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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Cataract and Ovarian Carcinoma: Is the Vitamin D Hypothesis Alive?

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Abstract

Background: The major health benefit of exposure to solar UV radiation is the production of vitamin D, which is implicated in protection against several human cancers, including ovarian carcinoma. On the other hand, solar UV radiation is a recognized risk factor for cataract.

Methods: This population-based case–control study of 709 women with primary invasive ovarian carcinoma and 1,101 controls examined the association of ovarian carcinoma risk with self-reported history of cataract as an indicator of high long-term exposure to UV radiation. ORs and 95% confidence intervals (CI) were estimated using multivariate logistic regression models.

Results: Among controls, older age ($P < 0.0001$), history of type 2 diabetes ($P = 0.04$), and skin cancer ($P = 0.03$) were significant cataract risk predictors. A history of cataract, reported by 14% of cases and 17% of controls, was significantly associated with a reduced ovarian carcinoma risk (OR = 0.6; 95% CI, 0.4–0.8; $P = 0.002$). No heterogeneity was observed by tumor histology, stage, grade, study site, body mass index, or other ovarian cancer risk factors ($P > 0.16$).

Conclusion: These findings add indirect evidence to the hypothesis that lifetime vitamin D exposure may be inversely associated with risk of ovarian carcinoma.

Impact: The study suggests some potential new avenues for research. Additional studies are needed to further investigate the potential behavioral and biologic factors that might influence association of cataract with ovarian cancer. *Cancer Epidemiol Biomarkers Prev; 1–5. ©2011 AACR.*

Introduction

Sunlight exposure is a recognized risk factor for developing cataract (1–3), a principal cause of blindness worldwide. According to the latest World Health Organization survey, age-related cataract is responsible for 48% of world blindness, representing about 18 million people (4). Solar radiation also contributes to nearly 1 million cases of basal and squamous cell skin cancers in the United States each year (5). Despite of these risks, public health recommendations about appropriate lower limits for sunlight exposure must consider the human requirement for UV radiation to catalyze vitamin D synthesis in the skin (6). Recent evidence suggests that colorectal cancer risk may be reduced through increased levels of circulating vitamin D (7, 8), but a role for vitamin D in the etiology of ovarian cancer remains controversial. Ecological studies have reported inverse associations between sunlight exposure and ovarian cancer incidence (9, 10) and mortality (11, 12). However, dietary studies of vitamin D exposure and ovarian carcinoma risk have been inconsistent (13). A recent meta-analysis of results from 10 longitudinal studies suggests a weak, nonsignificant inverse association between circulating 25(OH)D and ovarian cancer risk that was strongest among overweight women (14). Although evidence for a protective association of vitamin D with ovarian cancer is modest, a single blood measurement, while integrating dietary and nondietary sources of vitamin D, may not represent long-term vitamin D status.

We conducted a population-based study of ovarian carcinoma with a primary focus on dietary mechanisms in the etiology of ovarian cancer (15). Because of the complexity of ascertaining lifetime sunlight exposure, we asked study participants about their history of physician-diagnosed skin cancer and cataract as indicators of high long-term exposure to UV radiation.

Methods

Cases were women with histologically confirmed primary incident invasive ovarian carcinoma, 18 years or

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Table 1. Cataract association with selected participant characteristics among controls

