Published in final edited form as:

Cancer Causes Control. 2010 February ; 21(2): 259–268. doi:10.1007/s10552-009-9457-1.

Association of maternal and intrauterine characteristics with age at menarche in a multiethnic population in Hawaii

Meira Epplein,

Epidemiology Program, Cancer Research Center of Hawaii, University of Hawaii at Manoa, Honolulu, HI, USA

Rachel Novotny,

Epidemiology Program, Cancer Research Center of Hawaii, University of Hawaii at Manoa, Honolulu, HI, USA

Department of Human Nutrition, Food and Animal Science, College of Tropical Agriculture and Human Resources, University of Hawaii at Manoa, Honolulu, HI, USA

Kaiser Permanente, Center for Health Research Hawaii, Honolulu, HI, USA

Yihe Daida,

Department of Human Nutrition, Food and Animal Science, College of Tropical Agriculture and Human Resources, University of Hawaii at Manoa, Honolulu, HI, USA

Kaiser Permanente, Center for Health Research Hawaii, Honolulu, HI, USA

Vinutha Vijayadeva,

Epidemiology Program, Cancer Research Center of Hawaii, University of Hawaii at Manoa, Honolulu, HI, USA

Department of Human Nutrition, Food and Animal Science, College of Tropical Agriculture and Human Resources, University of Hawaii at Manoa, Honolulu, HI, USA

Alvin T. Onaka, and

Office of Health Status Monitoring, Hawaii State Department of Health, Honolulu, HI, USA

Loïc Le Marchand

Epidemiology Program, Cancer Research Center of Hawaii, University of Hawaii at Manoa, Honolulu, HI, USA

Abstract

This study seeks to further elucidate the mother–daughter hormonal relationship and its effects on daughter’s breast cancer risk through the association with early age at menarche. Four hundred and thirty-eight healthy girls, age 9–18 and of White, Asian, and/or Polynesian race/ethnicity, were recruited from an HMO on Oahu, Hawaii. Anthropometric measures were taken at a clinic visit, and family background questionnaires were completed. Cox proportional hazards regression was used to test the association of maternal and intrauterine hormone-related exposures with age at menarche. Weight and gestational age at birth and maternal pregnancy-induced nausea were not associated with age at menarche. Each year older of the mother’s age at menarche was associated with a 21% reduced risk of an early age at menarche for the daughter (95% CI: 0.73–0.86). This association between mother’s and daughter’s menarcheal age was statistically significant for girls of Asian, White, and

Mixed, Asian/White race/ethnicity, but not for girls of Mixed, part-Polynesian race/ethnicity ($p_{\text{interaction}} = 0.01$). There was a suggestion that maternal history of breast cancer was associated with an increased risk of early age at menarche (HR = 2.18, 95% CI: 0.95–4.98); there was no association with second-degree family history. These findings support the hypothesis that maternal and intrauterine hormone-related exposures are associated with age at menarche.

Keywords

Menarche; Breast cancer; Hormones; Mothers

Introduction

Early age at menarche, e.g., less than 12 years old, is a well-established risk factor for breast cancer [1–3]. It is thought to increase the risk in two ways: by resulting in a greater lifetime number of menstrual cycles, leading to a greater cumulative exposure to endogenous estrogens [4–6]; and through elevated circulating estrogen levels throughout the reproductive years [6–8].

Maternal and intrauterine characteristics related to increased estrogen exposure also have been investigated as risk factors for breast cancer. Trichopoulos proposed in 1990 that the mammary gland tissue in utero could be affected by high concentrations of maternal estrogens, creating a “fertile soil” for which breast cancer to begin [9]. A recent meta-analysis of the current literature found that factors possibly associated with high prenatal estrogen or growth hormone levels, including increased maternal age, higher birth weight, and greater birth length, were associated with an increased risk of breast cancer, whereas maternal pre-eclampsia and twin membership, possibly associated with decreased levels of in utero endogenous estrogens, were associated with a decreased risk of breast cancer [10]. Preterm birth has also been hypothesized to be a risk factor for breast cancer, as female infants’ urinary excretion of estrogens has been found to decrease from those born at 28 to those born at 41 weeks of gestation [11]. Preterm female infants are thought to have increased estradiol concentrations due to increased postnatal serum concentrations of gonadotropins [12], in addition to their greater likelihood for an increased rate of growth, leading to increased cell division, which would put them at a greater lifetime risk for cancer [13]. In the meta-analysis discussed earlier, however, the summary association of breast cancer with gestational age was not statistically significant, although this may be due to the varying definitions of early gestational age used in previous studies (ranging from 32 weeks or less to less than 39 weeks) and differing choices of adjustment variables. Additionally, another recent meta-analysis found no association between breast cancer risk and early gestational age, defined as either ≤ 36 weeks or ≤ 32 weeks, in separate analyses [14].

The present study reports on the relationships between maternal and intrauterine hormone-related exposures and age at menarche within a multiethnic study of adolescent and teenage girls in Hawaii. The suspected risk factors of greater birth weight and earlier gestational age, as discussed earlier, are examined in relation to age at menarche. Additionally, the associations of maternal history of breast cancer (as a possible indicator of greater levels of estrogens during pregnancy, although also linked to numerous other factors [15]), presence of severe pregnancy-induced nausea (potentially indicative of greater levels of maternal estradiol, as well as other hormones, during pregnancy [16,17]), and younger mother’s age at menarche (which could lead to elevated circulating estrogen levels during the reproductive years [6–8]) with early age at menarche are explored in this study. The overall aim of the study is to further elucidate the mother–daughter hormonal relationship and its effects on the daughter’s future breast cancer risk, through the association with daughter’s earlier age at menarche.

