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Research Article

Cancer Prevention Research

Association between Ambient Ultraviolet Radiation and Risk of Epithelial Ovarian Cancer

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Abstract

Evidence is accumulating to suggest that higher exposure to solar ultraviolet radiation (UVR) is associated with decreased risk of internal cancers, but data for ovarian cancer are unclear. We aimed to examine the association between lifetime ambient UVR and ovarian cancer in a population-based-case–control study. The study included women aged 18 to 79 years with a new diagnosis of invasive (n = 1,215) or borderline (n = 285) epithelial ovarian cancer identified through a network of clinics and state cancer registries throughout Australia. Controls (n = 1,459), frequency matched to cases by age (5-year groups) and state of residence, were randomly selected from the National Electoral Roll. We asked participants to report where they had lived at different periods of their life and assigned an estimate of UVR using data from NASA's Total Ozone Mapping Spectrometer database (1997–2003). We estimated the association between ambient UVR and risk of ovarian cancer using conditional logistic regression adjusted for potential confounders. Women in the highest third of average daily ambient UVR over their lifetime were at significantly lower risk of all epithelial ovarian cancers than those in the lowest third [OR, 0.70; 95% confidence interval (CI), 0.56–0.88]. The inverse association was stronger for borderline tumors (0.47, 0.31–0.71) than invasive tumors (0.78, 0.61–1.00). The effect sizes for overall and borderline tumors were unchanged after adjusting for confounders, whereas the inverse association for invasive tumors was attenuated. These data suggest that exposure to ambient UVR may reduce the risk of ovarian cancer. *Cancer Prev Res; 5(11); 1330–6. ©2012 AACR.*

Introduction

Ovarian cancer is the sixth most common cause of cancer death in women and has a poor overall 5-year survival rate of 40% (1). A number of factors such as nulliparity (2) and family history of breast or ovarian cancer (3) have consistently been found to increase the risk of ovarian cancer, whereas factors such as use of hormonal contraceptives (4) and having had a tubal ligation (5) are known to decrease risk. However, these factors account for only a relatively small proportion of the disease and thus obtaining a better understanding of the etiology of this disease remains a priority.

There is mounting interest in the role of sun exposure in the development of internal cancers including ovarian cancer. Ecological studies have shown an inverse association between latitude [as a proxy of ambient ultraviolet radiation (UVR)] and both ovarian cancer incidence and mortality (6–8). However, ecological studies are limited because of the lack of individual-level information about exposure and confounders, and there are few observational reports in the literature. One case–control study from the United States found that the level of ambient UVR estimated from the state of residence recorded on the death certificate was inversely associated with mortality from ovarian cancer (9), but there was no association with sun exposure estimated from usual occupation. Recently, a longitudinal study also in the United States showed no association between residential ambient UVR and risk of ovarian cancer (10).

A better understanding of the link between UVR and ovarian cancer could provide opportunities for prevention of ovarian cancer. We thus used data from a population-based case–control study to examine the association between lifetime ambient UVR and ovarian cancer risk.

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Materials and Methods

Study participants

The Australian Ovarian Cancer Study was a nationwide population-based case–control study. Women aged 18 to 79 years with epithelial ovarian, fallopian tube, or primary

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peritoneal cancer diagnosed between January 2002 and June 2005 were recruited through treatment clinics and state cancer registries throughout Australia. The study was approved by the Human Research Ethics Committees at the Queensland Institute of Medical Research (Brisbane, QLD, Australia), Peter MacCallum Cancer Center, University of Melbourne (Melbourne, VIC, Australia), and all participating cancer registries and hospitals. All participants provided informed consent.

The study protocol and procedures have been fully described elsewhere (11). Briefly, of 3,553 women identified with suspected ovarian cancer (most women were identified before surgery and thus before histologic diagnosis), 304 women died before contact could be made, 194 women could not be contacted, and 133 cases were too ill or unable to give informed consent. A further 167 patients (5%) were excluded on the basis of language difficulties (70 women), mental incapacity (33 women), and illness (64 women). The remaining 2,755 women were invited and 2,319 of them (84%) agreed to participate. After surgery, 590 women were excluded because their final diagnosis was not confirmed as epithelial ovarian cancer, 19 because their cancer was first diagnosed before the start of the study period, and one because she was not an Australian resident at the time of diagnosis. Of the final 1,710 eligible cases, 1,500 (88%) returned a completed questionnaire. Cases were classified as invasive or borderline (low malignant potential) and as serous, mucinous, endometrioid, clear cell, or mixed and other histologic subtypes, by reviewing pathologic reports.

