Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2011 December ; 20(12): 2507–2511. doi:
10.1158/1055-9965.EPI-11-0721.

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

Galina Lurie¹, Rayna K. Matsuno¹, Lynne R. Wilkens¹, Pamela J. Thompson¹, Nicholas J. Ollberding¹, Michael E. Carney², and Marc T. Goodman¹

¹Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI, USA

²Department of Obstetrics, Gynecology & Women's Health, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA

Abstract

Background—The major health benefit of exposure to solar ultraviolet 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 1101 controls examined the association of ovarian carcinoma risk with self-reported history of cataract as an indicator of high long-term exposure to ultraviolet radiation. Odds ratios (ORs) and 95% confidence intervals (CIs) 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 biological factors that might influence association of cataract with ovarian cancer.

Keywords

invasive ovarian carcinoma; cataract; case-control study

Introduction

Sunlight exposure is a recognized risk factor for developing cataract (1–4), a principal cause of blindness worldwide. According to the latest WHO survey, age related cataract is responsible for 48% of world blindness, representing about 18 million people (5). Solar radiation also contributes to nearly one million cases of basal and squamous cell skin

*Address for correspondence: Galina Lurie, MD, MPH, Cancer Epidemiology Program, University of Hawaii Cancer Center, 1236 Lauhala Street, Room 502E, Honolulu, HI 96813, Telephone: (808) 564-5981, Fax: (808) 586-2982, glurie@cc.hawaii.edu.

We do not have conflict of interest to disclose.

cancers in the United States each year (6). In spite of these risks, public health recommendations regarding appropriate lower limits for sunlight exposure must consider the human requirement for ultraviolet radiation to catalyze vitamin D synthesis in the skin (7). Recent evidence suggests that colorectal cancer risk may be reduced through increased levels of circulating vitamin D (8,9), 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 (10,11) and mortality (12,13). However, dietary studies of vitamin D exposure and ovarian carcinoma risk have been inconsistent (14). A recent meta-analysis of results from ten longitudinal studies suggests a weak, non-significant inverse association between circulating 25(OH)D and ovarian cancer risk that was strongest among overweight women (15). Although evidence for a protective association of vitamin D with ovarian cancer is modest, a single blood measurement, while integrating dietary and non-dietary 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 (16). 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 ultraviolet radiation.

Methods

Cases were women with histologically-confirmed primary incident invasive ovarian carcinoma, 18 years or older, who were identified through the rapid-reporting systems of the Hawaii Tumor Registry and the Los Angeles County Cancer Surveillance Program between 1993–2008 (16). 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, five-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, and written informed consent was obtained from all participants.

Statistical analysis was performed using SAS (release 9.2, SAS Institute Inc., Cary, NC). Multivariate unconditional logistic regression models were used to estimate odd ratios (ORs) and 95% confidence intervals (CIs) 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 performed excluding women of a younger age. All p-values were two-tailed.

Results

Controls with a history of cataract were older (mean age=70.0±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; $p=0.03$) compared to 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 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 non-significant 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 ultraviolet light is considered central to the pathogenesis of this disease (1–4). Ecological studies have shown strong correlations of cataract development with lifetime sun exposure (4), a factor hypothesized to affect several human cancers, including ovarian malignancy (10–13). 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, (17,18) perhaps through reduced receptor functionality. Furthermore, laboratory investigations demonstrating that vitamin D and its synthetic analogs inhibit growth and induce apoptosis in ovarian cells in culture and in animal models of ovarian cancer (19–21) 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. While 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, immunological) 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 to cataract prevalence data in Hawaii (22) for all females (19%), history of cataract may have been modestly under-reported (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 (23) and phenothiazines (24), have been found to be associated with an increased risk of cataract; and statin drugs may reduce the risk for cataract (25). Additional studies are needed to further investigate the potential behavioral (e.g., ultraviolet radiation exposure) and

biological (e.g., medication history) factors that might influence associations of cataract with ovarian cancer.

Acknowledgments

Financial Support: This work was supported by the National Institutes of Health (Grants R01 CA58598, N01-CN-55424, and N01-PC-67001 to MTG).

