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Exposure to natural vegetation in relation to mammographic density in a Massachusetts-based clinical cohort

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Background: Inverse associations between natural vegetation exposure (i.e., greenness) and breast cancer risk have been reported; however, it remains unknown whether greenness affects breast tissue development or operates through other mechanisms (e.g., body mass index [BMI] or physical activity). We examined the association between greenness and mammographic density—a strong breast cancer risk factor—to determine whether greenness influences breast tissue composition independent of lifestyle factors.
Methods: Women (n = 2,318) without a history of breast cancer underwent mammographic screening at Brigham and Women's Hospital in Boston, Massachusetts, from 2006 to 2014. Normalized Difference Vegetation Index (NDVI) satellite data at 1-km^2 resolution were used to estimate greenness at participants' residential address 1, 3, and 5 years before mammogram. We used multivariable linear regression to estimate differences in log-transformed volumetric mammographic density measures and 95% confidence intervals (CIs) for each 0.1 unit increase in NDVI.
Results: Five-year annual average NDVI was not associated with percent mammographic density in premenopausal (β = –0.01; 95% CI = –0.03, 0.02; *P* = 0.58) and postmenopausal women (β = –0.02; 95% CI = –0.04, 0.01; *P* = 0.18). Results were similar for 1-year and 3-year NDVI measures and in models including potential mediators of BMI and physical activity. There were also no associations between greenness and dense volume and nondense volume.
Conclusions: Greenness exposures were not associated with mammographic density.
Impact: Prior observations of a protective association between greenness and breast cancer may not be driven by differences in breast tissue composition, as measured by mammographic density, but rather other mechanisms.

Keywords: Breast; Greenness; Mammographic density; Mammography; Natural vegetation; Normalized Difference Vegetation Index

Introduction

In the United States, over 250,000 breast cancer cases are diagnosed annually, making it the most commonly diagnosed cancer among women (excluding nonmelanoma skin cancer).[1–3] International variation, migration studies, and changes over time in breast cancer incidence rates highlight the importance of environmental and modifiable factors in breast cancer etiology and prevention.[4–6] There is a growing body of scientific literature on environmental exposures and breast cancer epidemiology outcomes.[7–16] High mammographic density is one of the strongest breast cancer risk factors that quantifies the amount of radiographically dense, fibroglandular tissues and the amount of fatty breast tissue. Compared with women with less than 5% dense tissue, women with 75% or more dense tissue have a 4.6-fold increased risk of developing breast cancer.[17] Studies of mammographic density variation in relation to environmental exposures may provide novel insights into early drivers of breast tissue development and early markers of high breast cancer risk,

What this study adds

While higher exposure to natural vegetation (i.e., greenness) has been associated with lower breast cancer risk independent of physical activity and BMI, no studies have investigated whether greenness influences breast tissue composition that would elucidate whether greenness can impact normal breast tissue biology. We addressed this gap by examining greenness and volumetric mammographic density, a strong risk factor for breast cancer. Future studies are needed to determine whether greenness and breast cancer risk is driven by mammographic density or other unexplored mechanisms.

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which may further our understanding of the environment's role on normal breast tissue variation.

Natural vegetation exposure (also called "greenness") is increasingly considered to be a health-promoting contextual environmental factor that may be relevant to cancer prevention.[18] People who live in communities with more natural vegetation exposure (e.g., parks, gardens, and forests) have higher physical activity levels and lower body mass index (BMI),[19–23] both of which are breast cancer risk-reduction factors[24] that offer translational opportunities for breast cancer prevention. To date, three epidemiologic studies have reported that women residing in greener areas with more natural vegetation have lower breast cancer risk[25–27] after adjustment for breast cancer risk factors and socioeconomic status (SES).[25,26] One study investigated whether the association between greenness and breast cancer development was mediated by physical activity but did not observe mediation by physical activity.[26] Additionally, one recent study suggests that women with jobs in orchards, greenhouses, nurseries, and gardens had lower mammographic density but did not specifically examine greenness exposure.[28] Greenness has not been studied extensively in the context of breast cancer epidemiology, particularly in relation to mammographic density, although it may be a particularly relevant factor to promote breast cancer risk reduction.

The objective of this study was to examine the association between natural vegetation exposure and mammographic density. To test the hypothesis whether natural vegetation influences variation in normal breast tissue composition, we examined the association between greenness and volumetric mammographic density in a clinical cohort of adult women based out of Boston, Massachusetts. We additionally explored whether the association between greenness and mammographic density was independent of BMI and physical activity that may act as mediators.

