Contextual Impact of Neighborhood Obesogenic Factors on Postmenopausal Breast Cancer: The Multiethnic Cohort

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Abstract

Background: While obesity is well-understood to increase breast cancer risk, the role of the neighborhood obesogenic environment, encompassing social and built environment attributes that influence body size, is poorly understood.

Methods: Using principal components factor analysis, five composite factors [neighborhood socioeconomic status (nSES), urban, mixed-land development, unhealthy food environment, parks] on the basis of geospatial data were developed to characterize the obesogenic environment for 48,247 postmenopausal women in the Multiethnic Cohort, residing predominately in Los Angeles County. We used Cox proportional hazards regression to examine the association between neighborhood obesogenic factors and breast cancer risk ($n = 2{,}341$ cases after 17 years of follow-up), adjusting for body mass index (BMI), weight gain since age 21, education, established risk factors, other neighborhood factors, and clustering by block group.

Results: Lower nSES was associated with lower breast cancer risk [quintile 1 vs. 5: HR, 0.79; 95% confidence interval (CI), 0.66–0.95], with a more pronounced association observed in Latinos (quintile 1 vs. 5: HR, 0.60; 95% CI, 0.43–0.85). More urban environments were associated with lower breast cancer risk in Japanese Americans (quintile 5 vs. 1: HR, 0.49; 95% CI, 0.26–0.90), and lower mixed-land development was associated with higher breast cancer risk in Latinos (quintile 1 vs. 5: HR, 1.46; 95% CI, 1.10–1.93).

Conclusions: Obesogenic neighborhood environment factors, especially nSES, urbanicity, and mixed-land development, were differentially and independently associated with breast cancer risk in this multiethnic population.

Impact: These findings highlight the need for additional studies of the driving contextual aspects of nSES that influence breast cancer risk. *Cancer Epidemiol Biomarkers Prev; 26(4); 480–9. ©2017 AACR.*

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Introduction

Excess adiposity, measured by body mass index (BMI) or weight gain, is among the few modifiable risk factors for postmenopausal breast cancer (1–3). In a recent meta-analysis of 7 prospective studies, each 5-kg gain in weight since early adulthood increased the risk of postmenopausal breast cancer by 11%, at least among women who did not use hormone therapy (3). Excess adiposity has been shown to impact breast cancer risk differentially across race/ethnicity (4). In the Multiethnic Cohort (MEC), both BMI and adult weight gain were associated with a significantly higher risk of breast cancer overall, but the risks for Native Hawaiians and Japanese Americans with BMI > 30 kg/m^2 were higher than for white, African American, and Latino women of the same BMI (5). Overall, each 5 kg of weight gained since age 21 conferred an additional 4% increase in the risk of breast cancer, and weight gain was more important than baseline BMI in its association with breast cancer when modeled simultaneously (5).

A missing piece in our understanding of the relation between adiposity and the development of breast cancer, and potentially in our ability to address prevention, is the contribution of neighborhood obesogenic environments; specifically, the social and man-made ("built") physical attributes of an individual's residential surroundings relevant to energy balance that promote weight gain and obesity (6). As examples, greater adiposity has been associated with lower neighborhood socioeconomic status (nSES; refs. 7–10), proximity and density of grocery stores and supermarkets (11–13), fast food restaurants (12–15), and walkability (e.g., street connectivity, density of walkable destinations; refs. 16, 17). Walkability and availability of recreational facilities have been further associated with higher levels of physical activity (18–20). Despite the relationship of neighborhood environment to adiposity (reviewed in refs. 21–24) and the established role of excess adiposity as an

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important risk factor for postmenopausal breast cancer (5), to our knowledge, there have been no studies of associations between potentially obesogenic neighborhood characteristics and breast cancer risk or whether neighborhood obesogenic factors explain associations between BMI or weight gain and breast cancer risk. To quantify the influence of such neighborhoods on breast cancer risk independent of individual-level risk factors, we evaluated the association of a broad suite of neighborhood obesogenic factors with subsequent development of invasive breast cancer while accounting for prediagnostic BMI, weight gain, and established risk factors for breast cancer. Specifically, we examined 48,247 postmenopausal women in the MEC from 4 racial/ethnic groups living in California, who were followed prospectively for up to 17 years. Neighborhood characteristics were examined as factors derived from principal component factor analysis. We hypothesize that obesogenic neighborhood factors reflecting lower nSES, more urban environments, more unhealthy foods, lower mixed-land development, and fewer parks will be associated with increased breast cancer risk.

Materials and Methods

Study subjects

The MEC is a large prospective cohort study designed to investigate the role of lifestyle and dietary factors in the etiology of cancer among a multiethnic population of U.S. adults. Study recruitment and methods have been described in detail previously (25). Briefly, from 1993 through 1996, the MEC enrolled 215,521 men and women aged 45–75 years from 5 self-reported racial/ethnic groups (African Americans, Japanese Americans, Latinos, Native Hawaiians, and whites) residing in Hawaii or California (primarily Los Angeles County); the present analysis is limited to the California component of the cohort. At cohort entry, participants completed a 26-page mailed questionnaire with questions pertaining to demographic characteristics, anthropometrics, medical history, family history, physical activity, diet, reproductive history, mammography, and occupation. Participants were followed prospectively for diagnosis with incident, invasive breast cancer through routine linkage with regional member registries of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program. Tumor characteristics included SEER summary stage and hormone receptor status [estrogen receptor (ER) and progesterone receptor (PR)]. Information regarding tumor HER2 status was not available for all cases. Participants were followed for vital status through linkages to the National Death Index and death certificate files in Hawaii and California. Female MEC participants eligible for the present study ($n = 57{,}933$; Supplementary Fig. S1) belong to 1 of 4 racial/ethnic groups (African American, Japanese American, Latino, or white), completed a baseline questionnaire while living in California, had no invasive breast cancer diagnosis prior to cohort entry as reported on baseline questionnaire or through linkage with the tumor registry, and had plausible dietary data (5). We excluded those who were premenopausal or had unknown menopausal status ($n = 7{,}084$), had missing or extreme BMI (<15, >50 kg/m^2; $n = 1{,}555$), had residential addresses that could not be geocoded ($n = 1{,}045$), or had a date of cohort entry that coincided with the date of diagnosis and thus had zero follow-up ($n = 2$), providing an analytic cohort of 48,247 women.

