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Weight Gain in Pregnancy and Pre-menopausal Breast Cancer: a population-based case-control study

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WEIGHT GAIN IN PREGNANCY AND PRE-MENOPAUSAL BREAST CANCER: A POPULATION-BASED CASE-CONTROL STUDY

by

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ABSTRACT

Background: The risk of breast cancer increases transiently after pregnancy and then falls to a lower level than for age-matched nulliparous women. Higher levels of estrogen are known as the primary reason. Several pregnancy characteristics are thought to be confounding the above link; however, except for the age at first pregnancy no other pregnancy-related factor has been proved to be significant. Specifically, it has not been established that an excessive weight gain in pregnancy is linked to the maternal risk of breast cancer.

Objectives: To identify independent influence of weight gain in pregnancy on the risk of pre-menopausal breast cancer following a delivery. We also examine the effect of demographic factors and other relevant pregnancy characteristics on the risk of breast cancer.

Methods: Our cohort consisted of 213,250 women who gave birth to a live neonate from January 1, 1994 to December 31, 2003. We performed a nested population-based case-control study on 126 Nevada patients with a first lifetime breast cancer diagnosed from January 1, 1995 through December 31, 2003, and 504 Nevada participants without breast cancer. The two groups were matched on age at the recorded delivery. Our dataset was a linkage between the Nevada Cancer Registry database for the years 1995–2008 and birth certificates from the Nevada State Health Division for the years of 1994–2008.

Results: The excessive weight gain in none of the categories was associated with increased risk of premenopausal breast cancer. After adjustment for other pregnancy characteristics the results remained unchanged. Women whose pregnancies progressed beyond 40 weeks of gestation were at significantly lower risk of developing breast cancer up to five years following delivery, compared to the women who delivered at 37–40 weeks of gestation (OR 0.33, 95% CI 0.11–0.93), after adjustment for confounding variables.

Conclusions: Our study did not show an association between excessive weight gain in pregnancy and the risk of pre-menopausal breast cancer. However, pregnancies that extended beyond 40 weeks of gestation were strongly associated with a lower likelihood of pre-menopausal breast cancer up to 5 years after delivery. Biological plausibility for this may relate to the fact that as pregnancy develops into more advanced stages, mammary cells have more time to complete differentiation and maturation; a process that started earlier in the third trimester. The results of this study will therefore contribute to the literature and may provide a basis for future studies.

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I owe this milestone in my academic career to the generous support and encouragement of my committee and all my instructors in the School of Community Health Sciences. My teachers here have always been glad to offer advice and encouragement, not only in the classroom, but also when I brought in obscure questions and frustrations from my extracurricular research in public health. Their enthusiasm for teaching has greatly helped me begin to realize my potential as a student and a researcher.

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CONTENTS

CHAPTER 1: BACKGROUND

Breast cancer is the most common type of cancer among females and the second most common cause of overall cancer death in the United States. It is also the main cause of death in women between ages 40 to 59 worldwide.[79] Risk factors for breast cancer include age at menarche, age at first live birth, menopause, proliferative breast disease, race, reproductive history, family history and genetic predisposition.[76] The lifetime risk of developing breast cancer is one in nine overall.[23] The incidence of breast cancer increased continuously by 3.7 percent per year starting in the 1980s in the U.S..[43] That trend is attributed to factors such as changes in reproductive patterns, long-term menopausal hormone use, the rising prevalence of obesity, and increased detection through screening mammography.[63] The rates rose again from 1994 to 1999; however, it declined from 1999 to 2007 by 1.8 percent per year.[43] According to data from the Centers for Disease Control and Prevention (CDC), 211,731 women were diagnosed with breast cancer in 2009 in the U.S. and 40,676 of them died in the same year.[89]

Breast cancer is also the most frequently diagnosed cancer and the leading cause of cancer death in female worldwide.[37] Breast cancer is a disease of affluence and more commonly seen in communities with high socioeconomic status.[62] The incidence rates are highest in North America, Australia, New Zealand, and in western and northern Europe, and lowest in Asia and Sub-Saharan Africa.[63,37] Although the rates decreased after 2000 in North America, breast cancer incidence continued to rise in other parts of the world, such as Asia and Africa. These international differences are thought to be related to industrialization factors such as changes in fat intake, body weight, age at menarche, lactation, and reproductive patterns such as fewer pregnancies and later age at first birth.[66]

Pregnancy-associated breast cancer is defined as breast cancer that occurs during pregnancy or in the first year after delivery. The frequency of pregnancy-associated breast cancer ranges from 1 in 3,000 to 1 in 10,000 deliveries.[69] The risk of breast cancer however remains high in the first few years after delivery and then falls to a lower level

than for age-matched nulliparous women.[44,15] A plausible explanation for the above finding is that pregnancy increases the short term risk of breast cancer by stimulating the growth of cells that had already commenced early stages of malignant transformation. However, it provides long term protection by inducing the differentiation of normal mammary stem cells that are prone to malignant change.[53,72]

Pregnancy associated breast cancer increases in rate as women delay childbearing until later in life.[2,15,44] In a case-control study of a nation-wide cohort in Sweden, nulliparous women were found to be at a higher risk of breast cancer than age-matched multiparous women up to 15 years after delivery and at a lower risk thereafter. The excess risk was more prominent among women who were older at the time of their first pregnancy with odds ratio (OR) 1.26 for 5 years after delivery among women 35 years old at first delivery and 95% confidence interval (CI) 1.10–0.44. The study also showed that women with two pregnancies had a lower risk of breast cancer later in life compared to mothers of a single child.[44] This is due to a long term protection provided by the first pregnancy.[53]

Although age at the first full-term pregnancy is known to be a strong predictor of pregnancy-related breast cancer [2,4,44,46,88] other pregnancy characteristics and perinatal factors may additionally play roles or affect the risk of breast cancer independently. According to the results from a multi-center case-control study on 4,599 women of 20-55 years of age diagnosed with breast cancer as case subject and 4,536 controls, age at first full-term pregnancy had a strong influence on the risk of breast cancer (OR 1.97 for women older than 35 years compared to teen-aged women; 95% CI 1.30–2.97). After controlling for other perinatal factors, the number of children and duration of breastfeeding also significantly predicted the risk of breast cancer. Women of parity seven or more had an adjusted relative risk of 0.59 (95% CI; 0.44–0.79) compared with uniparous women for developing breast cancer, and there was a constant reduction in risk as women continued to have more children. Women who had breastfed for 25 months or longer had an adjusted relative risk of 0.67 (95% CI; 0.52–0.85), compared with parous women who had never breastfed. The results did not support the prominent importance of age at first full-term pregnancy among the reproductive determinants of breast

carcinogenesis in a multivariate model (adjusted OR 1.58 for women older than 35 compared to teenaged mothers; 95% CI 1.032–2.42).[46]

The results from epidemiological studies have shown that the long-term protective effect of pregnancy on breast cancer risk is preceded by a short-term adverse effect.[4,15,44] According to a population-based prospective study of 802,457 Norwegian parous women aged 20–56 years including 4,787 breast cancer cases, the risk of breast cancer was lowest during pregnancy among all age groups and parities.[4] Nonetheless, a short-term post-delivery increase of the risk was also observed with a peak in 3–4 years after the last birth, and the risk declined steadily thereafter. After the third or later pregnancies, the maximum risk presented earlier (1–2 years after the last delivery). Women with three or more children had lower risk than did nulliparous women in most categories of time since the last birth. The above risk slightly increased among multiparous women with highest risk after adjusting for only age at the time of delivery in all categories of time; however, the peak remained the same. The authors concluded that a non-linear relationship existed between breast cancer incidence and the time since the last birth.[4]

A study by Wohlfahrt *et al*. showed that following childbirth, breast cancer may occur in a more advanced stage, together with higher rates of the disease.[93] The risk of late-stage breast cancer increases in the first few years of childbirth, and it tends to appear at a later stage (a larger tumor, nodal involvement, or histologic grading II or III).[94] According to a population-based cohort study of 1.5 million Danish women, uniparous and bi-parous mothers experienced a transient increased risk of late-stage breast cancer that did not seem to be attributable to a delayed cancer diagnosis. The risk of having a tumor larger than 5 cm in at least one dimension was 53% higher during the first 10 years after childbirth compared with later in life.[93] The high rate of late-stage breast cancer in the first years after a birth might be attributed to delayed diagnosis or treatment of breast cancer during pregnancy.[60] This finding suggests that pregnancy-related factors can transiently induce a high growth rate in cells that are already malignant and stimulate new tumor growth.[93]

