

THE RELATIONSHIP BETWEEN MENSTRUAL FACTORS AND BREAST CANCER ACCORDING TO ESTROGEN RECEPTOR STATUS OF TUMOR: A CASE-CONTROL STUDY IN AFRICAN-AMERICAN WOMEN

Background: Exposure to estrogen is a risk factor for breast cancer. Since estrogen executes its effect through estrogen receptors (ERs), the relationship between menstrual factors, which are estrogen-related, and breast cancer may be different depending upon ER status of tumors. This case-control study aimed to examine such a relationship according to ER status of breast cancer in African-American women.

Methods: Cases were 304 African-American patients pathologically diagnosed with breast cancer during 1995–1998, who were 20–64 years old and lived in 3 Tennessee counties. Controls were 305 African-American women without breast cancer, selected through random-digit dialing and frequency matched to cases by age and county. Information on menstrual factors (age at menarche, age at menopause, time from menarche to menstrual regularity, cycle length, and length of flow) and other risk factors were collected through telephone interviews. Estrogen receptor status of tumor samples was defined based on immunohistochemical measurement. Logistic regression analysis was used to calculate odds ratios and 95% confidence interval (CI).

Results: Compared to women with an average cycle length less than 28 days, the risks of breast cancer for those with longer length were 0.62 (95% CI, 0.36–1.06) and 0.56 (95% CI, 0.32–1.00) for ER-positive and ER-negative tumors, respectively. The corresponding odds ratio (OR) estimates were 0.42 (95% CI, 0.20–0.86) and 0.38 (95% CI, 0.16–0.90) for postmenopausal women. Other menstrual factors were not significantly associated with breast cancer for either ER status.

Conclusions: Our results did not show a different menstrual factor/breast cancer relationship in terms of ER status in African-American women, although there might be an association between menstrual cycle length and the disease. (*Ethn Dis.* 2002;12[suppl3]:S3-23–S3-29)

Key Words: African-American Women, Breast Cancer, Case-Control Study, Estrogen Receptors, Menstrual Factors

From Department of Health Evaluation Sciences, College of Medicine, Pennsylvania State University, Hershey, Pennsylvania (KZ, JB, VMC, KHJ); Departments of Family and Community Medicine (SH, KPW, CLR,

Kangmin Zhu, MD, PhD; Jessica Beiler, MPH; Sandra Hunter, BS; Kathleen Payne-Wilks, BA; Chanel L. Roland, BS; Digna S. Forbes, MD; Vernon M. Chinchilli, PhD; Louis J. Bernard, MD; Kathryn H. Jacobsen, MPH; Robert S. Levine, MD

INTRODUCTION

Estrogen is important for the regulation of growth and differentiation of breast cells.¹ A substantial body of epidemiologic, experimental, and clinical evidence has shown that exposure to estrogen could increase breast cancer risk.² For target tissue to respond to estrogenic effects, the presence of estrogen receptors (ERA) is necessary.¹ Breast cancer has 2 subgroups, ER-positive (ER+) and ER-negative (ER-), according to the presence of estrogen receptors. Each subgroup has different clinical and prognostic implications.^{3–10} Because estrogen executes its effect through the estrogen receptors of breast cells,^{3,4} it is possible that estrogen-related factors play a greater role on ER-positive tumors.^{3,4}

Because menstrual characteristics may reflect hormonal status and thus different levels of estrogen exposure,^{5–7} the association between menstrual factors and breast cancer may be stronger for ER+ tumors. However, epidemio-

logical studies on menstrual factors according to ER status have been limited.^{4,8–13} These studies have primarily investigated age at menarche and age at menopause, and have obtained inconsistent results. To our knowledge, only one study investigated menstrual regularity in relation to breast cancer by ER status of tumors, finding no association for either ER type.¹² No previous studies have examined the relationship between breast cancer and other menstrual factors such as menstrual flow length and cycle length according to ER status. Also, no previous studies have investigated the menstrual factors/breast cancer relationship by ER type in African-American women. Compared with Caucasian women, African-American women are more likely to develop ER- breast cancer,^{5,14,15} which has more rapid tumor growth and lower survival rates.^{5,9,10} The distribution of menstrual factors may also vary between African-American and Caucasian women: African-American women may be, on average, of an earlier age at menarche,^{16–21} of an earlier age at menopause,¹⁶ and they may have shorter menstrual cycle lengths.^{18,22} Therefore, it would be interesting to know the relationship between menstrual factors, breast cancer, and the ER status of tumors in this population. This study aimed to provide data on whether menstrual factors are associated with breast cancer depending upon different ER status in African-American women.

