Published in final edited form as:

Breast Cancer Res Treat. 2016 August ; 159(1): 119–129. doi:10.1007/s10549-016-3913-x.

Race/ethnicity, genetic ancestry, and breast cancer-related lymphedema in the Pathways Study

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Abstract

Breast cancer-related lymphedema (BCRL) is a serious chronic condition after breast cancer (BC) surgery and treatment. It is unclear if BCRL risk varies by race/ethnicity. In a multiethnic prospective cohort study of 2953 BC patients, we examined the association of self-reported BCRL status with self-reported race/ethnicity and estimated genetic ancestry. Hazard ratios (HR) and 95 % confidence intervals (CI) were calculated by multivariable Cox proportional hazards models, with follow-up starting 6 months post-BC diagnosis. Estimates were further stratified by body mass index (BMI). By 48 months of follow-up, 342 (11.6 %) women reported having BCRL. Younger age at BC diagnosis, higher BMI at baseline, and lower physical activity were associated with greater BCRL risk. African American (AA) women had a 2-fold increased risk of BCRL compared with White women (HR = 2.04; 95 % CI 1.35–3.08). African genetic ancestry was also associated with an increased risk (HR = 2.50; 95 % CI 1.43, 4.36). Both risks were attenuated but remained elevated after adjusting for known risk factors and became more pronounced when restricted to the nonobese women (adjusted HR = 2.31 for AA and HR = 3.70 for African ancestry, both $p < 0.05$). There was also evidence of increased BCRL risk with Hispanic ethnicity in the nonobese women. Nonobese AA women had a higher risk of BCRL than White women, which cannot be fully explained by known risk factors. This is the first large-scale, prospective study demonstrating differences in BCRL risk according to race/ethnicity as assessed by both self-report and genetic ancestry data, with a potential ancestry–obesity interaction.

Keywords

Breast cancer-related lymphedema; Racial disparity; Ancestry; Genetics; Obesity; Interaction

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Marilyn L. Kwan and Song Yao contributed equally to this work and are co-first authors.

Compliance with ethical standards: **Conflict of Interest** The authors declare that they have no conflict of interest.

Introduction

Breast cancer-related lymphedema (BCRL) is a serious chronic condition characterized by lymphatic fluid retention and subsequent tissue swelling, typically in one or both arms [1, 2]. Other symptoms include pain, heaviness, discomfort, and reduced mobility and function [3]. BCRL can occur in about 20 % of patients after breast cancer (BC) surgery and treatment [1, 4]. Elevated risk is associated with younger age, higher body mass index (BMI), and less physical activity [5].

Only a few prospective studies have examined racial/ethnic differences in BCRL risk [6–8], including our group which found a nearly twofold elevated risk among African Americans (AA) [6]. However, the other studies found no association after 40 [7] and 123 months of follow-up [8] with multivariable adjustment accounting for BMI, chemotherapy, and hypertension. To our knowledge, studies of patients' genetic background with BCRL risk have not been conducted. Given that race/ethnicity is a complex construct of sociodemographic, cultural, and genetic factors, the investigation of genetic heterogeneity in BCRL risk may not only affirm the differences in BCRL risk by self-reported race, but also disentangle potential genetic from nongenetic contributing factors.

We examined the associations of race/ethnicity and genetic ancestry with self-reported BCRL status in a cohort of 2953 breast cancer patients with up to four years of follow-up, and investigated interactions of self-reported race/ethnicity and genetic ancestry with obesity on BCRL status.

Methods

Study population

The Pathways Study is a prospective cohort of women with newly diagnosed, invasive breast cancer at Kaiser Permanente Northern California (KPNC). Recruitment was from January 2006 to May 2013 through rapid case ascertainment procedures [9]. Briefly, cases were identified through daily scanning of computerized pathology records for new patients with recently diagnosed invasive breast cancer. Participation was restricted to KPNC female members of at least 21 years of age who had no previous history of malignancy other than nonmelanoma skin cancer and spoke English, Spanish, Cantonese, or Mandarin. The study was approved by the Institutional Review Boards of KPNC and Roswell Park Cancer Institute (RPCI), and written informed consent was obtained from all participants.