Address history and geocoding

The MEC actively maintains accurate and up-to-date addresses on all participants via periodic mailings of newsletters and follow-up questionnaires, as well as linkages with databases (e.g., U.S. Postal Service). Residential baseline addresses of MEC participants in California were geocoded to latitude and longitude coordinates using parcel data and then street centerline data for those that failed to geocode to a parcel. Geocodes of participants' addresses (at baseline, 1993–1996) were linked to 7,947 1990 U.S. Census block groups, each including an average of 1,475 residents in Los Angeles County or 9 MEC participants, representing our neighborhood unit.

Social and built environment data

We characterized the neighborhood obesogenic environment on the basis of the California Neighborhoods Data System, an integrated system of census, business, farmers market, park, traffic, and other small-area contextual data (26). We operationalized nSES as a composite measure by principal component analysis of census block group data (27) for education, housing, employment, occupation, income, and poverty, as described previously (28). Built environment characteristics included: (i) population density (persons per square kilometer) and (ii) percentage of residents who commute by car/motorcycle (per census block group) based on the census data (27); the number of (iii) businesses, (iv) recreational facilities, and (v) parks; unhealthy retail and restaurant environment, that is, (vi) restaurant environment index (REI), the ratio of the number of fast food restaurants to other restaurants, and (vii) the retail food environment index (RFEI), the ratio of the number of convenience stores, liquor stores, and fast food restaurants to supermarkets and farmers' markets (29) based on business listings from Walls & Associates' National Establishment Time-Series Database from 1990–2008 (30) and a 3-year business activity window (1990–1993), farmers' markets listings from the California Department of Food and Agriculture (31), and park listings from NavTeq's NavStreets database (32); (viii) traffic density from the California Department of Transportation (2000; refs. 33, 34); and (ix) street connectivity (35) based on the gamma index, defined as the ratio of actual number of street segments to maximum possible number of intersections, based on the data from NavTeq's NavStreets database (32).

To more fully characterize a neighborhood's obesogenic environment, we derived factors from principal components factor analysis (36, 37) of 9 built environment characteristics modeled as continuous variables and quantified for block groups using all California residents (Supplementary Table S1). All block groups in California in 1990 with at least 15 residents and non-missing data for the 9 built environment variables were included ($n = 20{,}874$ 1990 California block groups). For REI and RFEI, we set block groups with no restaurants or retail food outlets to zero and those with only unhealthy outlets to 2. The number of factors (components) retained for orthogonal varimax rotation was based on an eigenvalue criterion >1, screen plot analysis, and interpretability. Factor scores were linear combinations of the standardized scoring coefficients multiplied by the standardized built environment variables as continuous variables, only including the neighborhood variables with a loading >0.50 (38, 39). We identified 4 neighborhood factors: an "urban environment" factor, characterized by high population density (rotated factor

loading of 0.79), high street connectivity (0.70), low % commute by car/motorcycle (−0.68), and high traffic density (0.51); a "mixed-land development" factor, characterized by high recreational facilities per population (0.90), and high businesses per population (0.89); an "unhealthy food outlets" factor, characterized by a high ratio of unhealthy to healthy restaurants (0.82) and a high ratio of unhealthy to healthy retail establishments (0.81); and a "parks" factor, characterized by high number of parks per population (0.95). The "urban environment" and "mixed-land development" neighborhood factors were categorized into quintiles on the basis of the Los Angeles County distributions; the "unhealthy food outlets" factor was categorized as none, some, or more; and the "parks" factor was categorized as none versus any. Each MEC participant was assigned the 4 neighborhood obesogenic factors for her baseline residential block group. In a separate analysis, we examined the associations of these neighborhood obesogenic factors with baseline BMI and found that each factor was associated with an increased odds of obesity, although associations varied across race/ethnicity (40).

Health characteristics and breast cancer risk factors at baseline

Self-reported height and weight were used to calculate BMI (kg/m^2), which was categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥30 kg/m^2). Adult weight gain from age 21 was calculated as the difference between baseline weight and weight at age 21 categorized into quintiles according to the study participant distribution. Smoking exposure was based on smoking status and pack-years of smoking (never, current, former, missing) and pack-years of smoking (<20, ≥20 pack-years, unknown) as a combined variable. Physical activity was estimated as the number of hours per day spent engaging in moderate or vigorous activities, on average, in the previous year. Other risk factors for breast cancer included first-degree family history of breast cancer (yes, no, missing), age at menarche (≤12, 13–14, >14 years, missing), age at first live birth (no children, <20, 21–30, >30 years, missing), number of children (0, 1, 2–3, ≥4, missing), history of mammography (yes, no, missing), alcohol intake (non-drinker, drinker, missing), educational attainment (high school graduate or less, some college, college graduate, graduate and professional school, missing), and the use of hormone therapy (no estrogen use, past estrogen use, current estrogen use only, current estrogen use with past or current progesterone use, missing).

Statistical analyses

Associations of neighborhood obesogenic factors, weight gain and BMI with breast cancer were examined using multivariable Cox proportional hazards regression with adjustment for clustering by block group and individual-level breast cancer risk factors. Age from cohort entry to breast cancer diagnosis, death, or end of study follow-up (December 31, 2010) was used as the time metric. Models of obesogenic neighborhood factors were adjusted for individual risk factors and neighborhood clusters, as well as for other neighborhood obesogenic factors. Additional analyses included models for hormone receptor–positive (ER^+/PR^+) or negative (ER^-/PR^-) and early-stage (I–III) or late-stage (IV) disease breast tumors. There was no violation of the proportional hazards assumption as evidenced by the Schoenfeld residuals. Neighborhood or individual-level factors significantly associated with breast cancer ($P < 0.05$) in age- and race/ethnicity-adjusted models were included in fully-adjusted models (see Tables 2 and 3 for adjustments). Reference categories for the neighborhood factors were chosen to reflect their positive associations with obesity (e.g., higher obesity with lower SES, more urban areas, more unhealthy food, lower mixed-land development, and fewer parks). Trend tests were performed by entering the variable as an ordinal parameter representing categories in the corresponding models. We also tested for spatial autocorrelation with Moran's *I* and found no evidence of it. As a sensitivity analysis, gamma frailty models were fit with block group as a random-effect (41). As the random effect term was not statistically significant and the confidence intervals (CI) for the neighborhood obesogenic factors did not change, we present the fixed-effects models. All *P* values presented are 2-sided. A *P* value threshold <0.05 was used to determine statistical significance. Cox proportional hazards regression analyses were conducted using SAS (version 9.3) and gamma frailty models were conducted using R (version 3.2.2).

