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ORIGINAL REPORT

Association Between Inflammatory Biomarker C-Reactive Protein and Radiotherapy-Induced Early Adverse Skin Reactions in a Multiracial/Ethnic Breast Cancer Population

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ABSTRACT

Purpose
This study examined an inflammatory biomarker, high-sensitivity C-reactive protein (hsCRP), in radiotherapy (RT)-induced early adverse skin reactions or toxicities in breast cancer.

Patients and Methods
Between 2011 and 2013, 1,000 patients with breast cancer who underwent RT were evaluated prospectively for skin toxicities through the National Cancer Institute–funded Wake Forest University Community Clinical Oncology Program Research Base. Pre- and post-RT plasma hsCRP levels and Oncology Nursing Society skin toxicity criteria (0 to 6) were used to assess RT-induced skin toxicities. Multivariable logistic regression analyses were applied to ascertain the associations between hsCRP and RT-induced skin toxicities after adjusting for potential confounders.

Results
The study comprised 623 white, 280 African American, 64 Asian/Pacific Islander, and 33 other race patients; 24% of the patients were Hispanic, and 47% were obese. Approximately 42% and 15% of patients developed RT-induced grade 3+ and 4+ skin toxicities, respectively. The hsCRP levels differed significantly by race and body mass index but not by ethnicity. In multivariable analysis, grade 4+ skin toxicity was significantly associated with obesity (odds ratio [OR], 2.17; 95% CI, 1.41 to 3.34], post-RT hsCRP ≥ 4.11 mg/L (OR, 1.61; 95% CI, 1.07 to 2.44), and both factors combined (OR, 3.65; 95% CI, 2.18 to 6.14). Above-median post-RT hsCRP (OR, 1.93; 95% CI, 1.03 to 3.63), and change in hsCRP (OR, 2.80; 95% CI, 1.42 to 5.54) were significantly associated with grade 4+ skin toxicity in nonobese patients.

Conclusion
This large prospective study is the first to our knowledge of hsCRP as an inflammatory biomarker in RT-induced skin toxicities in breast cancer. We demonstrate that nonobese patients with elevated RT-related change in hsCRP levels have a significantly increased risk of grade 4+ skin toxicity. The outcomes may help to predict RT responses and guide decision making.

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INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in women and the second leading cause of cancer death in Americans.[1] With > 3 million breast cancer survivors in the United States, issues related to radiotherapy (RT)-induced normal tissue toxicities that significantly affect survivors' quality of life are important to address.[2,3] Compared with breast-conserving surgery alone, the addition of RT reduces the local recurrence rate.[4] However, under active debate is which patients can be successfully treated with surgery alone. Although well tolerated by most patients with cancer, those with breast cancer experience moist desquamation as early adverse skin reactions or toxicities during and up to 6 weeks after RT, 31% with intensity-modulated RT, and 48% with standard treatment.[5] The breast remains tender to palpation and the skin hyperpigmented for 6 to 9 months after treatment. The most common permanent effects in normal tissue are minor changes in the aesthetic appearance of the breast that results from volume loss, fibrosis, or retraction at the tumor bed site.[6-9] Breast or chest

ASSOCIATED CONTENT

Appendix
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wall pain, increased risk of rib fracture, increased risk of cardiac morbidity, and lymphedema also are known late adverse effects of radiation.[10-12]

Inflammation may play a critical role in RT-induced skin toxicities because RT has been observed to induce changes in proinflammatory, profibrotic, proangiogenic, and stem-cell–mobilizing cytokines as well as in growth factors that may contribute to normal tissue toxicities or tumor control.[13,14] C-reactive protein (CRP), an inflammatory biomarker, has been associated with vascular atherosclerosis, insulin resistance, type 2 diabetes mellitus, and cancer.[15-17] CRP levels have been associated with fatigue and sleep quality in patients with breast cancer and with RT-induced mucositis in patients with head and neck cancer.[18-20] Furthermore, CRP has prognostic value in patients with breast cancer, locoregionally advanced laryngeal carcinoma, and advanced esophageal cancer.[16,21-23] In a pilot study of 159 patients with breast cancer who underwent RT, we have shown that high-sensitivity CRP (hsCRP) predicts RT-induced skin toxicities.[24] To the best of our knowledge, the current study is the largest to investigate hsCRP and RT-induced skin toxicities in a multiracial/ethnic breast cancer population.

PATIENTS AND METHODS

Study Design

We used the plasma samples/data from 1,000 patients with breast cancer recruited through the National Cancer Institute–funded Wake Forest University Community Clinical Oncology Program Research Base during the period from October 31, 2011, through June 4, 2013. Each patient completed a self-administered questionnaire with demographic information, self-reported race and ethnicity, and smoking history/status. We also extracted clinical data from pathology reports and medical records. Blood samples (20 mL) were collected from each participant before the initiation of RT (pre-RT) and immediately after completion of the last RT (post-RT). The blood samples were processed within 24 hours of phlebotomy, and plasma was stored at −80°C until assay. This study was approved by the institutional review board at each participating site. After receiving a detailed description of the study protocol, signed informed consent was obtained from each participant.