References

1. Ayala MN, Michael R, Soderberg PG. In vivo cataract after repeated exposure to ultraviolet radiation. *Exp Eye Res*. 2000; 70(4):451–456. [PubMed: 10865993]
2. Ayala MN, Michael R, Soderberg PG. Influence of exposure time for UV radiation-induced cataract. *Invest Ophthalmol Vis Sci*. 2000; 41(11):3539–3543. [PubMed: 11006249]
3. West SK, Longstreth JD, Munoz BE, Pitcher HM, Duncan DD. Model of risk of cortical cataract in the US population with exposure to increased ultraviolet radiation due to stratospheric ozone depletion. *Am J Epidemiol*. 2005; 162(11):1080–1088. [PubMed: 16251390]
4. West SK, Longstreth JD, Munoz BE, Pitcher HM, Duncan DD. Model of risk of cortical cataract in the US population with exposure to increased ultraviolet radiation due to stratospheric ozone depletion. *Am J Epidemiol*. 2005; 162(11):1080–1088. [PubMed: 16251390]
5. World Health Organization. [accessed, August 31, 2011] Priority eye diseases. www.who.int/blindness/causes/priority/en/index1.html
6. Howlader, N.; Noone, AM.; Krapcho, M.; Neyman, N.; Aminou, R.; Waldron, W., et al. SEER Cancer Statistics Review, 1975–2008. National Cancer Institute; Bethesda, MD: http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011
7. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on Dietary Reference Intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. *J Clin Endocrinol Metab*. 2011; 96:53–58. [PubMed: 21118827]
8. Park SY, Murphy SP, Wilkens LR, Nomura AM, Henderson BE, Kolonel LN. Calcium and vitamin D intake and risk of colorectal cancer: the Multiethnic Cohort Study. *Am J Epidemiol*. 2007; 165:784–793. [PubMed: 17215380]
9. Woolcott CG, Wilkens LR, Nomura AM, Horst RL, Goodman MT, Murphy SP, et al. Plasma 25-hydroxyvitamin D levels and the risk of colorectal cancer: the multiethnic cohort study. *Cancer Epidemiol Biomarkers Prev*. 2010; 19:130–134. [PubMed: 20056631]
10. Garland CF, Mohr SB, Gorham ED, Grant WB, Garland FC. Role of ultraviolet B irradiance and vitamin D in prevention of ovarian cancer. *Am J Prev Med*. 2006; 31(6):512–514. [PubMed: 17169713]
11. Muir, C.; Waterhouse, J.; Mack, TPJ.; Whelan, S. Cancer Incidence in Five Continents, International Agency for Research on Cancer (IARC). IARC; Lyon, France: 1987. Report No.: Scientific Publication No. 88, Vol.V
12. Lefkowitz ES, Garland CF. Sunlight, vitamin D, and ovarian cancer mortality rates in US women. *Int J Epidemiol*. 1994; 23(6):1133–1136. [PubMed: 7721513]
13. Devesa, SS.; Grauman, MA.; Blot, WJ.; Pennello, GA.; Hoover, RN.; Fraumeni, JF, Jr. Atlas of Cancer Mortality in the United States, 1950–1994. NCI. National Institutes of Health; Bethesda, MD: 1999. Report No.: National Institute of Health Publication No.99–4564
14. Salazar-Martinez E, Lazcano-Ponce EC, Lira-Lira Gonzalez, Escudero-De los Rios P, Hernandez-Avila M. Nutritional determinants of epithelial ovarian cancer risk: a case-control study in Mexico. *Oncology*. 2002; 63:151–157. [PubMed: 12239450]
15. Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis: Circulating vitamin D and ovarian cancer risk. *Gynecol Oncol*. 2011; 121(2):369–375. [PubMed: 21324518]
16. Goodman MT, Wu AH, Tung KH, McDuffie K, Kolonel LN, Nomura AM, et al. Association of dairy products, lactose, and calcium with the risk of ovarian cancer. *Am J Epidemiol*. 2002; 156(2):148–157. [PubMed: 12117706]

