

Placental Characteristics and Reduced Risk of Maternal Breast Cancer

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Background: Women who have preeclampsia during pregnancy are at reduced risk of subsequent breast cancer. We examined whether other markers of reduced placental size or function, including increased blood pressure during pregnancy, predict a reduction in maternal breast cancer. **Methods:** The Child Health and Development Studies is a 40-year follow-up of pregnant women enrolled in the Kaiser Permanente health plan between 1959 and 1967. We identified 3804 white women for whom data were available on placental examinations and other study variables. As of 1997, 146 women had developed invasive breast cancer. Proportional hazards models were used to estimate associations of breast cancer with markers of placental function. All statistical tests were two-sided. **Results:** A blood pressure increase between the second and third trimesters exhibited a linear relationship with breast cancer rate, with the highest quartile showing a 51% reduction (95% confidence interval [CI] = 20% to 70%) that was not explained by preeclampsia. Smaller placental diameter was independently associated with a reduced breast cancer rate; the association increased with age at first pregnancy ($P = .008$). Maternal floor infarction of the placenta was associated with a 60% reduction in breast cancer rate (95% CI = 12% to 82%). In combination, placental risk factors were associated with a reduction in the breast cancer rate of as high as 94% (95% CI = 80% to 98%). **Conclusions:** Smaller placentas, maternal floor infarction of the placenta, and increasing blood pressure during pregnancy were associated with reduced maternal breast cancer. In the case of smaller placental diameter, the larger reduction observed with older age at first pregnancy suggests a process in which promotion of an existing lesion is

blocked. Elucidating the mechanisms for these associations could provide clues to breast cancer prevention and treatment. [J Natl Cancer Inst 2001;93:1133–40]

Much evidence indicates that pregnancy exerts a powerful influence on a woman's subsequent risk of developing breast cancer. Evidence suggests that immune, hormonal, or genetic mechanisms that induce hypertension or preeclampsia during pregnancy reduce the risk of breast cancer both in the mother (1–3) and in the daughter (4,5).

The clinical definitions of pregnancy-induced hypertension and preeclampsia may not be the only classifications of pregnancy blood pressure and placental pathology that are relevant to breast cancer etiology. Indeed, lesions of the placenta that are characteristic of preeclampsia are also found when neither preeclampsia nor pregnancy-induced hypertension is present (6,7). It is interesting that placental lesions seen in women with lupus anticoagulant syndrome, an immune disorder, are similar to those found in women with clinically defined preeclampsia (6).

In the present study, we defined possible markers of compromised placental function other than preeclampsia and examined whether these markers were associated with a reduced risk of maternal breast cancer. These markers included low placental weight, small placental diameter, and an increase in blood pressure during pregnancy throughout the range of blood pressures observed in pregnancy. We also investigated whether maternal floor infarction of the placenta, a placental anomaly that may also be a marker of compromised placental function, is associated with reduced breast cancer risk.

SUBJECTS AND METHODS

Subjects

Subjects were a subset of the Child Health and Development Studies (CHDS), a pregnancy cohort that has been followed for 40 years. The CHDS were originally designed to study the prenatal determinants of pregnancy outcome and child health and development. Women who were members of the Kaiser Permanente health plan, residents of the East Bay area of San Francisco, CA, and pregnant at some time during the period from June 1959 through September 1966 (with deliveries extending through

April 1967) were eligible for the CHDS (8). Nearly all of the women who met these criteria were enrolled in the CHDS. This high enrollment was accomplished by placing CHDS staff in the obstetric clinic that served all eligible women and by referring all women to the CHDS at the time that they first suspected they might be pregnant. CHDS paid for prenatal blood work as an incentive to participate.

Pregnant women provided information about demographics, reproductive history, and other social and behavioral factors during an in-person interview that was usually conducted as soon as possible after their first contact with the obstetrics department. Informed consent was obtained orally at the time of entry in the study. Approval from the Institutional Review Board of the Public Health Institute, Berkeley, CA, was obtained for this study. The original data collection predated the requirement for Institutional Review Board approval.

Clinical measurements were recorded during prenatal care visits and during labor and delivery. The timing of the data collection—i.e., concurrent with pregnancy—eliminated the problem of recall bias. Medical records were abstracted at each prenatal visit. These records are the source of data on blood pressure change, weight gain, and the diagnoses of preeclampsia used in this study.

Using a standardized protocol, the Benirschke protocol for gross examination (9), trained examiners conducted placental examinations at delivery. The protocol was designed to ensure uniform examination methods to maximize comparability, yet it is simple enough to be performed on a routine basis. The placenta was weighed after the membranes and the cord were trimmed and the blood clots were removed; thus, this procedure eliminated an important source of measurement variability and error (6). The placental examinations were a special feature of the CHDS; these examinations were conducted by CHDS-trained examiners and were not the standard clinical protocol for births at Kaiser Permanente Medical Center—Oakland, CA. Placental examinations were done without knowledge of interview information and for both normal and abnormal pregnancies. Delivery room nurses refrigerated the placentas, and an examiner was notified of the delivery as soon as possible. Refrigeration is the preferred method of storage before examination, and the placenta may be kept for days before macroscopic examination (6). Nevertheless, placental ex-

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aminations were usually completed within a few hours of delivery; however, for late-night and Sunday births, the examination was completed within 12–24 hours of delivery. Data from these examinations are the basis of previously published reports (10,11).