Patient Population

The inclusion criteria were female sex; new diagnosis of breast carcinoma (stage 0 to IIIA); post-lumpectomy, -quadrantectomy, or -mastectomy; plan to receive adjuvant RT to the whole breast or chest wall with or without regional lymph nodes (total dose ≥ 40 Gy, dose per fraction ≥ 1.8 Gy), use of two-dimensional, three-dimensional, conformal, or intensity-modulated RT; ability and willingness to sign the protocol consent form; age ≥ 18 years; white, black/African American (AA), Asian/Native Hawaiian/Pacific Islander, and Native American or Alaskan race; and Hispanic and non-Hispanic ethnicity.

Patients were allowed to receive adjuvant hormonal therapy and/or targeted therapies, such as trastuzumab, before, during, and/or after RT. The exclusion criteria were stage IIIB/C disease, prior radiation to the involved breast or chest wall, concurrent chemotherapy, immediate breast reconstruction after mastectomy, partial breast irradiation, planned use of skin-sparing intensity-modulated RT to treat the involved breast or chest wall, inability or unwillingness to sign informed consent, and inability to speak English or Spanish.

RT and Skin Toxicity Assessment

Patients with breast cancer usually begin RT approximately 4 to 6 weeks after surgery or completion of chemotherapy. RT to the whole breast/chest wall was given using standard opposed tangential fields alone or to the whole breast/chest wall plus regional lymph nodes at the treating physician's discretion. In general, patients received 10 to 33 fractions of 1.8 to 3.85 Gy for 3 to 7 weeks, depending on the fractionation scheme delivered to the whole breast/chest wall, with or without regional nodes. Skin toxicity was assessed by the treating physician at the completion of the last RT using the Oncology Nursing Society (ONS) skin toxicity scale as described previously.[25-27] The ONS skin toxicity scale separates grade 2 as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3) into three subcategories to capture more detailed information. It divides skin reactions into seven categories: 0, no changes noted; 1, faint or dull erythema and/or follicular reaction and/or itching; 2, bright erythema and/or tender to touch; 3, dry desquamation with or without erythema; 4, small or moderate amount of wet desquamation; 5, confluent moist desquamation; and 6, ulceration, hemorrhage, and/or necrosis.

hsCRP Assay

Plasma hsCRP levels were measured using the HS-CRP ELISA kit (Calbiotech, Spring Valley, CA) as described previously.[24] Briefly, frozen plasma samples were thawed and centrifuged. The supernatant was diluted and added to duplicate CRP-coated wells, and the enzyme conjugate was added. After a 1-hour incubation, the unbound mixture was removed and the wells washed three times. The plate was blotted and substrate added, and the plate was incubated for 15 minutes at room temperature before the addition of 50 μL stop solution. The absorbance at 450 mm was determined using the Safire microplate reader (Tecan US, Morrisville, NC). The standard curve was generated with each batch of samples to interpolate CRP levels. The average coefficient of variation of duplicate samples was 8.3%, and the interassay variation was < 10%. We always reran samples that were outside the standard curve range by adjusting the dilution ratio to ensure that all study samples were within the linear range of the standard curve.

Statistical Analysis

χ^2 and Fisher's exact tests were used to evaluate racial differences in patient demographics, clinical characteristics, and RT-induced skin toxicities. Analysis of variance was used to determine whether CRP log-transformed data, either at pre- or post-RT, differed by categories of demographic and clinical variables. Unadjusted logistic regression was used to determine whether hsCRP was associated with grade 3+ or grade 4+ post-RT skin toxicity. hsCRP was categorized into quartiles, and a linear tread was used to assess the association. Multivariable logistic regression was used to test whether pre-RT hsCRP (≥ 3.88 v < 3.88 mg/L), post-RT hsCRP (≥ 4.11 v < 4.11 mg/L), or hsCRP change (≥ 0.1 v < 0.1 mg/L [post-RT − pre-RT]) were significantly associated with grade 3+ or 4+ post-RT skin toxicity after adjustment for age, body mass index (BMI), race, ethnicity, diabetes, mastectomy, tumor stage, lymph node RT, prior chemotherapy, RT dose, and RT fractionation. Odds ratios (ORs) and 95% CIs were reported. All statistical analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC), and test results were considered significant at the two-sided 5% level.

RESULTS

Patient Population

As listed in Table 1, the study population comprised 623 white, 280 AA, 64 Asian/Pacific Islander, and 33 other race participants. No significant racial differences were observed for diabetes, current smoking status, tumor stage, progesterone receptor

