Mean Arterial Pressure, Pregnancy-induced Hypertension, and Preeclampsia: Evaluation as Independent Risk Factors and as Surrogates for High Maternal Serum \( \alpha \)-Fetoprotein in Estimating Breast Cancer Risk

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Abstract

Data from a nested case-control study were analyzed to examine high mean arterial pressure (MAP), hypertension of pregnancy, and preeclampsia as independent predictors and as surrogate markers for elevated \( \alpha \)-fetoprotein (AFP) levels in evaluating breast cancer risk. Cases (n = 205) were identified by the California Cancer Registry from a cohort of pregnant women who were part of the Kaiser Health Plan and took part in the Child Health and Development Studies initiated by the University of California, Berkeley, from June 1959 to September 1966. Controls (n = 337) were selected by randomized recruitment from the same cohort probability matched to cases by distribution of birth dates of cases. High MAP was associated with breast cancer risk and is different across quartile of age at first full-term pregnancy as is high AFP. Odds ratios (OR) across quartiles for MAP were 0.24 [95% confidence interval (CI), 0.08–0.71], 0.84 (95% CI, 0.39–1.66), 1.00 (referent), and 2.50 (95% CI, 1.21–5.13), and for AFP were 0.34 (95% CI, 0.13–0.93), 0.77 (95% CI, 0.36–1.67), 1.00 (referent), and 2.38 (95% CI, 1.13–5.00). Neither diagnosed preeclampsia nor hypertension of pregnancy showed any association with breast cancer risk. When both high AFP and high MAP were entered into the same analysis, neither changed the OR for the other more than 8%. Additionally, AFP level was not a linear function of MAP. Although the pattern of ORs across quartiles of age at first full-term pregnancy was similar for the two variables, it cannot be concluded that high MAP is an adequate surrogate for high levels of maternal serum AFP, but rather represents some related process that is in and of itself a risk factor for breast cancer.

Introduction

Pregnancy-induced hypertension, as a surrogate of elevated MSAFP\(^1\) levels, has been reported to have a protective effect against subsequent breast cancer risk in the mother (1–3). Although conditions defined by levels of maternal blood pressure, such as preeclampsia and hypertension of pregnancy, have been shown in some studies (4–9) to have an association with high AFP levels, other studies (10–13) have not supported this association. Thus, the validity of pregnancy-induced hypertension as a proxy indicator for AFP levels is called into question. The present study examines high MAP, hypertension of pregnancy, and preeclampsia as independent predictors of subsequent breast cancer risk. The performance of pregnancy-induced hypertension as a surrogate for AFP is evaluated further by comparing the hypertension risk estimates with those obtained from direct assessment of MSAFP levels.

Pregnancy-induced hypertension is a syndrome defined by maternal hypertension diagnosed during the later part of pregnancy, usually after the 20th week of gestation. When the diagnosis includes proteinuria, the condition is known as preeclampsia. The etiology of preeclampsia is controversial, but it involves the placenta as well as multiple organ systems and is resolved by delivery of the placental tissue whether or not a fetus is present (14).

AFP is a three-domain glycoprotein, structurally similar to serum albumin, that is synthesized by the fetal liver and yolk sac during embryonic development, enters the amniotic fluid through fetal renal excretion, crosses the placenta, and enters the maternal circulation (15). The hypothesis of a protective effect of AFP against breast cancer is based on the work of Mizjejewski et al. (16), Allen et al. (17), and Jacobson and Janeich (18), which has shown AFP to enhance or down-regulate growth in cell cultures, animal models, and two neoplastic cell lines (MCF-7 human breast cancer cell lines and MTW9A rat breast cancer cell lines; Ref. 19–22).