White, non-Hispanic women with a live-born or stillborn infant with a gestation of 28 weeks or more were eligible for this analysis. A total of 8230 CHDS subjects met these criteria. Of these, 3579 (43%) were excluded from this study because the placental examination was not completed. The availability of placental data was restricted primarily by funding limitations during periods of the study. During the time periods when the examiners were regularly

available (August 1960–December 1963 and October 1965–August 1966), a placental examination was done for 90% of eligible births. The second largest source of exclusion from the analysis subset was due to missing data on prenatal measurements required to calculate weight gain and blood pressure change between the second and third trimesters of pregnancy. This source accounted for deletion of an additional 762 subjects, or 9% of the eligible subjects. Finally, an additional 85 subjects (1% of the eligible subjects) were excluded because of missing data on age at first-term pregnancy, height, length of gestation, breast cancer status, or residence history, leaving 3804 subjects who are the basis of this report. The parity of women in this sample at the time

of the index pregnancy (i.e., the pregnancy included in the study) ranged from zero to nine; primiparous women (i.e., women with no previous live births) represented 40% of the study sample (Table 1). For women who were pregnant more than once during the duration of the study, only the first pregnancy was included in the study sample to maintain observation independence.

Follow-up

Assessment of cancer risk in the CHDS is based on linkage to the California Cancer Registry, vital status records, and knowledge of place of residence of subjects over time. Residence information allows

Table 1. Distribution of breast cancer risk factors and incidence rates*

Study variable	Mean (SD)	No. of case subjects	Person-years	Age-adjusted incidence	
				Rate per 1000†	95% CI
Age at study entry, y‡					
1st quartile, ≤22	20.42 (1.38)	18	17 178	1.05	0.62 to 1.66
2nd quartile, 23–26	24.48 (1.11)	26	18 490	1.41	0.92 to 2.06
3rd quartile, 27–31	28.77 (1.38)	38	18 513	2.05	1.45 to 2.82
4th quartile, >31	35.88 (3.18)	64	19 685	3.25	2.51 to 4.15
Age at first pregnancy, y‡					
1st quartile, ≤20	18.94 (1.13)	33	19 836	1.66	1.15 to 2.34
2nd quartile, 21–23	21.94 (0.83)	31	21 643	1.43	0.97 to 2.03
3rd quartile, 24–26	24.87 (0.81)	33	15 780	2.09	1.44 to 2.94
4th quartile, >26	30.18 (3.12)	49	16 607	2.95	2.18 to 3.90
Parity					
0	—	40	28 690	1.74	1.16 to 2.46
1 or 2	—	80	32 023	2.31	1.82 to 2.89
≥3	3.74 (1.07)	26	13 153	1.28	0.64 to 2.14
Placental diameter, cm					
1st quartile, ≤17	16.28 (1.09)	19	10 058	1.91	1.15 to 2.99
2nd quartile, 18–19	18.55 (0.50)	39	23 871	1.58	1.12 to 2.16
3rd quartile, 20	20.00 (0.00)	18	14 496	1.25	0.74 to 1.98
4th quartile, ≥21	22.18 (1.60)	70	25 441	2.54	1.97 to 3.22
Placental weight, decagrams					
1st quartile, <40	34.69 (4.00)	24	16 853	1.42	0.91 to 2.12
2nd quartile, ≥40 and <45.5	42.62 (1.74)	37	19 686	1.83	1.29 to 2.52
3rd quartile, ≥45.5 and <52	48.43 (1.72)	46	17 272	2.59	1.89 to 3.46
4th quartile, ≥52	58.54 (6.48)	39	20 055	1.78	1.26 to 2.45
Maternal floor infarction					
Present	—	7	6452	1.01	0.39 to 2.10
Absent	—	139	67 414	2.01	1.69 to 2.37
Systolic blood pressure change, mmHg, per wk§					
1st quartile, <0	−0.48 (0.35)	46	17 535	2.59	1.90 to 3.46
2nd quartile, ≥0 and ≤0.37	0.14 (0.13)	44	19 367	2.23	1.62 to 3.00
3rd quartile, ≥0.38 and ≤0.80	0.56 (0.12)	31	18 742	1.55	1.05 to 2.21
4th quartile, ≥0.81	1.30 (0.51)	25	18 222	1.30	0.84 to 1.92
Weight change, lbs, per wk§					
1st quartile, ≤0.57	0.38 (0.19)	33	18 472	1.53	1.03 to 2.18
2nd quartile, >0.57 and ≤0.76	0.68 (0.06)	35	18 751	1.72	1.19 to 2.40
3rd quartile, ≥0.77 and ≤0.98	0.87 (0.06)	40	18 513	2.17	1.55 to 2.96
4th quartile, ≥0.99	1.21 (0.20)	38	18 130	2.35	1.64 to 3.24
Infant's birth weight, ounces					
1st quartile, <108	95.84 (12.18)	32	17 930	1.78	1.22 to 2.51
2nd quartile, ≥108 and <120	113.72 (3.41)	31	18 183	1.69	1.14 to 2.39
3rd quartile, ≥120 and <131	124.73 (3.12)	43	18 062	2.35	1.70 to 3.17
4th quartile, ≥131	141.60 (9.46)	40	19 691	1.88	1.33 to 2.57
Preeclamptic pregnancy					
Present	—	2	1890	1.16	0.07 to 4.38
Absent	—	144	71 976	1.94	1.63 to 2.28

*SD = standard deviation; CI = confidence interval.