Table 1. Patient Demographic and Clinical Characteristics by Race/Ethnicity

Characteristic	Patients by Race, No. (%)					
	Total (N = 1,000)	White (n = 623)	AA (n = 280)	ASPI (n = 64)	Other (n = 33)	*P*
Ethnicity						**< .001**
Hispanic	241 (24)	218 (35)	3 (1)	2 (3)	18 (55)	
Not Hispanic	759 (76)	405 (65)	277 (99)	62 (97)	15 (45)	
Age, years						
Median (range)	58.4 (23-88)	59.4 (29-88)	57.9 (23-85)	54.3 (31-77)	52.7 (30-75)	**< .001**
≥ 60	446 (45)	299 (48)	117 (42)	21 (33)	9 (27)	**.010**
Menopausal status						**.024**
Pre	180 (18)	98 (16)	56 (20)	16 (25)	10 (30)	
Peri	106 (11)	64 (10)	27 (10)	12 (19)	3 (9)	
Post	714 (71)	461 (74)	197 (70)	36 (56)	20 (61)	
BMI, kg/m^2						**< .001**
Median (range)	29.7 (17.3-58.6)	28.9 (17.3-57.2)	31.8 (18.6-58.6)	26.0 (18.1-55.5)	30.2 (21.0-44.3)	
Underweight to normal (< 25)	216 (22)	158 (25)	28 (10)	25 (39)	5 (15)	
Overweight (25-30)	311 (31)	203 (33)	74 (26)	24 (38)	10 (30)	
Obese (≥ 30)	473 (47)	262 (42)	178 (64)	15 (23)	18 (55)	
Diabetes						.163
No	805 (81)	512 (82)	217 (78)	53 (83)	23 (70)	
Yes	194 (19)	111 (18)	62 (22)	11 (17)	10 (30)	
Hypertension						**.001**
No	534 (53)	357 (57)	121 (43)	37 (58)	19 (58)	
Yes	465 (47)	266 (43)	158 (57)	27 (42)	14 (42)	
Smoking history						**.004**
No	635 (64)	380 (62)	179 (66)	54 (84)	22 (67)	
Yes	350 (36)	235 (38)	94 (34)	10 (16)	11 (33)	
Current smoker						.350
No	901 (91)	563 (91)	250 (91)	61 (95)	27 (84)	
Yes	86 (9)	53 (9)	25 (9)	3 (5)	5 (16)	
Estrogen receptor						**.008**
Negative	181 (18)	95 (15)	65 (23)	11 (17)	10 (30)	
Positive	813 (82)	525 (85)	212 (77)	53 (83)	23 (70)	
Progesterone receptor						.192
Negative	276 (28)	159 (26)	89 (32)	17 (27)	11 (33)	
Positive	714 (72)	460 (74)	186 (68)	46 (73)	22 (67)	
HER2						.716
Negative	693 (83)	443 (84)	185 (81)	41 (80)	24 (80)	
Positive	141 (17)	83 (16)	42 (19)	10 (20)	6 (20)	
TNBC						**< .001**
No	860 (88)	552 (91)	228 (84)	57 (92)	23 (72)	
Yes	114 (12)	56 (9)	44 (16)	5 (8)	9 (28)	
Tumor stage						.054
0	204 (20)	121 (19)	63 (23)	16 (25)	4 (12)	
I	443 (44)	298 (48)	111 (40)	22 (34)	12 (36)	
II	280 (28)	167 (27)	78 (28)	20 (31)	15 (45)	
IIIA	73 (7)	37 (6)	28 (10)	6 (9)	2 (6)	
Breast surgery						
Lumpectomy	883 (88)	559 (90)	243 (87)	53 (83)	28 (85)	.251
Mastectomy	101 (10)	55 (9)	32 (11)	10 (16)	4 (12)	.267
Quadrantectomy	17 (2)	10 (2)	5 (2)	1 (2)	1 (3)	.720
Planned radiation						
Whole breast	910 (91)	575 (92)	251 (90)	55 (86)	29 (88)	.231
Chest wall	100 (10)	52 (8)	33 (12)	11 (17)	4 (12)	.081
Regional nodes	119 (12)	61 (10)	41 (15)	11 (17)	6 (18)	.055
Prior chemotherapy (yes)	401 (40)	232 (37)	126 (45)	27 (42)	16 (48)	.111
RT fractionation						.402
Standard (6 weeks)	863 (86)	539 (87)	236 (84)	59 (92)	29 (88)	
Hypo (3 weeks)	137 (14)	84 (13)	44 (16)	5 (8)	4 (12)	
Mean RT dose, Gy (SD)	58.8 (5.48)	58.8 (5.76)	58.9 (5.20)	59.3 (4.40)	58.9 (3.94)	.940

NOTE. Boldface indicates significance at $P < .05$.
Abbreviations: AA, African American; ASPI, Asian/Pacific Islander; BMI, body mass index; HER2, human epidermal growth factor receptor 2; RT, radiotherapy; SD, standard deviation; TNBC, triple-negative breast cancer.

status, human epidermal growth factor receptor 2 status, lumpectomy, mastectomy, RT treatment (ie, fractionation, dose, fractions), or prior chemotherapy. However, significant racial differences existed in ethnicity, age, menopausal status, BMI, hypertension, smoking history, estrogen receptor status, and triple-negative breast cancer status.

Table 2. RT-Induced Grade 3+ or 4+ Skin Toxicity by Demographic and Clinical Characteristics

