared to women of lower SES (11, 15). In recent decades, however, differences in incidence by SES have decreased among Black and White women, but increased in other racial/ethnic groups e.g. Hispanics and Asian-Americans (12). Among women < 40 years of age, Black women have higher age-specific incidence rates of breast cancer compared to White women, while after approximately age 45, incidence rates are higher among White women (2, 16). Though breast cancer disproportionately affects young Black

women and is more aggressive (2), the literature on breast cancer etiology among young Black women is sparse (17-32). Further, despite the fact that differences in breast cancer incidence by race are reflected in differences by SES (2, 12, 14, 19, 33, 34) , the contribution of SES to the increased incidence of breast tumors in young Black as compared to young White women has not been well-studied (1, 2, 12, 14, 19, 33).

Though the etiology of premenopausal breast cancer remains largely unknown, pregnancy is known to be a critically important time in relation to a women's subsequent risk of breast cancer (35, 36). Women diagnosed with breast cancer shortly following pregnancy are more likely to have advanced breast tumors (37), poorer tumor prognostic factors (38), and increased mortality risk compared to nulliparous premenopausal women (38-41). Earlier age at first birth and increased parity are established protective factors for long-term breast cancer risk (35, 42, 43). Though not as well-established, evidence suggests that pregnancy at any age is followed by a transient increase in breast cancer risk, with possibly a stronger effect in women with a later age at first birth (> 30 years) (44-50), and that later age at any birth (besides first) may also increase breast cancer risk (50-60).

The biological mechanisms underlying the role of pregnancy in premenopausal breast cancer are not clear (61, 62). The maternal hormonal environment during pregnancy (63, 64) or the mammary cell microenvironment following pregnancy have been hypothesized to promote tumor growth (61). **Perinatal factors** such as twinning and fetal growth, which are associated with

an altered maternal hormonal environment during pregnancy (63, 65, 66), could provide insight into the biological mechanisms for the relation between pregnancy and premenopausal breast cancer in mothers following pregnancy.

Research findings of the associations between perinatal factors and maternal premenopausal breast cancer risk (***maternal breast cancer*** refers to breast cancer in mothers following one or more completed pregnancies) remain inconclusive. Perinatal factors that have inconsistently been shown to influence maternal breast cancer risk include high fetal growth (birthweight alone or birthweight adjusted for gestational age as proxies for fetal growth) (63, 65), delivery of an infant at earlier gestational ages, including preterm (< 37 weeks gestation) and very preterm (< 32 weeks gestation) delivery (65-70), multiple births (twining and higher order deliveries) (65-67, 71-81), preeclampsia/pregnancy-induced hypertension (PIH) (65-67, 82-85), pregnancy weight gain (86, 87), offspring gender (88, 89), and diabetes during pregnancy (63, 66, 90, 91). Studies have found that the influence of **perinatal factors** may be modified by time since index pregnancy (e.g., < 5 years compared to ≥ 5 years)), age at index pregnancy (< 30 years; ≥ 30 years), infant gender for index pregnancy, and/or birth order (e.g., exposure in first birth or most recent birth) (65, 73, 74, 77, 79). Endogenous hormones and growth factors that are elevated during pregnancy and have been implicated in breast cancer etiology, may mediate the associations between **perinatal factors** and breast cancer risk (65, 79, 92-94) and include estrogens (95-97), progesterone (98, 99), androgens (100-102), human chorionic gonadotropin (HCG) (103, 104), insulin-like-growth-

factor-I (IGF-I) (105-108), prolactin (109), and alpha-feto protein (AFP) (92, 103, 110). For example, high fetal growth is associated with higher levels of maternal serum IGF-I (105-107, 111) and lower levels of prolactin (109), which may explain a positive association between fetal growth and maternal premenopausal breast cancer risk.

The purpose of this study is two-fold. First, we will conduct a systematic literature search to identify and synthesize all published studies of perinatal factors and maternal breast cancer. Second, we will investigate the associations between **pregnancy-related factors** (**later age at first and last delivery**, **number of live births**, and two **perinatal factors that have been very under-investigated —fetal growth and gestational age at delivery (GA)**), and maternal breast cancer risk among parous Black and White women 50 years of age or less (i.e., predominantly premenopausal women) in Michigan (MI), 1985-2004. We will examine associations for risk of maternal breast cancer overall and by two histologic tumor types (ductal and lobular). We will conduct a registry-linked population-based case-control study utilizing MI Resident Birth files (1978-2004), MI Statewide Cancer Registry data (1985-2004), and Detroit Metropolitan Surveillance Epidemiology End Results (Detroit SEER) Registry data (1978-2004). This investigation can provide insight into possible biological mechanisms for the role of pregnancy in premenopausal maternal breast cancer risk. The study results may lead to the identification of women who are at higher risk for premenopausal breast cancer following childbirth and can be targeted for early

prevention efforts, possibly contributing to a reduction of the breast cancer burden in premenopausal parous women.

2. Aims and Hypotheses

Aim 1. To systematically identify and descriptively summarize all published studies on perinatal factors and maternal breast cancer risk, including maternal conditions of pregnancy (preeclampsia, PIH, GDM, pregnancy weight gain) and infant birth characteristics (fetal growth, GA, multiple births, sex). These perinatal factors have been shown to reflect an altered hormonal environment during pregnancy, and may provide insight into the biological mechanisms underlying the role of pregnancy in breast cancer etiology. Given that that influence of many breast cancer risk factors depend on menopausal status (or by proxy age at diagnosis), we present findings stratified by menopausal status/attained age whenever available.

Aim 2. To investigate the associations between later age at first and last delivery, number of live births and breast cancer overall and by the two most common histologic types (ductal and lobular) among parous White and Black women 20-50 years of age in MI, 1985-2004. We will examine potential modification of the above associations by race (White, Black), and maternal education at first delivery (a measure of SES).

We hypothesize that women with a later age at first or last delivery (> 30 years) will have increased breast cancer risk compared to women with a younger age at first or last delivery (≤ 30 years). We further hypothesize that later age at first and last delivery and multiparity will be more strongly associated with

increased risk for lobular breast tumors as compared to ductal breast tumors, given the development of lobules during pregnancy and that lobular tumors have been hypothesized to be more strongly associated with hormonal-related factors in some studies (112).

Aim 3. To investigate the associations between fetal growth, gestational age at delivery (≥ 41 weeks (posterm), 37-41 weeks (term), 36-32 (preterm), < 32 weeks gestation (very preterm)), and breast cancer overall and by histologic type among parous White and Black women 20- 50 years of age in MI, 1985-2004. We will estimate fetal growth using published birthweight percentiles for gestational weeks 24-44, described in the methods section in Chapter 5. We will examine potential modification of the above associations by race (White, Black), maternal education at first delivery, later age at delivery (first and last), and shorter time since delivery last delivery. We will examine the perinatal exposures in first births and last births (among women with two or more births).

We hypothesize that women who deliver infants with higher fetal growth or have a preterm/very preterm delivery will have increased breast cancer risk compared to women who deliver infants with lower fetal growth or do not have a preterm/very preterm delivery.

3.1. We will examine the associations between fetal growth and gestational age at delivery and breast cancer histologic type (ductal and lobular). The sample will be limited to cases with these histologic types (n=5841) and their associated controls (n=21,325).

We hypothesize that mothers who delivery infants with high fetal growth or at earlier gestational ages may have stronger elevated risks associated with lobular tumors compared to ductal tumors. The overall rationale for this hypothesis is given by the finding that lobular tumors may be more strongly associated with hormonal factors related to pregnancy. However, this will be the first study of these two exposures and histologic type of breast tumors. Further, findings may vary for first births compared to last births, given development of the mammary gland during first pregnancy.

3. Organization of Dissertation

This dissertation includes 5 chapters and an epilogue. **Chapter** 1 is the introduction, aims, and hypotheses. **Chapter 2** is a systematic review of all epidemiologic studies of perinatal factors and maternal breast cancer (manuscript 1 of the dissertation: 'Perinatal factors and maternal breast cancer risk: a review of the epidemiologic literature'). **Chapter 3** describes the study design, data preparation, and related methodologic issues. **Chapters 4 and 5** are in the analytic manuscripts (abstract, introduction, methods, results, and discussion) that correspond to aim 2 (manuscript 2: 'Pregnancy-related factors and risk of breast cancer by histologic type, a registry-based study of parous black and white younger women') and aim 3 (manuscript 3: 'A population-based case-control study of fetal growth, infant gestational age at delivery, and maternal breast cancer among younger women'). The **epilogue** includes a brief summary of findings, main study strengths and limitations, conclusions, and recommendations for future research.

CHAPTER 2: Perinatal Factors and maternal breast cancer risk: a review of the epidemiologic literature

1. Abstract

Objective: Many reviews have been published on perinatal factors and offspring breast cancer risk; however, a review synthesizing the published literature on perinatal factors and breast cancer in mothers using systematic search methods is lacking. **Methods**: We conducted a systematic search to identify all published studies of perinatal factors and maternal breast cancer. We used PUBMED (to December 31, 2008) and identified 39 relevant articles. Results are summarized for each factor followed by a discussion of the findings. **Results**: Though inconsistent across 16 studies, evidence suggests multiple births may protect against breast cancer. Preeclampsia was found to decrease risk by up to 20% in all but two studies; results may be modified by infant sex. Breast cancer risk may be increased by delivery at earlier gestational ages or elevated fetal growth in a first or last birth, but data are sparse. Infant sex does not appear to be associated with breast cancer. Data on associations between gestational diabetes, pregnancy weight gain and breast cancer risk are limited and conflicting. **Conclusions**. Future research is needed to elucidate the associations between perinatal factors and maternal breast cancer, including studies of potential mechanisms for the role of perinatal factors in breast cancer etiology.

2. Introduction

Many review papers have been published on perinatal factors (reflecting the *in-utero* environment) and later female offspring breast cancer risk (113-116). Few reviews, however, have summarized epidemiologic findings for one or more perinatal factor and subsequent breast cancer in mothers (i.e., maternal breast cancer) (115, 117-119), and no review exists which synthesizes all the published literature on perinatal factors and maternal breast cancer using systematic search methods.

Epidemiologic studies of the association between perinatal factors and maternal breast cancer remain inconclusive. Perinatal factors that have inconsistently been shown to influence maternal breast cancer risk include fetal growth (birthweight alone or birthweight adjusted for gestational age) (63, 65), infant gestational age (GA) at delivery (65-67), multiple births (i.e., twining and higher order deliveries) (71, 80, 81), preeclampsia and/or pregnancy-induced hypertension (PIH) (66, 67, 82), placental characteristics (63, 120), pregnancy weight gain (66, 87), gestational diabetes mellitus (GDM) (66, 90, 91), and infant sex (65, 66). Perinatal factors are associated with altered levels of maternal hormonal factors during pregnancy, including estrogens (95-97), progesterone (98, 99), androgens (100-102), human chorionic gonadotropin (HCG) (103, 104), IGF-I, IGF-I binding proteins (105-108), prolactin (109), and AFP (92, 103, 110). These hormonal factors play a role in breast cancer etiology and have been proposed to mediate the associations between perinatal factors and maternal breast cancer risk (65, 79, 92, 93).

Pregnancy is known to be a critically important time in relation to a women's subsequent risk of breast cancer (35, 36). Earlier age at first birth and increased parity are established protective factors for long-term breast cancer risk (35, 42, 43). 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) (44-49). The biological mechanisms underlying the role of pregnancy in breast cancer etiology are not clear (61, 62), but several hypotheses, all of which involve alterations in the maternal hormonal environment during pregnancy, have been proposed to explain both the long-term decrease and short-term increase in breast cancer risk. For example, the long-term reduction in risk associated with early age at first full-term pregnancy and parity may be due to hormonally-induced terminal differentiation of the mammary gland, resulting in permanent changes in the breast tissue and protection against future carcinogens (36, 121). Alternatively, molecular changes in mammary epithelial stem cells during pregnancy, in response to the maternal hormonal environment, may influence later cellular proliferation and DNA repair in the mammary gland (62). The short-term increase in risk may be due to the promotion of tumor growth in response to elevated pregnancy hormones (63, 64). It is difficult to directly study the maternal hormonal environment during pregnancy and subsequent maternal breast cancer (122); however, perinatal factors (e.g., multiple births, high fetal growth), which may be proxies of this environment (63, 65, 66), can be used to provide insight

into the hormonal mechanisms underlying the influence of pregnancy on mammary carcinogenesis.

The purpose of this review is to summarize the epidemiologic evidence for the associations between perinatal factors and maternal breast cancer and to identify areas for future research. We focused on perinatal factors that have been shown to reflect an altered hormonal environment during pregnancy, and hence may provide insight into the biological mechanisms underlying the role of pregnancy in breast cancer, including maternal conditions of pregnancy (preeclampsia, PIH, GDM, pregnancy weight gain) and infant birth characteristics (fetal growth, GA at delivery, multiple births, sex). For each factor, we first describe and summarize the epidemiologic studies. This is followed by a commentary on the possible explanations for the findings, with a brief discussion on the postulated mechanisms that may help explain the associations between perinatal factors and maternal breast cancer.

3. Methods

3.1 Search strategy and study selection

The electronic database PUBMED was searched systematically by one reviewer (SN) for all articles published in peer-reviewed journals up to December 31, 2008. Searches included the medical subject heading (MeSH) "breast neoplasms" and the keyword "breast cancer" and terms for the exposures of interest (see appendix for terms and additional search strategy details). We included articles that were peer-reviewed epidemiologic studies using population-based case-control or cohort study designs that reported measures of

association (e.g., odds ratios (ORs), relative risks (RRs)) for one or more of the exposures of interest and maternal breast cancer. We excluded hospital-based case-control and cross-sectional studies (listed in appendix). The search strategy identified 1,501 possible articles. If the article title appeared relevant or if relevance was not clear from the title, the abstract was reviewed to confirm the study examined the outcome and exposure(s) of interest (n=211 abstracts). We excluded 1,435 articles based on title/abstract review. Full text of articles were obtained for review for both relevant studies and for studies where relevance was not clear from abstract review alone (n=66). Thirty four of these articles met the inclusion criteria and were included as original research studies, two articles were reviews of one or more relevant exposures of interest, and 30 articles were excluded for not meeting the inclusion criteria. The reference lists for each included study as well as review papers were hand searched for additional articles. Citations of all relevant studies were also searched in the citation index Web of Science- part of ISI Web of Knowledge (123). An additional five relevant reports not found in the PUBMED search were found through these methods. We did not attempt to identify unpublished articles or abstracts from scientific conferences.

We identified 39 relevant studies using the above search strategy. We descriptively summarized the studies for each perinatal exposure and breast cancer in tables, with the exception of placental characteristics, for which there were only two studies (Tables 1-7). Many breast cancer risk factors (including reproductive factors) differ in their effects by menopausal status (or attained age

which is a proxy for menopausal status) (124-126) and hence we include results stratified by menopausal status/age, whenever available. Data from each identified study were abstracted directly from the published manuscript of each individual study and tabulated by one author (SN). We did not conduct an overall quality assessment for the studies; all identified reports that met inclusion criteria are included in this review. Tables describe all studies that reported covariate-adjusted measures of association. Studies that did not provide covariate-adjusted measures of association with confidence intervals (CIs) were not tabulated, but are referenced in the text. Four redundant articles were not included as separate studies in the summary tables, but are discussed as appropriate in the text. One of these articles had been recently updated in a new published report (82) and only the new data is included; three articles were additional analyses on data from previously published reports (89, 127, 128). Studies nested within a cohort with follow-up were considered cohort studies. Age in the tables indicates age at diagnosis or at follow-up (attained age) unless otherwise noted.

3.2 Methodologic Issues

Three main issues to consider when interpreting the studies include: 1) the data source for exposure measurement (maternal self-report, birth registry, medical records), 2) potential confounding factors, and 3) potential effect modifiers. In addition, given that case-control studies are subject to systematic errors that could influence measures of associations (e.g., recall bias and participation bias), we include a separate discussion by study design, if possible. Most case-control studies were registry-based, however, and are not subject to

some well-known systematic errors that plague case-control studies, because exposure histories were collected from records prior to cancer diagnosis and contact with participants is not required via the use of linked records. However, registry-based studies may have limited information on potential confounding factors and hence be more subject to residual confounding.

Several characteristics of the index pregnancy (e.g., age at index birth, birth order) should be considered as potential effect modifiers of the associations between perinatal factors and breast cancer. Previous studies have examined perinatal exposures in first births, any birth, and last births (among women with 2 or more deliveries). It is important to examine exposures in first births given the established critical role of a first live birth on both the short- and long term risk of breast cancer. Exposure in the last birth, among multiparous women, may also be important because recency of exposure may reflect the growth-promoting influence of an altered maternal hormonal environment on the development of breast cancer. Alternatively, exposure in a birth prior to the most recent birth may be influenced by subsequent births and the characteristics of those births. In addition to birth order, age at the index birth and time since the index birth are important potential modifiers. Later ages at first and last birth are well-known risk factors for breast cancer which may modify the time-related effects of pregnancy on breast cancer risk (50). Finally, infant sex at index birth has been suggested as a potential effect modifier of the associations between other perinatal factors and breast cancer (e.g., preeclampsia).

4. Preeclampsia, Pregnancy-Induced Hypertension, and Placental Characteristics

4.1 Introduction

Preeclampsia is complication of pregnancy involving the placenta and multiple organ systems which occurs in about 4-6% pregnancies in the US and is a cause of both maternal and neonatal morbidity and mortality (129-133). Preeclampsia is defined by the presence of new onset hypertension, i.e., PIH (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) and proteinuria (≥ 300 mg per 24 hours) after 20 weeks of gestation (134). The etiology of preeclampsia is complex, and may originate with poor placentation that may involve both genetic and immunological mechanisms (129, 135). Abnormal placentation may lead to widespread endothelial dysfunction, which in turn results in the clinical manifestation seen in preeclamptic pregnancies (129, 135). Maternal risk factors for preeclampsia include nulliparity, family history of preeclampsia, pre-existing diabetes, insulin resistance, chronic hypertension, multiple gestations, older maternal age, and high pre-pregnancy body mass index (BMI) (134, 136).

4.2 Epidemiologic Studies

We found five case-control studies (65-67, 85, 137) and seven cohort studies (63, 81, 83, 84, 120, 138, 139) of preeclampsia and/or PIH and breast cancer risk (Table 2.1). Three of the twelve studies did not report measures of association (63, 81, 120). Among the nine other studies, exposure measurement was from birth registries for four studies, medical records for two studies, and maternal self-report for three studies.

Cohort studies. Two large cohort studies using registry-based data in Norway with overlapping populations (5,474 cases (2002) and 9,160 cases (2007)) reported that preeclampsia and/or PIH in a first birth is associated with a significantly reduced risk of breast cancer (84, 138). Odds ratios were not affected by age at breast cancer diagnosis (70). In contrast, a large cohort study (the Jerusalem Perinatal Cohort Study) used medical records and reported a significantly increased risk of breast cancer in two reports, one in 2004 (82) and also in an updated reported with further follow-up in 2008 (139). They also reported an increased risk of cancer at any site (hazard ratio (HR) = 1.23 95% CI: 1.05-1.45), which is inconsistent with a recent cohort study in Utah of all cancer sites and preeclampsia (140).

Case-control studies. Five case-control studies have reported evidence for an inverse association between preeclampsia and/or PIH and breast cancer, though only two studies reported significant findings (85, 137). One US interview-based case-control study with 1,310 cases examined the history of preeclampsia, PIH, or both conditions in any pregnancy and breast cancer risk, and was able to adjust for several known breast cancer risk factors (e.g., BMI, parity, age at menarche, lactation, family history). This study found that preeclampsia and PIH were inversely associated with breast cancer; results stratified by menopausal status revealed a stronger association among postmenopausal women (137).

Two studies (both case-control) considered age at index birth and/or time since index birth as effect modifiers of the association between preeclampsia and breast cancer. One registry-based case-control study of first births reported a

stronger inverse association between preeclampsia and breast cancer for women > 30 years at first birth and also in the first three years after the first birth (65). An interview-based case-control study found no evidence for effect modification by time since last birth (66).

In addition to age and time since birth, some studies (both case-control and cohort) have examined effect modification by length of gestation (84, 137), fetal growth (84), and offspring sex (65, 128, 137-139). In the largest cohort study, from Norway, Vatten and colleagues found the protective effect of preeclampsia and/or PIH was limited to women who delivered a male infant and in particular for preterm delivery of male infant (138). Troisi and colleagues conducted additional analyses using data from the registry-based case-control study of first births initially reported on by Innes and Byers (65), and found a stronger protective effect of preeclampsia for women who delivered a male than who delivered a female, but only among women > 30 years of age at first birth (128).

Two studies have examined placental characteristics and subsequent breast cancer risk (63, 120). Lower placental weight and other placental characteristics that may represent reduced placental functionality, could also reflect altered exposure to hormones and growth factors during pregnancy (141), and may have implications for breast cancer risk (63). Cohn and colleagues examined placental characteristics (e.g., placental weight, placental diameter) in a small (146 cases) cohort study that followed-up participants of the Child Health and Development Studies (120) and found some evidence for reduced breast

cancer risk associated with lower placenta weight or reduced placental diameter. Results from the Swedish registry-based cohort study conducted by Cnattingius and colleagues that also looked at several other perinatal factors including fetal growth, reported an increased risk of breast cancer per 100 gram increase in placenta weight, (HR = 1.07 95% CI : 1.02-1.13), adjusted for several other perinatal factors, including offspring birthweight (63). Further, women with a first birth and second birth placenta weighing > 700 grams, were at twice the adjusted risk of breast cancer compared to women for which both placentas weighed < 500 grams (63).

4.3 Summary

Most studies, based on both self-report and birth registry data have reported that preeclampsia and/or PIH is associated with a decrease in breast cancer risk (65-67, 84, 85, 137, 138). However, one large well-designed cohort study (Jerusalem Perinatal Cohort study) found an increased breast cancer risk among women with a history of preeclampsia. Authors of this cohort study speculated reasons for discrepancies between studies including residual confounding, varying exposure definitions (edema was a diagnostic requirement for preeclampsia in their study), or genetic and environmental differences in the populations studied (139). Overall, there is some evidence that infant sex and length of gestation may be effect modifiers of the association between preeclampsia and breast cancer, but results are not consistent across studies. Only two studies of placental characteristics, have been conducted, one of which was very small. However, this area of research is of interest because placental

characteristics are related to several other perinatal factors (including hypertensive disorders of pregnancy), as well as steroid hormone and HCG production during pregnancy, and hence may provide additional clues on the role of pregnancy hormones in breast cancer.

4.4 Commentary

The protective effect of preeclampsia and/or PIH on breast cancer risk may be mediated through lower levels of estrogen during pregnancy (65, 100, 117, 137), though studies of estriol and/or estradiol maternal blood levels during preeclamptic pregnancies have been inconsistent (98, 100, 101, 142-146). Other hormonal factors that have been implicated in breast cancer mechanisms and found to be altered in preeclamptic pregnancies include higher levels of progesterone (98, 117, 143), androgens (100, 101, 117, 142, 147), and HCG (117, 148). However, a recent US study found limited evidence for associations between androgens, estriol, and estradiol with blood pressure during the second and third trimester, as well as change in blood pressure between trimesters (149). Lower levels of maternal IGF-I during pregnancy may also play a role (117, 137), but studies of maternal serum IGF-I and preeclampsia/PIH are inconsistent and associations may depend on severity and/or length of gestation for preeclamptic pregnancies (108, 150-155). Alpha-fetoprotein (AFP), which may have "anti-estrogenic" effects in the breast tissue (117, 131), has been shown to be elevated in women with preeclampsia/PIH (156-158). This protein has been postulated to mediate the protective effect of preeclampsia/PIH on breast cancer risk (65, 85 , 117). However, not all studies have reported

increased AFP in pregnancies with hypertension (148) and a small cohort study did not find that AFP explained a decrease in breast cancer risk associated with elevated mean arterial pressure during pregnancy (83).

Alternative mechanisms to explain the association between preeclampsia/PIH and breast cancer have been postulated (117, 140, 159). Angiogenesis, (i.e., new blood vessel growth), is involved in tumor growth and metastasis (160). Preeclamptic pregnancies have been shown to be characterized by high levels of anti-angiogenic factors (e.g., soluble fms-like tyrosine kinase-1) and low levels of pro-angiogenic factors (e.g., vascular endothelial growth factor, placental growth factor) (161), which could lead to a reduction in cancer risk (140). Gago-Dominquez and colleagues postulated that lipid peroxidation may protect against breast cancer, possibly through inhibition of cell proliferation as well as increased cell differentiation and apoptosis. They hypothesized this may be a mechanism by which preeclampsia protects against subsequent breast cancer, given studies have found increased lipid peroxidation in preeclamptic pregnancies.

5. Multiple Births

5.1 Introduction

Multiple births may reflect an altered maternal hormonal environment, including elevated levels of estrogens, progesterone, HCG, and AFP, which may influence subsequent breast cancer risk (103, 162, 163). We use the term "multiple births" to indicate both twins only or twins and higher order births, with exact exposures definitions shown in Table 2. About 5% of multiple births in the

US in 2006 were triplets or higher order multiples (164). Multiple births may be spontaneous or due to the use of assisted reproduction. A study of 13,206 pregnant women in the US during 1986-1991 reported that about 35% of twins and 77% of higher order births were attributable to the use of assisted reproduction (165). Women with multiple births are at increased risk for PIH and GDM, and their infants are more likely to be born preterm and have lower birthweights (164, 166-169). Factors associated with spontaneous multiples include race/ethnicity, geographic location, maternal body size, maternal age, maternal nutrition, parity, being born a twin, and family history of twinning (164, 166, 170-172).

5.2 Epidemiologic Studies

We identified nine cohort (71, 76-81, 173, 174) and seven case-control (65-67, 72, 73, 75, 175) studies of the association between multiple births and breast cancer (Table 2.2). Several studies were of large sample size, and hence could examine exposure in any birth, a last birth, or prior to the last birth as well as effect modification by age at index birth, time since index birth or infant sex. The source of exposure data (e.g., birth records, maternal interview) is available in the Table 2, but not discussed below given that the exposure is unlikely to be misclassified regardless of data source.

Cohort studies. Three large cohort studies have reported a decreased risk of breast cancer associated with a delivery of multiples for any birth, a last birth, or a birth prior to the last birth (77, 78) The largest of these studies was conducted in Sweden with 19, 368 cases. This study examined results by age (< 55 years, ≥

55 years) and found the protective effect was limited to women < 55 years and was only significant for exposure in any birth, OR = 0.85, 95% CI: 0.74-0.98. The two other cohort studies were among women ≤ 56 years of age. A fourth cohort study of women < 50 years of age with 6,309 cases reported a small non-significant decrease in risk for exposure in any birth (76, 173). 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.

Case-control studies. One US case-control study of women aged 20-54 years with 3,918 cases reported a significant decrease in breast cancer risk associated with delivery of multiples in a last birth only (72). Other case-control studies of both younger and older women have found limited evidence for an association between multiple births and breast cancer (66, 73, 75). In contrast, a US case-control study in New York State with data on first births only reported a non-significant elevation in risk of breast cancer for having a multiple birth (65).

Several studies have examined potential effect modifiers of the association between multiple births and breast cancer. The US case-control study of first births in New York State 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; > 6 years) (65). Findings for the large Danish cohort study of latest births reported an elevated risk for mothers diagnosed with breast cancer <5 years after the birth (RR = 1.8; 95% CI: 1.1-2.8) (79). However, other studies that have investigated

time since a multiple birth (66, 72, 73, 75-77), or age at index birth (66, 72, 73, 75-77) have not found evidence for effect modification.

In addition to age at birth, time since birth, and birth order, other important confounding and/or modifying factors that have been examined include use of infertility treatments, length of gestation, and offspring sex. Studies could not distinguish between spontaneous multiple births or multiples due to assisted-reproduction, but three studies reported similar results when they either excluded women who reported infertility treatments or a history of infertility problems, or adjusted for these factors (66, 72, 73). Only one study considered gestational length; results were similar after adjustment (72). Studies that have examined same sex compared to different sex (a marker of zygosity) have found similar results (72, 73, 78). Some studies have examined multiple births with all females compared to all males, based on the hypothesis that infant sex is associated with hormonal differences during pregnancy (66, 76). Two studies reported that the non-significant protective effect of a multiple birth was limited to women who delivered all females compared to all males (66, 76).

5.3 Summary

Based on three large European cohort studies, multiple births appear to decrease risk of breast cancer among younger women, with possible modification by birth order (last, any), but results are inconsistent. The significant increase in risk for the first five years following a multiple birth, reported in a US case-control study of first births and in a large prospective cohort study in Denmark of last births, however, suggests the protective effect is not universal

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and/or may depend on characteristics of the birth. The determinants of natural multiples, spontaneous multiples, and zygosity may differ (discussed below); hence, future studies that differentiate between the type of multiple births may help clarify the association between multiple births and breast cancer.

5.4 Commentary

Postulated mechanisms to explain the association between multiple births and breast cancer involve the role of altered levels of maternal hormonal factors found in multiple pregnancies (65, 66, 72, 76-78, 80, 174). Elevated levels of estrogens (104, 162, 176), progesterone (163), HCG (103, 104, 177) , and AFP (103, 104, 110), have been found in multiple pregnancies compared to singleton pregnancies. Investigators have hypothesized that the elevated estrogens found in women with multiple pregnancies may help explain the increased short-term risk found in some studies of parous women with multiple births (65, 74, 79). Alternatively, elevated maternal HCG, progesterone, or AFP may mediate the protective effect of multiple births on breast cancer risk in parous women (65, 66, 72, 76, 77, 80, 174). Other researchers have proposed that protective effect may also be due to differences in hormone levels during the menstrual cycles and post-pregnancy in women who deliver multiples (78). For example, SHBG has been found to be higher in premenopausal women with a history of twins as compared to women with only singleton births (162, 178).

The association between multiple births and breast cancer may also be explained by characteristics of women who have multiple births that are also associated with breast cancer (77, 78). As noted above, factors associated with

spontaneous multiple births include race/ethnicity, maternal body size, maternal age, maternal nutrition, parity, being born a twin, and family history of twinning. Further, women with a multiple pregnancy are at increased risk for PIH, GDM, preterm delivery, and lower fetal growth. Though controversial, some studies have shown that infertility drugs may be associated with breast cancer risk (179), and it is not known if multiple births due to assisted-reproduction (compared to spontaneous multiple births) have different influences on breast cancer risk. Breastfeeding is a protective factor for breast cancer (180), and a few studies were able to adjust for this factor (72, 73). The role of breastfeeding, however, may be more complex given evidence that breastfeeding rates are lower in women with multiple births who deliver preterm compared to women who deliver full-term multiples or singletons (181).

