Inflammatory Cytokine Levels and Breast Cancer Risk Factors: Racial Differences of Healthy Caucasian and African American Women

Na-Jin Park, PhD, RN, and Duck-Hee Kang, PhD, RN, FAAN

Prominent racial differences have been noted in the incidence of and mortality from breast cancer (BC) between African American and Caucasian women in the United States (American Cancer Society [ACS], 2011). African American women have a lower overall lifetime incidence of BC but worse age-adjusted mortality rates than Caucasian women, resulting in a disproportionately higher (greater than 65%) risk of death (Joslyn & West, 2000). Earlier onset and more aggressive (e.g., triple-negative, inflammatory tumors) and more advanced forms of BC in African American women partially explain these mortality differences (Shavers, Harlan, & Stevens, 2003; Stead et al., 2009). Other potential sources of racial differences in BC outcomes include socioeconomic (e.g., income, health insurance coverage), healthcare system (e.g., screening, high-quality healthcare access), and tumor (e.g., tumor biology) factors (Amend, Hicks, & Ambrosone, 2006; Gerend & Pai, 2008). However, even after controlling for all these factors, racial differences in BC persist (Albain, Unger, Crowley, Coltman, & Hershman, 2009), suggesting that other contributors, such as biologic factors, may exist.

Chronic inflammation has been implicated as one of the biologic mechanisms underlying several types of cancer, including BC (Goswami, Rajappa, Sharma, & Sharma, 2008). Proinflammatory cytokines, such as interleukin (IL)-6, interferon-gamma (IFN-γ), and C-reactive protein (CRP), play a central role in sustaining chronic inflammation and have been reported to facilitate tumor growth and metastasis (Cole, 2009). Although the exact causality of inflammation has not been confirmed, higher levels of inflammatory cytokines are regarded as susceptibility or prognostic factors for BC incidence and mortality (Pierce et al., 2009). In addition, previous genetic studies have shown that polymorphisms of inflammatory cytokine genes (e.g., *–174G/C* for IL-6 and *874T/A* for IFN-γ) differ between African American and Caucasian women (Govan et al., 2003; Hassan, Aschner, Manning, Xu, & Aschner, 2003; Ness, Haggerty, Harger,

Purpose/Objectives: To examine racial differences in inflammatory cytokine levels (interleukin [IL]-6 and interferon-gamma [IFN-γ]) and breast cancer (BC) risk factors between healthy Caucasian and African American women; to examine differences in relationships of inflammatory cytokine levels with BC risk factors between these groups of women; and to determine the independent contribution of race to IL-6 and IFN-γ after controlling for relevant covariates.

Design: Cross-sectional and correlational descriptive design.

Setting: Community surrounding a state university health system in the southeastern United States.

Sample: 113 healthy women (65 Caucasians and 48 African Americans) aged 20 years or older and not pregnant.

Methods: Secondary analysis of data collected from self-report questionnaires and blood samples.

Main Research Variables: Inflammatory cytokine levels, BC risk factors (age, age at menarche, age at first live birth, family history of BC, breast biopsy, breastfeeding history and duration, body mass index, and physical activity), and race.

Findings: Significant racial differences were noted in IL-6 and IFN-γ levels, reproductive or hormonal and lifestyle BC risk factors, and relationships between African American and Caucasian women. Controlling for all other effects, race appeared to be a significant predictor for IL-6 and IFN-γ.

Conclusions: Racial differences in inflammatory cytokines and BC risk factors may provide partial evidence for existing racial disparities in BC for African American and Caucasian women. Additional studies are needed to confirm that potential.

Implications for Nursing: Additional biobehavioral research in racial disparities in BC may help to inform nurses to target race-specific modifications of lifestyle and behavioral factors to reduce BC health disparity between African American and Caucasian women.

Knowledge Translation: Being an African American woman predicted a higher level of inflammatory cytokine production after controlling for selected BC risk factors. Great potential exists for inflammatory responses as one of the underlying biologic mechanisms for existing BC disparity and for culturally tailored lifestyle or behavioral modification interventions for reducing BC risk and racial disparity.

& Ferrell, 2004), suggesting that genetic predisposition may explain higher inflammatory cytokine levels in African American women. Although intriguing, limited data currently exist on phenotypic differences of inflammatory cytokines between racial groups. Only a few population-based studies demonstrated higher circulating levels of inflammatory cytokines (e.g., IL-6, CRP) in African American women compared to Caucasians (Carroll et al., 2009; Stowe, Peek, Cutchin, & Goodwin, 2010). Although current evidence collectively suggests that racial differences in inflammatory cytokines may play a significant role in BC disparities (Berger, 2004; Zabaleta et al., 2008), few studies have examined this potential, and none of the genetic and population-based studies reporting these associations were conducted in relation to BC risk.

Major BC risk factors include age, familial or genetic factors, breast disease and biopsy, reproductive or hormonal factors (e.g., early menarche, late first live birth, no birth, no breastfeeding), and lifestyle factors (e.g., obesity, physical inactivity) (ACS, 2011). Current epidemiologic evidence suggests that African American women differ from Caucasian women in risk factor profiles by showing earlier menarche, more births at younger ages, higher levels of obesity, and less physical activity (Bernstein, Teal, Joslyn, & Wilson, 2003; Hall, Moorman, Millikan, & Newman, 2005). BC risk factors such as aging, obesity, and physical inactivity are known to increase circulating levels of inflammatory cytokines (Kasapis & Thompson, 2005; Stowe et al., 2010; Wee et al., 2008). In addition, psychosocial factors such as higher psychological stress and lower income have been associated with higher levels of inflammatory cytokines (Friedman & Herd, 2010; Howren, Lamkin, & Suls, 2009). Although prior studies have shown that racial differences exist in BC risk and other psychosocial factors as well as inflammatory cytokine levels, whether or not the types of relationships between BC risk factors and inflammatory cytokines are similar between Caucasian and African American women and whether race is an independent contributor to inflammatory cytokine levels after controlling for the effects of BC risk and other factors are unclear.

The Expanded Biobehavioral Interaction Model (Kang, Rice, Park, Turner-Henson, & Downs, 2010) provided the conceptual basis for the current exploratory study. Relationships depicted in this model identify factors in psychosocial, behavioral, individual, and environmental domains that may individually and/or interactively alter biologic responses to shape health and health outcomes. In the current study, race and BC risk factors are the individual and behavioral domains, and psychological stress and income are the psychosocial domain (covariates) that were examined to identify relationships with inflammatory cytokines (IL-6 and IFN-γ). Upregulated inflammatory cytokines have been related with health outcomes of BC incidence, advanced stage, and metastasis-related morbidity, as well as poor survival over time (Il'yasova et al., 2005; Pierce et al., 2009). Therefore, differences in inflammatory cytokines may help to explain disparities in BC-related health outcomes between African American and Caucasian women.

