Dairy, calcium, vitamin D and ovarian cancer risk in African–American women

Bo Qin *,1, Patricia G Moorman 2, Anthony J Alberg 3, Jill S Barnholtz-Sloan 4, Melissa Bondy 5, Michele L Cote 6, Ellen Funkhouser 7, Edward S Peters 8, Ann G Schwartz 6, Paul Terry 9, Joellen M Schildkraut 10 and Elisa V Bandera 1

1Population Science, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ 08903, USA; 2Department of Community and Family Medicine, Duke Cancer Institute, Durham, NC 27705, USA; 3Hollings Cancer Center and Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC 29425, USA; 4Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH 44106, USA; 5Cancer Prevention and Population Sciences Program, Baylor College of Medicine, Houston, TX 77030, USA; 6Department of Oncology and the Karmanos Cancer Institute, Population Studies and Disparities Research Program, Wayne State University School of Medicine, Detroit, MI 48201, USA; 7Division of Preventive Medicine, University of Alabama at Birmingham, Birmingham, AL 35205, USA; 8Epidemiology Program, Louisiana State University Health Sciences Center School of Public Health, New Orleans, LA 70112, USA; 9Departments of Public Health and Surgery, University of Tennessee-Knoxville, Knoxville, TN 37996, USA and 10Department of Public Health Sciences, University of Virginia, Charlottesville, VA 22908, USA

Background: No previous study has evaluated the associations of dairy products, lactose, calcium and vitamin D with the risk of ovarian cancer in African–American women, who are known to have high mortality from the disease, as well as to be at risk for calcium and vitamin D deficiency.

Methods: We evaluated these associations among 490 ovarian cancer cases and 656 age- and site-matched controls of African–American descent recruited into the African American Cancer Epidemiology Study, a population-based case-control study in 11 geographical areas in the US. Multivariable logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

Results: An increased ovarian cancer risk was observed for whole milk consumption and lactose intake (highest quartile vs lowest: OR = 1.97, 95% CI: 1.25–3.10; P-trend: 0.008). Calcium intake was associated with a decreased risk of ovarian cancer (OR = 0.51, 95% CI: 0.30–0.86; P-trend: 0.009), but vitamin D intake was not. Longer sun exposure in summer months was found to predict a lower risk (OR = 0.71, 95% CI: 0.51–0.99; P-trend: 0.049).

Conclusions: Our findings suggest that a high-calcium, low-lactose diet, and sun exposure in summer months may reduce the risk of ovarian cancer in African–American women.

Ovarian cancer is the fifth leading cause of cancer death among women in the US, of which nearly 90% are epithelial ovarian carcinomas (Berek et al., 2010). Because currently there is no reliable screening available for ovarian cancer and early-stage ovarian cancer often has no symptoms, most cases are diagnosed at an advanced stage, with a poor prognosis (Goff et al., 2000). Therefore, a better understanding of the aetiology and prevention is especially important for ovarian cancer. Although 5-year survival improved in Whites from 35% in 1975–1977 to 46% in 2005–2011, survival actually worsened in African Americans (AAs) during

*Correspondence: Dr B Qin; E-mail: bonnie.qin@rutgers.edu

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this period (rates went from 42% to 38%; Howlader et al, 2015). The widening gap suggests a critical need for identifying a modifiable risk factors in AA women, an understudied population.

The positive correlation between per capita milk consumption, lactase persistence (the ability to digest lactose), and ovarian cancer incidence (Cramer, 1989a) has led to the hypothesis that the lactose component of dairy – a disaccharide of galactose and glucose, may increase the risk of ovarian cancer through galactose’s direct toxicity on oocytes (Cramer et al, 1989b; Liu et al, 2000).

Although some studies found positive associations between dairy foods or lactose intake with the risk of ovarian cancer (Kushi et al, 1999; Fairfield et al, 2004; Larsson et al, 2004), others found null (Pan et al, 2004; Webb et al, 1998; Merritt et al, 2013) or inverse association (Goodman et al, 2002; Salazar-Martinez et al, 2002). These study populations were primarily of European ancestry, although no study has published among AAs. The inconsistencies might be attributed to other anti-tumorigenic nutrients in dairy foods, especially calcium and vitamin D. There is enticing evidence that vitamin D regulates multiple cancer risk and prognosis-relevant pathways, including tumorigenic pathways in ovarian carcinoma (Fleet et al, 2012). Co-administration of calcium was found to enhance the benefits of vitamin D on multiple health outcomes (Feldman et al, 2014). Calcium intake may also independently predict the lower risk of ovarian cancer as suggested by some observational studies (Bidoli et al, 2001; Goodman et al, 2002; Koralek et al, 2006; Merritt et al, 2013), albeit rather inconsistently (Tzonou et al, 1993; Kushi et al, 1999; Genkinger et al, 2006; Chang et al, 2007). It is possible that the opposing associations of calcium or vitamin D and lactose may explain the inconsistent findings between the dairy products and ovarian cancer risk in the current literature.