Materials and methods

The Boston Mammography Cohort Study (BMCS) is a clinical cohort of 2,821 adult women who underwent mammography visits at Brigham and Women's Hospital (BWH; Boston, Massachusetts) from 2006 to 2014. Participants were enrolled at the BWH mammography clinic and completed a baseline questionnaire at the time of enrollment to capture demographic factors, residential address, medical history including detailed breast health information (e.g., family history of breast cancer, personal history of breast cancer, benign breast disease [BBD]), reproductive factors (e.g., parity, age at birth(s), breastfeeding, menopause, menopausal hormone therapy use, use of oral contraceptives), anthropometrics (e.g., height, weight at enrollment, and body shape at various ages), and lifestyle factors, such as various types and frequency of physical activity (e.g., walking, jogging, running, bicycling, tennis). Participants who were seen for care at BWH were a part of the Mass General Brigham Healthcare Network that allowed for linkage to additional medical information. This included the Mass General Brigham Healthcare system databases and hospital-based registries for collection of digital mammograms and additional medical information such as the development of breast cancer through December 2017. Participants were also linked to the Massachusetts Cancer Registry to obtain clinical information on cancer diagnoses from 2006 to 2014. Participants' residential addresses at enrollment were geocoded to allow for linkage to environmental and neighborhood characteristics. A total of 89% of the residential addresses were geocoded to the street address level, and of these, >95% resided within the state of Massachusetts.

The study was approved by the Institutional Review Board at BWH, and participants provided informed consent before participating.

Greenness exposure

The Normalized Difference Vegetation Index (NDVI) is a commonly used measure of greenness.[21] For this study, we used greenness data captured from the National Oceanic and Atmospheric Administration's (NOAA) Advanced Very High Resolution Radiometer (AVHRR) sensor. The sensors measure the intensity of visible light (0.4–0.7 μm) and near-infrared wavelengths (0.7–1.1 μm) that can be used to derive estimates of vegetation levels (i.e., greenness) based on light absorption of chlorophyll in natural vegetation. The satellite-measured red and near-infrared bands reflected from the Earth's surface are used to derive NDVI values ranging from –1 to 1. High-vegetation areas have values closer to 1, low-vegetation areas have values closer to 0, and values approaching –1 indicate bodies of water. NDVI estimates were collected at 1-km2 scale resolution for every season (January to represent winter, April to represent spring, July to represent summer, and September/October to represent fall) and each participant was assigned the value for the pixel in which her address at time of enrollment was located. We estimated the annual average greenness across seasons and examined peak summer greenness (July). We estimated the annual average and summer greenness 1 year before the mammogram year to capture recent greenness exposure and averaged the annual and summer NDVI estimates across the 3 and 5 years before the mammogram year to capture long-term greenness exposures.

Mammographic density measurement

We collected digital mammogram mediolateral and craniocaudal images within the Partners HealthCare System for the left and right breast for all BMCS participants. Information on the type of visit (i.e., screening or diagnostic) was collected from the mammogram Digital Imaging and Communications in Medicine (DICOM) header input by the clinical personnel. We measured volumetric breast density (% volumetric density, total dense volume, and nondense volume) from the participant's baseline screening mammogram using a fully automated algorithm for raw, unprocessed images (Volpara Health, New Zealand), and we averaged the density measures across the left and right breast images. Volpara uses the measured breast thickness and x-ray attenuations on the raw images to estimate dense and nondense tissue volume for each pixel. Volumetric measures account for the fact that the breast is 3D, unlike the more common area-based measures of breast density from film mammograms that are not fully automated. Volpara's volumetric measurements have been shown to be associated with breast cancer risk on par with other area-based mammographic density measurement techniques and better than other fully automated methods.[29] The primary outcome was percent volumetric density (i.e., total dense volume divided by the total breast volume), and total dense and nondense volume were secondary outcomes.

Covariates

Covariate data were obtained from the enrollment questionnaire. Information was collected on age (years), race (Asian, Black, Hawaiian, Native, other race, and White), Hispanic ethnicity, menopausal status at enrollment, history of biopsy-confirmed benign breast disease (BBD), and hormonal use for postmenopausal women (never, current, past, unknown, and missing). The number of live births and stillbirths for pregnancies lasting 6 months or more was used to create categories of parity (nulliparous, parous, missing). Participants with a mother or sister with breast cancer were categorized as having a family history of breast cancer. Weight (pounds) and height (feet and inches) at enrollment were used to derive body mass index (BMI) (kg/m^2). To calculate physical activity, participants were asked their average time per week spent walking, jogging, running, bicycling,

lap swimming, playing tennis, other aerobic exercise (e.g., dance, ski, stair machine), low-intensity exercise (e.g., yoga), or other vigorous exercise (e.g., lawn mowing) during the past year. These responses were converted to metabolic equivalent (MET) hours per week according to established criteria.[30,31]

Neighborhood-level socioeconomic status (SES) was based on the census tract at baseline, linked with 5-year estimates from the American Community Survey (ACS). The ACS is an annual survey on demographic, social, economic, and housing factors conducted by the US Census Bureau from a sample of US addresses.[32] Participants that were enrolled in the study between 2006 and 2010 were linked to the ACS 2010 5-year estimates and participants enrolled after 2010 were linked to the ACS 2015 5-year estimates. SES variables that were included in the analysis were the percent of the census tract population with at least a high school diploma and the percent of the census tract population below the poverty level. We used the missing indicator method stratified by menopausal status, where participants living in census tracts with missing information on these variables were assigned the median value.