We randomly selected potential controls, frequency matched to the expected case series by age (in 5-year groups), and state of residence, from the Australian Commonwealth Electoral Roll between 2002 and 2005 (enrolment is compulsory in Australia). Of the 3,442 eligible women contacted, 1,615 (47%) agreed to participate and 1,459 of them (90%) provided a full residential history and were included in these analyses.

Data analysis

Participants completed a self-administered questionnaire, which included questions about demographics, medication use, reproductive status, family history of disease, and other potential risk factors. We used height and weight 1 year before diagnosis (for cases) or 1 year before interview (for controls) to calculate body mass index (BMI; kg/m^2) which was then classified into 4 groups according to the WHO categorization: "under-weight" <18.5 kg/m^2, "healthy weight" 18.5–25 kg/m^2, "overweight" 25–29.9 kg/m^2, and "obese" $\geq$30 kg/m^2.

To estimate residential ambient UVR, we asked participants to report where they were born and where they had mostly lived for the 5 age periods: 5–12, 13–19, 20–39, 40–59 years, and as they turned 60 (as applicable). Each location over their life was then mapped on a 1° latitude by 1.25° longitude grid to the NASA's Total Ozone Mapping Spectrometer database (TOMS; ref. 12). This database was used to assign the total erythemally weighted UVR dose (J/m^2) reaching the Earth at each location in one day, averaged between 1997 and 2003.

We estimated the cumulative ambient UVR for each age period by multiplying the number of days in the age period by the average daily UVR of the location where the participant had resided. For these calculations, we assumed that each participant resided continuously at the stated location during the entire interval for each age period (up to and including current age, as appropriate). Because changes of residence between birth and 5-year-olds were not recorded, we further assumed that all participants had resided at their place of birth for their first 5 years. Cumulative ambient UVR for different age periods was then summed to obtain the lifetime ambient UVR. Because this measure is strongly determined by current age, we estimated the average daily ambient UVR over the lifetime by dividing the lifetime ambient UVR by their age in days.

Differences in the distribution of demographic characteristics and potential risk factors between cases and controls were tested by the Student *t* test or the Pearson χ^2 statistics, as appropriate. We estimated the strength of associations between ambient UVR and ovarian cancer (overall, invasive, and borderline) by calculating crude and adjusted ORs and 95% confidence intervals (CI) using conditional logistic regression on age (5-year) and state of residence with adjustment for potential confounders. We included lifetime and average daily ambient UVR over the lifetime as both continuous and categorical measures.

For analyses of the continuous measure, we first estimated the effect size for an SD increase in lifetime and average daily ambient UVR over the lifetime and ovarian cancer risk. We also used generalized additive models adjusting for the potential confounders to identify possible nonlinear relationships between lifetime ambient UVR and ovarian cancer risk using restricted cubic splines. For categorical analyses, tertiles of the lifetime and average daily ambient UVR were used on the basis of the combined distribution of the cases and controls, and the lowest level was used as the reference category in a conditional logistic regression analyses with age and state as matching factors.

To adjust for potential confounding, we included in the models all variables that have been shown to be associated with ovarian cancer risk (parity, ever breastfed, use of hormonal contraceptives, BMI, and family history of ovarian or breast cancer), irrespective of their effect on the OR of interest. Other potentially confounding variables such as use of hormone replacement therapy, menopausal status, education, cumulative history of smoking in pack-years, and lifetime average alcohol consumption were also considered in a multivariable-adjusted model but they were not retained in the final models as they did not significantly alter the relevant ORs. Trend tests were based on the ordinal tertiles.

Statistical analyses were conducted in SAS version 9.2 (SAS Institute, Inc.). Generalized additive models were generated using R (version 2.10.1 with mgcv package).