Analyses presented here include 2953 women who completed the baseline interview, provided blood and/or saliva samples, and were eligible for the 48-month follow-up questionnaire as of September 2, 2014. Mean (standard deviation, SD) time from diagnosis to enrollment was 2.0 (± 0.7) months.

Data collection

To determine BCRL status, women were asked the following question on the 12-month follow-up questionnaire: "In the last 6 months, have you had lymphedema (Swelling of the arm and/or hand on the same side where you had your breast cancer surgery)?", and the date

of first being aware of the condition was recorded. Women were asked the same question, but referencing the previous 24 months, on the 48-month follow-up questionnaire.

At the baseline interview, sociodemographic and lifestyle information including race/ethnicity (White, AA, Hispanic, Asian, and Other) was asked by a trained interviewer. Height and weight were collected to calculate BMI (normal < 25 kg/m²; overweight 25–29 kg/m²; obese ≥ 30 kg/m²). Physical activity was assessed using a semiquantitative questionnaire to calculate metabolic equivalent (MET) hours/week of moderate–vigorous activity [10, 11].

Tumor and clinical characteristics were obtained from the KPNC Cancer Registry [12]. Information on breast surgery, adjuvant chemotherapy, radiation therapy, and hormonal therapy were collected from the KPNC Cancer Registry and KPNC electronic medical record.

History of comorbidities and hypertension at the time of breast cancer diagnosis was obtained from the KPNC electronic medical record and other data sources. Comorbidities were calculated using the Charlson comorbidity index [13].

Genetic ancestry

Germline DNA was available from blood or saliva samples collected around the time of the baseline interview the biospecimens were shipped to RPCI and processed under the auspices of the Data Bank and Biorepository, an RPCI Cancer Center Support Grant Shared Resource. Global genetic ancestry was estimated based on a validated panel of 124 ancestry informative markers (AIMs) selected and optimized by Kosoy et al. to distinguish continental origin in the major U.S. populations [14]. The AIMs were designed as part of a customized Illumina GoldenGate 1152-plex chip and genotyped at the RPCI Genomics Shared Resource. The ADMIXTURE program [15] was used to infer genetic ancestry, with ancestral genotype data from the same study that first developed the panel as controls in the estimation.

BCRL outcome

BCRL was considered as any event self-reported by the participant that was at least 6 months or more after the breast cancer diagnosis. This criterion was applied in order to minimize misclassification of BCRL as transient postoperative swelling due to the definitive breast cancer surgery.

Statistical analysis

Univariate analyses of patient and clinical characteristics between those with and without BCRL were conducted using Pearson Chi-square test for categorical variables or Satterthwaite *t* test for continuous variables. Associations of BCRL risk with patient factors were estimated by hazard ratios (HR) and 95 % confidence intervals (CI) from multivariable Cox proportional hazards models, with follow-up until the date of first self-reported BCRL, or the date of last follow-up questionnaire up to 48 months for those without BCRL. The estimated proportions of African, Asian, and Native American ancestry for each patient were

entered in the models as continuous variables, each with a range of 0–1, with European ancestry set as the default reference. Thus, the HRs for each of the three ancestries can be interpreted as the hazards of a “genetically pure” individual of the respective ancestry relative to a “genetically pure” individual of European ancestry.

Models were adjusted initially for education, household income, employment, American Joint Committee on Cancer (AJCC) stage, breast and lymph node surgery, number of lymph nodes examined, chemotherapy, and radiation therapy. The race/ethnicity and ancestry models were further adjusted for age at breast cancer diagnosis, baseline BMI, baseline physical activity, comorbidity, and hypertension, which are the recognized risk factors for BCRL. Finally, stratified analyses were conducted by obesity status (BMI < 30 vs. BMI ≥ 30 and BMI < 25 vs. BMI ≥ 25) to examine whether obesity modified the BCRL racial disparities. To test whether there was possible residual confounding by BMI after stratification, BMI was included in the multivariable models.

Based on the AIM genotypes, we identified outliers in each of the self-reported racial/ethnic populations using EIGENSOFT software [16, 17]. An individual who exceeded four standard deviations along the top three principal components was flagged as an outlier. Outliers were then excluded in sensitivity analyses for the genetic ancestry models.