Results

Overall, the 48,247 women were diverse with respect to race/ethnicity, with 35% African American and 39% Latino (Table 1). The median age at the time of cohort entry was 62 years [interquartile range (IQR), 56–68]. The prevalence of excess adiposity (being overweight or obese as defined by BMI ≥ 25 kg/m^2) at baseline varied substantially across race/ethnicity with a relatively higher proportion of overweight/obesity in African Americans (75%), Latinos (69%), and whites (53%) than among Japanese Americans (25%; Table 1). Similarly, a relatively higher proportion of African Americans (66%), Latinos (57%), and whites (50%) than Japanese Americans (23%) reported having gained at least 11.3 kg (25 pounds) since age 21. Compared with other racial/ethnic groups, Japanese Americans and whites were more likely to live in neighborhoods characterized by high SES (quintile 5) and more mixed-land development (quintile 5); conversely, African Americans and Latinos were more likely to live in more urban neighborhoods (quintile 5; Supplementary Table S2). During a median follow-up of 16.6 years (IQR, 14.5–17.3) from cohort entry, 2,341 women were diagnosed with invasive breast cancer; specifically, 1,542 (66%) ER^+/PR^+, 361 (15%) ER^-/PR^-, and 438 (19%) unknown hormone receptor status tumors. Most tumors ($n = 1{,}564$; 67%) were diagnosed at an early (localized) stage, whereas 741 (31%) were at late-stage (regional or distant) and 36 were unstaged (2%).

Women living in the lowest versus highest SES neighborhoods had 21% lower risk of breast cancer (quintile 1 vs. 5: HR, 0.79; 95% CI, 0.66–0.95; $P_{trend} = 0.02$), after adjustment for baseline BMI, weight gain, education, breast cancer risk factors, and other neighborhood obesogenic factors (Table 2). This nSES–breast cancer association was significant for Latinos ($P_{trend} = 0.01$) and suggestive for whites ($P_{trend} = 0.19$) but not evident for African Americans and Japanese Americans ($P_{trends} > 0.80$). The nSES–breast cancer associations appeared somewhat stronger for hormone receptor–positive tumors, compared with all tumors. Risk of hormone receptor–positive breast cancer among women living in the lowest versus the highest SES neighborhoods was 27% lower (quintile 1 vs. 5: HR, 0.73; 95% CI, 0.58–0.92). Overall associations were fairly similar with and without adjustment for weight gain and BMI.

Table 1. Distributions of breast cancer risk factors by race/ethnicity, postmenopausal women residing in California at baseline (n = 48,247), MEC, 1993–2010