Study population

Women with mammographic density readings from raw, unprocessed mammograms at the time of enrollment were included in this analysis (n = 2,696); the breast density outcome measurements were not available for women with processed images (n = 125). We included women who were going for a screening mammogram, which includes a routine visit, regardless of the breast density results of their mammogram. We excluded women with diagnostic images only (n = 141) or unknown type of mammogram visit (n = 7) given by the mammogram DICOM header, and participants with a personal history of breast cancer ascertained from the self-reported questionnaire (n = 12) or the registry databases (n = 4), and those missing data on personal history of breast cancer (n = 46). Women were also excluded if they were missing information on greenness NDVI exposure (n = 75) or BMI (n = 93). A total of 2,318 women remained in this analysis who were similar to the full cohort of BMCS participants (n = 2,821) in terms of age (53.1 vs. 53.4 years), BMI (26.6 vs. 26.6 kg/m^2), parity (82.1% vs. 81.7%), menopausal status (postmenopausal: 52.3% vs. 53.1%), current menopausal hormone therapy use (4.7% vs. 4.8%) and the greenness exposure, NDVI (0.441 for both).

Statistical analyses

Analyses were conducted separately for premenopausal women (n = 1,106) and postmenopausal women (n = 1,212) at the time of mammogram. Mammographic density measures were log-transformed to obtain normally distributed residuals. We used multivariable linear regression to estimate differences in log-transformed volumetric percent density and 95% confidence intervals (CIs) per 0.1 unit increase in NDVI adjusted for known breast density predictors: age (continuous, years), BMI (continuous, kg/m^2), categories of race/ethnicity (Hispanic of any race, non-Hispanic Black, non-Hispanic White, and non-Hispanic Asians, Hawaiians, Natives, other races, and missing), parity (nulliparous, parous, missing), family history of breast cancer (yes/no), history of biopsy-confirmed BBD (no, yes, missing), and menopausal hormone therapy use for postmenopausal analyses (never user, current user, past user, missing). We additionally considered smoking ≥20 packs of cigarettes (never, ever, missing), alcohol consumption per week (0–1 drinks, 2+ drinks) and oral contraceptive use (never, ever, missing), and percent of the census tract population who are below poverty level and percent of the census tract population who are high school graduates. Models separately considered BMI and physical activity (MET-hours/week) that potentially act as mediators. Participants with missing physical activity information were assigned the median value stratified by menopausal status (premenopausal women missing physical activity data, n = 64; postmenopausal women missing physical activity data, n = 71), and we included a missing indicator variable in the regression models. We used the likelihood ratio test (LRT) to identify statistically significant interactions between NDVI and categories of BMI (<25 kg/m^2, overweight with BMI 25 to <30 kg/m^2, obese with BMI ≥30 kg/m^2), quartiles of physical activity, and racial and ethnic groups. We used the Wald chi-square test *P* value for interaction terms between NDVI and continuous BMI, and NDVI and continuous physical activity levels. Analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

Results

The age-standardized characteristics of the study participants across quartiles of NDVI are provided for premenopausal women (Table 1) and postmenopausal women (Table 2). Compared with women residing in less green areas, women residing in greener areas had lower BMI, were more likely to be non-Hispanic White, parous, consume >1 alcoholic drink per week, be more physically active, and have biopsy-confirmed BBD for premenopausal (Table 1) and postmenopausal women (Table 2). Among premenopausal women, women residing in greener areas were slightly older, more likely to have breastfed for more than 6 months and be past smokers (Table 1). In postmenopausal women, women residing in greener areas were slightly younger, were more likely to have had a family history of breast cancer, be never smokers, and were more likely to have used oral contraceptives (Table 2).

Overall, there were no associations between NDVI and mammographic density among premenopausal or postmenopausal women (Table 3). For example, log-transformed percent volumetric mammographic density did not vary per 0.1 unit increase in 5-year annual average NDVI (adjusted β = –0.01; 95% CI = –0.03, 0.02; *P* = 0.58) or 5-year summer average NDVI (adjusted β = –0.01; 95% CI = –0.03, 0.01; *P* = 0.58) among 1,106 premenopausal women. Similarly, 5-year annual average NDVI (adjusted β = –0.02; 95% CI = –0.04, 0.01; *P* = 0.18) and 5-year summer average NDVI (adjusted β = –0.01; 95% CI = –0.03, 0.01; *P* = 0.30) were not associated with log-transformed percent mammographic density among 1,212 postmenopausal women. Results were similar for 1-year and 3-year NDVI measures and in models including potential mediators of BMI and physical activity (Table 3). Adjusting for smoking, alcohol consumption per week, and oral contraceptive use did not materially change the estimates (data not shown). Similarly, adjusting for percent of the census tract population who are below poverty level and percent of the census tract population who are high school graduates did not materially change the results (data not shown). The associations between greenness and dense volume and nondense volume were also consistent with the null (Supplemental Table 1; http://links.lww.com/EE/A191).