Results

Mean (SD) time from enrollment to end of follow-up was 38.1 (±17.0) months. A total of 342 (11.6 %) women reported having BCRL up to 48 month follow-up, with 59.7 % White, 10.8 % AA, 12.0 % Hispanic, and 14.3 % Asian (Table 1). Compared to patients with no BCRL, those with BCRL were more likely to be AA (10.8 vs. 6.6 %) and had a nonsignificantly higher proportion of African ancestry (0.80 vs. 0.77). Other factors associated with greater BCRL risk included younger age at breast cancer diagnosis (mean 56 vs. 60 years), higher BMI at baseline (mean 30.6 vs. 28.0 kg/m²), and less moderate–vigorous physical activity at baseline (26.8 vs. 30.3 MET-hours/week). Similar to the BMI pattern, increasing waist-to-hip ratio (WHR) was associated with higher BCRL risk, although the trend across WHR categories was not statistically significant. BCRL was not associated with socioeconomic status (SES) factors, such as education, marital status, household income, and being employed at breast cancer diagnosis, or with lifestyle factors such as smoking and alcohol intake.

Several tumor and clinical characteristics were associated with BCRL risk (Table 2). More advanced stage at diagnosis, mastectomy, greater number of lymph nodes examined, greater number of positive lymph nodes, and chemotherapy were each associated with elevated risk ($p < 0.05$). Women who had no radiation therapy (69.3 %) compared with those who had radiation therapy (30.7 %) were more likely to report having BCRL ($p < 0.05$). Among patients who reported BCRL compared with those who did not, sentinel lymph node biopsy only (8.4 vs. 17.0 %) was less common, whereas axillary lymph node dissection only (19.3 vs. 16.8 %) or both (54.2 vs. 49.9 %) were more common ($p = 0.0013$).

In the unadjusted model, AA women had a twofold increased risk of BCRL compared with White women (HR = 2.04; 95 % CI: 1.35, 3.08) (Table 3), also shown in cumulative incidence curves (Fig. 1a). The increased risk was attenuated (HR = 1.60, 95 % CI 1.04, 2.47) in the base model after adjusting for standard covariates. Upon further adjustment for BCRL risk factors including age at BC diagnosis, baseline BMI, baseline physical activity, comorbidity, and hypertension, the association was further attenuated (HR = 1.47; 95 % CI 0.94, 2.30). Identification with other racial/ethnic groups was not associated with BCRL risk in the adjusted models, except for an increased risk in Hispanics (HR = 1.47; 95 % CI 1.00, 2.15), which was substantially attenuated after adjustment for covariates (HR = 1.18; 95 % CI 0.78, 1.77).

Consistent with self-reported race, African genetic ancestry was associated with an increased risk of BCRL in the unadjusted model (HR = 2.50; 95 % CI 1.43, 4.36), which was attenuated in the base model (HR = 1.93; 95 % CI 1.08, 3.43), relative to European ancestry. After further covariate adjustment, the association was again less striking (HR = 1.73, 95 % CI 0.96–3.14) (Table 3). Native American and Asian ancestries were not associated with BCRL risk compared with European ancestry.

In stratified models by obesity status at baseline (BMI < 30 kg/m² vs. ≥ 30 kg/m²), AA women who were nonobese had a statistically significant elevated risk of BCRL in all models (fully adjusted HR = 2.20; 95 % CI 1.16, 4.19) (Table 4; Fig. 1b). However, there was no association with BCRL among obese AA women (HR = 1.21; 95 % CI 0.65, 2.26) (Fig. 1c). Consistent with self-reported AA race, African ancestry was associated with an increased BCRL risk among the nonobese (fully adjusted HR = 3.51; 95 % CI 1.50, 8.21), but not among the obese (fully adjusted HR = 1.14; 95 % CI 0.49, 2.65). Similar to AA women but to a lesser extent, Hispanic women who were nonobese had a nearly twofold increased risk of BCRL (HR = 1.96; 95 % CI 1.22, 3.15) (Table 4; Fig. 1b), even after adjustment for covariates (HR = 1.59; 95 % CI 0.95, 2.66). No such association was observed in their obese counterparts (HR = 0.70; 95 % CI 0.35, 1.43). In unadjusted models among the nonobese women, Native American ancestry was associated with increased risk of BCRL. However, due to small sample size and low percentage of Native American ancestry present in the study population, the CI was very wide and the risk estimate was nonsignificant after adjustment for covariates. Neither self-reported Asian race/ethnicity nor Asian ancestry was associated with BCRL in either the obese or nonobese group.