	All women (n = 48,247)[a] n (%)	African American (n = 16,703)[a] n (%)	Japanese American (n = 5,063)[a] n (%)	Latino (n = 18,752)[a] n (%)	White (n = 7,729)[a] n (%)
Age at baseline, y					
45–49	2,992 (6.2)	1,339 (8.0)	199 (3.9)	1,062 (5.7)	392 (5.1)
50–54	5,972 (12.4)	2,152 (12.9)	492 (9.7)	2,490 (13.3)	838 (10.8)
55–59	10,133 (21.0)	2,848 (17.1)	880 (17.4)	4,806 (25.6)	1,599 (20.7)
60–64	10,365 (21.5)	2,762 (16.5)	1,031 (20.4)	4,851 (25.9)	1,721 (22.3)
65–69	9,458 (19.6)	3,703 (22.2)	1,061 (21.0)	3,124 (16.7)	1,570 (20.3)
70–74	8,038 (16.7)	3,350 (20.1)	1,151 (22.7)	2,142 (11.4)	1,395 (18.0)
75+	1,289 (2.7)	549 (3.3)	249 (4.9)	277 (1.5)	214 (2.8)
BMI at baseline, kg/m^2					
Underweight, <18.5	868 (1.8)	171 (1.0)	354 (7.0)	177 (0.9)	166 (2.1)
Normal, 18.5–24.9	16,612 (34.4)	4,047 (24.2)	3,437 (67.9)	5,662 (30.2)	3,466 (44.8)
Overweight, 25.0–29.9	17,378 (36.0)	6,289 (37.7)	1,056 (20.9)	7,557 (40.3)	2,476 (32.0)
Obese, ≥30.0	13,389 (27.8)	6,196 (37.1)	216 (4.3)	5,356 (28.6)	1,621 (21.0)
Adult weight gain since age 21,[b,c] kg					
Quintile 1: −130.5 to <5.4	8,732 (18.1)	1,623 (9.7)	2,354 (46.5)	2,808 (15.0)	1,947 (25.2)
Quintile 2: 5.4 to <11.3	8,104 (16.8)	1,985 (11.9)	1,349 (26.6)	3,254 (17.4)	1,516 (19.6)
Quintile 3: 11.3 to <17.6	9,318 (19.3)	3,018 (18.1)	775 (15.3)	4,008 (21.4)	1,517 (19.6)
Quintile 4: 17.6 to <24.8	8,678 (18.0)	3,522 (21.1)	286 (5.6)	3,673 (19.6)	1,197 (15.5)
Quintile 5: 25.2 to <90.0	8,804 (18.2)	4,515 (27.0)	86 (1.7)	3,037 (16.2)	1,166 (15.1)
Education					
High school graduate or less	26,022 (53.9)	7,057 (42.2)	1,977 (39.0)	13,770 (73.4)	3,218 (41.6)
Some college/technical school	13,511 (28.0)	5,904 (35.3)	1,838 (36.3)	3,258 (17.4)	2,511 (32.5)
College graduate	4,155 (8.6)	1,821 (10.9)	761 (15.0)	647 (3.5)	926 (12.0)
Graduated and professional school	3,855 (8.0)	1,713 (10.3)	442 (8.7)	710 (3.8)	990 (12.8)
Smoking status					
Never smoker	25,784 (53.4)	7,266 (43.5)	3,403 (67.2)	11,594 (61.8)	3,521 (45.6)
Former smoker	14,335 (29.7)	5,864 (35.1)	1,196 (23.6)	4,479 (23.9)	2,796 (36.2)
Current smoker	6,858 (14.2)	3,334 (20.0)	415 (8.2)	1,806 (9.6)	1,303 (16.9)
Alcohol intake					
Non-drinker	29,123 (60.4)	10,172 (60.9)	3,653 (72.2)	11,838 (63.1)	3,460 (44.8)
Drinker	17,062 (35.4)	5,831 (34.9)	1,215 (24.0)	6,140 (32.7)	3,876 (50.1)
Moderate or vigorous physical activity,[c] h/d					
0	3,840 (8.0)	972 (5.8)	119 (2.4)	2,436 (13.0)	313 (4.0)
Quartile 1: <0.4	7,953 (16.5)	2,871 (17.2)	707 (14.0)	3,507 (18.7)	868 (11.2)
Quartile 2: 0.4 to <0.7	11,901 (24.7)	4,845 (29.0)	1,335 (26.4)	4,044 (21.6)	1,677 (21.7)
Quartile 3: 0.7 to <1.2	10,589 (21.9)	3,721 (22.3)	1,246 (24.6)	3,730 (19.9)	1,892 (24.5)
Quartile 4: 1.2 to <13.3	12,153 (25.2)	3,591 (21.5)	1,575 (31.1)	4,143 (22.1)	2,844 (36.8)
Energy,[c] kcal/d					
Quintile 1: 417.4 to <1,152.8	9,237 (19.1)	3,933 (23.5)	905 (17.9)	2,999 (16.0)	1,400 (18.1)
Quintile 2: 1,152.8 to <1,533.2	9,237 (19.1)	3,186 (19.1)	1,227 (24.2)	3,044 (16.2)	1,780 (23.0)
Quintile 3: 1,533.2 to <1,947.0	9,237 (19.1)	3,036 (18.2)	1,224 (24.2)	3,299 (17.6)	1,678 (21.7)
Quintile 4: 1,947.0 to <2,606.9	9,237 (19.1)	2,959 (17.7)	1,003 (19.8)	3,745 (20.0)	1,530 (19.8)
Quintile 5: 2,606.9 to <7,211.3	9,237 (19.1)	2,889 (17.3)	509 (10.1)	4,891 (26.1)	948 (12.3)
Ever had mammogram					
Yes	5,192 (10.8)	1,293 (7.7)	578 (11.4)	2,596 (13.8)	725 (9.4)
No	41,384 (85.8)	14,784 (88.5)	4,356 (86.0)	15,371 (82.0)	6,873 (88.9)
Family history of breast cancer[d]					
Yes	4,975 (10.3)	1,003 (13.0)	1,832 (11.0)	516 (10.2)	1,624 (8.7)
No	39,380 (81.6)	6,269 (81.1)	13,498 (80.8)	4,286 (84.7)	15,327 (81.7)
Age at first birth, y					
Nulliparous	5,691 (11.8)	2,261 (13.5)	800 (15.8)	1,528 (8.1)	1,102 (14.3)
<20	17,466 (36.2)	7,442 (44.6)	354 (7.0)	7,468 (39.8)	2,202 (28.5)
21–30	21,009 (43.5)	5,706 (34.2)	3,288 (64.9)	8,262 (44.1)	3,753 (48.6)
>30	2,665 (5.5)	668 (4.0)	516 (10.2)	960 (5.1)	521 (6.7)
Age at menarche, y					
<12	22,666 (47.0)	7,988 (47.8)	2,251 (44.5)	8,625 (46.0)	3,802 (49.2)
13–14	18,382 (38.1)	6,211 (37.2)	2,029 (40.1)	7,147 (38.1)	2,995 (38.8)
>14	6,344 (13.1)	2,139 (12.8)	713 (14.1)	2,646 (14.1)	846 (10.9)
Parity					
Nulliparous	5,691 (11.8)	2,261 (13.5)	800 (15.8)	1,528 (8.1)	1,102 (14.3)
1	5,432 (11.3)	2,651 (15.9)	581 (11.5)	1,271 (6.8)	929 (12.0)
2–3	18,106 (37.5)	5,825 (34.9)	2,784 (55.0)	5,811 (31.0)	3,686 (47.7)
≥4	18,342 (38.0)	5,735 (34.3)	868 (17.1)	9,805 (52.3)	1,934 (25.0)
Menopause status					
Natural menopause	26,584 (55.1)	7,611 (45.6)	3,354 (66.2)	11,121 (59.3)	4,498 (58.2)
Oophorectomy	7,685 (15.9)	3,198 (19.1)	718 (14.2)	2,395 (12.8)	1,374 (17.8)
Hysterectomy	9,441 (19.6)	4,153 (24.9)	552 (10.9)	3,402 (18.1)	1,334 (17.3)

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Table 1. Distributions of breast cancer risk factors by race/ethnicity, postmenopausal women residing in California at baseline (n = 48,247), MEC, 1993–2010 (Cont'd)

	All women (n = 48,247)[a] n (%)	African American (n = 16,703)[a] n (%)	Japanese American (n = 5,063)[a] n (%)	Latino (n = 18,752)[a] n (%)	White (n = 7,729)[a] n (%)
Hormone replacement therapy					
Never estrogen use	23,367 (48.4)	8,752 (52.4)	2,385 (47.1)	9,303 (49.6)	2,927 (37.9)
Past estrogen use	9,519 (19.7)	3,672 (22.0)	737 (14.6)	3,562 (19.0)	1,548 (20.0)
Current unopposed estrogen use	6,312 (13.1)	2,037 (12.2)	768 (15.2)	2,177 (11.6)	1,330 (17.2)
Current estrogen–progesterone use	6,083 (12.6)	1,231 (7.4)	1,008 (19.9)	2,183 (11.6)	1,661 (21.5)

[a]*N*s may not add to racial/ethnic totals and percentages may not add to 100 due to missing.
[b]Difference between baseline weight and weight at age 21.
[c]Quintiles or quartiles based on study population distribution.
[d]At least one of mother of sisters had breast cancer.