A previous study by Richardson et al. (23) has shown that a protective effect of high levels of MSAFP on subsequent breast cancer risk. In a nested case-control study, the highest quartile of measured MSAFP was shown to be protective against breast cancer risk among women who had their first pregnancy before age 27. High AFP after age 27 may have increased risk. The

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\(^1\) The abbreviations used are: MSAFP, maternal serum \( \alpha \)-fetoprotein; AFP, \( \alpha \)-fetoprotein; MAP, mean arterial pressure; CHDS, Child Health and Development Studies; OR, odds ratio; CI, confidence interval; LMP, last menstrual period.
Surrogates for High Maternal Serum α-fetoprotein

active portion of human AFP, which can elicit this biphasic response from cells, has recently been synthesized and characterized by Mizejewski et al. (24) and has been found to be in the ligand-binding region of the molecule.

Given the limited number of serum repositories available to study the effects of pregnancy serum components on long-term chronic diseases such as breast cancer, it would be advantageous to identify adequate surrogates for a range of serum biomarkers. Any such surrogates, however, should be validated before widespread use.

Materials and Methods

The CHDS were designed and initiated at the University of California, Berkeley in 1959 in cooperation with the Kaiser Foundation Research Institute and the Permanente Medical Group. These studies began with the enrollment of pregnant women who were members of the Kaiser Health Plan and who planned to deliver at Kaiser Foundation hospitals. Enrollment started in June 1959 and ended in September 1966 (25). During that period, 12,528 women were enrolled and interviewed. The present analysis of MSAFP levels, blood pressure, and subsequent breast cancer is limited to 542 women, 205 cases, and 337 controls.

To be enrolled in the present study, women in the CHDS cohort met the following eligibility criteria. Each woman must have: (a) completed an interview questionnaire; (b) been legally of age (21 years) or married; (c) delivered one or more (includes three sets of twins) live or stillborn infant(s) from the index pregnancy; (d) had a blood sample taken and frozen as serum during the last trimester of the index pregnancy, which was the last pregnancy experienced by cases and controls in the CHDS enrollment period, June 1959 to September 1966; (e) been a continuing California resident, therefore, had she developed breast cancer, she would be included in the California Cancer Registry or have had her death recorded in California; and (f) had her blood pressure measured and recorded at 9 days or less from the date of blood draw.

Cases were women in the CHDS cohort who met the eligibility requirements above and who had histologically confirmed primary breast carcinoma (ICD 174) identified in the files of the California Cancer Registry through 1994. Matching of the CHDS cohort to tumor registry data was done by the CHDS in cooperation with the California Cancer Registry, which is part of the California Public Health Foundation. The methodology used for linkage of the CHDS cohort minimizes the number of false positives. The initial linkage is done by matching name, also known as name, date of birth, sex, and race. Matches are assigned a probability score based on the degree of similarity of the matching records from the two files. Matches are reviewed carefully by project staff, and only high probability matches are included. Controls were eligible members of the cohort not diagnosed with breast cancer, probability matched to cases by distribution of birth dates of cases (using the requirement for an approved test for proteinuria. Blood pressure measurements from each prenatal visit were examined and used to assess the occurrence of gestational hypertension for each woman. A woman was designated as hypertensive if she had two or more instances of elevated blood pressure occurring ≥6 h apart, after the 22nd week of gestation.

Information on diastolic and systolic blood pressure within 9 days of blood draw was available from medical records. MAP was calculated using the equation: diastolic blood pressure + [1/3 × (systolic blood pressure − diastolic blood pressure)].

Levels of MSAFP were determined in the following way. From 1959 to 1966, serum samples from the CHDS population were stored at −20°C, shipped to NIH in Bethesda, Maryland, and held again at −20°C. AFP concentration is known to be relatively stable in human serum even when subjected to repeated freezing (at −20°C) and thawing and to hours at room temperature between each freezing episode (30, 31). To assess the possibility of protein degradation in the CHDS samples, two assays of serum levels of AFP were performed at the Reproductive Hormone Laboratory, Duke University Medical Center, Durham, North Carolina. The first, a radio immunoassay (Diagnostics Products Corporation), allows the assessment of both intact and fragmented AFP molecules; the second, an immunoenzymetric assay (Hybritech Corporation), uses two epitope-specific monoclonal antibodies to detect intact protein only. The average of the two assays characterized as ng AFP/ml of maternal serum was used as level of AFP exposure in the analysis presented below.