	Cataract			
Characteristics	**Yes**	**No**	**OR (95% CI)[a]**	***P*[a]**
No. of participants (%)	182 (17)	919 (83)		
Age, y				
<65	47 (6)	751 (94)	1.0	<0.0001
65–75	76 (38)	126 (62)	4.4 (2.7–7.2)	
>75	59 (58)	42 (42)	8.6 (4.7–16.4)	
Ethnicity				
Caucasian	72 (19)	311 (81)	1.0	0.22
Asian	82 (17)	393 (83)	0.6 (0.4–1.1)	
Mixed/other	28 (12)	215 (88)	0.8 (0.4–1.5)	
Education, y				
≤12	68 (21)	250 (79)	1.0	0.34
>12	114 (15)	669 (85)	1.1 (0.9–1.5)	
BMI, kg/m^2				
<25	114 (18)	537 (82)	1.0	0.12
≥25	68 (15)	382 (85)	0.7 (0.5–1.1)	
Parity				
Nulliparous	23 (13)	158 (87)	1.0	0.88
1–2	63 (14)	400 (86)	1.2 (0.6–2.2)	
≥3	96 (21)	361 (79)	1.1 (0.6–1.9)	
Use of contraceptive steroids				
Never	129 (30)	300 (70)	1.0	
<1 y	17 (12)	130 (88)	1.4 (0.7–2.8)	0.36
1–4 y	16 (6)	239 (94)	0.5 (0.3–1.1)	0.06
5–9 y	13 (8)	142 (92)	0.9 (0.5–2.1)	0.91
10+ y	7 (6)	108 (94)	0.8 (0.3–2.0)	0.60
Per year of use			0.99 (0.94–1.06)	0.80
Use of menopausal hormones				
Never	80 (28)	208 (72)	1.0	0.46
Estrogen only	46 (35)	87 (65)	1.4 (0.8–2.3)	
Estrogen and progestin	51 (20)	198 (80)	1.1 (0.6–1.6)	
Smoking				
never	117 (18)	539 (82)	1.0	0.99
Past or current	65 (15)	380 (85)	1.1 (0.7–1.5)	
Alcohol consumption				
No	120 (18)	544 (82)	1.0	0.78
Yes	62 (14)	375 (86)	1.1 (0.7–1.7)	
Type 2 diabetes				
No	152 (15)	854 (85)	1.0	0.04
Yes	30 (32)	65 (68)	1.9 (1.1–3.4)	
Thyroid disease				
No	139 (15)	791 (85)	1.0	0.61
Yes	43 (25)	128 (75)	1.1 (0.7–1.8)	
Skin carcinoma				
No	151 (15)	876 (85)	1.0	0.03
Yes	31 (42)	43 (58)	2.1 (1.1–4.0)	

Abbreviation: BMI, body mass index.

[a]ORs, 95% CIs, and *P* values from multivariate logistic regression model adjusted for age (continuous), ethnicity, center, education, BMI, menopausal status, use of contraceptive and menopausal hormones, alcohol consumption, smoking, and history of thyroid disease and type 2 diabetes mellitus.

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Table 2. Association of reported history of cataract with invasive ovarian carcinoma

Cataract	Controls	All cases		Serous		Nonserous		Stages I and II		Stages III and IV		Grade I and II (low)		Grade III and IV (high)	
	N (%)	*N* (%)	OR (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)	N	OR (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)
No	919 (83)	613 (86)	1.0	265	1.0	348	1.0	287	1.0	302	1.0	196	1.0	323	1.0
Yes	182 (17)	96 (14)	0.6 (0.4–0.8)	50	0.6 (0.4–0.9)	46	0.6 (0.4–0.9)	47	0.7 (0.5–1.1)	48	0.5 (0.4–0.8)	22	0.5 (0.3–0.8)	62	0.6 (0.5–0.9)
P^a			0.002		0.01		0.02		0.11		0.0009		0.01		0.02
P^b							0.92				0.16				0.59

[a]ORs, 95% CIs, and *P* values from the logistic regression models including age (continuous), ethnicity, center, education, body mass index, family history of ovarian cancer, parity, tubal ligation, hysterectomy, menopausal status, use of contraceptive and menopausal hormones, smoking, alcohol consumption, and history of thyroid disease and diabetes mellitus.

[b]Wald test *P* value for heterogeneity of cataract association with ovarian carcinoma by histology, stage, and grade strata.

older, who were identified through the rapid-reporting systems of the Hawaii Tumor Registry and the Los Angeles County Cancer Surveillance Program between 1993 and 2008 (15). In total, 709 women meeting these criteria were recruited, with a participation rate of 78%. Controls were women without a history of ovarian cancer or bilateral oophorectomy, randomly selected from participants in an annual survey of representative households in Hawaii and by random digit dialing in Los Angeles. Interviewed controls ($N = 1{,}001$) were frequency matched to cases on ethnicity, 5-year age group, and place of residence (participation rate was 80%). The study was approved by the Institutional Review Boards of the University of Hawaii and the University of Southern California, Los Angeles, CA, and written informed consent was obtained from all participants.

Statistical analysis was conducted using SAS (release 9.2, SAS Institute Inc.). Multivariate unconditional logistic regression models were used to estimate ORs and 95% confidence intervals (CI) for the association of age, education, and other exposures with the risk of cataract among controls (Table 1) and to assess the association of cataract with the risk of ovarian carcinoma among all subjects (see Table 2 for adjustment variables). Heterogeneity of effects by study site (Hawaii, Southern California), body mass index (treated as both a continuous and a categorical variable: underweight or normal vs. overweight; obese vs. nonobese), and other covariates were examined using Wald test of the cataract–covariate interaction term. Heterogeneity of ORs by histology, stage, and grade was examined using polytomous logistic regression; the estimated ORs were compared using the Wald test. In addition, a sensitivity analysis was conducted excluding women of a younger age. All *P* values were 2-tailed.