The nSES–breast cancer association was slightly attenuated with sequential modeling of individual risk factors (data not shown). For example among Latinos, the estimated minimally adjusted (age, race/ethnicity, clustering by block group) HR for the lowest versus highest nSES quintile of 0.55 (95% CI, 0.41–0.73) was attenuated 13% (HR, 0.62; 95% CI, 0.47–0.83) with adjustment for reproductive factors and hormone replacement therapy, an additional 3% (HR, 0.64; 95% CI, 0.48–0.85) with further adjustment for education, and an additional 2% (HR, 0.65; 95% CI, 0.49–0.88) with further adjustment for mammography screening, family history of breast cancer, alcohol intake, physical activity, energy intake, and smoking. Conversely, further adjustment for baseline BMI and weight change since age 21 slightly strengthened the association (HR, 0.64; 95% CI, 0.48–0.86), reflecting the positive association between adult weight change and breast cancer risk. Additional adjustment for the other neighborhood obesogenic factors attenuated the HR by 6% (HR, 0.60; 95% CI, 0.43–0.85).

Neighborhood obesogenic factors for unhealthy food outlets, mixed-land development, and urban environments were differentially associated with breast cancer risk in this multiethnic population, after adjustment for individual and other neighborhood obesogenic factors (Table 2). Women living in neighborhoods with more unhealthy foods outlets versus none had 10% higher breast cancer risk (HR, 1.10; 95% CI, 1.00–1.21; P_{trend} = 0.07). Living in neighborhoods characterized by the lowest versus highest quintile of mixed-land development was associated with higher breast cancer risk among Latinos (quintile 1 vs. 5: HR, 1.46; 95% CI, 1.10- 1.93; P_{trend} = 0.10). In contrast, Japanese Americans living in more urban environments had significantly lower breast cancer risk (quintile 1 vs. 5: HR, 0.49; 95% CI, 0.26–0.90; P_{trend} = 0.03). Overall, associations were attenuated in analyses limited to hormone receptor–positive tumors, except for nSES- and mixed-land development–breast cancer associations among Latinos, with evidence of a threshold effect of 50% higher risk for mixed-land development (quintile 4 vs. 5: HR, 1.50; 95% CI, 1.04–2.16; quintile 1 vs. 5: HR, 1.49; 95% CI, 1.02–2.16). Associations (overall and by tumor subtype) were fairly similar with and without adjustment for weight gain and BMI.

The associations between weight gain since age 21 and breast cancer risk persisted with adjustment for neighborhood obesogenic factors (Table 3). For African Americans and whites, who reported gaining at least 25 versus <5 kg since age 21, the risk of breast cancer was 85% and 60% higher, respectively, with adjustment for age, BMI, education, and other established risk factors (HR, 1.85; 95% CI, 1.30–2.61; P_{trend} < 0.01; and HR, 1.60; 95% CI, 1.06–2.41; P_{trend} = 0.08, respectively). For Japanese Americans and Latinos, associations of weight gain with breast cancer trended in the same direction. Further adjustment for nSES and neighborhood obesogenic factors did not strengthen nor attenuate these associations. Associations were generally higher for hormone receptor–positive than -negative subtypes while adjusting for individual and neighborhood factors (i.e., weight gain of >25 vs. <5 kg among all women: HR, 1.76; 95% CI, 1.40–2.22; P_{trend}< 0.01 for ER^+/PR^+; and HR, 1.42; 95% CI, 0.85–2.36; P_{trend} = 0.12 for ER^-/PR^-), and these associations also persisted after further adjustment for neighborhood obesogenic factors (data not shown).

Discussion

This study, to our knowledge, is the first assessment of the role of the neighborhood obesogenic environment and risk of postmenopausal breast cancer. Neighborhood SES was the strongest contextual characteristic associated with breast cancer risk independent of weight gain and established risk factors for breast cancer. Living in the lowest versus highest SES neighborhoods was associated with 21% lower breast cancer risk among all women and a more pronounced, 40% lower risk among Latinos. Having more compared with no unhealthy food retail establishments was associated with 10% higher risk overall. Notable associations for the other composite built environment factors included residence in the highest versus lowest quintile of urban neighborhoods was associated with a 51% lower risk among Japanese Americans and lowest versus highest quintile of mixed-land development was associated with a 46% higher breast cancer risk in Latinos. The higher breast cancer risk associated with weight gain since age 21 persisted after adjustment for neighborhood obesogenic factors.

The higher incidence of breast cancer among high SES neighborhoods is well described in population-based studies across multiple racial/ethnic groups (reviewed in ref. 42), with associations primarily observed in hormone receptor–positive tumors (43). In general, the magnitude of association has been reported to be greater in Latinos and Asians/Pacific Islanders than whites and African Americans (28, 44). Only a few studies have been able to examine nSES (mostly as a composite measure of block group census data) while accounting for individual-level SES (mostly measuring education) and established reproductive, hormonal, and behavioral risk factors for breast cancer (45–49). In 2 prior population-based case–control studies in Wisconsin (45) and Massachusetts (46), both including largely non-Hispanic, postmenopausal white women, living in the highest versus lowest nSES quintile was associated with 20% to 30% higher odds of breast cancer independent of reproductive history, BMI, alcohol

Table 2. Associations of neighborhood SES, neighborhood obesogenic factors, and risk of invasive breast cancer and hormone receptor–positive subtype by race/ethnicity, postmenopausal women residing in California at baseline (n = 48,247), MEC, 1993–2010