In addition to food and supplemental intakes, vitamin D in humans can also be produced through skin synthesis upon sun exposure. However, darker colour of the skin reduces the penetration of UVB, resulting in a subsequent less cutaneous synthesis of vitamin D (Webb, 2006). This, together with the tendency of AAs to consume less vitamin D and calcium from dietary sources, due to a higher prevalence of lactose intolerance (Suchy et al, 2010), and supplemental intake (Calvo et al, 2005; Kant et al, 2007) place AA women at risk for vitamin D deficiency. To our knowledge, this is the first study evaluating intakes of dairy foods, lactose, calcium, and vitamin D exposure (diet and sunlight) and the risk of ovarian cancer among AA women.

MATERIALS AND METHODS

Design and participants. This study was conducted among AA descent recruited into the African American Cancer Epidemiology Study (AACES), an ongoing population-based case-control study of ovarian cancer in AA women in 11 sites in the US (South: Tennessee, North Carolina, South Carolina, Georgia, Alabama, Louisiana, Texas; North: Michigan, Illinois, Ohio, New Jersey) (Schildkraut et al, 2014). Cases were identified by rapid case ascertainment utilising state cancer registries, SEER registries or hospitals’ gynaecologic oncology departments. Eligible cases include all self-identified AA women aged between 20 and 79 years, with newly diagnosed, histologically confirmed invasive epithelial ovarian cancer. Controls who self-identified as AAs were selected using random digit dialling and were frequency matched to cases by 5-year-age groups and state of residence. Women who had a previous history of ovarian cancer or a bilateral oophorectomy were ineligible controls. Among those who could be contacted, 66.5% of potential cases and 72% of potential controls agreed to participate in the main telephone interview (Schildkraut et al, 2014). The study was approved by the Institutional Review Boards at all study sites.

Data were collected by a computer-assisted telephone interview, which included detailed questions on demographic information, personal and family history of cancer, reproductive history, medication use, lifestyle characteristics, and other factors of particular relevance to AA women, such as pigmentation, perceived discrimination, and cultural beliefs. Daily hours spent outdoors in daylight were asked separately on weekdays or weekends, and in summer or the rest of the year.

The present study included 574 cases and 733 controls, who completed the baseline questionnaire via telephone interview by Jan 2016. Although a short version of the questionnaire was offered for those who were not willing to complete the full version (5.3%), they were not included in this study since sun exposure, pigmentation and some important covariates for this analysis (e.g., physical activity) were not asked. After excluding 78 cases and 68 controls who did not complete the food frequency questionnaire (FFQ) for dietary assessment, one case and three controls who reported an extreme energy intake (greater than twice the interquartile range of log energy intake), and five cases and six controls with covariates missing, a total of 490 cases and 656 controls remained for the analysis.

Dietary assessment. Dietary information was assessed via a self-administered Block 2005 FFQ, which included questions on frequency and portion size for 110 food and beverages consumed over the year preceding diagnosis for cases or the reference date for controls (Qin et al, 2016). Dietary intakes were calculated based on the MyPyramid Equivalents Database 2.0 (Bowman et al, 2008). One cup of milk or yogurt (8 fluid oz. or 237 ml) was counted as one milk cup equivalent, that is, one serving in our study. One serving of cheese was between 1 and 2 ounces of natural cheese or processed cheese depending on its calcium content. Milk-based desserts such as ice cream were also considered as dairy products with equivalent servings based on their milk ingredients.

Nutrient intakes were derived by Block Dietary Data Systems based on the USDA Food and Nutrient Database for Dietary Studies 1.0. Supplemental intake of calcium or vitamin D, including multivitamin sources was also collected. Total intake of calcium or vitamin D includes that from both dietary and supplemental sources. Validation studies of the Block FFQ have been described elsewhere (Mares-Perlman et al, 1993; Boucher et al, 2006). The reliability of total calcium or vitamin D intake between the first and second FFQs (2 month apart) were 0.80 and 0.76, respectively. The correlations between estimates from FFQ and two 24-h recalls were 0.71 and 0.54 for calcium and vitamin D, respectively.

Statistical analysis. We compared the distributions of characteristics between cases and controls using χ²-test or t-test as appropriate. We also compared the correlations between intakes of vitamin D, calcium, and lactose using Spearman’s rank correlations.

