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Gestational biomarkers of daughter's breast cancer in the Child Health and Development Studies

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Abstract

We examined the link between gestational biomarkers and breast cancer in 9169 daughters born into the Child Health and Development Studies from 1959 to 1967. We identified 137 breast cancer cases diagnosed by age 52 as of 2012. Markers of increased risk included higher placental volume and rapid 2nd trimester gestational weight gain. Protective markers were placental hemorrhage and fibrin deposition, indicators of resistance to placental trophoblast invasion. Paradoxically, higher ponderal index at birth was protective suggesting that fetal and placental pathways to breast cancer are multiple and distinct. Results link placental and fetal phenotypes to breast cancer, characterizing some as restrictive and others as permissive markers of tumor development. We found new biomarkers of breast cancer risk that can be mined to discover 'omic correlates in the pregnancy exposome using archived and contemporary pregnancy samples. This line of investigation may discover new pathways to risk and new opportunities for prevention.

Keywords

Breast cancer; Placental morphology; Fetal growth; Biomarkers; Intrauterine; Gestational; Child Health and Development Studies; Prospective

1. Introduction

Animal and human studies have demonstrated that certain placental phenotypes are related to subsequent risk of cancer [1–5]. The theoretical basis of this link between the feto-placental unit and cancer later in life emerges from a growing science that has revealed how conspicuously the trophoblast cells of the human placenta mimic those of malignant tumor cells – both exhibit properties of proliferation, migration and invasion [1,6]. However, human placental cells are generally bestowed with the ability to arrest these processes and finally assume a state of senescent apoptosis [6]. The placenta mobilizes nutrients to the fetus and screens toxins, organizes an immune balance with the fetal allograft and performs major endocrine functions. Impairment of these placental roles has the potential to lead to

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Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

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disordered developmental programming and alterations in the structure and function of major fetal organ systems through modification of gene expression or cell differentiation, which predispose offspring to disease [1,6].

The concept that the intrauterine environment plays a major role in establishing a growth and health trajectory that extends over the life-course of the offspring is widely supported by numerous studies [7–9]. Combining this concept with the rapidly increasing insight about the similarities between placenta trophoblast cells and tumor cells [1,6] forms the basis for our investigation of the link between the placenta, fetal growth and later life risk of breast cancer.

Previously we observed that clinical characteristics during pregnancy and placental morphology were associated with the mother's own subsequent risk of breast cancer. In brief, we found that smaller placentas, presence of maternal floor infarction of the placenta and more rapid blood pressure change between the 2nd and 3rd trimesters were associated with significant reduction in risk of maternal breast cancer, later in life [10]. The current study examines whether these factors are associated with risk of breast cancer in daughters. We also expand our search for daughters' breast cancer risk factors to include additional measures of placenta function and fetal growth which have been extensively implicated in the development of subsequent chronic disease [1,7,9,11].

2. Materials and methods

2.1. Study population

This study is based on the Child Health and Development Studies, a population-based, multi-generational cohort. The CHDS recruited more than 98% of women seeking obstetric care at the Kaiser Foundation Health Plan in the San Francisco East Bay Area from 1959 to 1967 [12]. Recruitment efforts enrolled 15,528 families into the cohort which is racially and ethnically diverse with a broad socio-economic base and uniform access to health care. Demographics and health-related behavior were collected from mothers during in-person interviews at enrollment, early in the first trimester. Clinical measures were abstracted from maternal medical records beginning 6 months prior to pregnancy through labor and delivery and are the source of data on baseline pregnancy weight, gestational weight gain, blood pressure change, length of gestation and birthweight. A standardized gross placental exam was conducted at delivery by trained examiners using the Benirschke protocol [13]. Delivery room nurses refrigerated the placentas, the preferred method of preservation for macroscopic exam, and an examiner was notified as soon as possible. Placental exams were usually completed within a few hours of delivery, except for late-night and Sunday births which were conducted within 12-24 hours of delivery. These exams were routinely performed for 95% of births during time periods when funding was available: August, 1960 – December, 1963 and October, 1965 – August, 1966. Thus availability of placental data for all CHDS births ranges from 56% to 78%, depending on the characteristic. For example placental weight is more widely available, for 78% of all births, whereas placental volume (which requires measurement of all three dimensions of the placenta – large diameter, small diameter, and thickness) is less frequently available, for nearly 60% of all births.

2.2. Cohort surveillance

Surveillance of CHDS participants has continued for 6 decades by annual linkage to: 1) the California Department of Motor Vehicles for a history of residence to identify the population at risk for cancer, 2) the California Department of Vital Statistics, for identifying deaths and cause [14–16] and 3) the California Cancer Registry, for identifying cancer diagnoses [10,17–21]. CHDS mothers and their families are regularly matched to these sources using an accumulated name and address history. This cumulative history protects against establishing false matches and failing to identify true matches. Surveillance efforts routinely identify over 80% of CHDS families.

Breast cancer cases in CHDS daughters were identified by linkage to the California Cancer Registry (CCR) and by self-report during a computer-assisted telephone interview in an adult follow-up study of CHDS daughters from 2010 to 2013. California hospitals and health care facilities that provide treatment to cancer patients are required by law to report cancer diagnoses to the California Cancer Registry. The CCR has established that its cancer coverage is more than 99% complete after a lag time of about 2 years [23]. Life table analyses using SEER rates to estimate expected numbers of breast cancer diagnoses in mothers (unpublished) and testicular cancer diagnoses in sons [19] in the CHDS show close comparability with observed cases identified through CCR linkage in both parent and offspring generations.