The specific aims of the current study were to (a) examine racial differences in inflammatory cytokine levels and BC risk factors (age, age at menarche, age at first live birth, family history of BC, breast biopsy, breastfeeding history and duration, body mass index [BMI], and physical activity) between healthy African American and Caucasian women; (b) examine racial differences in the relationships of inflammatory cytokine levels with BC risk factors between the two groups of women; and (c) determine the independent contribution of race to inflammatory cytokine levels after controlling for BC risk factors and covariates (psychological stress and income). The central hypothesis of the study was that racial differences would be noted in inflammatory cytokine levels, BC risk factors, and relationships. The study was a secondary analysis of data obtained for a prior study examining the influence of BC risk and psychological stress on immune responses in healthy women (Park, Kang, & Weaver, 2010).

Methods

A cross-sectional and correlational descriptive study design was used to examine racial differences in inflammatory cytokine levels, BC risk factors, and their relationships. Data were collected using self-report questionnaires and a blood sample.

Sample

Sample size was calculated based on a prior power analysis for the parent study with 0.05 significance level, 0.85 power, 0.13 (moderate) effect size, and five independent variables (Cohen, 1988). The parent study included 117 healthy women: 65 Caucasian, 48 African American, 1 Hispanic, and 3 Asian. Only Caucasian and African American women were included in the current study, resulting in a total sample size of 113 women. The authors' analysis indicated that a sample of 113 women would result in a moderate effect size for the study. The women identified themselves to be aged 20 years or older, healthy, and able to read and understand English. Women were excluded if they were pregnant, nursing, or reported (a) any prior or concurrent cancer, (b) chronic or acute infectious illnesses, (c) known mental illnesses or substance abuse, (d) immune disorders (e.g., autoimmune disease, HIV-positive status), or (e) currently using immunosuppressive drugs.

Procedures

The study protocol was approved by the University Institutional Review Board and the Human Subjects Research Review Board of the U.S. Army Medical Research and Materiel Command for the U.S. Department of Defense. Participants were recruited with advertisements posted on the campus of the University of Alabama at Birmingham. Eligibility criteria were self-determined when the potential participants called and then were checked by the investigator after they signed the informed consent form at a meeting in the School of Nursing at the University of Alabama at Birmingham.

After informed consent was obtained, participants were asked to complete a set of questionnaires (demographics, BC risk factors, and psychological stress) and give a blood sample. The investigator was available to answer any questions that participants might have while they completed the questionnaires. Blood samples (15 ml) for inflammatory cytokine assays using routine venipuncture technique were collected by a RN. Processing of blood samples and assay procedures were carried out in the laboratory by the same investigator immediately following sample collection. Participants received $20 and a breast self-examination instruction card for their time and efforts. Confidentiality was assured, and data handling and storage were confined to the authors.

Measurements

Inflammatory cytokine levels of interleukin-6 and interferon-gamma: All blood samples were collected into heparin-containing vacutainers from 9–11:30 am to minimize potential diurnal variation. Whole blood cell culture assay was used to better reflect the in vivo conditions (Kang et al., 2011). Briefly, heparinized blood was diluted 1:10 with the complete medium (Roswell Park Memorial Institute [RPMI] 1640 supplemented with HEPES 25 mM, L-glutamine 2 mM, penicillin 50 unit, and streptomycin 50 mcg/ml) and was incubated for four days at 37°C with 5% CO_2 in the presence of phytohemagglutinin 10 mcg/ml. Culture supernatant was collected and stored in aliquots at –80°C until batch assayed. Each cytokine level was determined by a standard two-step sandwich enzyme-linked immunosorbent assay (ELISA). The assay sensitivity for IL-6 and IFN-γ were 2 pg/ml and 4 pg/ml, respectively. Intra- and interassay coefficients of variation for both cytokines ranged from 2%–10%, indicating high sensitivity and precision.

Race: Participants identified their race or ethnic group from six categories: White/Caucasian or European-American, Black/African American or African ancestry, Latina/Latino or Hispanic (not including European Spanish or Portuguese), American Indian or Alaskan Native, Asian or Pacific Islander, and other. For the purpose of this study, White/Caucasian was coded with 0 and Black/African American with 1.

Breast cancer risk factors: BC risk factors were identified based on the **Gail Model** (age, age at menarche, age at first live birth, family history of BC, and previous breast biopsy) and current BC literature (breastfeeding history and duration, BMI, and physical activity). Based on the Gail Model (Gail et al., 1989), the National Cancer Institute (NCI) developed the Breast Cancer Risk Assessment Tool for public access at http://bcra.nci.nih.gov/brc with additional validation (Rockhill, Spiegelman, Byrne, Hunter, & Colditz, 2001) demonstrating validity and accessibility of the Gail Model (Tice et al., 2008). For the current study, individual risk factors were selected from this well-established Gail Model, including age (years), age at menarche (years), age at first live birth (younger than 20, 20–24, 25–29, 30 years or older, or nulliparous), number of first-degree relatives with BC (none, one, or two or more), and number of previous breast biopsy (none, one, or two or more).

Based on findings by Millikan et al. (2008) and Phipps et al. (2011), breastfeeding history (never or ever), total duration of previous breastfeeding (the total number of months for previous breastfeeding), BMI, and physical activity were assessed as additional risk factors. BMI was calculated from weight (kg) divided by height (m^2), and physical activity was assessed by an average number of days engaging in 30 minutes moderate physical activity or 20 minutes vigorous physical activity during a typical week per self-reports.

Income: Pre-tax household gross income for the prior 12 months also was assessed.

Psychological stress: The **Impact of Event Scale** (Horowitz, Wilner, & Alvarez, 1979) was used to measure psychological stress about developing BC. The 15-item scale measures the frequency of intrusive and avoidant thoughts about developing BC during the past seven days. Responses were weighted on a four-point Likert-type scale ranging from 0 (not at all) to 5 (often), with possible total scores ranging from 0–62. Higher scores indicate higher levels of BC-specific psychological stress. The Cronbach alpha was 0.93 in this study.