AFP levels for each woman during the index pregnancy were characterized as the difference (residual) between the woman’s assay value and the mean AFP level of all blood draws from that day of gestation (calculated from first day of LMP). This allowed adjustment for differing dates of blood draw throughout the data set. The mean AFP curve was estimated using local linear regression, or lowess, a nonparametric smoothing technique that uses a varying subset of the data to estimate the curve at each gestational age, i.e., a weighted average over days of gestation (32). For these data, a bandwidth of 70% of the data was used to estimate a given point on the curve. To contend with heteroscedasticity in the original scale of measurement, the lowess and the residual values were determined using logs of the original values. High AFP levels were defined as the top 25% of the AFP serum distribution among the controls compared with other controls (the other 75%).

Data Analysis. Multiple logistic regression in SAS Proc Genmod (33) was used to compute ORs for breast cancer risk. Proc Genmod allows offsets to adjust for the randomized recruitment sampling probabilities used to select controls. Information on potential confounders and effect modifiers was gathered from the interview data compiled from the questionnaires adminis-
Results

Table 1 shows selected sociodemographic characteristics and the number of women with hypertension of pregnancy and preeclampsia during the index pregnancy. The ages of the women in the study ranged from 17 to 44 years of age. Cases were 18 to 43 years of age at the end of index pregnancy (mean age, 31.00 years), and controls were 17 to 44 years of age (mean age, 31.03 years). Among controls, the incidence of diagnosed preeclampsia and gestational hypertension was 11.4%, and among cases, it was 12.2%. The percentage of preeclampsia among the study subjects was 3.9%, with both hypertension and preeclampsia being more prevalent in this study among women over age 30. More than 60% (68.3%) of cases of hypertension of pregnancy occurred among women over 30 years of age, as well as over 80% of the preeclampsia (81%) cases.

Neither preeclampsia alone (adjusted OR 1.57, 95% CI 0.63, 3.88), all of the hypertension of pregnancy (including preeclampsia; adjusted OR 1.07; 95% CI 0.60, 1.90), hypertension of pregnancy alone (no preeclampsia; OR 0.79; 95% CI 0.40–1.57), nor present and past preeclampsia (adjusted OR 1.31; 95% CI 0.55–3.12) showed any significant prediction of breast cancer risk. Even among women in a first pregnancy when the risk of preeclampsia is higher than subsequent pregnancies, no association with breast cancer risk was apparent for preeclampsia (OR 0.89; 95% CI 0.07–11.22). An interaction term for age at first full-term pregnancy × hypertension of pregnancy showed no significance ($P = 0.77$); neither did the interaction term for age at first full-term pregnancy × preeclampsia among women in a first pregnancy ($P = 0.39$). Only

Table 1  Distribution of mean maternal serum level of AFP (ng/ml) and average MAP (ml/Hg) by selected socio demographic characteristics and breast cancer risk factors among cases and controls, CHDS, 1959–1966