When models were stratified by overweight status at baseline (BMI < 25 kg/m² vs. ≥ 25 kg/m²), the associations had a similar pattern of increased BCRL risk with self-reported AA race/ethnicity and African ancestry among the nonoverweight women (data not shown). When genetic ancestry outliers were excluded from the models of genetic ancestry ($n = 30$), the results remained the same (data not shown).

Discussion

In this prospective study of BCRL in 2953 women with breast cancer, we confirm the risk factors for BCRL from previous studies, including younger age at breast cancer diagnosis, higher BMI, and lower physical activity. Further, we report increased risks of BCRL among

patients who self-reported their race as AA, and a similar increased risk associated with estimated African genetic ancestry, both of which could not be entirely explained by known BCRL risk factors. Intriguingly, these increased risks of BCRL appeared only among the nonobese women at breast cancer diagnosis. No associations were observed among the corresponding obese groups. To our knowledge, this is the first study to comprehensively examine potential racial/ethnic differences in risk of BCRL using both self-reported race/ethnicity and genetic ancestry information, and to investigate the interaction between race and obesity.

We previously reported a twofold increased risk of BCRL among AA women in our study cohort [6]. However, that analysis included only the first 997 enrolled women, with mean follow-up time of 20.9 months (0.7–31.8) after breast cancer diagnosis. Our current study builds upon the original study by increasing the sample size ($n = 2953$), having a longer mean follow-up of 38.5 months since breast cancer diagnosis, and including genetic ancestry markers. Our previous study also differed from the current analysis in ascertainment of BCRL. Previously, a BCRL diagnosis was determined by clinical indication from outpatient or hospitalization diagnosis codes, outpatient procedure codes, and durable medical equipment orders. In the present study, we focused on BCRL as a patient-reported outcome because of potential limitations in accurately classifying BCRL diagnoses by diagnosis and treatment codes using electronic data sources [18]. We conducted a validation analysis of the patient's self-report and compared with medical chart review in our analytic cohort ($n = 200$). While sensitivity and negative predictive value (NPV) were 92 and 98 %, respectively, specificity and positive predictive value (PPV) were lower at 56 and 22 %, respectively (unpublished data). When comparing ICD-9 diagnosis codes for lymphedema against chart review, the sensitivity, specificity, PPV, and NPV were 67, 52, 16, and 92 %, respectively.

A principal strength of our current study is the investigation of genetic ancestry in parallel with self-reported race/ethnicity. For all risk estimates, those associated with African genetic ancestry were consistently stronger and more robust to adjustment for known BCRL risk factors than those with self-reported African American race/ethnicity. These findings not only confirm the elevated risk observed in self-reported AA women, but also suggest that the this racial disparity in BCRL risk might be due, in part, to biological differences.

Obesity might contribute to some of these biological differences, given that it is an established BCRL risk factor with differences in prevalence among AA and White women, 45 and 31 % in our study, respectively. There are also reported differences in the relationship of BMI with body composition between AA and White women. Specifically, AA women are more likely to have higher lean mass and lower fat [19], and lower visceral adipose tissue and higher subcutaneous adipose tissue for a given BMI compared with White women [20]. Furthermore, differences in levels of obesity-related circulating adipokines and inflammatory biomarkers have been reported in AA and White women after adjusting for BMI, with AA women having higher levels of leptin, C-reactive protein and interleukin-6, and lower levels of adiponectin [21]. Given that the lymphatic system is critical in management of inflammatory, immune function, and obesity processes [22], one could hypothesize that these varying levels of obesity-related biomarkers could be differentially

affecting the lymphatic vessels of AA and White women, contributing to our observed elevated BCRL risk in AA women.