There was a statistically significant interaction between NDVI and BMI in premenopausal (*P* for interaction = 0.004) and postmenopausal women (*P* for interaction = 0.04) (Table 4). Among obese premenopausal women (n = 232), a 0.1 increase in NDVI was associated with lower log-transformed mammographic density (adjusted β = –0.05; 95% CI = –0.11, 0.02; LRT *P* for interaction = 0.02); however, among overweight premenopausal women (n = 284), there was a positive association (adjusted β = 0.05; 95% CI = –0.01, 0.11). There were no statistically significant interactions between NDVI and racial and ethnic groups or physical activity (*P* for interactions > 0.05) (Table 4).

Discussion

We observed no association between residential greenness exposure and mammographic density in premenopausal

Table 1.

Age-standardized characteristics at the time of enrollment for premenopausal women (n = 1,106) in the Boston Mammography Cohort Study by quartiles of 5-year annual NDVI before screening mammogram year

	NDVI	NDVI	NDVI	NDVI
No. of participants	**Quartile 1 (n = 274)**	**Quartile 2 (n = 279)**	**Quartile 3 (n = 276)**	**Quartile 4 (n = 277)**
NDVI range (minimum, maximum)	(0.12, 0.35)	(0.35, 0.46)	(0.46, 0.54)	(0.54, 0.67)
Volumetric percent density, mean (SD)	12.8 (7.5)	12.4 (7.4)	12.9 (7.1)	13.5 (6.8)
Age[a], mean (SD)	44.6 (5.6)	45.6 (5.1)	45.3 (5)	46 (4.7)
BMI, mean (SD)	26.4 (6.6)	27.5 (6.8)	25.7 (5.4)	25.1 (5)
Race and ethnicity, % (n)				
Hispanic of any race	23.2 (64)	22.6 (63)	10.8 (30)	2.0 (6)
Non-Hispanic Black	11.5 (32)	15.5 (43)	7.3 (20)	1.0 (3)
Non-Hispanic other/unknown	6.9 (19)	5.7 (16)	4.6 (13)	6.4 (18)
Non-Hispanic White	57.3 (157)	55.0 (153)	77.1 (213)	90.5 (251)
Missing	1.1 (3)	1.3 (4)	0.3 (1)	0.0 (0)
Parity, % (n)				
Nulliparous	23.0 (63)	19.1 (53)	12.4 (34)	8.9 (25)
Parous	74.3 (204)	78.1 (218)	86.5 (239)	90.1 (250)
Missing	2.6 (7)	2.8 (8)	1.1 (3)	1.0 (3)
Number of months breastfed among parous women, % (n)				
Parous did not breastfeed	13.6 (28)	19.6 (43)	12.3 (30)	13.3 (33)
0–6 months	24.1 (49)	26.0 (57)	22.2 (53)	22.3 (56)
>6 months	42.9 (88)	44.4 (97)	55.7 (134)	55.0 (137)
Missing	19.3 (39)	10.0 (22)	9.8 (23)	9.4 (23)
Mother or sister diagnosed with breast cancer, % (n)	21.5 (59)	21.1 (59)	18.3 (51)	23.1 (64)
Smoked 20 packs of cigarettes or more in lifetime, % (n)				
Never	69.9 (191)	67.5 (188)	68.9 (190)	68.6 (190)
Yes, past	21.5 (59)	23.2 (65)	24.2 (67)	26.1 (72)
Yes, currently	5.9 (16)	6.2 (17)	5.5 (15)	4.0 (11)
Missing	2.7 (7)	3.1 (9)	1.4 (4)	1.3 (4)
Alcohol consumption, % (n)				
0–1 drinks per week	59.0 (162)	63.4 (177)	60.4 (167)	53.5 (148)
2–6 drinks per week	27.6 (76)	23.2 (65)	29.3 (81)	35.4 (98)
7–13 drinks per week	9.0 (25)	6.8 (19)	6.4 (18)	8.1 (22)
14+ drinks per week	1.1 (3)	1.1 (3)	2.3 (6)	1.3 (4)
Missing	3.3 (9)	5.5 (15)	1.6 (4)	1.6 (5)
Total activity MET hours/week, mean (SD)	26.4 (29.3)	25.2 (35.3)	27.1 (34.7)	27.7 (27.2)
Oral contraceptive use, % (n)				
Never used oral contraceptives	17.0 (47)	20.7 (58)	11.2 (31)	16.1 (44)
Ever used oral contraceptives	80.9 (222)	77.6 (216)	88.0 (243)	83.0 (230)
Missing	2.1 (6)	1.7 (5)	0.7 (2)	1.0 (3)
Age at menarche, mean (SD)	12.8 (1.5)	12.6 (1.4)	12.8 (1.3)	13.0 (1.4)
BBD, % (n)				
No confirmed history of BBD	89.9 (246)	85.9 (240)	85.3 (235)	83.1 (230)
Biopsy-confirmed history of BBD	5.7 (16)	10.2 (29)	9.5 (26)	13.0 (36)
Missing	4.4 (12)	3.9 (11)	5.2 (14)	3.9 (11)