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 205)</th>
<th>Controls (n = 334)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean AFP</td>
<td>Mean MAP</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>180.9</td>
<td>83.6</td>
</tr>
<tr>
<td>Black</td>
<td>173.9</td>
<td>82.9</td>
</tr>
<tr>
<td>Asian</td>
<td>218.4</td>
<td>85.0</td>
</tr>
<tr>
<td><strong>Age at index pregnancy (yr)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>212.6</td>
<td>84.8</td>
</tr>
<tr>
<td>&gt;20 ≤23</td>
<td>217.9</td>
<td>85.3</td>
</tr>
<tr>
<td>&gt;23 ≤27</td>
<td>215.8</td>
<td>86.9</td>
</tr>
<tr>
<td>&gt;27 ≤30</td>
<td>209.2</td>
<td>85.4</td>
</tr>
<tr>
<td>&gt;30 ≤35</td>
<td>216.8</td>
<td>88.5</td>
</tr>
<tr>
<td>&gt;35</td>
<td>216.8</td>
<td>88.5</td>
</tr>
<tr>
<td><strong>Age at first full term pregnancy (yr)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>177.9</td>
<td>83.5</td>
</tr>
<tr>
<td>&gt;20 ≤23</td>
<td>204.3</td>
<td>87.2</td>
</tr>
<tr>
<td>&gt;23 ≤27</td>
<td>214.3</td>
<td>84.1</td>
</tr>
<tr>
<td>&gt;27 ≤30</td>
<td>214.3</td>
<td>84.1</td>
</tr>
<tr>
<td>&gt;30 ≤35</td>
<td>214.3</td>
<td>84.1</td>
</tr>
<tr>
<td>&gt;35</td>
<td>214.3</td>
<td>84.1</td>
</tr>
<tr>
<td><strong>Number of previous full term pregnancies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>207.6</td>
<td>87.1</td>
</tr>
<tr>
<td>1</td>
<td>212.2</td>
<td>87.2</td>
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<td>2</td>
<td>224.7</td>
<td>81.9</td>
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<td>3</td>
<td>158.3</td>
<td>70.3</td>
</tr>
<tr>
<td>4</td>
<td>255.5</td>
<td>96.9</td>
</tr>
<tr>
<td><strong>Blood pressure status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>190.1</td>
<td>92.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>222.3</td>
<td>82.4</td>
</tr>
<tr>
<td>Normotensive</td>
<td>242.7</td>
<td>89.6</td>
</tr>
</tbody>
</table>

*a Total number of observations in each category could differ due to missing data.
were assessed and found to be significantly different (means for the two groups across the weeks of the third trimester women with normal blood pressure. Using an ANOVA, the weeks of gestation of the third trimester when compared with as preeclamptic or hypertensive was higher during all of the drawn. However, the average MAP for those women diagnosed pressures obtained at or within 9 days of the time blood was enced preeclampsia. This results from using only those blood third trimester for the women who are hypertensive or experi- was not abnormally high over the weeks of gestation of the this period of gestation. It can be seen that the average MAP women with hypertension of pregnancy and preeclampsia and was not abnormally high over the weeks of gestation of the

The OR associated with each variable was estimated by logistic regression and adjusted for race and age at index pregnancy but not for high maternal MAP.

The OR associated with each variable was estimated by logistic regression and adjusted for race, age at index pregnancy, and high maternal MAP.

Lowest three quartiles of maternal MAP.

The OR associated with each variable was estimated by logistic regression and adjusted for race, age at index pregnancy, and high maternal serum AFP.

The OR associated with each variable was estimated by logistic regression and adjusted for race and index pregnancy but not for high maternal serum AFP.

Table 2 displays the relation of average MAP within 9 days of blood draw in the third trimester of pregnancy between women with hypertension of pregnancy and preeclampsia and women whose blood pressure was within normal values during this period of gestation. It can be seen that the average MAP was not abnormally high over the weeks of gestation of the third trimester for the women who are hypertensive or experienced preeclampsia. This results from using only those blood pressures obtained at or within 9 days of the time blood was drawn. However, the average MAP for those women diagnosed as preeclampsic or hypertensive was higher during all of the weeks of gestation of the third trimester when compared with women with normal blood pressure. Using an ANOVA, the means for the two groups across the weeks of the third trimester were assessed and found to be significantly different ($F = 50.94, P < 0.001$).

Both high MSAFP and high maternal MAP show interactions with age at first full-term pregnancy. Initially, it was expected that the variables were modeling aspects of the same underlying biological interactions and that both would not be significant in the same model. In the full model, however, each is independently significant, and each is modified little when the other is removed from the equation (<1% for the interaction ORs and <4% for the main effect terms).

The outcome of the analysis is shown in Tables 3 and 4, which show the ORs for high MAP and high AFP across quartiles of age at first full-term pregnancy, adjusted and un-adjusted for the other variable. There is a linear progression of ORs across the ages at first full-term pregnancy for high MAP very similar, although not identical, to high MSAFP ORs. The ORs for the lowest quartile of age at first full-term pregnancy for high MAP were not significant, whereas for high MSAFP the ORs were significant.