The influence of pregnancy characteristics on early breast cancer was studied in a large population-based case-control study of parous women aged 20–44 years, and the results partially opposed the previous findings. The study found that women who reported nausea or vomiting in their first pregnancy had a slightly lower risk of breast cancer [relative risk (RR) 0.87; CI 0.72–1.0].[88] This was attributed to relatively higher levels of human chorionic gonadotropin (HCG) in pregnancy.[51] Although the author found some evidence for reductions in pregnancies with female twins (RR 0.48; 95% CI 0.20–1.3) compared with singletons, the results did not reach a statistically significant level. Except for age at delivery (RR 1.4 for women older than 30 at delivery compared to teenaged mothers, CI 1–1.8) the study showed no associations for maternal risk related to pregnancy characteristics.[88] The authors support the idea that nulliparity is a risk factor for breast cancer and each pregnancy adds small additional protection on this risk.[40] A full-term pregnancy earlier than age 30 particularly provides a strong protection against breast cancer later in life. A plausible explanation for the observed difference is that during pregnancy the levels of reproductive hormones mainly alpha-fetoprotein (AFP) and HCG increase, and this can regress estrogen-dependent tumors.[74]

Although the hormonal effects of pregnancy on breast cancer are better known, it is still possible that other changes during pregnancy predispose mothers to breast cancer independently or through an effect on the estrogen levels. A plausible example of these pregnancy characteristics could be pregnancy weight gain. During pregnancy, the breast tissue undergoes proliferation in preparation for lactation. Estrogen stimulates normal breast cells to differentiate to milk-secreting alveoli, while cells with malignant degeneration may further develop into detectable tumors.[20] Androgen is aromatized to estrogen in adipose tissue[67]; thus a high body mass index is linked to elevated estrogen levels. As a result, excessive weight gain during pregnancy can potentially cause higher estrogen levels that may increase the risk of breast cancer later in life.[75] According to a case-control study within a cohort consisting of 2,089 Finnish women (123 cases of breast cancer, and 856 controls), a weight gain of more than 15 kg during pregnancy was associated with 62% higher risk of breast cancer (RR 1.62; 95% CI 1.03–2.53) compared to women with the recommended weight gain of 11–15 kg after adjusting for mother's

age at menarche, age at first birth, age at index pregnancy, parity at the index birth, and BMI before the index pregnancy. Further investigations determined that the excessive weight gain in pregnancy independently affected the risk of postmenopausal breast cancer in their study; and case subjects did not transfer their pregnancy weight gain into the postmenopausal period. Therefore, they did not have a higher BMI than the control subjects at the time of breast cancer diagnosis (P value<0.05).[42]

The influence of pregnancy weight gain on premenopausal breast cancer was studied with regards to BMI by Hilakivi-Clarck *et al.*[28] however; the results were not consistent with the previous findings. In a nested case-control study within a cohort of 22,610 Finnish women, 114 cases of premenopausal breast cancer were identified. A total of 98 cases of breast cancer and 392 controls were selected for the final model. According to the analysis, women who gained 16 kg (35.2 Ibs) during their last pregnancy had a significantly lower risk of breast cancer in the premenopausal period (OR 0.28; 95% CI 0.08–0.96) if their BMI increased >7 m/kg^2 after the age of 20; however, the risk of breast cancer increased later during post- menopause. The authors concluded that an excessive pregnancy weight gain may provide short-term protection, but cause a long-term hazardous effect on breast cancer following menopause. It remained to be determined why BMI and pregnancy weight gain affect premenopausal and postmenopausal breast cancer risks differently.[2]

CHAPTER 2: SPECIFIC AIMS

Although high levels of estrogen are known as cause of pregnancy-associated breast cancer, it is still possible that other perinatal factors interfere with this relationship or even cause breast cancer independently. The influence of different perinatal factors on resultant breast cancer has been studied; however, except for the mother's age at first full-term pregnancy,[2,4,44,46,88] other findings have not been consistent. A study by Luke *et al.* showed a protective effect of excessive weight gain in pregnancy on the risk of breast cancer in pre-menopausal women, although the risk rose later in postmenopausal life.[28] In this project, we aim to examine the independent effect of excessive weight gain in pregnancy on the premenopausal risk of breast cancer. Up to our knowledge, there have been only a couple of studies on this relationship that did not show consistent results.

The effect of weight gain during pregnancy on an early onset of breast cancer looks plausible. A few mechanisms such as the hormonal effects of estrogen on pre-malignant cells, increased testosterone aromatization in fat tissue, and increased cell proliferation and gene mutation in pregnancy can explain the plausibility of our hypothesis.[42,44] Although only a single study showed the above cause and effect relationship,[42] and this was not supported by other studies; it is still interesting to examine such a link in other populations.

For the purpose of this study we will utilize two linked datasets: the Nevada Cancer Registry (1995–2008), and the birth certificates of individuals born in Nevada (1994–2008). The overall goals of this population-based case-control study are as follow:

- To study whether changes occurring during pregnancy (mainly excessive weight gain as predictive variable) can play a role in developing breast cancer (outcome variable) in a period up to 5 years following delivery

- To study whether other perinatal and prenatal factors such as birth weight, birth order, gestational age, method of delivery and induction of labor, as well as mother's age at the time of delivery, race/ethnicity, level of education, plurality,

smoking and drinking habits can potentially influence the risk of breast cancer in a period of up to 5 years following delivery

CHAPTER 3: RESEARCH QUESTIONS

- Is an excessive weight gain during pregnancy associated with an increased risk of breast cancer in a period of 5 years following delivery?

- Can any variable of pregnancy or delivery such as birth weight, birth order, gestational age, method of delivery and induction of labor, as well as mother's age at delivery, race/ethnicity, and level of education, plurality, smoking and drinking habits, and marital status increase the risk of breast cancer during 5 years following delivery?

The independent variable is excessive weight gain during pregnancy and the dependent variable would be the new diagnosis of breast cancer during 5 years following delivery.

CHAPTER 4: MAIN HYPOTHESIS

The null and the alternative hypotheses are as follows:

Ho: Excessive weight gain during pregnancy does not increase the risk of breast cancer during 5 years following delivery.

Ha: Excessive weight gain during pregnancy is associated with an increased risk of breast cancer during 5 years following delivery.

CHAPTER 5: MATERIALS & METHODS

Data Source

Data for this population-based case-control study were obtained from two datasets: the Nevada Cancer Registry with all cancer diagnoses in the state from January 1, 1995 to December 31, 2008; and the birth certificates of individuals born from January 1, 1994 to December 31, 2008 in the state of Nevada. Data from the two sources were linked based on birth date; mother's name and mailing address (all identifiable variables which were not released with the working dataset) by the Nevada State Health Division. The data include information about all cancer types occurring among the mothers as well as all variables of pregnancy and delivery normally listed in a standard U.S. birth certificate. The dataset also provides an enumeration of the population from which controls can be sampled. Figure 2 illustrates the linkage between the two sources of data.

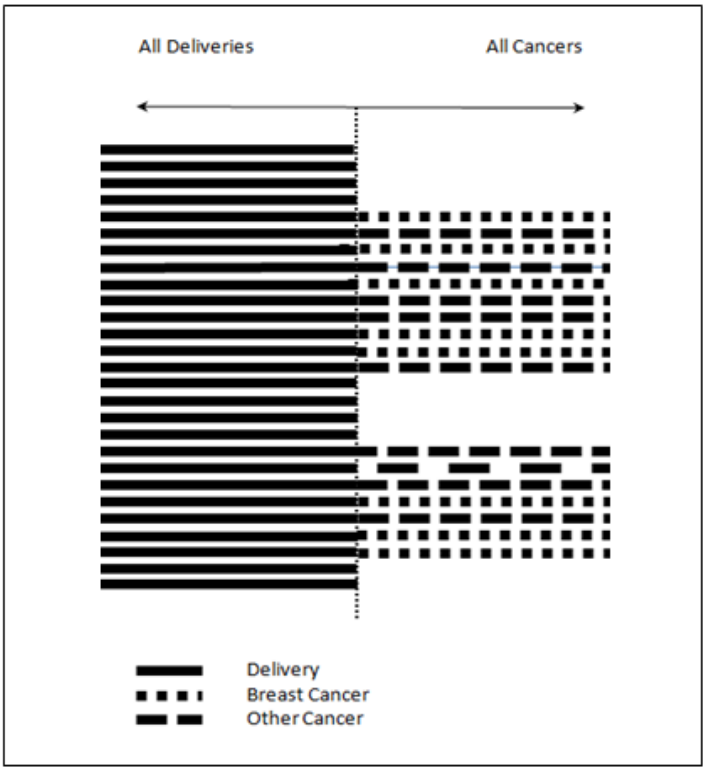


Figure 2. The linkage of the Nevada Cancer Registry database and the State of Nevada birth certificates