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Results

This study included 1,459 controls and 1,500 cases—1,215 had invasive tumors and 285 had borderline tumors (Table 1). Ninety-five percent of participants were of Caucasian origin. Twenty-six percent of participants were born overseas, and the proportion of people born overseas was significantly higher in cases than in controls ($P < 0.0001$). Cases were slightly older than controls ($P = 0.002$), and they were less likely to have continued their education beyond high school ($P = 0.02$). Compared with controls, cases were more likely to be nulliparous ($P < 0.0001$) and to have a family history of breast or ovarian cancer ($P = 0.0002$). In addition, cases were less likely than controls to report the use of oral contraceptives ($P < 0.0001$) and to have ever breastfed ($P = 0.0001$).

Lifetime ambient UVR in this study population ranged from 1.3×10^7 to 14×10^7 J/m^2 with a mean of 6.9×10^7 J/m^2 (SD, 1.9×10^7 J/m^2). For an SD increase in lifetime ambient UVR, the risk of ovarian cancer was reduced by 18% (OR, 0.82; 95% CI, 0.72–0.94). The inverse association was observed for both invasive (OR, 0.85; 95% CI, 0.74–0.97) and borderline (OR, 0.73; 95% CI, 0.56–0.95) tumors. The associations remained significant after adjustment for multiple variables. Results from the generalized

Table 1. Characteristics of cases and controls

	Controls	All cases	Invasive	Borderline
N	1,459	1,500	1,215	285
Age, mean (SD), y	56.4 (12.4)	57.8 (12.0)[a]	59.6 (10.8)[b]	50.0 (13.7)[b]
Overseas-born	309 (21.2)	406 (30.7)[b]	378 (31.1)[b]	82 (28.8)[a]
State at recruitment				
Queensland	477 (32.7)	452 (30.1)	348 (28.6)	104 (36.5)
New South Wales	325 (22.3)	372 (24.8)	316 (26.0)	56 (19.7)
Western Australia	174 (11.9)	202 (13.5)	162 (13.3)	40 (14.0)
Victoria	285 (19.5)	288 (19.2)	246 (20.2)	42 (14.7)
South Australia	147 (10.1)	121 (8.1)	98 (8.1)	23 (8.1)
Tasmania	51 (3.5)	65 (4.3)	45 (3.7)[a]	20 (7.0)[a]
Ethnicity				
White	1,392 (95.4)	1,424 (94.9)	1,158 (95.3)	266 (93.3)
Others	67 (4.6)	76 (5.1)	57 (4.7)	19 (6.7)
Education				
High school	719 (49.3)	810 (54.0)	669 (55.1)	141 (49.5)
Certificate/diploma	531 (36.4)	480 (32.0)	379 (31.2)	101 (35.4)
University	209 (14.3)	210 (14.0)[a]	167 (13.7)[a]	43 (15.1)
BMI, kg/m^2				
<18.5	32 (2.2)	31 (2.2)	27 (2.3)	4 (1.5)
18.5–24.9	632 (43.9)	588 (40.9)	471 (40.5)	117 (42.7)
25–29.9	440 (30.6)	471 (32.7)	398 (34.2)	73 (26.6)
30+	336 (23.3)	348 (24.2)	268 (23.0)	80 (29.2)
History of breast/ovarian cancer in first-degree relative				
No	1,268 (86.9)	1,228 (81.9)	978 (80.5)	250 (87.7)
Yes	191 (13.1)	272 (18.1)[b]	237 (19.5)[b]	35 (12.3)
Hormonal contraceptive use				
Never	305 (20.9)	482 (32.5)	426 (35.3)	56 (20.1)
<60 mo	356 (24.5)	401 (27.0)	320 (26.6)	81 (29.0)
>60 mo	794 (54.6)	601 (40.5)[b]	459 (38.1)[b]	142 (50.9)
Parity				
0	172 (11.8)	291 (19.4)	215 (17.7)	76 (26.7)
1–2	629 (43.1)	611 (40.8)	489 (40.3)	122 (42.8)
3+	658 (45.1)	596 (39.8)[b]	509 (42.0)[b]	87 (30.5)[b]
Ever breastfed (parous women only)				
No	237 (17.9)	301 (24.1)	241 (23.5)	60 (27.0)
Yes	1,088 (82.1)	947 (75.9)[b]	785 (76.5)[b]	162 (73.0)[b]

NOTE: Values were *n* (%) or otherwise stated.

[a]$P < 0.05$.

[b]$P < 0.001$.