Values are means (SD) for continuous variables, percentages (sample size, n) for categorical variables, and are standardized to the age distribution of the study population.

Values of polytomous variables may not sum to 100% due to rounding.

[a]Value is not age adjusted.

and postmenopausal women in this clinical cohort based in Massachusetts. While these null results still need to be confirmed in additional epidemiologic studies, these results suggest that recent exposure to greenness is unlikely to act biologically on normal breast tissue, as measured by mammographic density. Thus, it remains unknown whether mammographic density or other mechanisms could explain previous studies showing that women residing in greener areas have lower risk of breast cancer.

Prior literature on natural vegetation exposure in relation to breast cancer incidence is limited,[25–27] and to date, no literature has been published on natural vegetation exposure with regards to mammographic density. In a large statutory health insurance cohort of 1.9 million beneficiaries in Saxony, Germany, postal code-level estimates of greenness in 2007 were weakly associated with lower breast cancer risk for a 10% increase in greenness (relative risk [RR] = 0.96; 95% CI = 0.92, 0.99), but analyses were only adjusted for age.[27] In a large Spanish breast cancer population-based case-control study, compared with those who lived more than 300 m away from an urban green space, women living within 100 m of an urban green area had 44% lower odds of developing breast cancer (odds ratio [OR] OR = 0.56; 95% CI = 0.41, 0.76) and living within 100–300 meters was associated with a 29% lower odds of breast cancer (OR = 0.71; 95% CI = 0.53, 0.96) after adjusting for age, education, SES, and parity.[26] This association was not mediated by a binary measure of physical activity[26] and mediation by BMI was not assessed. In preliminary results from the US nationwide Nurses' Health Study II prospective cohort study (conference abstract), women who resided in the top quintile of greenness had a 13% lower rate of developing breast cancer compared with those in the lowest quintile of exposure (hazard ratio [HR] = 0.87; 95% CI = 0.75, 1.01; *P* for trend = 0.02) after adjusting for known and suspected breast cancer risk factors.[25] Additional studies are needed to determine whether the inverse association between greenness and breast cancer incidence is mediated by BMI and/or physical activity. Furthermore, while the results from the Nurses' Health Study II and the Spanish case-control study were adjusted for SES, it is possible that there may be residual confounding by other individual-level and neighborhood-level SES that could

Table 2.

Age-standardized characteristics at the time of enrollment for postmenopausal women (n = 1,212) in the Boston Mammography Cohort Study by quartiles of 5-year annual NDVI prior to screening mammogram year