Results

Controls with a history of cataract were older (mean age $= 70.0 \pm 9.2$ years vs. 53.3 ± 13.0 years; $P < 0.0001$), more likely to be diagnosed with type 2 diabetes mellitus (OR = 1.9; 95% CI, 1.3–3.4; $P = 0.04$), and at greater risk of skin cancer (OR = 2.1; 95% CI, 1.1–4.0; $P = 0.03$) than controls without a history of cataract (Table 1).

The prevalence of cataract among cases (14%) was significantly lower than among controls (17%), with an OR of 0.6 for ovarian carcinoma (95% CI, 0.4–0.8; $P = 0.002$) that was independent of known ovarian carcinoma risk factors (Table 2). Adding available potential risk factors for developing a cataract to the model, such as smoking, alcohol consumption, thyroid disease, and type 2 diabetes, did not substantially alter this association. No heterogeneity of the cataract–ovarian cancer association was observed by tumor histologic subtype ($P = 0.92$), stage ($P = 0.16$), or grade ($P = 0.59$; Table 2), and a history of cataract was associated with 50% lower risk of advanced high-grade serous carcinoma (95% CI, 0.3–0.9; $P = 0.02$). No heterogeneity was observed by study

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site ($P = 0.87$), body mass index ($P = 0.80$), or other known ovarian cancer risk factors. The association of cataract with ovarian carcinoma risk was consistent among women ≥50 years old (OR = 0.6; 95% CI, 0.4–0.8; $P = 0.001$); ≥60 years old (OR = 0.6; 95% CI, 0.4–0.9; $P = 0.003$); and ≥70 years old (OR = 0.5; 95% CI, 0.3–0.8; $P = 0.002$). A nonsignificant inverse association of skin carcinomas with ovarian cancer (OR = 0.7; 95% CI, 0.4–1.1; $P = 0.09$) was also observed.

Discussion

Although cataract etiology is not fully understood, oxidative stress associated with UV light is considered central to the pathogenesis of this disease (1–3). Ecological studies have shown strong correlations of cataract development with lifetime sun exposure (3), a factor hypothesized to affect several human cancers, including ovarian malignancy (9–12). In support of an association of vitamin D with ovarian cancer, we have compelling results from our genetic studies providing evidence that several *vitamin D receptor* genetic variants may influence ovarian cancer risk (16, 17), perhaps through reduced receptor functionality. Furthermore, laboratory investigations showing that vitamin D and its synthetic analogues inhibit growth and induce apoptosis in ovarian cells in culture and in animal models of ovarian cancer (18–20) strengthen the hypothesis that vitamin D may reduce ovarian cancer risk. Although no sun exposure information was collected in our study, we found a direct association of cataract with skin cancer for which sun exposure is an established risk factor. Although an inverse association between carcinomas of the skin and ovary was observed, it was not significant due to the small number of women with skin cancer ($N = 114$). Moreover, skin cancer and ovarian cancer might have other common mechanisms (e.g., genetic and immunologic) that would obscure this potential association.

This investigation has several strengths including its relatively large size, population-based design, standard histopathologic review of all cases, and full information on a variety of health-related characteristics that allowed us to account for confounding effects. Our study had several limitations. Information on cataract history was self-reported and might lead to misclassification bias. Compared with cataract prevalence data in Hawaii (21) for all females (19%), history of cataract may have been modestly underreported (17%) by our control study participants. However, the misclassification would likely have affected both cases and controls equally and thus would tend to attenuate the association. No data on cataract type and grade were available in our study.

These findings add indirect evidence to the hypothesis that lifetime vitamin D exposure is inversely associated with risk of ovarian carcinoma and suggest some potential new avenues for research. Aside from sunlight exposure, a variety of drugs, such as corticosteroids (22) and phenothiazines (23), have been found to be associated with an increased risk of cataract; and statin drugs may reduce the risk for cataract (24). Additional studies are needed to further investigate the potential behavioral (e.g., UV radiation exposure) and biologic (e.g., medication history) factors that might influence associations of cataract with ovarian cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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