†Per 1000 person-years.

‡Unadjusted rates per 1000 person-years.

§(Last 3rd trimester reading – first 2nd trimester reading)/(gestational days between the two readings).

us to compute the population at risk for cancer, corresponding to the geographic coverage of cancer surveillance. Residence history is required to determine when a subject ceases to be a California resident and, therefore, becomes lost to follow-up for the purposes of cancer surveillance.

We regularly match each member of our enrolled families to the California Department of Motor Vehicle files on full name and birth date. For each match, we get back all of the names that the individual has ever used and her current address. Next, we match our complete file to the California Vital Status records. If an individual does not match to either the motor vehicle or vital status files, we assume that she has left the state. We compare address history for all members of a family unit to verify that the match is good. All of the names that we have obtained for an individual are then submitted to the California Cancer Registry.

The match with the California Cancer Registry uses both fixed identifiers (i.e., birth date, sex, race, and name, which we consider fixed because we submit all names that the individual has used as determined from our matches with the Department of Motor Vehicle and California Vital Status files) and changeable identifiers (i.e., address and patient record number). After matching on fixed identifiers, changeable identifiers are used to verify the match.

Invasive breast cancer cases or deaths with an underlying cause of breast cancer as of 1997 were included in this study after a review of matches by the CHDS staff. There were 146 case patients in the population of 3804 women who are the basis for this report. Their mean age at diagnosis was 54.2 years.

Statistical Methods

Potential protective factors for maternal breast cancer were chosen on an *a priori* basis. These factors included greater rate of blood pressure increase between the second and third trimesters of pregnancy, any evidence of maternal floor infarction of the placenta, lower placental weight, and smaller placental diameter. We examined the full range of blood pressure increase and placental size, hypothesizing that prior breast cancer associations reported for preeclampsia might extend beyond the definition of clinically defined pregnancy-induced hypertension to the full continuum of blood pressure increase during gestation.

Systolic and diastolic blood pressure associations were examined with the use of the following classifications: mean blood pressure during the first, second, and third trimesters and the rate of change between the second and third trimesters calculated as a function of gestational time. The rate of blood pressure change was calculated as follows: (the last recorded third trimester blood pressure – the first recorded second trimester blood pressure)/(gestational days between dates of the third and second trimester measurements).

Maternal floor infarction of the placenta was defined as a dichotomous variable (present versus absent).

Placental weight was reported after the membranes and cord were trimmed and the clots were removed following the standardized protocol described above. Placental diameter was defined as the largest diameter. Many placentas are not circular, and the protocol for placental examination calls for measurement of both the smallest and the largest

diameters. The smaller diameter measure was not used in this study.

We also examined the following potential confounders: the woman's year of birth; age at index pregnancy; parity at index pregnancy; age at first full-term pregnancy (i.e., with duration of ≥ 7 months); presence of clinically diagnosed preeclampsia in the index pregnancy; rate of weight gain between the second and third trimesters of pregnancy, calculated as (the last recorded third trimester weight – the first recorded second trimester weight)/(gestational days between dates of the third and second trimester measurements); self-reported pre-pregnancy weight; age at menarche; the woman's height; birth weight of the index pregnancy; history of prior early fetal loss (< 20 weeks of gestation); history of late fetal loss (≥ 20 weeks of gestation); educational level; and smoking and alcohol consumption during pregnancy. Correlations among continuous variables were examined with the use of Pearson product moment correlations.

Residence history and vital status were used to calculate the person-years of breast cancer surveillance. This information was also used to construct a censoring variable for the Cox proportional hazards model, which was then used to estimate breast cancer associations. Statistical significance of associations was estimated with the use of the Wald test (12). We calculated rates of breast cancer per 1000 person-years adjusted to the age distribution of the analysis sample. We identified quartiles of placental weight, placental diameter, rate of blood pressure increase, and rate of weight change (Table 1) to examine the linearity of associations with breast cancer. When it appeared that extreme quartiles were the primary contributor to an observed association, as was the case for placental diameter and placental weight (Table 1), we dichotomized the risk factor by the extreme quartile versus the other three quartiles combined. These dichotomies were maintained in subsequent analyses.