Table 3 and 4 show that the ORs for high MAP and high AFP across quartiles of age at first full-term pregnancy, adjusted and un-adjusted for the other variable. There is a linear progression of ORs across the ages at first full-term pregnancy for high MAP very similar, although not identical, to high MSAFP ORs. The ORs for the lowest quartile of age at first full-term pregnancy for high MAP were not significant, whereas for high MSAFP the ORs were significant.

For these data, high MAP is not a linear predictor of AFP levels in maternal serum during the third trimester, adjusting for age at index pregnancy, first full-term pregnancy age, week of

### Table 2

<table>
<thead>
<tr>
<th>Wk of blood draw</th>
<th>Normal</th>
<th></th>
<th>Hypertensive</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAP</td>
<td>SD</td>
<td>AFP</td>
<td>SD</td>
</tr>
<tr>
<td>26–27</td>
<td>79.9</td>
<td>5.4</td>
<td>198.5</td>
<td>68.0</td>
</tr>
<tr>
<td>28–29</td>
<td>81.8</td>
<td>9.9</td>
<td>202.9</td>
<td>86.2</td>
</tr>
<tr>
<td>30–31</td>
<td>81.6</td>
<td>8.8</td>
<td>221.9</td>
<td>121.2</td>
</tr>
<tr>
<td>32–33</td>
<td>83.1</td>
<td>8.9</td>
<td>243.4</td>
<td>128.6</td>
</tr>
<tr>
<td>34–35</td>
<td>84.0</td>
<td>8.8</td>
<td>222.1</td>
<td>117.0</td>
</tr>
<tr>
<td>36–37</td>
<td>85.4</td>
<td>8.3</td>
<td>198.8</td>
<td>110.7</td>
</tr>
<tr>
<td>38–39</td>
<td>86.3</td>
<td>7.2</td>
<td>132.6</td>
<td>66.8</td>
</tr>
</tbody>
</table>

a Total number of observations in each category could differ due to missing data.

### Table 3

<table>
<thead>
<tr>
<th>Age at first full term pregnancy quartile</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Adjusted for high AFP</th>
<th>Adjusted for high AFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1 age ≤20 yr</td>
<td>44</td>
<td>88</td>
<td>0.24</td>
<td>0.11–0.52</td>
</tr>
<tr>
<td>Quartile 2 age &gt;20 Years to ≤23 Years</td>
<td>41</td>
<td>98</td>
<td>0.78</td>
<td>0.46–1.31</td>
</tr>
<tr>
<td>Quartile 3 age &gt;23 Years to ≤27 Years</td>
<td>61</td>
<td>75</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>Quartile 4 age &gt;27 Years</td>
<td>59</td>
<td>73</td>
<td>3.22</td>
<td>1.92–5.38</td>
</tr>
</tbody>
</table>

a Highest quartile of maternal MAP.

b Lowest three quartiles of maternal MAP.

c The OR associated with each variable was estimated by logistic regression and adjusted for race, age at index pregnancy, and high maternal serum AFP.

d The OR associated with each variable was estimated by logistic regression and adjusted for race and age at index pregnancy but not for high maternal serum AFP.

### Table 4

<table>
<thead>
<tr>
<th>Age at first full term pregnancy quartile</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Adjusted for high AFP</th>
<th>Adjusted for high AFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1 age ≤20 yr</td>
<td>44</td>
<td>88</td>
<td>0.28</td>
<td>0.14–0.58</td>
</tr>
<tr>
<td>Quartile 2 age &gt;20 Years to ≤23 Years</td>
<td>41</td>
<td>98</td>
<td>0.73</td>
<td>0.42–1.27</td>
</tr>
<tr>
<td>Quartile 3 age &gt;23 Years to ≤27 Years</td>
<td>61</td>
<td>75</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>Quartile 4 age &gt;27 Years</td>
<td>59</td>
<td>73</td>
<td>2.83</td>
<td>1.66–4.82</td>
</tr>
</tbody>
</table>

a Highest quartile of maternal MAP.

b Lowest three quartiles of maternal MAP.

c The OR associated with each variable was estimated by logistic regression and adjusted for race, age at index pregnancy, and high maternal MAP.

d The OR associated with each variable was estimated by logistic regression and adjusted for race and age at index pregnancy but not for high maternal MAP.

