Intake of vitamin D and calcium, sun exposure, and risk of breast cancer subtypes among black women

Bo Qin,1 Baichen Xu,1 Nan Ji,2 Song Yao,3 Karen Pawlish,4 Adana AM Llanos,1,5 Yong Lin,5 Kitaw Demissie,5,6 Christine B Ambrosone,5 Chi-Chen Hong,3 and Elisa V Bandera1,5

1Cancer Prevention and Control Program, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; 2Department of Environmental and Occupational Health, Rutgers School of Public Health, Piscataway, NJ, USA; 3Department of Cancer Prevention and Control, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; 4New Jersey State Cancer Registry, New Jersey Department of Health, Trenton, NJ, USA; 5Department of Biostatistics and Epidemiology, Rutgers School of Public Health, Piscataway, NJ, USA; and 6Department of Epidemiology and Biostatistics, School of Public Health, SUNY Downstate Medical Center, Brooklyn, NY, USA

ABSTRACT

Background: The randomized placebo-controlled Vitamin D and Omega-3 Trial suggested a possible benefit of vitamin D on cancer incidence among black individuals. However, data are limited regarding the impact of vitamin D on breast cancer subtypes among African-American/black women, who tend to develop more aggressive forms of breast cancer.

Objectives: We hypothesize that more vitamin D exposure (through diet, supplements, and sunlight) and higher intake of calcium are associated with decreased risk of estrogen receptor (ER)+ and ER− breast cancer, and of triple-negative breast cancer (TNBC) among black women.

Methods: This study was conducted among 1724 black cases and 1233 controls in the Women’s Circle of Health Study (WCHS) and WCHS2. Polytomous logistic regressions were used to estimate ORs and 95% CIs of ER+ and ER− breast cancer; logistic regressions were used for TNBC. The ORs from each study were pooled using an inverse-variance-weighted random-effects model.

Results: Dietary vitamin D and calcium intake were not associated with risk of breast cancer subtypes in the pooled analysis. For supplemental vitamin D, we observed possible inverse associations between intake of ≤800 IU/d (compared with nonuse) and risk of several subtypes, with effects that appeared strongest for TNBC (OR: 0.58; 95% CI: 0.35, 0.94); no association was found for >800 IU/d. More daylight hours spent outdoors in a year was associated with lowest quartile: TNBC OR: 0.53; 95% CI: 0.31, 0.91; P-trend = 0.02.

Conclusions: Moderate supplemental vitamin D intake was associated with decreased risk of TNBC, and increased sun exposure was associated with reduced risk of ER+, ER−, and TNBC among black women.

Keywords: epidemiology, cancer disparities, breast cancer risk, triple-negative breast cancer, vitamin D, calcium, sun exposure, African Americans, black women

Introduction

African-American/black women are about twice as likely to develop breast cancers with more aggressive phenotype [e.g., estrogen receptor-negative (ER−) and triple-negative breast cancer (TNBC)] as white women in the United States (1), which contributes to the notable racial disparities in breast cancer mortality (2).

Experimental studies have drawn attention to the potential antitumorigenic properties of vitamin D (3). Recent findings indicate that lower vitamin D levels are associated with increased risk of ER− and HER2− breast cancer subtypes in black women (2). A retrospective study of black women in the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute suggested a possible benefit of vitamin D on cancer mortality (4).

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Supplemental Figure 1 and Supplemental Tables 1–7 are available from the “Supplementary data” link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Data described in the article, code book, and analytic code will be made available upon request pending application and approval.

Address correspondence to BQ (e-mail: bonnie.qin@rutgers.edu).

Abbreviations used: BWHS, Black Women’s Health Study; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NJSCR, New Jersey State Cancer Registry; NYC, New York City; RCT, randomized controlled trial; TNBC, triple-negative breast cancer; VDR, vitamin D receptor; VITAL, Vitamin D and Omega-3 Trial; WCHS, Women’s Circle of Health Study; WHI, Women’s Health Initiative.

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trial (RCT), did not show that vitamin D supplementation (2000 IU/d) reduced the rate of invasive cancer, but results of subgroup analyses suggested a possible benefit of vitamin D on cancer incidence among black participants (HR: 0.77; 95% CI: 0.59, 1.01) (4). It also raised the possibility that BMI modifies the effect of vitamin D on cancer risk.

Most previous RCTs and observational studies were conducted among primarily white women and did not reveal significant associations of prediagnostic vitamin D exposure or circulating concentrations of vitamin D with breast cancer risk (5, 6). However, vitamin D deficiency is more prevalent among black than white women (7) owing to darker skin pigmentation, higher prevalence of lactose intolerance, and less use of supplements (8, 9). In addition, obesity, which is more prevalent among black women (10), may further lower the bioavailability of vitamin D (11, 12), considering that vitamin D is fat soluble and sequestered in adipose tissue. Three studies have evaluated vitamin D exposure in relation to breast cancer risk by subtypes among black women: 1 small study explored the relation with TNBC and suggested an inverse association (13); 1 study found a stronger association with ER+ than with ER− breast cancer (14); the other reported a null association (15). Co-administration of calcium may enhance the benefits of vitamin D on cancer risk (16, 17). Although the evidence on calcium intake and overall breast cancer risk was mixed (5), there was a suggestion that calcium intake was more strongly associated with the risk of ER− than ER+ tumors (18). No study, to our knowledge, has evaluated whether calcium intake alone or in combination with vitamin D is associated with breast cancer risk among black women. Population-based studies are needed to understand the effects of vitamin D and calcium on risk of aggressive breast cancer subtypes among black individuals, an understudied population.