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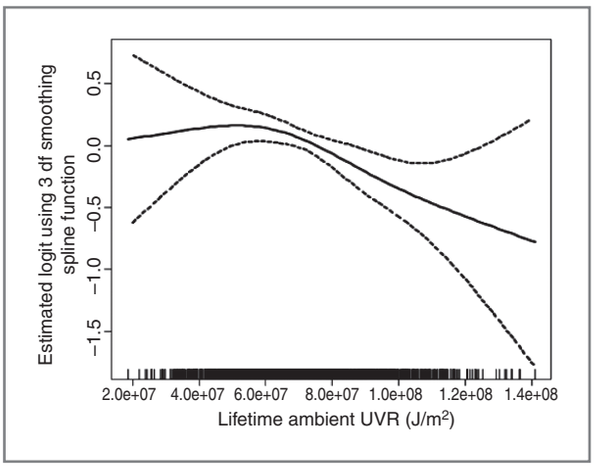

Figure 1. Dose–response effect of lifetime exposure to ambient UVR on risk of all ovarian cancers using a generalized additive model with 3 degrees of freedom (df) smoothing spline function adjusted for age, BMI, state of recruitment, full-term pregnancy, use of oral contraceptive, ever breastfed, and history family of ovarian/breast cancer.

additive regression analysis showed no evidence of a nonlinear association between lifetime ambient UVR and reduced risk of ovarian cancer ($P = 0.29$; Fig. 1).

In categorical analyses, women in the highest third of ambient lifetime UVR were at lower risk of ovarian cancer than those in the lowest third (OR, 0.78; 95% CI, 0.60–1.02; Table 2), with the magnitude of association being stronger for borderline than invasive tumors. Adjustment for further potential confounders slightly weakened the estimates of effect. These findings were supported by results of analyses in which average daily ambient UVR over the life course was used as the exposure measure. There was a significant inverse association overall (OR for highest third compared with lowest, 0.70; 95% CI, 0.56–0.88) which was more marked for borderline (OR, 0.47; 95% CI, 0.31–0.71) than for invasive tumors (OR, 0.78; 95% CI, 0.61–1.00; Table 2). The association between ambient UVR and ovarian cancer did not differ significantly by state of residence at recruitment (data not shown).

Analyses stratified by tumor type showed that a higher level of average daily ambient UVR over the lifetime was associated with reduced risk of invasive serous tumors (highest vs. lowest tertile adjusted OR, 0.75; 95% CI, 0.56–1.02), invasive mucinous tumors (OR, 0.71; 95% CI, 0.23–2.23) and endometrioid tumors (OR, 0.68; 95% CI, 0.37–1.27) but a suggestion of increased risk for clear cell tumors (OR, 2.37; 95% CI, 0.87–6.45). However, small numbers limit the power of these analyses, and the CIs are consistent with no association.

Discussion

In this Australian study, women who spent their lives in areas with higher levels of ambient UVR had a lower risk of developing epithelial ovarian cancer than those living in areas with lower levels of ambient UVR. The inverse association between high levels of ambient UVR and ovarian cancer risk was seen for all histologic subtypes (albeit nonsignificantly) of ovarian cancer except clear cell tumors. To the best of our knowledge, this study is the first to address the relationship between lifetime ambient UVR and ovarian cancer risk at the individual level.

These results are consistent with previous ecological studies showing that ovarian cancer incidence and mortality increase with decreasing ambient UVR or with markers of high UVR exposure such as non-melanoma skin cancer (6, 8, 13). Nevertheless, a recent cohort study that used the TOMS database to estimate ambient UVR found no association between ambient UVR and the risk of ovarian cancer (10). Notably, this study examined only the relationship with ambient UVR at the point of study entry, a maximum of 9 years before cancer diagnosis, unlike our study which considered the effect of total lifetime exposure.

The major strengths of this study include the population-based study design, with adequate sample size and high case response rate. Ambient UVR estimates for the entire life were obtained for almost 90% of all participants, as were data for known risk factors and potential confounders. It is possible that there are other unmeasured confounders, but any residual confounding would have to be of a large magnitude to explain the observed effects and we consider this to be unlikely. We have mapped ambient UVR using the satellite TOMS database to assign ambient UVR for each residential location. This was based on the recent time period (1997–2003) and thus may not be entirely indicative of the ambient UVR in earlier time periods. However, the correlation between ambient UVR estimated using the TOMS database and data obtained from Commonwealth Scientific and Industrial Research Organisation (CSIRO) in 1978 (14) was 0.98 indicating that use of the TOMS database is unlikely to have introduced an error.