Materials and methods

Study population

This analysis uses the female adolescent maturation (FAM) study, a longitudinal, observational study conducted by the collaborative efforts of Kaiser Permanente Hawaii, the University of Hawaii at Manoa and the Kapiolani Clinical Research Center [18,19]. The FAM study consists of healthy female residents of the island of Oahu, Hawaii, who were between the ages of 9 and 14 in 2000–2001, when they were selected from membership files of Kaiser Permanente Hawaii, a health maintenance organization with approximately 227,000 members. Individuals were excluded if they had a history of chronic disease, were using asthma, antiepileptic or steroid medication, or were of ethnic origin other than White, Asian, or Polynesian. FAM participants were then asked to return for two more exams, in 2002–2003 and 2004–2005, respectively. Additionally, new participants, this time aged 12–18 in 2005–2007, were recruited for the FAM study, with the same exclusions as mentioned earlier. The present analysis utilized a cross-sectional design, incorporating only the first visit of each FAM participant for all variables except for timing of menarche among girls not yet menstruating at the first visit. For already menstruating girls, the censor date was age at menarche. Pre-menarcheal girls at first visit were censored at age at menarche (if determined) or at last date of contact if no menarcheal age was given.

Race/ethnicity of each girl was determined by the racial/ethnic make-up of each of her biological parents [20]. For this analysis, we created four race/ethnicity categories. If both parents were fully Asian, the girl was classified as Asian (including individuals of Japanese, Korean, Chinese, Filipino, Indian, Thai, and Vietnamese origin.) If both parents were fully of European ancestry, the girl was classified as White. If one parent was Asian and the other parent White, or if both or either parent was of mixed Asian and White race/ethnicity, then the girl was classified as Mixed, Asian/White. If, *in addition to Asian and/or White*, one or both parents were of Polynesian ancestry (a Pacific Islander group that includes Native Hawaiian, Samoan, Tongan, Maori, Rapanui, and Rotuman), the girl was classified as Mixed, part-Polynesian. There were no fully Polynesian children. If either parent was part of any other race/ethnicity besides Asian, White or Polynesian, the girl was excluded from this analysis. Of the 529 individual girls who participated in the FAM study, 91 girls were not used in these analyses due to missing information on race/ethnicity ($n = 33$) or being part of a race/ethnic group other than White, Asian or Polynesian ($n = 58$), resulting in 438 subjects available for the present analysis.

Variable measurement

The girls and one of her parents (typically, the mother) completed a family background questionnaire that requested information on infant characteristics (including birth date, weight and length, and gestational age), mother's index pregnancy (including experience of morning sickness by trimester and severity), and maternal and second-degree family history of breast cancer. The age of the mother at the daughter's first visit averaged 45 years, with a range from 31 to 65 years. The girls kept a three-day food record (Thursday, Friday, and Saturday), with parental assistance. The shared nutrition food composition data base at the Cancer Research Centre of Hawaii was used to obtain nutrient variables [21]. For the analysis of dietary intake, we used nutrient averages of the 3 days of diet record. The girls also completed a past-year physical activity recall [22] with the help of the mother. They were asked to fill in activities that they engaged in more than ten times in the past year. For each activity they took part in, they were asked how many months a year, how many days a week and how many minutes each day they spent doing that particular activity. The MET values for all activities were calculated for the specified duration (MET of each activity times duration of each activity). The sum of all MET values was used as a proxy for physical activity in the past year. Questions were also

asked about the age at which both the mother and daughter began to menstruate. For those girls who had not yet begun menstruating at interview, information was sought again at the end of follow-up (August 2008).

Additionally, to complete missing information and to verify accuracy in recall, the records of all girls in the study were linked to the Hawaii State Department of Health birth record database for information on mother's date of last normal menses (for determination of gestational age) and daughter's birth weight. From the birth certificates, we obtained birth weight on 398 girls (75%), and gestational age on 348 girls (66%). Self-recalled and birth certificate information were significantly correlated at Spearman correlations of 0.9 for birth weight and 0.6 for gestational age. For the present analyses, weight and gestational age, when available from the birth certificates, were used in the models. When the birth certificate was not available, recall information was used.

Anthropometric measurements including weight, height, sitting height, waist and hip circumferences, and skinfolds measured on the trunk (subscapular and iliac skinfolds) and on the limbs (biceps, triceps, and calf skinfolds) were taken using standard measures [23] by research staff during a clinic visit. Weight was measured using a digital scale (Seca, Hanover, MD); height was measured using a digital stadiometer (Measurement Concepts, North Bend, WA). Body mass index-for-age percentiles, based on the Centers for Disease Control and Prevention United States growth charts for children and teens (for boys and girls separately), were calculated using the program developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion. A non-elastic tape measure (Rollfix) was used to assess waist and hip circumferences. Skinfolds were measured using a Lange Skinfold Caliper from Beta Technology Incorporated (Cambridge, Maryland). Each measurement was taken at least twice; a third measurement was taken if the two measures differed by two-tenths of a unit or more, with the average of the two closest values used in analysis. Body fat percent and distribution were measured with a GE Lunar Prodigy dual X-ray absorptiometry (DXA) machine. Trunk to periphery fat ratio was calculated by the following equation: $\text{DXA trunk fat} / (\text{DXA arm fat} + \text{DXA leg fat})$.

Statistical analysis

The risk factors of birth weight, gestational age, and mother's age at menarche were separately modeled as continuous variables and as dummy variables in the following categories: low ($\leq 2,500$ g), normal (2,500–4,000 g), and high ($\geq 4,000$ g) for birth weight; <36 , 36–41, and ≥ 42 weeks for gestational age; and <12 , 12–13, and >13 years for mother's age at menarche. Presence of severe pregnancy-induced nausea, mother's history of breast cancer, and second-degree family history of breast cancer were modeled as binary variables (yes/no).