The current study aimed to evaluate the associations of vitamin D exposure (through diet, supplements, and sunlight) and calcium intake with the risk of breast cancer by ER and TNBC status among black women. We also examined whether the associations were modified by BMI. The Women’s Circle of Health Study (WCHS) and the WCHS2, which were designed to identify risk factors for breast cancer among black women, provided a unique opportunity to examine these relations.

Methods

Study population

This study was conducted among African-American/black individuals recruited into the WCHS and the WCHS2. As previously described (19, 20), WCHS is a case-control study in metropolitan New York City (NYC) and 7 counties in New Jersey. Eligible cases included English-speaking women aged 20–75 y, with a newly diagnosed histologically confirmed ductal carcinoma in situ or invasive breast cancer, and who had no prior history of cancer except nonmelanoma skin cancer. Race was determined by self-report. Women who self-identified as black were eligible. Cases were identified in NYC hospitals with large referrals for black patients from 2002 to 2008, and by rapid case ascertainment by the New Jersey State Cancer Registry (NJSCR) from 2006 to 2012. Black controls were frequency matched by 5-y age groups using random-digit dialing in NYC and NJ supplemented by community recruitment efforts (20). The WCHS also recruited white women but these were not included in the current analysis owing to limited power for breast cancer subtype analysis. The WCHS2 started in 2012 with expansion of the target areas to 3 additional counties in NJ and some questionnaire changes (as described in more detail below), but following the same eligibility criteria and recruitment methods as in the WCHS. Because of financial constraints, recruitment of controls in the WCHS2 was stopped in 2015 to focus on case recruitment and follow-up for survival outcomes. Overall, the participation rate for black women who were contacted and were eligible was 82.4% in cases and 52.5% in controls (21). The study was approved by the Institutional Review Boards at all participating institutions and hospitals.

Data collection

Data were collected during in-person interviews for both the WCHS and WCHS2, including structured questions on sociodemographic, reproductive, lifestyle factors, and family history of cancer. Interviews were conducted at ∼9 mo since diagnosis and initiation of treatment. Information on hormone receptors and human epidermal growth factor receptor 2 (HER2) status were obtained from patients’ pathology reports, tissue microarrays, and NJSCR files.

“Usual” dietary intake over the year before diagnosis (for cases) or the reference date (for controls) was assessed via FFQs during in-person interviews. In the WCHS, the FFQ developed by Fred Hutchinson Cancer Research Center was used, which included questions on frequency and portion size for ∼125 foods and beverages (22). Nutrient intakes were calculated via Nutrition Data Systems for Research software (University of Minnesota Nutrition Coordinating Center). The Fred Hutchinson FFQ was validated in the Women’s Health Initiative (WHI) Dietary Assessment Study (23). The deattenuated correlations comparing FFQ estimates with four 24-h recalls and 4-d food records were >0.7 for both dietary calcium and vitamin D. Supplemental intakes were not assessed in the WCHS.

In the WCHS2, the 2001 FFQ of the Black Women’s Health Study (BWHS)—a modified National Cancer Institute–Block FFQ—was used, which included frequency and portion size questions for 85 food and beverage items (15). We slightly modified the BWHS FFQ by adding questions on types of cheese and yogurt (regular, reduced fat, or nonfat), and dairy products that are added to coffee and tea. Nutrient intakes were calculated mainly based on the food composition table and method for the National Cancer Institute’s Diet*Calc software as used in the BWHS’s FFQ (24), which was validated by 3 24-h recalls and 3-d food records (e.g., the deattenuated correlation for calcium was 0.79 compared with 3 nonconsecutive 24-h recalls) (25).

Supplemental intake of vitamin D and calcium was not assessed in the WCHS, but was ascertained through a detailed questionnaire asking brand, frequency, and dose of multivitamins, vitamin D, and/or calcium in the WCHS2. Multivitamin sources of vitamin D and calcium were calculated based on the Dietary Supplement Label Database (NIH Office of Dietary Supplements). The WCHS2 also included questions on daily hours spent outdoors in daylight and separately asked
for weekdays or weekends, and for summer or rest of the year.

**Analytic sample**

The present study included 1904 cases and 1270 controls recruited in the WCHS and WCHS2 through March 2017. ER status was available for 1803 cases (94.7%) at the time of analysis. After excluding 54 cases and 14 controls who did not provide all FFQs, 6 cases and 13 controls who reported an extreme energy intake [greater than twice the IQR of log energy intake (26)], and 19 cases and 10 controls with covariates missing, a total of 1724 cases (1213 ER+ and 511 ER−) and 1233 controls remained in the analysis. Among cases, 1461 (84.7%) had HER2+ results (Supplemental Figure 1).