	NDVI	NDVI	NDVI	NDVI
No. of participants	**Quartile 1 (n = 303)**	**Quartile 2 (n = 304)**	**Quartile 3 (n = 303)**	**Quartile 4 (n = 302)**
NDVI range (minimum, maximum)	(0.15, 0.35)	(0.35, 0.46)	(0.46, 0.53)	(0.53, 0.67)
Volumetric percent density, mean (SD)	8.0 (5.7)	7.8 (5.3)	8.1 (5.6)	8.6 (5.5)
Age[a], mean (SD)	60.5 (9.2)	59.8 (8.5)	60.6 (8.5)	59.5 (7.5)
BMI, mean (SD)	27.8 (7.1)	27.5 (6)	26.5 (5.2)	25.7 (5)
Race/ethnicity, % (n)				
Hispanic of any race	12.6 (38)	14.3 (44)	4.8 (15)	1.6 (5)
Non-Hispanic Black	16.6 (50)	19.6 (59)	6.6 (20)	1.0 (3)
Non-Hispanic other/unknown	5.2 (16)	4.4 (13)	3.2 (10)	3.0 (9)
Non-Hispanic White	65.4 (198)	61.7 (188)	85.1 (258)	94.1 (284)
Missing	0.2 (1)	0.0 (0)	0.4 (1)	0.2 (1)
Parity, % (n)				
Nulliparous	19.7 (60)	20.8 (63)	13.5 (41)	11.8 (36)
Parous	78.1 (237)	75.5 (229)	84.7 (257)	87.3 (264)
Missing	2.1 (6)	3.7 (11)	1.8 (5)	0.9 (3)
Number of months breastfed among parous women, % (n)				
Parous did not breastfeed	30.6 (72)	21.8 (51)	31.8 (82)	25.9 (68)
0–6 months	21.9 (52)	24.7 (58)	21.3 (55)	21.9 (58)
>6 months	30.1 (71)	37.0 (87)	34.7 (90)	41.9 (110)
Missing	17.4 (41)	16.5 (39)	12.1 (31)	10.4 (27)
Mother or sister diagnosed with breast cancer, % (n)	21.7 (66)	21.7 (66)	23.4 (71)	22.3 (67)
Smoked 20 packs of cigarettes or more in lifetime, % (n)				
Never	46.5 (141)	58.6 (178)	50.3 (152)	54.5 (165)
Yes, past	39.6 (120)	33.5 (102)	41.9 (127)	41.1 (124)
Yes, currently	10.6 (32)	5.3 (16)	5.9 (18)	2.7 (8)
Missing	3.4 (10)	2.6 (8)	1.9 (6)	1.7 (5)
Alcohol consumption, % (n)				
0–1 drinks per week	58.0 (176)	67.7 (206)	55.5 (168)	47.8 (144)
2–6 drinks per week	24.2 (73)	19.5 (59)	29.5 (89)	33.1 (100)
7–13 drinks per week	10.3 (31)	6.3 (19)	8.7 (26)	14.1 (43)
14+ drinks per week	4.8 (15)	2.9 (9)	3.9 (12)	2.3 (7)
Missing	2.7 (8)	3.7 (11)	2.4 (7)	2.7 (8)
Total activity MET hours/week, mean (SD)	19.9 (26)	21.1 (24.8)	25.3 (35.7)	28.4 (36.5)
Oral contraceptive use, % (n)				
Never used oral contraceptives	26.8 (81)	27.8 (84)	30.5 (92)	24.2 (73)
Ever used oral contraceptives	71.9 (218)	69.2 (210)	67.2 (204)	74.4 (225)
Missing	1.3 (4)	3.0 (9)	2.3 (7)	1.4 (4)
Age at menarche, mean (SD)	12.6 (1.5)	12.6 (1.5)	12.8 (1.6)	12.7 (1.4)
BBD, % (n)				
No confirmed history of BBD	79.7 (242)	77.7 (236)	77.0 (233)	73.8 (223)
Biopsy-confirmed history of BBD	16.0 (49)	14.4 (44)	18.1 (55)	19.7 (60)
Missing	4.3 (13)	7.9 (24)	4.8 (15)	6.5 (20)
Menopausal hormone therapy use, % (n)				
Never used	59.7 (181)	59.5 (181)	57.0 (173)	60.1 (182)
Current user	7.8 (24)	7.4 (23)	12.9 (39)	9.5 (29)
Past user	28.7 (87)	28.7 (87)	28.6 (87)	29.9 (90)
Missing	3.8 (12)	4.4 (13)	1.5 (5)	0.5 (1)

Values are means (SD) for continuous variables, percentages (sample size, n) for categorical variables, and are standardized to the age distribution of the study population.

Values of polytomous variables may not sum to 100% due to rounding.

[a]Value is not age adjusted.

explain these inverse associations between greenness and breast cancer incidence. It is notable that in our study of greenness and mammographic density, the results did not change materially when we adjusted for neighborhood-level SES, which is in line with prior research on mammographic density and SES that there is little association after adjustment for BMI.[33,34]

To our knowledge, this is the only study published on the association of natural vegetation exposure and mammographic density. A recent cross-sectional study in Madrid, Spain, of 1,362 premenopausal women observed that premenopausal women with jobs in orchards, greenhouses, nurseries, and gardens had lower mammographic density of borderline statistical significance after adjustment for age, education, BMI, parity, oral contraceptive use, breast biopsy, family history of breast cancer, smoking, energy intake, and alcohol consumption (P = 0.092).[28] While these occupations are characterized by higher greenness exposure, the association between greenness exposure and mammographic density was not examined explicitly in the Madrid study. Taken together with the current study, it is likely that greenness exposures are not associated with normal breast tissue variation.

There are multiple limitations and strengths of this study. There is a growing body of literature on mammographic density and environmental exposures, some of which are associated with greenness exposure that were not adjusted for in this analysis; however, the literature on particulate matter ($PM_{2.5}$) and mammographic density[14,16] and noise and mammographic density[35] is largely null and these exposures are unlikely to contribute substantially to confounding in this analysis. In this cross-sectional analysis, we were unable to examine early-life greenness exposure that may be a more relevant time window of susceptibility for breast development.[36] In any clinical population, selection bias

Table 3.