We identified 137 cases of incident invasive or in situ breast cancer cases in CHDS daughters via linkage to the CCR through 2012 (80% of cases) and direct self-report through 2013 (20% of cases). The self-reported cases were more recently diagnosed and most fell within the 2-year lag period required for CCR to completely capture these later diagnoses. Tumor stage and hormone receptor status were available from CCR records which abstracts information from pathology reports and medical records about timing of diagnosis, cancer site, tumor invasiveness, histology, grade and differentiation, and tumor biomarkers [22]. Cases were diagnosed from 1992-2012 at ages 32–52 years.

The institutional review board of the Public Health Institute approved the study protocols for this research. At enrollment CHDS mothers gave informed oral consent, as was customary in the 1960’s, for themselves and their children. Daughters who provided self-report of their breast cancer diagnoses from 2010-2013 gave full informed verbal consent before participating in the adult telephone survey.

2.3. Statistical methods

Main study variables comprised measures of fetal growth and development, prenatal conditions and characteristics of the placenta which are described as follows. *Birthweight-for-gestation z-scores* were calculated for female CHDS births by subtracting the individual birthweight from the mean for each gestational week and dividing the difference by the standard deviation of the mean. Scores below the 10th percentile of the birthweight-for-gestation distribution were used to identify small for gestational age (SGA) births vs. all other z-scores at or above the 10^{th} percentile. *Ponderal index* was calculated as [birthweight (g) / birth length (cm^3)] x 100 and represented as a 4-category ordinal variable where

categories were assigned the median value of each quartile. The *rates of maternal gestational weight gain* were calculated separately for *trimester 2* and *trimester 3* as: [(the last recorded maternal weight (lbs.) in each trimester – the first recorded maternal weight (lbs.) in each trimester) / (gestational days between dates of the first and last measurements in each trimester)]. Dose-response for rates of weight gain in each trimester was tested using 3 dummy variables representing quartile 2, quartile 3 and quartile 4, using the first as the reference quartile. Because risk for 2nd trimester rate of weight gain was concentrated in the highest quartile, trimester-specific rates of weight gain were thereafter classified as the highest quartile (quartile 4) versus all others, where the highest quartile of trimester 2 equated to a rate of weight gain ≥1.17 pounds per week and the highest quartile of trimester 3 was equivalent to a rate of gain ≥0.99 pounds per week [24]. *Placental volume* (cm^3) encompassed three dimensions – the largest diameter (cm) of the placenta, the smallest diameter (cm) and its thickness (cm). It was calculated based on the formula for the volume of an ellipse: 4/3 × 3.14 X [large diameter/2] X [small diameter/2] X [thickness/2]. *Fibrin deposition* was defined as the presence of maternal floor infarction of the placenta and/or massive or diffuse and patchy subchorionic fibrin. Evidence of *hemorrhage* in the placenta, recent or old, without designation of specific site; presence of *placental cysts;* and presence of *placental tumor* (reportedly benign chorioangioma [13]) were each captured as binary variables (1 = observed and 0 = not observed).

Adjustment variables included maternal and offspring variables and are outlined as follows. *Maternal ancestry* was determined from in-person interview at enrollment and was characterized as Eastern European, a proxy for Ashkenazi Jewish heritage vs. all other. *Maternal baseline pregnancy overweight* was defined as having a body mass index of ≥25 kg/m^2. Body mass index was calculated from weight (kg) divided by height (m) squared, measured or reported at interview or first prenatal visit. Weight was adjusted to compensate for variation in the timing of measurement by regressing weight on gestational age using the locally weighted scatterplot smoothing technique [25]. Adjusted weight was then imputed as the fitted mean weight at day 104 of gestation (median value for day of interview) plus the residual from the regression procedure. *Gestational age* was calculated as the time in completed weeks between date of delivery and date of last menstrual period. *Maternal history of breast cancer* was captured from maternal record linkage to the California Cancer Registry. *Daughter year of birth* was taken directly from labor and delivery records. Other maternal variables that were considered included: age at pregnancy (continuous), parity at pregnancy (continuous and dichotomized as primiparous vs. all other), maternal education (using two indicator variables for high school and some college vs. less than high school as the reference group), and total family income (using two indicator variables for at the median income adjusted for 1960 dollars and above the median vs. below the median as the reference group).

Daughter breast cancer incidence rates and 95% confidence intervals were calculated based on the discrete probability distribution for a binomial parameter. Hazard ratios were estimated using Cox proportional hazards models with the robust sandwich estimate option to account for family clusters since there were some sisters in the cohort [26]. Age at breast cancer diagnosis or follow-up was used as the censoring variable for these models. Since all cohort members are regularly monitored for residence, cancer and vital status, we used year

of last contact from all sources and from telephone contact during follow-up studies, to create the age at censorship. It was calculated by subtracting the year of diagnosis or censorship (last year of contact) from the year of birth, and ranged from 6 months to 52 ½ years from birth. Main study variables were tested in univariate models which included only the study variable of interest, then in models which included the main variable and the adjustment variables (maternal race, maternal baseline overweight, gestational age, maternal history of breast cancer and offspring year of birth) and finally in the fully adjusted model. The fully adjusted study model simultaneously estimated all main study variable associations and included the adjustment variables. Due to high collinearity, ponderal index and SGA were not both included in the fully adjusted model. To estimate the adjusted breast cancer association with ponderal index, SGA was omitted from the fully adjusted model, and to estimate the adjusted effect for SGA, ponderal index was omitted.

To investigate the effects of sample attrition due to missing on study variables, we used multiple imputation to estimate associations. Multiple imputation was implemented in SAS9.4 using the fully conditional algorithm (FCS) so that it could be applied to proportional hazards regression [27]. Estimates were based on 20 iterative imputations.