We used unconditional logistic regression models adjusting for the matching factors to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of ovarian cancer by levels of daily foods, nutrients (calcium, vitamin D, and lactose), and sun exposure. For total dairy, milk, cheese, total calcium or vitamin D, dietary calcium or vitamin D, lactose, and daylight hours spent outdoors in a year or in summer months, they were categorised into quartiles based on the distributions of controls. For yogurt, milk subtypes (whole milk, skim/low-fat milk), supplemental calcium or vitamin D, which had > 25% non-consumers, they were categorised into three groups, that is, non-consumers, below or above the median of consumption based on controls’ distributions. The median value of each category was treated as a continuous variable to test for linear trends.
The first model adjusted for age, geographic region, and total energy intake. Geographic region was grouped by UV index (≥5 and ≤5, i.e., South and North states) (NASA Earthdata, 2016). The second model further adjusted for a priori confounders or risk factors for ovarian cancer, including education (high school or less, some post-high school training, and college or graduate degree), parity (0, 1–2, >2), oral contraceptive use (never, <60 mo, ≥60 mo), menopause status (pre- and post menopause), tubal ligation (no and yes), first-degree family history of breast/ovarian cancer (no and yes), body mass index (BMI, calculated from self-reported weight and height 1 year before), recreational physical activity (0, <150 min per week, ≥150 min per week 1 year before), skin pigmentation (lighter, average, and darker), daylight hours spent outdoors in summer months (h per week) in models for dietary exposures, and additional covariates for corresponding models: models with dairy were controlled for supplemental calcium and were mutually adjusted for other types of dairy foods when applicable; models with nutrient intakes were adjusted for other sugar intakes (excluding lactose) and were mutually adjusted for each other; models with sun exposure were adjusted for total vitamin D intake from dietary and supplemental sources. Other covariates as listed in Table 1 (e.g., alcohol consumption, talc use, and occupational activity) were considered, but were not adjusted since none changed the effect estimates by >10%.

We tested for statistical interaction of total dairy, calcium, vitamin D, lactose, daylight hours spent outdoors (in a year or in summer months) between each other (except for dairy), and with skin pigmentation, BMI, menopausal status, and oral contraceptive use via likelihood ratio test. We also conducted analyses by the two histological subtypes contributing the largest number of cases (serous and endometrioid) and tested for heterogeneity. As the stratum sizes would be too small for interaction or histological subtype analyses, we evaluated the dietary exposure as a continuous variable, where 1 unit equals to the interquartile difference of controls’ dietary intake. All statistical analyses were performed using Stata (version 14.1; StataCorp LP, College Station, TX, USA).

RESULTS

Compared with controls, cases were older and less likely to reside in North (Table 1). We found the distributions of ovarian cancer risk factors were in the expected directions. Cases were less likely to have children, to have used oral contraceptives or to have had a tubal ligation, and were more likely to have a family history of breast or ovarian cancer.

The mean (s.d.) intake of dairy products were 6.9 (6.7) and 6.4 (5.8) servings per week among cases and controls, respectively (data not shown). As shown in Table 2, there was a suggestion of a positive association between total dairy or milk intake with ovarian cancer risk, though risk estimates were not statistically significant. In the analyses of milk subtypes, whole milk was significantly associated with a higher risk of ovarian cancer (OR = 1.85 comparing >2.3 serving per week vs non-consumers, 95% CI: 1.05–3.27; P-trend: 0.02), whereas skim/low-fat milk was not. No association was found for cheese or yogurt. Results remained essentially unchanged when adjusting for saturated fat (data not shown).

In the multivariable- and mutually adjusted model, we found calcium intake was consistently associated with a decreased risk of ovarian cancer, with a similar OR for calcium from food, supplement or total (from food plus supplement sources) comparing the highest to the lowest intake category (Table 3). For example, the highest quartile (Q4) of total calcium intake was associated with a 49% decreased OR (95% CI: 0.30–0.86, P-trend = 0.009). Although calcium intake was highly correlated with vitamin D intake (r = 0.64, P < 0.001; Supplementary Table 1), we found no association between total or dietary vitamin D with ovarian cancer risk. For supplemental vitamin D intake, we only observed a significant inverse association when comparing the intermediate category (i.e., ≤371.4 IU per day) vs non-consumers. Lactose intake was found to increase ovarian cancer risk, with an OR of 1.97 comparing Q4 vs Q1 (95% CI: 1.25–3.10; P-trend: 0.008).

In Table 4, the ORs for daylight hours spent outdoors in a year were in the inverse direction, but not statistically significant. The inverse association between outdoor hours in summer months and ovarian cancer risk comparing Q4 vs Q1 was statistical significant (OR = 0.71; 95% CI: 0.51–0.99; P-trend: 0.049).

DISCUSSION

In this population-based ovarian cancer study of AA women, the positive association between the total dairy intake and ovarian cancer risk seemed to be attributable to the consumption of whole milk. Calcium intake was significantly associated with a reduced risk of ovarian cancer, whereas lactose intake was associated with an increased risk. Sun exposure during the summer was found to decrease the risk of ovarian cancer, but total or dietary vitamin D intake was not.