Data Analysis

Data were examined for outliers and violating assumptions for regression analyses. Racial differences in inflammatory cytokine levels, BC risk factors, and sample demographic characteristics were compared using Student's t tests for continuous variables and a chi-square test for categorical variables. Pearson or nonparametric Spearman correlation coefficients then were used to examine the relationships between cytokine levels and BC risk factors for the total group and each

racial subgroup. The skewed data of psychological stress and total duration of previous breastfeeding were log transformed to meet the assumption of normal distribution. Hierarchical multiple regression analyses were used to determine the independent contribution of race to inflammatory cytokines after controlling for significant covariates. Potential covariates (BC risk factors, income, and psychological stress) showing statistically significant bivariate correlations with each cytokine at $p < 0.05$ were selected and entered for a regression analysis for each cytokine. Only variables that remained significant were retained and entered as significant covariates into the first block, followed by race in the second block of regression model for each cytokine. All analyses were performed using two-tailed tests with the alpha level at 0.05.

Results

Sample Characteristics

Descriptive characteristics of the sample are presented in Tables 1 and 2. The mean age of the participants was 36.6 (SD = 12.2 years). Most participants were relatively well educated and worked full-time. The average age at first live birth for 64 parous women was 24.3 years (range = 15–39). The average BMI was 26.7 kg/m^2, and about 50% of the participants were overweight (25–29.9) or obese (30 or higher). The mean levels of IL-6 and IFN-γ were 662.8 pg/ml (range = 2–1,410.7 pg/ml; SD = 322), and 862.8 pg/ml (range = 4–1,766.2 pg/ml; SD = 559.4), respectively.

Racial Differences

Inflammatory cytokine levels: Figure 1 shows differences in circulating levels of IL-6 ($t = -5.53$, $p < 0.001$) and IFN-γ ($t = -3.17$, $p = 0.002$) for Caucasian and African American women. African American women showed significantly higher mean levels of IL-6 (836.2 versus 534.7 pg/ml) and IFN-γ (1,049.4 versus 724.9 pg/ml) than did Caucasian women.

Sample characteristics and breast cancer risk factors: Education and income levels were significantly lower in African American women than Caucasian

Table 1. Sample Characteristics by Race (N = 113)

	Total		Caucasian (n = 65)		African American (n = 48)			
Characteristic	$\bar{X}$	**SD**	$\bar{X}$	**SD**	$\bar{X}$	**SD**	**t**	**p**
Psychological (breast cancer–specific) stress[a]	11.3	15.1	9.1	13.5	14.2	16.8	1.72	0.089
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**χ^2**	**p**
Marital status							5.61	0.06
Married or living together	57	50	39	60	18	38	–	–
Widowed, separated, or divorced	21	19	10	15	11	23	–	–
Single or never married	35	31	16	25	19	40	–	–
Employment							0.77	0.68
Not employed	14	12	7	11	7	15	–	–
Part-time	25	22	16	25	9	19	–	–
Full-time	74	66	42	65	32	67	–	–
Education							14.34	0.002
High school	13	12	3	5	10	21	–	–
Some college	40	35	19	29	21	44	–	–
College	38	34	25	38	13	27	–	–
Graduate or professional school	22	20	18	28	4	8	–	–
Income ($)							20.01	0.006
Less than 15,000	19	17	5	8	14	29	–	–
15,000–19,999	9	8	3	5	6	13	–	–
20,000–24,999	9	8	4	6	5	10	–	–
25,000–34,999	14	12	7	11	7	15	–	–
35,000–49,999	19	17	11	17	8	17	–	–
50,000–69,999	11	10	7	11	4	8	–	–
70,000–89,999	6	5	4	6	2	4	–	–
90,000 or greater	21	19	19	29	2	4	–	–
Missing	5	5	5	8	–	–	–	–
Having health insurance							3.4	0.065
Yes	103	91	62	95	41	85	–	–
No	10	9	3	5	7	15	–	–

[a] Range = 0–62. Higher scores indicate greater stress.

Note. Because of rounding, not all percentages total 100.

Table 2. Breast Cancer Risk Factors by Race (N = 113)

Characteristic[a]	Total $\bar{X}$	Total SD	Caucasian (n = 65) $\bar{X}$	Caucasian (n = 65) SD	African American (n = 48) $\bar{X}$	African American (n = 48) SD	t	p
Age (years)	36.6	12.2	38.8	13.2	33.5	10.1	2.35	0.02
Age at menarche (years)	12.6	1.5	12.9	1.4	12.1	1.6	2.86	0.005
Duration of previous breastfeeding (months)	3	8.9	4.5	11.4	0.9	2.3	2.48	0.016
Body mass index (kg/m²)	26.7	6	24.6	4.6	29.5	6.6	4.61	< 0.001
Physical activity (days per week)								
Moderate	3.1	2	3.4	1.9	2.7	2	2.13	0.035
Vigorous	2.1	2	2.1	1.9	2.2	2.2	0.059	0.953
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**χ^2**	**p**
Age at first live birth (years)							13.38	0.01
Younger than 20	15	13	3	5	12	25	–	–
20–24	20	18	10	15	10	21	–	–
25–29	17	15	13	20	4	8	–	–
30 or older	12	11	9	14	3	6	–	–
Nulliparous	49	43	30	46	19	40	–	–
Number of first-degree relatives with breast cancer							2.5	0.286
0	61	54	31	48	30	64	–	–
1	47	42	31	48	16	33	–	–
2 or more	5	5	3	5	2	4	–	–
Number of previous breast biopsies							0.64	0.726
0	103	91	59	91	44	92	–	–
1	6	5	3	5	3	6	–	–
2 or more	4	4	3	5	1	2	–	–
Breastfeeding history							4.01	0.045
Never	78	69	40	62	38	79	–	–
Ever	35	31	25	39	10	21	–	–

[a] Range for age is 21–70 years, 9–17 years for age at menarche, 0–78 months for duration of previous breastfeeding, and 16.6–54.2 kg/m² for body mass index.

Note. Because of rounding, not all percentages total 100.

women. However, no differences were noted in employment, marital status, health insurance status, and psychological stress level for African American and Caucasian women.

Racial differences were found in BC risk factors such as age, age at menarche, age at first live birth, breastfeeding history and duration, BMI, and moderate physical activity. African American women were significantly younger and experienced menstruation earlier than Caucasian women. Thirty-five percent of African American women reported menarche before age 12 years, compared with 12% of Caucasian women. Among 64 parous women, African American women gave first live birth at a younger age than their Caucasian counterparts (22.3 versus 26 years). Twenty-five percent of African American women had their first child before age 20 compared to 5% of Caucasian women. More Caucasian women were nulliparous or had their first live birth after age 30 than African American women (60% versus 46%). However, African American women reported less breastfeeding and a shorter duration of breastfeeding for all children (0.9 versus 4.5 months). Among parous women, 34% of African American women reported breastfeeding, compared with 71% of Caucasian women. BMI was significantly higher in African American women compared to Caucasian women: 29.5 versus 24.6 kg/m². African American women were less engaged in moderate physical activity than Caucasian women, but no difference was noted in vigorous physical activity. The number of first-degree relatives with BC and previous breast biopsy were similar between the two racial groups.