Potential confounders included the following: age at enrollment (as a continuous variable); race/ethnicity (Asian, White, Mixed Asian/White, and Mixed part-Polynesian); years of mother's education (as a continuous variable); average amount of physical activity (as a continuous variable in MET hours per week); mean total energy intake (mean of 3 days, as a continuous variable, in kilocalories); and mean percentage of calories from protein (mean of 3 days, as a continuous variable). Of the six variables, only age and race/ethnicity were found to be significantly associated with both the exposure and outcome of interest and thus were included in the models. Various measures of overall and central obesity, including body mass index (kg/m^2), waist circumference to height ratio, waist circumference (cm), hip circumference (cm), and trunk-to-peripheral fat ratio, based on DXA measurements, were examined to determine which one was most significantly associated with the outcome of daughter's age at menarche. Ultimately, waist circumference, modeled as a binary variable (less than versus greater or equal to the median waist circumference, 64 cm), was chosen to be included in the models as it was most strongly associated with the outcome. Additionally,

gestational age was included as a confounder when modeling the association of birth weight with age at menarche, and birth weight was included as a confounder when modeling the association of gestational age with age at menarche. Secondary models were also created to stratify by race/ethnicity to examine patterns of risk factors where the numbers in the subgroups, after stratification, allowed for cells not smaller than five.

Cox proportional hazards regression, with age as the time metric, was used to determine the association between the exposure and outcome variables. We considered subjects to have entered the study at birth and remained under follow-up until they reached menarche or until they were last contacted and reported that menarche had not yet begun. Thus, girls who had not reached menarche when they filled out the baseline questionnaire and who were not able to be reached for follow-up thereafter were considered censored at the age they filled out the questionnaire. A hazard ratio of greater than 1.0 indicates that the exposed group reached menarche at a younger age compared to the reference/unexposed group. Tests for interactions with race/ethnicity and mother's age at menarche were performed by including as variables in the model product terms of each racial/ethnic dummy variable by the continuous variable of mother's age at menarche, along with each of the individual main-effect variables. All *p* values included in these analyses are two sided, and all analyses were performed using SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina).

Results

Among the 320 girls for whom we obtained information on age at menarche, the age at menarche ranged from 9.0 to 17.6 years, the median age at menarche was 12.3 years, and 50% of girls reached menarche between the ages of 11.5–13.0. Compared to the 118 girls censored at date of last contact, as they had not yet reached menarche, girls for whom we obtained menarcheal age were similar on most baseline characteristics except that they more likely to be older (average age of 13 vs. 11 years), Asian (25 vs. 18%), and more physically active (average MET hours per week of 48 vs. 35).

Characteristics of the study participants are shown in Table 1. The median age at the first visit to complete the questionnaire and take anthropometric measurements was 12.8 years, with 50% of the girls between the ages of 10.8 and 13.9. Almost two-thirds of the girls were of Mixed race/ethnicity—31% were categorized as Mixed, part-Polynesian (within this category: 71% were Asian, White, and Polynesian; 18% were Asian and Polynesian; and 11% were White and Polynesian), and another 30% were Mixed, Asian/White only. The rest of the cohort consisted of subjects of Asian ancestry (23%) and White ancestry (16%). On average, girls of Mixed, part-Polynesian ancestry had a larger waist circumference and were more likely to be obese than girls of White, Asian, or Mixed Asian/White only ancestries.

Being Asian only, when compared to being White only, was associated with a significantly greater risk of an earlier age at menarche, adjusted for age and waist circumference at first visit (HR = 1.87, 95% CI: 1.29–2.71). (Being of Mixed race/ethnicity was not associated with relative timing of age at menarche, compared to being White or Asian.) Comparing within racial/ethnic groups, having a median or above-median (≥ 64 cm) waist circumference, versus a below-median waist circumference, at first visit was associated with an increased risk of a relatively earlier age at menarche, when compared to girls with a below-median waist circumference, adjusted for age (HR = 1.89, 95% CI: 1.48–2.42). The association between a median or above-median waist circumference, and a younger age at menarche was significant only for Asian (HR = 2.58, 95% CI: 1.58–4.20), White (HR = 2.56, 95% CI: 1.23–5.33), and Mixed, part-Polynesian girls (HR = 2.30, 95% CI: 1.42–3.73), and not for Mixed, Asian/White girls (HR = 1.21, 95% CI: 0.79–1.85; $p_{\text{interaction}} = 0.006$). No associations between age at

menarche and mother's education, physical activity, average daily energy intake, or average daily protein as a percent of energy were found.

The association of selected maternal and intrauterine estrogen-related exposures with age at menarche is presented in Table 2. As categorical or continuous variables, modeled linearly or as a quadratic, neither birth weight nor gestational age was significantly associated with age at menarche. Having a mother who experienced severe pregnancy-induced nausea was also not associated with age at menarche. A significant linear relationship was observed between mother's age at menarche and daughter's age at menarche, with each year older of mother's age at menarche being associated with a 21% reduced risk of early menarche for the daughter, adjusted for age, race/ethnicity, and waist circumference (95% CI: 0.73–0.86). There was a suggestion that having a mother with a history of breast cancer was associated with an increase in risk of an earlier age at menarche, although the confidence interval included 1.0, indicating the possibility of no association (HR = 2.18, 95% CI: 0.95–4.98). No association was observed between a second-degree family history of breast cancer and age at menarche.