Neighborhood measure	All women (n = 48,247) HR[a] (95% CI)	African American (n = 16,703) HR[a] (95% CI)	Japanese American (n = 5,063) HR[a] (95% CI)	Latino (n = 18,752) HR[a] (95% CI)	White (n = 7,729) HR[a] (95%CI)
Overall					
Neighborhood SES[b]					
Quintile 5: high	1.00	1.00	1.00	1.00	1.00
Quintile 4	0.92 (0.79–1.07)	0.88 (0.61–1.27)	0.88 (0.63–1.21)	0.95 (0.71–1.27)	1.01 (0.80–1.28)
Quintile 3	0.88 (0.76–1.03)	1.12 (0.79–1.58)	0.88 (0.63–1.25)	0.78 (0.59–1.04)	0.81 (0.61–1.07)
Quintile 2	0.89 (0.76–1.05)	1.03 (0.73–1.46)	0.73 (0.44–1.20)	0.83 (0.62–1.11)	0.89 (0.63–1.25)
Quintile 1: low	**0.79 (0.66–0.95)**	0.94 (0.65–1.36)	1.73 (0.86–3.48)	**0.60 (0.43–0.85)**	0.80 (0.50–1.29)
P_{trend}[c]	**0.02**	0.95	0.83	**0.01**	0.19
Urban environment[d]					
Quintile 1: low	1.00	1.00	1.00	1.00	1.00
Quintile 2	1.08 (0.95–1.23)	1.03 (0.80–1.34)	0.96 (0.70–1.34)	1.03 (0.82–1.28)	**1.36 (1.07–1.73)**
Quintile 3	1.03 (0.89–1.18)	1.13 (0.88–1.47)	0.95 (0.65–1.39)	0.97 (0.76–1.24)	1.07 (0.8–1.44)
Quintile 4	1.00 (0.86–1.15)	1.06 (0.82–1.37)	0.66 (0.41–1.08)	0.94 (0.72–1.22)	1.24 (0.91–1.69)
Quintile 5: high	1.02 (0.87–1.20)	1.10 (0.84–1.45)	**0.49 (0.26–0.90)**	1.07 (0.80–1.42)	1.13 (0.76–1.70)
P_{trend}[c]	0.87	0.56	**0.03**	0.98	0.45
Unhealthy food[e]					
None	1.00	1.00	1.00	1.00	1.00
Some	0.96 (0.84–1.09)	1.03 (0.82–1.28)	0.85 (0.58–1.26)	0.93 (0.74–1.17)	0.93 (0.69–1.25)
More	**1.10 (1.00–1.21)**	1.15 (0.97–1.35)	1.08 (0.82–1.42)	1.06 (0.89–1.27)	1.04 (0.84–1.29)
P_{trend}[c]	0.07	0.11	0.65	0.55	0.79
Mixed-land development[f]					
Quintile 5: high	1.00	1.00	1.00	1.00	1.00
Quintile 4	1.07 (0.92–1.25)	1.16 (0.84–1.59)	1.08 (0.76–1.56)	**1.38 (1.04–1.83)**	0.81 (0.61–1.09)
Quintile 3	1.02 (0.88–1.19)	1.16 (0.86–1.56)	1.00 (0.66–1.51)	1.29 (0.96–1.73)	0.76 (0.57–1.01)
Quintile 2	1.02 (0.88–1.18)	1.19 (0.89–1.58)	0.96 (0.66–1.41)	1.15 (0.86–1.53)	0.88 (0.67–1.14)
Quintile 1: low	1.11 (0.95–1.29)	1.24 (0.93–1.66)	0.78 (0.5–1.22)	**1.46 (1.10–1.93)**	0.87 (0.64–1.18)
P_{trend}[c]	0.36	0.18	0.24	0.10	0.49
Park[g]					
Some	1.00	1.00	1.00	1.00	1.00
None	1.03 (0.92–1.15)	0.93 (0.75–1.15)	1.05 (0.78–1.42)	1.00 (0.83–1.21)	1.12 (0.88–1.44)
P_{trend}[c]	0.66	0.52	0.76	0.97	0.36
ER^+/PR^+ subtype					
Neighborhood SES[b]					
Quintile 5: high	1.00	1.00	1.00	1.00	1.00
Quintile 4	0.89 (0.74–1.06)	0.85 (0.53–1.38)	0.82 (0.55–1.21)	0.87 (0.61–1.25)	0.99 (0.76–1.29)
Quintile 3	**0.82 (0.68–0.98)**	1.05 (0.65–1.68)	0.84 (0.57–1.26)	**0.65 (0.45–0.93)**	0.75 (0.54–1.03)
Quintile 2	**0.81 (0.67–0.99)**	0.99 (0.62–1.59)	**0.44 (0.23–0.86)**	**0.68 (0.47–0.99)**	0.88 (0.59–1.30)
Quintile 1: low	**0.73 (0.58–0.92)**	0.92 (0.56–1.53)	1.20 (0.54–2.66)	**0.52 (0.34–0.80)**	0.77 (0.45–1.31)
P_{trend}[c]	**0.01**	0.97	0.20	**<0.01**	0.18
Urban[d]					
Quintile 1: low	1.00	1.00	1.00	1.00	1.00
Quintile 2	**1.20 (1.03–1.39)**	1.11 (0.81–1.54)	1.20 (0.83–1.73)	1.15 (0.88–1.51)	**1.43 (1.09–1.88)**
Quintile 3	1.12 (0.95–1.33)	1.26 (0.92–1.75)	0.97 (0.60–1.56)	1.12 (0.84–1.50)	1.20 (0.86–1.69)
Quintile 4	1.04 (0.86–1.24)	1.19 (0.85–1.65)	0.82 (0.47–1.42)	0.86 (0.61–1.20)	1.32 (0.91–1.91)
Quintile 5: high	1.06 (0.87–1.29)	1.27 (0.91–1.79)	0.55 (0.27–1.09)	1.04 (0.73–1.49)	1.09 (0.69–1.72)
P_{trend}[c]	0.96	0.22	0.14	0.66	0.41
Unhealthy food[e]					
None	1.00	1.00	1.00	1.00	1.00
Some	0.95 (0.81–1.12)	1.02 (0.77–1.34)	0.94 (0.60–1.47)	0.96 (0.73–1.28)	0.86 (0.60–1.23)
More	1.09 (0.97–1.23)	1.05 (0.86–1.3)	1.14 (0.82–1.59)	1.07 (0.86–1.34)	1.08 (0.84–1.38)
P_{trend}[c]	0.19	0.63	0.47	0.57	0.61
Mixed-land development[f]					
Quintile 5: high	1.00	1.00	1.00	1.00	1.00
Quintile 4	1.07 (0.90–1.27)	1.18 (0.82–1.71)	1.13 (0.72–1.76)	**1.50 (1.04–2.16)**	0.75 (0.55–1.03)
Quintile 3	1.00 (0.83–1.20)	1.07 (0.75–1.5)	1.18 (0.71–1.96)	1.37 (0.94–2.00)	**0.67 (0.48–0.94)**
Quintile 2	0.98 (0.82–1.17)	0.96 (0.68–1.35)	1.12 (0.70–1.78)	1.29 (0.89–1.87)	0.84 (0.62–1.15)
Quintile 1: low	1.04 (0.87–1.25)	1.03 (0.74–1.44)	0.95 (0.56–1.61)	**1.49 (1.02–2.16)**	0.85 (0.60–1.19)
P_{trend}[c]	0.97	0.57	0.94	0.20	0.47
Park[g]					
Some	1.00	1.00	1.00	1.00	1.00
None	1.06 (0.93–1.22)	1.00 (0.77–1.3)	1.14 (0.79–1.64)	1.07 (0.84–1.36)	1.10 (0.82–1.47)
P_{trend}[c]	0.39	1.00	0.50	0.57	0.55