RSL), Pathology (DSF), and Surgery (LJB), Meharry Medical College, Nashville, Tennessee.

Address correspondence and reprint requests to Kangmin Zhu, MD, PhD; Department of Health Evaluation Sciences; College of Medicine; Pennsylvania State University; 600 Centerview Drive; Hershey, PA 17033-0855; 717-531-7178; 717-531-5779; kzhu@hes.hmc.psu.edu

METHODS

Study Subjects

A case-control study was conducted. The cases were 304 African-American female patients pathologically diagnosed with breast cancer during 1995–1998, who lived in Davidson, Shelby, or Hamilton Counties, Tennessee, and had telephone service at the time of the study. The controls were 305 African-American women without a history of breast cancer, selected through random-digit telephone dialing and frequency matched to cases by a 5-year-age range and county.

Cases were identified from the Tennessee Cancer Reporting System (TCRS) ($N=645$). We contacted each eligible patient's doctor for consent to contact the patients. Doctor's consent was given for 480 patients. These patients were contacted via mail, introducing the study procedures and rights as a study participant. A consent form for their participation in the study was also included in the initial packet. A second packet was mailed and subsequent reminder calls were made to those who did not respond. For women who did not respond to the second mailing and did not have a telephone listed, a home visit was made to seek their consent. Out of the 480 patients, 18 were deceased and 50 could not be located. Three hundred and four eligible patients (63% of those with a doctor's consent or 73.7% of those who could be contacted) agreed to participate in the study and were subsequently interviewed.

Controls were selected using random-digit telephone dialing techniques.²³ We first grouped cases diagnosed in the same calendar year with telephone area codes from the same county, and then formed the sampling frame by age distribution of the cases in the area, using an eligibility table. By randomly selecting one of the telephone prefixes of the cases and appending 4 random-selected digits, a call was made to find an eligible woman according to

ethnic background and age range. Up to 9 calls during a 2-week period, including 3 day-time, 3 evening, and 3 weekend calls, were made for each telephone number that was not answered. If an eligible woman was identified, we described the study purposes and procedures, and then asked whether she would be interviewed over the telephone. We identified 385 women eligible as frequency-matched controls. Of these 385 women, 305 (79.2%) participated in the study. To compensate for the participants' time and effort for the study, we paid \$25 for a completed interview and provided study subjects an opportunity to draw for \$200. We also provided \$10 for individuals in the case group if they agreed to release their tumor tissue specimens.

Data Collection

Interviews were conducted over the phone by trained interviewers. Information was obtained about the history of exposure to different factors at or before the reference date (date of diagnosis for cases and the corresponding date for controls). Information collected included: menstrual history (age at menarche, menopausal status, age at menopause, time from menarche to menstrual regularity, average cycle length, average length of period); reproductive history (age at first birth, number of pregnancies, history of infertility, miscarriage); medical history (history of benign breast disease, history of other cancers, and exogenous estrogen/progesterone use); family history of breast cancer; personal habits and lifestyle (smoking, alcohol use, exercise, dietary intake, contraceptive use, and use of electric bedding devices); anthropometric variables (weight and height); and demographic variables.

We determined menopausal status according to whether a woman was still having her menstrual periods 3 months before the reference date. A woman was considered pre-menopausal if she had menstrual periods during the 3-month period or did not have periods during

that time frame because of pregnancy. Post-menopausal status was defined as no periods during the time (except pregnancy). Body mass index (BMI) was defined as weight in kilograms divided by the height in meters squared. A family history of breast cancer was regarded as a history of breast cancer in either a primary (mother, sister, daughter) or secondary (grandmother, aunt) relative. Alcohol use was defined as consumption of at least one alcoholic beverage (beer, wine or liquor) per month for 6 or more months.