However, when we examined the associations separately among the nonobese and obese women, BCRL risk was higher in the nonobese, but not in the obese AA women and those with African ancestry. This is counterintuitive to the fairly established association of greater BMI, especially $\geq 30 \text{ kg/m}^2$, being associated with increased risk of BCRL [5, 23–25]. Nevertheless, our findings are conceptually similar to an earlier study of smoking-related lung cancer, which demonstrated a significantly higher risk in AAs than in Whites only among light and moderate smokers, but not among heavy smokers [26]. Specifically, the race- and ancestry–environment interaction might be explained by a hypothesis that any racial differences due to genetic susceptibility, such as the aforementioned differences in obesity-related adipokines and inflammation among AA and White women, may only be apparent without the presence of strong environmental risk factors, such as heavy smoking in the lung cancer study, or obesity in our current BCRL study. However, when such risk factors are present and become the major causal factors, differences in genetic susceptibility may be saturated by those exposures. These findings emphasize the importance of gene–environment interactions in health-related disparities and suggest striking disparities could exist among populations considered to be at low risk (e.g., nonobese women for BCRL). Further research is needed to understand the underlying mechanisms of these processes.

However, obesity is unlikely the only factor contributing to the observed BCRL racial disparity. In a recent study, Togawa et al. showed that a 1.6-fold increased risk of BCRL in AA women was almost entirely eliminated after adjusting for BMI, hypertension, and treatment-related factors [8]. However, in our analyses, controlling for these and other risk factors attenuated but did not completely explain the elevated risk in AA women or with African ancestry. The elevated risk became even more pronounced among nonobese women when adjusting for all other risk factors.

The proportion of women reporting BCRL in our study (11.6 %) is somewhat lower than that reported in the literature (8.4–21.4 %) [4]. Misclassification of BCRL status is certainly possible; however, our analyses excluded any reported BCRL event within the first 6 months of breast cancer diagnosis to minimize misclassification due to postsurgical swelling. Although we assessed self-reported BCRL only up to 48 months after cancer diagnosis, it was recently reported that BCRL incidence primarily occurs within the first five years [8]. While we fully acknowledge that self-report should ideally be validated against physical measures such as perometry, bioimpedance, or arm circumference measures, our proportion of women reporting BCRL was in the range of what has been reported in the literature. Alternatively, given that sentinel lymph node biopsy (SLNB) use is associated with lower BCRL risk [4, 5, 27, 28], this difference could be attributed to more SLNB being done in our contemporary cohort compared with older cohorts prior to the full endorsement of SLNB as the preferred method of axillary staging from 2005 to 2007 [29–31]. Indeed, women in our cohort were diagnosed with breast cancer from 2005 to 2013, and 77 % had SLNB with or without axillary lymph node dissection, compared with 4 % [32], 48 % [33], and 64 % [25] in other studies.

Interestingly, notable racial/ethnic differences in use of SLNB were recently reported in a large Surveillance, Epidemiology, and End Results Program (SEER)—Medicare study from 2002 to 2007 [34]. AA breast cancer patients were less likely to undergo SLNB compared with their White counterparts (odds ratio = 0.67; 95 % CI 0.60–0.75), which contributed to a statistically significant difference in 5-year cumulative risk of BCRL in Whites (8.2 %) vs. AAs (12.3 %) ($p < 0.001$). However, in our analysis, we did account for the type of lymph node surgery received, and the increased risk of BCRL remained among AA and with African ancestry.

To conclude, in this prospective cohort study of 2953 women with breast cancer, AA women had a greater risk of self-reported BCRL compared to White women. Moreover, African genetic ancestry was also linked with an increased risk of BCRL compared to European ancestry. This increased risk appears to be most pronounced for those who were nonobese at the time of breast cancer diagnosis. When identifying who might be at higher BCRL risk in breast cancer survivors, race/ethnicity might also be considered, along with the more established risk factors of age, BMI, and surgery, to direct appropriate surveillance or teach risk reduction interventions to these higher risk groups.

Acknowledgments

The authors thank the office and field staff for data collection, processing, and preparation. The authors thank all the Pathways Study participants for their numerous contributions to this study. This work was supported by the National Cancer Institute at the National Institutes of Health (Grant Number: R01 CA105274 to L.H.K) and the American Cancer Society (Grant Number: RSG-06-209-01-LR to M.L.K). The Roswell Park Cancer Institute Data Bank and Biorepository and Genomics Shared Resource are supported by a National Cancer Institute Cancer Center Support Grant (Grant Number: P30 CA16056). The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the funding agencies.