Our finding of increased risk with whole milk consumption is consistent with a meta-analysis of case-control and cohort studies, analysed either combined or separately by study design (Larsson et al, 2006). However, a pooled analysis of cohort studies found no association with whole milk intake (Genkinger et al, 2006). Their null findings for low-fat milk, cheese, and yogurt were similar to our observations. The previous meta-analysis or pooled analysis did not examine the stratified results among AA women, probably due to a limited statistical power as most study populations were primarily of European ancestry. Our results by milk type were not altered after adjusting for saturated fat intake. Our exploratory analysis showed that dairy fat tended to associate with an increased ovarian cancer risk, but the association was attenuated and became insignificant after adjusting for lactose intake (OR Q4 vs Q1 = 1.48; 95% CI: 0.88–2.47), which is similar to a previous finding (Bertone et al, 2002). Our results generally support the hypothesis that high-lactose dairy foods may raise the risk of ovarian cancer. Both whole milk and low-fat/skim milk, contain on average 12 g per serving of lactose, much higher than cheese and yogurt (e.g., one serving cheddar cheese contains 0.05 g lactose and 0.04 g galactose), although one serving of these dairy products all contain ~300 mg of calcium (Bowman et al, 2008; US Department of Agriculture ARS, Nutrient Data Laboratory, 2015). It is possible that the influence of lactose and potentially fat content in whole milk outweighs the benefits of rich calcium, leading to an increased risk of ovarian cancer risk.

Lactose metabolite, galactose, was found to invariably induce ovarian toxicity in rodent models (Liu et al, 2000). Excessive galactose and galactose metabolites, Gal-1-P and galactitol, may interfere with gonadotrophin signalling and ovarian apoptosis, contributing to the galactose-induced ovarian toxicity (Holschneider and Berek, 2000). Meanwhile, a higher incidence of ovarian failure was observed in patients with galactosemia, due
| Table 1. Selected characteristics of African–American women in AACES<sup>a</sup> | Cases (n = 490) | Controls (n = 656) | P<sup>b</sup> |
|---|---|---|---|
| **Age (y, mean ± s.d.)** | 57.3 ± 10.5 | 54.9 ± 11.5 | <0.001 |
| **Region<sup>c</sup>** | | | |
| South | 385 (78.6) | 448 (68.3) | <0.001 |
| North | 105 (21.4) | 208 (31.7) | |
| **Education** | | | 0.11 |
| High school or less | 211 (43.1) | 242 (36.9) | |
| Some post-high school training | 160 (32.7) | 240 (36.6) | |
| College or graduate degree | 119 (24.3) | 174 (26.5) | |
| **Parity** | | | 0.002 |
| 0 | 98 (20.0) | 83 (12.7) | |
| 1–2 | 214 (43.7) | 297 (45.3) | |
| >3 | 178 (36.3) | 276 (42.1) | |
| **Oral contraceptive use** | | | |
| Never | 142 (29.0) | 132 (20.1) | 0.002 |
| <60 months | 206 (42.0) | 294 (44.8) | |
| ≥60 months | 142 (29.0) | 230 (35.1) | |
| **Age at menarche** | | | 0.19 |
| <12 | 111 (22.7) | 179 (27.3) | |
| 12–13 | 255 (52.0) | 316 (48.2) | |
| >13 | 124 (25.3) | 161 (24.5) | |
| **Postmenopausal** | 350 (71.4) | 458 (69.8) | 0.55 |
| **Ever use of hormone replacement therapy<sup>d</sup>** | 91 (26.0) | 107 (31.0) | 0.66 |
| Tubal ligation | 171 (34.9) | 271 (41.3) | 0.03 |
| Hysterectomy | 124 (25.3) | 143 (21.8) | 0.17 |
| **Family history of breast/ovarian cancer (first-degree relative)** | | | 0.002 |
| No | 348 (71.0) | 517 (78.8) | |
| Yes | 131 (26.7) | 119 (18.1) | |
| Unknown | 11 (2.2) | 20 (3.0) | |
| **Diabetes** | 105 (21.4) | 155 (23.6) | 0.38 |
| **Body mass index (kg m<sup>-2</sup>, mean ± s.d.)** | 33.1 ± 8.8 | 32.2 ± 8.1 | 0.06 |
| **Ever smoked** | 217 (44.3) | 277 (42.2) | 0.49 |
| **Alcohol (drink per day)<sup>e</sup>** | | | 0.001 |
| 0 | 185 (37.8) | 202 (30.8) | |
| >0 –≤1 | 278 (56.7) | 379 (57.8) | |
| >1 | 27 (5.5) | 75 (11.4) | |
| **Talc use** | | | 0.003 |
| Never | 180 (36.7) | 305 (46.5) | |
| Any genital use | 211 (43.1) | 228 (34.8) | |
| Only non-genital use | 99 (20.2) | 123 (18.8) | |
| **Recreational physical activity** | | | 0.29 |
| No | 268 (54.7) | 377 (57.5) | |
| <150 min per week | 91 (18.6) | 130 (19.8) | |
| ≥150 min per week | 131 (26.7) | 149 (22.7) | |
| **Occupational activity** | | | 0.34 |
| Inactive (sitting or standing) | 132 (26.9) | 157 (23.9) | |
| Active (walking or active) | 120 (24.5) | 153 (23.3) | |
| Do not work outside the home | 238 (48.6) | 346 (52.7) | |
| **Daylight hours spent outdoors in summer months (h per week, mean ± s.d.)** | 15.5 ± 13.7 | 16.8 ± 13.4 | 0.12 |
| **Skin pigmentation** | | | 0.70 |
| Lighter than average | 131 (26.7) | 184 (28.0) | |
| About average | 298 (60.8) | 383 (58.4) | |
| Darker than average | 61 (12.4) | 89 (13.6) | |
| **Total energy intake (kcal, mean ± s.d.)** | 1758.7 ± 1190.6 | 1727.7 ± 1110.6 | 0.65 |