Tissue Collection and Laboratory Measurement

Paraffin-embedded tumor tissue samples were collected from the hospitals in which the cases had been pathologically diagnosed. ER status was measured using the immunohistochemical method.^{24,25} A pathologist read all tissue slides and determined the proportion of estrogen receptor positive cells and the intensity of stained cells. We calculated a histologic score to determine the ER status. The score was the sum of the proportion score and the intensity score. The proportion score was defined as 1 = $\leq 1\%$, 2 = $>1\%–10\%$, 3 = $>10\%–33.3\%$, 4 = $>33.3\%–66.6\%$, 5 = $>66.6\%–100\%$. The intensity score was defined as 0 = negative, 1 = weak, 2 = intermediate, and 3 = strong. A score of 3 or more was deemed ER-positive. Otherwise, ER status was determined to be ER-negative. ER status was determined for 272 (89.5%) of the 304 cases. For an additional 9 cases, ER status was available from the pathological reports. We included these patients in the analysis to increase the number of cases available for the study.

Data Analysis

ER-positive and ER-negative cases were each compared with the control group. The exposure variables of interest were menstrual factors including age at menarche, cycle length, length of flow,

Table 1. Demographic characteristics of African-American study subjects aged 20–64, 3 counties, Tennessee, 1995–1998

Characteristic	Cases (%)		Controls (%)
	ER+	ER–	
Age (years)			
20–39	10 (6.5)	20 (15.6)	33 (10.8)
40–49	54 (35.3)	44 (34.4)	105 (34.4)
50–59	56 (36.6)	43 (33.6)	109 (35.7)
≥60	33 (21.6)	21 (16.4)	58 (19.0)
Education			
High school	51 (33.3)	46 (35.9)	140 (46.1)
Vocational/technical	21 (13.7)	11 (8.6)	29 (9.5)
Some or junior college	35 (22.9)	41 (32.0)	77 (25.3)
College/graduate or professional school	45 (29.4)	30 (23.4)	55 (18.1)
Other	1 (0.7)	0 (0.0)	3 (1.0)
Income			
<\$15,000	35 (23.8)	36 (29.3)	107 (36.5)
\$15,000–\$29,999	40 (27.2)	26 (21.1)	88 (30.0)
\$30,000–\$44,999	35 (23.8)	24 (19.5)	56 (19.1)
≥45,000	37 (25.2)	37 (30.1)	42 (14.3)
Marital status			
Married	69 (45.1)	53 (41.4)	132 (43.6)
Separated	12 (7.8)	15 (11.7)	35 (11.6)
Divorced	41 (26.8)	31 (24.2)	61 (20.1)
Widowed	11 (7.2)	10 (7.8)	34 (11.2)
Never married	20 (13.1)	19 (14.8)	41 (13.5)
Employment status			
Yes	106 (69.3)	93 (72.7)	208 (68.7)
No	47 (30.7)	35 (27.3)	95 (31.4)

years from menarche to menstrual regularity, and age at menopause. As the first analytic step, we used dichotomized menstrual variables to assess whether they were related to the risk of breast cancer. Then, we analyzed whether there was a dose-response relation between different levels of menstrual factors and breast cancer risk. Finally, we stratified study subjects according to menopausal status to examine whether the relation between other menstrual factors and the disease differed by menopausal status. Odds ratios (OR) and 95% confidence intervals (CI) were computed using unconditional logistic regression method.²⁶

To control for potential confounding, we included demographic variables in the models to adjust for their complex effects. We also included as potential confounders those variables that

were either associated with the risk of breast cancer in the descriptive analysis or could logically confound the menstrual factor/breast cancer relationship.

RESULTS

Table 1 shows demographic features of study subjects. Cases in both ER groups tended to have more education and higher average incomes than controls. Cases with ER– tumors appeared to be younger than cases with ER+ tumors. The distributions in marital status and employment status were similar between cases and controls and between the 2 case subgroups.