17. Lurie G, Wilkens LR, Thompson PJ, McDuffie KE, Carney ME, Terada KY, et al. Vitamin D receptor gene polymorphisms and epithelial ovarian cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2007; 16(12):2566–2571. [PubMed: 18086759]
18. Lurie G, Wilkens LR, Thompson PJ, Carney ME, Palmieri RT, Pharoah PD, et al. Vitamin D receptor rs2228570 polymorphism and invasive ovarian carcinoma risk: pooled analysis in five studies within the Ovarian Cancer Association Consortium. *Int J Cancer.* 2011; 128(4):936–943. [PubMed: 20473893]
19. Saunders DE, Christensen C, Wappler NL, Schultz JF, Lawrence WD, Malviya VK, et al. Inhibition of c-myc in breast and ovarian carcinoma cells by 1,25-dihydroxyvitamin D3, retinoic acid and dexamethasone. *Anticancer Drugs.* 1993; 4:201–208. [PubMed: 8490200]
20. Jiang F, Bao J, Li P, Nicosia SV, Bai W. Induction of ovarian cancer cell apoptosis by 1,25-dihydroxyvitamin D3 through the down-regulation of telomerase. *J Biol Chem.* 2004; 279:53213–53221. [PubMed: 15485861]
21. Saunders DE, Christensen C, Lawrence WD, Malviya VK, Malone JM, Williams JR, et al. Receptors for 1,25-dihydroxyvitamin D3 in gynecologic neoplasms. *Gynecol Oncol.* 1992; 44:131–136. [PubMed: 1312051]
22. [accessed August 30, 2011] Vision problems in the U.S. - prevalence of adult vision impairment and age-related eye disease in America. Report of the National Eye Institute, National Institutes of Health and Prevent Blindness America: 2008 update to the fourth edition. <http://www.preventblindness.org/sites/default/files/national/documents/cataract.pdf>
23. Wang JJ, Rochtchina E, Tan AG, Cumming RG, Leeder SR, Mitchell P. Use of inhaled and oral corticosteroids and the long-term risk of cataract. *Ophthalmology.* 2009; 116(4):652–657. [PubMed: 19243828]
24. Cumming RG, Mitchell P. Medications and cataract. The Blue Mountains Eye Study. *Ophthalmology.* 1998; 105(9):1751–1758. [PubMed: 9754187]
25. Chodick G, Heymann AD, Flash S, Kokia E, Shalev V. Persistence with statins and incident cataract: a population-based historical cohort study. *Ann Epidemiol.* 2010; 20(2):136–142. [PubMed: 20123164]

Table 1

Cataract association with selected participant characteristics among controls.

Characteristics	Cataract		OR (95% CI) ^a	<i>P</i> ^a
	yes	no		
No. participants (%)	182 (17)	919 (83)		
Age (years)				
< 65	47 (6)	751 (94)	1.0	
65–75	76 (38)	126 (62)	4.4 (2.7–7.2)	
> 75	59 (58)	42 (42)	8.6 (4.7–16.4)	<0.0001
Ethnicity				
Caucasian	72 (19)	311 (81)	1.0	
Asian	82 (17)	393 (83)	0.6 (0.4–1.1)	
Mixed/Other	28 (12)	215 (88)	0.8 (0.4–1.5)	0.22
Education (years)				
≤ 12	68 (21)	250 (79)	1.0	
> 12	114 (15)	669 (85)	1.1 (0.9–1.5)	0.34
BMI (kg/m²)				
< 25	114 (18)	537 (82)	1.0	
≥ 25	68 (15)	382 (85)	0.7 (0.5–1.1)	0.12
Parity				
nulliparous	23 (13)	158 (87)	1.0	
1–2	63 (14)	400 (86)	1.2 (0.6–2.2)	
≥ 3	96 (21)	361 (79)	1.1 (0.6–1.9)	0.88
Use of contraceptive steroids				
never	129 (30)	300 (70)	1.0	
< 1 year	17 (12)	130 (88)	1.4 (0.7–2.8)	0.36
1–4 years	16 (6)	239 (94)	0.5 (0.3–1.1)	0.06
5–9 years	13 (8)	142 (92)	0.9 (0.5–2.1)	0.91
10+ years	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	
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)	0.46
Smoking				
never	117 (18)	539 (82)	1.0	
past or current	65 (15)	380 (85)	1.1 (0.7–1.5)	0.99
Alcohol consumption				
no	120 (18)	544 (82)	1.0	
yes	62 (14)	375 (86)	1.1 (0.7–1.7)	0.78
Type 2 diabetes				
no	152 (15)	854 (85)	1.0	

Characteristics	Cataract		OR (95% CI) ^a	<i>P</i> ^a
	yes	no		
yes	30 (32)	65 (68)	1.9 (1.1–3.4)	0.04
Thyroid disease				
no	139 (15)	791 (85)	1.0	
yes	43 (25)	128 (75)	1.1 (0.7–1.8)	0.61
Skin carcinoma				
no	151 (15)	876 (85)	1.0	
yes	31 (42)	43 (58)	2.1 (1.1–4.0)	0.03

^aOdds ratios (OR), 95% confidence intervals (CI) 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.

Table 2

Association of reported history of cataract with invasive ovarian carcinoma

Cataract	Controls		All cases		Serous		Nonserous		Stages I-II		Stages III-IV		Grade 1-2 (low)		Grade 3-4 (high)	
	N (%)	N (%)	N (%)	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)
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)	
<i>P^a</i>			0.002		0.01	0.02	0.02	0.11	0.0009		0.01					
<i>P^b</i>						0.92			0.16							

^a Odds ratios (OR), 95% confidence intervals (CI), and P values from the logistic regression models including age (continuous), ethnicity, center, education, BMI, 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.