Year of birth, age at index pregnancy, and age at first full-term pregnancy were represented as continuous variables in all Cox proportional hazards models. Parity at the time of the index pregnancy was represented initially as three indicator variables—parity of one, two, or three or more, with primiparous women (i.e., women whose index pregnancy was her first pregnancy) as the reference group. Because breast cancer risk did not differ for the primiparous women and the women of parity one or two in initial models (data not shown), parity was represented as parity three or more versus all others in subsequent models. Clinically diagnosed preeclampsia was coded as present versus absent. The rate of weight gain was represented initially as three indicator variables: quartiles 2, 3, and 4 versus the reference category quartile 1. However, because the relationship between the rate of weight gain and breast cancer rate appeared to show a trend across quartiles (Table 1), the rate of weight gain was entered into models as a continuous variable. Pre-pregnancy weight was entered as a continuous variable. Alcohol consumption was entered as three indicator variables: fewer than one drink per week, one drink per week, and two or more drinks per week versus no drinks per week. The study population had low alcohol consumption; 53% reported no alcohol consumption, 23% reported fewer than one drink per week, 11% reported one drink per week,

and 13% reported two or more drinks per week. Smoking status was examined as current versus not current. Age at menarche was entered as two indicator variables: less than 12 years old and 14 years old or older, versus the reference category of 12–13 years old. The woman's height and the infant's birth weight of the index pregnancy were entered as three indicator variables: quartiles 2, 3, and 4 versus quartile 1.

We retained in the Cox model only those variables that influenced the size of the coefficients of placental factors by 10% or more or that were known to be strong predictors of breast cancer risk. The adjustment variables retained were woman's birth year, age at index pregnancy, age at first full-term pregnancy, rate of weight gain (all continuous variables), and parity (three or more previous live births versus all others).

We examined the time dependence of placental factors by entering a time-dependent covariate representing the interaction between attained age (< 55 years old versus ≥ 55 years old) and each placental factor. This cut point was chosen as a crude indicator of menopausal status at attained age for control women or age at diagnosis for women with breast cancer.

We tested for two-way interactions between all placental risk factors and found that none of the interactions were statistically significant. Therefore, relative hazards for the combination of risk factors were calculated from the linear combination of coefficients in the fully adjusted Cox model (see last column of Table 2). To illustrate the combined effects of risk factors, we present bar graphs for all combinations of risk factors (Fig. 1, A and B). Combinations that included placental diameter depended on age at first pregnancy because of the statistically significant interaction between age at first pregnancy and placental diameter (Table 2). We graphed combinations that involved placental diameter for two different ages at first pregnancy, 19 years and 30 years. These ages correspond to the mean age at first pregnancy for the first quartile of age at first pregnancy and the mean age at first pregnancy for the fourth quartile in the study sample, respectively. Therefore, these two age groups were well represented in the study sample. All statistical tests were two-sided.

RESULTS

Distribution of Breast Cancer Risk Factors

Table 1 shows the distribution of breast cancer risk factors for the 3804 women with available data on all study variables. These women contributed 73 866 person-years of observation. Maternal floor infarction of the placenta was observed more frequently than preeclampsia, with 7.6% of the women showing involvement of less than 50% of the maternal surface, 0.2% showing involvement of 50% or more of the maternal surface, and 0.8% affected but with extent not specified. In contrast, 2.3% of the index pregnancies were affected by

Table 2. Association of placental factors with breast cancer

Factor	Relative hazard (95% confidence interval)	
	Age, parity, and weight adjusted*	Fully adjusted†
Systolic blood pressure change between trimesters 2 and 3		
Quartile		
1, <0 mmHg/wk	1.00 (referent)	1.00 (referent)
2, 0–0.37 mmHg/wk	0.89 (0.58 to 1.35)	0.92 (0.60 to 1.40)
3, 0.38–0.80 mmHg/wk	0.64 (0.40 to 1.02)	0.64 (0.40 to 1.02)
4, ≥0.81 mmHg/wk	0.50 (0.31 to 0.82)	0.49 (0.30 to 0.80)
<i>P</i> for trend‡	<i>P</i> = .0001	<i>P</i> = .0001
Maternal floor infarction of the placenta: present/absent	0.49 (0.23 to 1.05)	0.40 (0.18 to 0.88)
Lower placental weight,§ <400 g	0.66 (0.42 to 1.02)	0.74 (0.46 to 1.17)
Smaller placental diameter, <21 cm		
Age 19 y at first pregnancy	1.01 (0.60 to 1.69)	1.19 (0.70 to 2.04)
Age 30 y at first pregnancy	0.44 (0.28 to 0.71)	0.44 (0.27 to 0.71)
<i>P</i> for interaction¶	<i>P</i> = .03	<i>P</i> = .008

*All associations were estimated by a Cox model that included the indicated variable with adjustment for birth year (continuous), age at index pregnancy (continuous), age at first pregnancy (continuous), maternal weight gain (continuous), and parity (dichotomized as three or more versus all other).

†The fully adjusted model includes systolic blood pressure increase (quartile 2, quartile 3, and quartile 4, with quartile 1 as the reference group), maternal floor infarction of the placenta (present versus absent), placental weight (quartile 1 versus all others), placental diameter (quartiles 1–3 versus quartile 4), and the adjustment variables, birth year, age at first pregnancy, age at index pregnancy, maternal weight gain (continuous variables), and parity (dichotomized as three or more versus all other).

‡To test for trend, blood pressure was entered as a continuous variable into the designated Cox models.

§Placental weight classification is first quartile versus all others.

||Placental diameter classification is lower three quartiles versus fourth quartile. The interaction term was constructed as the product of smaller placental diameter (first, second, and third quartiles versus fourth quartile) by age at first full-term pregnancy (continuous variable).

¶To test for interaction, the Wald test was used to test the statistical significance of the product term between age at first pregnancy (continuous) and smaller placental diameter (lower three quartiles versus all other).

clinically diagnosed preeclampsia. Women with maternal floor infarction of the placenta contributed more person-years of observation than women with preeclampsia (Table 1).