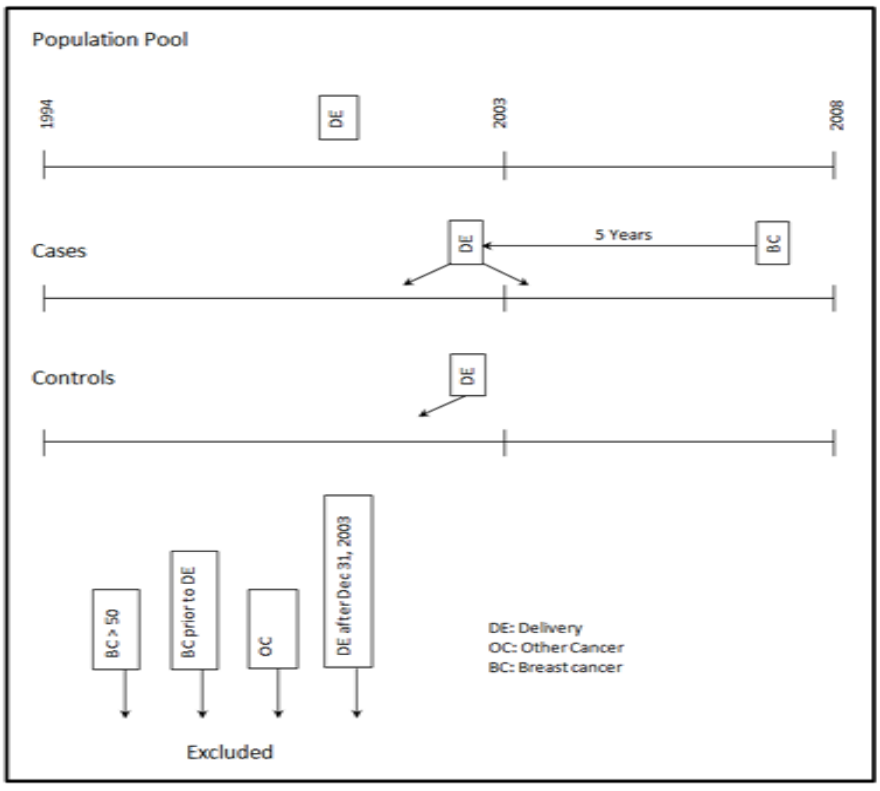
Participants

This is a population-based case control study. There is no interview or use of questionnaires. The initial dataset (population pool) consisted of all women who gave birth to a live baby from January 1, 1994 to December 31, 2008 in the state of Nevada.

The cases were defined as women who were diagnosed with premenopausal (<50 years of age) breast cancer from January 1, 1995 to December 31, 2008 in the state of Nevada after having delivered a live baby from January 1, 1994 to December 31, 2003 in the state of Nevada. The control group included women who gave birth to a live baby during the period of January 1, 1994 to December 31, 2003 and were not diagnosed with breast cancer from January 1, 1995 to December 31, 2008 in the state of Nevada (Figure 1).

Women who were diagnosed with breast cancer following menopause (>50 years of age was considered as cut-off point), women who were diagnosed with breast cancer prior to the recorded delivery, and women with a diagnosis of cancer other than breast cancer were excluded from the study (Figure 1).

Figure 1. The study population: inclusion and exclusion criteria



Study Population

Initially, the study pool included all women who gave birth to a live baby from January 1, 1994, to December 1, 2008 in the state of Nevada. A cohort of 461,766 women between the ages of 11 and 67 years whose delivery information was available through a birth certificate was identified.

Research Design

We performed a nested case-control study within the abovementioned residents of Nevada. Cases and controls were frequency-matched by the ratio of 1 to 4 by age of the mother at delivery in categories of 5-year age groups.

According to some of the previous studies, breast cancer is most commonly diagnosed within 3–4 years after a delivery,[4] and so we limited cases and controls to a delivery date of December 31, 2003; indicating the latest date of delivery providing enough time for the individuals to develop breast cancer up to the last diagnosis year covered in the dataset (2008).

The main predictor variable in our study was excessive weight gain during pregnancy, and the outcome variable was the occurrence of breast cancer diagnosed in 5 years following a full-term pregnancy, but prior to menopause. A weight gain of 36 Ibs or more during a full-term pregnancy was considered as an excessive weight gain. We examined the independent effect of 13 other covariates whose information is available in our dataset, and the effect of the main variable was adjusted for these covariates in the final model.

Selection of Cases and Controls

The initial dataset included 461,766 women who gave birth from Jan 1, 1994 to Dec 31, 2008 in the state of Nevada. The information about date of delivery (‘Date of Birth’) was not available in the data and we were required to add the values of Last Menstrual Period to that of the Gestational Week of mothers at the time of delivery in order to compute the

delivery date. The data missed the information of at least one of the above variables for a number of 83,735 women; therefore, these women were removed from the study.

A total of 213,250 mothers gave birth during the period of 1994–2003, of which 330 cases of breast cancer and 680 cases of other cancers were identified. The latter population was excluded from the study. Among the remaining breast cancer cases, only 126 individuals were diagnosed with breast cancer up to 5 years after delivery, and those were counted in the final model. The 126 cases of breast cancer did not include women older than 50 years old; thus no one had to be excluded from the cases for this reason. We selected four age matched controls for each case using frequency matching technique (504 controls). Our final model consisted of 630 individuals (Figure 3).

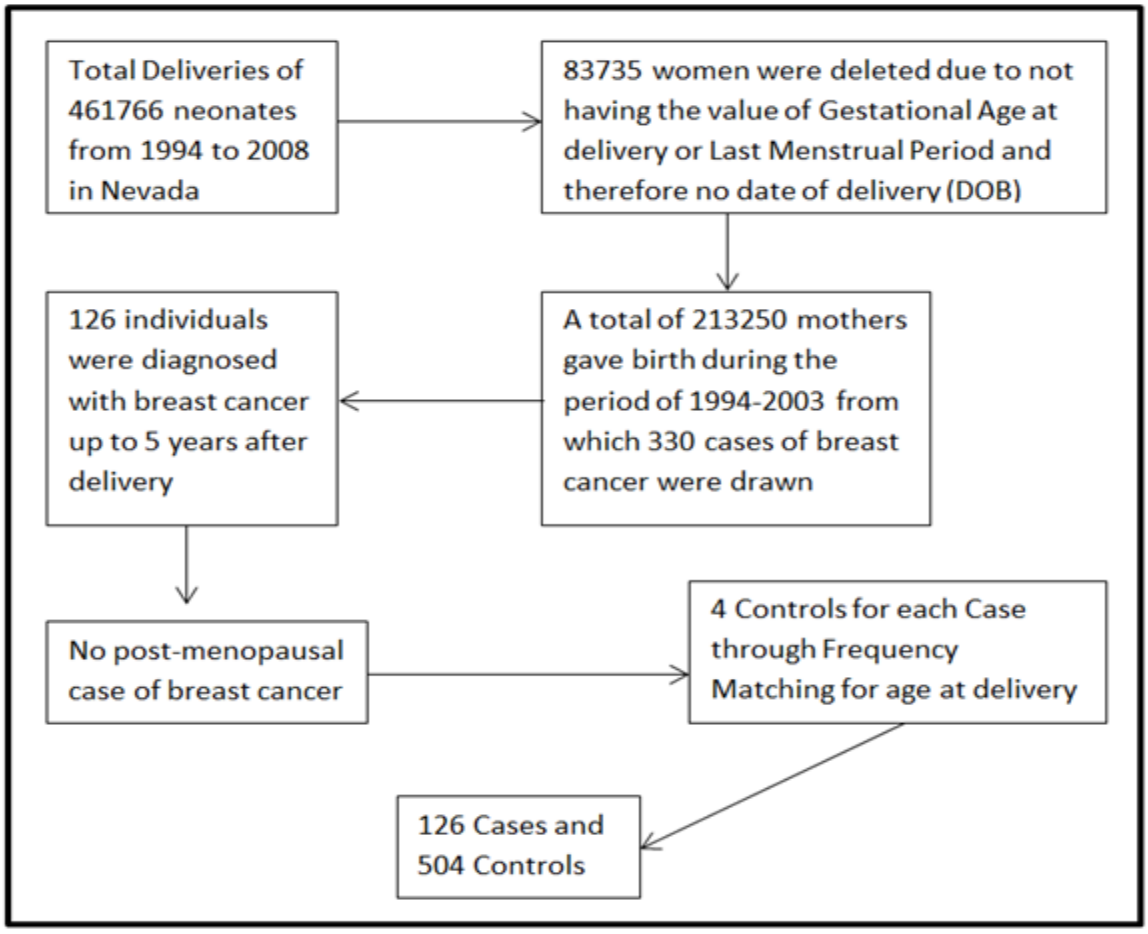


Figure 3. The selection model for Cases and Controls

Exposure Definition and Determination

Weight gain in pregnancy is defined as total extra weight that a mother gains during a pregnancy, and that was already calculated by subtracting mother's weight before pregnancy from mother's weight at delivery. The average weight gain in a normal pregnancy is expected to be 25–35 pounds, which includes the baby (6–8 lbs), placenta (1–2 lbs), uterus (1–2 lbs), amniotic fluid (2–3 lbs), breast (1–2 lbs), blood (3–4 lbs), and body fluid (3–4 lbs).[34]