2.4. Analysis sample

The present analysis is based on the 9169 live-born CHDS daughters who were followed for nearly 6 decades from birth and among whom we identified 137 cases of breast age through age 52. To ensure greater accuracy for the macroscopic placental exam we restricted analysis to births from 32 – 44 gestational weeks, excluding 418 observations. From the remaining observations, information required to calculate a standardized birthweight z-score and ponderal index was available for n = 8570 daughters including 127 cases. Among these, information on all adjustment variables (maternal race, maternal baseline overweight, gestational age and maternal history of breast cancer) was available for n = 7,534, including 109 cases. Additionally requiring prenatal measures in both 2nd and 3rd trimesters resulted in n = 5228 observations including 74 cases. And finally, requiring all placental measures yielded a final sample size of 2947 observations, including 44 offspring breast cancers.

3. Results

We identified 137 cases of *young* breast cancer among CHDS daughters. Cases were diagnosed between ages 32-52 years occurring from 1992 to 2012. The median age at diagnosis was between 43-44 years.

Unadjusted breast cancer incidence rates of daughter breast cancer reported in Table 1 support modeled results of breast cancer associations for study variables, provided in Table 2 and Fig. 1. All show that increased ponderal index is associated with decreased breast cancer risk in daughters, while small for gestational age is associated with increased risk. Rapid maternal weight gain in the 2nd trimester (4th quartile of weight gain rate), but not in the 3rd, predicted increased risk of breast cancer in daughters. Consistent with higher risk associated with rapid weight gain in the 2nd trimester, higher placental volume (greater than median) was also associated with higher risk that was marginally statistically significant, whereas the presence of fibrin deposition and indication of placental hemorrhage were

associated with lower risk. Although fibrin deposition and hemorrhage can occur in concert, most were unique events: 70% of fibrin deposition occurred in the absence of hemorrhage and conversely 85% of hemorrhage occurred in the absence of fibrin deposition. We also observed that the presence of placental tumor was associated with very high increased risk of daughter's breast cancer that was statistically significant; however, due to small numbers we consider this suggestive evidence that needs to be corroborated.

Table 2 presents associations of gestational variables with daughter breast cancer for increasing levels of adjustment and missingness due to sample attrition. Associations were not largely affected by adjustment for maternal variables. Table 2 also shows that associations are independent of one another and not explained by familial risk. Sensitivity analysis (data not shown) demonstrated that sample attrition had comparatively little impact on the associations and do not materially alter conclusions. Associations based on multiple imputation (Supplementary Table 1) were also highly comparable to those reported in Table 2, suggesting that sample attrition did not largely influence results. The primary impact of imputation was to slightly diminish the magnitude of associations and increase p-values; however, the direction and interpretation of results are not substantially altered from conclusions based on results in the smaller non-missing sample. In addition, rates of breast cancer were highly similar for daughters included in the fully adjusted model compared to daughters who were excluded due to one or more missing variables, incidence rates and 95% confidence intervals were: 4.21 per 10,000 (3.06 to 5.65) among daughters included in the fully adjusted model vs. 4.29 per 10,000 (3.46 to 5.25) among daughters not included.

Fig. 1 depicts breast cancer associations for placental and fetal markers as well as for selected maternal co-variables. Both maternal history of breast cancer and maternal East European ancestry were substantial predictors of daughter's breast cancer. East European ancestry includes countries of origin with high proportions of Ashkenazi Jews, who have a high prevalence of deleterious mutations in the BRCA1 and BRCA2 genes [28], and may therefore be a proxy marker of genetic risk. Maternal baseline pregnancy overweight was associated with decreased risk of breast cancer in daughters. Other maternal adjustment variables, age at pregnancy, parity at pregnancy, and education and total family income at pregnancy did not affect reported associations and were not themselves related to offspring breast cancer (data not shown).

Supplementary Table 2 provides associations for each quartile of trimester-specific rates of maternal weight gain and for each quartile of ponderal index, estimated from models adjusted for maternal variables only; and, from fully adjusted models. Quartile-specific associations for maternal rates of weight gain show no evidence of a dose-response and further show that risk is concentrated in the 4th quartile, suggesting that a dichotomy representing the highest quartile vs. all others provides the best categorization for trimester 2 and a homologous representation for trimester 3. Unlike rates of weight gain, the quartile-specific associations for ponderal index exhibited a consistent step-down gradient supporting the putative classification of this measure as a 4-category ordinal variable with values coded at the median of each quartile.

Supplementary Table 3 presents the results of a pilot study examining associations for early stage and for estrogen-receptor positive breast tumors. Tumors were predominantly diagnosed at an early stage (localized or in situ, 71%) and primarily identified as estrogen-receptor positive (ER+, 83%) and progesterone-receptor positive (PR+, 77%). Associations reported in Supplementary Table 3 are highly comparable to those observed for all tumors. However, due to small numbers available for examining these re-classified outcomes, we consider the tumor stage and hormone receptor associations as pilot results. Not shown in Supplementary Table 3 are the associations for progesterone-receptor positive – these were highly similar to those for ER+ results since most ER+ tumors were also PR+.

4. Discussion

We tested the hypothesis that the intrauterine environment, as characterized by fetal measures and placental morphology, aligns with vulnerability to tumor development and/or progression and therefore can serve as biomarkers of breast cancer risk. This hypothesis integrates two prominent concepts: 1) the *fetal* origins of adult disease concept, which postulates that events during gestation, such as malnutrition, can affect fetal programming and lead to perturbations in the body's structure, function and metabolism ultimately contributing to adult disease [9,29]; and, 2) the *placental* origins of disease concept based on the striking similarities between the placental trophoblast and malignant tumor cells [1,6]. Both concepts lead to the conclusion that the intrauterine environment plays a primary role in the determination of cancer susceptibility. Our results support this conclusion and provide evidence that both placental factors and fetal factors predict daughter breast cancer.