**Statistical analysis**

We compared the distributions of characteristics between cases and controls using the chi-square test, t test, or Kruskal–Wallis test as appropriate. We used polytomous logistic regression to estimate ORs and 95% CIs of ER+ and ER− breast cancer compared with controls by levels of vitamin D intake, calcium intake, and sun exposure, and unconditional logistic regression for TNBC compared with controls. Dietary vitamin D and calcium intake; total intake (dietary plus supplemental); and daylight hours spent outdoors in a year, in summer months, or the rest of the year, were categorized into quartiles based on controls’ distribution. Supplemental vitamin D and calcium, which had >25% nonconsumers, were categorized into 3 groups: nonconsumers and below or above the median of consumption among consumers based on the distribution of controls. We tested linear trends by creating a continuous variable for the exposure of interest using the median value of each category.

The first model controlled for age. The second model further adjusted for a priori potential confounders based on known or suspected breast cancer risk factors aided by backward stepwise elimination: education, age at menarche, menopausal status, age at first birth, ever breastfeeding, first-degree family history of breast cancer, history of benign breast disease, BMI (calculated from self-reported weight and height 1 y before), vigorous physical activity, and total energy intake. Models for vitamin D and calcium intakes further controlled for daylight hours spent outdoors in a year, and models for sun exposure further controlled for total vitamin D intake. Models with dietary and supplemental intakes mutually adjusted for each other. Other covariates including oral contraceptive use, parity, smoking, alcohol intake, and sunscreen use were considered, but were not included in the models because removing them did not change the effect estimates by >10%.

Because different FFQs were used, we pooled the multivariable-adjusted ORs from both studies using an inverse-variance-weighted random-effects model to calculate summary estimates. Because the information on supplemental intakes and sun exposure was collected in WCHS2 only, these analyses were limited to WCHS2 participants.

We examined the distributions of characteristics by levels of supplemental vitamin D intake and daylight hours spent outdoors among cases and controls, respectively. We stratified the ER+ and ER− analyses by menopausal status and obesity status. We also tested for statistical interactions by menopausal status and BMI, and the interactions of vitamin D intake with calcium intake or daylight hours spent outdoors via likelihood ratio tests. We repeated the analyses excluding noninvasive cases. To further ensure comparability between cases and controls (in terms of, e.g., age, year of diagnosis, or reference date), we conducted propensity score nearest-neighbor matching and repeated the analysis among matched samples. Our main analysis included adjustment for vigorous physical activity considering its strong evidence to reduce breast cancer risk (5). In the sensitivity analysis for sun exposure, we adjusted for time spent on any type of physical activity and excluded women who reported shift work. We used Stata version 15.1 (StataCorp LP) for all analyses and defined statistical significance at a 2-tailed P < 0.05.

**Results**

Distributions of key characteristics of cases and controls in the WCHS and WCHS2 are shown in Table 1. For both studies combined, we had 1213 ER+, 511 ER−, and 335 TNBC cases. Cases were less likely to have attended college and more likely to have a history of benign breast disease and a family history of breast cancer than controls. Cases in the WCHS were also older and less likely to be current smokers.

Results for age- and multivariable-adjusted models assessing vitamin D and calcium intakes in relation to breast cancer subtypes in individual cohorts are presented in Table 2. Results remained essentially unchanged with multivariable adjustment. Dietary vitamin D intake was not associated with risk of subtypes in either study. Supplemental vitamin D intake of ≥800 IU/d compared with nonusers was associated with significantly decreased risk of ER+ (OR: 0.68; 95% CI: 0.50, 0.94) and TNBC (OR: 0.58; 95% CI: 0.35, 0.94), but intake of >800 IU/d (median: 1800 and 1500 IU/d in cases and controls, respectively) was not. There were no clear associations for calcium intake after multivariable adjustment in both studies. We did not observe significant associations for dietary vitamin D or calcium intake from the pooled analysis (Table 3).

More daylight hours spent outdoors in a year, in summer months, or during other months were associated with a decreased risk of ER+ and ER− breast cancer in both age-adjusted and multivariable-adjusted models (Table 4). For example, comparing the highest quartile (Q4) of daylight hours spent outdoors in a year with the lowest (Q1), the OR was 0.43 (95% CI: 0.29, 0.61; P-trend < 0.001) for ER+ and 0.43 (95% CI: 0.27, 0.68; P-trend < 0.001) for ER−. The ORQ4 vs. Q1 for outdoor hours in summer months was 0.47 (95% CI: 0.31, 0.70) for ER+ and 0.47 (95% CI: 0.28, 0.78) for ER−. The highest quartile of daylight hours spent outdoors over the past year was also associated with a lower risk of TNBC (ORQ4 vs. Q1 = 0.53; 95% CI: 0.31, 0.91; P-trend = 0.016). In a sensitivity analysis adjusting for any physical activity (min/wk), we found these associations became slightly stronger. For example, ORQ4 vs. Q1 of outdoor hours in a year was 0.38 (95% CI: 0.26, 0.55) for ER+ and 0.39 (95% CI: 0.25, 0.62) for ER−. Only 5% of women in our study reported shift work and excluding them from analysis did not alter the associations for sun exposure (results not shown).
### TABLE 1  Selected characteristics of breast cancer cases and controls in the WCHS and WCHS2