Table 3 presents the age- and waist circumference-adjusted hazards ratios by race/ethnicity for the relative timing of girl's age at menarche based on mother's age at menarche. Having a mother who reached menarche before age 12 (when compared to age 12–13) more than tripled a White girl's risk of a relatively earlier age at menarche (HR = 3.82, 95% CI: 1.53–9.56), whereas for Mixed Asian/White girls the risk was not quite doubled (HR = 1.87, 95% CI: 1.16–3.02), and for Mixed, part-Polynesian and for Asian girls, there was no significant increase in risk (HR = 0.99, 95% CI: 0.62–1.59 and HR = 1.49, 95% CI: 0.86–2.59, respectively). Treated as a continuous, linear variable, mother's age at menarche was significantly associated with daughter's age at menarche for girls of White (HR = 0.53, 95% CI: 0.39–0.72), Mixed Asian/White (HR = 0.77, 95% CI: 0.64–0.92), and Asian ancestry (HR = 0.79, 0.70–0.90), but not for girls of Mixed, part-Polynesian race/ethnicity. The difference between the association of mother's age at menarche and daughter's age at menarche among Mixed, part-Polynesian girls when compared to White girls was significant (p for interaction = 0.01), and was of borderline significance for Asian girls compared to White girls (p for interaction = 0.06), while it was not significant when comparing Mixed Asian/White girls to White girls (p for interaction = 0.19).

Discussion

A trend toward an earlier age at menarche, a known risk factor for breast cancer, has been observed among girls in the United States, like in other industrialized countries, over recent decades [24]. This study was conducted to examine whether maternal and intrauterine hormone-related factors could be related to earlier age at menarche among a cohort of multiethnic teenage and adolescent girls in Hawaii. We did not find an association between a younger daughter's age at menarche and higher birth weight, younger gestational age, or severe pregnancy-induced nausea, three potential risk factors believed to be related to higher maternal estrogen levels. We did find a positive association between a mother's younger age at menarche with a daughter's younger age at menarche, as well as a suggestion of an increased risk of daughter's younger age at menarche with a mother's history of breast cancer, although this association was based on only seven girls who reported having a mother with a history of breast cancer.

While the present study did not observe an association between birth weight and age at menarche, findings from previous studies have been inconsistent. The most recent report from a study within the Nurses Health Study also observed no association between birth weight and age at menarche [25], and another recent US study found a non-significant association with higher birth weight, whereas the main finding was the positive association between rapid weight gain in childhood and early age at menarche [26]. Other studies have found an

association between birth weight and age at menarche only when including other factors such as birth length [27] and BMI in adolescence [27–29]. Another study found that girls born small for gestational age on average started menarche 5 months before “normal” children ($p = 0.03$) [30]. The present study could not examine this association as we had too few girls born small for gestational age. However, we did adjust for gestational age and current waist circumference when examining the association between birth weight and age at menarche.

Early gestational age has been associated with earlier age at menarche [31–33], although a study in Sweden, similar to the present study, did not find an association [30]. One possible reason for the null finding in the present study is the limited number of girls born premature in our sample. Most studies that have found a positive association have defined early gestational age in the range of less than 31–34 weeks, whereas in our study, we had only 6 girls who were born at or before 34 weeks of gestation, and thus to accrue enough power to see an association, if present, our category of early gestational age extended to those girls born at less than 36 weeks of gestation.

An association between mother’s and daughter’s menarcheal age, even independent from childhood body mass index, is well established in the literature [34–39]. In the one study that stratified by daughter’s body mass index taken postmenarche (median age of 15.6), a moderate positive correlation between the menarcheal ages of the girls and their mothers was observed for girls with a BMI of less than 25 kg/m² ($r = 0.282$, $p < 0.0001$), but no correlation was observed for girls with a BMI of greater than 25 kg/m² ($r = 0.004$, $p = 0.81$) [37]. In the present study, we observed a stronger correlation between the menarcheal ages of mothers and daughters for all girls ($r = 0.372$, $p < 0.0001$). To compare with the study mentioned earlier, the prevalence of girls with a body mass index of greater than 25 kg/m² is only 14% in our study. According to the CDC BMI-for-age index, of the present study population, 12% are categorized as overweight (in the 85th to 94th percentile) and an additional 12% are obese (equal to or above the 95th percentile). (Unfortunately, BMI-for-age was not calculated for the previously published study.) However, consistent with the study mentioned earlier, when examining the association between mother’s and daughter’s menarcheal age by race/ethnicity, we observed that the association was significant for all groups except for the Mixed, part-Polynesian girls, which comprises the population with the highest percentage of BMI-for-age determined overweight or obese (34%, compared to 14% for Asian, 18% for White, and 27% for Mixed, Asian/White). These girls on average have the same age at menarche (12.4 years) as girls in the other racial/ethnic groups, although incidence of breast cancer is significantly higher among women of part-Polynesian ancestry compared to women in the other racial/ethnic groups in Hawaii [40]. Additionally, a study on postmenopausal women found that Native Hawaiians, when compared to Whites in Hawaii, had higher levels of endogenous hormones (including total testosterone, bioavailable testosterone, estrone, total estradiol, and bioavailable estradiol) and lower levels of sex hormone binding globulin, after adjusting for age, known breast cancer risk factors, and lifestyle factors [41].

Whether the association between mother’s and daughter’s age at menarche is primarily genetic [42–44], whether it relates to estrogen exposure in utero, as mothers with an earlier age at menarche might have greater circulating levels of estrogen, or whether it is due to other contemporaneous behaviors was not determined by our study. Our study is the first, of which we are aware of, to examine this association in Polynesian mothers and daughters.

The suggestion of an association of a maternal history of breast cancer and younger age at menarche observed in this study has not, to our knowledge, been examined elsewhere. While one may argue that this finding is reflective of the genetic determinant of age at menarche only, the suggestion of an association persisted even after adjustment for mother’s age at menarche. Furthermore, no association between age at menarche was found with a second-degree family

history of breast cancer. This finding, while based on small numbers and only of borderline statistical significance after adjusting for waist circumference, gives support to the possibility that a woman who will later develop breast cancer may have higher circulating levels of estrogen while pregnant, creating a high estrogen in utero environment which could affect the daughter's earlier maturation.