Variable and Category	No. of Patients	Grade 3+ Skin Toxicity		Grade 4+ Skin Toxicity	
		No. (%)	*P*	No. (%)	*P*
Total No. of patients	979	415 (42)		151 (15)	
Race					
White	617	239 (39)	**.006**	96 (16)	.749
AA	268	127 (47)		44 (16)	
ASPI	61	28 (46)		7 (11)	
Other	33	21 (64)		4 (12)	
Ethnicity					
Hispanic	237	97 (41)	.601	35 (15)	.748
Not Hispanic	742	318 (43)		116 (16)	
Age ≥ 60 years					
No	544	258 (47)	**< .001**	89 (16)	.364
Yes	435	157 (36)		62 (14)	
Menopausal status					
Pre	176	95 (54)	**.001**	26 (15)	.796
Peri	102	49 (48)		18 (18)	
Post	701	271 (39)		107 (15)	
BMI					
Normal	213	66 (31)	**< .001**	16 (8)	**< .001**
Overweight	304	117 (38)		31 (10)	
Obese	462	232 (50)		104 (23)	
Diabetes					
No	789	328 (42)	.291	110 (14)	**.009**
Yes	190	87 (46)		41 (22)	
Hypertension					
No	522	212 (41)	.229	81 (16)	.931
Yes	457	203 (44)		70 (15)	
Smoking history					
No	621	269 (43)	.397	100 (16)	.338
Yes	348	141 (41)		48 (14)	
Current smoker					
No	885	376 (42)	.911	138 (16)	.688
Yes	86	36 (42)		12 (14)	
Estrogen receptor					
Negative	176	75 (43)	.985	29 (16)	.698
Positive	797	339 (43)		122 (15)	
Progesterone receptor					
Negative	269	105 (39)	.174	39 (14)	.638
Positive	700	307 (44)		110 (16)	
HER2					
Negative	679	276 (41)	**.024**	104 (15)	.138
Positive	137	70 (51)		28 (20)	
TNBC					
No	843	360 (43)	.882	132 (16)	.910
Yes	112	47 (42)		18 (16)	
Tumor stage					
0	201	90 (45)	**< .001**	22 (11)	**< .001**
I	436	152 (35)		55 (13)	
II	273	132 (48)		54 (20)	
IIIA	69	41 (59)		20 (29)	
Mastectomy					
No	882	359 (41)	**.001**	129 (15)	**.037**
Yes	97	56 (58)		22 (23)	
RT whole breast					
No	87	51 (59)	**.001**	19 (22)	.083
Yes	892	364 (41)		132 (15)	
RT chest wall					
No	882	358 (41)	**.001**	130 (15)	.074
Yes	97	57 (59)		21 (22)	
RT regional nodes					
No	862	348 (40)	**.001**	124 (14)	**.015**
Yes	117	67 (57)		27 (23)	
Prior chemotherapy					
No	588	231 (39)	**.016**	71 (12)	**< .001**
Yes	391	184 (47)		80 (20)	

(continued on following page)

Table 2. RT-Induced Grade 3+ or 4+ Skin Toxicity by Demographic and Clinical Characteristics (continued)

Variable and Category	No. of Patients	Grade 3+ Skin Toxicity		Grade 4+ Skin Toxicity	
		No. (%)	*P*	No. (%)	*P*
RT fractionation					
Standard	843	402 (48)	**< .001**	144 (17)	**< .001**
Hypo	136	13 (10)		7 (5)	
RT dose, Gy					
≤ 50.00	86	10 (12)	**< .001**	3 (3)	**.003**
50.01-60.00	317	128 (40)		58 (18)	
> 60.00	540	269 (50)		88 (16)	

NOTE. Boldface indicates significance at $P < .05$.
Abbreviations: AA, African American; ASPI, Asian/Pacific Islander; BMI, body mass index; HER2, human epidermal growth factor receptor 2; RT, radiotherapy; TNBC, triple-negative breast cancer.

RT-Induced Skin Toxicities by Demographic and Clinical Characteristics

Table 2 lists RT-induced ONS grade 3+ and 4+ skin toxicities by demographic and clinical characteristics. RT-induced grade 3+ and 4+ skin toxicities occurred in 42% and 15% of participants, respectively. Significantly lower percentages of white patients (39%) had grade 3+ skin toxicity, but no significant racial differences for grade 4+ skin toxicity were observed. Higher proportions of grade 3+ skin toxicity was observed in the following subgroups: age < 60 years, premenopausal, obese (BMI, ≥ 30 kg/m^2), human epidermal growth factor receptor 2 positive, advanced tumor stage, prior mastectomy, not whole-breast RT, chest wall RT, regional node RT, prior chemotherapy, standard fractionation, and higher RT doses. Higher proportions of grade 4+ skin toxicity were observed in patients who were obese and had diabetes, advanced tumor stage, prior mastectomy, RT to regional nodes, prior chemotherapy, standard fractionation, and higher RT doses.

hsCRP Levels by Demographic and Clinical Characteristics

Table 3 lists pre-RT, post-RT, and change in hsCRP levels by demographic and clinical characteristics. The hsCRP levels were highly skewed, so log-transformed data were used for the assessment of group differences. Pre-RT hsCRP levels differ significantly by race ($P < .001$), BMI categories ($P < .001$), diabetes ($P < .001$), and hypertension ($P < .001$). Post-RT hsCRP levels differ significantly by race ($P = .002$), BMI categories ($P < .001$), diabetes ($P < .001$), hypertension ($P < .001$), current smoking status ($P = .029$), and tumor stage ($P = .025$). A significant difference was found in the change of hsCRP by tumor stage only ($P = .019$).

Association Between RT-Induced Skin Toxicities and hsCRP

Table 4 lists the unadjusted association of ONS grade 3+ and grade 4+ RT-induced skin toxicities with quartiles of hsCRP levels. A significant association was found (P linear trend = .001) between increasing pre-RT hsCRP levels and ONS grade 4+ skin toxicity. Patients with the highest quartile of pre-RT hsCRP had a 2.45-fold (95% CI, 1.42- to 4.21-fold) elevated risk for grade 4+ skin toxicity. For post-RT hsCRP, a significant association existed between increasing hsCRP levels and both grade 3+ (P linear trend < .001) and 4+ (P linear trend < .001) skin toxicities. For change in hsCRP, the association was significant for grade 4+ but not 3+ skin toxicity.