The rate of change in systolic blood pressure between the second and third trimesters is shown in Table 1 and is used in subsequent analyses because this variable showed a stronger association with breast cancer rate than the mean systolic or diastolic blood pressure for any trimester or the rate of change for diastolic blood pressure (data not shown). During the second trimester, the mean systolic blood pressure in the study sample was 112.5 mmHg (standard deviation [SD] = 11.9), and the mean number of gestational days at that visit was 140, or 20 completed weeks (data not shown). During the third trimester, the mean systolic blood pressure was 120 mmHg (SD = 12.0), and the mean number of gestational days at the last visit was 277, or 39.5 completed weeks (data not shown).

Age-Adjusted Rates of Breast Cancer

The age-adjusted rates of breast cancer per person-year by various risk factors are

shown in Table 1. Established risk factors for breast cancer (i.e., age at entry, age at first pregnancy, and parity) were associated with breast cancer rate in the direction expected.

Markers of compromised placental function (i.e., smaller placental diameter, lower placental weight, maternal floor infarction of the placenta, and an increase in blood pressure during pregnancy) were each associated with reduced rates of breast cancer. However, a trend across quartiles (for continuous placental variables) was observed only for the increase in systolic blood pressure (Table 1). There was also a trend across quartiles of weight gain, with lower weight gain associated with reduced rates of breast cancer (Table 1). Generally, 95% confidence intervals (CIs) for rates within risk factor categories overlapped, reflecting the low power of the stratified analysis.

Breast cancer rates, age at first pregnancy, parity, age at entry, or mean follow-up time were very similar for women who could not be included in the study because of missing data on one or more study variables (see supplemental table on the Journal's Web site, <http://jnci.oupjournals.org>).

We conclude that exclusions for missing data are unlikely to have biased study results, particularly since women excluded for missing data had nearly identical rates of breast cancer as women not excluded.

Multivariate Models Predicting Breast Cancer Rates

Multivariate results estimated by the Cox model are shown in Table 2. Markers of compromised placental function (i.e., smaller placental diameter, lower placental weight, maternal floor infarction of the placenta, and greater increase in blood pressure during pregnancy) predicted lower rates of breast cancer. The fourth quartile of blood pressure increase was associated with a 51% reduction in breast cancer rate (95% CI = 20% to 70%) that was independent of other placental factors (calculated from Table 2). Maternal floor infarction was independently associated with a 60% reduction in the rate of breast cancer (95% CI = 12% to 82%). We tested interactions between each placental factor with mother's birth year, age at first pregnancy, age at index pregnancy, parity, weight gain, and pre-pregnancy weight. Only one interaction—between smaller placental diameter (quartiles 1–3 versus quartile 4) and age at first pregnancy—was statistically significant at $P < .05$ by the Wald test. Smaller placental diameter was associated with a larger rate reduction as age at first pregnancy increased ($P = .008$; Table 2).

A comparison of the second column of Table 2 (each placental association adjusted for age variables, parity, and weight gain) with the last column of Table 2 (each placental association additionally adjusted for all other placental factors) shows that breast cancer associations with placental factors were independent of each other. Breast cancer associations with placental factors were also largely independent of the woman's birth year, age at first pregnancy, age at index pregnancy, weight gain, length of gestation, infant's birth weight, pre-pregnancy weight, height, age at menarche, preeclampsia in index pregnancy, smoking, alcohol consumption, history of early and late fetal loss, and educational level (data not shown). Because of the collinearity of the two maternal age variables (i.e., birth year and age at index pregnancy), we compared the effect of adjusting for one versus adjusting for both simultaneously. There were no differences in the esti-