|                          | WCHS 2002–2012 | WCHS2 2012–2017 | \( P^1 \) | WCHS 2002–2012 | WCHS2 2012–2017 | \( P^1 \) |
|--------------------------|----------------|-----------------|------------|----------------|----------------|------------|
| **Total**                | 709            | 846             |            | 1015           | 387            |            |
| ER+                      | 486 (68.5)     | —               |            | 727 (71.6)     | —              |            |
| ER−                      | 223 (31.5)     | —               |            | 288 (28.4)     | —              |            |
| Triple-negative (ER−, PR−, HER2−) | 150 (21.2) | —               |            | 185 (18.2)     | —              |            |
| **Stage**                |                |                 |            |                |                |            |
| 0                        | 98 (13.8)      | —               |            | 200 (19.7)     | —              |            |
| I/II                     | 472 (66.6)     | —               |            | 669 (65.9)     | —              |            |
| III/IV                   | 100 (14.1)     | —               |            | 143 (14.1)     | —              |            |
| Unknown                  | 39 (5.5)       | —               |            | 3 (0.3)        | —              |            |
| **Age, y**               | 51.9 ± 10.3    | 50.4 ± 9.8      | 0.003      | 54.8 ± 10.8    | 54.0 ± 10.4    | 0.19       |
| Education                |                |                 |            |                |                |            |
| ≤High school graduate   | 344 (48.5)     | 330 (39.0)      | <0.001     | 427 (42.1)     | 135 (34.9)     | 0.01       |
| ≥Some college           | 365 (51.5)     | 516 (61.0)      |            | 588 (57.9)     | 252 (65.1)     |            |
| **Age at menarche, y**  |                |                 |            |                |                |            |
| <12                      | 197 (27.8)     | 239 (28.3)      |            | 289 (28.5)     | 105 (27.1)     |            |
| 12–13                    | 321 (45.3)     | 382 (45.2)      |            | 479 (47.2)     | 190 (49.1)     |            |
| >13                      | 191 (26.9)     | 225 (26.6)      |            | 247 (24.3)     | 92 (23.8)      |            |
| **Postmenopausal only** |                |                 |            |                |                |            |
| Ever received hormone therapy | 93 (26.4) | 83 (20.1)       | 0.09       | 140 (22.2)     | 43 (17.5)      | 0.08       |
| Age at menopause, y      | 49.7 ± 4.8     | 49.3 ± 4.5      | 0.30       | 49.1 ± 5.7     | 48.3 ± 5.8     | 0.07       |
| **Age at first birth, y**|                |                 |            |                |                |            |
| Nulliparous              | 110 (15.5)     | 142 (16.8)      | 0.98       | 166 (16.4)     | 61 (15.8)      | 0.85       |
| <25                      | 409 (57.7)     | 486 (57.4)      |            | 581 (57.2)     | 258 (56.3)     |            |
| ≥25                      | 190 (26.8)     | 218 (25.8)      |            | 268 (26.4)     | 108 (27.9)     |            |
| **Parity ≥ 3**           | 242 (34.1)     | 280 (33.1)      | 0.67       | 339 (33.4)     | 126 (32.6)     | 0.77       |
| **Ever breastfeeding**   | 287 (40.5)     | 349 (41.3)      | 0.76       | 392 (38.6)     | 152 (39.3)     | 0.82       |
| **BMI, kg/m²**           | 30.6 ± 7.2     | 31.0 ± 7.4      | 0.25       | 31.5 ± 6.9     | 31.5 ± 7.5     | 0.99       |
| **Alcohol intake, g/d**  | 2.8 ± 0.9      | 3.1 ± 10.5      | 0.10       | 2.8 ± 8.7      | 2.2 ± 5.2      | 0.41       |
| **Total energy intake, kcal/d** | 1798.2 ± 1165.5 | 1744.7 ± 1050.7 | 0.34  | 1786.0 ± 804.6 | 1727.2 ± 814.4 | 0.22       |
| **Supplemental vitamin D intake, IU/d** | — | — | 0.25 | 31.5 ± 6.9 | 31.5 ± 7.5 | 0.99 |
| **Among vitamin D supplement users** | 616 (60.7) | 240 (62.0) | 0.65 |
| Multivitamin use         | 491 (79.7)     | 195 (81.3)      | 0.61       |                |                |            |
| Single supplement use or in combination with calcium | 346 (56.2) | 112 (46.7) | 0.01 |

1Values are \( n \) (\%) or mean ± SD unless otherwise indicated. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; WCHS, Women’s Circle of Health Study.

2Based on interview dates.

3Chi-square test, Student’s \( t \) tests, and Kruskal–Wallis test were used as appropriate.

4Questions on use of sunscreen and dietary supplements were asked in the WCHS2 only.

5Among cases, there were 82.4% and 78.0% multivitamin users in the lower vitamin D supplement group (≤800 IU/d) and in the higher group (>800 IU/d), respectively; among controls, there were 83.5% and 79.0%, respectively.