6. Gestational Diabetes

6.1 Introduction

Gestational diabetes is defined as any degree of glucose intolerance with onset or first recognition during pregnancy and in the US is usually screened for at 24-28 weeks of pregnancy (182). Prevalence estimates for GDM vary (2-8%) depending on the population, and consistent with the high correlation between obesity and GDM as well as the increase in obesity in the US, rates of GDM appear to be also increasing (183, 184). Risk factors for GDM include maternal obesity, family history of diabetes, personal history of glucose intolerance, prior delivery of a high birthweight infant, and non-White race/ethnicity (185, 186)

6.2 Epidemiologic Studies

Few epidemiologic studies have examined the association between GDM and breast cancer (63, 66, 90, 91, 187) (Table 2.3). We found one registry-based cohort study, one cohort study that used medical records for exposures, and two interview-based case-control studies. One very small record-based study of maternal fasting plasma glucose and a hospital admission for breast cancer is included in Table 3, but not discussed below.

Cohort studies. Two record-based cohort studies (63, 90) have examined the association between GDM and breast cancer. One of these studies did not find an association, though had only 10 exposed cases and included all types of diabetes during pregnancy (gestational or pregestational (type I, type II)) (63). In contrast, in the Jerusalem perinatal cohort study, which used medical records for exposure data (90), reported a significant increase in risk of breast cancer for history of GDM among women ≥ 50 years, but not among women < 50 years was.

Case-control studies. Two US case-control studies of self-reported GDM (66, 91) reported conflicting findings. One study with 1,235 cases did not find an association between GDM and breast cancer risk (66), though when the study examined modification by years since last birth (< 5 years, and ≥ 5 years) it found a non-significant protective effect of GDM in the first five years and a non-significant elevated long-term risk (66). The other study, with 2,319 cases conducted among non-Hispanic White and Hispanic women, reported an inverse association between self-reported GDM and breast cancer among both pre- and postmenopausal women; results were only significant among postmenopausal

women (91). The authors further stratified the findings by age at onset of GDM (i.e., age at index delivery), and found an inverse association for women < 35 years and a positive association for women ≥ 35 years (91).

6.3 Summary

To date, studies of the association between GDM and breast cancer are few. Results include a significant protective effect in a large US case-control study conducted in the Southwestern states which appears to be limited to women < 35 years at index birth, a significant increased risk for women in the large Jerusalem Perinatal Cohort study, and no association in a US case-control study and Swedish cohort study. Given these discrepant findings, further studies are needed on this association. In particular, studies that also have information on post-pregnancy diabetes and biomarkers associated with diabetes development may provide more data to determine if GDM is an independent risk factor for breast cancer.

6.4 Commentary

The association between type 2 diabetes outside of pregnancy and breast cancer risk has been investigated in many studies, with evidence for a positive association that is more consistent and stronger among postmenopausal women (188). Several biological mechanisms have been proposed to explain an association between type 2 diabetes and breast cancer risk. For example, type 2 diabetes is characterized by elevated levels of insulin and increased sex hormones as well as decreased sex hormone binding globulin (SHBG) (188, 189). These increased hormonal factors could activate cell pathways that lead to

increased cellular proliferation and decreased apoptosis (189). Hyperglycemia, another feature of diabetes, may also be related to increased risk of breast cancer, and glucose may promote cell growth (188). Several of these mechanisms may provide reasoning for an increased risk of breast cancer following GDM. In addition, women with GDM are more likely to develop type II diabetes later in life (190), which could help explain an association between GDM and breast cancer. Finally, given that obesity is important in both the development of GDM (185), type 2 diabetes (189), and pre- and postmenopausal breast cancer, future studies with information on pre-pregnancy BMI, gestational weight gain, and pre and post-menopausal BMI could shed light on inconsistent findings.

7. Pregnancy Weight Gain

7.1 Introduction

Researchers have hypothesized that weight gain during periods of hormonal change over the life course (e.g., menarche, pregnancy, lactation, menopause) may be of particular importance in relation to subsequent breast cancer risk (191-193). Higher pregnancy weight gain may reflect increased exposure to maternal hormonal factors during pregnancy (e.g., estrogens), which could increase breast cancer risk(86). However, the study of pregnancy weight gain is complicated by the interrelationships between pre-pregnancy body mass, postpartum weight change, and adult adiposity.

7.2 Epidemiologic Studies

Few studies of the association of pregnancy weight gain and breast cancer have been published (66, 86, 87, 120, 194, 195) (Table 2.4). Two of the six studies did not report measures of association (120, 194). Measurement of pregnancy weight gain was via self-report in three studies and from hospital records in one study.

Cohort studies Two cohort studies of Finnish women with limited sample size (< 150 cases), (86, 87) have examined the association between pregnancy weight gain and breast cancer. One of these, with about 50% follow-up of the original cohort, reported a positive association between estimated weight gain during pregnancy > 15 kg (reference: 11-15 kg) and breast cancer risk. In stratified analyses, the association was limited to postmenopausal women, though authors noted that sample size for premenopausal cases was small (< 25 cases). To account for current BMI, the authors conducted a nested case-control study among the cohort for women with available hospital records on weight and height close to the time of diagnosis for cases (about 50% had data available), and found a non-significant positive association between pregnancy weight gain and breast cancer, adjusted for later BMI (87). The other study found no association between pregnancy weight gain and breast cancer risk in among predominantly premenopausal women (86). Neither study reported information on birth order with exposure (e.g., first, last)

Case-control studies. Three US case-control studies, of women aged 35-79 years (194), 20-44 years (66), and < 50 years (195), have reported limited evidence for an association between breast cancer risk and pregnancy weight

gain in the first pregnancy (66, 194), or most recent pregnancy (195) or for maximum weight gain in all pregnancies (66).

7.3 Summary

At present, there is limited evidence for an association between pregnancy weight gain and subsequent breast cancer risk, with the exception of perhaps an association among postmenopausal women, which was reported in 1 study with missing data on a high proportion of the cohort at follow-up. It is not clear, however, if this association is due to the known relation between high BMI, weight gain, and central adiposity and postmenopausal breast cancer risk (193), given that women who gain more weight during pregnancy retain more weight postpartum (196) and may also retain more weight into menopausal years (197, 198). Further, if the association is hypothesized to be due to the increase in adipose tissue during pregnancy, increased body fat may be a better exposure measure than pregnancy weight gain, which reflects several components (fetus, placenta, amniotic fluid, increased blood volume, and adipose tissue) (199).

7.4 Commentary

Researchers have hypothesized that pregnancy weight gain may increase risk due to an altered hormonal environment during pregnancy, in particular, due to elevated estrogens (87). Investigations of maternal serum estrogens and pregnancy weight gain, however, 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 (200), though subsequent studies have reported null results (96, 201-203). Alternatively, the underlying hormonal

mechanism may be due to lower levels of SHBG (96, 203) or progesterone (96) that have been reported in women with high weight gain during pregnancy. Recently, an animal study has reported that excessive weight gain during pregnancy increased carcinogen-induced breast tumors and the findings could not be accounted for via altered hormone levels of leptin, estradiol, or IGF-I (204). Another possible mediator may be hyperinsulimia, which may be associated with increased breast cancer risk (189), and also with higher weight gain during pregnancy (191), though the relationship is complex and the role of pre-pregnancy BMI, weight change following childbirth, as well as current body size should be considered.

8. Fetal Growth

8.1 Introduction

Fetal growth may reflect circulating levels of maternal hormones or growth factors important in breast cancer etiology (93, 95, 96, 105, 106, 109). Infant birthweight is influenced by both duration of gestation and rate of fetal growth (205). Fetal weight increases during pregnancy, with the highest weight gain in the third trimester, due to increased fetal fat mass, and a peak at about 34-35 weeks (206, 207). Weight at birth (birthweight) alone or birthweight adjusted for gestational age is used to estimate fetal growth because of the difficulties in directly measuring the rate of fetal growth in-utero using prenatal ultrasounds (208, 209). One method of adjustment for gestational age is to simply include gestational age as a covariate in the model. Another approach is to adjust for gestational age using reference birthweight percentiles for each gestational week

or to use the fetal growth ratio which is calculated by dividing the birthweight by a reference median birthweight for the given gestational age (210). A thorough discussion of the etiology of fetal growth is beyond the scope of this paper. Briefly, contributors to fetal growth that also may play a role in breast cancer etiology include maternal anthropometry (height, pre-pregnancy body mass index (BMI), gestational weight gain), maternal birthweight, parity, infant sex, race, physical activity, medical complications during pregnancy (e.g., preeclampsia, gestational diabetes), smoking, multiple births, maternal age, and socioeconomic status (210-213).

8.2 Epidemiologic Studies

Six studies have examined fetal growth and breast cancer (63, 65, 79, 81, 120, 175) (Table 2.5). Two of these studies did not report measures of association, and are not discussed further (81, 120). The remaining four studies were all registry-based with three studies adjusting for gestational age as a covariate and one study using birthweight alone as a proxy for fetal growth.

Cohort studies. Two cohort studies have examined the association between fetal growth and breast cancer. A cohort study in Sweden with about 2,200 cases reported a significant increase in breast cancer risk per 500 gram increase in birthweight for a first birth (63). This study adjusted for gestational age as a covariate (weeks: <37, 37, 38, 39, 40, 41, ≥ 42). A second cohort study in Denmark with 3,874 cases reported a non-significant elevation in breast cancer risk associated with delivery of an infant weighing >3500 grams compared to ≤

3000 grams (79). This study adjusted for extremely preterm delivery (< 32 weeks, ≥ 32 weeks, unknown).

Case-control studies. Two population-based case-control studies have examined fetal growth and breast cancer risk. A US registry based case-control study of first births reported a non-significant reduction in breast cancer associated with very low (< 1500 grams) and very high (≥ 4500 grams) birthweight (65). This study adjusted for gestational age as a covariate (weeks: < 32, 32-36, ≥ 37). A second case-control study of birthweight alone and breast cancer reported a non-significant increased risk for lower and higher birthweight in any birth (175).

Overall, consideration of effect modification by time or age at index birth has not been reported. The exception is the cohort study conducted in Denmark, where authors reported some evidence for a stronger increase in risk for the first five years following delivery. No studies reported results by menopausal status--though study populations were primarily among younger women (i.e., < 58 years of age).

8.3 Summary

In summary, evidence from two registry-based cohort studies that adjusted for gestational age suggest high fetal growth in a first or last birth may be associated with as small (~10%) increased risk of breast cancer. However, two registry-based case-control studies, one of first births and one of any births reported conflicting findings. The two case-control studies included women with

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multiple births and one study did not adjust for gestational age, which could be one factor to account for the differences.

8.4 Commentary

The association between high fetal growth and increased breast cancer is biologically plausible, given that high rates of fetal growth may be associated with elevated maternal estrogens and IGF-I levels during pregnancy (79). Most studies have found that fetal growth is positively associated with maternal estriol levels (primarily of fetal origin), mainly in the third trimester (93, 95, 96, 109, 214), while the evidence has been inconsistent for an association with maternal estradiol (93, 97, 214), which has been consistently implicated in breast cancer risk (215). Other hormones that may mediate a positive association between fetal growth and breast cancer include higher maternal serum levels of IGF-1 or low levels of IGF-binding protein-1, inconsistently associated with fetal growth/birthweight (particularly during late gestation) (105-107, 111) or lower levels of prolactin (109).

The observed association between fetal growth and breast cancer may be due to non-measured environmental, social, or genetic factors. Some key factors associated with both fetal growth and possibly breast cancer include maternal height, pre-pregnancy weight, maternal birthweight, parity, gestational weight gain, maternal age, smoking, hypertensive disease of pregnancy, and infant sex (211, 216). Cnattingius and colleagues did adjust for several maternal factors (maternal height, maternal BMI, pregnancy-induced hypertensive diseases), which were attenuated compared to the age-adjusted associations. In addition,

they also adjusted for placental weight (fetal growth depends on placental size (217)), which further attenuated results. Finally, no study to date has estimated fetal growth using approaches that are more appropriate than simple adjustment for gestational age as a covariate (e.g., reference birthweight percentiles for each gestational week).

9. Infant Gestational Age at Delivery

9.1 Introduction

Induced and spontaneous abortion, which reflect pregnancy interruption in early gestation (primarily first trimester), and breast cancer have been well-studied (218, 219). Few studies, however, have examined breast cancer and variation in gestational length in the third trimester of 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 a time of increasing hormone levels (65, 220). Variation in infant gestational age at delivery has been examined using established clinical cut points for preterm delivery (i.e., very preterm delivery (VTPD), defined as < 32 weeks gestation or preterm delivery (PTD), defined as < 37 weeks of gestation), or other arbitrary categorical cut points (see Table 6). From 1996-2006, the percentage of live singleton births in the US that were preterm increased from 9.7% to 11.1%, while the percentage of very preterm births was stable at 1.6% (221). PTD may broadly be divided into two types, spontaneous or due to medical intervention. Briefly, key risk factors for PTD include Black race, low and high maternal ages, lower socioeconomic status,

multiple births, history of prior preterm birth, pregnancy complications (e.g., preeclampsia, diabetes), cigarette smoking, and low or high pre-pregnancy BMI (222, 223).

9.2 Epidemiologic Studies

We identified seven studies of infant gestational age at delivery and breast cancer (63, 65-70) (Table 2.6). Six studies were registry-based and one study used an in-person interview for exposure assessment. Most birth registry studies did not report how they estimated gestational age. Two studies reported defining gestational age using the date of the last menstrual period (LMP) supplemented with the clinical estimate only (67) and both the clinical estimate and ultrasound data (68), while one study reported using the clinical estimate alone (65).

Cohort studies. Three of four registry-based cohort studies conducted in Sweden, Norway, or Denmark reported evidence for an increased risk of breast cancer associated with delivery of an infant at earlier gestational ages. Two cohort studies reported a significant trend for increasing breast cancer risk with decreasing gestational age in a last birth (68) and a first birth (70). Both of these studies reported increased risk for VPTD; the estimate for the smaller cohort (1,363 cases), but not the larger (5,474 cases) was significant. A third large cohort study reported a significant increase in breast cancer risk for PTD in a first birth among women ≥ 40 years of age, but not for women < 40 years of age (69).

Case-control studies. One small (275 cases) US registry-based case-control study conducted in 1983 reported a non-significant reduction in risk associated

with PTD and delivery at <30 weeks in a first birth (67), while a recent larger US registry-based case-control study for first births reported a non-significant increased risk for VPTD, but not delivery at 32-36 weeks of gestation. Finally, a population-based case-control study using maternal self-report for length of gestation did not find any association with breast cancer risk using varying definitions and examining exposure in first birth or ever (66).

Few studies have examined breast cancer risk associated with gestational age by effect modifiers. Hsieh and colleagues reported that the increased risk associated with PTD in a first birth may be limited to long-term risk (≥ 10 years since delivery) (69). Melbye and colleagues examined effect modification by attained age, age at index birth, or parity, but analyses were based on small sample sizes which limit interpretation (68). Other studies did not examine effect modification by age at index birth, years since index birth, or parity. Most studies were among younger women (< 57 years) (63, 65-68) and only one study reported results stratified by age (Hsieh et al., 1999) (69) with a meaningful sample size.

9.3 Summary

Based on findings from three large cohort and one large case-control study, earlier gestational age, may increase breast cancer risk, with a VPTD resulting in about a 20-70% increase in risk. However, one early small registry-based case-control study found a non-significant decreased risk for earlier gestational ages, and two studies which did not report effect estimates (one US case-control study using maternal self report and one Swedish registry-based

cohort study) reported null findings. Limited data exist, however, on whether the association is modified by birth order (e.g., first, last), age at birth, or time since birth. Further, it is not clear if results are modified by age/menopausal status with only one study reporting findings stratified by age.

9.4 Commentary

Researchers have proposed that PTD/VPTD may increase breast cancer risk due to the lack of complete terminal differentiation of the breast tissue during pregnancy (65, 68). Hormonal factors increase fairly progressively until the end of pregnancy, with the exception of HCG (224). The elevated levels of gestational hormones, coupled with lack of complete terminal differentiation of the mammary gland, could increase the susceptibility of the breast to the proliferating effects of the hormones, and explain the increased breast cancer risk following a PTD and VPTD (64, 65). Further, in prospective studies, shorter length of gestation at delivery (in continuous weeks) (96) and a PTD (225) have been found to be positively associated with maternal estrogen levels measured earlier in the index pregnancy.

The etiology of PTD is complex. Risk factors for either induced or spontaneous PTD that may also influence breast cancer risk include low or high maternal BMI, cigarette smoking, maternal age extremes, low SES, race/ethnicity, preeclampsia, multiple gestations, and a previous PTD (211, 216, 223). Most studies that have reported on PTD and breast cancer risk, have only adjusted for age, parity, and/or age at first birth. The fourth cohort study, which reported null findings, did have information on several maternal factors (body

size, conditions of pregnancy, smoking), but did not report the measure of association. The larger registry-based case-control study was able to additionally adjust for education, race and other pregnancy characteristics (e.g., preeclampsia), however, they adjusted for birthweight in their final fully adjusted model as well, which limits interpretation of the final model.

10. Infant Sex

10.1 Epidemiologic Studies

Maternal hormonal profiles during pregnancy may vary by infant gender, which could influence subsequent breast cancer risk (96, 226). We identified 7 original studies of infant sex and breast cancer (63, 65, 66, 76, 79, 88, 175) and two reports on additional analyses of the same cohorts (89, 127) (Table 2.7). Almost all studies (both cohort and case-control), reported no association for infant sex and breast cancer (63, 65, 66, 76, 175), including studies that examined the role of infant sex in the short- and long- term effects of a last birth (79, 89, 127). The one exception reported a reduced risk for women who had male offspring, in particular among women with two or more births who reported all males (compared to all females) and were < 40 years of age at diagnosis (88). However, they did not consider birth order in their study (e.g., sex in last birth) or modification of results by the time since birth on breast cancer risk (127).

10.2 Summary

Epidemiologic evidence to date provides little support for an overall association between infant sex and breast cancer, though this factor may be an

effect modifier for the associations between other perinatal factors (e.g., multiple births, preeclampsia) and breast cancer.

10.3 Commentary

Researchers have hypothesized that differences in gestational hormonal profiles of mothers of female compared to male offspring may influence breast cancer risk (128). However, as shown above, the epidemiologic literature provides limited evidence to suggest an association between infant sex and breast cancer. Studies, however, have shown some evidence for a role of infant sex as a modifier of the effects of other perinatal factors and breast cancer risk, namely, preeclampsia (128, 138) and multiple births (66, 76). Briefly, HCG levels in the third trimester have been shown to be higher for women carrying female fetuses (226), while levels of progesterone have been found to be lower (96). Higher levels of AFP have been reported for women carrying males fetuses, though results have been inconsistent (227-229).

11. Conclusion

Over the past thirty years, epidemiologic evidence has accumulated for associations between perinatal factors and maternal breast cancer. Preeclampsia and/or PIH is associated with a reduction in breast cancer risk in most studies, with some evidence for a stronger reduction in risk for women with male as compared to female preeclamptic pregnancies, which may depend on additional pregnancy characteristics. One exception is the Jerusalem Perinatal Cohort study, which reported a significant increase in breast cancer risk for women with a history of preeclampsia. Large cohort studies provide evidence

that having a multiple birth may protect against breast cancer, though two studies, including a large Danish cohort study reported a significantly increased risk in the first five years following delivery of a multiple birth. Few studies of GDM and breast cancer have been conducted, with a possible increased risk of breast cancer found in one large cohort in Israel and a reduced risk of breast cancer for GDM at < 35 years of age in a large case-control study in the Southwestern US. Pregnancy weight has also been little studied and a summary of findings suggests pregnancy weight gain itself may not be independently associated with breast cancer. Two large registry-based cohort studies suggest high fetal growth may slightly increase risk of breast cancer. Three large registry-based cohort studies and one registry-based case-control study suggest that delivery at earlier gestational ages, in particular a VPTD, may increase breast cancer risk. Infant sex does not appear to be associated with breast cancer.

One rationale for the study of perinatal factors and maternal breast cancer is that these exposures are proxies of the maternal hormonal milieu during pregnancy, given that it is difficult to directly study modification of the maternal hormonal environment and later breast cancer (though studies of pregnancy hormones and later breast cancer risk have begun to accumulate (230-234)). It has been shown, however, that some perinatal exposures may not accurately reflect hormonal exposures during pregnancy (83, 214). Researchers have also noted that comparison of hormonal factors during pregnancy between populations may be biased due to the variability in plasma volume expansion

during pregnancy (235). Further, more data on hormonal factors during pregnancy and the perinatal exposures is needed.

In conclusion, additional research in the area of perinatal factors and maternal breast cancer is needed, including studies of perinatal exposures and breast cancer risk with ample sample size to consider jointly several key effect modifiers (e.g., time, age, birth order, menopausal status) with data on all potential confounders, as well as studies of the maternal hormonal and metabolic profiles of exposed women during and following pregnancy.

12. Search Strategy

Search terms and limits used for PUBMED searches

12.1 Search terms used to conduct searches in pubmed

Used keywords and medical subject headings in PUBMED:

a. Breast Cancer: Breast Neoplasms [Mesh] OR ("breast cancer")
   i. Every search for each exposure of interest included the medical subject headings under "breast neoplasms" and the keyword "breast cancer".
b. Fetal-growth and birthweight: birthweight OR birthweights OR "birth weight" OR "fetal growth"
c. 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"
d. 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"
e. Preeclampsia: preeclampsia OR pre-eclampsia OR eclampsia OR toxemia OR preeclamptic OR pre-eclamptic
f. Pregnancy-induced hypertension: "pregnancy-induced hypertension" OR (pregnancy and hypertension) OR (pregnancy and "high blood pressure") OR "pregnancy-related hypertension"
g. Placental Characteristics: placenta OR placental OR "placental characteristics"

h. 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"
i. Pregnancy weight gain: (weight and pregnancy) OR ("weight gain" and pregnancy) OR "pregnancy weight gain"
j. Offspring sex: ((offspring and sex) or (offspring and sex))
k. Overall terms: "perinatal" OR "pregnancy factors" or "pregnancy characteristics" OR "prenatal" OR ("birth characteristics" and offspring) OR "pregnancy conditions" OR "pregnancy-related factors"

12.2 Search Limits:

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

13. Tables

Table 2.1. Preeclampsia, pregnancy-induced-hypertension, and maternal breast cancer risk[a]

Study	Study design[b]	Study population		Comparison	Measures of Association (95% confidence interval)	Comments
		Cases/ controls	Attained age (years)			
Polednak and Janerich,1983 (67) United States	Case-control Registry-based 1970-1976[c]	316/ 628	< 45	First birth: Preeclampsia/toxemia (yes vs. no)	RR = 0.28 (0.08-1.00)[d]	Matched on location and time of first delivery. Adjusted for maternal age at first birth.
Thompson et al., 1989 (85) United States	Case-Control In-person interview 1980-1982	4,668/ 4,653	20-54	Before the end of the most recent term birth: Hypertension (yes vs. no)	OR = 0.73 (0.59-0.92)	Matched on attained age and geographic area. Adjusted for attained age, geographic region, parity, age at first birth, total during of breastfeeding.

Table 2.1. Continued

Troisi et al, 1998 (66) United States	Case control In-person interview 1990-1992	1,236/ 1,162	20- 44	Any birth: Toxemia vs. never PIH vs. never	RR = 0.81 (0.61-1.1) RR = 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.
Innes and Byers, 2004 (65) United States	Case-control Registry-based 1977- 1995	2,522/ 10,052	22-55	First birth: Preeclampsia (yes vs. no)	OR = 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, multifetal gestation. Additional analyses were conducted to examine the role of offspring sex in the relation between preeclampsia and breast cancer (128), results are discussed in the text.
Terry et al., 2007 (137) United States	Case-Control In-person interviews 1996-1997	1,310/ 1,385[e]	20-98	Any birth: Preeclampsia vs. never Pregnancy-related	By menopausal status: Premenopausal: OR = 0.99 (0.52-1.88) Postmenopausal: OR = 0.63 (0.41-0.98) Premenopausal:	Matched on attained age. Adjusted for attained age, age at first birth, BMI at age 20 and at the reference date, parity, smoking status, age at menarche, lactation, family history of

Table 2.1. Continued

				hypertension vs. never	OR = 0.89 (0.51-1.56) Postmenopausal: OR = 0.78 (0.51-1.19)	breast cancer, ethnicity, education, and preeclampsia or PIH as appropriate.
Richardson et al., 2000 (83) United States	Cohort In-person interview, medical records 1959-1994	205/ 337	17-44[f]	Index birth: Preeclampsia alone PIH alone Both	 OR = 1.57 (0.63-3.88) OR = 0.79 (0.40-1.57) OR = 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. Can assume never. It was not indicated if the index birth was first/last etc.
Vatten et al., 2002 (84) Norway	Cohort Registry-based 1967-1998	5,474/ 689,183	< 30-80	First birth: Preeclampsia and/or PIH vs. neither	By attained age < 50 years: RR = 0.81 (0.7-0.9) ≥ 50 years: RR = 0.81 (0.6-1.1)	Adjusted for attained age, calendar period of diagnoses, age at first birth, and parity.
Vatten et al., 2007 (138)[g] Norway	Cohort Registry-based 1967-2002	9,160/ 691,846	NR	First birth: Preeclampsia and/or PIH vs. neither	Overall: RR= 0.86 (0.78-0.94) By offspring gender Male: RR = 0.79 (0.60-0.90) Female: RR = 0.94 (0.82-1.06)	Adjusted for attained age, age at first birth, length of gestation, parity, marital status and offspring sex (sex only for overall estimate).
Calderon-	Cohort	1,624/	<20-	Any birth:		Adjusted for age at first

Table 2.1. Continued

Margalit et al., 2008 (139)[h] Israel	Medical records 1964-2004	NR	≥40[i]	Preeclampsia vs. never	HR= 1.37 (1.06-1.78)	birth, and parity.

[a]Studies that did not report covariate-adjusted measures of association are not summarized in the Table (81) (preeclampsia only), (63) (hypertensive disorders of pregnancy)). Also, one study that used participants of the Child Health and Development cohort, as did Richardson et al., 2000 (83), looked at preeclampsia only, but did not report the covariate-adjusted measure of association and only 2 cases had preeclampsia (120).

[b]Years indicate years of data collection through cancer diagnosis/follow-up (e.g., year of first birth registry record to year of last follow-up) if available.

[c]When cancer was diagnosed- do not provide when birth records were available.

[d]This is a 90% confidence interval.

[e]Sample size for pregnancy-related hypertension was 1,278 cases and 1,319 controls.

[f]Age range of participants during the Child Health and Development enrollment period, 1959-1966, followed until 1994.

[g]This study includes overlapping data with Vatten et al., 2002 (84), but the study is not an update and used different exclusion criteria and modeling approaches, hence the two studies are summarized separately in the table.

[h]This study was an update of Paltiel et al., 2004 (82), with increased follow-up from June 1999 to December 31, 2004.

[i]Age of participants at enrollment (1964-1976), followed until 2004.

Table 2.2 Multiple births and maternal breast cancer risk[a]

Study	Study design[b]	Study population		Comparison	Measure of Association (95% confidence interval)	Comments
		Cases/ controls	Attained age (years)			
Polednak and Janerich 1983 (67) United States	Case-control Registry-based 1970-1976[c]	313/ 623	< 45	First birth: Twins verses singleton	RR = 1.33 (0.46-1.83)[d]	Matched on location and time of first delivery. No adjustment for covariates.
Jacobson et al., 1989 (72) United States	Case-control In-person interview 1980-1982	3,918/ 4047	20-54	Last birth: Multiple vs. all singletons Prior to last birth: Multiple vs. all singletons	OR = 0.60 (0.43-0.85) OR = 1.11 (0.79-1.57)	Matched on attained age and geographic area. Adjusted for age at first birth and parity.

Table 2.2. Continued

Nasca et al.,1992 (73) United States	Case-control Telephone interview 1982-1986	2,561/ 2,616	20-79	Any birth: ≥ 1 multiple birth vs. all singletons Last birth: Multiple vs. all singletons Prior to last birth: Multiple all singletons	By attained age: 20-55 years: OR = 1.10 (0.67-1.81) 55-79 years: OR = 1.01 (0.66-1.53) 20-55 years: OR = 0.97 (0.50-1.86) 55-79 years: OR = 1.00 (0.55-1.80) 20-55 years: OR = 1.31 (0.62-2.77) 55-79 years: OR = 1.02 (0.57-1.81)	Adjusted for attained age, county of residence, age at first birth and number of live births.
Dietz et al., 1995 (75) United States	Case-control Telephone interview 1988-1991	5,880/ 8,217	< 75	Any birth: ≥ 1 multiple all singletons Last birth: Multiple vs. all singletons Prior to last birth: Multiple vs. all singletons	OR = 0.94 (0.75-1.17) OR = 1.14 (0.80-1.62) OR = 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.
Olsen and Storm, 1998 (175)	Case-control Registry-based	5,213/ 20,025	NR[e]	Any birth: Twins vs. all singletons	OR = 1.07 (0.88-1.29)	Matched on parity, attained age, date of delivery, hospital of delivery. No adjustment for covariates.

Table 2.2. Continued

Denmark	1973-1993					
Troisi et al, 1998 (66) United States	Case control In-person interview 1990-1992	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	RR = 0.94 (0.58-1.5) RR = 0.80 (0.44-1.5) RR = 1.2 (0.56-2.6)	Matched on attained age and geographic area. Adjusted for age, site, race, parity/age at first birth, age at first birth.
Innes and Byers, 2004 (65) United States	Case control Registry-based 1977- 1995	2,522/ 10,052	22-55	First birth: Multiple vs. singleton	OR = 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, abruptio placentae.
Lambe et al., 1996 (77) Sweden	Cohort Registry-based 1958- 1990	19,368/ 100,459	≤ 65	Any birth: ≥ 1 multiple birth vs. all singletons	By attained age: < 55 years: OR = 0.85 (0.74-0.98) > 55 years: OR = 0.97 (0.76-1.29)	Matched on year and month of birth. Adjusted for parity and age at first-full term birth.