Our study does have a number of potential limitations. First, the ambient UVR was assigned for broad age periods, obscuring any changes due to change of address during these periods. To explore the possibility of differential error between cases and controls, we generated the ratio of the highest ambient UVR to the lowest as a surrogate measure for mobility between ambient UVR zones for each participant. The mean ratio was 1.4 for both cases and controls, suggesting that the difference in ambient UVR across the life course in both groups was similar and that any misclassification was unlikely to be differential. Second, we did not have measures of sun exposure behavior, possibly resulting in the misclassification of actual levels of personal exposure to UVR. However, the relation between sun exposure behavior and ambient UVR is unlikely to differ between cases and controls so this should not explain the observed results.

There was a relatively low participation rate among controls (47%) in this study raising a concern about possible selection bias. We assessed this issue by comparing data from our control group with data from the 2004 Australian National Health Survey (NHS, a representative survey of the Australian adult population; ref. 15). The distributions of educational level, BMI, and parity among our control women were almost identical to those in the NHS, suggesting

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Table 2. Association between ambient UVR exposure and ovarian cancer

			Condition on age (5 y) and state	
Cancer subtype	**Controls, *n* (%)**	**Cases, *n* (%)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)[a]**
All cases				
Lifetime UVR[b]				
Low	501 (34.3)	485 (32.3)	1.00	1.00
Medium	464 (31.8)	523 (34.9)	0.92 (0.73–1.15)	0.92 (0.72–1.19)
High	494 (33.9)	492 (32.8)	0.78 (0.60–1.02)	0.81 (0.60–1.08)
P_{trend}			0.06	0.15
Average lifetime daily UVR[c]				
Low	449 (30.8)	537 (35.8)	1.00	1.00
Medium	497 (34.1)	490 (32.7)	**0.76 (0.62–0.94)**	0.86 (0.68–1.08)
High	513 (35.1)	473 (31.5)	**0.70 (0.56–0.88)**	**0.73 (0.57–0.95)**
P_{trend}			**0.003**	**0.02**
Invasive cases				
Lifetime UVR				
Low	501 (34.3)	333 (27.4)	1.00	1.00
Medium	464 (31.8)	444 (36.5)	0.97 (0.76–1.24)	1.03 (0.79–1.36)
High	494 (33.9)	438 (36.1)	0.84 (0.64–1.11)	0.91 (0.67–1.24)
P_{trend}			0.21	0.50
Average lifetime daily UVR				
Low	449 (30.8)	437 (36.0)	1.00	1.00
Medium	497 (34.1)	397 (32.7)	0.78 (0.62–0.97)	0.88 (0.69–1.13)
High	513 (35.1)	381 (31.1)	**0.78 (0.61–1.00)**	0.82 (0.63–1.08)
P_{trend}			**0.04**	0.15
Borderline cases				
Lifetime UVR				
Low	501 (34.3)	152 (53.3)	1.00	1.00
Medium	464 (31.8)	79 (27.7)	0.78 (0.52–1.15)	0.69 (0.45–1.06)
High	494 (33.9)	54 (20.0)	**0.57 (0.34–0.95)**	**0.57 (0.33–0.99)**
P_{trend}			**0.03**	**0.04**
Average lifetime daily UVR				
Low	449 (30.8)	100 (35.1)	1.00	1.00
Medium	497 (34.1)	93 (32.6)	**0.67 (0.46–0.99)**	0.76 (0.49–1.17)
High	513 (35.1)	92 (32.3)	**0.47 (0.31–0.71)**	**0.51 (0.32–0.81)**
P_{trend}			**0.0003**	**0.004**

[a]Adjusted for BMI last year (<25, 25–29.9, 30–34.9, 35+ kg/m^2), parity (0, 1–2, 3+), ever breastfeeding (yes/no), use of hormonal contraceptive pills (never,<60, >60 months), and family history of breast/ovarian cancer.

[b]Cumulative lifetime ambient UVR tertiles based on distribution of all cases and controls: lowest third, <60,338,462; middle third, 60,344,079–76,808,619; highest third, >76,813,788 J/m^2.