Inflammatory cytokine levels and breast cancer risk factors: Table 3 shows bivariate relationships of IL-6 and IFN-γ with selected BC risk factors and potential covariates. Income showed a significant negative correlation with IL-6 (Spearman rho = –0.402, $p < 0.001$), whereas BC-specific psychological stress showed a significant positive correlation with IL-6 ($p = 0.002$). IL-6 also was correlated with duration of breastfeeding and BMI: increased levels of IL-6 were related with fewer months of previous breastfeeding ($p = 0.006$) and with higher BMI ($p = 0.002$). IFN-γ showed a negative relationship with age at first live birth (Spearman

rho = –0.197, p = 0.036), but not with any other BC risk factors.

Separate correlational analyses for each racial subgroup were performed to assess race-specific differences in the relationships. A significant negative relationship between IL-6 and income in the total group was sustained for Caucasian women (Spearman rho = –0.317, p = 0.011), but not for African American women. Similarly, duration of breastfeeding was negatively correlated with IL-6 only in Caucasian women (p = 0.014), but psychological stress was positively correlated with IL-6 only in African American women (p = 0.012). Another interesting finding related to age and IL-6 relationship, which showed race-specific relationships in an opposite direction, was that older age was correlated with lower levels of IL-6 in Caucasian women (p = 0.039) but with higher levels of IL-6 (p = 0.011) and IFN-γ (p = 0.013) in African American women. The significant relationships in age at first live birth with IFN-γ and in BMI with IL-6 from the total group did not hold for an individual racial group.

Independent Contribution of Race

Using bivariate correlations and regression analyses, significant covariates were identified for each inflammatory cytokine: income for IL-6 and age at first live birth for IFN-γ (see Table 4). The higher levels of IL-6 were associated with lower income (β = –0.41, $p \leq 0.001$). After controlling for income, race remained a statistically significant predictor for IL-6 ($\Delta R^2 = 0.096$, $p < 0.001$). The higher levels of IFN-γ were associated with younger age at first live birth (β = –0.188, p = 0.046), and after controlling for this factor, race also remained a significant predictor for IFN-γ ($\Delta R^2 = 0.064$, p = 0.006). In summary, race had a unique independent contribution to both IL-6 and IFN-γ after controlling for other factors.

Discussion

The major findings of this study include racial differences in IL-6 and IFN-γ levels, several BC risk factors, and some of their relationships, partially supporting the proposed hypothesis. Compared with Caucasian women, African American women had significantly higher levels of IL-6 and IFN-γ and were more likely to be younger at their menarche and first live birth, more parous, and less likely to breastfeed. African American women had higher BMI, less physical activity, and lower income and education than Caucasian women. As a total group, BC risk factors of BMI, breastfeeding, and age at first live birth, and covariates of income and psychological stress were significantly correlated with IL-6 or IFN-γ, but their relationships differed by race. More importantly, race remained a significant predictor for IL-6 and IFN-γ after controlling for all other factors of significance. Given the potential role of inflammatory markers in BC (Cole, 2009), the findings suggest that racial differences in inflammatory biologic responses may, in part, explain racial disparity in BC between African American and Caucasian women. More research with larger samples considering genetic and environmental or behavioral factors concurrently is necessary to verify these preliminary findings.

Racial Differences in Inflammatory Cytokines and Breast Cancer Risk Factors

Previous findings indicate different genetic variations in IL-6 (e.g., *–174G/C*) and IFN-γ (e.g., *874T/A*) genes between African American and Caucasian women (Govan et al., 2003; Hassan et al., 2003; Ness et al., 2004). For instance, African American women showed higher frequencies in the G allele (GG and GC genotypes) than Caucasian women (Hassan et al., 2003; Ness et al., 2004), thus contributing to higher IL-6 levels in African American women. Consistent with the authors' findings, prior studies also reported higher plasma concentrations of IL-6 and CRP in African American individuals than Caucasians (Carroll et al., 2009; Stowe et al., 2010). Whereas CRP and IL-6 have been studied more frequently, other inflammatory biomarkers such as IFN-γ have rarely been investigated for racial differences. Investigators have rarely studied racial disparity in BC risk factors and their relationships with inflammatory biomarkers among healthy women. Therefore, findings from this study provide intriguing information about potential racial differences in inflammatory cytokines including IFN-γ, established BC risk factors, and the relationships between the two in healthy African American and Caucasian women.

Of selected BC risk factors, reproductive or hormonal factors, including age at menarche, age at first live birth,

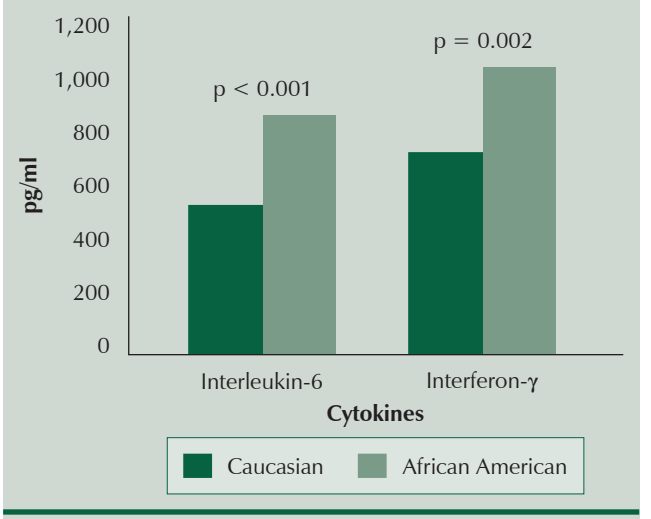

Figure 1. Racial Differences in Inflammatory Cytokines (N = 113)