4.1. Placental factors

Gestational weight gain in the 2nd trimester reflects rapid placental growth and output of hormones that lead to increasing blood volume [30]. We observed an association of higher 2nd trimester weight gain, but not 3rd trimester weight gain with increased risk of daughter breast cancer. Placental surface area, one component of volume is established by the 2nd trimester [1]. We found that placenta volume is also associated with increased risk of daughter breast cancer, further supporting the hypothesis that strong placental growth predicts a higher risk of daughter breast cancer. The observation that preeclampsia, a disorder of placentation with origins in early pregnancy [1], is associated with breast cancer protection in daughters [31] is further consistent with this hypothesis.

Other markers of placenta compromise, fibrin deposition and evidence of hemorrhage, were also associated with reduced risk of daughter breast cancer in this study. Fibrin deposition here includes the presence of subchorionic fibrin as well as report of maternal floor infarction. These are related placental lesions characterized by the marked fibrin deposition [32,33]. The etiology and full pathology of these lesions have yet to be elucidated but they are thought to result from an abnormal host-placenta interaction [32,33]. Angiongenic mechanisms may contribute to the association of these morphologic markers with breast cancer. In a small study, researchers found that angiogenic (P1GF) and anti-angiogenic (sVEGFR-1) factors and their ratio (PlGF/sVEGFR-1) were different for women who had massive perivillous fibrin deposition compared to those who did not [34].

We also found that presence of placental tumor (described generally as chorioangioma) was associated with very high risk of breast cancer. Although this association was statistically significant, the small number of events requires caution and we were unable to characterize the histology of the tumors found. However, we include it here because its magnitude warrants follow-up in other samples, both animal and human.

4.2. Fetal factors

Controlling for placenta factors we found that fetal adiposity, approximated by higher ponderal index at birth, had a protective association with daughter breast cancer while SGA was associated with increased risk. The association of higher ponderal index with lower risk of daughter breast cancer by age 52 in the CHDS corresponds with recent findings from the Premenopausal Breast Cancer Collaborative Group [35]. They found that increased body mass index (BMI) is associated with a reduced risk of premenopausal breast cancer and this inverse risk was stronger at younger ages, beginning at age 18 years. Studies of BMI in adolescence and earlier, including in early childhood, also provide evidence for an inverse relationship of adiposity with premenopausal breast cancer [36–38]. Thus, it is not surprising to find that the protective association between adiposity and early breast cancer appears to begin at birth. We did not find an independent association of breast cancer with birthweight which has been reported in a number of prior studies [31].

Whether the protective association of ponderal index with daughter breast cancer derives from a nutrient-rich uterine environment that promotes fetal growth and the development of particular defense mechanisms remains to be determined. Interestingly, higher maternal adiposity (BMI > 25) was also protective of daughter breast cancer in our study, rendering plausible support to this possibility. Further, we observed that fetal growth retardation was associated with higher risk of breast cancer lending additional evidence that strong fetal growth may decrease vulnerability to premenopausal breast cancer.

Indicators of advantaged fetal growth and development were protective of daughter breast cancer as were specific markers of placental compromise. These observations are paradoxical and likely reflect different pathways to risk. Clearly the fetoplacental system requires the coordination of a massive, complex and redundant repertoire of functions to establish a balance that enables both fetal development and maternal well-being. Placental compromise associations may signify barriers to tumor invasion and proliferation or lower exposures to tumor initiators in fetal life, while fetal growth associations may indicate a sound and progressive developmental process resulting in organs with resilient structure and function. Why and how rapid gestational weight gain distinctly in the 2nd trimester predicts increased risk of daughter breast question is an important question that may focus the search for key mechanisms which promote tumor development.

4.3. Strengths and limitations

The CHDS is one of few large multi-generational cohort studies able to examine the relationship between the intrauterine environment and breast cancer incidence in a population-based sample. Even so, small sample size particularly in the full subset of all study variables resulted in large estimates of variance and associations which are subject to

random error. The univariate associations estimated in considerably larger subsets show close comparability with those estimated in the small subset, indicating that associations are not likely the result of sample attrition, or of small sample aberration. The analogous rates of breast cancer incidence among daughters who were included in the fully adjusted model (small subset) and daughters who were not also demonstrates that sample attrition due to missing information was not likely biased according to eventual breast cancer status. In addition, results based on multiple imputation methods to address effects of sample attrition (Supplementary Table 1) support conclusions drawn from the smaller non-missing sample.

It is possible that we failed to identify some cases of breast cancer. Through regular linkage to the California Cancer Registry, and vital status and DMV records, 70% of daughters were under continual surveillance from birth onward, with a median follow-up-time of > 45 years. However, about 30% were lost-to-follow-up within 10 years of birth, representing early lost-to-follow-up and likely out-migration. Risk characteristics were represented proportionately according to early vs. continual surveillance status, i.e. daughters who were under continual surveillance did not over or under represent risk groups. This suggests that early loss was random and not biased according study characteristics; thus, we would expect that any missed cases would have the same distribution of risk characteristics as those observed for the study sample.

The standardization of the macroscopic placental exam performed by trained examiners ensured reliable accuracy for placental measures. The contemporaneous collection of prenatal, and labor and delivery information from obstetric records provided very high data quality. The pilot examination of tumor stage and hormone receptor status with placental and fetal characteristics produced associations that were highly similar to those observed for all tumors. This is not surprising since tumors were predominantly early stage and hormone-receptor (estrogen and progesterone) positive. However, we were unable to determine whether early stage associations were different from late stage associations, nor whether hormone receptor positive were different from receptor negative effects since the small numbers of late stage and receptor negative tumors did not support separate examination. Thus, we are unable to draw conclusions about what role tumor invasiveness and receptor status play in the reported relationships.