Abbreviation: AACES = African American Cancer Epidemiology Study.

<sup>a</sup>Values are n (%) unless otherwise noted.
<sup>b</sup>Student’s t-tests for continuous variables and χ²-tests for categorical variables.
<sup>c</sup>South includes states with average UV index ≥5: TA, NC, SC, GA, AL, LA and TX; and North includes those ≤5: MI, IL, OH and NJ.
<sup>d</sup>Restricted to postmenopausal women.
<sup>e</sup>One drink contains ~13 g of alcohol, equivalent to 12 fl oz of beer or 5 fl oz of table wine.
Table 2. Association between dairy products and ovarian cancer risk in AACES\(^a\)

| Cases (n = 490) | Controls (n = 656) | Model 1\(^b\) | Model 2\(^c\) |
|----------------|-------------------|--------------|--------------|
|                | n  | %  | n  | %  | OR  | 95% CI      | OR  | 95% CI      |
| Total dairy (serving per week) |      |     |      |     |     |              |     |              |
| Q1 (≤ 2.6)     | 103| 21.0| 168| 25.6| 1.00| Ref         | 1.00| Ref         |
| Q2 (2.7–4.7)   | 144| 29.4| 167| 25.5| 1.41| 1.01, 1.98  | 1.48| 1.04, 2.11  |
| Q3 (4.8–8.3)   | 118| 24.1| 157| 23.9| 1.22| 0.85, 1.75  | 1.32| 0.91, 1.92  |
| Q4 (>8.4)      | 125| 25.5| 164| 25.0| 1.37| 0.90, 2.08  | 1.48| 0.95, 2.28  |
| P for trend    |     |     |     |     |     | 0.36         |     | 0.25         |
| Milk (serving per week) |      |     |      |     |     |              |     |              |
| Q1 (≤ 0.8)     | 103| 21.0| 161| 24.5| 1.00| Ref         | 1.00| Ref         |
| Q2 (0.9–1.7)   | 121| 24.7| 161| 24.5| 1.15| 0.81, 1.64  | 1.20| 0.83, 1.74  |
| Q3 (1.8–4.1)   | 139| 28.4| 173| 26.4| 1.22| 0.86, 1.72  | 1.20| 0.83, 1.75  |
| Q4 (≥4.2)      | 127| 25.9| 161| 24.5| 1.26| 0.85, 1.88  | 1.34| 0.87, 2.05  |
| P for trend    |     |     |     |     |     | 0.38         |     | 0.30         |
| Whole milk (serving per week) |      |     |      |     |     |              |     |              |
| Non-consumer   | 356| 72.7| 511| 77.9| 1.00| Ref         | 1.00| Ref         |
| ≤2.3           | 56 | 11.4| 73 | 11.1| 1.13| 0.77, 1.66  | 1.20| 0.68, 2.12  |
| >2.3           | 78 | 15.9| 72 | 11.0| 1.61| 1.10, 2.35  | 1.85| 1.05, 3.27  |
| P for trend    |     |     |     |     |     | 0.01         |     | 0.02         |
| Skim/low-fat milk (serving per week) |      |     |      |     |     |              |     |              |
| Non-consumer   | 178| 36.3| 209| 31.9| 1.00| Ref         | 1.00| Ref         |
| ≤2.0           | 157| 32.0| 229| 34.9| 0.82| 0.61, 1.11  | 1.11| 0.69, 1.77  |
| >2.0           | 155| 31.6| 218| 33.2| 0.84| 0.63, 1.12  | 1.06| 0.66, 1.70  |
| P for trend    |     |     |     |     |     | 0.35         |     | 0.98         |
| Cheese (serving per week) |      |     |      |     |     |              |     |              |
| Q1 (≤ 0.9)     | 116| 23.7| 159| 24.2| 1.00| Ref         | 1.00| Ref         |
| Q2 (1.0–1.7)   | 119| 24.3| 158| 24.1| 1.08| 0.76, 1.52  | 1.10| 0.76, 1.58  |
| Q3 (1.8–3.1)   | 129| 26.3| 174| 26.5| 1.09| 0.77, 1.54  | 1.18| 0.82, 1.71  |
| Q4 (≥3.2)      | 126| 25.7| 165| 25.2| 1.19| 0.79, 1.79  | 1.25| 0.81, 1.92  |
| P for trend    |     |     |     |     |     | 0.42         |     | 0.34         |
| Yogurt (serving per week) |      |     |      |     |     |              |     |              |
| Non-consumer   | 213| 43.5| 263| 40.1| 1.00| Ref         | 1.00| Ref         |
| <0.5           | 144| 29.4| 218| 33.2| 0.82| 0.62, 1.09  | 0.84| 0.62, 1.13  |
| ≥0.5           | 133| 27.1| 175| 26.6| 0.95| 0.70, 1.27  | 0.93| 0.67, 1.28  |
| P for trend    |     |     |     |     |     | 0.96         |     | 0.88         |