[c]Average lifetime daily ambient UVR tertiles: lowest, <3,059; middle, 3,059–3,583.96; highest, >3,583.97 J/m^2.

that bias among our controls is likely to be minimal; current smokers were slightly underrepresented in our controls. We also considered the possibility that the findings were due to differential responses between cases and controls in different regions. However, the response rate for cases was slightly higher in areas with higher ambient UVR than in those with lower ambient UVR, whereas the response rate for controls was not related to levels of ambient UVR.

If the observed association between ambient UVR and ovarian cancer is causal, one plausible mechanism is through UVR-induced cutaneous production of vitamin D. Exposure to UVR is the main source of vitamin D synthesis which is estimated by measuring the serum concentration of 25-hydroxyvitamin D [25(OH)D]. *In vitro* studies have shown that the active metabolite of vitamin D [i.e., 1,25(OH)D] has the potential to inhibit the proliferation of ovarian cancer cells (16) and induce apoptosis (17). There is some evidence to support an inverse association between serum 25(OH)D and ovarian cancer risk, but a meta-analysis of 10 cohort and nested cases–control studies found that each 20 ng/mL (or 50 nmol/L) increase in serum 25(OH)D was associated with a 17% reduced risk of ovarian cancer, although the association was nonsignificant (95% CI, 0.63–1.08; ref. 18). Importantly, serum 25

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(OH)D measured at the point of entry into a cohort may not reflect lifetime levels, particularly if ambient UVR has changed.

Studies of vitamin D intake (either through diet or supplements) and risk of ovarian cancer have generated inconsistent results. A Mexican study (19) showed an inverse association between high levels of dietary vitamin D intake and ovarian cancer risk, whereas a nested hospital-based case–control study in Italy (20) and some cohorts in the United States (21–23) generated null findings. In contrast, a pooled analysis of 12 cohorts from North America and Western Europe showed that higher levels of dietary vitamin D intake were associated with increased risk of ovarian cancer (24), but there was no association between total vitamin D intake (from diet and supplements) and ovarian cancer risk.

We did not measure levels of 25(OH)D in this study as this would be inappropriate within the context of a case–control study of a serious disease in which participants are recruited *after* their diagnosis of cancer (by definition). Any results obtained from such an analysis would be essentially uninterpretable due to the changes in diet, physical activity, occupation, body mass, and outdoor exposure that occur around the time of cancer diagnosis. As epithelial ovarian cancer is usually symptomatic in the interval leading up to diagnosis, it is probable that behavior will have changed before diagnosis. In addition, because serum 25(OH)D has such a short half-life, it will reflect sun exposure and dietary intake within the month before blood draw, when patients are likely to have been undergoing diagnostic testing and/or initial treatment. Any difference in 25(OH)D than controls would almost certainly be attributable (at least in part) to reverse causality.

It is possible that any effect of ambient UVR on risk of ovarian cancer is independent of its effect on vitamin D synthesis. It appears that UVR and vitamin D have independent effects on the immune system (25), although the significance of this for cancer development is unclear. For other diseases, such as demyelination of the central nervous system, evidence of independent effects is emerging (26), and this is clearly an area which needs further exploration.

In conclusion, findings from this study support an inverse association between ambient UVR and risk of ovarian cancer. While this is consistent with results from ecological studies, it is in contrast with a recent cohort study. Further studies are needed to help resolve this issue.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: B. Tran, R. Neale
Development of methodology: B. Tran
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R. Lucas, P.M. Webb
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): B. Tran, S.J. Jordan, R. Lucas, P.M. Webb, R. Neale
Writing, review, and/or revision of the manuscript: B. Tran, S.J. Jordan, R. Lucas, P.M. Webb, R. Neale
Study supervision: R. Neale
Coordinated the original study: P.M. Webb

All authors read and approved the final version of the manuscript.