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Abbreviations

AA	African American
AIM	Ancestry informative marker
AJCC	American Joint Committee on Cancer
BC	Breast cancer
BCRL	Breast cancer-related lymphedema
BMI	Body mass index
CI	Confidence interval
HR	Hazards ratio
KPNC	Kaiser Permanente Northern California
MET	Metabolic equivalent
RPCI	Roswell Park Cancer Institute

SD	Standard deviation
SEER	Surveillance, epidemiology, and end results program
SES	Socioeconomic status
SLNB	Sentinel lymph node biopsy
WHR	Waist-to-hip ratio

Fig. 1. Kaplan–Meier curve showing cumulative incidence of BCRL in the entire cohort (a), nonobese only (b) and obese only (c) by self-reported race/ethnicity

Table 1
Patient characteristics of the Pathways Study cohort by self-reported BCRL status at 12 and 48 months postbreast cancer diagnosis (*n* = 2953)

	BCRL from self-report ^a		<i>p</i> value ^b
	No <i>n</i> = 2611 (88.4 %)	Yes <i>n</i> = 342 (11.6 %)	
	<i>N</i> (%)	<i>N</i> (%)	
Race/ethnicity			0.0093
White	1765 (67.6)	204 (59.7)	
African American	173 (6.6)	37 (10.8)	
Hispanic	312 (11.9)	41 (12.0)	
Asian	302 (11.6)	49 (14.3)	
Other	59 (2.3)	11 (3.2)	
Estimated ancestry, median (range)			
% European ancestry among whites	0.88 (0.03–1.00)	0.88 (0.46–1.00)	0.38
% African ancestry among African Americans	0.77 (0.06–0.98)	0.80 (0.01–0.95)	0.13
% Asian ancestry among Asians	0.83 (0.01–1.00)	0.81 (0.02–1.00)	0.14
% Native American ancestry among Hispanics	0.23 (0–0.83)	0.23 (0–0.74)	0.88
Age at breast cancer diagnosis			<0.0001
<50 years	550 (21.1)	108 (31.6)	
50–59 years	765 (29.3)	126 (36.8)	
60–69 years	768 (29.4)	68 (19.9)	
70 years	528 (20.2)	40 (11.7)	
Mean (SD)	60.0 (11.9)	56.0 (11.1)	<0.0001
Education at baseline			0.15
High school or less	416 (15.9)	43 (12.5)	
Some college	916 (35.1)	122 (35.7)	
College graduate	699 (26.8)	108 (31.6)	
Postgraduate	580 (22.2)	69 (20.2)	
Marital status at baseline			0.52
Married/marriage-like	1598 (61.3)	215 (63.1)	
Single/separated/widowed	1011 (38.7)	126 (36.9)	
Household income (\$) at baseline			0.57
<25,000	259 (11.1)	28 (9.2)	
25,000–49,999	516 (22.1)	61 (20.1)	
50,000–89,999	743 (31.8)	99 (32.7)	
>90,000	820 (35.0)	115 (38.0)	
Employment status at breast cancer diagnosis			0.97
Not working	1369 (53.0)	176 (52.9)	
Working	1215 (47.0)	157 (47.1)	
BMI (kg/m ²) at baseline			<0.0001
<25 (normal weight)	963 (37.2)	87 (25.6)	

	BCRL from self-report ^a		
	No <i>n</i> = 2611 (88.4 %)	Yes <i>n</i> = 342 (11.6 %)	<i>p</i> value ^b
	<i>N</i> (%)	<i>N</i> (%)	
25–29 (overweight)	814 (31.4)	99 (29.1)	
30 (obese)	815 (31.4)	154 (45.3)	
Mean (SD)	28.0 (6.4)	30.6 (7.9)	<0.0001
Waist-to-hip ratio (WHR) at baseline			0.04
Tertile 1 (<0.832)	894 (35.0)	98 (29.5)	
Tertile 2 (0.832–0.926)	850 (33.2)	107 (32.2)	
Tertile 3 (>0.926)	813 (31.8)	127 (38.3)	
Mean (SD)	0.87 (0.08)	0.88 (0.08)	0.072
Moderate-to-vigorous physical activity (MET-hours/week) at baseline			0.03
Quartile 1 (<8.2)	644 (24.8)	96 (28.2)	
Quartile 2 (8.2–21.1)	649 (25.0)	81 (23.8)	
Quartile 3 (21.2–42.5)	641 (24.7)	99 (29.0)	
Quartile 4 (>42.5)	664 (25.5)	65 (19.0)	
Mean (SD)	30.3 (31.4)	26.8 (27.9)	0.046
Smoking status at baseline			0.14
Never	1433 (54.9)	210 (61.4)	
Former	1047 (40.1)	119 (34.8)	
Current	130 (5.0)	13 (3.8)	
Alcohol intake at baseline (g/day)			0.09
Never	569 (28.0)	91 (34.6)	
Below (or equal) median	415 (20.5)	47 (17.9)	
Above median	1043 (51.5)	125 (47.5)	
Mean (SD)	6.5 (11.7)	5.6 (10.8)	0.20