The OR associated with each variable was estimated by logistic regression and adjusted for race, age at index pregnancy, and high maternal MAP.

d The OR associated with each variable was estimated by logistic regression and adjusted for race and age at index pregnancy but not for high maternal MAP.

For these data, high MAP is not a linear predictor of AFP levels in maternal serum during the third trimester, adjusting for age at index pregnancy, first full-term pregnancy age, week of...
blood draw, and race. Only race, week of blood draw, and body mass index contribute to the variance in AFP levels, and MAP still does not significantly augment prediction of MSAFP levels. With these three control variables in the equation, the linear regression parameter estimate for the relation of MAP and AFP is 0.4602 (P = 0.45; Ref. 34). Also, among women in the highest quartile of MAP there is an inverse relationship with levels of AFP, with the lowest number of women in the highest quartile of AFP. Of the women classified as having pregnancy-induced hypertension and those diagnosed with preeclampsia, only 19% were in the highest quartile of MSAFP. This is a lower percentage than that among women classified as being normotensive who were in the highest quartile of measured MSAFP (26%).

There is a marginally significant three-way interaction (P = 0.066) between high MAP at or near time of blood draw and age at first full-term pregnancy and age at index pregnancy. The three-way interaction indicates that when a woman in the study was 21 years of age or less at first full-term pregnancy, the OR for MAP for subsequent breast cancer is ~0.50 across all three tertiles of age at index pregnancy (≤28, >28 to ≤34, and >34 years of age). For women in the study who had first given birth between 22 and 25 years of age, the ORs for high MAP appear to increase across the three tertiles of age at the time of the index pregnancy (adj. OR 0.77, CI 0.18–3.34; OR 0.82, CI 0.23–2.86; OR 1.41, CI 0.27–7.21). When women were ≥26 years of age at first full-term pregnancy, the ORs decrease across the tertiles of age at index pregnancy (adj. OR 8.34, CI 1.11–62.72; OR 1.98, CI 0.63–6.29; OR 1.40, CI 0.52–3.76).

Diagnosis of breast cancer at ≤15 years after index pregnancy was examined to assess possible differences in action of either high MAP or high AFP on breast tissue soon after a full-term pregnancy. Small numbers (n = 22) contributed to the instability of the data, but the ORs for both high MAP and high AFP indicated a protective effect for those women with a first full-term pregnancy before age 27, although the CIs included the null values. For those women ≤27 years of age at first full-term pregnancy, the ORs for high AFP and high MAP for diagnosis ≤15 years after index pregnancy were 0.33 (95% CI 0.10–1.14) and 0.62 (95% CI 0.22–1.74). For those women with a diagnosis at <15 years but first full-term pregnancy when they were older than age 27, the ORs for high AFP and high MAP were 0.69 (95% CI 0.15–3.12) and 1.28 (95% CI 0.38–4.28), which might mean that high AFP is still protective for those women or that it is essentially neutral.

High MAP and high AFP had a slightly stronger protective effect for first pregnancies than for subsequent pregnancies, but the relation to breast cancer risk was the same.

Discussion
Contrary to expectations, in these data high levels of MSAFP and high MAP are separate and distinct risk factors for subsequent breast cancer risk. There is also an indication of effect modification of high MAP by both age at index pregnancy and age at first full-term pregnancy that is not true for high maternal serum levels of AFP. High AFP as a predictor of breast cancer risk seems only to be modified by age at first full-term pregnancy.