and breastfeeding, showed notable racial differences: African American women had their menarche and first child at younger age with higher parity but were less likely to breastfeed relative to Caucasian women, consistent with previous reports (Bernstein et al., 2003; Hall et al., 2005). Early menarche (before age 12 years) indicates early and longer lifetime exposure to estrogen that can damage DNA through alkylation of molecules and active radical production, which can lead to BC development and proliferation of BC cells (Clemons & Goss, 2001; Pike, Spicer, Dahmoush, & Press, 1993). Full-term pregnancy, particularly at a young age (younger than 30 years), is known to reduce BC risk by inducing differentiation of mammary glands, thereby making them less susceptible to carcinogenic stimuli (Russo, Tay, & Russo, 1982). However, this relationship is particularly complex in African American women because of the dual effects of parity on BC risk: BC risk increases after full-term pregnancy but decreases generally after 10 years post-pregnancy (Liu et al., 2002; Palmer, Wise, Horton, Adams-Campbell, & Rosenberg, 2003). Although parity and first live birth at younger age reduced BC risk in Caucasian women, higher parity was associated with an increased BC risk among younger (20–49 years) African American women but with a decreased risk among older (aged 50 years and older) African American women (Hall et al., 2005). Because African American women are more likely to experience multiple pregnancies and deliveries in their earlier life (Bernstein et al., 2003), younger African American women may have prolonged transient increases in BC risk than Caucasian women. Breastfeeding is known to lower the risk of BC, including triple-negative tumors (Collaborative Group on Hormonal Factors in Breast Cancer, 2002; Millikan et al., 2008). A significant lack of breastfeeding in African American women may account for the higher incidence rates of aggressive breast tumors among younger African American women (Bernstein et al., 2003; Palmer et al., 2003). However, direct evidence is limited without prospective longitudinal data clearly indicating the causality. More research on racial differences in BC risk, particularly with premenopausal women, is warranted with additional reproductive or hormonal risk factors incorporated.

Obesity and physical inactivity generally are categorized as major risk factors for BC (Phipps et al., 2011). Consistent with previous findings (Bernstein et al., 2003; Forshee, Storey, & Ritenbaugh, 2003), the authors' data demonstrated higher BMI and less moderate physical activity in African American women than Caucasian counterparts. In previous epidemiologic studies, however, higher BMI or obesity was associated with higher BC risk in postmenopausal women but lower BC risk in premenopausal women (Lahmann et al., 2004; Ursin, Longnecker, & Haile, 1995). Because race was not considered in these studies, whether this relationship differs by race is unclear. In a prospective cohort study with postmenopausal women, the relationship between BMI and BC risk was weaker in African American women than Caucasian women (McCullough et al., 2005), but data were unavailable for premenopausal women. Physical activity is known to reduce lifetime exposure to endogenous estrogens (e.g., delaying menarche), decrease obesity and central adiposity, and increase immune function, thereby decreasing BC risk (Friedenreich & Orenstein, 2002). Although one epidemiologic study demonstrated a stronger inverse relationship between physical activity and BC mortality in African American women than

Table 3. Racial Differences in Relationships Between Inflammatory Cytokines and BC Risk Factors (N = 113)

	Total		Caucasian (n = 65)		African American (n = 48)	
Variable	**IL-6**	**IFN-γ**	**IL-6**	**IFN-γ**	**IL-6**	**IFN-γ**
Race[a]	0.465***	0.288**	–	–	–	–
BC risk factor						
Age	ns	ns	–0.257*	ns	0.366*	0.356*
Age at menarche	ns	ns	ns	ns	ns	ns
Age at first live birth[b]	ns	–0.197*	ns	ns	ns	ns
Number of FDRs with BC[b]	ns	ns	ns	ns	ns	ns
Number of breast biopsies[b]	ns	ns	ns	ns	ns	ns
Breastfeeding history	ns	ns	ns	ns	ns	ns
Duration of breastfeeding[c]	–0.255**	ns	–0.304*	ns	ns	ns
Body mass index	0.295**	ns	ns	ns	ns	ns
Moderate physical activity	ns	ns	ns	ns	ns	ns
Vigorous physical activity	ns	ns	ns	ns	ns	ns
Potential covariate						
Income[b]	–0.402***	ns	–0.317*	ns	ns	ns
Psychological stress[c]	0.292**	ns	ns	ns	0.358*	ns

* $p \leq 0.05$; ** $p \leq 0.01$; *** $p < 0.001$

[a] Caucasian was noted as 0 and African American as 1.

[b] Nonparametric Spearman correlation coefficients were used to test bivariate relationships.

[c] Log-transformed data were used.

BC—breast cancer; FDRs—first-degree relatives; IFN-γ—interferon-gamma; IL-6—interleukin-6; ns—not statistically significant

Caucasian women (John, Horn-Ross, & Koo, 2003), little data exist on racial differences in physical activity and their relationship with BC risk (McCullough et al., 2005). Existing data (Forshee et al., 2003) including the current study, however, indicate that African American women may have unhealthier lifestyles (e.g., poor diet, physical inactivity) than Caucasian women, which may contribute to racial disparity in BC. Most epidemiologic studies of lifestyle risk factors have been predominantly with Caucasian women, leaving a significant gap to understand BC risk in African American women (Bernstein et al., 2003; McCullough et al., 2005). Future studies need to include various lifestyle factors and diverse racial and ethnic groups in sufficient numbers so that the findings of the studies provide meaningful comparisons and ways to tailor future interventions to be culturally sensitive, which may ultimately reduce racial health disparities.

Table 4. Multiple Regressions: Independent Contribution of Race to Interleukin-6 and Interferon-Gamma Controlling for Covariates

Covariate	Model	R^2	AdjR^2	B	β	p
Interleukin-6[a]						
Step 1	F(1,109) = 22.045***	0.168	0.161	–	–	–
Income	–	–	–	–52.845	–0.41	< 0.001
Step 2	F(2,108) = 19.427***	0.265	0.251	–	–	–
Income	–	–	–	–33.061	–0.257	0.006
Race[b]	–	–	–	225.303	0.346	< 0.001
Interferon-gamma[c]						
Step 1	F(1,111) = 4.056*	0.035	0.027	–	–	–
Age at first live birth	–	–	–	–69.45	–0.188	0.046
Step 2	F(2,110) = 6.061**	0.099	0.083	–	–	–
Age at first live birth	–	–	–	–48.363	–0.131	0.161
Race[b]	–	–	–	292.171	0.259	0.006

* $p \leq 0.05$; ** $p \leq 0.01$; *** $p < 0.001$

[a] $\Delta R^2 = 0.096$, $\Delta F = 14.149$, $p < 0.001$

[b] Caucasian was noted as 0 and African American as 1.