Abbreviations: AACES—African American Cancer Epidemiology Study; CI—confidence interval; OR—odds ratio.
\(^a\)Exposures were categorised into quartiles based on the distribution of controls. For exposures with >25% non-consumers, they were categorised into non-consumers, below or above the median of consumption based on controls’ distributions.
\(^b\)Model 1 adjusted for age, region, and total energy intake.
\(^c\)Model 2 further adjusted for education, parity, oral contraceptive use, menopausal status, tubal ligation, family history of breast/ovarian cancer, daylight hours spent outdoors in summer months, pigmentation, recreational physical activity, body mass index, supplemental calcium intake, and mutually adjusted for other types of dairy products when applicable.

Examination Survey AA adults had much lower intake of total dairy or milk (mean ± s.d.: 0.48 ± 0.06 serving per day) compared with other races (0.93 ± 0.07 serving per day; Fulgoni et al, 2007), which is consistent with our findings. Because of the lower intakes in the reference group, we may be more likely to detect the relation with milk and lactose than other case-control studies.

The other two abundant nutrients from dairy foods are calcium and vitamin D, which represent the largest contributor of total calcium and vitamin D intake of the US population (37% and 49%, respectively) regardless of supplemental intake (Baraina et al, 2014; Hoy and Goldman, 2014). We identified a consistent inverse association with total, dietary and supplemental intakes of calcium, independent of a wide array of non-dietary and dietary factors. For vitamin D intake, we only observed a suggestive decreased risk with that from supplemental sources. Although we have mutually adjusted for each other, the high correlations between calcium and vitamin D made it challenging to evaluate their independent associations with ovarian cancer, particularly between supplemental calcium and vitamin D, which often go together in available supplements. Our findings with calcium were supported by some
Cohort and case-control studies (Bidoli et al., 2001; Goodman et al., 2002; Koralek et al., 2006; Merritt et al., 2013), but not all (Tzonou et al., 1993; Kushi et al., 1999; Genkinger et al., 2006; Chang et al., 2007). A recent case-control study suggested that the association was stronger for mucinous ovarian cancer (Merritt et al., 2013). Considering that mucinous tumours of the ovary usually originate from the colorectum, and exhibit similar mutational patterns as mucinous carcinomas of the colorectum (Kelemen and Kobel, 2011), the protective effect of calcium intake on colorectal cancer may also apply to the mucinous type ovarian cancer (Cho et al., 2004). Because of the small number of mucinous cases \((n = 25)\), we were not able to restrict analyses to this subtype. However, our findings were not altered when mucinous cases were excluded.

Calcium may also protect against advanced ovarian cancer, as a mediator of vitamin D-induced apoptosis (Sergeev, 2004). Data from animal models of ovarian cancer showed consistent evidence that calcitriol, the active form of vitamin D, could suppress the growth of ovarian cancer (Zhang et al., 2005). However, evidence from epidemiological studies was rather inconsistent (Cook et al., 2010). Except a few (Salazar-Martinez et al., 2002; Merritt et al., 2013), most studies including ours did not observe a decreased risk with vitamin D intake (Kushi et al., 1999; Genkinger et al., 2006; Koralek et al., 2006; Chang et al., 2007). However, the ecological