Beyond the relatively small size of the cohort in the present study, other limitations to the analyses relate to missing or unavailable data. Specifically, the large amount of missing data on birth weight and gestational age led the authors to link to birth certificates from the Hawai'i State Department of Health. However, even with the linkage, birth weight and/or gestational age was missing for 30% (134/438) of the study population. The present study also lacked data on mother's history of preeclampsia, and did not comprise enough twins to examine dizygotic twin pregnancies, the other two risk factors that have been deemed significant from previous studies of maternal/intrauterine exposures and daughter's subsequent risk of breast cancer. The present study also lacked information on childhood growth tempo, considered a potentially important determinant of age at menarche, as noted earlier in the study that found a strong association with rapid childhood weight gain [26].

The other main limitation is the possibility of memory/recall issues when ascertaining mother's age at menarche. A recent study in England, Scotland, and Wales found that when 48-year-old women were asked to recall their age at menarche (which had previously been obtained from them when they were 14–15 years old), 43.6% (412/946) correctly recalled the exact age at menarche, and 41.6% (394/946) recalled their age at menarche as 1 year higher or lower than recorded in their adolescence. Even when grouped into categories similar to those in the current study (≤ 11 , 12–13, ≥ 14 years), there was only moderate agreement ($\kappa = 0.43$) between age at menarche recalled at 48 years and that recorded at age 14 or 15 (Pearson's correlation coefficient $r = 0.66$, $p < 0.001$), although the agreement was best for women in the highest and lowest categories (71.3% agreement for ≤ 11 years and 79.4% agreement for ≥ 14 years) [45]. However, in another study where age at menarche was established at the actual time of menarche, including the month, when the women were contacted, up to 33 years later, 55% recalled age at menarche within 6 months, and 79% recalled age at menarche within 1 year (Pearson $r = 0.79$, $p < 0.001$) [kappa could not be calculated from published data] [46].

There are many strengths to the present study. The unique multiethnic population in Hawaii allowed for stratification by race/ethnicity, including separate categories for racial admixture. Both maternal and intrauterine exposures were assessed through obtaining information from the study participant and her mother. The outcome, daughter's age at menarche, was obtained soon after the actual event, so it is more likely to be accurate than in studies where adult women were asked to recall their menarcheal age. A number of anthropometric measures were taken of the study participants, allowing the authors to select, as the adjustment variable, the best measure for central obesity as it relates to age at menarche. And, while our anthropometric measurements on over half of the participants were taken after menarche began, secondary analyses separating these participants from those whose measurements were assessed prior to menarche did not produce qualitatively different results. Finally, with the linkage to the Hawaii state birth certificates, birth weight, and gestational age were ascertained from an objective source.

In conclusion, this study found only one statistically significant risk factor supporting the hypothesis that maternal and intrauterine hormone-related exposures affect a girl's risk for earlier age at menarche, which then increases her risk of breast cancer. As the literature is already quite large on the association of adolescent central obesity and earlier age at menarche, the present study was able to show that, above and beyond the association with central obesity, a younger mother's age at menarche increases a girl's risk for younger age at menarche. While

this risk factor for early age at menarche may not be very modifiable, it is possible that other steps can be taken among girls at increased risk of early menarche to delay the onset of maturation. Specifically, in a school-based randomized intervention study focused on reducing obesity, it was found that pre-menarcheal girls in the intervention schools had delayed menarche, compared to those girls in the control schools (RR = 0.76, 95% CI: 0.66–0.87), due to increased physical activity and reduced television viewing and resultant changes in BMI and fat distribution [47]. Furthermore, knowledge of the risk factors for early age at menarche, and future research to understand the entire scope of maternal and intrauterine risk factors, especially when able to examine their direct relationship with breast cancer risk, will help in identifying women at increased risk, and hopefully lead to earlier detection, and greater survival, through better screening.

Acknowledgments

Financial support This study was partially supported by Department of Defense grant BC032028, USDA Grant # 99-00700, and a Research Centers in Minority Institutions award, P20 RR11091, from the National Center for Research Resources, National Institutes of Health. One of the authors (ME) was supported by a postdoctoral fellowship on grant R25 CA 90956.

References

1. Colditz, GA.; Baer, HJ.; Tamimi, RM. Breast cancer. In: Schottenfeld, D.; Fraumeni, JF., editors. *Cancer epidemiology and prevention*. 3rd edn. New York: Oxford University Press; 2006. p. 995–1012.
2. Kelsey JL, Bernstein L. Epidemiology and prevention of breast cancer. *Annu Rev Public Health* 1996;17:47–67. [PubMed: 8724215]
3. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. *Epidemiol Rev* 1993;15(1):36–47. [PubMed: 8405211]
4. Chavez-MacGregor M, van Gils CH, van der Schouw YT, Monninkhof E, van Noord PA, Peeters PH. Lifetime cumulative number of menstrual cycles and serum sex hormone levels in postmenopausal women. *Breast Cancer Res Treat* 2008;108(1):101–112. [PubMed: 18274909]
5. Clavel-Chapelon F. Cumulative number of menstrual cycles and breast cancer risk: results from the E3 N cohort study of French women. *Cancer Causes Control* 2002;13:831–838. [PubMed: 12462548]
6. Bernstein L. Epidemiology of endocrine-related risk factors for breast cancer. *J Mammary Gland Biol Neoplasia* 2002;7(1):3–15. [PubMed: 12160084]
7. MacMahon B, Trichopoulos D, Brown J, Andersen AP, Cole P, de Waard F, et al. Age at menarche, urine estrogens and breast cancer risk. *Int J Cancer* 1982;30(4):427–431. [PubMed: 7141738]
8. Windham GC, Elkin E, Fenster L, Waller K, Anderson M, Mitchell PR, et al. Ovarian hormones in premenopausal women: variation by demographic, reproductive and menstrual cycle characteristics. *Epidemiology* 2002;13(6):675–684. [PubMed: 12410009]
9. Trichopoulos D. Hypothesis: does breast cancer originate in utero? *Lancet* 1990;335(8695):939–940. [PubMed: 1970028]
10. Xue F, Michels KB. Intrauterine factors and risk of breast cancer: a systematic review and meta-analysis of current evidence. *Lancet Oncol* 2007;8(12):1088–1100. [PubMed: 18054879]
11. Robine N, Relier JP, Le Bars S. Urocytogram, an index of maturity in premature infants. *Biol Neonate* 1988;54(2):93–99. [PubMed: 3167137]
12. Ekblom A, Erlandsson G, Hsieh C, Trichopoulos D, Adami HO, Cnattingius S. Risk of breast cancer in prematurely born women. *J Natl Cancer Inst* 2000;92:840–841. [PubMed: 10814680]
13. Forman MR, Cantwell MM, Ronckers C, Zhang Y. Through the looking glass at early-life exposures and breast cancer risk. *Cancer Invest* 2005;23:609–624. [PubMed: 16305989]
14. Park SK, Kang D, McGlynn KA, Garcia-Closas M, Kim Y, Yoo KY, et al. Intrauterine environments and breast cancer risk: meta-analysis and systematic review. *Breast Cancer Res* 2008;10(1):R8. [PubMed: 18205956]
15. Cnattingius S, Torrang A, Ekblom A, Granath F, Petersson G, Lambe M. Pregnancy characteristics and maternal risk of breast cancer. *JAMA* 2005;294(19):2474–2480. [PubMed: 16287958]