RT-Induced Skin Toxicities Associated With hsCRP and/or Obesity

BMI correlates with hsCRP and contributes to ONS grade 3+ or 4+ skin toxicity, so we ran models to determine whether hsCRP was associated with skin toxicities after adjustment for BMI (Table 5). In addition to BMI, results were adjusted for age, race, ethnicity, tumor stage, diabetes, mastectomy, lymph node RT, prior chemotherapy, RT dose, and RT fractionation. Obesity was significantly associated with RT-induced ONS grade 3+ and 4+ skin toxicities after adjustment for pre-RT, post-RT, and change in hsCRP and other covariates, with ORs between 1.6 and 1.8 for grade 3+ skin toxicity and between 2.2 and 2.5 for grade 4+ skin toxicity. Patients with above-median post-RT hsCRP levels had a significantly higher risk for both grade 3+ (OR, 1.46; 95% CI, 1.08 to 1.98) and 4+ (OR, 1.61; 95% CI, 1.07 to 2.44) skin toxicities after adjustment for obesity and other factors. Grade 4+ skin toxicity was significantly associated with obesity (OR, 2.17; 95% CI, 1.41 to 3.34), post-RT hsCRP ≥ 4.11 mg/L (OR, 1.61; 95% CI, 1.07 to 2.44), and both factors combined (OR, 3.65; 95% CI, 2.18 to 6.14). Above-median change in hsCRP (OR, 2.80; 95% CI, 1.42 to 5.54) was significantly associated with grade 4+ skin toxicity in nonobese but not in obese patients. Change in hsCRP was not associated with grade 3+ skin toxicity. We also performed subgroup analyses for specific races or race/ethnicity combinations (Data Supplement) and found a minimal association between obesity and CRP on grade 3+ skin toxicity for AA and Hispanic white patients. The strongest association was observed in non-Hispanic white patients. With limited sample size, we observed similar racial/ethnic differences for grade 4+ skin toxicity.

DISCUSSION

Postoperative adjuvant RT significantly reduces locoregional recurrence and improves survival.[28,29] Thus, there has been increasing use of adjuvant RT in patients with early-stage breast

Table 3. hsCRP Levels by Demographic and Clinical Characteristics

Variable and Category	Pre-RT hsCRP, mg/L				Post-RT hsCRP, mg/L				Change of hsCRP by RT, mg/L			
	No.	Mean	SD	*P*	No.	Mean	SD	*P*	No.	Mean	SD	*P*
All	976	6.05	6.17		946	6.32	7.07		932	0.28	5.60	
Race												
White	608	5.97	6.26	**< .001**	591	6.22	6.75	**.002**	582	0.23	5.12	.514
AA	272	6.89	6.32		264	7.14	8.23		260	0.33	6.94	
ASPI	63	3.30	4.39		59	4.10	4.78		58	1.00	3.40	
Other	33	5.95	4.33		32	5.45	4.95		32	−0.54	4.92	
Ethnicity												
Hispanic	235	6.29	6.51	.175	221	6.48	7.65	.589	219	0.10	6.72	.633
Not Hispanic	741	6.97	6.06		725	6.27	6.89		713	0.33	5.21	
Age ≥ 60 years												
No	543	6.12	6.22	.933	526	6.49	7.35	.732	519	0.35	5.58	.847
Yes	433	5.96	6.11		420	6.11	6.70		413	0.19	5.62	
Menopausal status												
Pre	178	5.48	5.28	.311	177	5.61	5.20	.254	175	0.20	3.32	.471
Peri	105	6.12	6.26		100	6.19	7.35		100	0.10	6.93	
Post	693	6.19	6.36		669	6.52	7.44		657	0.33	5.86	
BMI												
Normal	210	2.85	4.05	**< .001**	201	2.86	4.04	**< .001**	197	0.12	4.49	.675
Overweight	306	5.11	5.66		298	5.07	6.15		295	0.02	5.84	
Obese	460	8.13	6.51		447	8.70	7.83		440	0.52	5.88	
Diabetes												
No	786	5.66	5.74	**< .001**	763	5.93	6.74	**< .001**	752	0.30	5.83	.749
Yes	190	7.68	7.49		183	7.93	8.14		180	0.21	4.51	
Hypertension												
No	517	4.94	5.14	**< .001**	506	5.17	5.30	**< .001**	497	0.21	4.27	.125
Yes	459	7.30	6.94		440	7.64	8.49		435	0.36	6.81	
Smoking history												
No	624	5.82	5.66	.427	603	5.89	6.58	.114	595	0.08	5.68	.217
Yes	341	6.48	7.02		335	7.02	7.85		329	0.58	5.36	
Current smoker												
No	882	6.00	6.22	.116	859	6.25	7.22	**.029**	845	0.25	5.78	.542
Yes	85	6.82	5.73		81	7.21	5.48		81	0.60	3.56	
Estrogen receptor												
Negative	177	6.58	6.73	.289	170	7.08	8.52	.338	167	0.54	6.20	.298
Positive	793	5.94	6.05		770	6.12	6.70		759	0.19	5.42	
Progesterone receptor												
Negative	267	6.21	6.43	.825	262	6.81	8.26	.649	255	0.69	6.49	.173
Positive	699	6.00	6.09		674	6.11	6.54		667	0.09	5.19	
HER2												
Negative	679	6.28	6.60	.993	657	6.41	7.26	.936	648	0.14	5.63	.494
Positive	136	5.58	4.85		130	6.26	7.96		129	0.66	7.03	
TNBC												
No	840	5.88	5.95	.078	815	6.09	6.63	.054	804	0.21	5.41	.191
Yes	110	7.62	7.75		106	8.32	9.95		103	0.66	7.00	
Tumor stage												
0	199	5.48	5.74	.430	196	5.40	4.85	**.025**	192	−0.05	4.44	**.019**
I	433	6.23	6.28		418	6.11	7.14		413	0.01	6.04	
II	273	6.07	6.43		266	6.78	7.24		262	0.55	4.56	
IIIA	71	6.48	5.55		66	8.46	10.31		65	1.90	8.58	
Mastectomy												
No	875	6.08	6.26	.859	855	6.34	7.20	.725	841	0.28	5.78	.539
Yes	101	5.77	5.27		91	6.13	5.69		91	0.26	3.55	
RT whole breast												
No	89	5.49	5.05	.753	80	6.01	5.62	.941	79	0.49	3.36	.299
Yes	887	6.11	6.27		866	6.35	7.19		853	0.26	5.76	
RT chest wall												
No	876	6.06	6.24	.717	856	6.30	7.19	.448	842	0.27	5.80	.743
Yes	100	5.98	5.48		90	6.45	5.88		90	0.34	3.20	
RT regional nodes												
No	858	6.06	6.25	.989	833	6.26	6.85	.775	820	0.21	5.34	.239
Yes	118	6.00	5.55		113	6.72	8.53		112	0.82	7.22	
Prior chemotherapy												
No	585	5.86	5.94	.329	570	5.89	5.91	.225	562	0.09	4.92	.108
Yes	391	6.34	6.50		376	6.97	8.50		370	0.57	6.49	