Weight gain in pregnancy depends on the Body Mass Index (BMI) before conception. The guidelines for pregnancy weight gain are issued by the Institutes of Medicine (IOM). According to the most recent recommendation, as of 2009, a woman with a normal BMI (18.5–24.9) is expected to gain between 25 and 35 pounds during pregnancy. This is equivalent to 1 to 5 pounds in the first trimester and an average of 1 pound per week for the rest of the pregnancy for an optimal growth of the baby. Table 1 illustrates the normal weight gain and the break, respectively, in a full-term pregnancy.[30]

According to the standard birth certificate issued by the Centers for Disease Control, the subgroup recommended that mother's pregnancy weight (Item 33) and mother's weight at delivery (Item 34) be added to replace the previous 'weight gained during pregnancy' item in an effort to gain more accurate information on the weight gained during pregnancy. The height and the pre-pregnancy weight are needed in order to calculate maternal BMI. As a matter of fact, maternal weight gain is of little value without the knowledge of maternal BMI. Maternal BMI alone and in combination with maternal weight gain during pregnancy is associated with the pregnancy outcome and maternal morbidity and mortality.[18]

The weight gain during pregnancy can be measured using the Pregnancy Weight Gain Calculator software which needs current information about mother's weight and height, and the gestational age of the fetus.[33] For a twin pregnancy, the IOM recommends a gestational weight gain of 16.8–24.5 kg (37–54 lbs) for women of normal weight, 14.1–22.7 kg (31–50 lbs) for overweight women, and 11.3–19.1 kg (25–42 lbs) for obese

women. There is no guideline available for estimating weight gain in a multiple gestation pregnancy.[33]

There is also no clear definition for 'excessive weight gain' during pregnancy. A previous study categorized total weight gain of more than 15 kg (33 Ibs) as more than normal regardless of BMI and number of gestations.[42]However, by considering table 1 and for the purpose of our study, we defined a weight gain of 35 Ibs or more as excessive weight gain in pregnancy regardless of mother's body mass index or number of fetuses, and we classified it as mild (36–50 Ibs), moderate (51–65 Ibs), or severe (>65 Ibs) excessive weight gain. Table 1 illustrates the Institute of Medicine's weight gain guidelines for pregnancy.[78]

Table 1. The Institutes of Medicine's weight gain recommendations for pregnancy.

Prepregnancy Weight Category	Body Mass Index*	Recommended Range of Total Weight (lb)	Recommended Rates of Weight Gain† in the Second and Third Trimesters (lb) (Mean Range [lb/wk])
Underweight	Less than 18.5	28–40	1 (1–1.3)
Normal Weight	18.5–24.9	25–35	1 (0.8–1)
Overweight	25–29.9	15–25	0.6 (0.5–0.7)
Obese (includes all classes)	30 and greater	11–20	0.5 (0.4–0.6)

*Body mass index is calculated as weight in kilograms divided by height in meters squared or as weight in pounds multiplied by 703 divided by height in inches.

†Calculations assume a 1.1–4.4 lb weight gain in the first trimester.

Modified from Institute of Medicine (US). Weight gain during pregnancy: reexamining the guidelines. Washington, DC. National Academies Press; 2009. ©2009 National Academy of Sciences.

Ethical Considerations

Approval from the UNLV Institutional Review Board (IRB) was obtained. Our database does not include names or patient identifications, and as a result the study was exempt from IRB approval.

CHAPTER 6: COVARIATES

Out of a total of 64 variables present in the database, we included only 13 covariates that were believed to be relevant for the study through a plausible relationship with the outcome variable. We studied the effect of each of these 13 predictor variables on the outcome variable in both univariate and multivariate models.

The selected covariates included birth weight, birth order, gestational age and induction of labor, as well as mother's age at delivery, race/ethnicity, and levels of education, plurality, smoking and drinking habits, gestational hypertension, and gestational diabetes.

Some of the covariates play the role of confounding factors in our study, and therefore we computed and adjusted the influence of each of them on the risks of breast cancer in a multivariate model. All variables were already measured and the results were available as yes/no or a number (string and numeric) in our dataset. Table 2 shows the frequency of each variable. Some of the covariates are defined below:

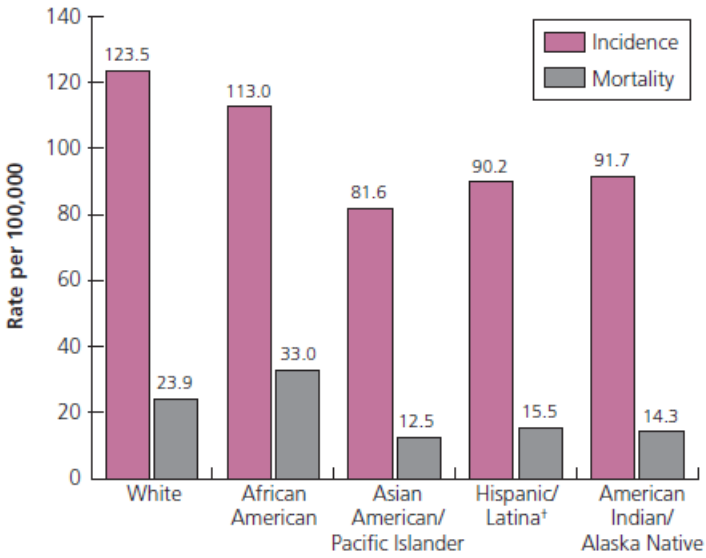
Age

Age is the second strongest risk factor for breast cancer following sex. Incidence rates increase along with age steadily until about the age of 45 to 50, then the increase continues but at a slower rate.[38] Hormonal change due to menopause taking place at this time may explain this pattern. The curve flattens at 75 to 80 years of age, and decreases only mildly thereafter.[14] According to data from 2002−2006, 95% of new cases and 97% of deaths due to breast cancer occurred in women aged 40 and older; and the average age at the time of diagnosis was 61 years.[7]

Pregnancy related breast cancer also increases in rate as women delay childbearing until later in life; when the incidence of breast cancer would normally increase.[2,38,44,46,88] However, it peaks at an earlier age than that of nulliparous women or women who gave birth at younger ages.

Race

According to the National Cancer Institute, white non-Hispanic women have the highest overall incidence rate for breast cancer among U.S. ethnic groups, while Asian-American women have the lowest rate (Fig. 4).[8,38] Among women of ages 40─50, African-American women have the highest incidence of breast cancer.[35] Black women also have the highest mortality rates from breast cancer in all age groups.[16] Among women of all races and ages, breast cancer mortality rates declined at an average rate of 2.3% per year between 1990 and 2002, which reflects development in both early detection and treatment.[81]



*Rates are age-adjusted to the 2000 US standard population. †Persons of Hispanic origin may be any race.

Figure 4. U.S. female breast cancer profile for 2002–2006: incidence and mortality rates by age and race (American Cancer Society, Surveillance Research, 2009)

Birth Weight

Birth weight is the first weight of the baby measured right after being born. Birth weight is measured on pounds scale, and a range of 5.5 to 10.5 Ibs is considered as normal birth weight.[36] A low birth weight of neonates (also known as 'small for gestational age') can be due to prematurity or other reasons such as health issues of mother, genetic factors,

problems with the placenta, and substance abuse by the mother.[58] The term Fetal Growth Restriction (FGR) (also called intrauterine growth restriction: IUGR) is used when a fetus has not reached its expected growth; mainly due to genetic or environmental factors.