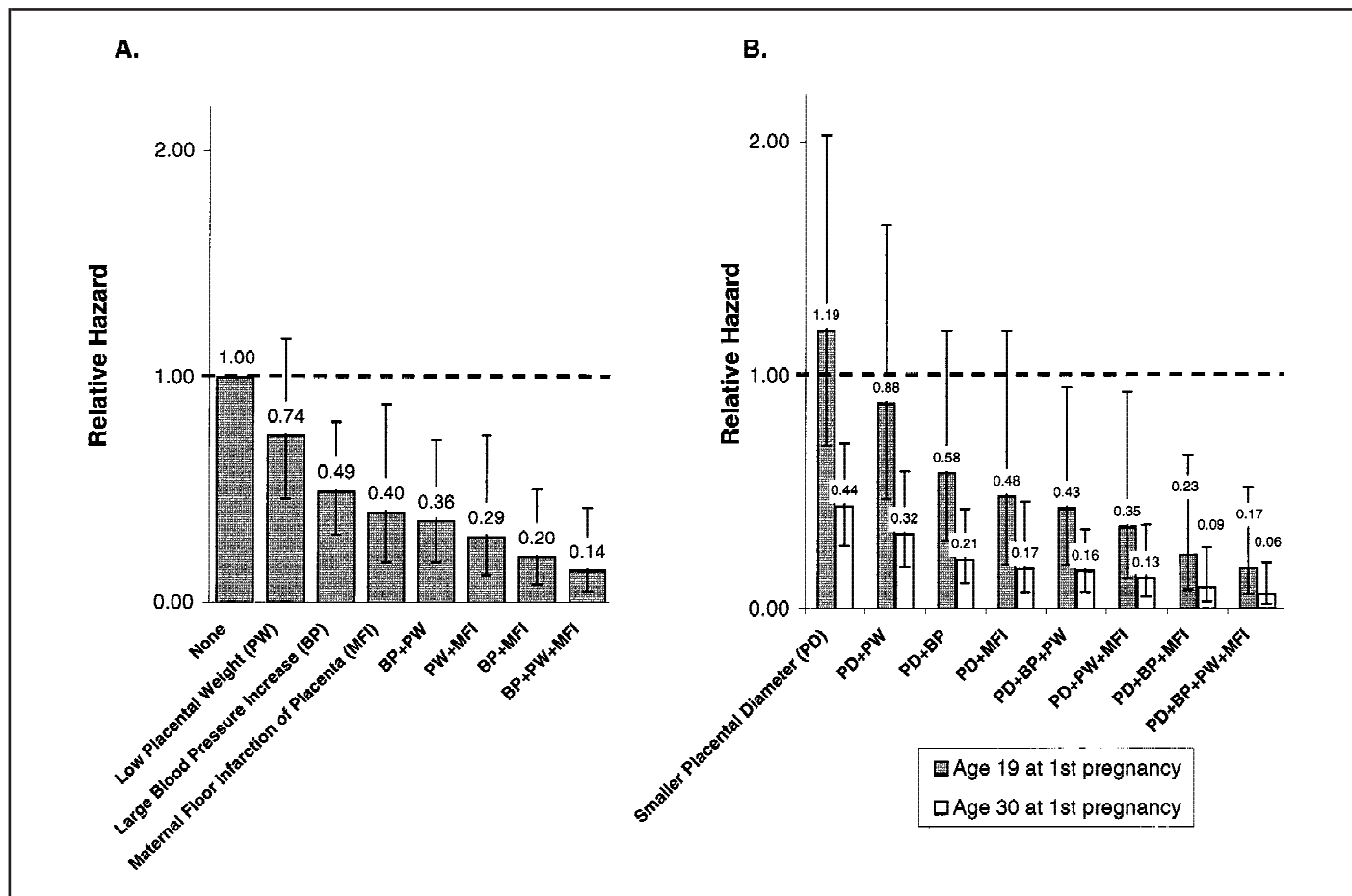


Fig. 1. Estimated effects of placental factors on maternal breast cancer risk. **A)** Effects considered one at a time and in combination. Relative hazards were estimated from a single Cox proportional hazards model adjusted for all placental risk factors shown, as well as for mother's birth year, age at first pregnancy, age at index pregnancy, parity, weight gain, and an interaction between age at first pregnancy and placental diameter. As noted in the text, there were no other interactions between any other variables in this model. In this model, age variables are represented as continuous variables, parity is dichotomized as three or more versus all others, weight gain is represented as a continuous variable, blood pressure increase is represented as three indicator variables—quartile 2, quartile 3, and quartile 4—with the lowest quartile as the reference group, placental weight is dichotomized as the first quartile versus all others, and placental diameter is

dichotomized as the lower three quartiles versus the highest. Maternal floor infarction of the placenta is coded as present versus absent, lower placental weight is defined as the first quartile versus all others, higher blood pressure increase is defined as the fourth quartile versus the first quartile, and smaller placental diameter is defined as the lower three quartiles versus the first quartile. **B)** Effects on risk of placental factor combinations that involve placental diameter. Because of the interaction between placental diameter and age at first pregnancy (P for interaction = .008), risk factor combinations that involve placental diameter are shown for two specific ages. Age 19 years is the mean for the first quartile of age at first pregnancy for the study sample, and age 30 years is the mean for the fourth quartile. **Error bars** in both graphs reflect boundaries for upper and lower 95% confidence limits.

mated placental factor associations between models adjusted for only one maternal age variable versus models adjusted for both.

The independence of placental associations was somewhat unexpected, but it is consistent with the moderate to low correlation among most placental variables. The largest correlation was between placental weight and placental diameter (Pearson $r = .56$; $P = .0001$). The rate of blood pressure increase did not show a statistically significant correlation with any other placental factor (data not shown). Placental weight was statistically significantly increased, by a mean of 12.6 g ($P = .02$; 95% CI = 1.8 g to 23.3 g), in the presence of maternal floor infar-

tion (data not shown), presumably as a result of the density of the fibrin deposits. Adjustment for placental weight actually increased the rate reduction associated with maternal floor infarction of the placenta (data not shown). There was no evidence that associations with placental factors depended on attained age or that the assumption of proportionality for placental factor associations with breast cancer was violated.

Effects of Combinations of Placental Risk Factors

Panels A and B of Fig. 1 illustrate the effects of combinations of placental risk factors on breast cancer rates. Because age at first pregnancy modifies the effect

of placental diameter on breast cancer rates, it is necessary to illustrate two groups of risk factor combinations: those that do not include placental diameter (Fig. 1, A) and those that do (Fig. 1, B).