NOTE: Values in bold represent $P < 0.05$.

[a]Models [invasive breast cancer overall and hormone receptor–positive ($ER^+/PR+$) subtype] adjusted for age at entry, clustering effect of block group, race/ethnicity for all women, risk factors (family history of breast cancer, age at menarche, age at first live birth, number of children, hormone replacement therapy, ever had mammography, alcohol use, physical activity, education), baseline BMI and adult weight change, neighborhood SES, and all neighborhood obesogenic factors in table.

[b]Composite measure of 7 indicator variables for U.S. census block groups (Liu education index, proportion with a blue collar job, proportion older than age 16 in the workforce without a job, median household income, percent below 200% of the poverty line, median rent, median house value); categories based on distribution for block groups in Los Angeles County.

[c]Trend analysis excluding underweight and missing values. Trend variable was assigned ordinal value (i.e., 1, 2, 3) corresponding to categories.

[d]Composite measure of high population density, low commute by car, high traffic density, high street connectivity.

[e]Composite measure of high number of fast food restaurants and unhealthy retail food outlets. Unhealthy food environment index was categorized into none (no fast food restaurant and no unhealthy food outlet/minimal factor index value), some (factor index value greater than minimal and less than the median of non-minimal values), more (factor index value greater than or equal to the median of non-minimal values).

[f]Composite measure of high number of businesses and high number of recreational facilities.

[g]Number of parks categorized into none (no park/minimal factor index value) and any (≥1 parks/factor index value greater than minimal).

Table 3. Associations of body size and adult weight gain and risk of invasive breast cancer and hormone receptor subtypes by race/ethnicity, postmenopausal women residing in California at baseline (n = 48,247), MEC, 1993–2010

	All women (n = 48,247) HR (95% CI)	African American (n = 16,703) HR (95% CI)	Japanese American (n = 5,063) HR (95% CI)	Latino (n = 18,752) HR (95% CI)	White (n = 7,729) HR (95% CI)
Independent of individual-level factors[a]					
BMI at baseline, kg/m^2					
Underweight	0.83 (0.57–1.21)	1.00 (0.44–2.27)	0.61 (0.31–1.21)	1.19 (0.53–2.69)	1.00 (0.50–1.98)
Normal	1.00	1.00	1.00	1.00	1.00
Overweight	1.01 (0.89–1.14)	0.85 (0.69–1.05)	1.28 (0.86–1.90)	1.11 (0.90–1.38)	0.93 (0.71–1.22)
Obese	0.98 (0.84–1.14)	0.83 (0.65–1.05)	0.97 (0.41–2.34)	1.20 (0.93–1.55)	0.84 (0.57–1.22)
P_{trend}[b]	0.80	0.15	0.52	0.17	0.36
Adult weight gain since age 21,[c] kg					
−130.5 to <5.4	1.00	1.00	1.00	1.00	1.00
5.4 to <11.3	1.07 (0.92–1.25)	1.23 (0.87–1.74)	1.04 (0.76–1.41)	0.99 (0.75–1.31)	1.02 (0.77–1.34)
11.3 to <17.6	1.17 (1.00–1.37)	1.22 (0.87–1.71)	1.34 (0.87–2.06)	1.18 (0.88–1.56)	0.97 (0.71–1.33)
17.6 to <24.8	**1.35 (1.13–1.61)**	**1.56 (1.11–2.17)**	1.76 (0.96–3.26)	1.11 (0.81–1.52)	**1.44 (1.01–2.04)**
25.2 to <90.0	**1.56 (1.29–1.88)**	**1.85 (1.30–2.61)**	1.51 (0.51–4.44)	1.32 (0.94–1.83)	**1.60 (1.06–2.41)**
P_{trend}[b]	**<0.01**	**<0.01**	0.08	**0.05**	0.08
Independent of individual-level + neighborhood-level factors[d]					
BMI at baseline, kg/m^2					
Underweight	0.83 (0.57–1.21)	0.99 (0.43–2.24)	0.61 (0.31–1.2)	1.17 (0.52–2.65)	0.98 (0.49–1.95)
Normal	1.00	1.00	1.00	1.00	1.00
Overweight	1.01 (0.89–1.15)	0.85 (0.69–1.04)	1.30 (0.88–1.94)	1.13 (0.91–1.41)	0.94 (0.72–1.23)
Obese	0.99 (0.85–1.16)	0.83 (0.65–1.05)	1.02 (0.42–2.47)	1.23 (0.96–1.59)	0.84 (0.57–1.22)
P_{trend}[b]	0.91	0.15	0.46	0.12	0.37
Adult weight gain since age 21,[c] kg					
−130.5 to <5.4	1.00	1.00	1.00	1.00	1.00
5.4 to <11.3	1.07 (0.92–1.25)	1.24 (0.88–1.74)	1.02 (0.75–1.4)	1.00 (0.75–1.32)	1.00 (0.76–1.32)
11.3 to <17.6	1.17 (0.99–1.37)	1.23 (0.88–1.72)	1.32 (0.86–2.03)	1.18 (0.88–1.56)	0.97 (0.71–1.33)
17.6 to <24.8	**1.34 (1.13–1.60)**	**1.55 (1.11–2.16)**	1.79 (0.96–3.32)	1.10 (0.81–1.51)	1.41 (0.99–2.00)
25.2 to <90.0	**1.56 (1.29–1.88)**	**1.84 (1.30–2.60)**	1.59 (0.53–4.72)	1.30 (0.94–1.82)	**1.58 (1.05–2.39)**
P_{trend}[b]	**<0.01**	**<0.01**	0.08	0.05	0.09

NOTE: Values in bold represent $P < 0.05$.