Small for gestational age (SGA) refers to a weight below the 10th percentile for gestational age. Most of the fetuses who weigh below the 10th percentile for gestational age are small only because of constitutional factors such as female sex or maternal ethnicity, parity, or body mass index; and they are not at high risk of perinatal mortality or morbidity.[12] The incidence of FGR varies among populations, and increases with decreasing gestational age. Approximately 23% of full-term infants in developing countries are SGA; compared to only 10% of term infants in developed countries.[10]
High birth weight of neonates is often constitutional or due to maternal conditions during pregnancy, mainly diabete.[58] Infants are considered large for gestational age (LGA) if their birth weight is greater than the 90th percentile for gestational age (equal to 3,800 grams).[5]

Factors related to intrauterine growth in the female offspring may increase adult risk of breast cancer. A high birth weight is thought to be linked with risk of breast cancer later in life.[55,56,90] A high level of estrogen during embryonic life is thought to be the main reason. Trichpopolos hypothesized this link in 1990; and it was subsequently supported by a few studies; although some studies have been inconclusive or found no association.

Although the above link has been investigated by many studies and is generally supported by the literature, there is little evidence that birth weight is associated with maternal risk of breast cancer. To our knowledge, none of the case-control studies on the association between pregnancy characteristics and maternal breast cancer have been able to provide significant results on birth weight. This link has not been examined in an observational study so far, or the results were inconclusive.

Twin Pregnancy (Plurality)

Twin pregnancies have been increasing in proportion among total pregnancies in the developed countries; which seems to be due to the expanded use of fertility treatments and older maternal age at childbirth.[8,71] In the United States, twin births accounted for 3.3% of live births in 2008.[50] Multiple gestations are associated with higher rates of almost every complication of pregnancy except for post-term pregnancy and fetal macrosomia.[19, 82]

It has been hypothesized that the relatively higher estrogen levels in twin pregnancies might be linked with higher risk of maternal breast cancer.[21] However, support for this seems to be insufficient, and in fact there are studies showing opposite results.[27,39, 45,57,59,85,88] The higher levels of other pregnancy hormones such as progesterone and HCG are suggested as a likely mechanism for association between multiple gestations and reduced risk of maternal breast cancer.

Gestational Age

Gestational Age (GA) is defined as the length of the pregnancy, and is measured in weeks by subtracting the date of the Last Menstrual Period (LMP) from the date of delivery minus another 2 weeks.[31] It is assumed that fertilization in humans normally occurs 14 days after the onset of the LMP.[92] By agreement, only completed weeks of gestation are counted. If a more precise gestational age is required, the number of remaining days is added to the calculated complete weeks of gestation.[52] A value of 37–40 weeks is referred as normal GA for delivery or a normal full-term pregnancy. According to data from CDC in 2005, the mean gestational age for singletons was 38.7 weeks.[49]

According to the World Health Organization, the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG), premature birth is defined as the delivery of an infant prior to completion of 37 weeks of gestation.[52] Infants born between 34 and 36 weeks of gestation are called as late preterm.[22] Some studies have defined late preterm birth as 35─36 weeks.[32] Post-term pregnancy is defined as a pregnancy that has extended beyond 42.0 weeks of gestation or 294 days from the

first day of the last menstrual period.[1] In 2005, around 6% of pregnancies continued beyond 42 weeks of gestation.[49] The prevalence of post-term pregnancy in a population is influenced by several factors, but mainly by performing an early ultrasound assessment of gestational age. The use of ultrasound for detection of gestational age early in pregnancy has reduced the prevalence of post-term pregnancy to 2%.[17,52]

The incidence of premature births has increased from 10.6 percent in 1990 to 12.8 percent of all live births in 2006; and declined over three consecutive years to 12.2% of all births in 2009.[52] Changes in rates of late preterm birth (35^{th} and 36^{th} weeks of gestation) is known to be the cause of this trend in 2006 and from 2007 to 2009.[25]

A preterm delivery was thought to be associated with increased risk of breast cancer. This idea originated from a study that showed mammary cells proliferate in the first and second trimester of pregnancy and differentiate in the last trimester among animals.[73] It was then hypothesized that a full term pregnancy is required for complete differentiation of the mammary cells, and that early pregnancy termination or a pre-term labor may elevate the risk of breast cancer. The assumption was examined a few times thereafter and some evidence was found to support such link.[29, 54,91] According to the results of a study by Melbye *et al.*, parous women who gave birth prior to 32nd week of gestation for any reason had significantly higher risk of pre-menopausal breast cancer compared to women who delivered at 40 weeks of pregnancy (RR 1.72; 95% 1.14−2.59). However, a pre-term delivery after 32 weeks of gestation did not significantly change the risk of breast cancer.[54]

Gestational Hypertension

Gestational hypertension or Pregnancy Induced Hypertension (PIH) is defined as systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg detected after 20 weeks of gestation in a previously normotensive pregnant woman.[70,77] The blood pressure readings have to be documented on at least two occasions six hours apart. Gestational hypertension is a temporary diagnosis for hypertensive pregnant women who do not meet criteria for preeclampsia (both hypertension and proteinuria) or chronic

hypertension (hypertension first detected before the 20th week of pregnancy). Gestational hypertension occurs in about 6% of pregnancies.[97]

Preeclampsia is defined as hypertension after 20 weeks of gestation associated with proteinuria (presence of protein> 3grams in a 24-hour urine sample), and is characterized by dysfunction of the maternal endothelium.[47] Given that many hormonal changes occur with preeclampsia, it is possible that these changes influence the risk of maternal breast cancer.[41] According to a meta analysis of 13 relevant articles about preeclampsia and six relevant publications about PIH, both preeclampsia[84] (OR 0.86; 95% CI 0.73−1.01), and PIH[86] (OR 0.83; 95% CI 0.66−1.06) were found to have a protective effect on maternal risk of breast cancer later in life.[41]

Gestational Diabetes

Women are normally prone to insulin resistance in pregnancy that predisposes them to develop diabetes. The resistance is mainly caused by placental secretion of diabetogenic hormones such as growth hormone, placental lactogenic hormone, and progesterone, as well as an increased maternal adipose deposition, decreased exercise, and increased caloric intake.[46] Gestational diabetes is defined as having an abnormal glucose tolerance test detected for the first time during the n pregnancy.[68]

According to the recent guideline issued by the American Diabetes Association in order to diagnose a woman with gestational diabetes, she either has to have a fasting plasma glucose ≥92 mg/dl and <126 mg/dl at any gestational age or to have an abnormal oral glucose tolerance test (GTT). An abnormal GTT is defined as having a fasting plasma glucose ≥92 mg/dL but <126 mg/dL or an one-hour blood sugar ≥180 mg/dL or a two-hour blood sugar ≥153 mg/dL after a two-hour GTT with 75 grams of glucose.[9]

The prevalence rates of gestational diabetes are higher in African-American, Hispanic-American, Native American, and Asian women than in white women in the United States.[11] Up to 16% of patients with breast cancer have type-1 or type-2 diabetes. According to a meta-analysis of data on 43 studies, a significantly elevated risk of breast

cancer was found to be associated with diabetes in women (OR 1.20; 95% CI 1.13−1.29). The author concluded that diabetes independently increases the lifetime risk of breast cancer in women.[26] Gestational diabetes might also be associated with excess risk of breast cancer.[95]

CHAPTER 7: STATISTICAL ANALYSIS

The data were collected, cleaned, and recoded for use in this study. We compared the demographic features and prevalence of major risk factors between case and control subjects. We performed a case-control study of the association between excessive weight gain during pregnancy and a breast cancer diagnosis. We measured the odds of excessive weight gain during pregnancy in case patients in relation to breast cancer.

Regression analyses were conducted with the logistic procedure of SPSS 20. We utilized unconditional logistic regression to determine the adjusted estimates of odds ratios and respective 95% confidence intervals. Unadjusted odds ratios at 95% CI; as well as P-values for each variable were computed. The odds ratio for each one of the abovementioned weight gain was adjusted for the potential confounding variables described above. The background characteristics of the recorded pregnancies are shown in table 2.