Table 2.2. Continued

				Last birth: Multiple vs. all singletons Prior to last birth: Multiple vs. all singletons	< 55 years: OR = 0.88 (0.74-1.03) > 55 years: OR = 0.94 (0.66-1.33) < 55 years: OR = 0.80 (0.62-1.03) > 55 years: OR = 0.97 (0.61-1.54)	
Murphy et al,, 1997 (78) Sweden	Cohort Registry-based 1961-1989	4,790/ 46,571	< 50	Any birth: ≥ 1 twin vs. all singletons Last birth: Twins vs. all singletons Prior to last birth: Twins vs. all singletons	OR = 0.71 (0.55-0.91) OR = 0.67 (0.49-0.91) OR = 0.81 (0.52-1.27)	Matched on maternal year of birth. Adjusted for parity and age at first-full term birth.
Albrektsen et al. 1995 (76) Norway	Cohort Registry-based 1955-1991	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	IRR = 0.89 (0.73-1.09) IRR = 0.85 (0.66-1.09) IRR = 0.96 (0.69-1.34)	Adjusted for attained age, birth cohort, number of full term pregnancies.

Table 2.2. Continued

Wohlfahrt and Melbye, 1999 (79) Denmark	Cohort Registry-based 1968-1994	9,495/ 989,004	< 58	Last birth: Multiple vs. singleton	RR = 1.1 (1.0-1.3)	Adjusted for attained age, calendar period, age at first birth, number of births, and extremely preterm birth.
Neale, et al., 2004 (80) United States	Cohort Registry-based 1912-1999	536/ 15,261	15-71[f]	Any birth: Multiple vs. all singletons	By attained age: ≤ 50 years: RR = 1.02 (0.69-1.51) > 50 years: RR = 1.03 (0.84-1.26)	Matched to unexposed on birth year and year of index delivery. Adjusted for number of pregnancies and age at first and last birth.
Neale, et al., 2005[g] (173) Sweden	Cohort Registry-based 1961-1996	6,309/ NR	< 50	Any birth: Multiple vs. all singletons	RR = 0.91 (0.75-1.09)	Adjusted for number of births, age at first birth, and date of birth of mother.
Ji et al., 2007[h] (174) Sweden	Cohort Registry-based 1958-2004	1,010[i]/ NR	NR	Any birth: Twin vs. all singletons	RR = 0.85 (0.74-0.98)	Adjusted for attained age, period, age at first childbirth, and number of pregnancies.

Table 2.2. Continued

[a]Studies that did not report covariate-adjusted measures of association are not summarized in the Table (81). 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) (71).

[b]Years indicate years of data collection and cancer diagnosis/follow-up (e.g., year of first birth registry record to year of last follow-up) if available.

[c]When cancer was diagnosed- do not provide when birth records were available.

[d]90% confidence interval.

[e]Age range of participants is not clear

[f]Age at enrollment, follow-up ended in 1999.

[g]This study used data that partly overlaps with the study population used by Lambe et al., 1996 (77), though there are differences in study design and exclusions, hence it is included as a separate study.

[h]This study used data that overlaps with Lambe et al., 1996 (77) and Neale 2005 (173), though they used difference in designs, exclusions, and analyses and do not mention that their study is using the same data.

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

Table 2.3. Gestational diabetes and maternal breast cancer risk[a]

Study	Study design[b]	Study population		Comparison	Measure of Association (95% confidence interval)	Comments
		Cases/ controls	Attained age (years)			
Troisi et al, 1998 (66) United States	Case control In-person interview 1990-1992	1,235/ 1,163	20- 44	Any birth: GDM vs. never	RR = 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 et al., 2007 (91) United States	Case control In-person interview 1999-2004	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: OR = 0.79 (0.52-1.21) < 35 years: OR = 0.61 (0.36-1.02) ≥ 35 years: OR = 1.41 (0.67- 2.98) Postmenopausal: OR = 0.60 (0.37-0.97) < 35 years: OR = 0.47 (0.27-0.82) ≥ 35 years: OR =1.33 (0.44-4.02)	Matched on attained age. Adjusted for attained age, BMI at 15 years, and number of full-term pregnancies.

Table 2.3. Continued

Cnattingius et al, 2005 (63) Sweden	Cohort Registry-based 1982-2001	2,216 /311,803	95% < 50	First birth: Diabetes vs. no[c]	RR = 1.07 (0.51-2.25)	Adjusted for maternal age at first birth, gestational age, infant sex, age at first birth, height, maternal BMI, smoking, family situation, country of birth, PIH, diabetes mellitus, vaginal bleeding in late pregnancy, parity, birthweight, placenta weight.
Dawson (187) Scotland	Cohort Registry-based 1979-1998	18/ 753	NR	Log of fasting glucose at about 32 weeks gestation 4.06-4.28 4.29-4.32 4.33-4.38 4.39-4.67	1.00 (REF) RR = 2.59 (0.23-28.75) RR = 7.18 (0.85-60.43) RR = 10.7 (1.34-85.01)	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)
Perrin et al., (90) Israel	Cohort Medical records 1964-2004	1,626/ 37, 926	43-94	Ever GDM vs. never,	By age at diagnosis: < 50: HR = 1.0 (0.5-2.1) ≥ 50: HR = 1.7 (1.1-2.5)	Adjusted for attained age, birth order at first observed birth, social class, ethnic origin, education, and immigration status.

[a] Studies that did not report covariate-adjusted measures of association are not summarized in the Table.

[b] Years indicate years of data collection and cancer diagnosis/follow-up (e.g., year of first birth registry record to year of last follow-up) if available.

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

Table 2.4. Pregnancy weight gain and maternal breast cancer risk[a]

Study	Study design[b]	Study population		Comparison	Measures of Association (95% confidence interval)	Comments
		Cases/ Controls	Attained age (years)			
Troisi et al., 1998 (66) United States	Case control In-person interview 1990-1992	954/889	20- 44	First birth: Weight gain (lbs) ≤ 22.5 22.6-27.5 27.6-32.5 32.6-37.5 37.6-42.5 > 42.5	 RR = 1.0 (0.78-1.4) 1.0 (REF) RR = 0.93 (0.68-1.3) RR = 1.10 (0.74-1.6) RR = 0.75 (0.52-1.1) RR = 1.10 (0.79-1.5)	Matched on attained age and geographic area. Adjusted for attained age, site, race, parity/age at first birth, current BMI, age at menarche, recent alcohol intake, and oral contraceptive use.
Kinnunen et al., 2004 (87) Finland	Cohort Hospital records 1954-2001	123/ 2,089	35-74	Any birth (see comments): Pregnancy weight gain (kg) >15 vs. 11-15	By menopausal status: Premenopausal: RR = 1.0 (0.40-2.48) Postmenopausal: RR = 1.80 (1.05-3.07)	Adjusted for age at menarche, age at first birth, age at index pregnancy, parity, and pre-pregnancy BMI. Index birth could have been a first birth, second birth, etc.
Hilakivi-Clarke et al., 2005 (86) Finland	Cohort Mailed survey 1990-1996	98/ 392	32-58	Any birth (see comments): Pregnancy weight gain (kg) <10	 1.0 (REF)	Matched on attained age and use of the intrauterine device Mirena. Adjusted for education, age at menarche, age at first birth,

Table 2.4. Continued

				10-15 16-20 20+	OR = 0.80 (0.44-1.47) OR = 1.0 (0.47-2.04) OR = 0.80 (0.27-2.13)	family history of breast cancer, change in BMI during adult life. Index birth could have been a first birth, second birth, etc.
Peterson et al., 2008 (195) United States	Case-control Telephone interview 1996-2001	1,706/ 1,756	< 50	Last birth: Percent weight change[c] < 20 20-28 ≥ 29	 1.0 (REF) OR = 0.92 (0.76-1.11) OR = 0.87 (0.72-1.07)	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.

[a]Studies that did not report covariate-adjusted measures of association are not summarized in the Table ((120) (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), (194) (reported no association for weight gain in first pregnancy and pre or postmenopausal breast cancer risk)).

[b]Years indicate years of data collection and cancer diagnosis/follow-up (e.g., year of first birth registry record to year of last follow-up) if available.

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

Table 2.5. Fetal growth and maternal breast cancer risk[a]

Study	Study design[b]	Study population		Birthweight (g)	Measure of association (95% confidence interval)	Comments
		Cases/ controls	Attained age (years)			
Olsen and Storm, 1998 (175) Denmark	Case-control Registry-based 1973-1993	5,213/ 20,025	NR[c]	Any birth: (< 2500) vs. (2500-4000)[d] (> 4000) vs. (2500-4000)[d]	OR = 1.27 (0.77-2.08) OR = 1.09 (0.80-1.49)	Matched on parity, attained age, date of delivery, hospital of delivery. No adjustment for covariates. Did not adjust for gestational age.
Innes and Byers, 2004 (65) United States	Case-control Registry-based 1977- 1995	2,522/ 10,052	22-55	First birth: < 1500 1500-1999 2000-2499 2500-3499 3500-3999 4000-4499 ≥ 4500	OR = 0.82 (0.39-1.74) OR = 0.96 (0.55-1.68) OR = 0.96 (0.72-1.28) 1.0 (REF) OR = 0.99 (0.88-1.12) OR = 0.94 (0.77-1.14) OR = 0.64 (0.38-1.06)	Matched on county of residence and date of delivery. Adjusted for attained age, maternal age at first birth, race, education, gestational age at delivery (< 32, 32-36, ≥ 37), infant sex, preeclampsia, abruptio placentae, multifetal gestation.
Wohlfahrt and Melbye, 1999 (79)	Cohort Registry-based	3874/NR	< 58	Last birth:[e] ≤ 3000 3000-3250 3250-3500	1.0 (REF) RR = 1.0 (0.9-1.1) RR = 1.0 (0.9-1.1)	Adjusted for attained age, calendar period, age at first birth, number of births, and extremely preterm birth

Table 2.5. Continued

Denmark	1968-1994			3500-3750 > 3750	RR = 1.0 (0.9-1.1) RR = 1.1 (1.0-1.2)	(<32 weeks, ≥ 32 weeks, unknown).
Cnattingius et al, 2005 (63) Sweden	Cohort Registry-based 1982-2001	2,216/ 311,803	95% < 50	First birth:[e] per 500 g increase ≥ 4500 vs. 2500-3499	HR = 1.11 (1.04-1.18) HR = 1.22 (0.86-1.73)	Adjusted for maternal age at first birth, gestational age (<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, parity.

[a] Results by menopausal status/age estimate of menopausal status were not reported for any of the studies, though studies include mainly premenopausal women (i.e., women of premenopausal age, 58 years of age or less). Studies that did not report covariate-adjusted measures of association are not summarized in the Table (81, 120).

[b] Years indicate years of data collection and cancer diagnosis/follow-up (e.g., year of first birth registry record to year of last follow-up) if available.

[c] Age range of participants is not clear.

[d] Reference group and parity at index birth not stated, we assume that the results are for any birth and that the reference group is 2,500-4,000.

[e] Limited to singleton births.

Table 2.6. Infant gestational age at delivery and maternal breast cancer[a]

Study	Study design[b]	Study population		Gestational age (weeks)	Measure of Association (95% confidence interval)	Comments
		Cases/ controls	Attained age (years)			
Polednak and Janerich, 1983 (67) United States	Case-control Registry-based 1970-1976[c]	275/ 550	< 45	First birth: < 30 vs. ≥ 37 < 37 vs. ≥ 37	 RR = 0.33 (0.06-1.00)[d] RR = 0.81 (0.45-1.38)[d]	Matched on location and time of first delivery. No adjustment for covariates.
Innes and Byers, 2004 (65) United States	Case-control Registry-based 1977- 1995	2,522/ 10,052	22-55	First birth: < 32 32-36 ≥ 37	 OR = 1.43 (0.90–2.28) OR = 0.91 (0.72–1.13) 1.00 (REF)	Matched on county of residence and date of delivery. Adjusted for attained age and maternal age at first birth.
Melbye et al., 1999 (68) Denmark	Cohort Registry-based 1973-1992	1,363/ 472,793	15-57	Last birth: < 29 29-31 32-33 34-35 36-37 38-39 40 ≥ 41	 RR = 2.11 (1.00-4.45) RR = 2.08 (1.20-3.60) RR = 1.12 (0.62-2.04) RR = 1.08 (0.71-1.66) RR = 1.04 (0.83-1.32) RR = 1.02 (0.89-1.17) 1.00 (REF) RR = 1.03 (0.90-1.18)	Adjusted for attained age, calendar period, parity, and age at first birth.

Table 2.6. Continued

				Ever VPTD vs. never	RR = 1.72 (1.14-2.59)	
Hsieh et al., 1999 (69) Sweden	Cohort Registry based 1973-1989	2,318/ 10,199	NR	First birth: <37 weeks vs. ≥ 37 weeks	By attained age < 40 years: OR = 1.03 (0.79-1.35) ≥ 40 years: OR = 1.30 (1.02-1.65)	Matched on maternal birth year. Adjusted for age at first birth.
Vatten et al., 2002 (70) Norway	Cohort Registry-based 1967-1998	5,474/ 689,183	< 30-80	First birth < 32 32-36 37-39 ≥ 40	 RR = 1.22 (0.97-1.53) RR = 1.11 (0.97-1.19) RR = 1.03 (0.98-1.05) 1.00 (REF)	Adjusted for attained age, calendar period of diagnosis, age at first birth, and total number of births.

[a]Studies that did not report covariate-adjusted measures of associations are not summarized in the Table (63, 66) and both reported null results for infant gestational age at delivery and maternal breast cancer.

[b]Years indicate years of data collection and cancer diagnosis/follow-up (e.g., year of first birth registry record to year of last follow-up) if available.

[c]When cancer was diagnosed- do not provide when birth records were available.

[d]90% confidence interval.

Table 2.7. Infant sex and maternal breast cancer risk[a]

Study	Study design[b]	Study population		Comparison	Measures of Association (95% confidence interval)	Comments
		Cases/ controls	Attained age (years)			
Olsen and Storm, 1998 (175) Denmark	Case-control Registry-based 1973-1993	5,213/ 20,025	NR	Any birth: Sex ratio (male to female)	OR = 1.01 (0.95-1.08)	Matched on parity, attained age, date of delivery, hospital of delivery. No adjustment for covariates.
Innes and Byers, 2004 (65) United States	Case-control Registry-based 1977- 1995	2,522/ 10,052	22-55	First birth: Female vs. male[c]	OR = 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, multifetal gestation.
Wohlfahrt and Melbye, 1999 (79) Denmark	Cohort Registry-based 1968-1994	9,495/ 989,004	< 58	Last birth: Female vs. male[c]	RR = 1.0 (1.0-1.0)	Adjusted for attained age, calendar period, age at first birth, number of births, and extremely preterm birth.

Table 2.7. Continued

Hsieh et al., 1999 (88) Sweden	Cohort Registry-based 1973-1989	2,328/ 10,250	16-64	Infant sex distribution among biparous women vs. all females[c]	By age at diagnosis < 40 years: All males: OR = 0.63 (0.49-0.81) Mixed sex: OR = 0.85 (0.69-1.04) ≥ 40 years: All males: OR = 1.13 (0.81-1.57) Mixed: OR = 1.09 (0.82-1.46)	Matched on maternal birth year. Adjusted for attained age and age at first birth.
Albrektsen et al., 1995 (76) Norway	Cohort Registry-based 1953-1991	4,782/ 797,487	20-56	First birth[c] Male vs. female Last birth[c] Male vs. female	IRR = 0.99 (0.93-1.05) IRR = 1.03 (0.96-1.09)	Adjusted for attained age, birth-cohort, and parity.

[a]Studies that did not report covariate-adjusted measures of association are not summarized in the Table ((63, 66) (both reported no association between infant sex and maternal breast cancer)).

[b]Years indicate years of data collection and cancer diagnosis/follow-up (e.g., year of first birth registry record to year of last follow-up) if available.

[c]Singleton births only.

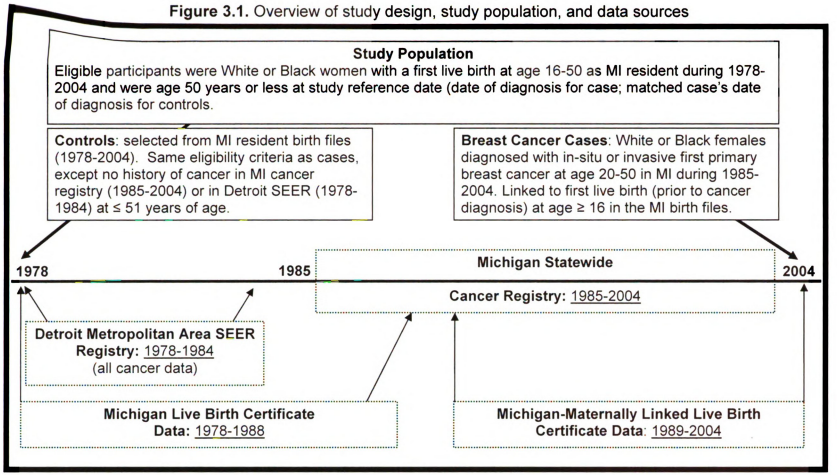
CHAPTER 3: STUDY DESIGN, DATA PREPARATION, AND METHODOLOGIC ISSUES

1. Study Design and Study Population

1.1 Overview of Study Design

We conducted a population-based, case-control study among parous MI women 20-50 years of age to investigate the associations between pregnancy-related factors and maternal premenopausal breast cancer risk. This study utilized MI Resident Birth files (MI birth files), MI Statewide Cancer Registry data (MSCR), and Detroit Metropolitan Area Surveillance, Epidemiology, and End Results (SEER) Registry data. Figure 3.1 summarizes the study design, study population, and data sources.

Figure 3.1. Overview of study design, study population, and data sources



1.2 Study Population

1.2.1. Cases

Eligible breast cancer cases were identified from the MSCR (1985-2004) and linked to their first live birth in the MI birth files (1978-2004). Eligibility criteria included: (1) diagnosed with *in situ* or invasive first primary breast cancer between 1985 and 2004 in the MSCR; (2) age 20-50 years at breast cancer diagnosis; (3) no previous diagnosis of any cancer with the exception of basal and squamous cell carcinoma; (4) White or Black race based on MI birth file; (5) first live birth in MI at age 16 years or older during 1978-2004; and (6) residing in MI at time of diagnosis. The study reference date for cases was the case's date of diagnosis.

1.2.2. Source Population

The source population (the population that gave rise to the cases in this study) could not be defined until after linkage of eligible cases to the MI birth files. The source population included parous White and Black women aged 20-50 years during 1985-2004, who had a first live birth at age ≥ 16 years while residing in MI during 1978-2004, and who are assumed to not have been lost to follow-up (i.e., died before study reference date or moved out of MI prior to the study reference date). In addition, the source population has restrictions on the possible range of age at first births that depend on both the age at study reference date and year of study reference date. This is due to the use of pre-existing data files to identify our study cases with restrictions on both the year of

first birth (1978-2004) and year of diagnosis (1985-2004). This issue is discussed further in the methodologic issues section below (***see section 4.1***).

1.2.3. Controls

Eligible controls were selected from the source population described above, identified in the MI birth files (after linkage of the birth files to MSCR). The eligibility criteria for controls included: (1) no history of cancer in MI between 1985-2004 or in the Detroit SEER Registry for the years 1978-1984 (area covered by Detroit SEER accounted for 43.6% of MI's population in 1980; 42.1% in 1990) (240).; (2) age 20-50 years at study reference date (individually-matched case's diagnosis date); (3) White or Black race based on MI birth file; and (4) first live birth in MI at age 16 years or older during 1978-2004. Control Sampling Strategy. We individually matched four controls from the source population to each eligible case on calculated maternal year of birth (+/- 1 year) and maternal race (White; Black). Controls were required to have their first live birth in MI prior to the study reference date. The first step in control sampling was to identify the sample of eligible controls that matched a single case on maternal race and calculated maternal year of birth. This sample was further limited by requiring the first live delivery date of controls to be prior to the date of diagnosis for the case. Four controls were then randomly selected from this sample and matched to the case with a unique number.

2. Data Sources and Measurement of Study Variables

2.1 Michigan Statewide Cancer Registry

Cancer data in MI has been collected since 1947, but the MSCR was not fully established until January 1,1985. MI Hospitals, physician offices, and laboratories (~180 facilities) are required to report *in situ* and invasive malignancies (with the exception of non-genital basal and squamous cell carcinomas) to the MSCR. In addition, nursing homes, hospice care facilities, and 15 other state registries provide case information to the MSCR. The registry includes National Cancer Institute (NCI) SEER registry data for metropolitan Detroit area residents. The MSCR is a member of the North American Association of Central Cancer Registries (NAACCR) and is certified as meeting all NAACCR standards for quality, completeness, timeliness, and unresolved duplicate records. Data quality criteria for the MSCR (2004) are as follows: case ascertainment (≥ 95%), passing edits (99.8%), cases identified from death certificates only (1.7%), missing sex (0.04%), missing age, (0.0%), and missing race (2.56%)(241).

2.2 Metropolitan Detroit Cancer Surveillance System

The Metropolitan Detroit Cancer Surveillance System (MDCSS) or the Detroit SEER registry has conducted comprehensive cancer surveillance since 1969 for the Detroit metropolitan area which includes Wayne, Oakland and Macomb counties (242). The registry became an official part of NCI's SEER Program on January 1, 1973. NCI's SEER program includes 18 population-based cancer registries across the US that comprise about 26 percent of the US population (243). The population covered by MDCSS included approximately 3.9 million people in 1990, encompassing 42% of the state population (240). Since

1973, data on approximately 692,300 SEER reportable cases have been collected by MDCSS (242). MDCSS data have been used extensively for cancer research (244-246). MDCSS collects data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status (243). The registry also collects social security number (SSN) for cancer patients and has a unique registry number which enables MDCSS patients to be identified in the MDCH statewide cancer registry. Data quality criteria for the MDCSS (2004) are as follows: case ascertainment (90-94%), passing edits (100%), cases identified from death certificates only (1.0%), missing sex (0.0%), missing age, (0.0%), and missing race (2.24%) (241).

2.3 Michigan Birth Certificate Data

The Michigan Department of Community Health (MDCH), Vital Records and Data Development Section has maintained computerized records of all MI births since 1970 (MI birth files) (247). We elected to initiate this study in 1978 because maternal SSN, the main record linkage variable used in this study, is missing for > 11% of mothers prior to 1978 (248). MI birth data is used at the county, state, and national level to monitor maternal and infant health trends and to create vital statistics reports (249). MI birth certificate forms are completed by mothers after delivery and by the hospital staff, filed and reviewed at the local registrar office, and forwarded to the registration unit at MDCH where the certificates are checked for completeness, consistency, and appropriateness. The certificates are then coded using standard instructions. Data items available

from the birth certificate have changed over the study years (1978-2004), with a major revision in 1989. This revision included new methods for the collection of pregnancy complications and the addition of data items including obstetrics procedures, labor complications, maternal risk factor data (e.g., alcohol use, weight gain during pregnancy, tobacco use), and the addition of maternal identifying information (e.g., name, address, and date of birth) to the electronic birth files.

MDCH Maternally-linked birth dataset. MDCH currently has available a maternally-linked live birth dataset of MI birth files (1989-2004) created using a multi-stage deterministic approach to link live delivery records for the same women (250). This file has been used for research purposes (250, 251).

2.4 Measurement of Study Variables

The data sources for the study variables were the MI Birth files and MSCR. The statistical definitions of the variables used in the analyses for each aim are defined in the statistical analysis section of the methods for Chapter 4 and 5.

2.4.1 Case-Control Matching Variables

Data from both the MI birth files and MSCR were used to match controls to cases on maternal race at first live delivery and maternal year of birth. Prior to 1989, maternal DOB was not electronically available in the MI birth files, hence age at first delivery (years) and year of first infant birth were used to estimate maternal year of birth for all cases and controls for consistency. Controls were required to have had their first delivery prior to study reference date (i.e.,

matched case's date of diagnosis). Maternal race was self-reported White or Black race and information on ethnicity was not available prior to 1997 in the MI birth files.

2.4.2 Outcome

The study outcome was primary breast cancer status (yes/no), obtained from MSCR. Cases were women diagnosed with first primary *in-situ* or invasive breast (210) cancer (***see eligibility criteria, section 1.2.1***). Controls were women without a history of cancer diagnosis. Breast cancer histologic type was available for all cases. Histologic types with ample sample sizes for analyses included ductal (International Classification of Diseases for Oncology (ICD-O-3) code 8500, 8521, 8541, 8543) and lobular (ICD-O-3 code 8520).

2.4.3 Exposures

The main exposures of interest (i.e., age at first and last delivery, years since last delivery, birthweight, fetal growth (birthweight-for-gestational age), and infant gestational age), were assessed for each live birth delivery using the MI birth files and were available for all study years 1978-2004. Again, please note that the statistical definitions of the variables used for the analyses are defined in the analytic sections for manuscript 2 (chapter 4) and manuscript 3 (chapter 5). Maternal age at each live delivery was continuous and in years. Years since index delivery was defined using both data from the MI birth files and MSCR (i.e., reference mo/year – delivery mo/year). Gestational age (GA) is calculated by MDCH registry staff as the interval between first day of the women's last normal menstrual period (LMP) and date of delivery (252). Gestational age in weeks

based on the clinical estimate was also used. Infant birthweight in grams was available for each week. It is important to note that we obtained raw data on gestational age and birthweight from the MI birth files and we conducted our own cleaning of these variables using published methods (***please see section 4.3 and chapter 5***).

2.4.4 Covariates

Covariates measured using the MI birth files and not described above include multiple births for each live delivery (defined as the birth of two or more children from a single term of pregnancy), maternal education at each live delivery (to be defined further in the statistical analysis sections of Chapter 4 & 5), number of prior children now living and number of prior children now dead at each live delivery (used to determine number of live births or parity), prior stillbirths/miscarriages/abortions (note: the quality of this variable is uncertain), infant year and month of birth, and infant gender at each live delivery (male; female). Variables will be considered as potential confounders, effect modifiers, and mediators where appropriate.

2.4.5 Accuracy of Michigan Birth Certificate Data: Exposure and Covariates.

Information from MI birth files used in this study (described above in **Measurement of Study Variables**) have been validated in several states in the US, though we were unable to identify validation studies specific to MI birth files (253-266). Overall, most studies have found that demographics (e.g., maternal race, ethnicity, and age) are accurately recorded (sensitivity and specificity >93%) compared to both in-person interviews (254) and medical records (255,

256, 258, 260). Most investigators have also found that number of previous live births (257, 260) and birthweight categorized (258-260, 263) are accurately reported on the birth certificate compared to medical records. For example, a large (n = 33,000) study in Ohio, reported high sensitivity and specificity for birthweight ≥ 3000 g vs. < 3000 g (99.4% and 98.8%, respectively) and prior pregnancy (95.3% and 97.5%, respectively) comparing birth certificates to medical records (260).

Though LMP is known be flawed in its assessment, even from antenatal medical records, it is widely used to estimate gestational age (267). The agreement percentage for LMP (within one week or less) between birth certificate data and medical records has been shown to be above 90% in two previous validation studies (257, 258). Some studies, however, have reported agreement < 80% (264, 265) and have found overestimation of gestational age by LMP to be higher among infants with low birthweight (265). A recent study compared birth certificate LMP (using California live birth records from 2002) to a population-based database of prenatal records (considered the gold standard). This study reported a high proportion of misclassification for both preterm and post-term births and also found that about 15% of preterm births were missed using LMP from the birth record, although overall agreement in LMP (within 1 week) between the two data sources was 89% (268). We used published approaches to clean gestational age and birthweight which are discussed below (***please see section 4.3 and chapter 5 methods***).

3. Dataset Creation Procedures

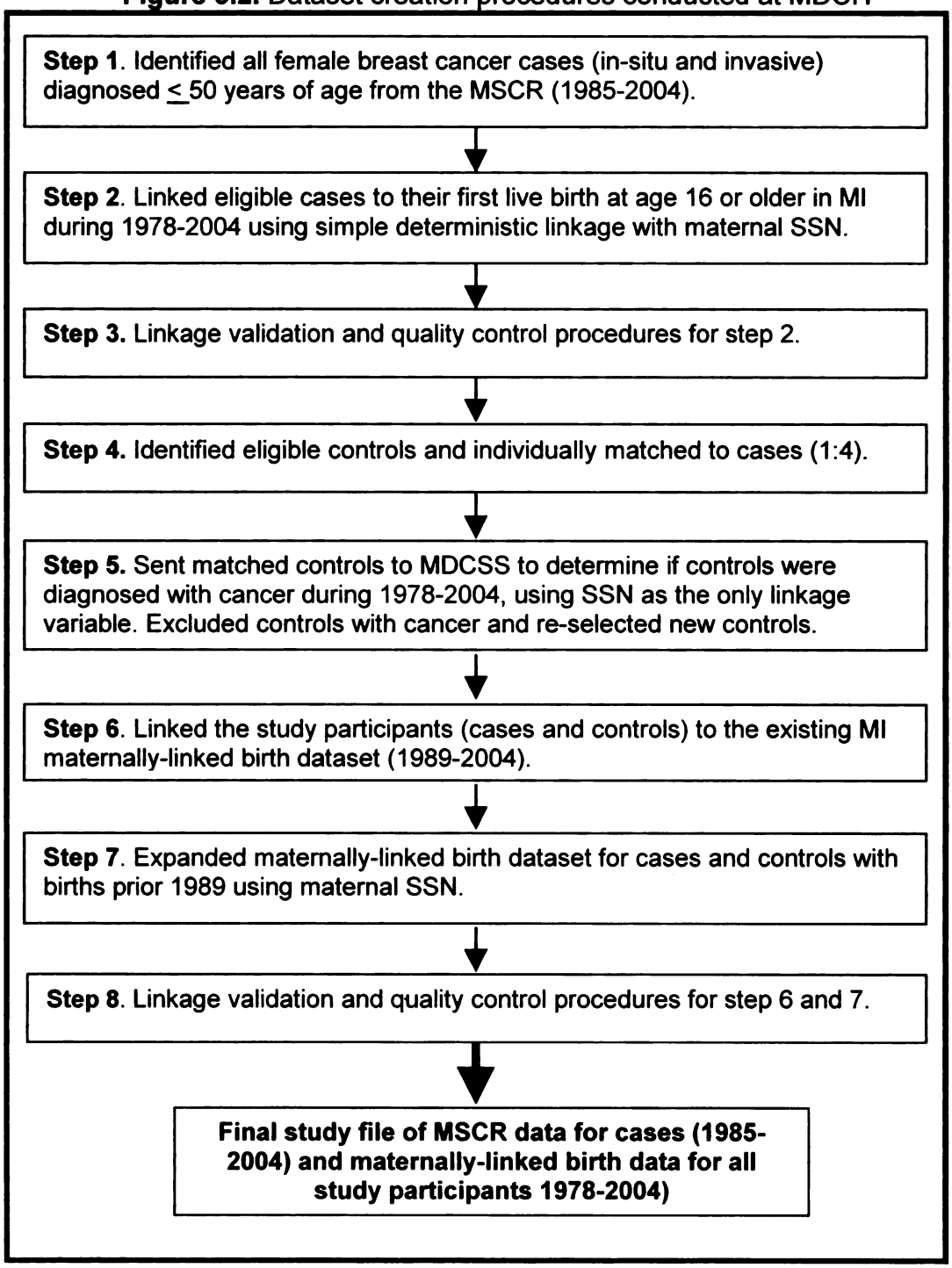
3.1 Summary of Dataset Creation Procedures Conducted at MDCH

This study involved the linkage of pre-existing registry data from the MI birth files, the MSCR, and MDCSS during the years 1978-2004. The dataset creation procedures are shown in figure 3.2. In Step 1, we identified all female breast cancer cases (*in-situ* and invasive) diagnosed ≤ 50 years of age from the MSCR (1985-2004). In Step 2, we linked eligible cases to their first live birth at age 16 or older in MI during 1978-2004 using simple deterministic linkage with maternal SSN as the only linkage variable. In Step 3, we conducted several linkage validation/quality control procedures for the birth-cancer linkages, which are described in detail below. In Step 4, we identified eligible controls from the birth files and individually matched four controls to each case (***see Control Sampling Strategy in section 1.2.3***). In Step 5, we linked all controls (n = 33,004) to the MDCSS using SSN alone to determine if controls were diagnosed with cancer at ≤ 50 years of age during the study years, 1978-2004. We then excluded controls with cancer (n = 95) and re-selected new controls.