The relationship between menstrual factors and breast cancer is presented in Table 2. Compared to women with a shorter cycle length, those with a longer

cycle length tended to have decreased risk of breast cancer despite ER status, with the confidence intervals of the ORs marginally including one. Other menstrual factors including age at menarche, menopausal status, length of flow, and time from menarche to menstrual regularity were not associated with breast cancer risk: the confidence intervals contained the null for all these variables. No significant differences in ORs were found between ER+ and ER– breast cancers. We repeated analysis with the exclusion of 9 cases whose ER status was based on their pathological reports and obtained similar results. We also estimated ORs and their confidence intervals for breast cancer according to different levels of a menstrual factor (cycle length, age at menarche, age at menopause, length of flow, and time from menarche to menstrual regularity). While the OR estimates were lower than one with longer cycle length, trend test did not reach significance (data not shown). No consistent patterns were shown in terms of exposure levels and ER status for other menstrual factors.

When data were stratified by menopausal status, the inverse association between cycle length and breast cancer was found only in post-menopausal women (Table 3). The OR estimates were 0.41 (95% CI, 0.20–0.86) and 0.38 (0.16–0.90) for ER+ and ER– tumors, respectively, in post-menopausal women. The corresponding estimates contained the unity for both ER types in pre-menopausal women. Earlier age at menarche tended to be related to both ER+ and ER– tumors inversely in pre-menopausal women and positively in post-menopausal women. However, the confidence intervals included one for all the OR estimates. Longer length of flow seemed to increase the risk of post-menopausal tumors, but the OR estimates were not significantly different from one. Time between menarche and menstrual regularity had the OR estimates close to the null, except for an OR of 0.50 (95% CI, 0.14–1.71) for pre-menopausal ER– tumors.

Table 2. Odds ratios for menstrual factors in relation to breast cancer according to ER status in African-American women aged 20–64, 3 counties, Tennessee, 1995–1998

Characteristic	Controls‡	Cases‡			
		ER+	OR* (95% CI)†	ER–	OR* (95% CI)†
Cycle length (days)					
<28	74	44	reference	43	reference
≥28	161	68	0.62 (0.36–1.06)	60	0.56 (0.32–1.00)
Age at menarche (years)					
>12	119	55	reference	55	reference
≤12	116	57	1.04 (0.62–1.75)	48	0.83 (0.48–1.45)
Menarche to regularity (years)					
<1	166	81	reference	76	reference
≥1	69	31	0.93 (0.52–1.66)	27	0.78 (0.43–1.41)
Length of flow (days)					
<5	91	37	reference	42	reference
≥5	144	75	1.24 (0.73–2.13)	61	0.95 (0.55–1.63)
Menopausal status					
Pre-menopausal	101	41	reference	51	reference
Post-menopausal	135	71	1.04 (0.55–1.97)	52	0.67 (0.34–1.32)

* Adjusted for marital status, education, age, family history of breast cancer, history of benign breast disease, alcohol use, smoking, oral contraceptive use, number of pregnancies, age at first birth, age at first sexual intercourse, body mass index, daily energy intake (kcal), physical activity, electric bedding device use, history of infertility, and the other variables in the table.

† CI = confidence interval.

‡ Subjects with a missing value on any variables in the model were excluded; women whose menstruation has never been regular were excluded.

DISCUSSION

Our study results showed that a short cycle length might be related to increased risk of breast cancer in African-American women. This association existed primarily in post-menopausal women and did not vary depending on ER status. Other menstrual factors did not increase or decrease breast cancer risk, and no risk pattern could be identified according to ER status of cancer.

The association of short cycles with increased risk of breast cancer is biologically plausible. It is known that there are higher estrogen levels in the normal luteal phase than nonovulatory phase during a menstrual cycle.²⁷ Since the length of luteal phase is constant (about 14 days) for short and long menstrual cycles,²⁸ a short menstrual length represents more cycles and thus more luteal phases,^{29,30} given the same ages at menarche and at menopause. Therefore, fre-

quency of cycles may be an index of cumulative estrogen exposure³¹ and short menstrual cycles (thus more cycles) may stand for more estrogen exposure than long cycles.^{32,33} Although inconsistent,^{36–38} some epidemiological studies have shown the increased breast cancer risk related to short menstrual cycles.^{33–35}

While the menstrual cycle length/breast cancer association should be stronger for ER+ tumors if cycle length influences the risk of breast cancer through estrogen, our data did not support this. Our search of the currently available literature did not produce any other studies examining the association between cycle length and breast cancer by ER status. Additionally, no other studies investigated cycle length in relation to breast cancer risk in African-American women. As the first study examining the hypothesized association in terms of ER status and the first one investigating the effect of menstrual cycle

length in African-American women, we found an increased breast cancer risk associated with a short cycle length in postmenopausal African-American women despite ER status of tumors. These results suggest no differences between ER+ and ER– tumors in the cycle length/breast cancer association.