(continued on following page)

Table 3. hsCRP Levels by Demographic and Clinical Characteristics (continued)

Variable and Category	Pre-RT hsCRP, mg/L				Post-RT hsCRP, mg/L				Change of hsCRP by RT, mg/L			
	No.	Mean	SD	*P*	No.	Mean	SD	*P*	No.	Mean	SD	*P*
RT fractionation												
Standard	846	6.07	6.11	.438	816	6.38	7.24	.565	807	0.31	5.74	.743
Hypo	130	5.93	6.57		130	5.92	5.94		125	0.11	4.61	
RT dose, Gy												
≤ 50.00	84	6.70	7.18	.137	79	6.49	6.31	.340	77	0.03	4.49	.855
50.01-60.00	310	5.71	6.20		303	5.93	6.39		297	0.20	4.65	
> 60.00	538	6.17	6.07		530	6.44	7.08		525	0.27	5.69	

NOTE. Boldface indicates significance at $P < .05$.
Abbreviations: AA, African American; ASPI, Asian/Pacific Islanders; BMI, body mass index; HER2, human epidermal growth factor receptor 2; hsCRP, high-sensitivity C-reactive protein; RT, radiotherapy; SD, standard deviation; TNBC, triple-negative breast cancer.

cancer. However, RT is associated with skin toxicities and other late effects that negatively affect quality of life and prognosis of breast cancer survivors.[30,31] We evaluated whether the inflammatory biomarker hsCRP is associated with RT-induced skin toxicities. To the best of our knowledge, this study is the largest to date to report a significant association between RT-induced skin toxicities and post-RT hsCRP. Of note, above-median change in hsCRP was significantly associated with RT-induced grade 4+ skin toxicity among nonobese women.

The data show that AA patients are more likely to develop RT-induced grade 3+ skin toxicity, which is consistent with the results from a previous study that used a self-administered questionnaire to assess skin toxicities.[32] In the current study, radiation oncologists used the well-established ONS grading system for RT-induced skin toxicities, which may present a more consistent and objective evaluation of skin toxicities. Patients with elevated post-RT hsCRP experienced an increase in RT grade 4+ skin toxicity, even after adjusting for BMI and other factors. This is supported by a previous study in which expression of human CRP in mice was associated with upregulation of the transforming growth factor-β/Smad3 signaling pathway, which has been associated with RT-induced fibrosis or moist desquamation of the skin.[33] Other risk factors, particularly obesity, have been related to skin toxicities and late effects,[26,27,34] which could be due to dosimetric variation across the breast related to skin folding in patients with a higher BMI. Similarly, we reported an association between obesity and RT-induced skin toxicities.

