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

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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

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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). Dairy 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 χ^2 -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 dairy 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).

We did not find significant interaction between any two nutrients – total calcium, total vitamin D, and lactose; or between these nutrients and total dairy with sun exposure hours (in a year or in summer months), skin pigmentation, BMI, menopausal status, and oral contraceptive use. In the analyses by serous and endometrioid histologic subtypes (Supplementary Table 2), we observed similar magnitude of associations with continuous scale of total dairy, nutrients, or sun exposure across tumour subtypes. No significant heterogeneity was found.

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^a

	Cases (n = 490) n (%)	Controls (n = 656) n (%)	P ^b
Age (y, mean $\pm$ s.d.)	57.3 $\pm$ 10.5	54.9 $\pm$ 11.5	<0.001
Region ^c			<0.001
South	385 (78.6)	448 (68.3)	
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			0.002
Never	142 (29.0)	132 (20.1)	
< 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 ^d	91 (26.0)	107 (23.4)	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 ⁻² , mean $\pm$ s.d.)	33.1 $\pm$ 8.8	32.2 $\pm$ 8.1	0.06
Ever smoked	217 (44.3)	277 (42.2)	0.49
Alcohol (drink per day) ^e			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 $\pm$ s.d.)	15.5 $\pm$ 13.7	16.8 $\pm$ 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 $\pm$ s.d.)	1758.7 $\pm$ 1190.6	1727.7 $\pm$ 1110.6	0.65

Abbreviation: AACES = African American Cancer Epidemiology Study.

^aValues are n (%) unless otherwise noted.^bStudent's t-tests for continuous variables and χ^2 -tests for categorical variables.^cSouth includes states with average UV index >5: TX, NC, SC, GA, AL, LA and TX; and North includes those ≤ 5 : MI, IL, OH and NJ.^dRestricted to postmenopausal women.^eOne 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.

^aExposures 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.

^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, 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.

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

^aExposures 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.

^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, 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.

to a deficient activity of galactose-1-phosphate uridyl transferase (GALT) (Kaufman *et al*, 1981), which, in turn, is caused by GALT gene mutations. Among several polymorphisms, S135L is almost exclusively found in AAs (Tyfield *et al*, 1999). It is possible that a higher lactose consumption, which is beyond the GALT activity, may introduce a greater risk of ovarian cancer.

Consistent with this hypothesis, and the findings from a pooling study and a meta-analysis of prospective studies (Genkinger *et al*, 2006; Larsson *et al*, 2006), we found lactose intake increased ovarian cancer risk in AAs. Two cohort studies found this association was stronger for serous tumours (Fairfield *et al*, 2004; Larsson *et al*, 2004), whereas most case-control studies did not observe this positive relation among all cases or across tumour subtypes (Webb *et al*, 1998; Pan *et al*, 2004; Merritt *et al*, 2013). Compared with the previous studies that were mainly conducted in European or European-American women, our study of AA women had, on average, lower intakes of milk and lactose. AAs are more likely to have lactose intolerance than European Americans (Suchy *et al*, 2010), which may, in part, explain the reduced intake of milk and lactose in this population. For example, in the National Health and Nutrition

Examination Survey AA adults had much lower intake of total dairy or milk (mean $\pm$ 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 (Barainca *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

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 ^b		Model 2 ^c	
	n	%	n	%	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
Q2 (478.7–784.1)	306	26.7	164	25.0	1.00	0.72, 1.39	0.89	0.61, 1.31
Q3 (784.2–1233.6)	272	23.7	164	25.0	0.70	0.48, 1.00	0.62	0.39, 0.96
Q4 (≥1233.7)	270	23.6	164	25.0	0.63	0.42, 0.94	0.51	0.30, 0.86
P for trend					0.012		0.009	
Dietary calcium (mg per day)								
Q1 (≤362.4)	123	25.1	164	25.0	1.00	Ref	1.00	Ref
Q2 (362.5–546.8)	128	26.1	164	25.0	0.98	0.70, 1.37	0.79	0.54, 1.17
Q3 (546.9–819.5)	126	25.7	164	25.0	0.94	0.65, 1.35	0.75	0.47, 1.20
Q4 (≥819.6)	113	23.1	164	25.0	0.77	0.48, 1.23	0.52	0.28, 0.98
P for trend					0.26		0.049	
Supplemental calcium (mg per day)								
Non-consumer	231	47.1	240	36.6	1.00	Ref	1.00	Ref
≤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
P for trend					<0.001		0.007	
Total vitamin D (IU per day)								
Q1 (≤130.8)	313	27.3	164	25.0	1.00	Ref	1.00	Ref
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
P for trend					0.27		0.60	
Dietary vitamin D (IU per day)								
Q1 (≤48.5)	124	25.3	164	25.0	1.00	Ref	1.00	Ref
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
P for trend					0.41		0.69	
Supplemental vitamin D (IU per day)								
Non-consumer	200	40.8	189	28.8	1.00	Ref	1.00	Ref
≤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
P for trend					0.03		0.20	
Lactose (g per day)								
Q1 (≤2.3)	104	21.22	170	25.9	1.00	Ref	1.00	Ref
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
P for trend					0.11		0.008	

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

^aExposures 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.

^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, 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.

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 4. Daylight hours spent outdoors 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
Weekly average of daylight hours spent outdoors in a year (h per week)								
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)								
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.

^aExposures 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.

studies that evaluated UVB radiation and ovarian mortality rates invariably found an inverse correlation (Grant, 2012), which supported our finding that sun exposure in summer months predicted a lower risk of ovarian cancer. Vitamin D synthesis was thought to be the most important physiological effect of sun exposure, despite other pathways such as circadian rhythm that have been proposed as well (van der Rhee *et al*, 2013). Although we were not able to collect serum samples before diagnosis, a meta-analysis or a pooling study of circulating vitamin D concentration found a tentative inverse association among all women (Yin *et al*, 2011), or an inverse association among women who were overweight or obese (Zheng *et al*, 2010). Relatively similar findings for vitamin D status and sun exposure in relation to ovarian cancer may be explained by the observation that the circulating level of vitamin D is determined primarily by exposure to sunlight (Adams *et al*, 1982). It is suggested that sun exposure for 5–15 min between 1000 hours and 1500 hours during spring, summer, and fall can help produce an adequate amount of vitamin D for Whites, AAs need 5–10 times longer exposure to synthesise the same amount of vitamin D, as their skin pigment reduce the penetration of UVB (Holick, 2011). However, because the benefits of sun exposure may be offset by increased risk of skin cancer, a combination of moderate sun exposure and sufficient vitamin D intakes from diet and supplements may be a safer solution for an adequate vitamin D status. In our study, <20% of AA women achieved the recommended daily vitamin D intake of at least 600 IU (or 800 IU if beyond 70 years; Ross *et al*, 2011), a threshold mainly based on the evidence in skeletal health. It has been hypothesised, but remains to be explored whether higher daily doses of vitamin D would be required for anticancer actions than that for bone health (Feldman *et al*, 2014).

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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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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