Table 2. Background characteristics of the recorded pregnancies

Risk Factors	Cases N=126 (%)	Controls N=504 (%)
Age (years)		
≤24	2 (1.5)	7 (1.3)
25–29	14 (11.2)	79 (15.6)
30–34	42 (33.3)	164 (32.5)
35–39	46 (36.6)	194 (38.4)
40–44	21 (16.6)	56 (11.1)
≥45	1 (0.7)	4 (0.7)
Race		
White	80 (63.8)	290 (57.7)
Black	11 (8.7)	26 (5.1)
Hispanic	21 (16.6)	140 (27.7)
Native	1 (0.7)	2 (0.3)
Asian	12 (9.5)	38 (7.5)
Unknown	1 (0.7)	8 (1.5)
Education (years)		
≤6	2 (1.5)	30 (5.9)
7–12	52 (41.2)	197 (39.4)
13–14	26 (20.6)	109 (21.6)
15–16	26 (20.6)	93 (18.4)
≥17	16 (12.6)	62 (12.3)
Unknown	1 (0.7)	13 (2.5)
Birth Weight (lbs)		
≤5.49	15 (11.9)	57 (11.3)
5.50–10.49	110 (87.3)	446 (88.4)
≥10.50	0	1 (0.7)
Unknown	1 (0.7)	0
Plurality		
1	121 (97.0)	489 (96.0)
2	5 (2.3)	12 (3.9)
3	0	2 (0.3)
4	0	1 (0.1)

Risk Factors	Cases N=126 (%)	Controls N=504 (%)
Parity		
1	125 (99.3)	499 (99.1)
2	1 (0.7)	5 (0.9)
Gestational Age (w)		
≤34	4 (3.2)	21 (4.1)
35–36	10 (7.9)	28 (5.5)
37–40	108 (85.7)	406 (80.5)
≥41	4 (3.2)	49 (9.7)
Weight Gain		
≤24	26 (24.4)	123 (24.4)
25–35	47 (37.4)	185 (36.7)
36–50	34 (26.9)	124 (24.7)
51–65	8 (6.3)	21 (4.1)
≥66	11 (8.7)	51 (10.1)
Alcohol		
No	121 (96.1)	487 (96.6)
Yes	3 (2.3)	12 (2.5)
Unknown	2 (1.5)	5 (0.9)
Tobacco		
No	107 (84.9)	437 (86.7)
Yes	18 (14.4)	62 (12.4)
Unknown	1 (0.7)	5 (0.9)
Induction of Labor		
No	94 (74.6)	368 (73.1)
Yes	32 (25.4)	136 (26.9)
Hypertention		
No	121 (96.1)	490 (97.2)
Yes	5 (3.9)	14 (2.8)
Diabetes		
No	124 (98.4)	497 (98.6)
Yes	2 (1.6)	7 (1.4)

CHAPTER 8: RESULTS

In the initial cohort, 330 women developed breast cancer from 1995 to 2008. A total of 126 cases aged 21─46 were eligible and entered the final model. The cases of breast cancer had a mean age of 34.37 ± 4.57 at delivery and mean age of 37.88 ± 4.58 at the time of diagnosis. The average time difference between the ages at the time of breast cancer diagnosis and age at recorded delivery was 5.19 ± 1.46 years. The cases and controls were matched on age at the time of delivery; thus we did not study the effect of age on the risk of premenopausal breast cancer, although the values of every other variable were adjusted for that. The unadjusted odds ratio of maternal breast cancer by pregnancy characteristics is shown in Table3.

Table 3. Unadjusted odds ratio of maternal breast cancer by pregnancy characteristics

Risk Factors	OR	95% CI	P value
Race			
White	Referent		0.135
Black	1.58	0.74–3.37	0.239
Hispanic	0.56	0.33–0.94	0.029
Native	2.02	0.18–22.94	0.571
Asian	1.14	0.96–2.29	0.718
Unknown	0.46	0.05–3.78	0.469
Education (years)			
≤6	Referent		0.337
7–12	4.24	0.97–18.49	0.055
13–14	3.77	0.84–16.92	0.084
15–16	4.31	0.96–19.42	0.056
≥17	4.63	1.00–21.39	0.051
Unknown	1.11	0.09–13.57	0.933
Birth Weight (lbs)			
1–5.49 lbs	1.11	0.60–1.99	0.768
5.5–10.49	Referent		0.957
Plurality			
1	Referent		0.871
2	1.61	0.54–4.67	0.398
Parity			
1	Referent		0.999
2	0.81	0.09–7.12	0.839
Gestational Age (weeks)			
17–34	0.63	0.21–0.95	0.446
35–36	1.33	0.62–2.86	0.464
37–40	Referent		0.122
41–48	0.32	0.11–0.92	0.034

Risk Factors	OR	95% CI	P value
Weight Gain (lbs)			
0–24	1.17	0.68–2.00	0.558
25–35	Referent		0.662
36–50	1.32	0.74–2.23	0.337
51–65	1.88	0.74–4.74	0.183
66+	0.99	0.46–2.18	0.996
Alcohol			
No	Referent		0.891
Yes	1.09	0.30–3.98	0.506
Unknown	1.77	0.32–9.57	0.118
Tobacco			
No	Referent		0.838
Yes	0.18	0.67–2.09	0.562
Unknown	0.88	0.10–8.01	0.915
Induction of Labor			
No	Referent		
Yes	0.85	0.61–1.50	0.956
Hypertention			
No	Referent		
Yes	1.33	0.45–3.89	0.607
Diabetes			
No	Referent		
Yes	1.27	0.26–6.26	0.769

The average weight gain in pregnancy among cases was 38.34 ± 20.50 Ibs and for that of controls was 37.33 ± 2.19 Ibs. An excessive weight gain was found among 42% of cases and 39% of controls. Excessive weight gain was identified in 42% of patients with breast cancer diagnosis and 39% of controls, giving odds ratio of 1.32, 1.87, and 0.99 for weight gains of 36–50, 51–65, and +66 Ibs, respectively compared to the weight gain category of 25–35 Ibs as reference group. However, the values did not reach significant levels (Table 4).

A total of 17 mothers had twin pregnancies (5 cases and 12 controls). Two mothers had triplet pregnancy and one had a quad pregnancy. Six mothers (1 case and 5 controls) had their second pregnancy recorded in the dataset. Due to the low number of cases with multiple gestational pregnancies as well as those with a second pregnancy, the results were inconclusive on these variables.

Pregnancies that progressed beyond 40 weeks of gestation were associated with a significant lower risk of premenopausal breast cancer compared to gestational week of 37−40 at the time of delivery (OR 0.32; CI 0.11─ 0.92). After adjustment for other covariates in a multivariate model, the odds ratio remained significant (OR 0.32; CI 0.11─0.94). Preterm deliveries were not associated with changes in the risk of maternal breast cancer.

The mean birth weight was 6.89 ± 1.38 Ibs for cases and 6.82 ± 1.57 Ibs for controls. Among neonates, 556 were born in the normal range of birth weight, 72 were SGA, one was LGA, and one neonate was with no value. The birth weight of the neonate did not predict the maternal risk of premenopausal breast cancer in any category.

Whites made up the majority of the mothers in our study population (370), followed by Hispanic (161), Asian (50), African-American (37), and Native American (3). Hispanic background protected mothers against breast cancer compared to mothers of white background (OR 0.56; 95% CI 0.33─0.94). Use of tobacco and alcohol, gestational

diabetes, gestational hypertension, and induction of labor were not associated with significant changes in the risk of premenopausal breast cancer.

Table 4. Distribution of risk factors and associated odds ratio for premenopausal breast cancer among parous cases and controls after frequency-matching for the age of the mother

Risk Factors	OR	95% CI	P Value
Race			
White	Referent		0.282
Black	1. 75	0.80-3.80	0.161
Hispanic	0.61	0.35-1.11	0.114
Native	1.92	0.17-22.47	0.626
Asian	1.13	0.55-2.32	0.739
Unknown	0.62	0.06-6.08	0.687
Education (years)			
≤6	Referent		0.755
7-12	2.58	0.55-12.01	0.229
13-14	2.34	0.48-11.49	0.294
15-16	2.62	0.53-12.98	0.239
≥17	2.65	0.52-13.66	0.244
Unknown	0.76	0.05-11.07	0.833
Birth Weight (lbs)			
≤5.49	0.98	0.43-2.20	0.998
5.50-10.49	Referent		0.951
Plurality			
1	Referent		0.947
2	1.52	0.39-5.93	0.456
Parity			
1	Referent		
2	0.48	0.03-6.99	0.595

Risk Factors	OR	95% CI	P Value
Gestational Age (weeks)			
≤34	0.77	0.19-3.09	0.714
35-36	1.3	0.53-3.19	0.564
37-40	Referent		0.171
≥41	0.33	0.11-0.93	0.038
Weight Gain (lbs)			
≤24	1.07	0.61-1.86	0.815
25-35	Referent		0.707
36-50	1.21	0.66-2.20	0.941
51-65	2.03	0.74-5.20	0.167
≥66	1.03	0.44-2.41	0.953
Alcohol			
No	Referent		0.766
Yes	0.81	0.20-3.20	0.999
Tobacco			
No	Referent		0.999
Yes	1	0.53-1.90	0.985
Induction of Labor			
No	Referent		
Yes	0.92	0.58-1.48	0.743
Hypertention			
No	Referent		
Yes	1.5	0.46−4.88	0.497
Diabetes			
No	Referent		
Yes	1.62	0.30−8.68	0.575

CHAPTER 9: DISCUSSION

A relatively higher level of estrogen during pregnancy associated with early stages of malignant transformation is known as a likely cause of the elevated rates of breast cancer.[72] Mammary cells in a few percent of women might be in early stages of malignant transformation at the time of pregnancy and raising estrogen to higher levels enhances the growth of cells in an already malignant region. This theory is consistent with the fact that the risk of breast cancer increases as women delay the age of their first pregnancy.[2,4,44,46,88] In fact, the chances of showing early stages of malignancy or being in higher stages of malignant transformation increases with the pregnancy occurring at relatively older ages. The theory of higher levels of estrogen during a delayed first-time pregnancy as a possible mechanism to increase the risk of a subsequent breast cancer[65] seems to lack sufficient scientific basis, this is because the ovaries start regressing in size and function as the woman ages.