The CRP level in normal human serum ranges from 0.2 to 10 mg/L; 90% of apparently healthy individuals have CRP levels < 3 mg/L, and only 1% have levels > 10 mg/L. In this study, 22% and 23% of patients had pre-RT and post-RT hsCRP ≥ 10 mg/L, respectively (data not shown). We also observed that a higher proportion of AA patients had hsCRP ≥ 10 mg/L at both pre-RT (27%) and post-RT (27%), which is consistent with previous findings that reported higher hsCPR levels in AA compared with white, Chinese, and Japanese patients in a multiethnic study of women without cardiovascular disease.[35,36] Furthermore, in multiple inflammatory cytokine polymorphisms, AA populations have a higher frequency of cytokine variants responsible for the regulation of immune/inflammatory responses.[37-39] Similarly, we report that AA patients had higher pre-RT and post-RT hsCRP levels than white patients. Another consideration is that racial differences in skin

Table 4. Association Between hsCRP and RT-Induced Grade 3+ or 4+ Skin Toxicity

hsCRP, mg/L in Quartiles	No.	Grade 3+ Skin Toxicity			Grade 4+ Skin Toxicity		
		No. (%)	OR (95% CI)	*P**	No. (%)	OR (95% CI)	*P**
Pre-RT							
< 1.37	242	98 (40)	Referent		22 (9)	Referent	
≥ 1.37 to < 3.88	237	89 (38)	0.88 (0.61 to 1.28)		36 (15)	**1.79 (1.02 to 3.15)**	
≥ 3.88 to < 9.10	241	113 (47)	1.30 (0.91 to 1.86)		43 (18)	**2.17 (1.26 to 3.76)**	
≥ 9.10	239	110 (46)	1.25 (0.87 to 1.80)	.070	47 (20)	**2.45 (1.42 to 4.21)**	**.001**
Post-RT							
< 1.42	235	87 (37)	Referent		22 (9)	Referent	
≥ 1.42 to < 4.11	235	83 (35)	0.93 (0.64 to 1.35)		25 (11)	1.15 (0.63 to 2.11)	
≥ 4.11 to < 9.21	235	111 (47)	**1.52 (1.05 to 2.20)**		39 (17)	**1.93 (1.10 to 3.36)**	
≥ 9.21	234	119 (51)	**1.76 (1.22 to 2.55)**	**< .001**	56 (24)	**3.05 (1.79 to 5.18)**	**< .001**
Change by RT							
< −1.06	231	98 (42)	Referent		30 (13)	Referent	
≥ −1.06 to < 0.10	231	92 (40)	0.90 (0.62 to 1.30)		28 (12)	0.92 (0.53 to 1.60)	
≥ 0.10 to < 1.57	232	95 (41)	0.94 (0.65 to 1.36)		33 (14)	1.11 (0.65 to 1.89)	
≥ 1.57	231	112 (48)	1.28 (0.89 to 1.84)	.185	50 (22)	**1.85 (1.13 to 3.04)**	**.008**

NOTE. Boldface indicates significance at $P < .05$.
Abbreviations: hsCRP, high-sensitivity C-reactive protein; OR, odds ratio; RT, radiotherapy.
**P* for linear trend.

Table 5. RT-Induced Grade 3+ or 4+ Skin Toxicity Associated With hsCRP and/or Obesity

BMI, kg/m^2	hsCRP, mg/L	No.	Grade 3+ Skin Toxicity			Grade 4+ Skin Toxicity		
			No. (%)	OR (95% CI)	*P*	No. (%)	OR (95% CI)	*P*
Pre-RT								
< 30	NA	508	182 (36)	Referent		47 (9)	Referent	
≥ 30	NA	451	228 (51)	**1.77 (1.31 to 2.39)**	**< .001**	101 (22)	**2.42 (1.60 to 3.67)**	**< .001**
NA	< 3.88	479	187 (39)	Referent		58 (12)	Referent	
NA	≥ 3.88	480	223 (46)	1.10 (0.82 to 1.48)	.513	90 (19)	1.23 (0.83 to 1.81)	.307
< 30	< 3.88	331	120 (36)	Referent		28 (8)	Referent	
< 30	≥ 3.88	177	62 (35)	0.94 (0.62 to 1.42)	.763	19 (11)	1.31 (0.70 to 2.47)	.395
≥ 30	< 3.88	148	67 (45)	1.49 (0.97 to 2.29)	.071	30 (20)	**2.56 (1.43 to 4.58)**	**.002**
≥ 30	≥ 3.88	303	161 (53)	**1.95 (1.37 to 2.77)**	**< .001**	71 (23)	**3.01 (1.83 to 4.94)**	**< .001**
Post-RT								
< 30	NA	496	178 (36)	Referent		45 (9)	Referent	
≥ 30	NA	443	222 (50)	**1.58 (1.16 to 2.15)**	**.004**	97 (22)	**2.17 (1.41 to 3.34)**	**< .001**
NA	< 4.11	470	170 (36)	Referent		47 (10)	Referent	
NA	≥ 4.11	469	230 (49)	**1.46 (1.08 to 1.98)**	**.014**	95 (20)	**1.61 (1.07 to 2.44)**	**.024**
< 30	< 4.11	333	111 (33)	Referent		24 (7)	Referent	
< 30	≥ 4.11	163	67 (41)	1.45 (0.95 to 2.20)	.084	21 (13)	**1.93 (1.03 to 3.63)**	**.040**
≥ 30	< 4.11	137	59 (43)	1.56 (0.99 to 2.44)	.053	23 (17)	**2.59 (1.38 to 4.87)**	**.003**
≥ 30	≥ 4.11	306	163 (53)	**2.30 (1.62 to 3.27)**	**< .001**	74 (24)	**3.65 (2.18 to 6.14)**	**< .001**
Change by RT								
< 30	NA	489	177 (36)	Referent		45 (9)	Referent	
≥ 30	NA	436	220 (50)	**1.82 (1.36 to 2.43)**	**< .001**	96 (22)	**2.54 (1.69 to 3.83)**	**< .001**
NA	< 0.10	462	190 (41)	Referent		58 (13)	Referent	
NA	≥ 0.10	463	207 (45)	1.14 (0.86 to 1.52)	.356	83 (18)	1.40 (0.96 to 2.05)	.079
< 30	< 0.10	249	83 (33)	Referent		13 (5)	Referent	
< 30	≥ 0.10	240	94 (39)	1.35 (0.91 to 2.01)	.138	32 (13)	**2.80 (1.42 to 5.54)**	**.003**
≥ 30	< 0.10	213	107 (50)	**2.16 (1.43 to 3.25)**	**< .001**	45 (21)	**4.76 (2.44 to 9.28)**	**< .001**
≥ 30	≥ 0.10	223	113 (51)	**2.07 (1.38 to 3.10)**	**< .001**	51 (23)	**4.63 (2.39 to 8.96)**	**< .001**