[c] $\Delta R^2 = 0.064$, $\Delta F = 7.816$, $p = 0.006$

AdjR^2—adjusted R^2

Race and Relationships for Inflammatory Cytokines and Breast Cancer Risk Factors

IL-6 showed significant bivariate relationships with BMI and duration of breastfeeding in this study. Because adipocytes are a major source of IL-6 (Mohamed-Ali et al., 1997), the positive relationship between IL-6 and BMI is not surprising, as found in other studies (Hamer & Steptoe, 2009; Wee et al., 2008). However, a negative relationship between IL-6 and duration of breastfeeding is new information that adds to the current knowledge base. Benefits of breastfeeding have been documented from short- and long-term health outcomes in children to mental health and weight and metabolic benefits in lactating mothers (Groer, Davis, & Hemphill, 2002; Ip, Chung, Raman, Trikalinos, & Lau, 2009). However, breastfeeding behavior has not been studied for its relationship with IL-6 or other inflammatory markers. The negative relationship between the two in the current study suggests potential long-term benefits of breastfeeding on women's health. However, that relationship was significant only in Caucasian women, indicating a potential racial disparity. Although the limited variability in breastfeeding duration in African American women could be a reason for the nonsignificant relationship, the exact reason is unclear. Another intriguing finding is the relationship of lower levels of IFN-γ with older age at first live birth or nulliparity. Given that normal reproductive processes including pregnancy are associated with upregulation of inflammatory cytokine levels (Jabbour, Sales, Catalano, & Norman, 2009), the relationship between nulliparity and lower inflammatory level seems reasonable, but the relationship was limited only to IFN-γ. Implications of these findings for BC are not clear.

Racial differences in the nature of relationships between inflammatory cytokines and BC risk factors were noted between African American and Caucasian women in the current study. Most strikingly, the directions of the relationships between age and IL-6 and IFN-γ were opposite between two racial groups: Increased age was associated with lower levels of IL-6 in Caucasian women but with higher levels of IL-6 and IFN-γ in African American women. In the general population, aging has been consistently associated with increased IL-6 levels (Ershler & Keller, 2000; Kiecolt-Glaser, Preacher, MacCallum, Atkinson, & Malarkey, 2003). Although reasons for this racially discrepant finding are unclear, limited variations in age of the study sample, with most being premenopausal women (79%), and a relatively small sample size may have contributed to these findings. Lower income and higher psychological stress were significantly related with higher levels of IL-6, consistent with previous findings (Friedman & Herd, 2010; Howren et al., 2009). However, subgroup analyses showed that the inverse income to IL-6 relationship was significant only in the Caucasian group, whereas the positive stress to IL-6

relationship was significant only in African American women, perhaps reflecting differential cultural values and sensitivity to psychosocial and environmental factors. Additional studies are warranted in these areas.

For exploratory purpose, the independent contributions of race were examined for each inflammatory cytokine using regression models controlling for selected BC risk factors and psychosocial factors. After controlling for finalized covariates, age at first live birth and income, race remained a significant predictor for inflammatory cytokine levels—being African American predicted higher levels of IL-6 and IFN-γ. These findings extend previous findings on racial differences in inflammatory markers between African American and Caucasian individuals (Carroll et al., 2009; Stowe et al., 2010). In addition, income remained a significant contributor to IL-6 along with race at the final step of the regression model. Because lower socioeconomic status in African American women is regarded as one of major sources of racial disparity in BC (Gerend & Pai, 2008), conceptual and contextual overlaps may exist between income and race in the relationship with IL-6. In the current study, income and race showed a weak-to-moderate negative relationship ($r = –0.442$, $p < 0.001$), indicating no concern for multicollinearity in the analysis. Because the current study design and approach with controlling some selected variables allowed room for effects of other variables, caution needs to be taken in interpreting these findings. In addition, whether and how inflammatory cytokines contribute to BC outcomes require more in-depth investigations using additional pro- and anti-inflammatory biomarkers and BC risk factors.

Limitations

Limitations include the cross-sectional design, which precludes definitive causal interpretation. Sampling was limited to one locality, reducing generalizability to broad populations. Although the sample met the required estimate for a moderate effect size, whether or not a moderate effect size would be sufficient to identify clinical significance of the relationships is unclear. Because of a relatively small sample size, separate racial subgroup analyses are likely underpowered, and the one-time assessment of cytokines may not adequately represent persistent inflammatory cytokine responses. Although evidence suggests that IL-6 levels are relatively stable for an extended period (Rao, Pieper, Currie, & Cohen, 1994), multiple assessments for a longer period may increase reliability of interindividual variability in inflammatory cytokine production. Also, reliance on self-report could have been verified with objective measures for greater accuracy, and more sensitive and reliable measurements of the study variables might have yielded more accurate data. Although analysis of the genetics of inflammatory cytokines was beyond the scope of this study, simultaneous investigations on both genotypic and phenotypic expressions of inflammatory biomarkers in relation to BC risk and risk factors would generate rich data in this field.

Conclusion and Implications for Nursing

This study is the first demonstrating racial differences in IL-6 and IFN-γ inflammatory cytokine levels in relation to BC risk factors. Of BC risk factors, notable racial differences were found in reproductive or hormonal and lifestyle factors, but not in family history of BC or breast biopsy history. Although higher levels of IL-6 and IFN-γ in African American women than Caucasian women may be attributed to differences in BC risk and other lifestyle factors, race independently predicted inflammatory cytokines controlling for other effects. Acknowledging that there may be other effects not considered in this exploratory study, the study findings need to be validated through larger studies using a more rigorous prospective design and reliable and sensitive instruments and incorporating both genetic and environmental BC risk factors.

Racial differences in lifestyle and behavioral factors provide opportunities for developing culturally sensitive interventions to reduce BC risk and racial disparity. Millikan et al. (2008) estimated that promoting breastfeeding and reducing obesity could prevent about 68% of triple-negative BC development among younger African American women, demonstrating significant clinical implications for this line of research. Future studies should be conducted to enhance understanding of the complex interactions between biologic mechanisms and behavioral aspects underlying health disparity in BC. Cumulative findings of biobehavioral research will inform nurses to target race-, ethnic-, and culture-specific assessment and modifications of lifestyle or behavioral factors, contributing to reducing health disparity in BC.

Na-Jin Park, PhD, RN, is an assistant professor in the School of Nursing at the University of Pittsburgh in Pennsylvania, and Duck-Hee Kang, PhD, RN, FAAN, is a professor in the School of Nursing at the University of Texas Health Science Center at Houston. Support for this research was provided through a Department of Defense Medical Research, Breast Cancer Research Program, Predoctoral Traineeship Award (No. W81XWH-04-1-0352) and a grant from the National Institute of Nursing Research (No. R01 NR004930). Preparation of this manuscript was supported by a grant from the National Center for Advancing Translational Science of the National Institutes of Health (No. KL2TR000146). The content is solely the responsibility of the authors and does not necessarily reflect the official views of the National Institutes of Health and the U.S. government. Park can be reached at parknj@pitt.edu, with copy to editor at ONFEditor@ons.org. (Submitted August 2012. Accepted for publication January 15, 2013.)