5. Conclusions

We found that very rapid 2nd trimester gestational weight gain and higher placental volume predicted increased risk of daughter breast cancer. Consistent with this observation placental fibrin deposition and hemorrhage, all markers of placental compromise, predicted reduced risk. Fetal predictors did not align completely with placental predictors – higher ponderal index was protective for daughter breast cancer and fetal growth retardation was associated with increased risk – suggesting separate pathways to risk for fetal growth and placental function: These fetal and placental associations with breast cancer were independent of one another and were not explained by familial risk or maternal adiposity. Findings in this prospective study add strong support for the fetal and placental origins of disease hypotheses. We found new biomarkers of risk that can be mined to discover ‘omic correlates

in the pregnancy exposome using archived and contemporary pregnancy samples. This line of investigation may discover pathways to risk and new opportunities for prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CHDS	Child Health and Development Studies
CCR	California Cancer Registry
SGA	small-for-gestational age
BMI	body mass index

References

[1]. Burton GJ, Fowden AL, Thornburg KL, Placental origins of chronic disease, Physiol. Rev 96 (4) (2016) 1509–1565. [PubMed: 27604528]

[2]. Barker DJ, Osmond C, Thornburg KL, Kajantie E, Eriksson JG, The shape of the placental surface at birth and colorectal cancer in later life, Am. J. Hum. Biol 25 (4) (2013) 566–568. [PubMed: 23754589]

[3]. Barker DJ, Osmond C, Thornburg KL, Kajantie E, Eriksson JG, The intrauterine origins of Hodgkin's lymphoma, Cancer Epidemiol. 37 (3) (2013) 321–323. [PubMed: 23403130]

[4]. Eriksson JG, Thornburg KL, Osmond C, Kajantie E, Barker DJ, The prenatal origins of lung cancer. I. The fetus, Am. J. Hum. Biol 22 (4) (2010) 508–511. [PubMed: 20309990]

[5]. Barker DJ, Thornburg KL, Osmond C, Kajantie E, Eriksson JG, The prenatal origins of lung cancer. II. The placenta, Am. J. Hum. Biol 22 (4) (2010) 512–516. [PubMed: 20309992]

[6]. Soundararajan R, Rao AJ, Trophoblast' pseudo-tumorigenesis': significance and contributory factors, Reprod. Biol. Endocrinol 2 (2004) 15. [PubMed: 15043753]

[7]. Barker DJP, The origins of the developmental origins theory, J. Intern. Med 261 (5) (2007) 412–417. [PubMed: 17444880]

[8]. Swanson JM, Entringer S, Buss C, Wadhwa PD, Developmental origins of health and disease: environmental exposures, Semin. Reprod. Med 27 (5) (2009) 391–402. [PubMed: 19711249]

[9]. Wadhwa PD, Buss C, Entringer S, Swanson JM, Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms, Semin. Reprod. Med 27 (5) (2009) 358–368. [PubMed: 19711246]

[10]. Cohn BA, Cirillo PM, Christianson RE, van den Berg BJ, Siiteri PK, Placental characteristics and reduced risk of maternal breast cancer, J. Natl. Cancer Inst 93 (15) (2001) 1133–1140. [PubMed: 11481384]

[11]. Gluckman PD, Hanson MA, Cooper C, Thornburg KL, Effect of in utero and early-life conditions on adult health and disease, New Engl. J. Med 359 (1) (2008) 61–73. [PubMed: 18596274]

[12]. van den Berg BJ, Christianson RE, Oechsli FW, The California child health and development studies of the school of public health, University of California at Berkeley, Paediatr. Perinat. Epidemiol 2 (3) (1988) 265–282. [PubMed: 3070486]

[13]. Benirschke K, Examination of the placenta, Obstet. Gynecol 18 (3) (1961) 309–333.

[14]. Cirillo PM, Cohn BA, Pregnancy complications and cardiovascular disease death: 50-year follow-up of the child health and development studies pregnancy cohort, Circulation 132 (13) (2015) 1234–1242. [PubMed: 26391409]

[15]. Wang ET, Cirillo PM, Vittinghoff E, Bibbins-Domingo K, Cohn BA, Cedars MI, Menstrual irregularity and cardiovascular mortality, J. Clin. Endocrinol 96 (1) (2011) E114–8.

[16]. Mongraw-Chaffin ML, Cirillo PM, Cohn BA, Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort, Hypertension 56 (1) (2010) 166–171. [PubMed: 20516394]

[17]. Cirillo PM, Wang ET, Cedars MI, Chen LM, Cohn BA, Irregular menses predicts ovarian cancer: Prospective evidence from the Child Health and Development Studies, Int. J. Cancer 139 (5) (2016) 1009–1017. [PubMed: 27082375]

[18]. Cirillo PM, Benz CC, Cohn BA, Comment on:' hypertensive diseases in pregnancy and breast cancer risk', Br. J. Cancer 114 (11) (2016) e10. [PubMed: 27140311]

[19]. Cohn BA, Cirillo PM, Christianson RE, Prenatal DDT exposure and testicular cancer: a nested case-control study, Arch. Environ. Occup. Health 65 (3) (2010) 127–134. [PubMed: 20705572]

[20]. Cohn BA, Wolff MS, Cirillo PM, Sholtz RI, Christianson RE, van den Berg BJ, Siiteri PK, Timing of DDT Exposure and Breast Cancer Before Age 50, Epidemiology, Vancouver, Canada, 2002, p. S197.