The distributions of some characteristics of cases and controls varied by levels of supplemental vitamin D intake and daylight hours spent outdoors (Supplemental Tables 1 and 2). Results remained relatively consistent between pre- and postmenopausal women (Supplemental Tables 3 and 4) and between nonobese and obese women (Supplemental Tables 5 and 6) in each study. Although there was a suggestion that higher calcium intake was associated with ER− risk among postmenopausal women, we did
|                       | ER+          | ER−          | TNBC         |
|-----------------------|--------------|--------------|--------------|
| **Controls**          |              |              |              |
| **Age-adjusted**      |              |              |              |
| **Multivariable-**    |              |              |              |
| **adjusted**<sup>2</sup> |              |              |              |
| **Dietary vitamin D, IU/d** |          |              |              |
| Q1 (≤88.1)            | 213 (25.2)   | 109 (22.4)   | 1.00 (reference) |
| Q2 (88.2–154.0)       | 211 (24.9)   | 116 (23.9)   | 1.00 (0.78, 1.49) |
| Q3 (154.1–262.1)      | 211 (24.9)   | 122 (25.1)   | 1.16 (0.84, 1.61) |
| Q4 (≥262.2)           | 211 (24.9)   | 139 (28.6)   | 1.37 (0.99, 1.88) |
| P-trend               | 0.04         | 0.38         |              |
| **Dietary calcium, mg/d** |          |              |              |
| Q1 (≤434.0)           | 212 (25.1)   | 117 (24.1)   | 1.00 (reference) |
| Q2 (434.1–677.6)      | 211 (24.9)   | 110 (22.6)   | 0.98 (0.71, 1.35) |
| Q3 (677.7–1002.3)     | 212 (25.1)   | 125 (25.7)   | 1.07 (0.78, 1.47) |
| Q4 (≥1002.4)          | 211 (24.9)   | 134 (27.6)   | 1.23 (0.90, 1.69) |
| P-trend               | 0.13         | 0.10         |              |
| **Total vitamin D, IU/d** |          |              |              |
| Q1 (≤56.2)            | 97 (25.1)    | 180 (24.8)   | 1.00 (reference) |
| Q2 (56.3–762.2)       | 97 (25.1)    | 174 (23.9)   | 0.99 (0.70, 1.41) |
| Q3 (762.3–1212.1)     | 96 (24.8)    | 154 (21.2)   | 0.85 (0.59, 1.21) |
| Q4 (≥1212.2)          | 96 (24.8)    | 219 (30.1)   | 1.21 (0.86, 1.71) |
| P-trend               | 0.23         | 0.24         |              |
| **Dietary vitamin D, IU/d** |          |              |              |
| Q1 (≤88.7)            | 97 (25.1)    | 169 (23.2)   | 1.00 (reference) |
| Q2 (88.8–129.2)       | 97 (25.1)    | 157 (21.6)   | 0.93 (0.65, 1.33) |
| Q3 (129.3–192.0)      | 97 (25.1)    | 189 (26.0)   | 1.14 (0.81, 1.62) |
| Q4 (≥192.1)           | 96 (24.8)    | 212 (29.2)   | 1.31 (0.92, 1.85) |
| P-trend               | 0.07         | 0.33         |              |
| **Supplemental vitamin D, IU/d** |          |              |              |
| Nonconsumer           | 147 (38.0)   | 290 (39.9)   | 1.00 (reference) |
| ≤800                  | 121 (31.3)   | 174 (23.9)   | 0.71 (0.52, 0.96) |
| >800                  | 119 (30.7)   | 263 (36.2)   | 1.08 (0.80, 1.45) |
| P-trend               | 0.47         | 0.46         |              |
| **Total calcium, mg/d** |          |              |              |
| Q1 (≤506.9)           | 98 (25.3)    | 167 (23.0)   | 1.00 (reference) |
| Q2 (507.0–831.0)      | 98 (25.3)    | 172 (23.7)   | 1.05 (0.74, 1.50) |
| Q3 (831.1–1278.0)     | 97 (25.1)    | 195 (26.8)   | 1.20 (0.84, 1.70) |
| Q4 (≥1278.1)          | 94 (24.3)    | 193 (26.5)   | 1.21 (0.85, 1.72) |
| P-trend               | 0.25         | 0.74         |              |

*Q1*: First quartile; *Q2*: Second quartile; *Q3*: Third quartile; *Q4*: Fourth quartile; *P-trend*: *P*-value for trend.
TABLE 2

| Age-adjusted | Multivariable-adjusted2 | Multivariable-adjusted2 |
|--------------|-------------------------|-------------------------|
| Controls     | Age-adjusted2           | Age-adjusted2           |
| Dietary calcium, mg/d | Q1 (396.6) 99 (25.6) 148 (20.4) 1.00 (reference) 1.00 (reference) 76 (26.4) 1.00 (reference) 1.00 (reference) 48 (26.0) 1.00 (reference) 1.00 (reference) |
|              | Q2 (396.7–558.2) 96 (24.8) 184 (25.3) 1.28 (0.90, 1.83) 1.20 (0.83, 1.74) 55 (19.1) 0.75 (0.48, 1.17) 0.72 (0.45, 1.14) 34 (18.4) 0.73 (0.43, 1.23) 0.67 (0.38, 1.17) |
|              | Q3 (558.3–818.2) 95 (24.5) 220 (30.3) 1.60 (1.12, 2.27) 1.48 (0.98, 2.21) 75 (26.0) 1.03 (0.67, 1.58) 1.02 (0.62, 1.66) 49 (26.5) 1.06 (0.65, 1.74) 1.08 (0.61, 1.93) |
|              | Q4 (≥P)         1.00 (reference) 1.00 (reference) 1.00 (reference) 1.00 (reference) 1.00 (reference) 1.00 (reference) 1.00 (reference) 1.00 (reference) 1.00 (reference) |