It is also possible that there are other pregnancy-related factors confounding this relationship, producing relatively higher levels of estrogen in some pregnant women, or even causing breast cancer independently. Examples of such confounding factors may include an excessive weight gain in pregnancy and preterm delivery.[42,54] A few other pregnancy-related factors such as breastfeeding,[46] female twins,[88] and preeclampsia[41] have also been suggested to have protective effects against premenopausal breast cancer among mothers, although not consistently.

It is not clear whether the number of parities is associated with the risk of premenopausal breast cancer. While some studies showed that the rates decrease following a second, third or a subsequent pregnancy[4,44,46] other studies were not consistent with this finding or even showed opposite results.[88] The mechanism of this protection if it even exists is not well understood. The long term protective effect of first pregnancy through the introduction of mature mammary cells is known as a likely mechanism of risk reduction of breast cancer later in life.[53]

Our study did not support a likely role of weight gain during pregnancy on the risk of premenopausal breast cancer. Although there is little evidence for such link drawn from a single study by Kinnunen *et al*..[42] To our knowledge, the only significant results on the above link should be due to the protective effects of weight gain during pregnancy on the premenopausal risk of breast cancer,[28] in which the postmenopausal increased risk of breast cancer is only partially explained by the known mechanisms of hormonal stimulation of pregnancy on the premalignant proliferation of mammary cells.

Although the information about BMI at delivery was not available in our dataset and a couple of previous studies controlled for it, this should not alter our definition of excessive weight gain during pregnancy; and we are not concerned whether the mothers normally gained weight during pregnancy. With regard to the theory of conversion of testosterone to estrogen in fat tissue,[80] the total weight gain in pregnancy was targeted as a likely predictor of breast cancer rather than the value of the basal BMI. Although higher baseline estrogen levels might correlate with higher BMI, we are mainly looking for the differences in estrogen levels due to changes during pregnancy. It is also not feasible, perhaps even in a prospective study, to monitor the levels of estrogen hormone through pregnancy due to the diurnal variation in its levels.[83,96]

Our study had a high level of strength and validity. The fact that it was a nested case-control study within a cohort of Nevada residents enabled us to minimize the risk of selection bias (the whole population is included) or recall bias (the data contained measurable variables which were already measured and listed in our dataset; there are no subjective characteristics of pregnancy listed in our dataset). In addition, the design of the study allowed us to examine the aforementioned link over a population from all socioeconomic classes. We were also able to examine a large number of variables as likely causes of breast cancer following a pregnancy.

Our study, like many other previous studies, had a number of limitations. The linking of the two sources of data (Cancer Registry database and birth certificates) based on name, date of birth, and residential information but no social security number could be a source

of incomplete matching or misclassification. In fact, it is possible that a portion of the control subjects actually had breast cancer and their information is not recorded in the dataset. It is also possible that some patients left the state of Nevada following a pregnancy and developed breast cancer elsewhere. We are not able to clarify whether the individuals who are counted as control subjects developed breast cancer while they moved and lived in a different state. However, the probability of this is negligible given the low incidence of premenopausal breast cancer in the population at large.

In our analysis, we were not able to control the study for some of the confounding factors such as BMI at baseline, age at menarche, history of breast feeding, using mammography as a screening tool, family history of breast cancer, and genetic predispositions (e.g., BRCA 1 and BRCA 2 genes) due to unavailability of the information. Breastfeeding is shown to protect women against breast cancer.[46,61] The effects of genetic factors and familial predispositions are also already known and the use of mammography has caused higher and earlier rates of detecting breast cancer cases.[24] A long duration of exposure to estrogen due to early menarche or late menopause or both is known to be a risk factor for breast cancer.[13]

The most interesting finding of our study was the effect of gestational age at the time of delivery on the risk of maternal breast cancer, which is plausible.[54,75] The theory of proliferation of mammary cells in the first and second trimester and cell differentiation and maturation in the third trimester[73] explains the positive influence of pre-term delivery on the risk of premenopausal breast cancer among mothers.[54] This theory also applies for the protective effects of late deliveries on premenopausal risk of breast cancer. We suggest that as pregnancy progresses beyond 40 weeks of gestation, mammary cells have more time for complete differentiation and maturation; a process that started earlier in the third trimester. To our knowledge, this link was not previously shown. The results of this study will therefore contribute to the literature and may provide a basis for future studies.

CHAPTER 10: CONCLUSIONS

Our study did not find a role of excessive weight gain on the risk of premenopausal breast cancer. There is little to no evidence that weight gain in pregnancy is associated with maternal risk of breast cancer. This link can potentially be examined in a different population, a larger number of participants, or a different study design controlling for BMI at baseline. The association of pregnancy progressing beyond 40 weeks of gestation and reduced risk of maternal breast cancer is significant and plausible. This link needs to be studied further in a cohort study with different populations.

The impact of such a finding on public health could be significant. Delivery through elective cesarean section or induction of labor has been increasingly performed for the past couple of decades. The procedures are both normally preferred after the completion of a minimum of 38 weeks of pregnancy.[64,86] In order to minimize the premenopausal risk of breast cancer for women with known risk factors, it may be beneficial to schedule a relatively later gestational age for the aforementioned procedures — beyond 40 weeks of gestation if the delivery does not progress naturally before then.

APPENDIX

Protocol Logged In Notice

Biomedical IRB

DATE: Friday, May 17, 2013

TO: **Dr. Paulo Pinheiro, Community Health Sciences, School of**

FROM: Office of Research Integrity – Human Subjects (ORI – HS)

RE: Protocol Title: **Weight Gain in Pregnancy and Pre-menopausal Breast Cancer, a population-based case-control study**
Protocol #: 1305-4461M

This memorandum is notice that the protocol named above has been entered into the ORI – HS protocol database system.

Please be aware:

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Please allow 14 days before contacting the ORI – HS staff regarding the status your protocol. You will be notified via email and/or campus mail after the protocol has been reviewed.

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Stage 1. Basic Course Passed on 11/22/12 (Ref # 9182756)

Required Modules	**Date Completed**	
Introduction	11/15/12	no quiz
History and Ethical Principles – SBR	11/16/12	4/5 (80%)
Defining Research with Human Subjects – SBR	11/16/12	3/5 (60%)
The Regulations and The Social and Behavioral Sciences - SBR	11/16/12	4/5 (80%)
Assessing Risk in Social and Behavioral Sciences - SBR	11/17/12	4/5 (80%)
Informed Consent – SBR	11/18/12	5/5 (100%)
Privacy and Confidentiality – SBR	11/18/12	3/5 (60%)
Research with Prisoners – SBR	11/19/12	3/4 (75%)
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International Research – SBR	11/20/12	3/3 (100%)
Internet Research – SBR	11/21/12	4/5 (80%)

Avoiding Group Harms: U.S. Research Perspectives	11/21/12	3/3 (100%)
Vulnerable Subjects - Research Involving Workers/Employees	11/22/12	4/4 (100%)
Conflicts of Interest in Research Involving Human Subjects	11/22/12	4/5 (80%)
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Visa Status: U.S. Permanent Resident

EDUCATION AND QUALIFICATIONS
2013 USMLE Step3 Passing Score
2012 Australian Medical Council (AMC) MCQ Exam Certificate
2011 Masters of Public Health (MPH) Candidate, University of Nevada, Las Vegas, School of Public Health (Concentration: Epidemiology & Biostatistics, GPA: 3.80, Graduation Date: August 2013)
2008 ECFMG Certificate
2002 MOH License of UAE as General Practitioner, Abu Dhabi, UAE
1996 MD, Tehran University of Medical Sciences, Tehran, Iran