[21]. Whittemore AS, Cirillo PM, Feldman D, Cohn BA, Prostate specific antigen levels in young adulthood predict prostate cancer risk: results from a cohort of Black and White Americans, J. Urol 174 (3) (2005) 872–876 discussion 876. [PubMed: 16093978]

[22]. Cancer reporting in California: abstracting and coding procedures for hospitals. California Cancer Reporting System standards Vol I California Department of Health Services, Cancer Surveillance Section, Sacramento, CA, 2012.

[23]. Kwong SL, Perkins CI, Morris CR, Cohen R, Allen M, Wright WE, Cancer in California: 1988–1999, California Department of Health Services, Cancer Surveillance Section, Sacramento, CA, 2001.

[24]. Greenland S, Avoiding power loss associated with categorization and ordinal scores in dose-response and trend analysis, Epidemiology 6 (4) (1995) 450–454. [PubMed: 7548361]

[25]. Cleveland WS, Robust locally weighted regression and smoothing scatterplots, J. Am. Stat. Assoc 74 (1979) 829–836.

[26]. Gharibvand L, Liu L, Analysis of survival data with clustered events, SAS Global Forum (2009) 1–11.

[27]. U.S.C. Group, Multiple Imputation in SAS Part 1, (2019) (Accessed 10 April 2019), https://stats.idre.ucla.edu/sas/seminars/multiple-imputation-in-sas/mi_new_1/.

[28]. Liede A, Paterson C, Serruya C, Allingham-Hawkins D, Warner E, Glendon G, Ozcelik H, Brunet J-S, Honeyford J, Blondal J, Di Prospero L, Klein M, Hamel N, Goodwin P, Goss P, Moslehi R, Narod S, Contiga V, Meschino W, Foulkes W, Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer, JNCI: J. Natl. Cancer Inst 91 (14) (1999) 1241–1247. [PubMed: 10413426]

[29]. Barker D, Fetal and infant origins of adult disease, British Medical Journal Monographs, London, (1992).

[30]. Hytten FE, Leitch I, The Physiology of Human Pregnancy, 2nd edition, Blackwell Scientific Publications, Oxford, England, 1971.

[31]. Xue F, Michels KB, Intrauterine factors and risk of breast cancer: a systematic review and meta-analysis of current evidence, Lancet Oncol 8 (12) (2007) 1088–1100. [PubMed: 18054879]

[32]. Romero R, Whitten A, Korzeniewski SJ, Than NG, Chaemsaithong P, Miranda J, Dong Z, Hassan SS, Chaiworapongsa T, Maternal floor infarction/ massive perivillous fibrin deposition: a manifestation of maternal antifetal rejection? Am. J. Reprod. Immunol 70 (4) (2013) 285–298. [PubMed: 23905710]

[33]. Benirschke K, Kaufman P, Pathology of the Human Placenta, third edition ed., Springer-Verlag New York, Inc., New York, NY, 1995.

[34]. Whitten AE, Romero R, Korzeniewski SJ, Tarca AL, Schwartz AG, Yeo L, Dong Z, Hassan SS, Chaiworapongsa T, Evidence of an imbalance of angiogenic/antiangiogenic factors in massive perivillous fibrin deposition (maternal floor infarction): a placental lesion associated with recurrent miscarriage and fetal death, Am. J. Obstetrics Gynecol 208 (4) (2013) 310.e1–310.e11.

[35]. T.P.B.C.C. Group, Association of body mass index and age with subsequent breast cancer risk in premenopausal women, JAMA Oncol. (2018) e181771. [PubMed: 29931120]

[36]. Baer HJ, Tworoger SS, Hankinson SE, Willett WC, Body fatness at young ages and risk of breast cancer throughout life, Am. J. Epidemiol 171 (11) (2010) 1183–1194. [PubMed: 20460303]

[37]. Hilakivi-Clarke L, Forsen T, Eriksson JG, Luoto R, Tuomilehto J, Osmond C, Barker DJ, Tallness and overweight during childhood have opposing effects on breast cancer risk, Br. J. Cancer 85 (11) (2001) 1680–1684. [PubMed: 11742488]

[38]. De Stavola BL, dos Santos Silva I, McCormack V, Hardy RJ, Kuh DJ, Wadsworth ME, Childhood growth and breast cancer, Am. J. Epidemiol 159 (7) (2004) 671–682. [PubMed: 15033645]