The next goal was to identify all live births for study cases and controls in the MI birth files. In step 6, we linked study participants to the existing MDCH MI maternally-linked birth dataset (1989-2004) to identify any additional births during these study years. In step 7, we expanded this maternally-linked birth dataset specific for cases and controls to locate births prior to 1989 in the MI Birth files (1978-1988). We again used simple deterministic linkage with maternal SSN alone for the initial linkage. Finally, in step 8, we conducted several linkage

validation and quality control procedures for the maternal birth-birth linkages, described in detail below. The final analytic file includes breast cancer data from the MSCR for cases (1985-2004) and maternally-linked birth data for all study participants with a first birth after 1978 (1978-2004).

Figure 3.2. Dataset creation procedures conducted at MDCH



3.2 Selection and Linkage Procedures: Breast Cancer Cases

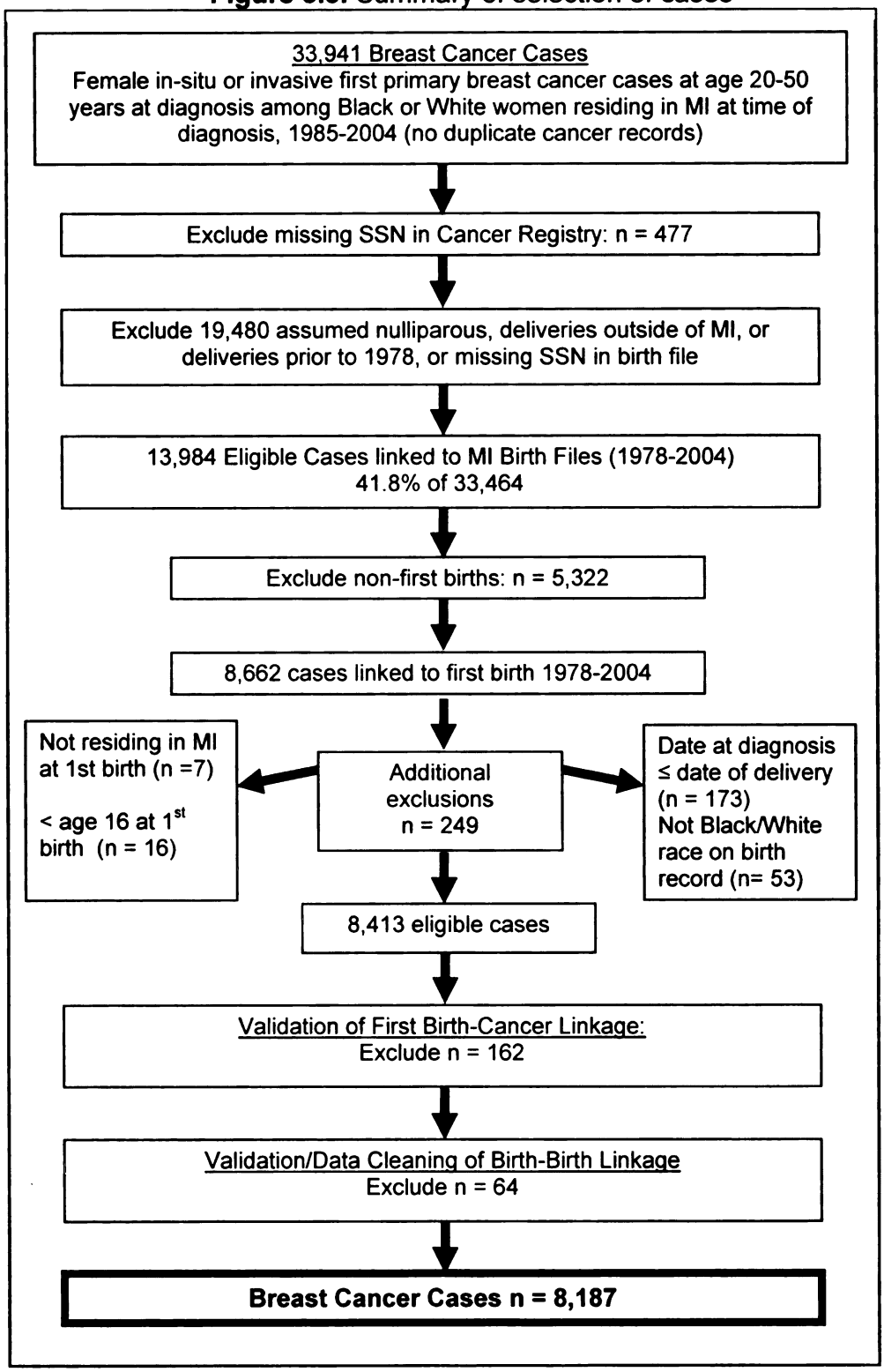
We identified all first primary female breast cancer cases (*in-situ* and invasive) diagnosed ≤ 50 years of age from the MSCR for the study years, 1985-2004 (n = 33, 941) (see Figure 3.3). After excluding cases missing SSN in the cancer file (n = 477, 1.4%), we linked cases to the MI birth files (1978-2004) using simple deterministic linkage with maternal SSN as the only linkage variable (see Step 2 in Figure 3.1). SSN is the only linkage variable used because other identifying variables such as maternal date of birth (DOB) and name are not available in MI birth files prior to 1989 (248). However, SSN is a unique identifier and has been shown to have high validity as a linkage variable both in previous work and in the current study (our validation results are described below). For example, Simon and colleagues conducted a study using MDCSS data linked to MI birth data (1989-1994) and compared two linkage approaches, SSN alone and deterministic linkage with seven linkage variables (maternal first name, maternal last name, maternal maiden name, child's last name, maternal alias, maternal DOB, maternal SSN) and 14 steps (245). All linkages were manually reviewed by hand and were considered valid if all linkage variables from the birth data matched all linkage variables from the cancer data. They found that use of SSN alone identified 98% of valid linkages that would have been found using the seven identifiers (245).

After linkage with SSN alone, a total of 19,480 cases did not link to the MI birth files, 1978-2004 (Figure 3.3). Reasons for non-linkage and ineligibility included: 1) had a first birth or all births outside of MI, 2) had all births prior to

1978, 3) were nulliparous, or 4) were missing SSN in the MI birth files (*note: is impossible to know how many cases were missing SSN in the birth file and not linked because the only way to know this would be to link them to the birth file*). Eligible women may have not linked due to inaccuracies in SSN alone linkage. We conducted several validation procedures to demonstrate the validity of SSN alone linkage, which are described below.

Based on SSN alone, 13,984 (41.2% of cases diagnosed between 1985 and 2004), were linked to a birth in MI resident files (Figure 3.3). We then excluded non-first births between 1978-2004 (n = 5,322), women with month/year of diagnosis ≤ month/year of first delivery (n = 173), women who were not Black or White race based on the birth record (we based race on the birth record because this was all that was available for controls) (n = 53), women not residing in MI at first birth (n = 7) and women < 16 years at first birth (n = 16, 0.1% of 8,429 otherwise eligible women). The case sample size prior to validation work was **8,413 eligible cases**.

Figure 3.3. Summary of selection of cases



3.3 Case Linkage Validation Procedures and Results

We conducted several linkage validation and quality control procedures for the first birth-cancer linkages. These procedures included a) identifying invalid linkages by checking women with inconsistencies in maternal age based on birth compared to cancer data, b) manual verification of a random sample of linkages, c) checking multiple first birth records linked to the same women, and d) comparing simple deterministic linkage (SSN alone) to multi-stage deterministic linkage (SSN, maternal name, infant's last name, maternal DOB). We had two primary goals in conducting the validation work. First, to demonstrate that SSN alone is a valid linkage approach we asked, 'Were cases truly matched with their first birth or were cases falsely matched to a wrong child?' Second, we were interested in completeness. How certain were we that all eligible women who had a first live birth in MI and were diagnosed with breast cancer at ≤ 50 years in MI are included in the study? Below is a description of each validation procedure (summarized in Table 3.1).

a) Maternal age check. For this procedure we calculated the case age at first birth using the age on the cancer record and the year of first delivery from the birth record. This age was compared with maternal age on the birth record. If the age did not match within 1 year, the linkage was manually verified. Manual verification of the linkages involved using additional identifying variables to verify the cancer to birth linkages by hand. The variables needed to validate the linkages were available in electronic files only for births after 1988. For earlier births, paper birth certificates were checked to verify linkages. A birth-cancer

linkage was considered valid if maternal SSN, first name, and last name on the cancer record matched maternal SSN, first name, and last name (maiden, child's, or father's) on the birth record. We identified 227 linkages where age at first birth based on cancer record did not match within 1 year to age at first birth based on the birth record, 1978-2004. Of these, 154 were found to be invalid after manual review, with a total percent invalid linkages among cases = 1.83% (154/8413). Among, the 227 linkages flagged by the maternal age check as possible invalid linkages, 73 were valid and 154 were invalid for a percent invalid among these flagged linkages = 67%. This procedure demonstrated that about 70% of cases with unmatched age are truly invalid linkages. Further, if we exclude all cases with unmatched age, we will exclude about 0.8% of truly valid first birth to cancer linkages (73/8,413).

b) Manual verification for random sample of cases. We selected a random sample of cases linked to their first birth (n = 299 for 1978-1988 births; n = 292 for 1989-2004 births). Linkages were considered valid if SSN, age (+/- 1 year), first name, and last name on the cancer record matched the SSN, age, first name, and last name (including maiden name, child's last name, or father's last name) on the birth record. Linkages where last name only did not match out of the 4 record linkage variables were also considered valid (women could have married or remarried in-between birth and cancer diagnosis). For cases linked to their first birth in 1978-1988, the percent valid = 97.7%, for cases linked to their first birth in 1989-2004, the percent valid = 98.3%, and for all years combined, the percent valid = 98.0% (Table 3.1). In addition, we determined that the number

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of invalid linkages identified by a maternal age check was 11 out of 12. When we excluded the invalid linkages identified by the maternal age check the percent valid increased to 99.8%. This demonstrates that linkage via SSN alone is a highly valid linkage approach for this dataset and that checking for discrepancies in age between linked records can identify close to all of the false positive linkages that may occur with SSN alone linkage.

c) Multiple linked records check. We conducted a check for multiple linked first birth records for the same case to identify invalid linkages and/or inaccurate data. We found 110 breast cancer cases linked to more than one first birth record (n = 224 records). The 224 linkages were manually verified to determine if they were valid linkages (using the same approach described in the above paragraph). We found the following: 182 linkages were valid first, second or third births for the same case (the birth registry parity variables were inaccurate), 39 linkages were invalid (34 would have been caught by maternal age check), and 3 were duplicate birth certificate records.

d) *Multi-stage deterministic and simple deterministic linkage for first births 1989-2004*. We compared two linkage approaches for birth-cancer record linkages (multi-stage deterministic and simple deterministic linkage with SSN alone). In the multi-stage deterministic approach, additional linkage variables were used to ensure no linkages were missed. We used seven linkage variables (mother's first name, mother's last name, maiden name, infant's last name, alias, mother's date of birth, SSN) and 14 successive matching steps, the same variables and steps used by Simon et al., 2004 (245). The comparison of the two

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linkage approaches was made only for births in 1989-2004, because prior to 1989 maternal personal identifiers such as name and DOB are not available in the electronic MI birth files and hence cannot be used for computerized linkage. Using simple deterministic linkage (SSN alone) 2,414 cases were linked to their first births; using multi-stage deterministic linkage, 2,444 cases were linked. The percentage of possible cases missed using the SSN alone approach compared to the deterministic approach was 1.2%. We also checked the reverse and confirmed that all cases found by simple deterministic linkage were also found by multi-stage deterministic linkage. This procedure shows that linkage using only SSN resulted in fairly complete linkage. Because we do not have computerized information on maternal name and DOB prior to 1989, we have to assume that we would find a similar low percentage of missed cases during 1978-1988. This assumption is reasonable given the similar results obtained in our random sample manual verifications of SSN linkage for cases with first births prior to 1989 and after 1989. See Table 3.1 for the results.

In summary, we found a total of 162 invalid/duplicate birth to cancer linkages which were excluded from the final case file (see Table 3.1). The total case sample size at this stage (prior to additional validation procedures after the next phase of the study described below) was **8,251 eligible cases**.

Table 3.1. Summary of validation results for cancer to birth registry linkages

Maternal age check and manual verification results	
N = 8,413 cases; among these 227 (2.7%) where age on first birth record did not match age on cancer record +/1 year	
First birth: 1978-1988	**First birth: 1989-2004**
Percent invalid among cases with unmatched age: **93/151 = 61.6%**	Percent invalid cases women with unmatched age: **61/76 = 80.3%**
Percent invalid among cases with unmatched age for all birth years: **154/227 = 67.8%**	
Manual verification for a random sample of cases	
Sample of n = 591 First Births of all Cases	
First birth: 1978-1988	**First birth: 1989-2004**
Percent valid: 292/299 = 97.7 *Number of invalids that would have been caught by age check (n=6/7)*	Percent valid: 287/292 = 98.3 *Number of invalids that would have been caught by age check (n=5/5)*
Percent valid for all birth years: 579/591 = 98%	
Multiple linked first birth records check	
n = 110 women linked to 224 birth records	
Results from manual verification: 182 linkages were valid first, second or third births 39 linkages were invalid (5 not caught by age check) 3 duplicate birth certificate records were found	
Multi-stage deterministic linkage compared to simple deterministic (SSN alone) linkage for 1989-2004 first births	
30 'new' cases found using multi-stage deterministic 2444 total number of cases found using multi-stage deterministic **Percentage of cases missed using SSN alone = 1.2** *(Have to assume same quality for 1989 prior)*	
Total Invalid Linkages/Duplicate Records : 162*	

*These invalid linkages were excluded from the final case file.

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3.4 Control Selection and Matching Procedures

We identified eligible controls from the birth files and individually matched four controls to each case (n = 33,004) on maternal year of birth +/- 1 (1935-1981) and race (White; Black) (***see Control Sampling Strategy, in section 1.2.3***). We then had all controls matched to MDCSS to determine if controls were diagnosed with cancer at ≤ 50 years of age. Using SSN alone as the linkage variable, MDCSS registry staff identified 179 linkages. Out of these 179 linkages, 2 controls were linked to males cancer cases (we are assuming this is due to inaccuracies in SSN reported in the birth file and/or the MDCSS file), there was 1 duplicate record, and 81 were linked to cancers occurring in 2005 or later. This left 95 controls diagnosed with cancer in MDCSS during the study years, 1978-2004 (77 diagnosed prior to 1985; 18 diagnosed in 1985 or later). Of these cancers, 12 were breast cancer (4 were diagnosed after 1984). We excluded these 95 controls (95/33,004 = 0.29% of study controls) and re-selected new controls from the eligible control file by hand.

3.5 Creation of Maternally-linked Birth Dataset for Cases and Controls

The next step was to create the maternally-linked birth dataset for cases and controls. The goal was to identify all children born in MI to study cases and controls. We had **33,004 controls** and **8,251 cases** prior to linkage of additional births (beyond first births) for study women.

3.5.1 Birth-Birth Linkage Procedures

The goal of this step was to identify and link all live births for study cases and controls to create a final study data file of maternally-linked birth records (for

women with more than one live birth). The procedures used for linkage of births were similar to those used for linkage of cases to their first live birth. We had an additional resource, however, because MDCH currently has a maternally-linked live birth dataset (1989-2004). This dataset has been used for research purposes and was created using a multi-stage deterministic approach to link birth records for multiple deliveries for the same women (250). The first step for our study was to link our cases and controls to this existing database. We then linked the database to the MI birth files for 1978-1988 using SSN alone to identify all births for study participants during these years. The following sections describe the validation and quality control work for birth-birth linkages for cases and controls.

3.5.2 Birth-Birth Validation Procedures and Results

Prior to any validation or quality control work, we had **84,747** records linked to **41,255** cases and controls. Because of the large number of linkages, manual verification of all birth-birth linkages or even a random sub-sample of birth-birth linkages was not feasible given study time constraints. Instead, we used procedures to identify possible invalid birth-birth linkages for study cases and controls through several "checks". The checks included looking for discrepancies between infant birth year, maternal age, and parity at each birth for women with 1 or more births (i.e., we compared birth 2 to birth 1, birth 3 to birth 2 and 1, and so on). For birth certificate data, parity is determined by combining 'nowlive' and 'nowdead', which indicate the number of children now living and the number of children born alive but now dead at the current live birth.

We identified **1,668** women (4% of all participants) with birth-birth linkages where birth year, maternal age, or parity did not match or were implausible across birth histories (figure 3.4). Of these 1,668, we generated computer reports to validate all birth-birth linkages for women with first births in 1989 or later (n = 461) because we could use computerized records for these pregnancies. We used the same approach to validate birth-birth linkages as was used to validate the birth-cancer linkages (**see section 3.3**). Similar to the criteria for a valid birth-cancer linkage, a birth-birth linkage was considered valid if maternal SSN, first name, and last name on the first birth record matched maternal SSN, first name, and last name on the subsequent birth record.

For these 461 women with all their births after 1989, we determined why there were inconsistencies in birth year, age, and parity. The reasons for inconsistencies for women with validated birth-birth linkages included (Figure 3.4):

1) **Multiple births** (the checking mechanism we used identified these women as possible problems because of the way 'nowlive' and 'nowdead' and birth year are recorded for multiple births);

2) **Inaccurate parity data;**

3) **Selected as a control twice** (this was due to inaccurate 'nowlive' or 'nowdead' variables (i.e., the same women had more than one "first" birth due to inaccurate data and we happened to select two of her births as controls)); and

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4) **Now ineligible** (this was due to linkage to earlier births prior to what we had thought was the participant's first birth). These women are now ineligible because they were linked to earlier births that were prior to 1978 or births that occurred out of MI.

5) **Unknown in parity variables**

6) **Maternal age inconsistency for subsequent births**.

We also found a few women with invalid birth-birth linkages (Figure 3.4). As described later, we excluded the invalid birth records, but not the study participant.

While checking the 461 women with first births after 1989, we found 155 participants who we had thought had a first birth in 1989 or later, but were linked to earlier births before 1989 when we created the maternally linked birth file (Figure 3.4). This is the same issue that led to the women that were selected as a control twice (number 3 above) and "now ineligible" women above (number 4) above. What we had thought was the first birth, was actually not the first birth because the parity data was inaccurate. For these 155 women, we validated their birth-birth linkages with the birth certificate paper birth files using the same manual validation procedure described above and also for birth to cancer linkages (***see section 3.3***). Among the 155 women, we identified 48 women with 1 or more invalid linked births, and 35 of these women had an age that didn't match across birth-records (73%) (Figure 3.4). Among the 106 women with valid birth histories, only 1 women had age that did not match across birth records (0.94%) (Figure 3.4).

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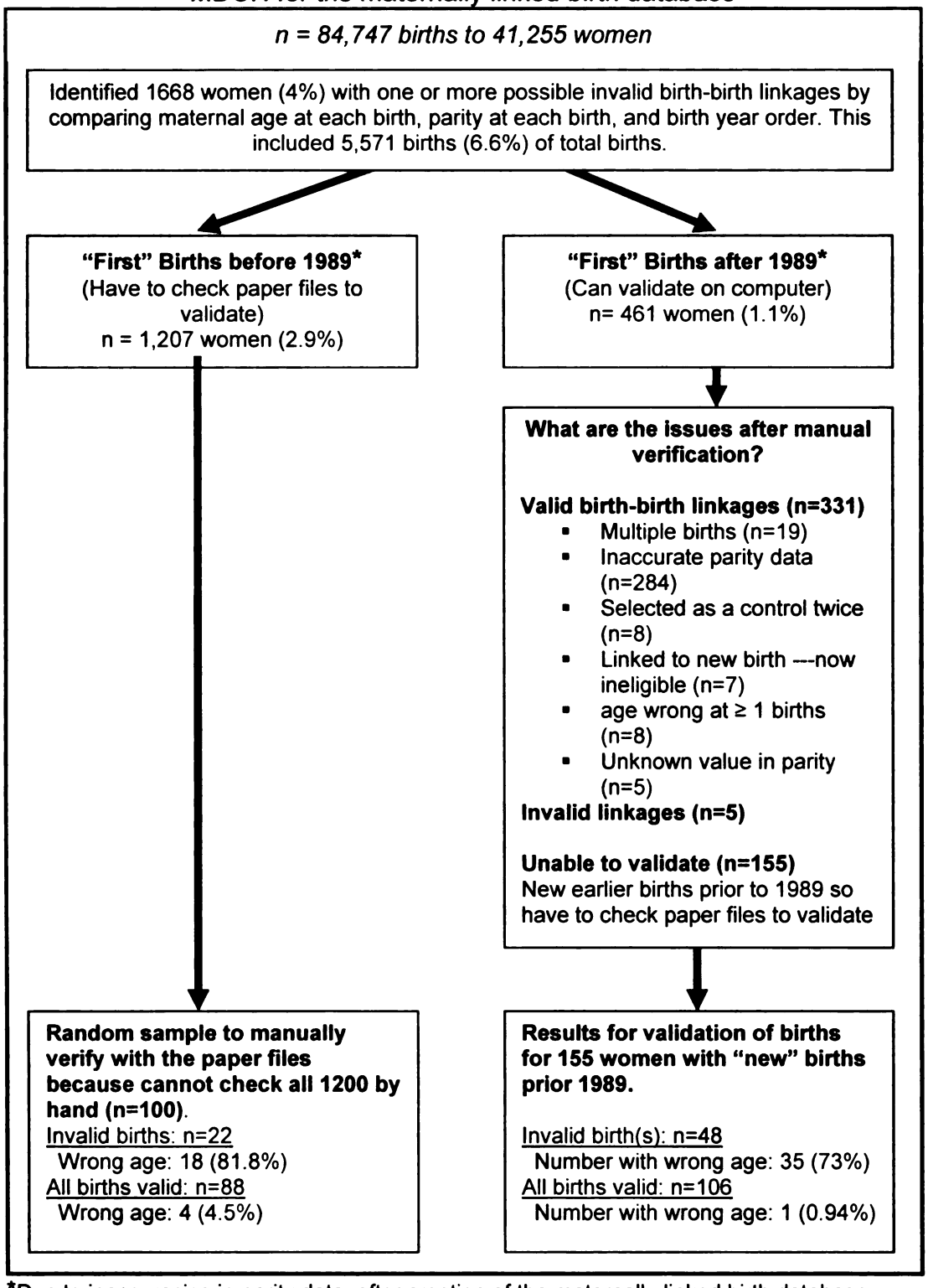
Given the birth data is not computerized prior to 1989, we next identified a random sample (n = 100) of the 1207 women who had their first birth prior to 1989 and where discrepancies were identified in **maternal age, parity, and birth year order across their pregnancies** (figure 3.4). We validated the birth-birth linkages for these 100 women using the same approach used above and also for birth to cancer linkages (***see section 3.3***). We identified 22 women (22%) of the 100 who had one or more invalid births linked to their "first" birth (or index birth). Of these 22 women, 82% would have been identified by checking for inconsistencies in maternal age across births. Of the 88 women with all valid birth-birth linkages, 4 or about 4.5% had inaccurate maternal ages (Figure 3.4). For all the women with validated birth histories, we ordered their births by birth year and the parity data ('nowlive' and 'nowdead' variables) were corrected by hand. We also hand fixed parity data for women that we did not manually validate among the original problematic sample prior to 1989 (1207- 100 = 1107). This number was further reduced with exclusions due to new ineligibility (linked earlier births that were prior to 1978 or out of state births) and women with inconsistencies in age across births (described below and in shown figure 3.5). The number left from the original 1207 that were hand fixed was 762.

Figure 3.4. Summary of validation procedures at MDCH for the maternally linked birth database



*Due to inaccuracies in parity data, after creation of the maternally-linked birth database, original first births for some study participants were found to be non-first births, with linkage to earlier "new" births. Some of these new earlier births occurred prior to 1978 or out of state, which made the study participant ineligible.

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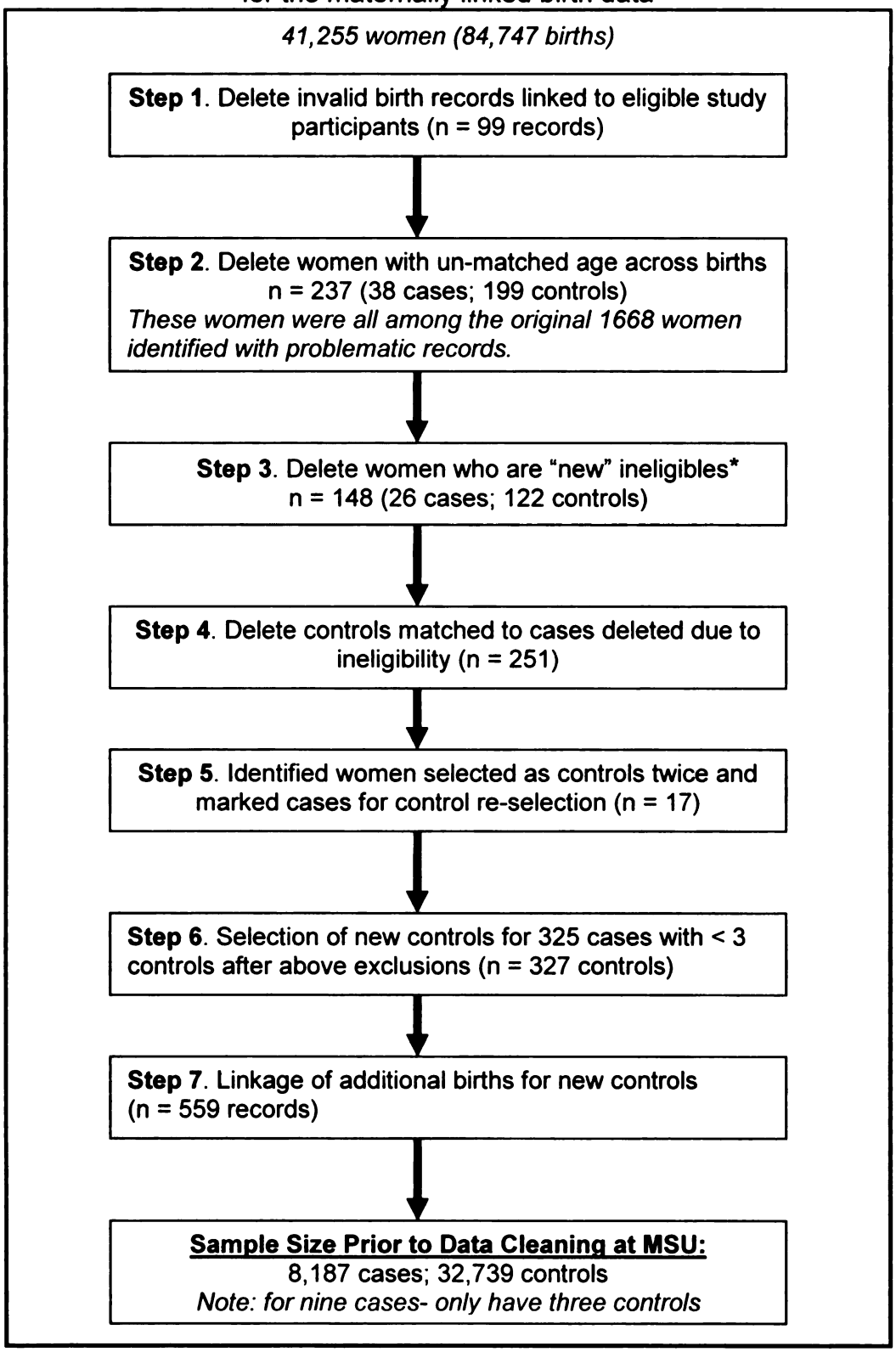
Applying the results from the validation procedures described above, we created the final study dataset. These procedures are summarized in Figure 3.5. The first step was to delete birth records determined to be invalid and linked to eligible study participants (n = 99 records). This ensured that we did not delete these study participants in the next step (if they had an age discrepancy because of linkage to a birth record that was not one of their births). In the second step, we deleted women with discrepancies in reported age across births (0.6% of study participants), with the goal of removing the large majority of women with invalid births linked to them. By removing these study participants, several concerns arise. These include: (1) we will not identify all women with invalid births linked to them using this exclusion method (estimated to be missing about 20-25% among the 4% of the study population with possible problematic linkages (See Figure 3.4)); (2) we are excluding the entire participant, not just the invalid birth record; and (3) some women with inaccurate ages may have valid birth histories (~ 1-4.5%, see figure 3.4) among the 4% of the study population with possible problematic linkages. The third step was to delete women who were identified as ineligible with creation of the maternally-linked birth database and linkage of "new" earlier births to cases and controls. Ineligibility was due to: 1) first birth at < age 16 years; 2) first live birth prior to 1978; or 3) earlier births outside of MI. In step 4 we deleted the controls matched to any case that was deleted in previous steps. In step 5 we identified women selected as a control more than once and marked the matched case for control re-selection. In step 6, we re-selected controls for 325 cases where 1 or more controls were deleted in

above steps or had duplicate control selection (327 controls (2 cases needed 2 controls)). Finally, we linked additional births for the new controls. The final sample size was 8,187 cases and 32,739 controls.