| Dietary vitamin D intake | Nonconsumer | Q1 (568–818.2) 189 (48.8) 216 (29.7) 0.86 (0.65, 1.14) 0.84 (0.62, 1.12) 64 (29.2) 0.91 (0.64, 1.29) 0.93 (0.57, 1.50) 42 (24.7) 0.93 (0.57, 1.50) 0.93 (0.57, 1.50) |
|                        | Q2 (588–758.2) 175 (49.1) 249 (30.8) 0.95 (0.67, 1.33) 0.90 (0.62, 1.30) 66 (29.9) 0.94 (0.65, 1.35) 0.93 (0.57, 1.50) 42 (22.7) 0.93 (0.57, 1.50) 0.93 (0.57, 1.50) |
|                        | Q3 (≥758)       1.00 (reference) 1.00 (reference) 1.00 (reference) 1.00 (reference) 1.00 (reference) 1.00 (reference) 1.00 (reference) 1.00 (reference) 1.00 (reference) |

1Values are OR (95% CI). After calculating study-specific multivariable-adjusted ORs, we combined the log, ORs, weighted by the inverse of their variances, by using a random-effects model. ER, estrogen receptor; TNBC, triple-negative breast cancer; WCHS, Women’s Circle of Health Study.

not detect any significant interactions by menopausal status. We did not find significant interactions by BMI or obesity status, or between vitamin D intake and calcium intake or daylight hours spent outdoors in a year. We observed similar associations after limiting the analyses to invasive cases with controls (data not shown). The sensitivity analysis using propensity score matching did not materially alter the observed associations (Supplemental Table 7).

Discussion

In this population-based breast cancer study of black women, a moderate intake of supplemental vitamin D was associated with decreased risk of several breast cancer subtypes, with effects that appeared strongest for TNBC. More sunlight exposure was associated with decreased risk, including ER− and TNBC. Prior studies have shown the etiological heterogeneity of breast cancer by ER status among black women (27–29), indicating a need to evaluate risk factors separately for different subtypes. The current study is the largest investigation to date to systematically evaluate vitamin D exposure from diet, supplements, and sun exposure, and calcium intake in relation to risk of breast cancer subtypes including the aggressive TNBCs, among black women.

Several RCTs have examined the effect of vitamin D supplementation on cancer risk, but few had enough breast cancer cases and even fewer included enough black participants. For example, Lappe et al. (17) did not find an effect of supplemental calcium plus 1100 IU vitamin D/d on the incidence of breast cancer. The number of breast cancer cases was small with 19 cases in the intervention group and 24 in the placebo group. Another RCT, the Vitamin D Assessment study, with 36 breast cancer cases, was also not optimally powered to detect the effect on incidence (30). VITAL, which had 246 breast cancer cases, found no significant difference in breast cancer incidence comparing the vitamin D supplementation group with the control group (4). The study included 20% black participants and suggested that vitamin D supplementation may reduce the risk of invasive cancer of any type among them. However, the results on site-specific cancers among black participants were not reported, possibly owing to lack of power. The WHI, with >2000 cases (85% white and 8% black participants), was well powered to evaluate the
### TABLE 4  Daylight hours spent outdoors in relation to ER+, ER−, and TNBC in WCHS2