| Table 3. Association between intakes of calcium, vitamin D and lactose with ovarian cancer risk in AACES$^a$ |
|---------------------------------------------------------------|
| **Cases (n = 490)** | **Controls (n = 656)** | **Model 1** | **Model 2** |
|                  |                  | OR      | 95% CI | OR      | 95% CI |
| **Total calcium (mg per day)**                              |                  |         |        |         |        |
| Q1 (<478.6)      | 298              | 26.0    | 164    | 25.0    | 1.00    | Ref    | 1.00    | Ref    | 0.012  | 0.097  |
| Q2 (478.7–784.1) | 306              | 26.7    | 164    | 25.0    | 1.00    | 0.72, 1.39 | 0.89 | 0.11  | 0.26, 1.31 |
| Q3 (784.2–1233.6)| 272              | 23.7    | 164    | 25.0    | 0.70    | 0.48, 1.00 | 0.62 | 0.26, 0.96 |
| Q4 (>1233.7)     | 270              | 23.6    | 164    | 25.0    | 0.63    | 0.42, 0.94 | 0.51 | 0.30, 0.86 |
| **Dietary calcium (mg per day)**                            |                  |         |        |         |        |
| Q1 (<362.4)      | 123              | 25.1    | 164    | 25.0    | 1.00    | Ref    | 1.00    | Ref    | 0.26  | 0.49  |
| Q2 (362.5–546.8) | 128              | 26.1    | 164    | 25.0    | 0.98    | 0.70, 1.37 | 0.79 | 0.34, 1.17 |
| Q3 (546.9–819.5) | 126              | 25.7    | 164    | 25.0    | 0.94    | 0.65, 1.35 | 0.75 | 0.30, 1.17 |
| Q4 (>819.6)      | 113              | 23.1    | 164    | 25.0    | 0.77    | 0.48, 1.23 | 0.52 | 0.26, 0.98 |
| **Supplemental calcium (mg per day)**                       |                  |         |        |         |        |
| Non-consumer     | 231              | 47.1    | 240    | 36.6    | 1.00    | Ref    | 1.00    | Ref    | <0.001 | 0.007  |
| <240.0           | 143              | 29.2    | 214    | 32.6    | 0.69    | 0.52, 0.91 | 0.62 | 0.41, 0.92 |
| >240.0           | 116              | 23.7    | 202    | 30.8    | 0.57    | 0.43, 0.77 | 0.52 | 0.35, 0.79 |
| **Total vitamin D (IU per day)**                            |                  |         |        |         |        |
| Q1 (<130.8)      | 313              | 27.3    | 164    | 25.0    | 1.00    | Ref    | 1.00    | Ref    | 0.27  | 0.30  |
| Q2 (130.9–292.8) | 262              | 22.9    | 164    | 25.0    | 0.63    | 0.45, 0.89 | 0.72 | 0.49, 1.04 |
| Q3 (292.9–523.9) | 282              | 24.6    | 164    | 25.0    | 0.77    | 0.55, 1.07 | 0.89 | 0.60, 1.32 |
| Q4 (>524.0)      | 289              | 25.2    | 164    | 25.0    | 0.75    | 0.54, 1.05 | 1.00 | 0.65, 1.54 |
| **Dietary vitamin D (IU per day)**                          |                  |         |        |         |        |
| Q1 (<48.5)       | 124              | 25.3    | 164    | 25.0    | 1.00    | Ref    | 1.00    | Ref    | 0.41  | 0.69  |
| Q2 (48.6–80.8)   | 114              | 23.3    | 164    | 25.0    | 0.90    | 0.64, 1.27 | 0.84 | 0.57, 1.25 |
| Q3 (80.9–141.1)  | 115              | 23.5    | 164    | 25.0    | 0.91    | 0.64, 1.30 | 0.85 | 0.54, 1.33 |
| Q4 (>141.2)      | 137              | 28.0    | 164    | 25.0    | 1.12    | 0.75, 1.66 | 1.02 | 0.58, 1.79 |
| **Supplemental vitamin D (IU per day)**                     |                  |         |        |         |        |
| Non-consumer     | 206              | 40.8    | 189    | 28.8    | 1.00    | Ref    | 1.00    | Ref    | 0.03  | 0.20  |
| <371.4           | 134              | 27.4    | 257    | 39.2    | 0.49    | 0.37, 0.66 | 0.54 | 0.39, 0.74 |
| >371.4           | 156              | 31.8    | 210    | 32.0    | 0.67    | 0.50, 0.89 | 0.78 | 0.55, 1.12 |
| **Lactose (g per day)**                                     |                  |         |        |         |        |
| Q1 (<2.3)        | 104              | 21.22   | 170    | 25.9    | 1.00    | Ref    | 1.00    | Ref    | 0.01  | 0.008  |
| Q2 (2.4–4.6)     | 137              | 27.96   | 164    | 25.0    | 1.41    | 1.00, 1.98 | 1.44 | 1.00, 2.08 |
| Q3 (4.7–8.8)     | 108              | 22.04   | 158    | 24.1    | 1.12    | 0.78, 1.61 | 1.19 | 0.79, 1.78 |
| Q4 (>8.9)        | 141              | 28.78   | 164    | 25.0    | 1.53    | 1.02, 2.29 | 1.97 | 1.25, 3.10 |

Abbreviations: AACES = African American Cancer Epidemiology Study; CI = confidence interval; IU, international unit; OR = odds ratio.