Adjusted estimates (95% CI) of the difference in log-transformed volumetric percent mammographic density for a 0.1 unit increase in NDVI measures in premenopausal (n = 1,106) and postmenopausal women (n = 1,212)

	5-year annual average NDVI	5-year summer average NDVI	3-year annual average NDVI	3-year summer average NDVI	1-year annual average NDVI	1-year summer average NDVI
Premenopausal (n = 1,106)						
Basic[a]	0 (–0.02, 0.03)	0 (–0.02, 0.02)	0 (–0.02, 0.02)	0 (–0.02, 0.01)	0 (–0.02, 0.03)	0 (–0.02, 0.01)
Multivariable[b]	–0.01 (–0.03, 0.02)	–0.01 (–0.03, 0.01)	–0.01 (–0.03, 0.02)	–0.01 (–0.03, 0.01)	0 (–0.03, 0.02)	–0.01 (–0.03, 0.01)
Multivariable excluding BMI[c]	–0.02 (–0.05, 0.01)	–0.02 (–0.04, 0.01)	–0.02 (–0.05, 0.01)	–0.02 (–0.05, 0.002)	–0.02 (–0.05, 0.02)	–0.02 (–0.04, 0.003)
Multivariable + physical activity[d]	–0.01 (–0.03, 0.02)	0 (–0.02, 0.02)	–0.01 (–0.03, 0.02)	–0.01 (–0.03, 0.01)	0 (–0.03, 0.02)	–0.01 (–0.02, 0.01)
Postmenopausal (n = 1,212)						
Basic[a]	–0.02 (–0.04, 0.01)	–0.01 (–0.03, 0.01)	–0.02 (–0.04, 0.01)	–0.01 (–0.03, 0.01)	–0.01 (–0.03, 0.01)	0 (–0.02, 0.01)
Multivariable[b]	–0.02 (–0.04, 0.01)	–0.01 (–0.03, 0.01)	–0.01 (–0.04, 0.01)	–0.01 (–0.03, 0.01)	–0.01 (–0.03, 0.01)	0 (–0.02, 0.02)
Multivariable excluding BMI[c]	–0.01 (–0.04, 0.02)	–0.01 (–0.03, 0.02)	0 (–0.03, 0.03)	0 (–0.03, 0.02)	0 (–0.03, 0.03)	0.01 (–0.01, 0.03)
Multivariable + physical activity[d]	–0.02 (–0.04, 0.01)	–0.01 (–0.03, 0.01)	–0.01 (–0.04, 0.01)	–0.01 (–0.03, 0.01)	–0.01 (–0.03, 0.01)	0 (–0.02, 0.02)

[a]Basic: Adjusted for age and BMI.

[b]Multivariable: Adjusted for age, BMI, race/ethnicity (Hispanic of any race, non-Hispanic Black, non-Hispanic White, non-Hispanic other races and missing), parity (nulliparous, parous, missing), family history of breast cancer, BBD (no confirmed history of BBD, biopsy-confirmed history of BBD, missing), and menopausal hormone therapy use (never user, current user, past user, missing) for postmenopausal models.

[c]Multivariable excluding BMI: Adjusted for multivariable model covariates without BMI.

[d]Multivariable + physical activity: Adjusted for multivariable model covariates and physical activity.

Table 4.

Adjusted estimates[a] (95% CI) of the difference in log-transformed volumetric percent mammographic density for a 0.1 unit increase in 5-year annual average NDVI with interaction terms with continuous BMI, categories of BMI, race/ethnicity, continuous physical activity, and categories of physical activity

	n	Premenopausal	n	Postmenopausal
Effect modification by BMI (continuous)	1,106		1,212	
Main effect of NDVI		0.15 (0.04, 0.26)		0.10 (–0.02, 0.21)
Main effect of BMI per 1 kg/m^2		–0.04 (–0.06, –0.02)		–0.04 (–0.06, –0.03)
Interaction for BMI × NDVI		–0.006 (–0.011, –0.002)		–0.004 (–0.008, –0.0002)
P for interaction		0.0037		0.04
Main effects of NDVI on mammographic density by BMI categories				
BMI <25 kg/m^2	591	–0.01 (–0.04, 0.02)	571	–0.01 (–0.05, 0.03)
BMI 25 to 29.9 kg/m^2	284	0.05 (–0.01, 0.11)	323	–0.02 (–0.06, 0.31)
BMI ≥ 30 kg/m^2	231	–0.05 (–0.11, 0.02)	318	0 (–0.04, 0.04)
LRT *P* for interaction between BMI categories and NDVI		0.02		0.66
Main effects of NDVI on mammographic density by race/ethnicity				
Hispanic of any race	162	0.01 (–0.08, 0.10)	104	0.02 (–0.07, 0.12)
Non-Hispanic Black	105	0 (–0.11, 0.11)	131	–0.04 (–0.15, 0.06)
Non-Hispanic other or unknown race	73	0.01 (–0.08, 0.10)	52	–0.02 (–0.13, 0.09)
Non-Hispanic White	766	–0.01 (–0.04, 0.02)	925	–0.02 (–0.05, 0.01)
LRT *P* for interaction between race and NDVI interaction		0.93		0.84
Effect modification by PA (continuous), total MET hours/week	1,106		1,212	
Main effect of NDVI		–0.02 (–0.06, 0.01)		–0.03 (–0.06, 0.003)
Main effect of PA per 1 MET-hour increase		0.001 (–0.005, 0.0025)		–0.002 (–0.006, 0.002)
Interaction for PA × NDVI		0.0005 (–0.0003, 0.0013)		0.0005 (–0.0004, 0.001)
P for interaction		0.21		0.25
Main effects of NDVI on mammographic density by PA quartiles, total MET hours/week				
Quartile 1	280	–0.03 (–0.09, 0.03)	306	–0.04 (–0.10, 0.01)
Quartile 2	241	0.03 (–0.03, 0.09)	264	–0.01 (–0.06, 0.04)
Quartile 3	309	–0.02 (–0.07, 0.03)	336	0.02 (–0.03, 0.07)
Quartile 4	276	–0.01 (–0.05, 0.04)	306	–0.02 (–0.07, 0.02)
LRT *P* for interaction between PA categories and NDVI		0.15		0.19