|                  | ER+ (ca/con: 727/387) | ER− (ca/con: 288/387) | TNBC (ca/con: 185/387) |
|------------------|-----------------------|------------------------|------------------------|
|                  | Controls              | Age-adjusted           | Multivariable-adjusted | Controls              | Age-adjusted           | Multivariable-adjusted | Controls              | Age-adjusted           | Multivariable-adjusted |
| **Weekly average of daylight hours spent outdoors in a year, h/wk** |                       |                        |                        |                       |                        |                        |                       |                        |                        |
| Q1 (<9.0)        | 95 (24.5)             | 246 (33.8)             | 1.00 (reference)       | 99 (34.4)             | 1.00 (reference)       | 1.00 (reference)       | 52 (28.1)             | 1.00 (reference)       | 1.00 (reference)       |
| Q2 (9.1–14.1)    | 95 (24.5)             | 193 (26.5)             | 0.79 (0.56, 1.11)      | 71 (24.7)             | 0.72 (0.47, 1.09)      | 0.71 (0.46, 1.08)      | 51 (27.6)             | 0.98 (0.60, 1.58)      | 0.91 (0.56, 1.50)      |
| Q3               | 96 (24.8)             | 166 (22.8)             | 0.68 (0.48, 0.96)      | 68 (23.6)             | 0.68 (0.45, 1.03)      | 0.67 (0.43, 1.02)      | 47 (25.4)             | 0.89 (0.54, 1.44)      | 0.86 (0.52, 1.43)      |
| Q4 (≥24.3)       | 101 (26.1)            | 122 (16.8)             | 0.47 (0.33, 0.67)      | 50 (17.4)             | 0.47 (0.31, 0.74)      | 0.43 (0.27, 0.68)      | 35 (18.9)             | 0.63 (0.38, 1.05)      | 0.53 (0.31, 0.91)      |
| **P-trend**      | <0.001                | <0.001                 |                       | 0.001                 |                        |                       | 0.058                 |                        | 0.016                 |
| **Weekly average of daylight hours spent outdoors in summer months, h/wk** |                       |                        |                        |                       |                        |                        |                       |                        |                        |
| Q1 (<9.5)        | 80 (20.7)             | 199 (27.4)             | 1.00 (reference)       | 75 (26.0)             | 1.00 (reference)       | 1.00 (reference)       | 41 (22.2)             | 1.00 (reference)       | 1.00 (reference)       |
| Q2 (9.6–20.5)    | 110 (28.4)            | 251 (34.5)             | 0.91 (0.65, 1.29)      | 101 (35.1)            | 0.98 (0.65, 1.48)      | 0.94 (0.62, 1.44)      | 62 (33.5)             | 1.10 (0.67, 1.79)      | 1.07 (0.64, 1.77)      |
| Q3               | 117 (30.2)            | 173 (23.8)             | 0.60 (0.42, 0.85)      | 72 (25.0)             | 0.66 (0.43, 1.01)      | 0.62 (0.40, 0.95)      | 52 (28.1)             | 0.87 (0.53, 1.43)      | 0.77 (0.46, 1.30)      |
| Q4 (≥34.8)       | 80 (20.7)             | 104 (14.3)             | 0.53 (0.36, 0.78)      | 40 (13.9)             | 0.53 (0.33, 0.87)      | 0.47 (0.28, 0.78)      | 30 (16.2)             | 0.73 (0.41, 1.28)      | 0.62 (0.34, 1.13)      |
| **P-trend**      | <0.001                | <0.001                 |                       | 0.001                 |                        |                       | 0.155                 |                        | 0.051                 |
| **Weekly average of daylight hours spent outdoors in spring, fall, and winter months, h/wk** |                       |                        |                        |                       |                        |                        |                       |                        |                        |
| Q1 (<8.5)        | 104 (26.9)            | 271 (37.3)             | 1.00 (reference)       | 107 (37.2)            | 1.00 (reference)       | 1.00 (reference)       | 58 (31.4)             | 1.00 (reference)       | 1.00 (reference)       |
| Q2 (8.6–10.5)    | 117 (30.2)            | 207 (28.5)             | 0.68 (0.49, 0.94)      | 79 (27.4)             | 0.66 (0.44, 0.97)      | 0.66 (0.44, 0.98)      | 58 (31.4)             | 0.89 (0.57, 1.40)      | 0.88 (0.55, 1.40)      |
| Q3               | 59 (15.2)             | 128 (17.6)             | 0.85 (0.58, 1.24)      | 48 (16.7)             | 0.79 (0.50, 1.26)      | 0.78 (0.49, 1.26)      | 32 (17.3)             | 0.96 (0.56, 1.65)      | 0.98 (0.56, 1.71)      |
| Q4 (≥21.2)       | 107 (27.6)            | 121 (16.6)             | 0.44 (0.31, 0.62)      | 54 (18.8)             | 0.49 (0.32, 0.75)      | 0.45 (0.29, 0.70)      | 37 (20.0)             | 0.62 (0.38, 1.01)      | 0.52 (0.31, 0.88)      |
| **P-trend**      | <0.001                | <0.001                 |                       | 0.002                 |                        |                        | 0.050                 |                        | 0.012                 |

1 Values are n (%) or OR (95% CI). ER, estrogen receptor; TNBC, triple-negative breast cancer; WCHS2, Women’s Circle of Health Study 2.

2 Polytomous logistic regression was used for ER+ and ER− breast cancer compared with controls, and unconditional logistic regression was used for TNBC compared with controls. Model adjusted for age, education (≤high school graduate, ≥some college), age at menarche (<12, 12–13, >13 y), menopausal status (pre-, postmenopause), age at first birth (nulliparous, <25 y, ≥25 y), ever breastfeeding (yes, no), first-degree family history of breast cancer (yes, no), history of benign breast disease (yes, no), BMI (kg/m²), vigorous physical activity (yes, no), total energy intake (kcal/d), and total vitamin D intake (quintile).
effect of calcium (1 g/d) plus vitamin D supplementation (400 IU/d) on breast cancer incidence (31). After an average of 7.0 y of intervention and 4.9 y postintervention follow-up, a lower incidence of in situ breast cancer was observed among women randomly assigned to supplementation, suggesting extended follow-up may be required to observe the potential effects of supplementation.

In the current study, we observed a suggested lower risk among several breast cancer subtypes compared to a moderate intake of supplemental vitamin D (>0 to 800 IU/d; median: 730 IU/d in cases and 700 IU/d in controls) without users. Among users, 40.8% of cases and 43.3% of controls reported that they had consumed vitamin D supplementation for >4 y. In the WHI, an increased incidence of invasive tumors was observed in the supplementation group who had a higher baseline intake of vitamin D (31), suggesting a threshold effect is possible by which high-dose vitamin D no longer has the favorable health effects (32, 33). Most prospective observational studies on supplemental vitamin D intake compared any consumption or a low dose at >400 IU/d with 0 IU/d and found a nonsignificant inverse association (5), except that 1 compared 800–3200 IU/d with 0 IU/d and reported null results (34). Similarly, we did not find that the highest vitamin D supplementation (>800 IU/d; median: 1800 IU/d in cases and 1500 IU/d in controls) was associated with risk. Another possibility is residual confounding or prevalent health conditions for which the highest use of dietary supplementation is indicated.