Figure 3.5. Exclusions based on validation results for the maternally linked birth data

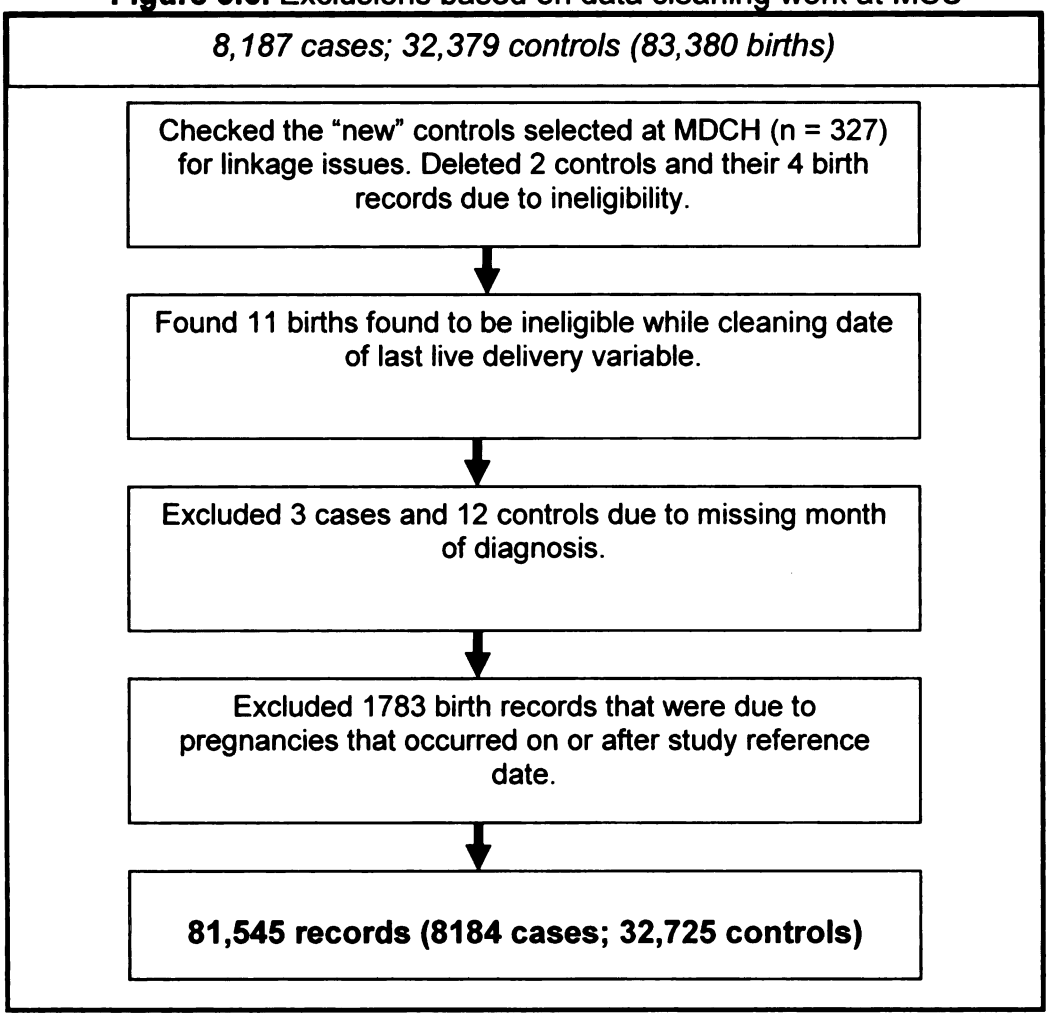


*Reasons for new ineligibility include earlier births that were prior to age 16, prior to 1978 or births not in MI.

3.6. Data Cleaning-Management at MSU

Figure 3.6 displays additional exclusions made for either women or births during the data management phase at MSU with the final study files from MDCH. It is important to note that data management work, including additional study population exclusions made, is mostly described as relevant in chapter 4 and chapter 5.

Figure 3.6. Exclusions based on data cleaning work at MSU



4. Methodologic Issues

4.1 Identifying the Study base and Implications for Bias

We used control selection procedures that ensured that controls were selected from the same population that gave rise to the cases. Selection of cases in this study was limited by the year of first birth (1978-2004) and year of first cancer diagnosis (1985-2004). Because of these two data restrictions, we selected a group of cases where the age at first birth range is restricted, in particular for older cases, because cases with older ages at diagnosis (e.g., 40 years) have a larger plausible age range at which a first birth could occur as compared to cases diagnosed at younger ages (e.g., 30 years). Thus, we know that our source population is not representative of all women in MI with a first live birth at age 16-50 during the years 1978-2004 who could have been diagnosed with breast cancer at age 50 years or less (assuming women did not move out of state or die).

To understand how the age at first birth restriction impacts the age distribution of our study population, we created excel spreadsheets that list the age at first birth ranges by case age and year of cancer diagnosis. These spreadsheets demonstrate how as a case's age increases, the likelihood of capturing the entire true range of age at first birth for a case population is reduced (and hence it is reduced for controls as well). For example (***see Figure 3.7***), at the most extreme, for a 50 year old case diagnosed in 1985 in our study population, her possible age at first birth range is limited to 43-50 years because she had to have a first birth in 1978 or later. This implies that our sample will not

include any 50 year old cases diagnosed in 1985 who had a first birth at age ≤ 42 years. To address this issue we will conduct analyses stratified by attained age and examine age at first and last birth by maternal birth cohort and years of study (please see Chapter 4 and Chapter 5 discussion sections for more details).

Figure 3.7. Age at first birth range for a 50 year old case by year of diagnosis

	Age at First Birth for study births years 1978-2004																										
Age at Dx	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04
50 in 1985	43	44	45	46	47	48	49	50																			
50 in 1986	42	43	44	45	46	47	48	49	50																		
50 in 1987	41	42	43	44	45	46	47	48	49	50																	
50 in 1988	40	41	42	43	44	45	46	47	48	49	50																
50 in 1989	39	40	41	42	43	44	45	46	47	48	49	50															
50 in 1990	38	39	40	41	42	43	44	45	46	47	48	49	50														
50 in 1991	37	38	39	40	41	42	43	44	45	46	47	48	49	50													
50 in 1992	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50												
50 in 1993	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50											
50 in 1994	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50										
50 in 1995	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50									
50 in 1996	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50								
50 in 1997	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50							
50 in 1998	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50						
50 in 1999	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50					
50 in 2000	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50				
50 in 2001	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50			
50 in 2002	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50		
50 in 2003	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	
50 in 2004	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50

4.2 Incomplete Follow-up: Cases and Controls

4.2.1 Movement Out of State

Cases may have had a first live birth in MI, moved out of state and had additional birth(s), moved back into the state, and then be diagnosed with breast cancer in MI before age 50. Controls may have also had a first live birth in MI and then moved out of state and had additional births. The original proposed solution was to obtain address histories for a sub-sample of randomly selected cases and controls. We would have used this data to obtain an estimate of the number of women who have a first live birth in MI and then moved out of state. We would have also used this data to estimate the likelihood of selected controls moving out of state during the study years (1978-2004) and before the reference age by key factors (i.e., SES, infant birthweight) to determine the possible effect of bias on the study effects estimates.

In lieu of data on study participants who have moved out of MI, we have data from a US census report for characteristics of persons who moved out of any state during the period 1990-1995. Interstate moving rates were higher for White non-Hispanics (compared to Black non-Hispanics, Asian and Pacific Islanders, and Hispanics) (269). Moving rates increased as education level increased, the rates were the highest for those with a professional or graduate degree. Moving rates were higher for married individuals and those with higher incomes. The age groups with the highest moving rates were 25-29 years and those older than age 65 years (269). This same report examined characteristics of outmigration from the Midwest, but did not look at characteristics of persons

who moved out of specific states. Please see **chapter 4 and 5 discussion sections** for the implications of this potential bias in the context of the study results.

4.2.2 Time Lag between Exposure and MSCR creation (1978-1984)

Due to the restrictions of the data files, we have a time lag between exposure and the start of statewide cancer registry surveillance (1978-1984). To address this issue, we linked selected controls to MDCSS to identify any cancers diagnosed before age 51 during 1978-1984. We found 77 controls diagnosed with cancer (8 were breast cancers). We excluded these women and selected new controls. This data is reassuring, with only 8 women from the study population diagnosed with breast cancer during 1978-1984 in MDCSS, which accounted for 44% of the population in MI in 1980 (240).

4.2.3 Controls that Died before Reference Date

It is possible that selected controls may have died before the study reference date. One proposed solution to address this was to link selected controls to the National Death Index and exclude those who died before their matched case was diagnosed with breast cancer, but this would be very costly ($5.46 per control). It is reassuring however, that the probability of death in this young population is very low (270).

4.3 Use of Birth Certificate Data for Exposure Measurement: Birthweight and gestational age

Two published approaches for cleaning gestational age, Alexander et al.,1996 (271) and Zhang and Bowes, 1995 (209), are widely used in perinatal

epidemiology research. The method proposed by Zhang and Bowes involves using birthweight-gestational age combinations for weeks 25-35 to identify births for replacement with the clinical estimate of gestational age and if the clinical estimate is missing or is the same poor quality as LMP-based gestational age then the births will be excluded. The Alexander et al., method provides cut points for implausible birthweights for gestational weeks 20-38. A recent study conducted by Parker and colleagues compared the use of these two approaches and concluded that there is no optimal approach and with both approaches, higher birthweights are more likely to be excluded, higher risk women's births are more likely to be excluded, and the edits modify lower gestational ages more than higher gestational ages (272). We decided to use the Zhang and Bowes method given this method excludes fewer births and we have the clinical estimate of gestational age available for all study years in MI, 1978-2004. Additional details on the exclusions made are described in the methods section of chapter 5.

4.4 Exclusions and Selection Bias: SSN, Age, and Race

We compared characteristics for women diagnosed with cancer in MSCR at age 50 or less during 1978-2004, by missing SSN status (yes (n=200,380; no (n=15,437)). Compared to cases with SSN, those missing SSN were younger, diagnosed with cancer at earlier years, had a higher percentage of *in-situ* cancers or unstaged/unknown cancers at diagnosis, and a greater percentage were missing race (Table 3.2).

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Table 3.2. Distributions of select characteristics by missing SSN status for women diagnosed with cancer at ≤ 50 years in the Michigan Statewide Cancer Registry

	No		Yes	
	n	(%)	n	(%)
Age at Diagnosis (years)				
20-24	16,271	(8.0)	2,722	(17.6)
25-29	23,543	(11.8)	3,488	(22.6)
30-34	26,676	(13.3)	2,860	(18.5)
35-39	30,369	(15.2)	2,158	(14.0)
40-44	41,061	(20.5)	1,960	(12.7)
45-50	62,460	(31.2)	2,249	(14.6)
Year of Diagnosis				
1985-1989	31,487	(15.7)	3,726	(24.1)
1990-1994	42,100	(21.0)	3,561	(23.1)
1995-1999	55,880	(27.9)	4,000	(25.9)
2000-2004	70,913	(35.4)	4,150	(26.9)
Stage at Diagnosis				
In situ	72,392	(36.1)	9,819	(63.6)
Localized	57,136	(28.5)	1,993	(12.9)
Regional	26,572	(13.3)	516	(3.3)
Distant metastases	16,645	(8.3)	350	(2.3)
Unknown/unstaged	27,635	(13.8)	2,759	(17.9)
Race				
Black	164,626	(82.2)	9,189	(59.5)
White	25,500	(12.7)	988	(6.4)
Other	2,448	(1.2)	226	(1.5)
Missing	7,806	(3.9)	5,034	(32.6)

We compared select available characteristics of first births in MI during 1978-2004 by missing SSN status (yes (n=1,460,217); no (n=38,119)) (Table 3.3). Compared to women with SSN, women missing SSN at their first live birth in MI were younger and had their first birth in earlier years. Very few (~ 0.04%) first live birth records were missing maternal age and 0.4% of records were missing race.

Table 3.3. Distributions of select characteristics by missing SSN status for women with a first birth in the Michigan during 1978-2004

	No		Yes	
	n	(%)	n	(%)
Age at First Live Birth (years)				
< 16	24,430	(1.7)	4,813	(12.7)
16-19	318,473	(21.8)	14,277	(37.8)
20-24	477,751	(32.7)	9,559	(25.3)
25-29	397,428	(27.2)	6,284	(16.6)
30-34	184,170	(12.6)	2,250	(6.0)
35-39	50,204	(3.4)	550	(1.5)
≥ 40	7,525	(0.52)	72	(0.2)
Missing Age at First Birth				
Yes	236	(0.02)	314	(0.8)
No	1,459,981	(99.9)	37,805	(99.2)
Year of First Live Birth				
1978-1982	279,512	(19.1)	17,363	(45.5)
1983-1987	266,889	(18.3)	11,293	(29.6)
1988-1992	290,420	(19.9)	2,054	(5.4)
1993-1997	269,358	(18.5)	405	(1.1)
1998-2004	354,038	(24.3)	7,004	(18.3)
Race				
Black	1,183,612	(81.3)	27,121	(71.4)
White	239,111	(16.4)	8,702	(22.9)
Other	32,394	(2.2)	2,147	(5.7)
Missing Race				
Yes	5,100	(0.4)	149	(0.4)
No	1,455,117	(99.6)	37,970	(99.6)

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CHAPTER 4: Pregnancy-related factors and risk of breast cancer by histologic type, a registry-based study of parous black and white younger women

1. Abstract

Pregnancy-related factors such as age at first birth and parity have been well-studied in relation to risk of breast cancer, yet few studies have examined risk of breast cancer by histologic type for these factors, in particular among younger women. The identification of differences in risk by histologic type can help elucidate biological mechanisms for the role of pregnancy in breast cancer etiology. We conducted a population-based case-control study among parous Michigan (MI) women aged ≤ 50 years with singleton births using linked MI Cancer Registry (1985-2004) with MI Live Birth records (1978-2004). Cases (n=7,837) were matched 4:1 on maternal birth year and race to controls (n=30,159). We used conditional logistic regression models to examine associations between age at first and last birth, number of live births, and breast cancer risk overall and by histologic type (ductal, lobular). Later age at first (odd ratio (OR) per 5 year increase = 1.16, 95% Confidence Interval (CI): 1.13-1.20) and last birth (OR per 5 year increase = 1.11, 95% CI: 1.04-1.18), and multiparity vs. uniparity (OR for 2 births = 1.36, 95% CI: 1.28-1.44, 3 births = 1.29, 95% CI: 1.19-1.40, 4 births = 1.25; 95% CI: 1.11-1.42), were independently associated with increased breast cancer risk, with ORs of similar magnitude by histologic type. Results were similar by maternal education (≤ high school, > high school). Some differences were observed by race (White, Black), including an increased risk of lobular tumors for age at last birth ≥ 30 years (vs. < 30 years) among

White women only (OR = 1.70, 95% CI: 1.21-2.40). Pregnancy-related factors were not significantly associated with risk of ductal or lobular tumors among Black women. Our results suggest that among parous women ≤ 50 years of age, later age at first and last birth and multiparity are associated with increased risk of both ductal and lobular breast cancer with associations of similar magnitude by histologic type.

2. Introduction

Later age at first birth is a well-established breast cancer risk factor (35, 42, 43). Later age at last birth has also been shown to increase breast cancer risk independently of age at first birth, though there have been fewer studies and findings have been less consistent (48, 54, 55, 57, 59, 60, 273). Multiparity has also been well-studied, but findings have been inconsistent across populations and by age at diagnosis and/or menopausal status (24, 25, 35, 43, 124, 274-276). Few studies, however, have examined these factors and breast cancer risk by histologic type among younger women (112, 277-281). Understanding how pregnancy-related risk factor profiles differ by risk of histologic breast cancer subtypes could generate biological hypotheses for the influence of pregnancy on mammary carcinogenesis (280, 282).

Several studies have examined associations between pregnancy-related factors and breast cancer risk for different histologic types among older/postmenopausal women only or mixed age populations (112, 277-279, 281-286). Research in young women is needed given that the distribution of tumor characteristics and the influence of reproductive risk factors on breast cancer risk

have both been shown to vary by age/menopausal status (3-6, 124, 287), and few studies have examined risk in younger women (288). We found only one study that reported findings by tumor histologic type stratified by menopausal status. Li et al., reported findings from a population-based case-control study of risk for both ductal and lobular breast cancer and age at first birth among premenopausal White and Black women (288). They reported some evidence that later age at first birth was more strongly related to increased risk of lobular as compared to ductal tumors among White premenopausal women only (compared to Black women).

Using data from a large, population-based case-control study conducted using state-wide birth and cancer registry data in Michigan (MI), we first examined the associations of age at first and last birth, and number of live births with breast cancer risk overall. We next examined these associations by histologic breast cancer subtype, focusing on the two most common subtypes (ductal and lobular), which had adequate samples sizes. We further examined the associations for pregnancy-related factors and breast cancer overall and for ductal and lobular tumors by race and maternal education. We hypothesized that later age at first and last birth and multiparity would be more strongly associated with increased risk for lobular breast tumors as compared to ductal breast tumors, given the development of lobules during pregnancy and that lobular tumors have been hypothesized to be more strongly associated with hormonal-related factors in some studies (112).

3. Methods

3.1 Study Design

We conducted a population-based, case-control study among parous MI women aged ≤ 50 years who had a live birth in MI during 1978-2004 at age 16-50. This study was registry-based, using linked MI birth files (1978-2004) and the MSCR (1985-2004). We created a complete live birth history for cases and controls through linkage of all of a woman's MI births. The study protocol was approved by the institutional review board at Michigan State University and the Michigan Department of Community Health (MDCH).

3.2 Study Population

Cases. Eligible breast cancer cases were identified from the MSCR (1985-2004) and linked to their first live birth in the MI birth files (1978-2004). Eligibility criteria included: (1) diagnosed with *in situ* or invasive first primary breast cancer between 1985 and 2004 in the MSCR; (2) age 20-50 years at breast cancer diagnosis; (3) no previous diagnosis of any cancer with the exception of basal and squamous cell carcinoma; (4) White or Black race based on MI birth file; (5) first live birth in MI at age 16 years or older during 1978-2004; and (6) residing in MI at time of diagnosis. The study reference date for cases was the date of diagnosis.

Controls. Eligible controls were selected from the MI birth files (after linkage of the birth files to MSCR). Eligibility criteria included: (1) no history of cancer in MI between 1985-2004 or in the Detroit Surveillance, Epidemiology, & End Results Registry (SEER) for the years 1978-1984 (area covered by Detroit

SEER accounted for 43.6% of MI's population in 1980; 42.1% in 1990) (240); (2) age 20-50 years at study reference date (individually-matched case's diagnosis date); (3) White or Black race based on MI birth file; and (4) first live birth in MI at age 16 years or older during 1978-2004. Control Sampling Strategy. We individually matched four controls to each eligible case on maternal year of birth (+/- 1 year) and maternal race (White; Black). Controls were required to have their first live birth in MI prior to the study reference date.

3.3 Data Sources

MSCR. The MSCR, which was fully established in 1985, is a member of the North American Association of Central Cancer Registries (NAACCR) and is certified as meeting all NAACCR standards for quality, completeness, timeliness, and unresolved duplicate records. Data quality criteria (2004) are as follows: case ascertainment (≥ 95%), passing edits (99.8%), cases identified from death certificates only (1.7%), missing sex (0.04%), missing age, (0.04%), and missing race (2. 6%) (241). Available data items utilized for the present study included stage, behavior, histologic type, age and date at diagnosis.

MI birth files. MDCH-Vital Records and Data Development Section has maintained computerized records of all MI births since 1970. We elected to initiate this study in 1978 because maternal SSN, the main record linkage variable used in this study, is missing for ≥ 10% of mothers prior to 1978 and < 10% after 1978. Data items available from the MI birth certificate have changed over the study years (1978-2004), with a major revision in 1989. Data items utilized for the present study, available for each live delivery, included maternal

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age, month/year of delivery, clinical estimate of gestational age, multiple births (defined as the birth of two or more children from a single term of pregnancy), maternal education, number of prior children now living, and number of prior children now dead.

3.4 Dataset Creation Procedures

We conducted several steps to create the final analytic file of cancer data from the MSCR for cases (1985-2004) and maternally-linked birth data for all study participants (1978-2004). ***Cancer to birth linkages***. First, we identified all female breast cancer cases diagnosed ≤ 50 years of age during 1985-2004 from the MSCR (n=33,941). Second, we linked eligible cases to their first live birth at age 16 or older in MI during 1978-2004 using simple deterministic linkage with maternal social security number (SSN) as the only linkage variable (n=8,662; excludes 477 cases missing SSN in the MSCR, and 19,480 cases assumed nulliparous, first delivery outside of MI, first delivery prior to 1978, or missing SSN in birth file). Additional reasons for exclusions after linkage included: not residing in MI at 1st birth (n=7), < age 16 years at 1st birth (n=16), date at diagnosis ≤ date of delivery (n=173), and non-Black or White race (n=53), leaving 8,413 eligible cases.

Next, we conducted linkage validation/quality control procedures for the birth-cancer linkages. Two main findings from this work include: (1) we found, in a random sample of 591 linkages manually verified, that the proportion of correct linkages was 98%, and (2) for the years 1989-2004, when additional maternal identifiers were available, comparing SSN alone linkage with multi-stage

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deterministic linkage (which used additional identifiers to ensure no linkages were missed), the percentage of possible cases missed using SSN alone was 1.2%. After the validation work, we excluded 162 cases with invalid/duplicate linkages. Then we identified eligible controls from the MI birth files and individually matched four controls to each case (cases=8,251; Controls=33,004) on maternal year of birth +/- 1 (1935-1981) and race (White, Black). Finally, we linked all controls to the Detroit SEER registry using SSN to determine if controls were diagnosed with cancer at ≤ 50 years of age during the study years, 1978-2004. We then excluded controls with cancer (n=95; 0.29% of study controls) and re-selected new controls.

Birth-Birth Linkages. We next identified all live MI births for study participants. First, we linked participants to the existing MDCH MI maternally-linked birth dataset (1989-2004) (250) and then expanded this to include births prior to 1989 in the MI Birth files. We used maternal SSN alone for linkages. We again conducted validation procedures, including manual verification, to determine the accuracy of linkages among 4% of the participants identified as having possible invalid birth-birth linkages (i.e., non-matching maternal age, parity, birth year order) and found an estimated 20% had invalid linkages in this subset. We excluded 68 cases and 267 controls with invalid linkages or where age at each delivery (a good indicator of invalid birth-birth linkages) did not match across live birth histories.

3.5 Data analyses

Outcome. Histology information was available from the MSCR for both *in-situ* and invasive cases and is based on medical records and pathology reports when available. Histology was defined using International Classification of Diseases for Oncology (ICD-O-3) codes with ductal breast cancer defined as ICD-0-3 code 8500 and lobular breast cancer defined as ICD-0-3 code 8520. We did not examine other rarer histologic sub-types due to limited sample sizes, in particular for stratified analyses.

Exposures and covariates. Study exposures were categorized using cut points selected *a priori* based on previous literature (57), including age at first birth in years (< 20 (reference), 20-24, 25-29, 30-34, ≥ 35), age at last birth in years (< 25 (reference), 25-29, 30-34, 35-39, ≥ 40) among women with ≥ 2 live births, and number of live births (1 (reference), 2, 3, ≥ 4). We also examined age at first and last birth per five year increase. Matching factors included race (White, Black) and maternal year of birth (continuous). Covariates included year of first live birth (1978-1983, 1984-1988, 1989-1993, 1994-1998, 1999-2004), maternal education at first birth (< high school (HS), ≥ high school), and years since last birth (< 5, ≥ 5). For cases only additional variables were year of diagnosis (1985-1989, 1990-1994, 1995-1999, 2000-2004) and stage at diagnosis (in-situ, invasive).

Demographic and pregnancy-related factors were compared between cases and controls, and also between ductal and lobular cases using frequencies and proportions and means (where appropriate). We examined separately the associations between age at first birth, number of live births, and age at last birth

and breast cancer risk overall and separately by histologic type (ductal, lobular). Odds ratios and 95 percent confidence intervals (CIs) were obtained by fitting conditional logistic regression models to the data, using maternal race and maternal year of birth as conditioning variables. Covariates and study exposures were considered as potential confounders when not the main effects of interest, selected *a priori* based on previous literature. Each potential confounder was tested individually in conditional logistic regression models for each exposure and breast cancer risk. Though not all potential confounders resulted in a change of ≥ 5 percent for the main effects parameter estimate, we adjusted all final models for the same covariate set (age at first birth, maternal education, and number of live births).

We also examined associations for pregnancy-related factors and both overall breast cancer risk and breast cancer risk for ductal and lobular tumors by race and maternal education at first birth. For these stratified analyses, we dichotomized study exposures (age at first birth and last birth (< 30 years, ≥ 30 years) and number of birth (uniparous, multiparous)). To test for multiplicative interactions, we used the likelihood ratio test to compare models with and without the multiplicative term for the potential modifiers and exposure of interest. For subgroup analyses and analyses by histologic type, we present only the results from fully adjusted models. P-values for case-case comparisons were calculated by fitting unconditional logistic regression models to compare ductal and lobular cases, adjusted for age at first birth, number of births, maternal education, race, and maternal year of birth (as appropriate) (11). SAS version 9.2 was used for all

analyses. All tests were two-sided and p-values < 0.05 indicated statistical significance.

3.6 Original Sample and Analytic Sample for the Present Study

The original study sample of eligible women included 8,251 cases and 33,004 controls. During validation of linkages, as described above, we excluded 331 women (64 cases; 267 controls). We also excluded 15 women (3 cases, 12 controls) missing study reference month and 66 cases diagnosed with breast cancer during pregnancy. Finally, we excluded 264 controls who were matched to excluded cases.

The initial eligible sample for the present study included 8,118 cases and 32,461 controls. We then excluded 247 cases and 1,130 controls with missing/implausible (< 24 weeks) gestational length for any birth. We required participants to have pregnancies lasting at least 24 weeks to compare to previous studies. A total of 34 cases and 115 controls were missing information on education. In sum, 3.5% of cases and 3.8% of controls were excluded due to missing/implausible data. Finally 1,057 controls that were matched to excluded cases were also excluded. The final analytic sample size was 7,837 cases and 30,159 controls. Sample sizes for analyses by histologic subtypes of breast cancer are shown in the Tables 4-6.

4. Results

Table 4.1 displays descriptive and pregnancy-related characteristics for ductal and lobular breast tumors. The mean age at diagnosis was 40.4 (standard deviation (SD): 5.61) for ductal cases (67.7% of all cases) and 43.1 (SD: 4.63)

for lobular cases (8.7% of all cases). Compared to cases with lobular tumors, cases with ductal tumors were more likely to be younger at diagnosis, be invasive tumors , have ≤ H.S. education, and be younger at first and last birth. Number of births did not differ by tumor histologic type.

Table 4.2 shows the distributions by case-control status for age at first birth, number of live births, and age at last birth. Controls were more likely than cases to have earlier age at first and last birth. The mean and median ages at first birth were 27.3 (SD: 5.04) and 27.0 for cases, and 26.7 (SD: 5.23) and 26 for controls. Data from the National Center for Health Statistics based on the U.S. natality files reported that the mean age at first birth increased from 21.4 in 1970 to 24.9 in 2000, while the median age of mother increased from 25.4 to 27.1 (289). The mean number of live births for cases was 2.2 (SD: 0.87) and for controls 1.9 (SD: 0.92). Among women with ≥ 2 live births, the mean age at last birth for cases and controls was 31 (SD: 4.49) and 30.5 (SD: 4.66), respectively. Controls were more likely than cases to have earlier ages at first and last birth.

In models conditioned on age and race, later age at first birth and later age at last birth were significantly associated with increased risk of breast cancer and adjustment for potential confounders did not substantially alter the results (Table 4.2). ORs adjusted for maternal education at first birth, number of live births, and age at first birth (for last birth models only), were elevated for each category for age at first birth (reference = < 20 years) and last birth (reference = < 25). For example, women with a first birth at ≥ 35 years had an 80% increase in risk compared to women < 20 years at first birth, while women with a last birth at

≥ 40 years had a 36% increase in risk compared to women < 25 years (Table 4.2). In models conditioned on age and race, women with 2 or 3 live births (compared to uniparous women), had an increased risk of breast cancer, with similar ORs for further adjusted analyses (Table 4.2).

We further examined the associations between pregnancy-related factors and breast cancer risk by race (White, Black) and maternal education at first birth (≤ H.S., > H.S.) (Table 4.3). Age at first birth was associated with increased risk of breast cancer for both Black and White women and women of lower and higher education at first birth. Multiparous women had an increased risk of breast cancer for 2, 3, or ≥ 4 births compared to uniparous women for all subgroups with the exception of Black women, who had a decreased risk for ≥ 4 births ($p_{interaction}$ for race = 0.04). Later age at last birth was also associated with increased risk of increased breast cancer risk; ORs tended to be higher in magnitude for Black women compared to White women ($p_{interaction}$ = 0.01) and among women with > H.S. education compared to H.S. education or less ($p_{interaction}$=0.41).

Results for adjusted associations between pregnancy-related factors and risk of ductal and lobular breast cancer are displayed in Table 4.4. Later age at first birth for each age group (reference: < 20 years) was significantly associated with increased risk of ductal breast cancer. Results were similar for lobular cancer except the OR for age at first birth at 20-24 years was close to 1.0 and not significant. In the case-case comparison, the p-value was significant for a difference in ductal compared to lobular tumors for age at first birth. ORs for number of live births were elevated and fairly similar for both ductal and lobular

breast cancer risk. Later age at last birth also increased risk of breast cancer for both histologic types, for lobular breast cancer only the OR for 30-34 years at last birth (reference: < 25 years) was significant (OR = 2.11, 95% CI: 1.17, 3.83).

We further examined pregnancy-related factors and risk of ductal and lobular breast cancer by race (Table 4.5). Among White women, later age at first birth ≥ 30 years (reference: < 30 years) was associated with increased risk of both ductal and lobular cancer. Among Black women, age at first birth was not significantly related to risk of ductal or lobular breast cancer, and the non-significant OR for lobular cancer was in the opposite direction compared to White women (OR = 0.62, 95% CI: 0.26, 1.48). Multiparity was associated with increased risk of both ductal and lobular breast cancer among White women only. Later age at last birth (≥ 30 years; < 30 years) was associated with a 70% increase in risk of lobular breast cancer (OR = 1.70, 95% CI: 1.21, 2.40), but not related to risk of ductal breast cancer among White women, while ORs for Black women were in the direction of reduced risk and nonsignificant. Tests for effect modification by race on a multiplicative scale were significant only for age at last birth and risk of ductal breast cancer ($p_{interaction}$ = 0.01).