There may be several possible explanations of the results. First, different ER status does not represent different disease entities. It is possible that all breast cancers initially contain estrogen receptors and ER– cancers result from the lost ability to synthesize estrophilin during clonal evolution of estrogen receptors.^{1,39,40} If this is true, menstrual cycle length may be associated with all breast tumors, independent upon ER status of the cancer, which can be measured when cancer develops to an identifiable stage. The second possible explanation is that misclassification in determining ER status may dilute the differences between ER+ and ER– tumors. ER levels may be influenced by hormones, such as contraceptive pill use and estrogen replacement therapy.^{41,42} The sampling errors in taking breast cancer tissue may be another source of misclassification due to intra-tumor ER heterogeneity: ER+ tumor can be falsely regarded as negative when an ER– area is sampled.⁴³ Cellularity of tissue samples may also affect the determination of ER status: a highly cellular tumor consisting of cells of low ER content may be classified as receptor-positive and a tumor with sparse distribution of ER+ cells in a connective tissue stroma may be defined as negative.⁴⁴ The misclassification of ER status may attenuate the differences in hypothesized association between the 2 types of cancer, although it may not fully explain the lack of the differences.

Other menstrual factors (age at menarche, age at menopause, length of flow, and time from menarche to menstrual regularity) were not associated with either ER+ or ER– tumor in our study. Previous studies primarily conducted in Caucasian women have ob-

Table 3. Odds ratios for menstrual factors in relation to breast cancer according to menopausal and ER states in African-American women aged 20–64, 3 counties, Tennessee, 1995–1998

Characteristic	Controls‡	Cases‡			
		ER+	OR* (95% CI)†	ER–	OR* (95% CI)†
Pre-menopausal					
Cycle length (days)					
<28	37	15	reference	20	reference
≥28	63	26	0.65 (0.20–2.12)	31	1.00 (0.31–3.22)
Age at menarche (years)					
>12	45	20	reference	27	reference
≤12	55	21	0.70 (0.24–2.05)	24	0.52 (0.18–1.54)
Menarche to regularity (years)					
<1	67	29	reference	38	reference
≥1	33	12	1.06 (0.33–3.40)	13	0.50 (0.14–1.71)
Length of flow (days)					
<5	38	13	reference	23	reference
≥5	62	28	1.21 (0.41–3.59)	28	0.84 (0.28–2.50)
Post-menopausal					
Cycle length (days)					
<28	37	29	reference	23	reference
≥28	98	42	0.41 (0.20–0.86)	29	0.38 (0.16–0.90)
Age at menarche (years)					
>12	74	35	reference	28	reference
≤12	61	36	1.26 (0.62–2.57)	24	1.16 (0.52–2.60)
Menarche to regularity (years)					
<1	99	52	reference	38	reference
≥1	36	19	1.11 (0.49–2.53)	14	1.06 (0.47–2.40)
Length of flow (days)					
<5	53	24	reference	19	reference
≥5	82	47	1.23 (0.60–2.54)	33	1.36 (0.60–3.08)

* Adjusted for marital status, education, age, family history of breast cancer, history of benign breast disease, alcohol use, smoking, oral contraceptive use, number of pregnancies, age at first birth, age at first sexual intercourse, body mass index, daily energy intake (kcal), physical activity, electric bedding device use, history of infertility, and the other variables in the table.

† CI = confidence interval.