We observed strong inverse associations between daylight hours spent outdoors and risk of all breast cancer subtypes. This observation is in line with previous ecological studies which repeatedly found an inverse correlation between UV exposure and breast cancer risk in the United States (35–37). Prospective investigations conducted in the United States also found that increased sunlight exposure was associated with reduced risk of breast cancer (38–40). These studies were conducted among primarily white women, who can be more efficient at producing vitamin D owing to light skin pigmentation (41). They reported similar or less time spent outside in daylight compared with the black women enrolled in our study (39, 40). Studies conducted among European women living at high latitudes did not observe such associations (42–44), suggesting the vitamin D concentrations necessary to reduce breast cancer risk may be difficult to achieve through skin synthesis in regions with low solar radiance. We found similar results for sunlight exposure in summer and other seasons combined. This could be explained by errors in reporting (some women may not accurately separate exposure in summer from other seasons) or the storage of vitamin D in adipose tissue that potentially extends its effects accumulated through summer to other seasons (45). A low amount of sun exposure may also be a reflection of disrupted daily (circadian) rhythms, which may induce breast carcinogenesis via altering endocrine timing (46), but excluding women who had shift work did not change our results. Physical activity was considered to be a confounding factor, but we observed weak correlations between daylight hours outdoors and time spent on physical activity including walking (Spearman’s $r = 0.16$). Results remained significant with adjustment for vigorous or any physical activity. It seems unlikely that our findings for sun exposure were explained by physical activity levels. More studies are needed to understand the contribution of sun exposure to breast cancer risk among black women.

Because vitamin D is the precursor to the steroid hormone calcitriol, several specific mechanisms in regulating ER+ development have been proposed, including inhibiting estrogen synthesis in breast cancer cells or surrounding adipose tissue (3, 47), and downregulating ER in breast cancer cells to inhibit estrogen signaling (48). Vitamin D may also play a role in the pathways against more aggressive breast cancer subtypes. In addition to ER+ cells, vitamin D receptors (VDRs) are also present in ER− cells including two-thirds of TNBC (49). Acting on VDRs, vitamin D compounds could trigger growth arrest and apoptosis via estrogen-independent mechanisms (50), and inhibit the expression of several myoepithelial markers associated with more aggressive breast cancers (51).

Black women are more likely to develop ER− and TNBC than white women (1), but few studies have investigated the role of vitamin D on risk of breast cancer subtypes among them (13–15). In the BWHS, dietary vitamin D or calcium intake was not associated with risk of ER+ or ER− disease, which is consistent with our observations (15). Supplemental vitamin D intake and sun exposure were not evaluated. To our knowledge, only 1 study has evaluated vitamin D status (serum 25-hydroxyvitamin D3 concentration) in relation to TNBC among black women, finding a significant inverse association (13), which supports our observations. However, these findings need to be interpreted with caution because blood samples in the previous study were collected at the time of diagnosis and more studies among this minority group are needed.

We recognize the potential of recall bias is a concern in case-control studies. However, the largely unknown associations of sun exposure, vitamin D, and calcium-rich foods, such as dairy, with breast cancer risk, and therefore, lack of awareness of these relations in this population should minimize this concern. Undetected disease may influence recall, and one might expect to observe more dietary changes and less sun exposure among cases with advanced stages. However, we did not find differences in vitamin D and calcium intakes or sun exposure between cases at early compared with advanced stages. The potential for selection bias is another concern, but we found that the distributions of the main risk factors among WCHS and WCHS2 cases and controls were in the expected directions compared with other studies among black women (27–29), which corroborates the validity of our findings. Furthermore, some degree of residual confounding may have remained despite the multivariable- and mutually adjusted models. For example, residual confounding by physical activity is still possible, although it was carefully adjusted for in the main model and the sensitivity analysis.

A major strength of this study is that we were able to recruit a large sample of black breast cancer cases and controls and to collect detailed information on lifestyle and tumor characteristics, which allows us to examine risk factors for breast cancer subtypes in this understudied population. Another strength is the detailed information on dietary supplements in the WCHS2, which allowed us to compile a fairly accurate estimate of supplemental intake. Our study builds on the recent findings from VITAL and adds to the scarce evidence on vitamin D exposure in relation to risk of breast cancer subtypes, in particular TNBC, among black women.
In conclusion, our findings suggest that moderate supplemental vitamin D intake and sun exposure may reduce the risk of several breast cancer subtypes including TNBC among black women. Considering the high prevalence of aggressive subtypes in this group, efforts to identify risk factors for ER− and TNBC may have important implications for reducing the sizable racial disparities in breast cancer outcomes.

The authors’ responsibilities were as follows—BQ and EVB: designed the study; BQ, KP, AAML, KD, CBA, C-CH, and EVB: acquired the data; BQ, BX, and NJ: analyzed the data; BQ: drafted the paper and had primary responsibility for the final content; and all authors: critically revised the paper and read and approved the final manuscript. The authors report no conflicts of interest.

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