16. Goodwin TM. Nausea and vomiting of pregnancy: an obstetric syndrome. *Am J Obstet Gynecol* 2002;186:S184–S189. [PubMed: 12011884]
17. Lagiou P, Tamimi R, Mucci LA, Trichopoulos D, Adami HO, Hsieh CC. Nausea and vomiting in pregnancy in relation to prolactin, estrogens, and progesterone: a prospective study. *Obstet Gynecol* 2003;101(4):639–644. [PubMed: 12681864]
18. Lee SK, Novotny R, Daida YG, Vijayadeva V, Gittelsohn J. Dietary patterns of adolescent girls in Hawaii over a 2-year period. *J Am Diet Assoc* 2007;107(6):956–961. [PubMed: 17524716]
19. Novotny R, Daida Y, Grove J, Le Marchand L, Vijayadeva V. Asian adolescents have higher trunk: peripheral fat ratio than Whites. *J Nutr* 2006;136(3):642–647. [PubMed: 16484537]
20. Novotny R, Daida Y. Mixed race/ethnicity assessment using the BLEND method. *Hawaii J Public Health*. 2009 in press.
21. Murphy SP. Unique nutrition support for research at the Cancer Research Center of Hawaii. *Hawaii Med* 2002;61(1):15, 7.
22. Aaron DJ, Kriska AM. Modifiable activity questionnaire for adolescents. *Med Sci Sports Exer* 1997;29(6):S79–S82.
23. Lohman, TB.; Roche, AF.; Martorell, R. Anthropometric standardization reference manual. Champaign: Human Kinetics Publishers, Inc; 1988.
24. Euling SY, Herman-Giddens ME, Lee PA, Selevan SG, Juul A, Sørensen TI, et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. *Pediatrics* 2008;121:S172–S191. [PubMed: 18245511]
25. Colbert LH, Graubard BI, Michels KB, Willett WC, Forman MR. Physical activity during pregnancy and age at menarche of the daughter. *Cancer Epidemiol Biomarkers Prev* 2008;17(10):2656–2662. [PubMed: 18843007]
26. Terry MB, Ferris JS, Tehranifar P, Wei Y, Flom JD. Birth weight, postnatal growth, and age at menarche. *Am J Epidemiol* 2009;170(1):72–79. [PubMed: 19439580]
27. Tam CS, de Zegher F, Garnett SP, Baur LA, Cowell CT. Opposing influences of prenatal and postnatal growth on the timing of menarche. *J Clin Endocrinol Metab* 2006;91(11):4369–4373. [PubMed: 16926251]
28. Blell M, Pollard TM, Pearce MS. Predictors of age at menarche in the Newcastle thousand families study. *J Biosoc Sci* 2008;40:563–575. [PubMed: 18198007]
29. Sloboda DM, Hart R, Doherty DA, Pennell CE, Hickey M. Age at menarche: Influences of prenatal and postnatal growth. *J Clin Endocrinol Metab* 2007;92:46–50. [PubMed: 17062767]
30. Persson I, Ahlsson F, Ewald U, Tuvemo T, Meng QY, von Rosen D, et al. Influence of perinatal factors on the onset of puberty in boys and girls. *Am J Epidemiol* 1999;150:747–755. [PubMed: 10512428]
31. Windham GC, Zhang L, Longnecker MP, Klebanoff M. Maternal smoking, demographic and lifestyle factors in relation to daughter's age at menarche. *Paediatr Perinat Epidemiol* 2008;22(6):551–561. [PubMed: 19000293]
32. Bhargava SK, Ramji S, Srivastava U, Sachdev HP, Kapani V, Datta V, et al. Growth and sexual maturation of low birth weight children: a 14 year follow up. *Indian Pediatr* 1995;32:963–970. [PubMed: 8935258]
33. Ruder EH, Dorgan JF, Kranz S, Kris-Etherton PM, Hartman TJ. Examining breast cancer growth and lifestyle risk factors: early life, childhood, and adolescence. *Clin Breast Cancer* 2008;8(4):334–342. [PubMed: 18757260]
34. Adair LS. Size at birth predicts age at menarche. *Pediatrics* 2001;107:e59–e65. [PubMed: 11335780]
35. Chang SR, Chen KH. Age at menarche of three-generation families in Taiwan. *Ann Hum Biol* 2008;35(4):394–405. [PubMed: 18654871]
36. Ellis BJ, Essex MJ. Family environments, adrenarche, and sexual maturation: a longitudinal test of a life history model. *Child Dev* 2007;78(6):1799–1817. [PubMed: 17988322]
37. Ersoy B, Balkan C, Gunay T, Egemen A. The factors affecting the relation between the menarcheal age of mother and daughter. *Child Care Health Dev* 2005;31(3):303–308. [PubMed: 15840150]