ORs for ductal and lobular breast cancer by maternal education at first birth (≤ H.S.; > H.S) are shown in Table 4.6. For women of both education level groups, age at first birth ≥ 30 years and multiparity was associated with increased risk of ductal cancer, while multiparity and age at last birth ≥ 30 years were associated with increased risk of lobular breast cancer.

5. Discussion

In this large, population-based registry-linked case-control study of parous Black and White MI women ≤ 50 years of age, later age at first and last birth, and multiparity were associated with increased risk of breast cancer overall and both ductal and lobular breast cancer. Later age at first (odds ratio per 5 year increase = 1.16, 95% CI: 1.13-1.20) and last birth (OR per 5 year increase = 1.11, 95% CI: 1.04-1.18), and multiparity vs. uniparity (OR for 2 births = 1.36, 95% CI: 1.28-1.44, 3 births = 1.29, 95% CI: 1.19-1.40, 4 births = 1.25, 95% CI: 1.11-1.42), were independently associated with increased breast cancer risk, with ORs of similar magnitude by histologic type. Results were similar by maternal education (≤ high school, > high school). Some differences were observed by race (White, Black), including an increased risk of lobular tumors for age at last birth ≥ 30 years (vs. < 30 years) among White women only (OR = 1.70, 95% CI: 1.21-2.40). Further, associations by histologic type among Black women tended to be nonsignificant and risk did not appear to be elevated, but sample size was limited.

Few studies have examined the effect of age at first birth and risk of ductal or lobular breast cancer among younger women. We identified only two reports, both using the Women's Contraceptive and Reproductive Experiences Study (CARE) case-control data, which have examined reproductive factors and histologic type among younger/premenopausal women. Results from the first report suggested that later age at first birth was associated with an increased risk for lobular tumors (e.g., OR for 25-29 years vs. ≤ 19 years = 2.31, 95% CI: 1.11-

2.47, OR for ≥ 30 years vs. ≤ 19 years = 1.61, 95% CI: 0.89-2.91), but not ductal tumors ((e.g., OR for 25-29 years vs. ≤ 19 years = 1.13, 95% CI: 0.96-1.33, OR for ≥ 30 years vs. ≤ 19 years = 1.05, 95% CI: 0.86-1.27) and findings were not modified by age (280). A second study, using the same data, reported findings for risk of both ductal and lobular breast cancer and age at first birth jointly by menopausal status and race (for premenopausal women only) (288). They found some evidence that later age at first birth was more strongly related to increased risk of lobular as compared to ductal tumors among White women and associations were null among Black women.

We found only one study of later age at last birth and histologic type of breast cancer, and findings were similar for ductal and lobular tumors, though the study was among women 50 years or older (278). As with age at first birth, studies of number of live births and breast cancer by histologic type are among older women or mixed age populations and/or use nulliparous women as the reference group (112, 277-281), which hinders comparison to our study.

The maternal hormonal milieu during pregnancy is thought to underlie the associations between pregnancy-related factors and breast cancer. Researchers have hypothesized that later age at first birth may be more strongly associated with lobular tumors as compared to ductal tumors, given that lobular tumors have been proposed to be more hormonally sensitive and are more likely to be estrogen receptor positive (282, 290). However, in the present study associations for pregnancy-related factors and risk of ductal and lobular cancer were similar.

In our study we also confirmed the well-known association for increased breast cancer risk overall for later age at first birth and the less consistently reported increased risk for later age at last birth (26, 46, 54, 55, 57, 59, 60, 273). Number of births has also been well-studied in relation to breast cancer (24, 124, 274, 275), but has been less studied among younger women, and in particular among parous younger women. Among parous younger women, some studies have reported an increased risk of breast cancer for increased number of births (35, 43). However, two large U.S. population-based case control studies (i.e., the Women's CARE study and the Cancer and Steroid Hormone Study), have not reported an increased risk for parity among women 35-49 years (25) and 20-55 years (276), or evidence for an effect of years since last birth on breast cancer risk. For example, in contrast to our findings, the CASH study of women aged 20-50 years of age reported a significant protective effect for increasing number of births and breast cancer risk, independent of age at first birth (276).

Several limitations must be considered when interpreting the results of our study. First, we only had pregnancy-related variables available in the birth registry to consider as covariates. However, several other studies with this information have not found that adjustment for other known breast cancer risk factors substantially alters age at birth associations or have also only adjusted for pregnancy-related factors (278, 281, 288). A second limitation is the potential for underestimates of parity due to potential movement out of state for women who had more than one live birth. This could lead to an underestimation of the number of live births, incorrect classification of a birth as a last birth (for age at

last birth), and lack of complete adjustment for number of live births as a confounder. Further, it could be said that it is more likely that controls moved out of state and had additional births because cases were required to have both their births and cancer diagnosis in MI; hence it is possible that our controls were more likely to have underestimated number of births and ORs for the association between multiparity and breast cancer risk could be biased away from the null. Third, the source of histology data for this study was from the statewide MI cancer registry, which routinely abstracts tumor histology data from pathology reports and medical records, and though information is complete, there is no centralized pathology review to assure consistency and accuracy in histological classification.

Several limitations of our study are related to the use of registry-linked data. First, SSN alone was used to link cancer and birth data as well as additional births for study women. However, our validation work demonstrated that linkages were correct and complete above 98% (see Chapter 3, Methods). Simon and colleagues also demonstrated that SSN was a highly valid approach, with only 2% of possible linkages missed using SSN as the only linkage variable (245). Second, we had to exclude women missing SSN in either the cancer or birth registry. Few women, however, were missing SSN in the cancer registry (1.4% of cases) or birth files (1-5% among all births per year) and missing SSN is unlikely to be related to case-control status. Third, outcome misclassification is a concern because some controls may have developed breast cancer either during the time lag between exposure and the start of the MSCR (1978-1984) or in a

different state. However, breast cancer diagnosis, before the age of 50 is rare. Further, we found by linking to the Detroit SEER registry that only 8 controls in Detroit were diagnosed with breast cancer before age 51 during 1978-1984; if this estimate is extended to the entire state, only about 0.05% of our controls could have been misclassified.

Our study population has a much higher percentage of women with later age at first births and last births, as compared to other population based studies. Table 4.7 displays distributions for age at first birth overall and by birth cohort for controls, with a comparison to a recent birth registry-based study among younger women conducted in Sweden (63). We expected these higher distributions, which are due to the data restrictions of our study (i.e., first live birth in 1978-2004 and year of first diagnosis during 1985-2004). Further, we ensured that controls were selected from the same population that gave rise to the cases by using the same selection criteria for cases and controls, with the exception of cancer diagnosis, and requiring controls to have their first live birth before the matched case's date of diagnosis. Hence, the higher age at first and last birth distribution should only influence the generalizability of our study findings, and not bias the odds ratios.

Main strengths of our study include the large sample size, population-based state-wide design, and use of registry data. Registry-based studies are less subject to key bias found in case-controls studies, because exposure data is collected before breast cancer diagnosis, though recall for important reproductive events such as age at births and number of births is unlikely to be a large

concern. Further, using existing registry data provided us the opportunity to select controls from the same study base as the cases, without being subject to potential bias due to low participation rates. In addition, we had high quality cancer registry data that meets NAACCR standards.

In this large, population-based registry-linked study of parous women ≤ 50 years of age, we found that later age at first and last births, as well as multiparity were associated with an increased risk of breast cancer overall and for both lobular and ductal histologic types. We did not find that associations varied by histologic type among all women. Some differences were found by race and education subgroups, most notably a 70% significant increase in risk of lobular, but not ductal breast cancer among White women only. Very few studies, however, have examined histologic type among younger women and results require confirmation in future studies. Future studies that jointly examine histology and other tumor characteristics (e.g., estrogen receptor status) can further contribute to the understanding of pregnancy-related factors and risk of breast cancer by histologic type.

6. Tables

Table 4.1. Distribution of characteristics for ductal and lobular breast tumors, Pregnancy Factors and Breast Cancer Registry-Based Study in Michigan (1985-2004)

	Ductal cases (n=5,305)		Lobular cases (n=682)		p-value
	n	(%)	n	(%)	
Maternal race					
White	4,713	(88.8)	625	(91.6)	
Black	592	(11.2)	57	(8.4)	0.03[1]
Age at diagnosis (years)					
< 40	2,153	(40.6)	141	(20.7)	
≥ 40	3,152	(59.4)	541	(79.3)	<.0001[1]
Year of Diagnosis					
1985-1989	252	(4.8)	22	(3.2)	
1990-1994	790	(14.9)	68	(10.0)	
1995-1999	1,647	(31.1)	201	(29.5)	
2000-2004	2,616	(49.3)	391	(57.3)	<.0001[1]
Stage of breast cancer at diagnosis					
In-situ	722	(13.6)	303	(44.4)	
Invasive	4,583	(86.4)	379	(55.6)	<.0001[1]
Year of first live birth					

Table 4.1. Continued

1978-1983	2,411 (45.5)	361 (52.9)	
1984-1988	1,470 (27.7)	178 (26.1)	
1989-1993	916 (17.3)	107 (15.7)	
1994-1998	398 (7.5)	29 (4.3)	0.0003[1]
1999-2004	110 (2.1)	7 (1.0)	
Education at first birth[2]			
≤ High School/GED	2,400 (45.2)	269 (39.4)	
> High School	2,905 (54.8)	413 (60.6)	0.0041[1]
Number of Live Births			
1	1,657 (31.2)	203 (29.8)	
2	2,510 (47.3)	319 (46.8)	
3	865 (16.3)	125 (18.3)	
≥ 4	273 (5.2)	35 (5.1)	0.5822[3]
Age at First Birth (years)			
< 20	331 (6.2)	26 (3.8)	
20-24	1,318 (24.8)	124 (18.2)	
25-29	2,031 (38.3)	291 (42.7)	
30-34	1,209 (22.8)	157 (23.0)	
≥ 35	416 (7.8)	84 (12.3)	<.0001[3]
Age at last birth (years)[4]			
< 25	278 (7.6)	26 (5.4)	
25-29	1,123 (30.8)	111 (23.2)	
30-34	1,468 (40.2)	224 (46.8)	
35-39	675 (18.5)	110 (23.0)	
≥ 40	104 (2.9)	8 (1.7)	0.0017[3]
Years since last birth[4]			
< 5	1,270 (23.9)	83 (12.2)	
≥ 5	4,035 (76.1)	599 (87.8)	<.0001[1]

Table 4.1. Continued

[1]Chi-square test for general association.

[2]Includes women aged 16, 17, or 18 at first birth.

[3]Mantel-haenszel chi-square test for trend.

[4]Among women with 2 or more live births.

Table 4.2. Odds ratios for pregnancy-related factors and risk of breast cancer, Pregnancy Factors and Breast Cancer Registry-Based Study in Michigan (1985-2004)

	Cases (n=7,837)		Controls (n=30,159)			
	n	(%)	n	(%)	OR (95%CI)[1]	OR (95%CI)[2]
Age at first birth (years)						
< 20	464	(5.9)	2,439	(8.1)	1.00 (reference)	1.00 (reference)
20-24	1,881	(24.0)	8,189	(27.2)	**1.27 (1.13-1.42)**	**1.29 (1.15-1.45)**
25-29	3,030	(38.7)	11,021	(36.5)	**1.60 (1.42-1.79)**	**1.65 (1.46-1.86)**
30-34	1,800	(23.0)	6,083	(20.2)	**1.75 (1.55-1.98)**	**1.85 (1.62-2.12)**
≥ 35	662	(8.5)	2,427	(8.1)	**1.63 (1.03-1.41)**	**1.80 (1.54-2.10)**
Age at first birth (per 5 years)					**1.14 (1.11-1.17)**	**1.16 (1.13-1.20)**
Number of live births						
1	2,436	(31.1)	10,661	(35.4)	1.00 (reference)	1.00 (reference)
2	3,719	(47.5)	12,905	(42.8)	**1.28 (1.20-1.35)**	**1.36 (1.28-1.44)**
3	1,299	(16.6)	5,013	(16.6)	**1.15 (1.07-1.24)**	**1.29 (1.19-1.40)**
≥ 4	383	(4.9)	1,580	(5.2)	1.08 (0.95-1.22)	**1.25 (1.11-1.42)**
Age at last birth (years)[3]						
< 25	396	(7.3)	2,086	(10.7)	1.00 (reference)	1.00 (reference)
25-29	1,594	(29.5)	6,104	(31.3)	**1.50 (1.31-1.71)**	**1.40 (1.21-1.61)**
30-34	2,221	(41.1)	7,406	(38.0)	**1.79 (1.57-2.05)**	**1.57 (1.33-1.84)**
35-39	1,036	(19.2)	3,360	(17.2)	**1.79 (1.54-2.07)**	**1.48 (1.21-1.81)**
≥ 40	154	(2.9)	542	(2.8)	**1.71 (1.35-2.17)**	**1.36 (1.02-1.81)**
Age at last birth (per 5 years)					**1.17 (1.12-1.22)**	**1.11 (1.04-1.18)**

[1] ORs derived by conditional logistic regression models with maternal year of birth and maternal race as conditioning variables. ORs statistically significant at $\alpha \leq 0.05$ level are in bold print.

Table 4.2. Continued

[2]In addition to conditioning variables, models also included age at first birth, number of live births, and maternal education at first birth.

[3]Among women with 2 or more live births.

Table 4.3. Odds ratios for pregnancy-related factors and risk of breast cancer by maternal race and maternal education at first birth, Pregnancy Factors and Breast Cancer Registry-Based Study in Michigan (1985-2004)

	White Cases=6,970	Black Cases=867	≤ H.S. Education Cases=3,491	> H.S. Education Cases=4,346
	OR (95%CI)[1]	OR (95%CI)[1]	OR (95%CI)[1]	OR (95%CI)[1]
Age at first birth (years)				
< 20	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
20-24	**1.33 (1.16-1.52)**	1.09 (0.84-1.40)	**1.32 (1.17-1.50)**	1.40 (0.86-2.26)
25-29	**1.70 (1.48-1.95)**	**1.39 (1.04-1.86)**	**1.57 (1.37-1.79)**	**1.95 (1.21-3.15)**
30-34	**1.92 (1.65-2.22)**	**1.53 (1.09-2.14)**	**1.94 (1.66-2.26)**	**2.09 (1.29-3.39)**
≥ 35	**1.89 (1.60-2.25)**	1.26 (0.83-1.92)	**1.58 (1.28-1.96)**	**2.16 (1.32-3.52)**
Number of live births				
1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
2	**1.38 (1.29-1.47)**	**1.25 (1.05-1.49)**	**1.30 (1.19-1.42)**	**1.41 (1.30-1.53)**
3	**1.32 (1.21-1.44)**	1.08 (0.84-1.39)	**1.20 (1.07-1.34)**	**1.37 (1.23-1.52)**
≥ 4	**1.36 (1.19-1.55)**	0.76 (0.53-1.10)	**1.20 (1.02-1.42)**	**1.30 (1.08-1.56)**
Age at last birth (years)[2]				
< 25	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
25-29	**1.34 (1.15-1.56)**	**2.20 (1.49-3.26)**	**1.37 (1.17-1.60)**	**1.71 (1.22-2.39)**
30-34	**1.55 (1.30-1.84)**	**1.56 (1.00-2.42)**	**1.50 (1.26-1.79)**	**1.97 (1.40-2.77)**
35-39	**1.45 (1.17-1.79)**	1.68 (0.94-3.00)	**1.40 (1.12-1.76)**	**1.87 (1.30-2.70)**
≥ 40	1.30 (0.96-1.76)	2.12 (0.85-5.30)	1.09 (0.70-1.68)	**1.83 (1.19-2.83)**

[1] ORs derived by conditional logistic regression models with maternal year of birth and maternal race as conditioning variables and adjusted for age at first birth, number of live births, and maternal education at first birth.

[2] Among women with 2 or more live births.

Table 4.4. Odds ratios for pregnancy-related factors and risk of breast cancer by histologic type, Pregnancy Factors and Breast Cancer Registry-Based Study in Michigan (1985-2004)

	Ductal		Lobular		
	Cases	OR (95% CI)[1]	Cases	OR (95% CI)[2]	P-value[3]
Age at first birth (years)					
< 20	331	1.00 (reference)	26	1.00 (reference)	
20-24	1,318	**1.32 (1.14-1.51)**	124	1.06 (0.66-1.71)	
25-29	2,031	**1.65 (1.42-1.90)**	291	**1.68 (1.04-2.73)**	
30-34	1,209	**1.85 (1.58-2.17)**	157	**1.68 (1.01-2.80)**	
≥ 35	416	**1.72 (1.42-2.07)**	84	**2.09 (1.20-3.65)**	0.03
Number of live births					
1	1,657	1.00 (reference)	203	1.00 (reference)	
2	2510	**1.34 (1.24-1.44)**	319	**1.38 (1.13-1.69)**	
3	865	**1.26 (1.14-1.39)**	125	**1.35 (1.04-1.76)**	
≥ 4	273	**1.30 (1.12-1.51)**	35	1.41 (0.93-2.15)	0.18
Age at last birth (years)[4]					
< 25	278	1.00 (reference)	26	1.00 (reference)	
25-29	1,123	**1.35 (1.14-1.60)**	111	1.34 (0.79-2.27)	
30-34	1,468	**1.39 (1.15-1.69)**	224	**2.11 (1.17-3.83)**	
35-39	675	1.26 (0.99-1.60)	110	**1.52 (0.74-3.11)**	
≥ 40	104	1.27 (0.89-1.80)	8	0.48 (0.16-1.43)	0.16

Table 4.4. Continued

[1]ORs (ductal vs. control) derived by conditional logistic regression models with maternal year of birth and maternal race as conditioning variables and also adjusted for age at first birth, number of live births, and maternal education at first birth (Cases=5,305; Controls=15,844).

[2]ORs (lobular vs. controls) derived by conditional logistic regression models with maternal year of birth and maternal race as conditioning variables and also adjusted for age at first birth, number of live births, and maternal education at first birth (Cases=682; Controls=2,618).

[3]p-values are for case-case comparisons (286). Specifically, unconditional logistic regression models were fit to compare ductal vs. lobular tumors for the study exposures, adjusted for age, race, education, age at first birth, and number of births.

[4]Among women with 2 or more live births (3,648 ductal cases and 9,336 controls; 479 lobular cases and 1,217 controls).

Table 4.5. Odds ratios for pregnancy-related factors and risk of ductal and lobular breast cancer by maternal race, Pregnancy Factors and Breast Cancer Registry-Based Study in Michigan (1985-2004)[1]

	White Women				Black Women			
	Ductal		Lobular		Ductal		Lobular	
	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
Age at first birth (years)								
< 30	3,234	1.00 (reference)	396	1.00 (reference)	446	1.00 (reference)	45	1.00 (reference)
≥ 30	1,479	**1.21 (1.11-1.31)**	229	**1.24 (1.01-1.54)**	146	1.10 (0.85-1.43)	12	0.62 (0.26-1.48)
Number of live births								
Uniparous	1,397	1.00 (reference)	178	1.00 (reference)	260	1.00 (reference)	25	1.00 (reference)
Multiparous	3,316	**1.35 (1.26-1.46)**	447	**1.42 (1.16-1.75)**	332	1.08 (0.88-1.33)	32	0.96 (0.51-1.83)
Age at last birth (years)[2]								
< 30	1,233	1.00 (reference)	124	1.00 (reference)	168	1.00 (reference)	13	1.00 (reference)
≥ 30	2,083	1.08 (0.96-1.22)	323	**1.70 (1.21-2.40)**	164	0.73 (0.51-1.05)	19	0.97 (0.26-3.67)

[1]ORs derived by race-specific conditional logistic regression models with maternal year of birth as a conditioning variable and adjusted for age at first birth, number of live births, and maternal education at first birth. p-values for a case-case comparisons by race (derived from unconditional logistic regression models to compare ductal vs. lobular tumors, adjusted for age, education, age at first birth, and number of births) were as follows: White women and age at first birth (p=0.85), number of births (p =0.14), and age at last birth (p=0.04); Black women and age at first birth (p=0.05), number of births (p=0.89), and age at last birth (p=0.50).

[2]Among women with 2 or more live births.

Table 4.6. Odds ratios for pregnancy-related factors and risk of ductal and lobular breast cancer by maternal education at first birth, Pregnancy Factors and Breast Cancer Registry-Based Study in Michigan (1985-2004)[1]

	H.S. Education or Less				> H.S. Education			
	Ductal		Lobular		Ductal		Lobular	
	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
Age at first birth (years)								
< 30	1,929	1.00 (reference)	211	1.00 (reference)	1,751	1.00 (reference)	230	1.00 (reference)
≥ 30	471	**1.37 (1.21-1.55)**	58	1.17 (0.83-1.65)	1,154	**1.11 (1.02-1.22)**	180	1.19 (0.94-1.52)
Number of live births								
Uniparous	751	1.00 (reference)	78	1.00 (reference)	880	1.00 (reference)	86	1.00 (reference)
Multiparous	1,649	**1.30 (1.22-1.40)**	191	**1.37 (1.13-1.67)**	769	**1.43 (1.31-1.57)**	105	**1.39 (1.08-1.78)**
Age at last birth (years)[2]								
< 30	880	1.00 (reference)	86	1.00 (reference)	521	1.00 (reference)	51	1.00 (reference)
≥ 30	769	1.04 (0.91-1.20)	105	**1.58 (1.04-2.42)**	1,478	1.05 (0.91-1.21)	237	**1.71 (1.14-2.55)**

[1] ORs derived by conditional logistic regression models with maternal year of birth and maternal race as conditioning variables and adjusted for age at first birth and number of live births. p-values for a case-case comparisons by education (derived from unconditional logistic regression models to compare ductal vs. lobular tumors, adjusted for age, race, age at first birth, and number of births) were as follows: ≤ H.S. and age at first birth (p=0.29), number of births (p=0.04), and age at last birth (p=0.13), > H.S. and age at first birth (p=0.04), number of births (p=0.19), and age at last birth (p=0.02).

[2] Among women with 2 or more live births.

Table 4.7. Distribution of age at first Birth by maternal birth cohort among controls, Pregnancy Factors and Breast Cancer Registry-Based Study in Michigan (1985-2004)

	Maternal Birth Year									
	Total		1937-1947		1948-1958		1959-1969		1970-1981	Cnattingius et al., 2005[1]
	n	(%)	n	(%)	n	(%)	n	(%)	n (%)	%
Age at first birth (years)										
< 20	2,439	(8.1)		0		0	2179	(18.2)	260 (28.6)	7.0
20-24	8,189	(27.2)		0	3,610	(21.8)	4,256	(35.5)	323 (35.6)	38.0
25-29	11,021	(36.5)		0	7,435	(44.8)	3,343	(27.9)	243 (26.8)	36.5
30-34	6,083	(20.2)	348	(51.1)	4,000	(24.1)	1,653	(13.8)	82 (9.0)	14.2
≥ 35	2,427	(8.1)	333	(48.9)	1,542	(9.3)	552	(4.6)	0	4.2

[1] Age at first birth distribution for all births in a cohort study conducted among Swedish women with first births during 1982-1989 and breast cancer at ≤ 50 years of age for 95% of the sample.

CHAPTER 5: A population-based case-control study of fetal growth, infant gestational age at delivery, and maternal breast cancer among younger women

1. Abstract

Variation in fetal growth (FG) or gestational age (GA) in a woman's own pregnancies may serve as indirect markers of the hormonal environment during pregnancy, which may play a role in both the short-term increase and long-term decrease in risk of breast cancer following childbirth. We conducted a population-based case-control study among parous Michigan (MI) women aged ≤ 50 years with singleton births using linked MI Cancer Registry (1985-2004) with MI Live Birth records (1978-2004). Cases (n=7,591) were matched 4:1 on maternal birth year and race to controls (n=28,382). Using conditional logistic regression, we examined the associations for breast cancer and GA (< 32 wks, 32-36 wks, 37-41 wks, ≥ 42 wks) and FG (defined using BW percentiles for GA ((SGA) < 10th, (AGA) 10-90th (referent), (LGA) > 90th) in both first and last births. Delivery of an SGA or an LGA infant in a first or last birth was not significantly associated with breast cancer risk. However, among women with a last birth at age ≥ 30 years, delivery of an SGA infant in a last birth was associated with a reduced risk of breast cancer (OR=0.82, 95% CI: 0.68-0.98). A first delivery at < 32 weeks or at > 41 weeks (reference: 37-41 week) was associated with a reduced risk (ORs: 0.80, 95% CI: 0.62-1.04 and 0.92, 95% CI: 0.85-0.99, respectively). Our study provides limited evidence for an association between low or high FG and overall breast cancer risk among women ≤ 50 years of age. Delivery of an infant < 32 weeks in a first birth may reduce breast cancer risk, though this finding was in

contrast to our hypothesis and the underlying biologic mechanism is not clear. Little work has been done in the area of infant birth characteristics and maternal breast cancer and future studies with information on biologic measures during pregnancy and other potential confounding factors (e.g., maternal body size) are needed to further characterize these associations.

2. Introduction

Breast cancer following childbirth has been shown to be associated with a poorer prognosis and higher mortality risk (as compared to nulliparous women of the same age) (38-41). Little is known, however, about the hormonal mechanisms underlying the role of pregnancy in breast cancer development among premenopausal parous women. The observed short-term increase and long-term decrease in breast cancer risk following childbirth, which depends on age at pregnancy, has been proposed to be due to maternal hormonal factors during pregnancy (61, 62, 291). The direct study of maternal hormones during pregnancy and subsequent breast cancer risk, however, is difficult due to methodologic and practical issues (e.g., long time span between exposure measurement and breast cancer diagnosis) (122).

In lieu of biologic measures, infant birth characteristics such as fetal growth or gestational age at live delivery, which may reflect altered exposure to maternal hormones during pregnancy, could serve as proxy measures of the maternal hormonal environment (65, 66, 79). Few studies, however, have examined fetal growth (estimated using birthweight adjusted for gestational age) (63, 65, 79, 81, 120, 175) or infant gestational age at delivery (including preterm

(> 37 weeks of gestation) and/or very preterm (< 32 weeks of gestation delivery)) (63, 65-70) in a women's own pregnancies and subsequent maternal breast cancer risk. Though limited, evidence from two large registry-based cohort studies of birthweight adjusted for gestational age and breast cancer suggests that delivery of a high birthweight baby in a first birth (≥ 4500 g vs. 2500-3499 g) (63) or most recent birth (≥ 3.75 kg vs. ≤ 3.0 kg) increases breast cancer risk, and the effect may be more pronounced in the first five years following delivery (79). One case-control study (65) and three cohort studies (68-70) have reported evidence for an increased risk of breast cancer for earlier gestational ages at delivery, though other studies have reported conflicting findings (63, 66, 67). Finally, the etiologies of breast tumor histologic sub-types may vary (282), but no study has examined variation in the associations between the infant birth characteristics and risk of breast cancer for different histologic types.

In summary, studies of the association between infant gestational age and fetal growth for a woman's own pregnancies and breast cancer risk are sparse and several questions remain. To estimate fetal growth, previous researchers have used birthweight alone or adjusted for gestational age as a covariate (birthweight is influenced by both duration of gestation and rate of fetal growth (211)). No study has defined fetal growth using percentiles for infant birthweights for each gestational week based on published national reference values, which allows for more complete adjustment for gestational age and hence improves estimation of the independent effect of fetal growth on breast cancer risk (210). Second, though studies have examined exposure in first births, given the

importance of a first full-term (full-term is defined as a pregnancy lasting ≥ 24 weeks in breast cancer research) pregnancy in relation to subsequent breast cancer risk (35, 36), as well as exposure in last births, no study has examined exposure to fetal growth and gestational age in both first and last births.

In light of the few studies and remaining questions, we conducted a registry-linked, population-based case-control study among parous Michigan (MI) women ≤ 50 years (predominantly premenopausal) using MI Resident Live Birth files 1978-2004 (MI birth files) and MI Statewide Cancer Registry data 1985-2004 (MSCR). We investigated associations between fetal growth and gestational age overall and the two most common histologic types (ductal and lobular) in first and last births. We also examined associations of interest by the *a priori* effect modifiers age at first/last birth and years since first/last birth.

3. Methods

3.1 Study Design

We conducted a population-based, case-control study among parous MI women aged ≤ 50 years who had a live birth in MI during 1978-2004 at age 16-50. This study was registry-based, using linked MI birth files (1978-2004) and the MSCR (1985-2004). We created a complete live birth history for cases and controls through linkage of all of a woman's MI births. The study protocol was approved by the institutional review board at Michigan State University and the Michigan Department of Community Health (MDCH).

3.2 Study Population

Cases. Eligible breast cancer cases were identified from the MSCR (1985-2004) and linked to their first live birth in the MI birth files (1978-2004). Eligibility criteria included: (1) diagnosed with *in situ* or invasive first primary breast cancer between 1985 and 2004 in the MSCR; (2) age 20-50 years at breast cancer diagnosis; (3) no previous diagnosis of any cancer with the exception of basal and squamous cell carcinoma; (4) White or Black race based on MI birth file; (5) first live birth in MI at age 16 years or older during 1978-2004; and (6) residing in MI at time of diagnosis. The study reference date for cases was the date of diagnosis.

Controls. Eligible controls were selected from the MI birth files (after linkage of the birth files to MSCR). Eligibility criteria included: (1) no history of cancer in MI between 1985-2004 or in the Detroit Surveillance, Epidemiology, & End Results Registry (SEER) for the years 1978-1984 (area covered by Detroit SEER accounted for 43.6% of MI's population in 1980; 42.1% in 1990) (240); (2) age 20-50 years at study reference date (individually-matched case's diagnosis date); (3) White or Black race based on MI birth file; and (4) first live birth in MI at age 16 years or older during 1978-2004. Control Sampling Strategy. We individually matched four controls to each eligible case on maternal year of birth (+/- 1 year) and maternal race (White; Black). Controls were required to have their first live birth in MI prior to the study reference date.

3.3 Data Sources

MSCR. The MSCR, which was fully established in 1985, is a member of the North American Association of Central Cancer Registries (NAACCR) and is

certified as meeting all NAACCR standards for quality, completeness, timeliness, and unresolved duplicate records. Data quality criteria (2004) are as follows: case ascertainment (≥ 95%), passing edits (99.8%), cases identified from death certificates only (1.7%), missing sex (0.04%), missing age, (0.04%), and missing race (2. 6%) (241). Available data items utilized for the present study included stage, behavior, histologic type, age and date at diagnosis.