In combination, placental factors predicted substantial reductions in breast cancer rates, ranging as high as a 94% reduction (95% CI = 80% to 98%) for women with all four risk factors and age 30 years at first pregnancy (Fig. 1, B). All of the combinations shown in Fig. 1 occurred in the study population, although some were rare (Table 3). For example, combinations including maternal floor infarction ranged from less than 1% of the study sample (maternal floor infarction and low placental weight, low placental

Table 3. Prevalence of placental risk factor combinations in study sample

Placental characteristic(s)	No.	% of sample
None	847	22
Smaller placental diameter (PD) only	1148	30
Large systolic blood pressure increase (BP) only	274	7
Low placental weight (PW) only	55	1
Maternal floor infarction of the placenta (MFI) only	89	2
PD + PW only	548	14
PD + BP only	395	10
PD + MFI only	117	3
BP + PW only	14	<1
PW + MFI only	6	<1
BP + MFI only	20	1
PD + BP + PW	193	5
PD + PW + MFI	47	1
PD + BP + MFI	34	1
BP + PW + MFI	1	<1
PD + BP + PW + MFI	16	<1
Total	3804	100

diameter, and large blood pressure increase) to 3% (maternal floor infarction and smaller placental diameter). However, some three-way combinations of placental risk factors were surprisingly common. For example, 5% of the study sample had low placental weight, smaller placental diameter, and large blood pressure increase. Among the women in this group, both those with young age at first pregnancy and those with older age at first pregnancy had a statistically significant reduction in rate of breast cancer: 57% reduction (95% CI = 5% to 81%) for women aged 19 years at first pregnancy and 84% reduction (95% CI = 66% to 93%) for women aged 30 years at first pregnancy (Fig. 1, B).

DISCUSSION

In this study, we considered markers of placental function, other than preeclampsia, as potential protective factors for maternal breast cancer. These markers were lower placental weight, smaller placental diameter, maternal floor infarction of the placenta, and increase in blood pressure between the second and third trimesters of pregnancy. We found substantial reductions in the rate of maternal breast cancer among women with each of these markers that could not be explained by the presence of preeclampsia or other known breast cancer risk factors.

Rationale for Choosing Placental Variables

We selected the markers of compromised placental function on the basis of previous research in perinatal and breast cancer epidemiology before examining

the data in the present study. One of us (13) reported previously that primigravida (i.e., women pregnant for the first time) experience a larger rise in blood pressure between the second and third trimesters of pregnancy than multigravida (i.e., women with previous pregnancies). In addition, primigravid pregnancies are characterized by a slow rate of intrauterine growth and lower birth weights (14) and a higher incidence of preeclampsia (7). We reasoned that the larger increase in blood pressure experienced by the primigravida could reflect similar but more subtle defects of placental function, analogous to some of the processes that occur in preeclampsia.

Several lines of evidence suggest an immune etiology for preeclampsia, including higher incidence in primigravida (7), in multigravida with changed paternity (15–20), and in pregnancies occurring after shorter periods of cohabitation with the father (21). Thus, the greater increase in blood pressure during pregnancy in the primigravida may reflect greater disparity between maternal and paternal antigens even in the absence of preeclampsia. Although the protective mechanism for preeclampsia remains unknown, we reasoned that larger increases in blood pressure in women of any parity might extend some protection against developing breast cancer. This prediction is supported by our findings. We observed a substantial, linear, inverse association between increasing blood pressure during pregnancy and breast cancer rates (Table 2); this association was independent of preeclampsia and parity.

To our knowledge, no previous study has examined the relation between breast

cancer risk and change in blood pressure throughout the entire range in pregnancy. Retrospective studies (1,2) have reported protective associations for hypertension during pregnancy. However, one study (3) found only a weak protective association, possibly because of poor recall of pregnancy events. A nested case-control study in the CHDS cohort (22) reported a protective association for third-trimester mean arterial pressure for women with a young age at first pregnancy but not for women with an older age at first pregnancy. The discrepancies between these findings and the findings in the present study may reflect differences in the coding of blood pressure. In particular, high third-trimester blood pressures that were measured in the case-control study could be confounded by higher pre-pregnancy blood pressure. We found the mean blood pressure to be a poorer predictor of breast cancer than a change in blood pressure during pregnancy.

We examined small placental size as a protective risk factor for breast cancer because the placenta is smaller both in women with preeclampsia and in primigravida (6). We did find independent rate reductions associated with the lowest quartile of placental weight and with the lowest three quartiles of placental diameter (Table 2; Fig. 1). However, these associations were not linear across the continuum of placental weight or diameter (Table 1).

The rate reduction associated with smaller placental diameter was larger for women with older age at first pregnancy (Table 2; Fig. 1, B). This finding is consistent with the hypothesis that smaller placental diameter is associated with a factor that blocks the growth of a pre-existing lesion. Women who are older at first pregnancy are more likely to have transformed breast epithelial cells as a result of longer exposure of undifferentiated cells that are more vulnerable to carcinogens. Pregnancy decreases the population of vulnerable breast cells via differentiation (23).