NOTE. Boldface indicates significance at $P < .05$.
Abbreviations: BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; NA, not applicable; OR, odds ratio; RT, radiotherapy.

toxicities may be attributed to multiple genetic risk factors. For example, racial/ethnic differences in RT-induced skin reactions in *ATM* variant carriers (17% Hispanic, 23% AA, and 8% white patients) have been found.[40,41] Therefore, genetic studies are warranted to elucidate the contribution of genetic variants in racial/ethnic differences of RT-induced skin toxicities.

Radiation sensitivity is a complex and inherited polygenic trait with many genes in multiple biologic pathways.[41-47] Previous studies have suggested that RT-induced changes in proinflammatory cytokines and growth factors may contribute to normal tissue toxicities.[13,14] However, whether tumor or skin was the source of circulating CRP is questionable. A recent study demonstrated that CRP deposition was found on the basal keratinocyte membrane in normal human skin, and skin inflammation may be regulated by CRP modulation of keratinocytes.[48] The current data provide evidence that a plasma inflammatory biomarker, hsCRP, is associated with RT-induced skin toxicities in patients with breast cancer who undergo RT. These findings have several clinical implications. First, elevated plasma hsCRP has been associated with cancer prognosis, vascular atherosclerosis, insulin resistance, and type 2 diabetes mellitus that also may affect overall survival. Therefore, patients with elevated post-RT hsCRP levels should be actively monitored for various medical conditions that may affect overall survival. Second, with consideration of the involvement of CRP in fatigue and prognosis of patients with breast cancer, a future follow-up study will focus on monitoring CRP levels, quality of life, and clinical outcomes. Third, growing evidence suggests that serum CRP is positively associated with sugar intake and negatively associated with dietary intakes of minerals, vitamins, and polyunsaturated fatty acids.[49] Therefore, CRP concentrations can be modulated by dietary intake, and dietary modification may provide a promising intervention strategy for risk reduction. Finally, we observed that above-median change in hsCRP was significantly associated with RT-induced grade 4+ skin toxicity only in nonobese patients. Of note, a recent study showed that prediagnosis hsCRP levels are not associated with postmenopausal breast cancer incidence or survival; however, increased risks may be found among leaner women.[23] Because CRP and BMI are highly correlated, breast cancer risk associated with CRP may be masked by obesity but not in nonobese patients.[24]

This study had several strengths and limitations. First, we used a prospective study design that is particularly suitable to conduct a comprehensive evaluation of biomarkers and RT-induced skin toxicities. We collected biologic samples from patients over time and recorded clinician-reported skin toxicities on the last day of RT to minimize recall bias, which provides more-precise estimates of biomarkers and skin toxicities. Second, this study is the largest to date of racial/ethnic differences in RT-induced skin toxicities among patients with breast cancer. Third, we are currently evaluating genome-wide single nucleotide polymorphisms in building predictive models of hsCRP in RT-induced skin toxicities. The first limitation is that the study design mainly focused on RT-induced early skin toxicities, and whether

hsCRP can predict late effects, such as fibrosis, is unclear. A long-term follow-up study is needed to assess RT-related late effects. Second, although we had a large sample size for evaluating hsCRP in RT-induced skin toxicities, the results must be validated externally in other study populations. If validated, these results pave the way for testing anti-inflammatory agents in reducing RT-induced skin toxicities.[50] Third, only 45 patients had a grade 4+ skin toxicity (Table 5); therefore, spurious significant findings are a possible limitation. Finally, lack of ancestry analysis needs to be addressed in the future.

In summary, the current results validate a previous report on the association between hsCRP and RT-induced skin toxicities in patients with breast cancer.[24] More importantly, we demonstrate for the first time that nonobese patients with elevated changes in hsCRP level have a significantly increased risk of grade 4+ skin toxicity. Therefore, these data demonstrate the association between inflammatory response and RT-induced skin toxicities.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Association Between Inflammatory Biomarker C-Reactive Protein and Radiotherapy-Induced Early Adverse Skin Reactions in a Multiracial/Ethnic Breast Cancer Population

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Appendix

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