38. Ong KK, Northstone K, Wells JC, Rubin C, Ness AR, Golding J, et al. Earlier mother's age at menarche predicts rapid infancy growth and childhood obesity. *PLoS Med* 2007;4(4):e132. [PubMed: 17455989]
39. van den Berg SM, Boomsma DI. The familial clustering of age at menarche in extended twin families. *Behav Genet* 2007;37(5):661–667. [PubMed: 17541737]
40. Pike MC, Kolonel LN, Henderson BE, Wilkens LR, Hankin JH, Feigelson HS, et al. Breast cancer in a multiethnic cohort in Hawaii and Los Angeles: risk factor-adjusted incidence in Japanese equals and in Hawaiians exceeds that in whites. *Cancer Epidemiol Biomarkers Prev* 2002;11(9):795–800. [PubMed: 12223421]
41. Setiawan VW, Haiman CA, Stanczyk FZ, Le Marchand L, Henderson BE. Racial/ethnic differences in postmenopausal endogenous hormones: the multiethnic cohort study. *Cancer Epidemiol Biomarkers Prev* 2006;15(10):1849–1855. [PubMed: 17035391]
42. Zhao J, Xiong DH, Guo Y, Yang TL, Recker RR, Deng HW. Polymorphism in the insulin-like growth factor 1 gene is associated with age at menarche in caucasian females. *Hum Reprod* 2007;22(6):1789–1794. [PubMed: 17376820]
43. Yang F, Xiong DH, Guo Y, Shen H, Xiao P, Zhang F, et al. The chemokine (C-C-motif) receptor 3 (CCR3) gene is linked and associated with age at menarche in Caucasian females. *Hum Genet* 2007;121(1):35–42. [PubMed: 17146638]
44. Guo Y, Xiong DHYTL, Guo YF, Recker RR, Deng HW. Polymorphisms of estrogen-biosynthesis genes CYP17 and CYP19 may influence age at menarche: a genetic association study in Caucasian females. *Hum Mol Genet* 2006;15(16):2401–2408. [PubMed: 16782804]
45. Cooper R, Blell M, Hardy R, Black S, Pollard TM, Wadsworth ME, et al. Validity of age at menarche self-reported in adulthood. *J Epidemiol Community Health* 2006;60(11):993–997. [PubMed: 17053289]
46. Must A, Phillips SM, Naumova EN, Blum M, Harris S, Dawson-Hughes B, et al. Recall of early menstrual history and menarcheal body size: after 30 years, how well do women remember? *Am J Epidemiol* 2002;155:672–679. [PubMed: 11914195]
47. Chavarro JE, Peterson KE, Sobol AM, Wiecha JL, Gortmaker SL. Effects of a school-based obesity-prevention intervention on menarche (United States). *Cancer Causes Control* 2005;16(10):1245–1252. [PubMed: 16215875]
48. Cavill N, Biddle S, Sallis J. Health enhancing physical activity for young people. *Pediatr Exerc Sci* 2001;13:12–25.

Table 1

Main characteristics of participants by race/ethnicity

Variable	Asian (n = 101)	White (n = 71)	Mixed, Asian/White (n = 132)	Mixed, part-Polynesian (n = 134)	All girls (n = 438)
Age at first visit (years)					
9–10	28 (28%)	24 (34%)	43 (33%)	31 (23%)	126 (29%)
11–12	23 (23%)	19 (27%)	34 (26%)	33 (25%)	109 (25%)
13–14	36 (36%)	25 (35%)	37 (28%)	47 (35%)	145 (33%)
15–16	12 (12%)	2 (3%)	12 (9%)	21 (16%)	47 (11%)
17–18	2 (2%)	1 (1%)	6 (5%)	2 (1%)	11 (3%)
Median (IQR)	13.0 (10.9–13.8)	12.4 (10.3–13.8)	12.7 (10.6–13.8)	13.2 (11.2–14.1)	12.8 (10.8–13.9)
Years of mother's education ^a					
≤12	6 (9%)	7 (15%)	20 (21%)	31 (33%)	64 (21%)
13–15	23 (33%)	11 (24%)	30 (31%)	29 (31%)	93 (30%)
≥16	41 (59%)	28 (61%)	46 (48%)	34 (36%)	149 (49%)
Median (IQR)	16 (15–17)	16 (14–18)	15 (13–17)	14 (12–16)	15 (13–17)
Waist circumference (cm)					
<64 .25	59 (58%)	39 (55%)	71 (54%)	49 (37%)	218 (50%)
≥64 .25	42 (42%)	32 (45%)	61 (46%)	85 (63%)	220 (50%)
Median (IQR)	62.6 (58.4–66.9)	63.4 (58.3–68.9)	62.9 (58.9–70.5)	67.2 (61.4–74.2)	64.0 (59.0–70.1)
Trunk to peripheral fat ratio ^b					
<1.0	42 (60%)	36 (77%)	51 (54%)	46 (49%)	175 (57%)
≥1.0	28 (40%)	11 (23%)	44 (46%)	48 (51%)	131 (43%)
Body mass index-for-age ^c					
Underweight (<5th percentile)	11 (11%)	5 (7%)	14 (11%)	2 (1%)	32 (7%)
Healthy weight (5th–84th)	76 (75%)	53 (75%)	82 (62%)	87 (65%)	298 (68%)
Overweight (85th–94th)	8 (8%)	6 (8%)	20 (15%)	20 (15%)	54 (12%)
Obese (≥95th)	6 (6%)	7 (10%)	16 (12%)	25 (19%)	54 (12%)
Physical activity ^d					
Not active (<42 MET h/wk)	59 (60%)	29 (41%)	66 (50%)	56 (42%)	210 (49%)
Active (≥42 MET h/wk)	39 (40%)	42 (59%)	65 (50%)	76 (58%)	222 (51%)
Median METs (IQR)	31 (15–66)	51 (33–84)	40 (19–74)	50 (26–89)	45 (21–79)