[a]Estimates are adjusted for age, BMI, race and ethnicity (Hispanic of any race, non-Hispanic Black, non-Hispanic White, non-Hispanic other races and missing), parity (nulliparous, parous, missing), family history of breast cancer, BBD (no confirmed history of BBD, biopsy-confirmed history of BBD, missing), and menopausal hormone therapy use (never user, current user, past user, missing) for postmenopausal models.

PA indicates physical activity.

is a potential concern if participation depends on the exposure and the outcome; however, in our study, we observed a range of volumetric percent mammographic density that is consistent with other registry-based studies for largely postmenopausal women without breast cancer.[37,38] Additionally, during this time period (2006–2014), many women were unaware of their mammographic density due to a lack of reporting breast density results to patients (legislation was only recently put in place in 2015 in Massachusetts requiring physicians to report breast density to patients). Thus, we do not believe that participation is related to the outcome in this study. Additionally, our NDVI range of 0.12–0.67 is capturing a large range of greenness, although may not be capturing people in the extreme green or least green areas. Therefore, the actual potential for selection bias in this study is unlikely. Exposure measurement error is likely given that we used natural vegetation at each participant's residence at the time of enrollment, which may not reflect the natural vegetation exposure levels where the participants spend their time. The observed null

associations may be due to nondifferential exposure measurement error that could mask a true effect because this exposure measurement error is unlikely to differ by mammographic density measurement error. Additionally, the NDVI measure of natural vegetation used in this study does not account for the type of green space (e.g., agricultural, gardens, parks, etc.) or qualities of the green space that make vegetation appealing or usable for recreation or potential chemicals that may be used on natural vegetation; however, consistent with other studies,[19–23] we observed that those residing in the most green areas had lower BMI and higher physical activity levels (Tables 1 and 2) suggesting that the NDVI metric is informative for health behaviors in this cohort. Another limitation of this study is that we did not have prior residential history to capture different addresses before enrollment; therefore, it is possible that we may have a higher degree of measurement error for the 3-year and 5-year greenness estimates before enrollment. However, it was a strength of the study that we were able to examine multiple time windows of greenness exposure in relation to variation in mammographic density. There are strengths of the residential vegetation metrics used, including using the satellite-based NDVI measures that provide an objective and quantitative measure of vegetation that is not subject to errors of self-reported use of green spaces or differences in administrative reporting of green areas across towns and cities.

Furthermore, the BMCS is a relatively large clinical cohort of women who, despite the cohort name, reside across Massachusetts with a large geographic catchment area, providing variation in greenness. The participants represent a more racially and ethnically diverse cohort than most studies of mammographic density, and this allowed for the examination of effect modification by race and ethnicity. The BMCS participants provided detailed information from questionnaires on demographic factors, medical history, reproductive factors, anthropometrics, and lifestyle factors that allowed us to account for confounding by individual-level factors. The use of a fully automated software to estimate volumetric mammographic density is a strength of this study as well, as most research on mammographic density has historically relied on semiautomated area-based measures of mammographic density that can introduce outcome measurement errors from the readers.

In conclusion, while the results were null, this was the first study to examine the association between surrounding natural vegetation exposure and possible direct effects on breast tissue composition. The implication of this finding, if it can be replicated in other populations, is that there may be other pathways through which previously observed protective associations between higher greenness exposure and lower breast cancer risk remain to be elucidated, and/or there may be residual confounding to be addressed in studies of greenness and breast cancer incidence. Additional studies are needed to replicate the current findings, and studies of greenness exposure and risk of breast cancer that can address mechanisms such as mediation by physical activity and BMI or residual confounding by SES to determine whether higher greenness exposure and lower risk of developing breast cancer is reflecting a true phenomenon.

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Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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