‡ Subjects with a missing value on any variables in the model were excluded; women whose menstruation has never been regular were excluded.

tained inconsistent results. While some studies suggested an increased risk for ER+ tumors in women with an earlier age at menarche,⁹ other studies suggested a possible association of earlier¹¹ or later⁴ age at menarche with increased risk of ER– tumors, or of earlier⁷ or later¹³ age at menarche with both ER statuses, or found no association with either ER status.¹² Similarly, no coherent results have been obtained for age at menopause.^{4,9,11,12} The only study we found on menstrual regularity did not report an association between menstrual

regularity and breast cancer for both ER types.¹² Theoretically, early age at menarche and late age at menopause may represent the greater exposure to estrogen^{27,29,38} because of more menstrual cycles. A short interval between menarche and menstrual regularity may also be related to higher estrogen exposure because rapid establishment of regular cycles increases cumulative number of ovulatory cycles when other menstrual factors are the same.²⁷ Many previous investigations have demonstrated increased risk of breast cancer due to early

age at menarche^{36,45–47} and late age at menopause,^{36,37,46–48} while, although suggestive,^{46,49,50} results were less consistent for menstrual regularity.^{37,38,47} Limited studies by ER status generally did not find the relatively consistent association between age at menarche or age at menopause and breast cancer and did not show a clear pattern in terms of ER status. Our study in African-American women also did not find a pattern according to ER status, while studies without considering ER status in African Americans did not generate results as consistent as those conducted in Caucasians.^{51–53} Our study also agreed to the previous investigation by ER status,¹² finding no differences between ER+ and ER– tumors in menstrual regularity in relation to breast cancer. Apart from the possible explanations of the results as previously mentioned, a smaller number of cases, due to subdividing case group by ER status, may also contribute to less consistent results. Length of flow, which has been seldom studied previously and was not related to either ER status in our study, possesses large individual variation^{24,54} and deserves more research on its value as a marker of hormonal exposure.

To our knowledge, this study is the first to provide data on the association of menstrual factors with breast cancer by ER status in African-American women and the first to examine menstrual cycle length and length of flow in relation to breast cancer by ER status. Because African-American women are different from Caucasian women in the distribution of ER status of tumors, menstrual factors, and other factors that may influence study results, an exploration of the hypothesized relationship in the population is desirable. To ensure good quality in determining ER status for the study, we processed tissue samples at the same laboratory and one pathologist read all tissue slides (except for 9 patients whose ER status was defined based on their pathological reports). These standardized procedures mini-

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mized inter-laboratory variations due to the use of medical records from different hospitals for defining ER status, which was common in previous studies.^{4,9,14,15} Since we collected detailed information on different factors including dietary intake, we were able to control for potential confounders more thoroughly.

However, this study had some limitations. First, a substantial proportion of eligible patients did not participate due to the lack of a doctor's consent, being unable to be located, deceased status, or patient's refusal. The results might be biased if non-participants differed from the participants. However, we did not expect a substantial bias because non-participation might not be related to menstrual factors. Second, the sample size of this study was not sufficient for more detailed analysis (eg, analysis on dose-response relation by both ER and menopausal status). Third, it has been suggested that a combination of ER and progesterone receptor (PR) statuses may be important for examining risk factors for breast cancer.^{9,10,12} Although PR status was also measured in this study, a very small number of cases with discordant ER and PR statuses prevented us from stratifying study subjects by both hormone receptors. Finally, the modest sample size confined our ability in subdividing post-menopausal status according to whether a menopause was natural or resulted from a surgical procedure. Women with a surgical menopause may differ from those with a natural menopause in hormone-related factors. Combining these two subgroups might have influenced the results. Our study showed that African-American women had a high proportion of menopause through hysterectomy (40% for cases and 35% for controls) and many of those with hysterectomy were unable to tell if they had had their ovaries removed during the procedure. This may imply the importance of addressing these factors in future research.

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AUTHOR CONTRIBUTIONS

Design and concept of study: Zhu, Bernard
Acquisition of data: Zhu, Hunter, Payne-Wilks, Roland, Forbes
Data analysis and interpretation: Zhu, Beiler, Hunter, Roland, Payne-Wilks, Forbes, Chinchilli, Bernard, Jacobsen, Levine
Manuscript draft: Zhu, Beiler, Hunter, Chinchilli, Jacobsen, Levine
Statistical expertise: Zhu, Chinchilli, Jacobsen
Acquisition of funding: Zhu, Bernard
Administrative, technical, or material assistance: Zhu, Beiler, Hunter, Payne-Wilks, Roland, Forbes, Levine
Supervision: Zhu