Although hypertension of pregnancy and preeclampsia have been used as surrogates for high MSAFP, the association between the two conditions is not clear. The two variables, levels of MSAFP and MAP, do not demonstrate a significant linear relationship to one another. It is possible that this lack of correlation between the two conditions is unique to the women in this study or to the relation of MAP to AFP level during the third trimester only. However, researchers (10, 11) who have examined a possible relationship between hypertension of pregnancy or preeclampsia and MSAFP levels during the second trimester of pregnancy have found that high MSAFP levels do not predict hypertensive disorders of pregnancy or preeclampsia. Other researchers (5, 7) have found that high maternal serum levels of AFP were predictive of severe (or proteinuric) preeclampsia but not of mild preeclampsia or of gestational hypertension. Wenstrom et al. (8) have found that amniotic fluid AFP can be elevated without an elevation in MSAFP, and a combination of elevations in both amniotic fluid and MSAFP has been found to be more predictive of preeclampsia than either elevation alone. In contrast, among a cohort of women with elevated MSAFP in the second trimester of pregnancy, William v et al. (9) estimated the adjusted relative risk of preeclampsia at 3.8. However, Pouta et al. (11) found a sensitivity of elevated AFP to predict preeclampsia of only 3% among 637 women screened for elevated midtrimester MSAFP levels. To add to the confusion, there has been at least one study (13) that found lower maternal serum levels of AFP among women with toxemia of pregnancy. All of these studies examined the relation of AFP and MAP during the second trimester rather than the third trimester during which AFP levels peak and would, therefore, presumably have the greatest effect on breast cancer risk.

Three studies have examined preeclampsia and hypertension of pregnancy and breast cancer risk. Polednak and Janerich (1) conducted a case-control study among women whose disease was diagnosed at <45 years of age (n = 314) and controls (n = 628) matched to cases on occurrence of fetal death. Among the cases and controls with a live birth, preeclampsia diagnosis was reported less frequently on birth records of cases than on those of controls, with an estimated relative risk of 0.28 (90% CI 0.08–1.00). Troisi et al. (3) analyzed data from a large case control study (n = 1239) with in-person interviews. In this study, women with self-reported hypertension during any pregnancy were estimated to have a relative risk of 0.94 (95% CI 0.73–1.2) and those with toxemia during any pregnancy a relative risk of 0.81 (95% CI 0.61–1.1). No effect modification by age at first full-term pregnancy was evaluated. Thompson et al. (2), evaluating data from the Cancer and Steroid Hormone Study of the Centers for Disease Control, found that among 1375 cases and controls women whose pregnancies lasted longer than 6 months with self-reported occurrence of hypertension during the most recent term pregnancy had a risk of breast cancer (estimated by the OR) of 0.68 (95% CI 0.47–0.99). Although age at first full-term pregnancy was included as a control variable, no interaction term was evaluated.

The etiology of preeclampsia is still not completely understood, although many facets of the disease have been illuminated. Endothelial cell dysfunction would seem to be the common denominator in the various stages of preeclampsia and appears to be present from the first trimester of pregnancy (35). It is also generally accepted that placental ischemia is present. Additionally, various investigators (36, 37) have suggested that an immune dysfunction may be involved in the preeclamptic syndrome. AFP is an important plasma protein in the fetus which is involved in both cell regulation and fetal growth partly by binding and transporting free fatty acids, particularly polyunsaturated fatty acids in the fetus (38). The fatty acids are transported in the maternal circulation by albumin and are exchanged across the placenta to the fetus where fetal demand for free fatty acids is very high. It is conceivable that low levels
of fetal AFP would leave large circulating levels of fatty acids in the maternal blood stream, which would be consistent with the finding that preeclamptic women have, among other symptoms, an elevated ratio of circulating free fatty acid:albumin (39). AFP also helps to down-regulate the immune system during pregnancy, e.g., by inhibiting certain T lymphocytes (40). A low level of AFP in fetal and maternal circulation could hamper this process. AFP is a growth-regulating protein and can specifically down-regulate estrogen-dependent cell growth (16). It is logical that a condition that increases or decreases the amount of circulating MSAFP would impact this function.