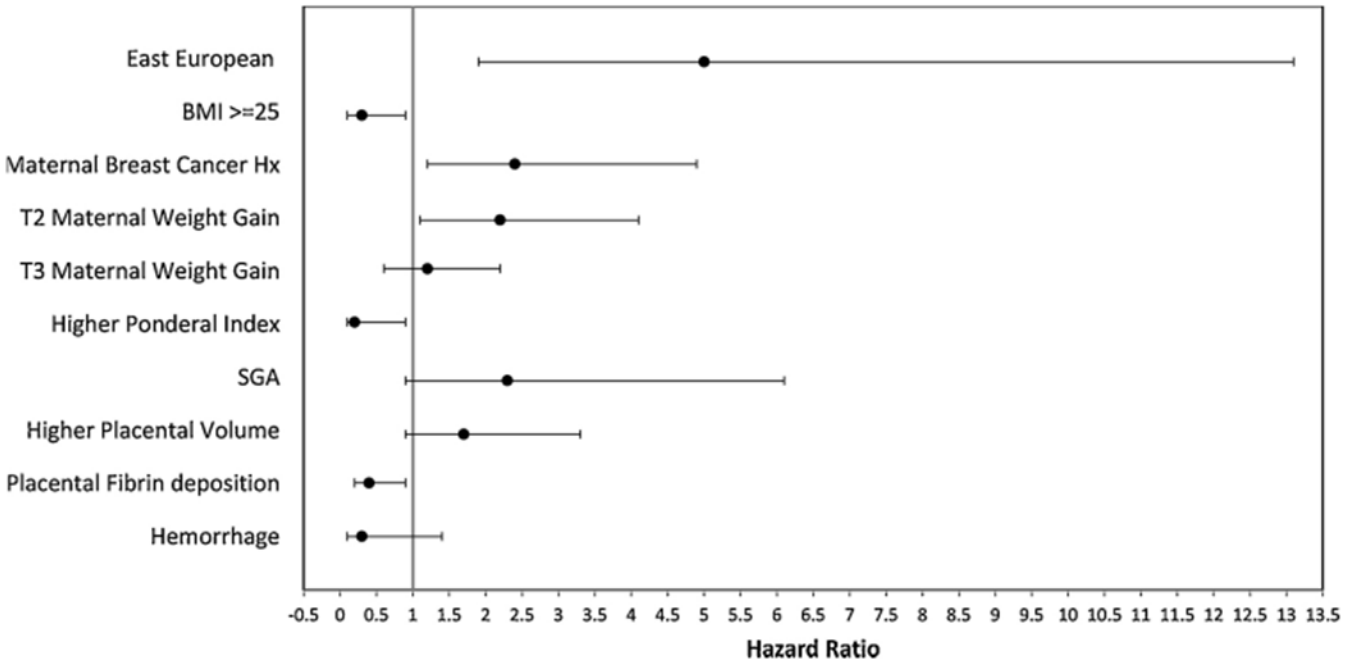

Fig. 1.

Associations of maternal and fetal factors with daughter breast cancer in the CHDS, predicted from proportional hazards model simultaneously adjusted for all variables. The top three factors are maternal characteristics; T2 and T3 refer to the rate of maternal pregnancy weight gain in Trimesters 2 and 3, respectively. Ponderal index and SGA are markers of fetal growth. The bottom three factors are placental characteristics.

Maternal characteristics were classified as follow: maternal history of breast cancer (yes vs. no), race (East-European vs. all other), overweight at pregnancy baseline measure (BMI > 25 kg/m2 vs. other), and week of gestation (continuous). Ponderal index was calculated as [birthweight (g) / birth length (cm3)]*100 and represented as a 4-category ordinal variable coded at quartile medians: 2.14, 2.35, 2.51 and 2.75 respectively for quartiles 1-4. The hazard ratio shown is for an increment of one unit. Small for gestational age was defined as the lowest decile of the birth-weight-for gestation standardized score vs. all other. High trimester-specific rates of maternal weight gain were represented as the 4th quartile of weight gain for each trimester vs. all lower quartiles. High 2nd trimester rate of weight gain was equivalent to > 1.1690 pounds per week and high 3rd trimester rate of weight gain was equal to>0.9996 pounds per week. High placental volume was represented as a dichotomous variable,>360 cm^3 (above the median) vs.<360 cm^3 (at or below the median). Fibrin deposition was defined as the presence of maternal floor infarction and/or massive or diffuse and patchy subchorionic fibrin vs. absence. Hemorrhage was classified as observed vs. not observed.

Table 1

Distribution of fetal and maternal factors and breast cancer incidence rates in CHDS daughters.

				Age-adjusted Incidence	
Study variable	**Mean (SD)[a] / N (%)**	**No. of case subjects**	**Person-years**	**Rate per 10,000**	**95% CI[b]**
Year of Birth					
1959-1961	2,716 (29.62%)	59	100,548	5.87	4.47 to 7.57
1962	1,454 (15.86%)	25	52,204	4.79	3.10 to 7.07
1963	1,456 (15.88%)	19	50,884	3.73	2.25 to 5.83
1964	1,499 (16.35%)	17	51,636	3.29	1.92 to 5.27
1965-1967	2,044 (22.29%)	17	66,086	2.57	1.50 to 4.12
Maternal Ancestry					
Eastern European	213 (2.36%)	8	6,915	11.57	5.00 to 22.80
All other	8546 (94.54%)	126	310,244	4.06	3.38 to 4.84
Maternal history of breast cancer					
Yes	722 (7.87)	32	29,269	10.93	7.48 to 15.43
No	8447 (92.13)	105	292,089	3.59	2.94 to 4.35
Maternal baseline pregnancy BMI, kg/m^2					
Overweight, ≥ 25	28.60 (3.74)[c]	16	60,591	2.64	1.51 to 3.82
All other	21.22 (1.93)[c]	103	220,292	4.68	3.82 to 5.67
Ponderal Index [(g/cm^3) x 100]					
1st quartile, ≤ 2.259	2.11 (0.12)[d]	43	80,166	5.36	3.88 to 7.23
2nd quartile, > 2.259 – 2.426	2.34 (0.05)[d]	36	78,977	4.56	3.19 to 6.31
3rd quartile, > 2.426 – 2.613	2.51 (0.05)[d]	29	81,576	3.56	2.38 to 5.11
4th quartile, > 2.613	2.81 (0.40)[d]	27	79,448	3.40	2.24 to 4.94
Small-for-gestational age (SGA)					
Lowest decile	2539 (283.67)[e]	14	29,324	4.77	2.61 to 8.01
All other	3351 (448.43)[e]	115	274,342	4.19	3.46 to 5.03
Rate of maternal weight gain in 2nd trimester, lbs/week					