^aSelf-reported BCRL from the 12-month or 48-month Health Status Updates

^bFrom Pearson Chi-square test (categorical variables) and Satterthwaite t-test (continuous variables)

Not reported, missing, unknown are as follows: Marital status *n* = 3, Household income *n* = 312, Employment status *n* = 36, BMI at baseline *n* = 21, WHR at baseline *n* = 64, Moderate-to-Vigorous physical activity *n* = 14, Alcohol intake at baseline *n* = 663

Table 2
Clinical characteristics of the Pathways Study cohort by self-reported BCRL status at 12 and 48 months postbreast cancer diagnosis (*n* = 2953)

	BCRL from self-report ^a		<i>p</i> value ^b
	No <i>n</i> = 2611 (88.4 %)	Yes <i>n</i> = 342 (11.6 %)	
	<i>N</i> (%)	<i>N</i> (%)	
AJCC stage at breast cancer diagnosis			<0.0001
I	1475 (56.5)	89 (26.0)	
II	883 (33.8)	161 (47.1)	
III	215 (8.2)	90 (26.3)	
IV	38 (1.5)	2 (0.6)	
Breast surgery ^c			<0.0001
Lumpectomy only	1628 (62.4)	161 (47.1)	
Mastectomy	961 (36.8)	177 (51.7)	
None	21 (0.8)	4 (1.2)	
Lymph node surgery			0.0013
Axillary lymph node dissection	404 (16.8)	62 (19.3)	
Sentinel lymph node biopsy	409 (17.0)	27 (8.4)	
Both	1199 (49.9)	174 (54.2)	
none	389 (16.2)	58 (18.1)	
Number of lymph nodes examined			<0.0001
Mean [SD (range)]	5.6 (6.3 [0–50])	11.2 (8.4 [0–44])	
Number of positive lymph nodes			<0.0001
Mean [SD (range)]	1.0 (3.1 [0–49])	2.6 (4.3 [0–32])	
Chemotherapy			<0.0001
No	1401 (53.9)	72 (21.1)	
Yes	1198 (46.1)	270 (78.9)	
Radiation therapy			<0.0001
No	1494 (57.2)	237 (69.3)	
Yes	1117 (42.8)	105 (30.7)	
Hormonal therapy			0.09
No	640 (24.7)	99 (28.9)	
Yes	1954 (75.3)	243 (71.1)	
Comorbidity history at BC diagnosis			0.22
No	2239 (85.9)	302 (88.3)	
Yes	369 (14.2)	40 (11.7)	
Hypertension history at BC diagnosis			0.60
No	1419 (54.3)	191 (55.9)	
Yes	1192 (45.7)	151 (44.2)	

^aSelf-reported BCRL from the 12-month or 48-month Health Status Updates

^bFrom Pearson Chi-square test (categorical variables) and Satterthwaite *t* test (continuous variables)

^cBilateral surgery, $n = 146$ (4.94 %), Unilateral surgery, $n = 2767$ (93.70 %), No surgery, $n = 26$ (0.88 %), NOS/Unknown, $n = 14$ (0.47 %)

Not reported, missing, unknown are as follows: Lymph node surgery $n = 231$, Chemotherapy $n = 12$, Hormonal therapy $n = 17$, Comorbidity history $n = 3$

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Table 3
Associations of self-reported race/ethnicity with self-reported BCRL status