Elevated MAP is a fundamental part of the syndromes of preeclampsia and hypertension of pregnancy. Because of this, it is also intimately related to AFP, although the association in these data does not appear to be linear. Therefore, it is somewhat surprising that high MAP represents such a limited amount of the variation of high AFP. It can also be seen in tables 3 and 4 that the pattern of variation of the ORs for breast cancer over the quartiles of age at first full-term pregnancy is very similar for both variables even when controlling for the other. However, if high MAP were used as a surrogate for high AFP using these data, the estimated risk of breast cancer among those women with high AFP at each quartile of age at first full-term pregnancy would be different by 10–28%. It seems then that we cannot conclude that high MAP is an adequate surrogate for high levels of MSAFP but rather represents some related process which is in and of itself a risk factor for breast cancer. Neither preeclampsia nor pregnancy-induced hypertension represents in any fashion the risk estimated for high AFP in third trimester pregnant women. Given the complex nature of hypertension of pregnancy, it is not completely surprising that MSAFP levels do not have a direct relation to this condition.

Although misclassification of blood pressure status and hypertension status are possible, it is unlikely they would be differential by case or control status because the diagnosis of breast cancer was many years in the future. It is also possible that some cases were classified in this study as controls. Cases reported to the California Cancer Registry for the five-county Bay area where the large majority of the CHDS members lived have been complete since 1969 and became complete for the entire state in 1988. To establish complete ascertainment of cases outside the five-county Bay area, breast cancer deaths were also recorded from state death records beginning in 1960. Follow-up status was determined by personal contact (both telephone and written), by accessing and scanning the death files, and by matching California Department of Motor Vehicle files to names and birth dates of cohort members. Three women did not have confirmed follow-up and were removed from the data set. Neither selection of controls nor cases had any relation to MSAFP level or blood pressure measurements, neither of which was known at the time of selection. It also seems unlikely that follow-up was related to AFP level or MAP during a previous pregnancy.

Approximately 20% of the women in this study were in their first full-term pregnancy. This allowed us to compare the effects of high MSAFP and high MAP on breast cancer risk for nulliparous women and for women with higher parity and to assess whether parity changed the direction of risk of breast cancer for the exposures. This did limit the number of women in each parity category.

Ascertainment of the day of gestation might have been inaccurate because at the time of the data collection for the women in this study, the day of gestation was based on the first day of LMP. To confirm that bias would not influence the association of the exposure and outcome, an additional analysis was done removing any women whose days of gestation were >280 days from LMP. The results of the analysis were essentially the same, although the CIs were wider. The distribution of days of gestation among cases and controls and top quartile versus bottom quartiles of MAP and AFP were examined, and there was essentially no difference in the mean days of gestation for any of the groups with the means ranging from 279.8 (SD = 12.6) to 281.3 (SD = 11.3). Using the Mantel-Haenszel $\chi^2$ test for differences in the mean days of gestation between groups, the following results were obtained: (a) cases and controls, 68.9, $P = 0.48$; (b) high and low AFP, 67.2, $P = 0.53$; (c) high and low MAP, 64.6, $P = 0.63$. We therefore feel that although there may have been inaccuracy in ascertainment of days of gestation using the LMP date, this method was not differential by exposure or case status.

In every study there is the possibility of uncontrolled confounding. In this study, the data were limited to the biological and lifestyle data collected during the CHDS enrollment period. Therefore, lifestyle and other health-related factors that may have changed or may have occurred since the conclusion of the CHDS study such as family history of breast cancer, long-term smoking, alcohol intake, time since last pregnancy, and exact age at menopause could not be assessed as potential confounders or effect modifiers.

In summary, this study has demonstrated an inverse association between MAP and maternal breast cancer risk that is similar but not identical to the pattern observed for AFP levels as a risk factor for breast cancer. Despite previous use as such, the evidence does not support a role for pregnancy-induced hypertension as a surrogate indicator of AFP exposure when evaluating maternal breast cancer risk.

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