WORK EXPERIENCE
March 2012-November 2012
Primary Care Office, Generation Medical Center, Las Vegas, NV
Physician Assistant
 Dealt with different cases such as hypertension, hyperlipidemia, diabetes mellitus, osteoporosis, elderly care, and mental disorders
 Responsibilities included: taking histories, reviewing lab and imaging results, analyzing data and starting assessment and plan, prescribing medications, patient education and follow up
 Worked with a medical software called 'Athena Health' for entering and accessing patient information

July 2012
Internship in Public Health, Nevada Department of Health and Human Services, Office of Public Health Informatics and Epidemiology, Las Vegas, NV
Intern
 Research on Rocky Mountain and Registry Plus Cancer Data System

July 2011
Internal Medicine Department, Reading Hospital and Medical Center, Reading, PA
Clinical Observer
 Participated in daily morning reports and conferences, prepared and presented subject-specific
lectures, observed patient admission and discharge, and participated in graduate medical education teaching and training classes
 Visited patients as part of the inpatient team, discussing diagnosing and work up, assessment and plan, and patient follow-up

March 2011-July 2011
Genetics Department, New York -Presbyterian Hospital, Columbia University, New York, NY
Research Associate
 Worked on Metabolic and Genetic Disease Registries such as Fabry's Disease & Wolman Disease

June 2011-July 2011
Fertility Research Foundation, New York, NY
Medical Associate
 Worked with Dr. Masood Khatamee sorting patient records and creating a new file system for the Foundation

May 2009–September 2009
Research Lab of Sleep and Wake Disorders, Hackensack University Medical Center, Hackensack, NJ
Research Assistant
 Observed and monitored patients under treatment with various sleep disorders utilizing both the PSG, polysomnography, in the initial screening as well as MSLT, multiple sleep latency test, to monitor and record patient's EEG, muscle activity, and eye movements
 Trained in techniques such as MSLT and CPAP Titration Test
 Shared readings and data analysis with technician responsible for writing the final reports presented to the doctor for diagnosis
 Assisted with study to measure level of nitrous oxide (NO) in patients with sleep apnea, educated patients in using NO machine and wrote report summarizing results

January 2008–April 2008
Bronx-Lebanon Health Care Center/Williamsbridge Manor Health Care Center, Bronx, NY
Physician assistant
 Reviewed patient charts and obtained detailed medical histories upon each new admission
 Performed physical exams along with the physician, monitored lab results, followed up with consults as needed, and checked on medications to ensure that all medications were dispensed as prescribed

May 2003–May 2007
Al Noor Hospital Emergency Room/DAMAN clinic, Abu Dhabi, UAE
Emergency Room Physician/Primary Care Physician
 Managed various cases and maintained responsibilities including but not limited to; immunizations,
common cold, influenza, asthma, hypertension, hyperlipoproteinemia, diabetes, headache, anemia, osteoporosis, contraception, prenatal care, bronchitis & pneumonia, otitis media, lower back pain, travel disorders, peptic ulcer disease, irritable bowel

syndrome, tobacco dependency, elderly care, and patient education on chronic diseases such as; diabetes mellitus and hypertension
 Treated patients in ER and outpatient clinic; attended to house visits several times per week
 Served as sole physician during night shifts in ER; managed nursing team of six
 Effectively treated diverse, Arabic-speaking population

September 1998–May 2003
Five-Azar University Hospital (primary public hospital in province with 450 beds), Gorgan, Iran
Emergency Room Physician
 Dealt with various critical medical and surgical emergencies
 Trained in various medical and surgical

May 1998–May 2003
Falsafi Private Hospital, Gorgan, Iran
Emergency Room Physician & Outpatient Clinic General Practitioner
 Admitted and treated patients with various medical problems
 Managed all wards and Cardiac Care Unite during night shifts
 Managed different cases such as upper & lower respiratory tract diseases, diabetes mellitus,
hypertension, hyperlipopeoteinema, gout, premenstrual syndrome, gastrointestinal diseases,
depressive disorders, asthma, thyroid diseases, osteoarthritis, and routine prenatal care

Jun 1996–Apr 1998
Zagheh Health Care Center (affiliated with satellite clinics in remote rural areas in province),
Khorramabad, Iran, Primary Care Physician
 Managed eleven satellite clinics focusing on pregnancy and infant care, cancer screening, and elderly care
 Monitored and reported on public health indicators throughout district; presented reports to municipal officials
 Worked as Family Practitioner at a central outpatient clinic. Treated all emergency cases and traumas and referred patients to urban hospitals when appropriate

SKILLS
 Clinical & Procedural Skills: performing and interpreting ECG and ABG, IV cannulation,
intramascular/ subcutaneus injections, use of nebulizer, blood sampling, ACLS/defibrillation,
endotracheal intubation, and pleural & ascitis tap, NG tube/urinary catheter insertion, wound
Suturing, management of burns, abscess drainage, splint application, ingrown toe nail removal,

subcutaneous lipoma removal, deep vein catheterization, nasal tamponing, and local anesthesia,
natural vaginal delivery/episiotomy
 Computer Skills: Statistical Package for the Social Sciences (SPSS), Microsoft Excel
 Languages: Farsi, Arabic, English

ARTICLES & RESEARCH
 An epidemiologic review on an article named 'Pattern of Asthma Mortality in Philadelphia from 1969 to 1991'. University of Nevada, Las Vegas, School of Public Health; September 2012
 A bio statistical review on an article named 'Damp housing and asthma: a case-control study'.
University of Nevada, Las Vegas, School of Public Health; July 2012
 Smoke cessation, Health Belief Model, Evaluation of a Minimal-Contact Smoking Cessation
Intervention in an Outpatient Setting. University of Nevada, Las Vegas, School of Public Health; May 2012
 Effect of Levetiracetam on Chronic Pain in Multiple Sclerosis; A literature review. University of Nevada, Las Vegas, School of Public Health; February 2012
 Contraceptives-Hormonal Effects. University of Nevada, Las Vegas, School of Public Health; February 2012
 Epidemiology of Pancreatic Cancer. University of Nevada, Las Vegas, School of Public Health; December 2011
 PLCO trial, Progression of low-grade dysplasia in Ulcerative Colitis; effect of colonic location. University of Nevada, Las Vegas, School of Public Health; October 2011
 Sleep Disorders in the General Population. Persian Heritage Magazine, Paramus, NJ; August 2009
 Common Sleep Disorders in Fibromyalgia; A Literature Review. Hackensack University Hospital, Hackensack, NJ; September 2009
 Pheochromocytoma in Surgery: A Ten-Year Case Review. Imam Khomeini University Hospital, Tehran, Iran; March 1996

ORAL PRESENTATIONS
 Acceptance of Hepatitis B Vaccine among 5-Azar Hospital Personnel in Gorgan, Iran; An Application of The Health Belief Model. University of Nevada, Las Vegas, School of Public Health; June 2012
 Increased Unrecognized Coronary Heart Disease and Sudden Deaths in Rheumatoid Arthritis; A Population-Based Cohort Study. University of Nevada, Las Vegas, School of Public Health; May 2012
 Epidemiology of Pancreatic Cancer. University of Nevada, Las Vegas, School of Public Health; December 2011
 Anal HPV prevalence among HIV-seropositive men under antiretroviral treatment, A Cross-Sectional Study. University of Nevada, Las Vegas, School of Public Health; December 2011
 Increased Prevalence of Aortic Stenosis in Patients with Atriovenous Malformations of the

Gastrointestinal Tract in Heyde's Syndrome. Reading Hospital and Medical Center, Reading, PA; July 2011
 Peak Expiratory Flow Rate Monitoring in Asthma. Reading Hospital and Medical Center, Reading, PA; July 2011
 Tardive Dyskinesia; A Case Report and Management. Williamsbridge Manor Health Care Center, Bronx, NY; March 2008
 Management of Upper GI Bleeding. 5-Azar University Hospital, Gorgan, Iran; April 2001.
 Herpes Simplex Encephalitis; A Case report and Management. Bahrami University Hospital, Tehran, Iran; October 1994

RESEARCH PROJCTS & INDEPENDENT STUDIES
 Master's Degree Thesis: Pregnancy Characteristics & Premenopausal Breast Cancer; A Population-Bcase-control Study. University of Nevada, Las Vegas, School of Public Health; July 2013.
 Increased Cancer Survival in Married Population; A Cross-Sectional Study. University of Nevada, Las Vegas, School of Public Health; December 2011

REFERENCES
 Available Upon Request