$^a$Exposures were categorised into quartiles based on the distribution of controls. For exposures with >25% non-consumers, they were categorised into non-consumers, below or above the median of consumption based on controls’ distributions.

$^b$Model 1 adjusted for age, region, and total energy intake.

$^c$Model 2 further adjusted for education, parity, oral contraceptive use, menopausal status, tubal ligation, family history of breast/ovarian cancer, daylight hours spent outdoors in summer months, pigmentation, recreational physical activity, body mass index, other sugar intake excluding lactose, plus quartiles of total calcium, total vitamin D, and lactose when applicable. When examining dietary or supplemental intake of calcium (or vitamin D), the model was also mutually adjusted for the other source.
We recognised the limitations of dietary recall in case-control studies. However, the largely unknown relation between intakes of vitamin D, calcium or dairy foods, and ovarian cancer and, as a result, lack of awareness of this link in this population should minimise this problem. To reduce the potential that undetected disease influenced dietary recall, cases were asked to report their diet 1 year before diagnosis that is beyond the median pre-diagnostic symptom duration (4 months) for invasive cases (Vine et al, 2001). The potential for selection bias is another concern, especially when the participation rates in population-based epidemiologic studies have been declining. However, the distribution of risk factors among cases and controls in our study were in the expected directions compared with other studies among AA women (Moorman et al, 2009), which increased our confidence in the validity of our findings. In addition, residual confounding is possible despite the multivariable and mutually adjusted models. We did not have information on sunscreen use or clothing habits, which could attenuate the negative associations between daylight outdoor hours in the summer and the risk of ovarian cancer. Nevertheless, the prevalence of sun-protection behaviours among AAs is low (e.g., 63% never used sunscreen; Hall and Rogers, 1998).

A main strength of our study is that we were able to recruit a large sample of AA ovarian cancer cases and controls from various geographic regions, and with diverse socioeconomic and lifestyle characteristics, which imparts our ability to generalise the results to the AA population. Our study adds to the scarce literature on the aetiology of ovarian cancer in AA women.

Considering that there is no effective screening tool for ovarian cancer and the poorer survival of AA patients, prevention is critical, particularly through lifestyle or dietary modifications, which are less costly and risky than medical treatments. Our findings suggest that sun exposure in summer months and a high-calcium, low-lactose diet may benefit ovarian cancer prevention in AA women.

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Table 4. Daylight hours spent outdoors and ovarian cancer risk in AACES*

| Weekly average of daylight hours spent outdoors in a year (h per week) | Cases (n = 490) | Controls (n = 656) | Model 1b | Model 2c |
|---|---|---|---|---|
| **Q1 (≤5)** | 146 | 29.8 | 163 | 24.9 | 1.00 | Ref | 1.00 | Ref |
| **Q2 (6–10)** | 88 | 18.0 | 120 | 18.3 | 0.85 | 0.59, 1.22 | 0.82 | 0.57, 1.20 |
| **Q3 (11–16)** | 131 | 26.7 | 198 | 30.2 | 0.76 | 0.55, 1.04 | 0.72 | 0.52, 1.00 |
| **Q4 (≥17)** | 125 | 25.5 | 175 | 26.7 | 0.85 | 0.61, 1.19 | 0.84 | 0.59, 1.20 |
| P for trend | | | | | 0.43 | | 0.46 | |

| Weekly average of daylight hours spent outdoors in summer months (h per week) | Cases (n = 490) | Controls (n = 656) | Model 1b | Model 2c |
|---|---|---|---|---|
| **Q1 (≤6)** | 160 | 32.7 | 178 | 27.1 | 1.00 | Ref | 1.00 | Ref |
| **Q2 (7–11)** | 135 | 27.6 | 176 | 26.8 | 0.86 | 0.63, 1.18 | 0.86 | 0.62, 1.20 |
| **Q3 (12–22)** | 76 | 15.5 | 105 | 16.0 | 0.87 | 0.60, 1.25 | 0.91 | 0.62, 1.34 |
| **Q4 (≥23)** | 119 | 24.3 | 197 | 30.0 | 0.71 | 0.52, 0.98 | 0.71 | 0.51, 0.99 |
| P for trend | | | | | 0.041 | | 0.049 | |

Abbreviations: AACES = African American Cancer Epidemiology Study; CI = confidence interval; OR = odds ratio.

*Exposures were categorised based on approximate quartiles among controls.

bModel 1 adjusted for age, region, and total energy intake.

cModel 2 further adjusted for education, parity, oral contraceptive use, menopausal status, tubal ligation, family history of breast/ovarian cancer, pigmentation, recreational physical activity, body mass index, and total vitamin D intake.
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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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