Digital Object Identifier: 10.1188/13.ONF.40-05AP

References

Albain, K.S., Unger, J.M., Crowley, J.J., Coltman, C.A.J., & Hershman, D.L. (2009). Racial disparities in cancer survival among randomized clinical trials patients of the Southwest Oncology Group. *Journal of the National Cancer Institute, 101,* 984–992. doi:10.1093/jnci/djp175

Amend, K., Hicks, D., & Ambrosone, C.B. (2006). Breast cancer in African American women: Differences in tumor biolgoy from European American women. *Cancer Research, 66,* 8327–8330.

American Cancer Society. (2011). *Breast cancer facts and figures 2011–2012.* Atlanta, GA: Author.

Berger, F.G. (2004). The interleukin-6 gene: A susceptibility factor that may contribute to racial and ethnic disparities in breast cancer mortality. *Breast Cancer Research and Treatment, 88,* 281–285.

Bernstein, L., Teal, C.R., Joslyn, S., & Wilson, J. (2003). Ethnicity-related variation in breast cancer risk factors. *Cancer, 97*(1, Suppl.), 222–229.

Carroll, J.F., Fulda, K.G., Chiapa, A.L., Rodriquez, M., Phelps, D.R., Cardarelli, K.M., . . . Cardarelli, R. (2009). Impact of race/ethnicity on the relationship between viscerall fat and inflammatory biomarkers. *Obesity, 17,* 1420–1427.

Clemons, M., & Goss, P. (2001). Estrogen and the mechanism of breast cancer. *New England Journal of Medicine, 344,* 276–285.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Erlbaum.

Cole, S.W. (2009). Chronic inflammation and breast cancer recurrence. *Journal of Clinical Oncology, 27,* 3418–3419. doi:10.1200/JCO.2009.21.9782

Collaborative Group on Hormonal Factors in Breast Cancer. (2002). Breast cancer and breastfeeding: Collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50,302 women with breast cancer and 96,973 women without the disease. *Lancet, 20,* 187–195.

Ershler, W.B., & Keller, E.T. (2000). Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. *Annual Review of Medicine, 51,* 245–270.

Forshee, R.A., Storey, M.L., & Ritenbaugh, C. (2003). Breast cancer risk and lifestyle differences among premenopausal and postmenopausal African American women and White women. *Cancer, 97*(1, Suppl.), 280–288.

Friedenreich, C.M., & Orenstein, M.R. (2002). Physical activity and cancer prevention: Etiologic evidence and biological mechanisms. *Journal of Nutrition, 132*(Suppl.), 3456S–3464S.

Friedman, E.M., & Herd, P. (2010). Income, education, and inflammation: Differential associations in a national probability sample (the MIDUS Study). *Psychosomatic Medicine, 72,* 290–300. doi:10.1097/PSY.0b013e3181cfe4c2

Gail, M.H., Brinton, L.A., Byar, D.P., Corle, D.K., Green, S.B., Schairer, C., & Mulvihill, J.J. (1989). Projecting individualized probabilities of developing breast cancer for White females who are being examined annually. *Journal of the National Cancer Institute, 81,* 1879–1886.

Gerend, M.A., & Pai, M. (2008). Social determinants of Black-White disparities in breast cancer mortality: A review. *Cancer Epidemiology, Biomarkers and Prevention, 17,* 2913–2923. doi:10.1158/1055-9965.EPI-07-0633

Goswami, B., Rajappa, M., Sharma, M., & Sharma, A. (2008). Inflammation: Its role and interplay in the development of cancer, with special focus on gynecological malignancies. *International Journal of Gynecological Cancer, 18,* 591–599.

Govan, V.A., Carrara, H.R.O., Sachs, J.A., Hoffman, M., Stanczuk, G.A., & Williamson, A.L. (2003). Ethnic differences in allelic distribution of IFN-γ in South African women but no link with cervical cancer. *Journal of Carcinogenesis, 2,* 3. doi:10.1186/1477-3163-2-3

Groer, M.W., Davis, M.W., & Hemphill, J. (2002). Postpartum stress: Current concepts and the possible protective role of breastfeeding. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 31,* 411–417.

Hall, I.J., Moorman, P.G., Millikan, R.C., & Newman, B. (2005). Comparative analysis of breast cancer risk factors among African American women and White women. *American Journal of Epidemiology, 161,* 40–51.

Hamer, M., & Steptoe, A. (2009). Prospective study of physical fitness, adiposity, and inflammatory markers in healthy middle-aged men and women. *American Journal of Clinical Nutrition, 89,* 85–89. doi:10.3945/ajcn.2008.26779

Hassan, M.I., Aschner, Y., Manning, C.H., Xu, J., & Aschner, J.L. (2003). Racial differences in selected cytokine allelic and genotypic frequencise among healthy, pregnant women in North Carolina. *Cytokine, 21,* 10–16.

Horowitz, M., Wilner, N., & Alvarez, W. (1979). Impact of Event Scale: A measure of subjective stress. *Psychosomatic Medicine, 41,* 209–218.

Howren, M.B., Lamkin, D.M., & Suls, J. (2009). Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. *Psychosomatic Medicine, 71,* 171–186.

Il'yasova, D., Colbert, L.H., Harris, T.B., Newman, A.B., Bauer, D.C., Satterfield, S., & Kritchevsky, S.B. (2005). Circulating levels of inflammatory markers and cancer risk in the Health Aging and Body Composition Cohort. *Cancer Epidemiology, Biomarkers and Prevention, 14,* 2413–2418.

Ip, S., Chung, M., Raman, G., Trikalinos, T.A., & Lau, J. (2009). A summary of the Agency for Healthcare Research and Quality's evidence report on breastfeeding in developed countires. *Breastfeeding Medicine, 4*(Suppl. 1), S17–S30. doi:10.1089/bfm.2009.0050

Jabbour, H.N., Sales, K.J., Catalano, R.D., & Norman, J.E. (2009). Inflammatory pathways in female reproductive health and disease. *Reproduction, 138,* 903–919.

John, E.M., Horn-Ross, P.L., & Koo, J. (2003). Lifetime physical activity and breast cancer risk in a multiethnic population: The San Francisco Bay Area Breast Cancer Study. *Cancer Epidemiology, Biomarkers and Prevention, 12,* 1143–1152.

Joslyn, S.A., & West, M.M. (2000). Racial differences in breast carcinoma survival. *Cancer, 88,* 114–123.

Kang, D.H., McArdle, T., Park, N.J., Weaver, M.T., Smith, B., & Carpenter, J. (2011). Dose effects of relaxation practice on immune responses in women newly diagnosed with breast cancer: An explorary study [Online exclusive]. *Oncology Nursing Forum, 38,* E240–E252. doi:10.1188/11.ONF.E240-E252

Kang, D.H., Rice, M., Park, N.J., Turner-Henson, A., & Downs, C. (2010). Stress and inflammation: A biobehavioral approach for nursing research. *Western Journal of Nursing Research, 32,* 730–760.