Study variable	Mean (SD)[a] / N (%)	No. of case subjects	Person-years	Age-adjusted Incidence	
				Rate per 10,000	95% CI[b]
4th quartile, > 1.1690	1.53 (0.45)[f]	31	52,866	5.86	3.98 to 8.32
1st – 3rd quartiles, < 1.1690	0.68 (0.39)[f]	58	162,083	3.58	2.72 to 4.63
Rate of maternal weight gain in 3rd trimester, lbs/week					
4th quartile, > 0.9996	1.32 (0.45)[f]	37	76,600	4.83	3.40 to 6.66
1st – 3rd quartiles, < 0.9996	0.49 (0.50)[f]	94	227,453	4.13	3.33 to 5.06
Placental volume, cubic cm					
Above the median, > 360	447.12 (75.41)[g]	39	89,862	4.34	3.09 to 5.93
Below the median, ≤ 360	300.14 (48.42)[g]	34	91,241	3.73	2.58 to 5.21
Fibrin deposition					
Present	1077 (20.51 %)[h]	11	39,608	2.78	1.39 to 4.97
Absent	4173 (79.49%)[h]	62	145,512	4.26	3.27 to 5.46
Hemorrhage					
Present	485 (6.79%)	3	17,938	5.00	4.13 to 6.00
Absent	6660 (93.21%)	117	234,141	1.67	0.34 to 4.89
Placental tumor					
Present	10 (0.2%)[i]	1	385	25.97	0.66 to 144.72
Absent	5211 (99.81%)[i]	72	183,552	3.92	3.07 to 4.94

[a] SD, Standard Deviation of the Mean.

[b] CI, Confidence Intervals are calculated based on the discrete probability distribution for a binomial parameter.

[c] BMI, body mass index.

[d] Mean ponderal index [(g/cm^3) x 100] (standard deviation of the mean) for each quartile.

[e] Mean birthweight in grams (standard deviation of the mean) for each category.

[f] Mean trimester-specific maternal weight gain in lbs. per week (standard deviation of the mean) for each category.

[g] Mean placental volume [cm^3] (standard deviation of the mean) for each category.

[h] Presence of maternal floor infarction and/or massive or diffuse and patchy subchorionic fibrin.

[i] Placental tumors were reportedly benign chorioangiomas as described by Benirschke [K. Benirschke, Examination of the placenta, Obstet. Gynecol. 18(3) (1961) 309-333].

Table 2

Effect of Adjustment on Associations of Daughter Breast Cancer with Main Study Variables.

	Univariate				Adjusted for Maternal Factors[a]				Fully Adjusted[b], (N_{cases} = 44) N_{total} = 2947		
Study Variable	**(N_{cases}) N_{total}**	**HR**	**95% CI**	**p-value**	**(N_{cases}) N_{total}**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Fetal/*In utero* Factors											
Ponderal Index[c]	(129) 8719	0.46	0.20 – 1.03	0.058	(111) 7667	0.41	0.21 – 0.97	0.043	0.21	0.05 – 0.88	0.033
Small-for-gestational age (SGA)[d]	(129) 8600	1.12	0.64 – 1.96	0.685	(111) 7562	1.33	0.75 – 2.33	0.327	2.44	0.94 – 6.33	0.067
High weight gain (2nd trimester)[e]	(86) 5935	1.60	1.03 – 2.48	0.035	(78) 5337	1.74	1.11 – 2.73	0.017	2.28	1.19 – 4.35	0.013
High weight gain (3rd trimester)[e]	(86) 5935	1.19	0.75 – 1.90	0.328	(78) 5337	1.26	0.79 – 2.01	0.328	1.09	0.55 – 2.15	0.809
Placental Factors											
High placental volume[f]	(70) 4918	1.36	0.82 – 2.25	0.236	(64) 4481	1.36	0.82 – 2.25	0.236	1.76	0.89 – 3.48	0.106
Presence of fibrin deposition[g]	(70) 5032	0.53	0.28 – 1.02	0.055	(64) 4575	0.55	0.29 – 1.08	0.081	0.39	0.15 – 0.99	0.047
Occurrence of hemorrhage	(116) 6834	0.29	0.09 – 0.90	0.033	(99) 6090	0.34	0.11 – 1.05	0.061	0.17	0.02 – 1.20	0.076
Presence of placental tumor[h]	(70) 5004	6.58	0.99 – 43.89	0.052	(64) 4552	6.02	0.88 – 41.34	0.068	7.34	2.27 – 23.79	0.001

HR = Hazard Ratio; 95% CI = 95% Confidence Interval, estimated from proportional hazards models.

[a] Maternal characteristics include maternal history of breast cancer (yes vs. no), race (East-European vs. all other), overweight at pregnancy baseline measure (BMI $\geq$ 25 kg/m^2 vs. other), and week of gestation (continuous).

[b] The fully adjusted model included the maternal adjustment variables and all main study variables entered concurrently, except for ponderal index and small-for-gestational age. Due to high collinearity the fully adjusted model for ponderal index did not include small for gestational age and conversely the fully adjusted SGA model did not include ponderal index.

[c] Ponderal index was calculated as [birthweight (g) / birth length (cm^c)] x 100 and represented as a 4-category ordinal variable coded at quartile medians: 2.14, 2.35, 2.51 and 2.75 respectively for quartiles 1-4. The hazard ratio shown is for an increment of one unit.

[d] Small for gestational age was defined as the lowest decile of the birth-weight-for gestation standardized score vs. all other.

[e] High trimester-specific rates of maternal weight gain were represented as the 4th quartile of weight gain for each trimester vs. all lower quartiles. High 2nd trimester rate of weight gain was equivalent to $\geq$ 1.1690 pounds per week and high 3rd trimester rate of weight gain was equal to $\geq$ 0.9996 pounds per week.

[f] High placental volume was represented as a dichotomous variable, > 360 cm^3 (above the median) vs. $\leq$ 360 cm^3 (at or below the median).

[g] Fibrin deposition was defined as the presence of maternal floor infarction and/or massive or diffuse and patchy subchorionic fibrin vs. absence.

[h] Placental tumors were reportedly benign chorioangiomas as described by Benirschke [K. Benirschke, Examination of the placenta, Obstet. Gynecol. 18(3) (1961) 309-333].