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References

1. Australian Institute of Health and Welfare (AIHW), National Breast and Ovarian Cancer Centre (NBOCC). Ovarian cancer in Australia: an overview, 2010. Canberra, Australia: AIHW; 2010. Report No.: AIHW Cat. No. CAN 32.
2. Negri E, Franceschi S, Tzonou A, Booth M, La Vecchia C, Parazzini F, et al. Pooled analysis of 3 European case-control studies: I. Reproductive factors and risk of epithelial ovarian cancer. Int J Cancer 1991;49:50–6.
3. Stratton JF, Pharoah P, Smith SK, Easton D, Ponder BA. A systematic review and meta-analysis of family history and risk of ovarian cancer. Br J Obstet Gynaecol 1998;105:493–9.
4. Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet 2008;371:303–14.
5. Cibula D, Widschwendter M, Majek O, Dusek L. Tubal ligation and the risk of ovarian cancer: review and meta-analysis. Hum Reprod Update 2011;17:55–67.
6. 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;31:512–4.
7. Parkin DM. Cancers of the breast, endometrium and ovary: geographic correlations. Eur J Cancer Clin Oncol 1989;25:1917–25.
8. Boscoe FP, Schymura MJ. Solar ultraviolet-B exposure and cancer incidence and mortality in the United States, 1993–2002. BMC Cancer 2006;6:264.

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9. Freedman DM, Dosemeci M, McGlynn K. Sunlight and mortality from breast, ovarian, colon, prostate, and non-melanoma skin cancer: a composite death certificate based case-control study. Occup Environ Med 2002;59:257–62.
10. Lin SW, Wheeler DC, Park Y, Cahoon EK, Hollenbeck AR, Michal Freedman D, et al. Prospective study of ultraviolet radiation exposure and risk of cancer in the U.S. Int J Cancer 2012;131:E10105–23.
11. Olsen CM, Nagle CM, Whiteman DC, Purdie DM, Green AC, Webb PM. Body size and risk of epithelial ovarian and related cancers: a population-based case-control study. Int J Cancer 2008;123:450–6.
12. NASA GSFC Total Ozone Mapping Spectrometer. Available from: http://iridl.ldeo.columbia.edu/SOURCES/.NASA/.GSFC/.TOMS/. [Cited date: June 2012.]
13. Grant WB. An ecologic study of cancer mortality rates in Spain with respect to indices of solar UVB irradiance and smoking. Int J Cancer 2007;120:1123–8.
14. Paltridge GW, Barton IJ.Erythemal ultraviolet radiation distribution over Australia - the calculations, detailed results and input data. Commonwealth Scientific and Industrial Research Organisation; 1978. Printed by CSIRO, Melbourne.
15. Australian Bureau of Statistics (ABS).2004–05 National Health Survey: summary of results. Cat. No. 4364. Australia: Australian Bureau of Statistics, 2006. p. 92.
16. 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;4:201–8.
17. 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;279:53213–21.
18. Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis: circulating vitamin D and ovarian cancer risk. Gynecol Oncol 2011;121:369–75.
19. Salazar-Martinez E, Lazcano-Ponce EC, Gonzalez Lira-Lira G, Escudero-De los Rios P, Hernandez-Avila M. Nutritional determinants of epithelial ovarian cancer risk: a case-control study in Mexico. Oncology 2002;63:151–7.
20. Bidoli E, La Vecchia C, Talamini R, Negri E, Parpinel M, Conti E, et al. Micronutrients and ovarian cancer: a case-control study in Italy. Ann Oncol 2001;12:1589–93.
21. Kushi LH, Mink PJ, Folsom AR, Anderson KE, Zheng W, Lazovich D, et al. Prospective study of diet and ovarian cancer. Am J Epidemiol 1999;149:21–31.
22. 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;156:148–57.
23. Cramer DW, Kuper H, Harlow BL, Titus-Ernstoff L. Carotenoids, antioxidants and ovarian cancer risk in pre- and postmenopausal women. Int J Cancer 2001;94:128–34.
24. Genkinger JM, Hunter DJ, Spiegelman D, Anderson KE, Arslan A, Beeson WL, et al. Dairy products and ovarian cancer: a pooled analysis of 12 cohort studies. Cancer Epidemiol Biomarkers Prev 2006;15:364–72.
25. Hart PH, Gorman S, Finlay-Jones JJ. Modulation of the immune system by UV radiation: more than just the effects of vitamin D? Nat Rev Immunol 2011;11:584–96.
26. Lucas RM, Ponsonby AL, Dear K, Valery PC, Pender MP, Taylor BV, et al. Sun exposure and vitamin D are independent risk factors for CNS demyelination. Neurology 2011;76:540–8.

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