Kasapis, C., & Thompson, P.D. (2005). The effects of physical activity on serum C-reactive protein and inflammatory markers: A systematic review. *Journal of the American College of Cardiology, 45,* 1563–1569.

Kiecolt-Glaser, J.K., Preacher, K.J., MacCallum, R.C., Atkinson, C., & Malarkey, W.B. (2003). Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proceedings of the National Academy of Sciences, 100,* 9090–9095.

Lahmann, P.H., Hoffmann, K., Allen, N., van Gils, C.H., Khaw, K.T., Tehard, B., . . . Elio, R. (2004). Body size and breast cancer risk: Findings from the European Prospective Investigation into Cancer and Nutrition (EPIC). *International Journal of Cancer, 111,* 762–771.

Liu, Q., Wuu, J., Lambe, M., Hsiech, S.F., Ekbom, A., & Hsieh, C.C. (2002). Transient increase in breast cancer risk after giving birth: Postpartum period with the highest risk (Sweden). *Cancer Causes and Control, 13,* 299–305.

McCullough, M.L., Feigelson, H.S., Diver, W.R., Patel, A.V., Thun, M.J., & Calle, E.E. (2005). Risk factors for fatal breast cancer in African American women and White women in a large U.S. prospective cohort. *American Journal of Epidemiology, 162,* 734–742.

Millikan, R.C., Newman, B., Tse, C.K., Moorman, P.G., Conway, K., Dressler, L.G., . . . Perou, C.M. (2008). Epidemiology of basal-like breast cancer. *Breast Cancer Research and Treatment, 109,* 123–139.

Mohamed-Ali, V., Goodrick, S., Katz, R.D.R., Miles, J.M., Yudkin, J.S., Klein, S., & Coppack, S.W. (1997). Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. *Journal of Clinical Endocrinology and Metabolism, 82,* 4196–4200.

Ness, R.B., Haggerty, C.L., Harger, G., & Ferrell, R. (2004). Differential distribution of allelic variants in cytokine genes among African Americans and White Americans. *American Journal of Epidemiology, 160,* 1033–1038. doi:10.1093/aje/kwh325

Palmer, J.R., Wise, L.A., Horton, N.J., Adams-Campbell, L.L., & Rosenberg, L. (2003). Dual effect of parity on breast cancer risk in African American women. *Journal of the National Cancer Institute, 95,* 478–483.

Park, N.J., Kang, D.H., & Weaver, M.T. (2010). Objective and subjective breast cancer risk: Relationships with natural killer cell activity and psychological distress in healthy women. *Cancer Nursing, 33,* 411–420. doi:10.1097/NCC.0b013e3181dc37a1

Phipps, A.I., Chlebowski, R.T., McTiernan, A., Stefanick, M.L., Wactawski-Wende, J., Kuller, L.H., . . . Li, C.I. (2011). Body size, physical activity, and risk of triple-negative and estrogen receptor-positive breast cancer. *Cancer Epidemiology, Biomarkers and Prevention, 20,* 454–463. doi:10.1158/1055-9965.EPI-10-0974

Pierce, B.L., Ballard-Barbash, R., Bernstein, L., Baumgartner, R.N., Neuhouser, M.L., Wener, M.H., . . . Ulrich, C.M. (2009). Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. *Journal of Clinical Oncology, 27,* 3437–3444. doi:10.1200/JCO.2008.18.9068

Pike, M.C., Spicer, D.V., Dahmoush, L., & Press, M.F. (1993). Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. *Epidemiologic Reviews, 15,* 17–35.

Rao, K.M., Pieper, C.S., Currie, M.S., & Cohen, H.J. (1994). Variability of plasma IL-6 and crosslinked fibrin dimers over time in community dwelling elderly subjects. *American Journal of Clinical Pathology, 102,* 802–805.

Rockhill, B., Spiegelman, D., Byrne, C., Hunter, D.J., & Colditz, G.A. (2001). Validation of the Gail model of breast cancer risk prediction and implications for chemoprevention. *Journal of the National Cancer Institute, 93,* 358–366. doi:10.1093/jnci/93.5.358

Russo, J., Tay, L.K., & Russo, I.H. (1982). Differentiation of the mammary gland and susceptibility to carcinogenesis. *Breast Cancer Research and Treatment, 2,* 5–73. doi:10.1007/BF01805718

Shavers, V.L., Harlan, L.C., & Stevens, J.L. (2003). Racial/ethnic variation in clinical presentation, treatment, and survival among breast cancer patients under age 35. *Cancer, 97,* 134–147. doi:10.1002/cncr.11051

Stead, L.A., Lash, T.L., Sobieraj, J.E., Chi, D.D., Westrup, J.L., Charlot, M., . . . Rosenberg, C.L. (2009). Triple-negative breast cancers are increased in Black women regardless of age or body mass index. *Breast Cancer Research, 11,* R18. doi:10.1186/bcr2242

Stowe, R.P., Peek, M.K., Cutchin, M.P., & Goodwin, J.S. (2010). Plasma cytokine levels in a population-based study: Relation to age and ethnicity. *Journal of Gerontology: Medical Sciences, 65A,* 429–433. doi:10.1093/gerona/glp198

Tice, J.A., Cummings, S.R., Smith-Bindman, R., Ichikawa, L., Barlow, W.E., & Kerlikowske, K. (2008). Using clinical factors and mammographic breast density to estimate breast cancer risk: Development and validation of a new predictive model. *Annals of Internal Medicine, 148,* 337–347. doi:10.7326/0003-4819-148-5-200803040-00004

Ursin, G., Longnecker, M., & Haile, R. (1995). A meta-analysis of body mass index and risk of premenopausal breast cancer. *Epidemiology, 6,* 137–141. doi:10.1097/00001648-199503000-00009

Wee, C.C., Mukamal, K.J., Huang, A., Davis, R.B., McCarthy, E.P., & Mittleman, M.A. (2008). Obesity and C-reactive protein levels among White, Black, and Hispanic U.S. adults. *Obesity, 16,* 875–880. doi:10.1038/oby.2008.7

Zabaleta, J., Schneider, B.G., Ryckman, K., Hooper, P.F., Camargo, M.C., Piazuelo, M.B., . . . Ochoa, A.C. (2008). Ethnic differences in cytokine gene polymorphisms: Potential implications for cancer development. *Cancer Immunology and Immunotherapy, 57,* 107–114. doi:10.1007/s00262-007-0358-4