MI birth files. MDCH-Vital Records and Data Development Section has maintained computerized records of all MI births since 1970. We elected to initiate this study in 1978 because maternal SSN, the main record linkage variable used in this study, is missing for ≥ 10% of mothers prior to 1978 and < 10% after 1978. Data items available from the MI birth certificate have changed over the study years (1978-2004), with a major revision in 1989. Data items utilized for the present study, available for each live delivery, included maternal age, month/year of delivery, last menstrual period (LMP) estimate of gestational age (calculated as interval between first day of the women's last normal menstrual period and date of delivery), clinical estimate of gestational age, infant birthweight, multiple births (defined as defined as the birth of two or more children from a single term of pregnancy), maternal education, infant gender, number of prior children now living, and number of prior children now dead.

3.4 Dataset Creation Procedures (please see Chapter 3 for more details)

We conducted several steps to create the final analytic file of cancer data from the MSCR for cases (1985-2004) and maternally-linked birth data for all study participants (1978-2004). ***Cancer to birth linkages***. First, we identified all

female breast cancer cases diagnosed ≤ 50 years of age during 1985-2004 from the MSCR (n=33,941). Second, we linked eligible cases to their first live birth at age 16 or older in MI during 1978-2004 using simple deterministic linkage with maternal social security number (SSN) as the only linkage variable (n=8,662; excludes 477 cases missing SSN in the MSCR, and 19,480 cases assumed nulliparous, first delivery outside of MI, first delivery prior to 1978, or missing SSN in birth file). Additional reasons for exclusions after linkage included: not residing in MI at 1st birth (n=7), < age 16 years at 1st birth (n=16), date at diagnosis ≤ date of delivery (n=173), and non-Black or White race (n=53), leaving 8,413 eligible cases.

Next, we conducted linkage validation/quality control procedures for the birth-cancer linkages. Two main findings from this work include: (1) we found, in a random sample of 591 linkages manually verified, that the proportion of linkages correct was 98%, and (2) for the years 1989-2004, when additional maternal identifiers were available, comparing SSN alone linkage with multi-stage deterministic linkage (which used additional identifiers to ensure no linkages were missed), the percentage of possible cases missed using SSN alone was 1.2%. After the validation work, we excluded 162 cases with invalid/duplicate linkages. Then we identified eligible controls from the MI birth files and individually matched four controls to each case (cases=8,251; Controls=33,004) on maternal year of birth +/- 1 (1935-1981) and race (White; Black). Finally, we linked all controls to the Detroit SEER registry using SSN to determine if controls were diagnosed with cancer at ≤ 50 years of age during the

study years, 1978-2004. We then excluded controls with cancer (n=95; 0.29% of study controls) and re-selected new controls.

Birth-Birth Linkages. We next identified all live MI births for study participants. First, we linked participants to the existing MDCH MI maternally-linked birth dataset (1989-2004) (250) and then expanded this to include births prior to 1989 in the MI Birth files. We used maternal SSN alone for linkages. We again conducted validation procedures, including manual verification, to determine the accuracy of linkages among 4% of the participants identified as having possible invalid birth-birth linkages (i.e., non-matching maternal age, parity, birth year order) and found an estimated 20% had invalid linkages in this subset. We excluded 68 cases and 267 controls with invalid linkages or where age at each delivery (a good indicator of invalid birth-birth linkages) did not match across live birth histories.

3.5 Study Variables

Gestational age data cleaning. We used published methods to clean gestational age (209, 210, 271). First, we used the clinical estimate to replace missing/implausible values(i.e., < 20 weeks or > 44 weeks) for the LMP estimate of gestational ages for 3,837 births (4.6% of all births) (210, 271). Next, we used published cut points for gestational weeks 25-35 to identify births with implausibly high birthweights (e.g., week 25, exclude birthweights > 1250 g); *see Zhang and Bowes (1995) for all cut points (209)*) and substituted the clinical estimate for the LMP estimate, when available (615 births; 0.7% of births) (209). After the above described modifications, 57 cases and 303 controls were excluded due to

missing/implausible gestational age, gestational age 20-23 weeks (to compare to previous breast cancer studies which exclude pregnancies lasting < 24 weeks (291)), or implausible birthweight for gestational age where the clinical estimate unavailable for substitution.

Exposures. Birthweight was defined using *a priori* categories based on previous studies (< 1500 g, 1500-1999 g, 2000-2499 g , 2500-3499 g (reference), 3500-3999 g, 4000-4499 g, 4500 g) (63, 65). We defined gestational age both as a continuous variable (24-44 weeks), as well as using clinically relevant definitions of gestational age (< 32 (very preterm delivery (VPTD)), 32-36 (preterm delivery (PTD)), 37-41 (term) (reference), 42+ (postterm)) (292). Fetal growth was defined using published birthweight percentiles based on US Natality data for each week of gestation (24-44 weeks) for percentiles 1-99 (210). We examined this as a continuous variable. We also categorized this variable using *a priori* categories (271, 272). Small for gestational age (SGA) included infants with birthweights < 10^{th} percentile by gestational week, appropriate for gestational age (AGA) included infants with birthweights between the 10-90^{th} percentile by gestational week (reference), and large for gestational age (LGA) included infants with birthweights > 90^{th} percentile by gestational week. Birthweight adjusted for gestational age as a covariate has been used by all previous studies as an estimator of fetal growth; however, we use the term 'fetal growth' in the Tables and Results to indicate when we are using the birthweight percentiles for each gestational week definition. All exposure variables were created for first and last births among women with ≥ 2 live births.

Covariates. All covariates were created for first births and last births (except parity, maternal education, and age at reference) and were categorized based on previous studies (57, 66, 68, 69, 79). Categorical variables included age at first birth in years (< 20 (reference), 20-24, 25-29, 30-34, ≥ 35), age at last birth in years (< 25 (reference), 25-29, 30-34, 35-39, ≥ 40), age at reference in years (< 25 (reference), 25-29, 30-34, 35-39, 40-44, ≥ 45), years since first birth and last birth (< 5, ≥ 5 (reference)), infant gender (female, male (reference)), maternal education at first birth (< high school, ≥ high school (reference)). Parity (i.e., number of live births) was determined by the sum of number of prior children now living/now dead at the last birth (1, 2, 3, ≥ 4). Binary categories for the potential modifiers included years since first/last birth (same as above), age at first/last birth (< 30 years, ≥ 30 years), and age at reference (< 40 years, ≥ 40 years) were also selected *a priori* based on previous studies (66, 68, 69, 79).

3.6 Original Sample and Analytic Sample for the Present Study

The original study sample of eligible women included 8,251 cases and 33,004 controls. During validation of linkages, as described above, we excluded 331 women (64 cases; 267 controls). We also excluded 15 women (3 cases, 12 controls) missing study reference month and 63 cases diagnosed with breast cancer during pregnancy. For the present analyses, we excluded 1,115 women (231 cases; 884 controls) with ≥ 1 multiple birth. Finally, we excluded 1,149 controls that were matched to excluded cases.

Our initial eligible sample for the present study included 7,890 cases and 30,692 controls with singleton births. We excluded 57 cases and 303 controls

with missing/implausible gestational age, 16 cases and 42 controls with missing/implausible birthweight, 33 cases and 116 controls missing education or infant gender, and 193 cases and 728 controls with missing/inaccurate parity data (3.8% of cases and 3.9% of controls excluded due to missing data). Finally we excluded 1,121 controls matched to excluded cases. The final analytic sample size was 7,591 cases and 28,382 controls.

3.7 Statistical analyses

Demographic and pregnancy-related factors were compared between cases and controls using frequencies and proportions. Statistical significance testing of these differences was conducted using the chi-square tests for categorical variables (age at reference, year of first live birth, education at first birth, infant sex in first birth, infant sex in last birth), the Mantel-Hansel chi-square for trend for variables with three or more ordered categories (parity, age at first birth, age at last birth, birthweight, gestational age, and fetal growth).

We examined separately the associations between breast cancer risk and birthweight, gestational age, and fetal growth in first births for all women and last births for women with ≥ 2 live births. Odds ratios (ORs) and 95 percent confidence intervals (CIs) were obtained by fitting conditional logistic regression models to the data, using maternal race and maternal year of birth as conditioning variables. Several potential confounders were considered, selected *a priori* based on previous literature, including age at first birth and last birth, maternal education at first birth, parity, gestational age in first and last birth, and fetal growth in first and last birth. Each factor was tested individually in

conditional logistic regression models for each exposure and breast cancer risk. Though not all potential confounders resulted in a change of ≥ 5 percent for the main effects parameter estimate, we adjusted all final models for first birth exposures for the same covariate set (shown in Table 2) and all final models for last birth exposures for the same covariate set (shown in Table 4).

To examine whether associations were modified by covariates hypothesized *a priori* to be potential effect modifiers (age at first/last delivery, years since first/last delivery, age at reference, race, and maternal education), we included a multiplicative term for the potential modifier and exposure of interest. We used the likelihood ratio test to compare models with and without the interaction term. The Wald test was used to test for trend for ordered categorical variables.

We also conducted conditional logistic regression analyses by histologic type. Specifically, we modeled the associations for gestational age and fetal growth in first and last births separately with the following outcomes with ductal cases compared to matched controls and lobular cases compared to matched controls (sample sizes for first birth and last birth analyses are shown in Table 6). For subgroup analyses and analyses by histologic type, we present only the results from fully adjusted models. SAS version 9.2 was used for all analyses. All tests were two-sided and p-values < 0.05 indicated statistical significance.

4. Results

4.1 Description of Sample

Table 5.1 displays descriptive characteristics for cases and controls. By design, cases and controls had similar attained age and race distributions. Cases were more likely than controls to have a first live delivery later in the study years, > high school education at first birth, 2 or 3 live births, and be older at their first birth. Infant gender in first and last birth did not differ for cases and controls. Over 75% of first deliveries for both cases and controls occurred prior to 1989. About 38% of cases were diagnosed before the age of 40 and 62% between 40-50, with a mean age at diagnosis of 41 years (SD) =5.64).

4.2 Birthweight, gestational age, and fetal growth in first birth

Table 5.2 reports the overall associations between birthweight (an estimate of fetal growth), gestational age, and fetal growth (estimated via established reference birthweight percentiles for gestational week) in first births and breast cancer risk. ***Birthweight***. In unadjusted models, birthweights of < 1500 g and 1500-1999 (vs. 2500-3499 g) were associated with a reduced risk of breast cancer (< 1500 g OR = 0.80, 95% CI: 0.61, 1.05; < 1500-1999 g OR = 0.73, 95% CI: 0.56, 0.93), while birthweights above 4000 or 4500 g were suggestively associated with a slight elevated risk of breast cancer (ORs, respectively, 1.04 (95% CI: 0.95, 1.14) and 1.08 (95% CI: 0.89, 1.32)). Only the ORs for delivery of an infant weighing 1500-1999 g were significant. Adjustment for gestational age in first birth, age at first birth, parity, and infant gender in first birth did not appreciably alter results (Table 5.2).

Gestational age. Women with a first live delivery at < 32 weeks or 32-36 weeks had a nonsignificant decreased risk of breast cancer compared to women

who delivered a term infant, with similar unadjusted and adjusted ORs (adjusted OR for < 32 weeks = 0.80, 95% CI: 0.62, 1.04; for 32-36 weeks OR = 0.95, 95% CI: 0.85, 1.05). Women with a post-term first delivery had a significant decreased risk of breast cancer (OR = 0.89, 95%CI: 0.83, 0.96) and adjustment for potential confounders (age at first birth, parity, infant gender in first birth, and fetal growth in first birth) did not appreciably alter the OR (Table 5.2).

Fetal Growth. ORs for delivery of an SGA infant or an LGA infant were nonsignificant and close to 1.0, with similar results for unadjusted and adjusted models (Table 5.2). Additional adjustment for education at first birth did not appreciably alter the results for any models for the three exposures of interest (data not shown). We also examined fetal growth for all birthweight percentiles (1-99) by gestational week in unadjusted and adjusted models (adjusted for age at first birth, parity, infant gender in first birth, and gestational age in first birth), rather than using the SGA, AGA, and LGA categories. We found limited evidence for an association per 1 percentile (adjusted OR = 1.00, 95% CI: 1.00-1.00; p for trend = 0.18) or per 10 percentile change in birthweight-for-gestational age (adjusted OR = 1.01, 95% CI: 1.00-1.02).

We next examined potential modification of associations between birthweight, gestational age, and fetal growth and breast cancer risk by age at first birth and years since first birth (Table 5.3). For birthweight adjusted for gestational age and fetal growth, results were similar by age at first birth (< 30, ≥ 30), with close to null results for low birthweight (< 2500 g) or delivery of an SGA infant and a slight nonsignificant increase in risk for high birthweight (≥ 4000g) or

delivery of an LGA infant. For gestational age, the nonsignificant decreased risks observed for delivery at < 32 weeks or 32-36 weeks (vs. term) were similar by age at first birth; the decrease in risk for a posterm first delivery was stronger and significant in women 30 years or older at their first birth (OR = 0.80, 95% CI: 0.68, 0.94). We found limited evidence for modification of results by years since first birth. Statistical tests for multiplicative interactions were not significant (Table 5.3).

4.3 Birthweight, gestational age, and fetal growth in last birth

Table 5.4 reports the overall associations between birthweight, gestational age, and fetal growth in last births and breast cancer risk among women with ≥ 2 live births. Adjusted results for lower birthweights were all fairly close to 1.0 and nonsignificant, as were results for higher birthweights with a slight increase above 1.0 for the highest birthweight category ≥ 4500 g (vs. 2500-3499) adjusted OR = 1.08, 95% CI: 0.88, 1.31. In contrast to first births, adjusted ORs for a last delivery at < 32 weeks of 32-36 weeks (vs. term) were above 1.0, though nonsignificant. A posterm last delivery was unrelated to breast cancer (adjusted OR = 0.97, 95% CI: 0.86-1.09). Delivery of an SGA infant in a last birth as compared to delivery of an AGA infant, was associated with a non-significant reduction in risk of about 12%; the OR was slightly attenuated after adjustment for potential confounders. Delivery of an LGA infant in a last birth was unrelated to breast cancer risk (Table 5.4). Adjustment for education did not appreciably alter any of the findings in Table 5.4 (data not shown).

We further examined whether age at last birth or years since last birth modified the associations between birthweight, gestational age, and fetal growth and breast cancer risk (Table 5.5). In general, results for birthweight and gestational age were similar to overall findings, and all ORs were non-significant as were tests for multiplicative interaction. As for overall results, delivery of an SGA infant (reference: AGA infant) was associated with a reduced risk of breast cancer, but this finding was only found among women ≥ 30 years at last birth or with ≥ 5 years since last birth (OR among women ≥ 30 years at last birth: 0.82, 95% CI: 0.68, 0.98; OR for ≥ 5 years since last: 0.88 95% CI: 0.75, 1.02). Delivery of an LGA infant among women < 30 years at last birth was associated with a non-significant decrease in breast cancer risk of about 10%. The multiplicative interaction between fetal growth and age at last birth was significant (Table 5.5).

4.4 Birthweight, gestational age, and fetal growth by histologic type

We further examined the associations between gestational age and fetal growth and breast cancer by the two most frequent histologic tumor sub-types (Tables 5.6 and 5.7). The mean age at diagnosis for cases by histologic type was as follows: 40 years (SD=5.64) for ductal cases and 43 years (SD=4.70) for lobular cases.

Overall, none of the effect estimates were significant for analyses by histologic types. Findings for risk of ductal tumors for both first and last births for the three exposures of interest, tended to parallel overall findings. For first births (Table 5.6), a non-significant reduction in risk was found for ductal tumors (OR =

0.86, 95% CI: 0.63-1.17), but not lobular tumors. For last births (Table 5.7), a VPTD was associated with a non-significant increased risk for ductal tumors and a reduction in risk of both ductal and lobular tumors for delivery of an SGA infant. Sample sizes became quite small for lobular tumors and. We did not examine the exposures of interest by other histologies because of too small sample sizes.

4.5 Gestational age and fetal growth by attained age, race, and education

Attained age. Results by age at study reference date (< 40 years, 40-50 years) for the associations between breast cancer risk and gestational age and fetal growth in first births and last births are presented in Tables 5.8 and 5.9, respectively. For gestational age, results were fairly similar by age, though the protective effect of a posterm delivery was significant only among women < 40 years (OR = 0.87, 95% CI: 0.77-0.98). For fetal growth, ORs were below 1.0 for both delivery of an SGA or LGA infant among women < 40 years, while for women 40-50 years the OR for delivery of an LGA infant was above 1.0 and non-significant (OR =1.11, 95% CI: 0.99-1.25). Results for last births were fairly similar by age, though delivery at earlier gestational ages was associated with non-significant increased risks only for women < 40 years and a posterm delivery in a last birth was associated with a non-significant reduction in risk only for women 40-50 years of age.

Race and maternal education. We also examined the associations between breast cancer risk and gestational age and fetal growth in both first and last births by maternal race and education at first birth (data not shown). Overall, results were fairly similar by race (White; Black) and education at first birth (≤

H.S.; > H.S). However, for gestational age in first births, protection for delivery at 32-36 weeks (vs. term) was only found for Black women OR = 0.68, 95% CI: 0.53, 0.89). Further, the OR for decreased risk due to a posterm first delivery (vs. term) was stronger and only significant among Black women (Black: OR = 0.65 95% CI: 0.50, 0.80; White: OR = 0.95, 95% CI: 0.88, 1.03, $p_{interaction}$= 0.005) and women with > H.S. education (≤ H.S.: OR = 0.99, 95% CI: 0.89, 1.09; > H.S. OR = 0.86, 95% CI: 0.77, 0.95, $p_{interaction}$ = 0.07).

5. Discussion

Using data from a large, registry-linked, population-based case-control study among MI women ≤ 50 years of age, we found limited evidence for an association between low or high FG and overall breast cancer risk among women ≤ 50 years of age. Delivery of an infant at < 32 weeks in a first birth may reduce breast cancer risk, though this finding was in contrast to our hypothesis and the underlying biological mechanism is not clear. We also found that a posterm delivery was associated with an eight percent decreased risk of breast cancer.

We found that low or higher birthweights adjusted for gestational age in a first birth were associated with breast cancer risk. We observed a 23-30% reduction in risk for lower birthweights. Results were statistically significant only for the association between breast cancer risk and delivery of an infant weighing 1500-1999 g compared to 2500-3499 g. These findings for first births are consistent with two previous large registry-based cohort studies which estimated fetal growth by birthweight adjusted for gestational age as a covariate. The first of

these, conducted in Sweden with 2,216 cases for first births, reported a non-significant increase in breast cancer risk for delivery of an infant weighing ≥ 4500 vs. 2500-3499 g and a significant increase in breast cancer risk per 500 g increase in infant birthweight (63). This study also reported a non-significant reduction in risk for birthweight < 2500 g vs. 2500-3499. A second study in Denmark of infant birthweight in the most recent birth, with 3,874 cases, reported a non-significant elevation in breast cancer risk associated with delivery of an infant weighing >3500 grams vs. ≤ 3000 grams, but did not look at lower birthweights and breast cancer risk (79). A US registry-based case-control study of 2,522 cases, similarly found a non-significant reduction in risk for very low (< 1500 g) birthweight in first births, but not for birthweights 1500-1999 g. This study also reported a non-significant reduction in risk for very high birthweights (≥ 4500 g) (65).

When we examined the association between fetal growth, defined using birthweight percentiles for each gestational week, and breast cancer risk, we found limited evidence for an overall association for fetal growth in a first birth and breast cancer risk, though ORs were in the hypothesized direction (i.e., slight decreased risk for delivery of an SGA infant and slight increased risk for delivery of an LGA infant). For last births, delivery of an SGA infant was associated with a non-significant reduced risk of breast cancer, which was limited to women ≥ 30 years at last birth and for women with ≥ 5 years since last birth in stratified analyses. No previous study has examined fetal growth estimated using percentiles for infant birthweights for each gestational week based on published

national reference values, which allows for more complete adjustment for gestational age and hence improves estimation of the independent effect of fetal growth on breast cancer risk (210).Elevation in risk of breast cancer for high fetal growth and decreased risk for low fetal growth may reflect altered exposure to maternal hormonal factors during pregnancy that are important to breast cancer etiology. Most studies have found that fetal growth is positively associated with maternal estriol levels (primarily of fetal origin), mainly in the third trimester (93, 95, 96, 109, 214) while studies did not find an association with maternal estradiol (93, 97, 214), which has been consistently implicated in breast cancer risk (215). Other hormones that may mediate a positive association between fetal growth and breast cancer risk include higher maternal serum levels of IGF-1 or low levels of IGF binding protien-1, which have been inconsistently associated with fetal growth (particularly during late gestation) (105-107, 111), or lower levels of prolactin (109).

We found that delivery of an infant at < 32 weeks gestation in a first birth was associated with a non-significant 20% reduction in breast cancer risk, which was in the opposite direction of our hypothesis and most previous literature to date. For last births, we found slight non-significant elevations in breast cancer risk of about 9-10% for delivery at < 32 weeks and 32-36 weeks. We also found a significant decreased risk of breast cancer associated with a posterm first delivery and breast cancer risk, which was more pronounced and significant only among women < 40 years in age and not among women 40-50 years in stratified analyses. Our findings for a protective effect on breast cancer risk for delivery at

early gestational ages in a first birth is not consistent with one case-control and three cohort studies. Two European registry-based cohort studies, have reported a significant trend for increasing breast cancer risk with decreasing gestational age in both last birth (68) and first births (70). Both studies reported an increased risk for VPTD; the estimate for the smaller cohort (1,363 cases), but not the larger cohort (5,474 cases), was significant. A third cohort study with 2,318 cases reported a significant increase in breast cancer risk for PTD in a first birth among women ≥ 40 years of age, but not for women < 40 years of age (69) and one US case-control study reported a non-significant increased risk of breast cancer for a first delivery at < 32 weeks (65). In contrast, and similar to our findings, a small US registry-based study with 275 cases reported a non-significant reduction in risk associated with PTD and delivery at <30 weeks in a first pregnancy (67). Finally, a registry-based cohort study (63) and a population-based case-control study using self-report data (66) reported no association between gestational age and breast cancer.

Pregnancies that are shorter in duration during the third trimester have been hypothesized to increase breast cancer risk, due to possible lack of full terminal differentiation of the mammary gland followed by a time of increasing hormone levels (65, 220). However, gestational age is inversely correlated with AFP (229), which has been hypothesized to decrease breast cancer risk through inhibiting estrogen-dependent tumor (94, 230, 231, 233, 293), and hence could explain our findings of a protective effect of VPTD in a first birth. Alternatively, our findings could be attributed to confounding by factors that we could not adjust for,

such as low or high prepregnancy BMI or a more accurate measure of SES (222, 223).

We found a significant decreased risk of breast cancer associated with a posterm first delivery and breast cancer risk, which was more pronounced and significant only among women < 40 years in age stratified analyses. To the best of our knowledge, only one study has investigated posterm delivery and breast cancer risk. In contrast to our findings, a cohort study in Sweden reported no association for delivery at > 40 weeks (231), though they examined exposure in last births. The mechanism for our finding of a protective effect of a posterm first delivery, which appears to be mostly among women < 40 years, is not clear. One possible explanation could be maternal obesity, given that high maternal pre-pregnancy BMI is associated with posterm delivery (294) and overweight/obesity during early adulthood may increase premenopausal breast cancer risk (295). However, this explanation does not fit with the null findings for last births.

In this first investigation of gestational age and fetal growth by histologic type of breast cancer, we did not find much evidence that fetal growth or gestational age were associated with risk of ductal or lobular tumors. Findings were non-significant, though the direction of the ORs for ductal tumors (the most common histologic type (68% of breast tumors)) tended to parallel overall findings. Sample sizes were small in several strata, in particular for exposures in last births and risk of lobular tumors.

Percentages of very low birthweight (1.1), low birthweight (6.3), VPTD (1.1), and PTD (8.1) for first births among controls in our study were fairly similar

to NCHS data for 1996-2004 (very low birthweight: 1.1% for all years, low birthweight: 6.0-6.5%, VPTD: 1.6% for all years, PTD: 9.7-10.8%) (221). However, our posterm birth rates for both first births (15.2) and last births (9.9) were high compared to data from the 1980/early 1990's (296), which encompasses most of the years of the current study.

Several limitations must be considered when interpreting the results of our study. First, the use of registry data for study exposures and covariates meant we had little control over how variables were measured. Overall, most studies have found that demographics (e.g., maternal race, ethnicity, and age) are accurately recorded (sensitivity and specificity >93%) compared to both in-person interviews (254) and medical records (255, 256, 258, 260). Most investigators have also found that number of previous live births (257, 260) and birthweight (258-260, 263) are accurately reported on the birth certificate compared to medical records. The accuracy of gestational age from birth certificates using LMP, however, is a concern (272). Studies have shown, there is misclassification at lower gestational ages where birthweights appear to be higher than plausible for a given week and also at late gestational ages (> 41 weeks), which may incorrectly include term births (209, 272). Gestational age quality is dependent on year in the US, however, and has improved over the years (297). To address this concern, we used published cleaning methods, (209, 271) to reduce misclassification in our data.

We were also concerned that our findings may have differed from other studies due to the way we defined gestational age (e.g., LMP-based estimate)

and methods we used to 'clean' LMP. Though it is difficult to compare both our definition and cleaning approach to other studies, because this information is not reported in detail (63, 66, 67, 69, 79), we conducted two sensitivity analyses to compare findings. First, we re-analyzed the association between breast cancer risk and birthweight and gestational age in first births, using the clinical estimate of gestational age, with no modifications and excluding only births with gestational age < 24 weeks or missing values. Results were similar to the presented findings. We also re-ran the analyses using the LMP estimate of gestational age with these same exclusions applied and again found similar results.

Several limitations of our study are related to the use of registry-linked data. First, SSN alone was used to link cancer and birth data as well as additional births for study women. However, our validation work demonstrated that linkages were correct and complete above 98% (see Chapter 3, Methods). Simon and colleagues also demonstrated that SSN was a highly valid approach, with only 2% of possible linkages missed using SSN as the only linkage variable (245). Second, we had to exclude women missing SSN in either the cancer or birth registry. Few women, however, were missing SSN in the cancer registry (1.4% of cases) or birth files (1-5% among all births per year) and missing SSN is unlikely to be related to case-control status. Third, we may have missing exposure or inaccurate parity data if women moved out of state and had additional births, which could be a possible explanation for the null findings for last births. Fourth, outcome misclassification is a concern because some controls

may have developed breast cancer either during the time lag between exposure and the start of the MSCR (1978-1984) or in a different state. However, breast cancer diagnosis, before the age of 50 is rare. Further, we found that only 8 controls were diagnosed with breast cancer before age 51 during 1978-1984 by linking to the Detroit SEER registry, which if this estimate is extended to the entire state, indicates only about 0.05% of our controls could have been misclassified.

Finally, as have most previous studies, we only had variables available in the birth registry to consider as covariates. For example, we did not have information on maternal pre-pregnancy BMI, which is an important determinant of both birthweight and length of gestation and also breast cancer risk. Hence, residual confounding cannot be ruled out as a possible explanation for our finding. However, most previous studies have also only had information on pregnancy-related factors such as age at deliveries, number of births, race, maternal education, and infant gender (65, 67-70, 79).

Main strengths of our study include the large sample size, population-based state-wide design, and use of registry data. Registry-based studies are less subject to key bias found in case-control studies, because exposure data is collected before breast cancer diagnosis. Further, using existing registry data provided us the opportunity to select controls from the source population that gave rise to the cases, without being subject to potential bias due to lower participation rates among controls. In addition, we had high quality cancer registry data that meets NAACCR standards. Finally, this is the first study to

examine fetal growth defined using birthweight percentiles for gestational week, to examine exposures in both first and last births, and to investigate birth characteristics and breast cancer risk for specific histologic sub-types.

In summary, we found limited evidence that fetal growth influences breast cancer risk overall and some evidence that earlier or late gestation in a first birth may be associated with a reduction in breast cancer risk. We did find a non-significant reduction in risk for delivery of an SGA infant in last birth, but not an LGA infant, which was statistically significant among women older than 30 years at their last birth in stratified analyses. This finding could reflect the influence of lower levels of maternal estrogens or IGF-I levels during pregnancy on subsequent breast cancer risk. The suggestion of a reduced breast cancer risk for a first delivery at < 32 weeks could reflect elevated levels of maternal alpha-fetoprotein, but this finding is in the opposite direction of our hypothesis and most previous literature to date. Our finding of a protective effect of a posterm delivery in a first birth, which has not been previously reported, warrants further study. Few studies have examined infant birth characteristics and maternal breast cancer and further work is needed to characterize these associations among different populations, including studies with information available on other potential confounding factors (e.g., body size).

6. Tables

Table 5.1. Descriptive characteristics for cases and controls, Pregnancy Factors and Breast Cancer Registry-Based Study in Michigan (1985-2004)

	Cases n=7,591		Controls n=28,382		p-value
	n	(%)	n	(%)	
Maternal race in first birth					
White	6,738	(88.8)	25,358	(89.4)	
Black	853	(11.2)	3,024	(10.7)	0.15[a]
Maternal year of birth					
1937-1947	184	(2.4)	685	(2.4)	
1948-1958	4,249	(56.0)	15,995	(56.4)	
1959-1969	2,938	(38.7)	10,874	(38.3)	
1970-1981	220	(2.9)	828	(2.9)	0.94[a]
Age at reference date (years)					
< 25	28	(0.4)	106	(0.4)	
25-29	222	(2.9)	841	(3.0)	
30-34	925	(12.2)	3,469	(12.2)	
35-39	1,731	(22.8)	6,419	(22.6)	
40-44	2,542	(33.5)	9,494	(33.5)	

Table 5.1. Continued

≥ 45	2,143 (28.2)	8,053 (28.4)	0.93[b]
Year of first live birth			
1978-1983	3,572 (47.1)	14,888 (52.5)	
1984-1988	2,082 (27.4)	7,143 (25.2)	
1989-1993	1,266 (16.7)	3,981 (14.0)	
1994-1998	524 (6.9)	1,695 (6.0)	
1999-2004	147 (1.9)	675 (2.4)	<0.0001[a]
Education at first birth[c]			
≤ High School/GED	3,388 (44.6)	13,507 (47.6)	
> High School	4,203 (55.4)	14,875 (52.4)	<0.0001[a]
Parity[d]			
1	2,410 (31.8)	10,359 (36.5)	
2	3,589 (47.3)	12,049 (42.5)	
3	1,241 (16.4)	4,558 (16.1)	
≥ 4	351 (4.6)	1,416 (5.0)	< 0.0001[a]
Age at First Birth (years)			
< 20	455 (6.0)	2,199 (7.8)	
20-24	1,815 (23.9)	7,687 (27.1)	
25-29	2,939 (38.7)	10,467 (36.9)	
30-34	1,750 (23.1)	5,762 (20.3)	
35+	632 (8.3)	2,267 (8.0)	< 0.0001[b]

Table 5.1. Continued

Age at last birth (years)[e]			
< 25	384 (7.4)	1,910 (10.6)	
25-29	1,531 (29.6)	5,661 (31.4)	
30-34	2,152 (41.5)	6,889 (38.2)	
35-39	977 (18.9)	3,064 (17.0)	
≥ 40	137 (2.6)	499 (2.8)	< 0.0001[b]
Infant sex in first birth			
Male	3,839 (50.6)	14,514 (51.1)	
Female	3,752 (49.4)	13,868 (48.9)	0.38[a]
Infant sex in last birth[e]			
Male	2,693 (52.0)	9,190 (51.0)	
Female	2,488 (48.0)	8,833 (49.0)	0.21[a]

[a]Chi-square test for general association.