[a]Adjusted for individual-level factors: age at entry, race/ethnicity for all women, family history of breast cancer, age at menarche, age at first live birth, number of children, hormone replacement therapy, ever had mammography, alcohol use, physical activity, and education, baseline BMI and adult weight change.

[b]Trend analysis excluding underweight and missing values. Trend variable was assigned ordinal value (i.e., 1, 2, 3) corresponding to categories.

[c]Difference between baseline weight and weight at age 21 categorized into quintiles based on study population distribution.

[d]Adjusted for individual-level factors with further adjustment for neighborhood SES and all neighborhood obesogenic factors (urban environment, unhealthy food, mixed-land development, parks).

intake, and mammography, as well as urban environments. In the Black Women's Health Study of African American women, aged 21–69 years from all regions in the United States., higher nSES was associated with increased ER$^+$ breast cancer risk ($P_{trend} = 0.02$; $n = 621$ after 14 years of follow-up), but associations were slightly attenuated after adjustment for parity and age at first birth ($P_{trend} = 0.14$) and further attenuated after additional adjustment for education, reproductive history, including lactation, BMI, vigorous exercise, alcohol intake, and mammography ($P_{trend} = 0.59$; ref. 48). Limited number of cases and geographical variation in nSES may account for the lack of association in the other prospective studies of mostly white, postmenopausal women in Washington state ($n = 856$ cases; ref. 47) and Maryland ($n = 272$; ref. 49).

Individual-level risk factors did not explain the nSES–breast cancer risk associations in our prospective study. Significant nSES–breast cancer risk associations remained among all women after adjustment for BMI, adult weight gain, education, established reproductive and hormonal risk factors, behavioral risk factors (alcohol intake, vigorous activity), and mammography. The lower nSES–lower breast cancer risk associations were unlikely to be related to access to mammographic screening, as analyses were adjusted for ever having had a mammogram, similar to other studies (45, 46) and analyses specific for early- or late-stage breast cancer did not yield different results. Residual confounding related to individual-level SES is likely unaccounted for in our analysis that lacked detailed data on income, wealth, or occupation. However, education is a stable measure that is typically attained relatively early in life and that has been associated more consistently with breast cancer incidence than has income (50).

A notable contribution of this study, conducted using the California component of the MEC, is the examination of neighborhood effects for four distinct racial/ethnic groups. Differential associations across racial/ethnic groups were evident with a more pronounced lower nSES–lower breast cancer risk among Latinos and more urban environments–lower breast cancer risk among Japanese Americans. In general, established breast cancer risk factors have less of an influence on breast cancer risk in Latino (51) and Japanese American (52) compared with white women, which may account for the persistent association among these racial/ethnic groups while accounting for individual-level breast cancer risk factors. These associations may also reflect early-life exposures that are more prevalent in Latinos living in lower SES neighborhoods or Japanese Americans living in more urban environments such as exposures related to hygiene and infectious diseases (53). It is plausible that in low nSES environments, the development and maintenance of closer ethnic ties, stronger cultural mores and ethnically distinct resources for Japanese Americans and Latinos may

have beneficial effects on breast cancer risk. Further studies are needed to understand the racial/ethnic-specific contextual role of the neighborhood on breast cancer risk (54).

More unhealthy food environments among all women and lower mixed-land development among Latinos were associated with higher breast cancer risk while accounting for body size and individual breast cancer risk factors. It is plausible that the higher breast cancer risk associated with more unhealthy food outlets and less mixed-land development operates via mechanisms involving physical or social stressors. Exposure to psychological stress has been implicated in breast cancer development (55). Further studies are needed that incorporate neighborhood characteristics associated with physiological stress [e.g., neighborhood safety/disorder (56, 57), neighborhood stability (58)], especially as chronic physiological stress can lead to the accumulation of excess body fat (59), and whether associations with breast cancer risk differ by race/ethnicity.

Strengths of our study include large sample size allowing for race/ethnicity-specific associations, data on prediagnostic BMI and adult weight gain, extensive questionnaire data on individual-level breast cancer risk factors, and 17 years of follow-up. However, there were limitations to our study. We characterize neighborhoods using census data, as opposed to detailed audits or self-reported perceived neighborhood data, potentially misclassifying neighborhoods attributes (60). However, census block group boundaries have been shown to correlate well with perceived neighborhoods (61). While the models we present did not account for length of stay at residence or change in environment (due to changes in neighborhood factors or relocations), we did conduct time-dependent analysis that accounted for change in obesogenic neighborhood factors and observed similar associations of lower nSES and lower breast cancer risk (data not shown). Furthermore, among participants who changed residences, more than 57% had little or no change in nSES level, whereas 27% increased and 16% decreased in nSES levels. We could not address the contextual influences of non-residential environments like workplace (62), geographic health care access (63), crime/disorder (64, 65), and psychosocial stress (66) or contextual exposures during early adulthood. We were not able to examine early life exposures (67) or breast cancer subtypes defined jointly by ER, PR, and HER2. We did not adjust for multiple comparisons; some of the reported differential associations across racial/ethnic groups may be due to chance.

This detailed assessment of the association between the neighborhood obesogenic environment and breast cancer risk adds to the evidence of a strong, contextual influence of nSES on breast cancer development. It suggests that there are additional operating exposures associated with breast cancer risk beyond body size, adult weight gain, and known reproductive and behavioral risk factors. Further research is needed to delineate the unique contextual aspects of high nSES, more urban environments, and less mixed-land development neighborhoods that place residents of specific racial/ethnic groups at higher risk for breast cancer or promote an unhealthy breast cancer risk profile over the life course, perhaps with a focus on early life exposures.

Disclosure of Potential Conflicts of Interest

C.A. Clarke is a Population Health Scientist at GRAIL, Inc. No potential conflicts of interest were disclosed by the other authors.

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