Variable	Asian (n = 101)	White (n = 71)	Mixed, Asian/White (n = 132)	Mixed, part-Polynesian (n = 134)	All girls (n = 438)
Average daily energy intake (kcal) ^e					
Mean (± standard deviation)	1,715 (± 389)	1,823 (± 464)	1,784 (± 554)	1,750 (± 513)	1,764 ± 492
Average daily protein as a percent of energy ^e					
Mean (± standard deviation)	20 ± 8	20 ± 10	22 ± 10	22 ± 11	21 ± 10

^a30% of subjects missing mother's education: Asian = 31 (31%); White = 25 (35%); Mixed Asian/White = 36 (27%); Mixed part-Polynesian = 40 (30%)

^b30% of subjects missing central obesity (trunk-to-peripheral fat ratio) information: Asian = 31 (31%); White = 24 (34%); Mixed Asian/White = 37 (28%); Mixed part-Polynesian = 40 (30%)

^cBody mass index-for-age percentiles developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000)

^d1% of subjects missing physical activity: Asian = 3 (3%); White = 0 (0%); Mixed Asian/White = 1 (1%); Mixed part-Polynesian = 2 (1%); categories based on the 2001 international recommendations for youth to have 60 min/day moderate-to-vigorous activity [48]

^e3% of subjects missing information on diet: Asian = 4 (4%); White = 2 (3%); Mixed Asian/White = 6 (5%); Mixed part-Polynesian = 2 (1%)

Table 2

Multivariate-adjusted proportional hazards ratios for the association of maternal and intrauterine estrogen-related exposures and relative timing of menarche

	n (%)	Adjusted for age and race/ethnicity ^a			Adjusted for age, race/ethnicity, and waist circumference ^d		
		Hazards ratio	95% confidence interval	p value	Hazards ratio	95% confidence interval	p value
Birth weight ^b (g)							
Low (≤2,500)	19 (5%)	1.28	0.75, 2.18	0.37	1.17	0.69, 2.00	0.56
Normal (2,500–4,000)	315 (90%)	1.00	Reference		1.00	Reference	
High (≥4,000)	14 (4%)	1.08	0.53, 2.20	0.84	1.01	0.49, 2.07	0.98
As a continuous variable		1.00	1.00, 1.00	0.33	1.00	1.00, 1.00	0.14
Gestational age ^b (weeks)							
<36	12 (3%)	1.65	0.85, 3.19	0.14	1.61	0.83, 3.10	0.16
36–41	281 (81%)	1.00	Reference		1.00	Reference	
≥42	55 (16%)	1.03	0.72, 1.49	0.86	1.08	0.75, 1.55	0.69
As a continuous variable		1.00	0.99, 1.01	0.51	1.00	0.99, 1.01	0.66
Presence of severe pregnancy-induced nausea ^c							
No	277 (91%)	1.00	Reference		1.00	Reference	
Yes	26 (9%)	0.93	0.61, 1.43	0.75	0.87	0.57, 1.34	0.53
Mother's age at menarche ^d (years)							
<12	106 (25%)	1.49	1.14, 1.93	0.003	1.45	1.12, 1.90	0.006
12–13	233 (56%)	1.00	Reference		1.00	Reference	
>13	79 (19%)	0.55	0.40, 0.77	0.004	0.51	0.37, 0.71	<0.0001
As a continuous variable		0.79	0.73, 0.86	<0.0001	0.79	0.73, 0.86	<0.0001
Mother history of breast cancer	7 (2%)	2.60	1.14, 5.94	0.02	2.18	0.95, 4.98	0.06
2° family history of breast cancer	85 (19%)	1.12	0.85, 1.48	0.43	1.08	0.82, 1.42	0.59

^aBirth weight also adjusted for gestational age; gestational age also adjusted for birth weight

^b90 subjects missing birth weight and/or gestational age

^c90 subjects missing presence of severe pregnancy-induced nausea

p 20 subjects missing mother's age at menarche

Table 3

Multivariate-adjusted proportional hazards ratios for the association of mother's age at menarche and relative timing of daughter's menarche, stratified by race/ethnicity

Mother's age at menarche (years)	<i>n</i> (%)	Hazards ratio ^a	95% confidence interval	<i>p</i> value
Asian ^b				
<12	28 (30%)	1.49	0.86, 2.59	0.15
12–13	42 (45%)	1.00	Reference	
>13	24 (26%)	0.43	0.22, 0.81	0.01
As a continuous variable		0.79	0.70, 0.90	0.0003
White ^c				
<12	8 (12%)	3.82	1.53, 9.56	0.004
12–13	44 (66%)	1.00	Reference	
>13	15 (22%)	0.27	0.11, 0.67	0.004
As a continuous variable		0.53	0.39, 0.72	<0.0001
Mixed, Asian/White ^d				
<12	34 (27%)	1.87	1.16, 3.02	0.01
12–13	71 (55%)	1.00	Reference	
>13	23 (18%)	0.73	0.39, 1.36	0.32
As a continuous variable		0.77	0.64, 0.92	0.004
Mixed, part-Polynesian ^e				
<12	36 (28%)	0.99	0.62, 1.59	0.96
12–13	76 (59%)	1.00	Reference	
>13	17 (13%)	0.58	0.29, 1.13	0.11
As a continuous variable		0.88	0.76, 1.03	0.10

^a Adjusted for age and waist circumference

^b 7 subjects missing mother's age at menarche

^c 4 subjects missing mother's age at menarche

^d 4 subjects missing mother's age at menarche

^e 5 subjects missing mother's age at menarche