We examined maternal floor infarction because of its unique pathologic characteristics (6,24). This placental anomaly, a condition of excessive fibrin deposition on the maternal side of the placenta (6,24), is detected easily by macroscopic examination (6). The cause of maternal floor infarction is unknown, although it has been proposed to result from abnormal maternal-fetal interaction (6,24). We

reasoned that, as in preeclampsia, maternal floor infarction could lower exposure to factors that initiate or promote tumor growth or, alternatively, increase exposure to factors that block tumor initiation or growth. As predicted, maternal floor infarction was associated with a substantial reduction in breast cancer rate (Table 2; Fig. 1).

Study Limitations

Although our study's prospective design addressed methodological problems in previous studies, including poor recall for pregnancy events (25–29), it has some limitations. If some breast cancer cases were missed in this record linkage study or if some control subjects were censored incorrectly, the associations may have been attenuated. In addition, bias would occur if misclassification of case or control subjects depended differentially on placenta variables studied. However, it is unlikely that misclassification of case status would occur according to the woman's rate of blood pressure increase in pregnancy or according to the size or characteristics of her placenta. Thus, bias is unlikely to explain the consistency or the size of the associations observed. Selection bias due to missing data on study variables was also possible but unlikely because subjects included in the study did not differ from excluded subjects in breast cancer rates, age at observed pregnancy, age at first pregnancy, parity, or follow-up time.

Another possible limitation was the lack of information on family history of breast cancer. Thus, it is possible that a common familial factor related both to breast cancer and to placental factors explains the observed associations. We used attained age as an indirect indication of menopausal status at the time of breast cancer diagnosis. Although we observed no time dependence of placental associations on attained age (age <55 years versus age ≥55 years), we cannot rule out an interaction with menopausal status.

We also lack data on subsequent pregnancies for most of our sample. High parity is associated with a reduced rate of breast cancer, but we believe it unlikely that women with the placental factors that we studied went on to have higher parities. The factors tend to be associated with pregnancy complications (6) rather than with reproductive efficiency.

Although we adjusted for history of pregnancy loss, we had no data on pla-

cental factors in other pregnancies for most women in the study. Nevertheless, the strong associations of the placental characteristics of the index pregnancy with breast cancer rate imply that a woman's pregnancies may resemble each other. Other evidence of correlation of events from one pregnancy to the next is the strong correlations between levels of estradiol in successive pregnancies (30) and among pregnancy outcomes within a woman (31).

Possible Mechanisms for Placental Factor Effects

We can only speculate on the mechanism(s) by which placental factors might affect breast cancer, in some cases many years later. The several independent associations that we observed suggest that more than one aspect of pregnancy may protect against breast cancer.

First, placental size may be related to maternal exposures in pregnancy. Placental steroid and protein hormone production is roughly proportional to the mass of trophoblastic cells. Thus, lower placental estrogen production by a relatively small placenta may explain the reduced breast cancer risk in the daughters of women who developed preeclampsia in pregnancy (5,32) and might reduce maternal risk as well.

Placental estrogen production also depends on the amount of dehydroepiandrosterone sulfate (DHEAS) produced by both the maternal and the fetal adrenal glands and the normal expression of sulfatase, 3-β-hydroxysteroid dehydrogenase, and aromatase enzymes (33) by placental trophoblastic cells. However, the relatively small variations in extremely high plasma estrogen levels resulting from differences in placental size are unlikely to have etiologic significance or to influence growth rates of pre-existing transformed breast epithelial cells. Other placental hormones may also influence breast epithelial cell growth, differentiation, or tumorigenesis (34).

Estrogen antagonism by androgens could also explain the associations that we observed. Levels of plasma testosterone increase twofold to threefold during the last weeks of a normal pregnancy, and the rise is even greater in women who develop preeclampsia (35). Placental release of testosterone likely occurs when proximal substrates begin to saturate the rate-limiting placental aromatase enzyme because of the exponential growth and se-

cretion of DHEAS by the fetal adrenal glands late in gestation. Accordingly, maternal plasma testosterone levels will be inversely related to placental size. This mechanism could explain the higher than normal levels of testosterone found in women with preeclampsia. Thus, antagonism of estrogens by greater amounts of androgens rather than by reduced estrogen levels may explain the reduced breast cancer risk associated with preeclampsia. Perhaps the level of testosterone also increases as a result of small placental size or maternal floor infarction of the placenta or if maternal blood pressure increases during pregnancy.

Alternatively, α-fetoprotein (AFP) may antagonize estrogen-stimulated growth and/or differentiation of breast cells during pregnancy. AFP antagonizes estrogen stimulation of the rodent uterus and a series of human breast cancer lines (36–40). These findings, together with reports indicating that high maternal AFP levels during pregnancy reduce the risk of breast cancer (41,42) and its severity at diagnosis (42), suggest that the protective effect of pregnancy may be related to maternal exposure to AFP. AFP has also been suggested to explain the protective association between hypertension in pregnancy and breast cancer risk (2,41,42). However, some studies (43,44) reported reduced levels of maternal AFP in pregnancy-induced hypertension, and in one study (22), AFP levels did not explain the observed associations between mean arterial blood pressure and breast cancer risk.

Whatever their explanation, the reductions in breast cancer rate among women with smaller placentas, maternal floor infarction of the placenta, and larger increases in blood pressure in pregnancy that we observed are among the largest ever reported. We believe that these findings warrant investigation of biologic factors that may explain these observations. This line of investigation could lead to prevention and treatment strategies for all women.

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NOTES

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