	<i>n</i>	# Events ^a	Unadjusted model HR (95 % CI)	Base Model ^b HR (95 % CI)	Further adjusted for age BC Dx, baseline BMI, baseline PA, comorbidity, HTN HR (95 % CI)
Race/ethnicity from self-report					
White	1969	133	Ref	Ref	Ref
African American	210	27	2.04 (1.35, 3.08)	1.60 (1.04, 2.47)	1.47 (0.94, 2.30)
Hispanic	351	33	1.47 (1.00, 2.15)	1.28 (0.86, 1.90)	1.18 (0.78, 1.77)
Asian	353	30	1.31 (0.88, 1.95)	1.18 (0.78, 1.79)	1.24 (0.81, 1.92)
Other	70	7	1.57 (0.73, 3.36)	1.20 (0.55, 2.59)	1.21 (0.56, 2.61)
Genetic ancestry ^c					
European ancestry	–	–	Ref	Ref	
African ancestry	–	–	2.50 (1.43, 4.36)	1.93 (1.08, 3.43)	1.73 (0.96, 3.14)
Native American ancestry	–	–	2.70 (0.79, 9.23)	1.91 (0.52, 7.07)	1.33 (0.32, 5.51)
Asian ancestry	–	–	1.23 (0.73, 2.05)	1.14 (0.66, 1.94)	1.21 (0.69, 2.11)

^aFollow-up starting at 6 months postbreast cancer diagnosis until BCRL self-report or date of last patient contact (12- or 48-month follow-up), whichever occurred first

^bCox proportional hazards models, adjusted for education, household income, employment, AJCC stage, breast and lymph node surgery, number of lymph nodes examined, chemotherapy, radiation therapy

^cThe estimated percentages of African, Asian and Native American ancestry for each patient were entered in the models as continuous, each with a range of 0–1 and European ancestry set as the default reference. Thus, the HRs with each of the three ancestries should be interpreted as the hazards of a “genetically pure” individual of the respective ancestry relative to a genetically pure individual of European ancestry

Table 4
Associations of self-reported race/ethnicity and genetic ancestry with self-reported BCRL status by BMI (nonobese vs. obese)

		NonObese (BMI < 30) n = 1810			Obese (BMI ≥ 30) n = 930		
		n	# Events ^a	Unadjusted model	Base model ^b	Further adjusted for age BC Dx, baseline BMI, baseline PA, comorbidity, HTN	HR (95 % CI)
Race/ethnicity from self-report							
White		1188	72	Ref	Ref	Ref	Ref
African American		94	12	2.33 (1.27, 4.29)	2.33 (1.25, 4.36)	2.20 (1.16, 4.19)	1.22 (0.66, 2.27)
Hispanic		199	21	1.96 (1.22, 3.15)	1.73 (1.05, 2.84)	1.59 (0.95, 2.66)	0.73 (0.36, 1.48)
Asian		292	22	1.29 (0.80, 2.07)	1.12 (0.68, 1.84)	1.07 (0.64, 1.81)	1.80 (0.83, 3.90)
Genetic Ancestry ^c							
European ancestry		–	–	Ref	Ref	Ref	Ref
African ancestry		–	–	3.63 (1.63, 8.06)	3.67 (1.61, 8.39)	3.51 (1.50, 8.21)	1.52 (0.69, 3.32)
Native American ancestry		–	–	6.66 (1.49, 29.7)	4.10 (0.80, 21.0)	3.02 (0.56, 16.25)	0.26 (0.02, 3.29)
Asian ancestry		–	–	1.35 (0.74, 2.46)	1.24 (0.66, 2.34)	1.20 (0.62, 2.33)	1.47 (0.50, 4.32)

^a Follow-up starting at 6 months postbreast cancer diagnosis until BCRL self-report or date of last patient contact (12- or 48-month follow-up), whichever occurred first

^b Adjusted for education, household income, employment, AJCC stage, breast and lymph node surgery, number of lymph nodes examined, chemotherapy, radiation therapy

^c The estimated percentages of African, Asian and Native American ancestry for each patient were entered in the models as continuous, each with a range of 0-1 and European ancestry set as the default reference. Thus, the HRs with each of the three ancestries should be interpreted as the hazards of a “genetically pure” individual of the respective ancestry relative to a genetically pure individual of European ancestry