[b]Mantel-haenszel chi-square test for trend.

[c]Includes women aged 16, 17, or 18 at first birth.

[d]We only had birth records for live births so parity is number of live births with length of gestation ≥ 24 weeks.

[e]Among women with ≥ 2 live births.

Table 5.2. Odds ratios for infant birthweight, gestational age, and fetal growth in First birth and maternal breast cancer at age ≤ 50 years, Pregnancy Factors and Breast Cancer Registry-Based Study in Michigan (1985-2004)[a]

	Cases (n=7,591)		Controls (n=28,382)			
	n	(%)	n	(%)	OR (95%CI)[b]	OR (95%CI)[c]
Birthweight (g)						
< 1500	64	(0.8)	298	(1.1)	0.80 (0.61-1.05)	0.77 (0.51-1.16)
1500-1999	68	(0.9)	345	(1.2)	**0.73 (0.56-0.95)**	**0.70 (0.53-0.93)**
2000-2499	317	(4.2)	1,139	(4.0)	1.03 (0.91-1.17)	1.01 (0.88-1.15)
2500-3499	4,112	(54.2)	15,277	(53.8)	1.00 (reference)	1.00 (reference)
3500-3999	2,235	(29.4)	8,477	(29.9)	0.98 (0.93-1.04)	0.99 (0.94-1.05)
4000-4499	661	(8.7)	2,381	(8.4)	1.04 (0.95-1.14)	1.05 (0.96-1.16)
≥ 4500	134	(1.8)	465	(1.6)	1.08 (0.89-1.32)	1.11 (0.91-1.36)
Gestational age (weeks)						
< 32	71	(0.9)	324	(1.1)	0.80 (0.62-1.04)	0.80 (0.62-1.04)
32-36	518	(6.8)	1,991	(7.0)	0.95 (0.86-1.05)	0.95 (0.86-1.05)
37-41	5,949	(78.4)	21,755	(76.7)	1.00 (reference)	1.00 (reference)
≥ 42	1,053	(13.9)	4,312	(15.2)	0.89 (0.83-0.96)	**0.92 (0.85-0.99)**
Fetal growth[d]						
SGA	861	(11.3)	3,331	(11.7)	0.96 (0.88-1.04)	0.97 (0.89-1.05)
AGA	6,072	(80.0)	22,713	(80.0)	1.00 (reference)	1.00 (reference)
LGA	658	(8.7)	2,338	(8.2)	1.05 (0.96-1.16)	1.06 (0.97-1.16)

[a]ORs were derived by conditional logistic regression models with maternal year of birth and maternal race as conditioning variables. ORs statistically significant at $\alpha \leq 0.05$ level are in bold print.

Table 5.2. *Continued*

[b]Models only include conditioning variables.

[c]Adjusted for age at first birth, infant gender in first birth, parity, fetal growth in first birth (only for models where gestational age model is the main effect), gestational age in first birth (only for models where the main effect are birthweight or fetal growth).

[d]SGA - infants with birthweights < 10th percentile, AGA -infants with birthweights between the 10-90th percentile, LGA - infants with birthweights > 90th (by gestational week).

Table 5.3. Adjusted odds ratios for infant birthweight, gestational age, fetal growth and maternal breast cancer at age ≤ 50 years by age at first birth and years since first birth, Pregnancy Factors and Breast Cancer Registry-Based Study in Michigan (1985-2004)[a]

	Age at first birth				Years since first birth			
	< 30 years		≥ 30 years		< 5 years		≥ 5 years	
	Cases (n=5,209)	OR (95%CI)	Cases (n=2,382)	OR (95%CI)	Cases (n=579)	OR (95%CI)	Cases (n=7,012)	OR (95%CI)
Birthweight (g)								
≤ 2500	278	0.91 (0.78-1.05)	174	0.99 (0.82-1.20)	46	1.02 (0.72-1.45)	406	0.93 (0.81-1.06)
500-3999	4,393	1.00 (reference)	1,951	1.00 (reference)	474	1.00 (reference)	5,870	1.00 (reference)
≥ 4000	538	1.06 (0.96-1.18)	257	1.10 (0.95-1.28)	59	0.90 (0.67-1.22)	736	1.08 (0.99-1.18)
Gestational age (weeks)								
< 32	45	0.78 (0.56-1.08)	26	0.82 (0.53-1.26)	8	1.32 (0.59-2.97)	63	0.76 (0.58-1.00)
32-36	325	0.94 (0.83-1.07)	193	0.96 (0.81-1.13)	47	0.88 (0.63-1.23)	471	0.95 (0.86-1.06)
37-41	4,005	1.00 (reference)	1,944	1.00 (reference)	482	1.00 (reference)	5,467	1.00 (reference)
≥ 42	834	0.94 (0.86-1.02)	219	0.80 (0.68-0.94)	42	0.78 (0.55-1.10)	1,011	0.93 (0.86-1.00)
Fetal growth[b]								
SGA	583	0.93 (0.85-1.03)	278	1.00 (0.86-1.15)	65	0.95 (0.71-1.27)	796	0.96 (0.88-1.04)
AGA	4,191	1.00 (reference)	1,881	1.00 (reference)	458	1.00 (reference)	5,614	1.00 (reference)
LGA	435	1.05 (0.94-1.17)	223	1.12 (0.96-1.32)	56	0.99 (0.73-1.36)	602	1.07 (0.97-1.18)

[a] ORs derived by conditional logistic regression models with maternal year of birth and maternal race as conditioning variables and are adjusted for parity, years since first birth (when appropriate), age at first birth (when appropriate), infant gender in first birth, fetal growth in first birth (only for models where gestational age model is the main effect), gestational age in first birth (only for models where birthweight or fetal growth is the main effect).

[b] SGA - infants with birthweights < 10th percentile, AGA -infants with birthweights between the 10-90th percentile, LGA - infants with birthweights > 90th (by gestational week).

Table 5.4. Odds ratios for infant birthweight, gestational age, and fetal growth in last birth and maternal breast cancer at age ≤ 50 years, Pregnancy Factors and Breast Cancer Registry-Based Study in Michigan (1985-2004)[a]

	Cases (n=5,181)		Controls (n=18,023)			
	n	(%)	n	(%)	OR (95%CI)[b]	OR (95%CI)[c]
Birthweight (g)						
< 1500	35	(0.7)	110	(0.6)	1.18 (0.76-1.82)	1.02 (0.57-1.85)
1500-1999	35	(0.7)	134	(0.7)	1.01 (0.67-1.51)	0.96 (0.62-1.49)
2000-2499	126	(2.4)	447	(2.5)	1.04 (0.83-1.29)	1.01 (0.80-1.27)
2500-3499	2,391	(46.2)	8,260	(45.8)	1.00 (reference)	1.00 (reference)
3500-3999	1,758	(33.9)	6,229	(34.6)	0.98 (0.90-1.05)	0.98 (0.91-1.06)
4000-4499	674	(13.0)	2,331	(12.9)	1.01 (0.91-1.13)	1.02 (0.91-1.13)
≥ 4500	162	(3.1)	512	(2.8)	1.07 (0.88-1.03)	1.08 (0.88-1.31)
Gestational age (weeks)						
< 32	38	(0.7)	118	(0.7)	1.08 (0.71-1.65)	1.10 (0.72-1.69)
32-36	319	(6.2)	1,040	(5.8)	1.08 (0.94-1.25)	1.09 (0.95-1.26)
37-41	4,339	(83.8)	15,079	(83.7)	1.00 (reference)	1.00 (reference)
≥ 42	485	(9.4)	1,786	(9.9)	0.93 (0.83-1.04)	0.97 (0.86-1.09)
Fetal growth						
SGA	342	(6.6)	1,362	(7.6)	0.88 (0.77-1.01)	0.91 (0.79-1.04)
AGA	4,107	(79.3)	14,113	(78.3)	1.00 (reference)	1.00 (reference)
LGA	732	(14.1)	2,548	(14.1)	0.99 (0.90-1.09)	0.98 (0.89-1.08)

[a]ORs derived by conditional logistic regression models with maternal year of birth and maternal race as conditioning variables. Table includes women with two or more live births (n=23,204).

[b]Models only include conditioning variables.

[c]Also adjusted for age at first birth, age at last birth, infant gender in last birth, parity, gestational age in

Table 5.4. Continued

last birth (where birthweight/fetal growth is the main effect), and fetal growth in last birth (where gestational age is the main effect).

[d] SGA - infants with birthweights < 10^{th} percentile, AGA -infants with birthweights between the $10\text{-}90^{th}$ percentile, LGA - infants with birthweights > 90^{th} (by gestational week).

Table 5.5. Adjusted odds ratios for infant birthweight, gestational age, fetal growth in last birth and maternal breast cancer at age ≤ 50 years by age at last birth and years since last birth, Pregnancy Factors and Breast Cancer Registry-Based Study in Michigan (1985-2004)[a]

	Age at last birth				Years since last birth			
	< 30 years		≥ 30 years		< 5 years		≥ 5 years	
	Cases (n=1,915)	OR (95%CI)	Cases (n=3,266)	OR (95%CI)	Cases (n=1,244)	OR (95%CI)	Cases (n=3,937)	OR (95%CI)
Birthweight (g)								
≤ 2500	82	1.05 (0.78-1.40)	115	0.96 (0.74-1.25)	46	0.95 (0.64-1.41)	151	1.01 (0.81-1.27)
2500-3999	1,572	1.00 (reference)	2,576	1.00 (reference)	991	1.00 (reference)	3,157	1.00 (reference)
≥ 4000	261	0.96 (0.82-1.12)	575	1.09 (0.97-1.22)	207	1.07 (0.89-1.30)	629	1.03 (0.93-1.15)
Gestational age (weeks)								
< 32	18	1.36 (0.74-2.48)	20	0.94 (0.53-1.69)	11	1.18 (0.51-2.71)	27	1.09 (0.67-1.77)
32-36	124	1.14 (0.91-1.42)	195	1.06 (0.89-1.28)	81	1.08 (0.81-1.43)	238	1.10 (0.93-1.29)
37-41	1,553	1.00 (reference)	2,786	1.00 (reference)	1,059	1.00 (reference)	3,280	1.00 (reference)
≥ 42	220	0.93 (0.79-1.10)	265	1.00 (0.85-1.17)	93	1.05 (0.80-1.37)	392	0.94 (0.83-1.07)
Fetal growth[b]								
SGA	157	1.01 (0.83-1.23)	185	0.82 (0.68-0.98)	83	1.00 (0.76-1.32)	259	0.88 (0.75-1.02)
AGA	1,536	1.00 (reference)	2,571	1.00 (reference)	981	1.00 (reference)	3,126	1.00 (reference)
LGA	222	0.90 (0.76-1.07)	510	1.02 (0.91-1.15)	180	0.99 (0.81-1.20)	552	0.98 (0.88-1.09)

[a]ORs were derived by conditional logistic regression models with maternal year of birth and maternal race as conditioning variables and adjusted for parity, age at first birth, years since last birth, infant gender in last birth, gestational age at last birth (only for models where birthweight or fetal growth is the main effect), fetal growth in last birth (only for models where gestational age is the main effect). Table limited to women with two or more live births (n = 23,204). ORs statistically significant at $\alpha \leq 0.05$ level are in bold print.

[b]SGA - infants with birthweights < 10th percentile, AGA -infants with birthweights between the 10-90th percentile, LGA - infants with birthweights > 90th (by gestational week).

Table 5.6. Adjusted odds ratios for gestational age and fetal growth in first birth and maternal breast cancer at age ≤ 50 years by histologic type, Pregnancy Factors and Breast Cancer Registry-Based Study in Michigan (1985-2004)[a]

	Ductal (cases=5,191; controls=19,673)		Lobular (cases=650; 1,652=controls)	
	Cases	OR (95%CI)	Cases	OR (95%CI)
Gestational age (weeks)				
< 32	52	0.86 (0.63-1.17)	8	0.96 (0.44-2.09)
32-36	345	0.96 (0.85-1.09)	47	0.94 (0.66-1.32)
37-41	4,068	1.00 (reference)	511	1.00 (reference)
≥ 42	726	0.94 (0.86-1.02)	84	0.82 (0.63-1.07)
Fetal growth[d]				
SGA	585	0.94 (0.85-1.03)	73	0.94 (0.71-1.25)
AGA	4,147	1.00 (reference)	525	1.00 (reference)
LGA	459	1.09 (0.97-1.22)	52	0.96 (0.70-1.34)

[a]ORs were estimated separately for ductal vs. control and lobular vs. control derived by conditional logistic regression models with maternal year of birth and race as conditioning variables and adjusted for parity, age at first birth, infant gender in first birth, fetal growth in first birth (only where gestational age is the main effect), gestational age in first birth (only where fetal growth is the main effect). Ductal tumors were classified using ICD-O-3 code 8500 and lobular tumors classified using ICD-O-3 code 8520.

[b]SGA - infants with birthweights < 10th percentile, AGA -infants with birthweights between the 10-90th percentile, LGA - infants with birthweights > 90th (by gestational week).

Table 5.7. Adjusted odds ratios for gestational age and fetal growth in last births and maternal breast cancer at age ≤ 50 years by histologic type, Pregnancy Factors and Breast Cancer Registry-Based Study in Michigan (1985-2004)[a]

	Ductal (cases=3,538; controls=8,671)		Lobular (cases=449;controls=1,093)	
	Cases	OR (95%CI)	Cases	OR (95%CI)
Gestational age (weeks)				
< 32	29	1.35 (0.82-2.20)	3	0.54 (0.11-2.52)
32-36	225	1.16 (0.97-1.37)	24	0.81 (0.49-1.35)
37-41	2,929	1.00 (reference)	391	1.00 (reference)
≥ 42	355	1.02 (0.89-1.16)	31	0.72 (0.46-1.12)
Fetal growth[b]				
SGA	228	0.89 (0.76-1.05)	26	0.74 (0.46-1.20)
AGA	2,809	1.00 (reference)	364	1.00 (reference)
LGA	501	0.97 (0.86-1.09)	59	1.03 (0.73-1.46)

[a]ORs were estimated separately for ductal vs. control and lobular vs. control derived by conditional logistic regression models with maternal year of birth and race as conditioning variables and adjusted for age at first birth, age at last birth, infant gender in last birth, parity, gestational age at last birth (only where fetal growth is the main effect), fetal growth in last birth (only where gestational age model is the main effect). Last birth analyses limited to women with two or more live births. Ductal tumors were classified using ICD-O-3 code 8500 and lobular tumors classified using ICD-O-3 code 8520.

[b]SGA - infants with birthweights < 10th percentile, AGA -infants with birthweights between the 10-90th percentile, LGA - infants with birthweights > 90th (by gestational week).

Table 5.8. Adjusted odds ratios for gestational age and fetal growth in first and births and maternal breast cancer by attained age, Pregnancy Factors and Breast Cancer Registry-Based Study in Michigan (1985-2004)[a]

	< 40 years		40-50 years	
	Cases (n=2,906)	OR (95%CI)	Cases (n=4,685)	OR (95%CI)
Gestational age (weeks)				
< 32	28	0.82 (0.54-1.23)	43	0.79 (0.56-1.10)
32-36	192	0.90 (0.76-1.06)	326	0.97 (0.86-1.11)
37-41	2,313	1.00 (reference)	3,636	1.00 (reference)
≥ 42	373	0.87 (0.77-0.98)	680	0.95 (0.87-1.04)
Fetal growth[b]				
SGA	343	0.96 (0.85-1.10)	518	0.96 (0.86-1.06)
AGA	2,326	1.00 (reference)	3,746	1.00 (reference)
LGA	237	0.98 (0.84-1.14)	421	1.11 (0.99-1.25)

[a]ORs were derived by conditional logistic regression models with maternal year of birth and race as conditioning variables and adjusted for parity, age at first birth, infant gender in first birth, fetal growth in first birth (only for models where gestational age is the main effect), gestational age in first birth (only for models where fetal growth is the main effect). ORs statistically significant at $\alpha \leq 0.05$ level are in bold print.

[d]SGA - infants with birthweights < 10^{th} percentile, AGA -infants with birthweights between the 10-90^{th} percentile, LGA - infants with birthweights > 90^{th} (by gestational week).

Table 5.9. Adjusted odds ratios for gestational age and fetal growth in last births and maternal breast cancer by attained age, Pregnancy Factors and Breast Cancer Registry-Based Study in Michigan (1985-2004)[a]

	< 40 years		40-50 years	
	Cases (n=1,969)	OR (95%CI)	Cases (n=3,212)	OR (95%CI)
Gestational age (weeks)				
< 32	20	1.29 (0.69-2.43)	18	0.99 (0.56-1.76)
32-36	135	1.20 (0.97-1.50)	184	1.02 (0.85-1.23)
37-41	1,622	1.00 (reference)	2,717	1.00 (reference)
≥ 42	192	1.06 (0.88-1.27)	293	0.91 (0.78-1.06)
Fetal growth[b]				
SGA	137	0.92 (0.75-1.14)	205	0.89 (0.75-1.05)
AGA	1,579	1.00 (reference)	2,528	1.00 (reference)
LGA	253	0.93 (0.79-1.09)	479	1.01 (0.89-1.14)

[a]ORs were derived by conditional logistic regression models with maternal year of birth and maternal race and adjusted for parity, age at first birth, age at last birth, infant gender in last birth, fetal growth in last birth (only for models where gestational age is the main effect), gestational age in last birth (only for models where fetal growth is the main effect). ORs statistically significant at $\alpha \leq 0.05$ level are in bold print.

[b]SGA - infants with birthweights < 10th percentile, AGA -infants with birthweights between the 10-90th percentile, LGA - infants with birthweights > 90th (by gestational week).

EPI-logue

1. Summary of findings

This dissertation began with a systematic review of the literature to identify studies of the associations between perinatal factors in a woman's own pregnancies and maternal breast cancer risk. This work was initiated due to an interest in understanding the biological mechanisms underlying the role of pregnancy in relation to maternal breast cancer risk. Direct study of maternal hormones during pregnancy and subsequent breast cancer is difficult due to methodologic and practical issues (e.g., long time span between exposure measurement and breast cancer diagnosis) (122). In lieu of biologic measures, perinatal factors, which may be proxy measures of this environment (65, 66, 79), can be examined (118). As an example, figure 6.1 summarizes the proposed relationships between fetal growth and later maternal breast cancer, as well as the potential biological mechanisms underlying this association. After an extensive literature review and considering the study design and data limitations for conducting a registry-based birth and cancer linked study in MI, we decided to focus on the two perinatal exposures that have been least studied, gestational age and fetal growth, and which are measured fairly well and were available in the MI birth files for all years of the planned study.

Aim 1. (Perinatal factors and maternal breast cancer risk: a review of the epidemiologic literature)

To systematically identify and descriptively summarize all published studies on perinatal factors and maternal breast cancer risk, including maternal

conditions of pregnancy (preeclampsia, PIH, GDM, pregnancy weight gain) and infant birth characteristics (fetal growth, GA, multiple births, sex). These perinatal factors have been shown to reflect an altered hormonal environment during pregnancy, and may provide insight into the biological mechanisms underlying the role of pregnancy in breast cancer etiology. Given that that influence of many breast cancer risk factors depend on menopausal status (or by proxy age at diagnosis), we present findings stratified by menopausal status/attained age whenever available.

In this first paper, we summarized data on published studies for seven perinatal exposures, including preeclampsia/PIH, multiple births, GDM, pregnancy weight gain, fetal growth, gestational age, infant sex. Briefly, we found across 16 studies, that multiple births may protect against breast cancer. Preeclampsia was found to decrease risk by up to 20% in all but two studies; results may be modified by infant sex. Breast cancer risk may be increased by delivery at earlier gestational ages or elevated fetal growth in a first or last birth, but data is sparse. Infant sex does not appear to be associated with breast cancer. Data on associations between gestational diabetes, pregnancy weight gain and breast cancer risk is limited and conflicting. In summary, we found that additional research in the area of perinatal factors and maternal breast cancer is needed, including studies of perinatal exposures and breast cancer risk with ample sample size to consider jointly several key effect modifiers (e.g., time, age, birth order, menopausal status) with data on potential confounders, including non-pregnancy-related factors.

Aim 2. (Pregnancy-related factors and risk of breast cancer overall and by histologic type, a registry-based study of parous black and white younger women)

To investigate the associations between later age at first and last delivery, number of live births and breast cancer overall and by the two most common histologic types (ductal and lobular) among parous White and Black women 20-50 years of age in MI, 1985-2004. We will examine potential modification of the above associations by race (White, Black), and maternal education at first delivery (a measure of SES).

As hypothesized, we found that women with a later age at first or last birth had increased breast cancer risk. We also found that multiparity was associated with increased risk compared to women who had only one birth. Further, we found that later age at first and last birth increased risk of both ductal and lobular breast cancer. Contrary to our hypothesis, we did not find evidence that risks for age at first and last birth were more strongly associated with lobular as compared to ductal breast cancer. We also found that multiparity (versus primiparity) increased breast cancer risk similarly for both ductal and lobular cancer. Some differences by race were found, in particular, we found that among White women, later age at last birth significantly increased lobular breast cancer risk, but was not associated with ductal cancer. Among Black women, associations between pregnancy-related factors and risk of ductal or lobular tumors were non-significant, though number of lobular cases were small. Notably, we found a non-significant reduction in risk associated with both later age at first birth and risk of

lobular tumors and later age at last birth and risk of ductal tumors. These pregnancy-related factors were associated with increased risk among White women.

Aim 3. (A population-based case-control study of fetal growth, infant gestational age at delivery, and maternal breast cancer among younger women)

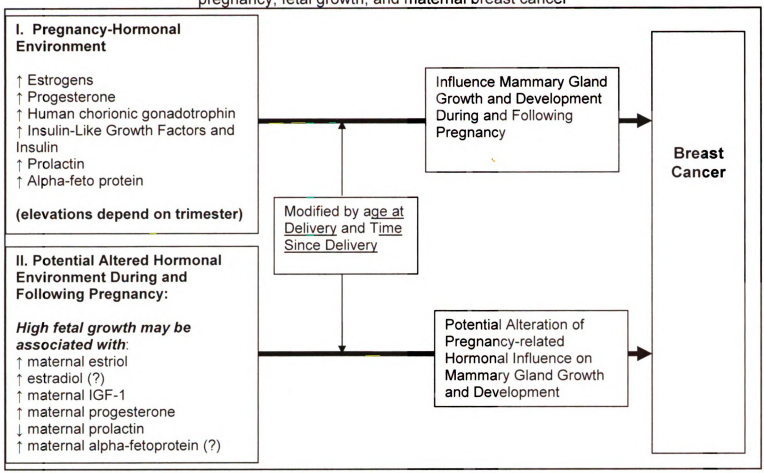
To investigate the associations between fetal growth, gestational age at delivery (≥ 41 weeks (postterm), 37-41 weeks (term), 36-32 (preterm), < 32 weeks gestation (very preterm)), and breast cancer overall and by histologic type among parous White and Black women 20- 50 years of age in MI, 1985-2004. We will estimate fetal growth using published birthweight percentiles for gestational weeks 24-44, described in the methods section in Chapter 5. We will examine potential modification of the above associations by race (White, Black), maternal education at first delivery, later age at delivery (first and last), and shorter time since delivery last delivery. We will examine the perinatal exposures in first births and last births (among women with two or more births).

Using data from a large, registry-linked, population-based case-control study among MI women ≤ 50 years of age, we found that low or higher birthweights adjusted for gestational age in a first birth, an approach commonly used by cancer epidemiologists to estimate fetal growth, were associated with breast cancer risk, including a 23-30% reduction in risk for lower birthweights and an 11% increase in risk for high birthweights. Results were statistically significant only for the association between breast cancer risk and delivery of an infant

weighing 1500-1999 g compared to 2500-3499 g. When we examined the association between fetal growth, defined using birthweight percentiles for each gestational week, and breast cancer risk, we found limited evidence for an overall association for fetal growth in a first birth and breast cancer risk, though ORs were in the hypothesized direction (i.e., slight decreased risk for delivery of an SGA infant and slight increased risk for delivery of an LGA infant). For last births, delivery of an SGA infant was associated with a non-significant reduced risk of breast cancer, which was limited to women ≥ 30 years at last birth and for women with ≥ 5 years since last birth in stratified analyses.

We found that delivery of an infant at < 32 weeks in a first birth was associated with a non-significant 20% reduction in breast cancer risk, which was in the opposite direction of our hypothesis and most previous literature to date. For last births, we found slight non-significant elevations in breast cancer risk of about 9-10% for delivery at < 32 weeks and 32-36 weeks. We also found a significant decreased risk of breast cancer associated with a posterm first delivery and breast cancer risk, which was more pronounced and significant only among women < 40 years in age and not among women 40-50 years in stratified analyses.

Figure 6.1. The maternal hormonal environment during pregnancy, fetal growth, and maternal breast cancer



2. Limitations and Strengths

Two main limitations should be considered when interpreting our results. First, it is possible that parity data is inaccurate for some women due to movement out of state for women who had more than one live birth, which could lead to underestimation of number of live births, incorrect classification of a birth as a last birth (for age at last birth), and lack of complete adjustment for number of live births as a confounder. Further, it could be said that it is more likely that controls moved out of state and had additional births because cases were required to have both their births and cancer diagnosis in MI; hence it is possible that our controls were more likely to have underestimated number of births and ORs could be biased away the null.

The other key limitation is that our study population has a much higher percentage of women with later age at first births and last births, as compared to other population-based studies. Table 4.7 displays distributions for age at first birth overall and by birth cohort for controls, with a comparison to a recent birth registry-based study among younger women conducted in Sweden (63). We expected these higher distributions, which are due to the data restrictions of our study (i.e., first live birth in 1978-2004 and year of first diagnosis during 1985-2004), and we carefully ensured that controls were selected from the same population that gave rise to the cases, so this should only influence the generalizability of our study findings, and not the bias the odds ratios.

Main strengths of our study include the large sample size, population-based state-wide design, and use of registry data. Registry-based studies are

less subject to key bias found in case-control studies, because exposure data is collected before breast cancer diagnosis. Further, using existing registry data provided us the opportunity to select controls from the source population that gave rise to the cases, without being subject to potential bias due to lower participation rates among controls. In addition, we had high quality cancer registry data that meets NAACCR standards. Finally, this is the first study to examine fetal growth defined using birthweight percentiles for gestational week, to examine exposures in both first and last births, and to investigate birth characteristics and breast cancer risk for specific histologic sub-types.

3. Conclusions

To date, few studies have been conducted in the area of perinatal factors in a women's own pregnancy and subsequent maternal breast cancer risk. The first manuscript of this dissertation will be the first published review focusing specifically on perinatal factors and maternal breast cancer and using systematic search methods. This paper can help guide researchers interested in this area of research when they are planning and conducting studies. The main conclusion of this work is that future research is needed to elucidate the associations between perinatal factors and maternal breast cancer, including studies of potential mechanisms for the role of perinatal factors in breast cancer etiology.

The second manuscript, which examined the *a priori* effect modifiers for the third aim of this dissertation, also makes an important contribution. Though ages at first and last birth and low parity have been well-studied, the associations of these factors by histologic type, in particular among younger women, have

been little described. We found that later age at first and last births, as well as multiparity, were associated with an increased risk of breast cancer overall and for both lobular and ductal histologic types. We did not find that associations varied by histologic type among all women. Some differences were found by race and education subgroups, but very few studies have examined histologic type among younger women and results require confirmation in future studies, particularly given limitations in sample size in subgroups.

The third paper of this manuscript is the first study to examine fetal growth defined using birthweight percentiles for gestational week, to examine infant birth characteristics in both first and last births, and to investigate at infant birth characteristics and breast cancer risk for specific histologic sub-types. We found limited evidence that fetal growth influences breast cancer risk overall and some evidence that earlier or late gestation in a first birth may be associated with a reduction in breast cancer risk. We did find a non-significant reduction in risk for delivery of an SGA infant in last birth, but not an LGA infant, which was statistically significant among women older than 30 years (vs. < 30 years) at their last birth in stratified analyses (OR = 0.82, 95% CI: 0.68-0.98). This finding could reflect the influence of lower levels of maternal estrogens or IGF-I levels during pregnancy on subsequent breast cancer risk. The suggestion of a reduced breast cancer risk for a first delivery at < 32 weeks gestation (vs. 37-41 weeks) (OR = 80, 95% CI: 0.62-1.04) could reflect elevated levels of maternal alpha-fetoprotein, but this finding is in the opposite direction of our hypothesis and most previous literature to date. Our finding of a protective effect of a posterm delivery in a first

birth (OR for > 42 weeks vs. < 37-41 weeks gestation = 0.92, 95% CI: 0.85-0.99), which has not been previously reported, warrants further study.

4. Recommendations

In summary, few studies have been conducted in the area of perinatal factors in a women's own pregnancy and subsequent maternal breast cancer risk. The study of breast cancer in premenopausal parous women is of particular importance given the increasing trend in delayed childbearing (289) and because women diagnosed with breast cancer shortly following pregnancy are more likely to have advanced breast tumors (37) and poorer tumor prognostic factors (38), as well as increased mortality risk compared to nulliparous premenopausal women (38-41). Additional research in the area of perinatal factors and maternal breast cancer, which incorporates epidemiologists trained in both perinatal and cancer epidemiology (113), is needed. Future studies of perinatal factors and maternal breast cancer should have ample sample size to consider jointly several key effect modifiers (e.g., time, age, birth order, menopausal status) with information on other potential confounding factors (e.g., body size). To improve biological hypotheses for studies of perinatal factors and breast cancer, future work is also needed to further characterize the maternal hormonal and metabolic profiles of exposed women during and following pregnancy.

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