

Circulating 25-hydroxyvitamin D and survival in women with ovarian cancer^{1,2}

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ABSTRACT

Background: Vitamin D status might be associated with cancer survival. Survival after ovarian cancer is poor, but the association with vitamin D has rarely been examined.

Objective: We evaluated the association between serum 25-hydroxyvitamin D [25(OH)D], a marker of vitamin D status, and ovarian cancer survival.

Design: Participants were women with invasive ovarian cancer diagnosed between 2002 and 2005 who participated in the Australian Ovarian Cancer Study. Serum samples, collected at diagnosis ($n = 670$) or after completion of primary treatment and before recurrence ($n = 336$), were assayed for 25(OH)D. Sociodemographic, dietary, and lifestyle data came from questionnaires self-completed at recruitment, and clinical and survival data were from medical records, supplemented by linkage to the Australian National Death Index (October 2011). Cox proportional hazards regression was used to estimate HRs and 95% CIs for the association between circulating 25(OH)D and survival.

Results: Overall, 59% of the women died during follow-up, with 95% of deaths resulting from ovarian cancer. Circulating 25(OH)D concentrations (mean: 44 nmol/L) were significantly associated with age, state of residence, season of blood collection, and body mass index but not with tumor histology, stage or grade, or comorbidities. Higher 25(OH)D concentrations at diagnosis were significantly associated with longer survival (adjusted HR: 0.93; 95% CI: 0.88, 0.99 per 10 nmol/L), but there was no significant association with progression-free survival or for 25(OH)D measured after primary treatment.

Conclusions: In our cohort, higher serum 25(OH)D concentrations at diagnosis were associated with longer survival among women with ovarian cancer. If confirmed in other studies, this suggests that vitamin D status at diagnosis may be an independent predictor of prognosis. Furthermore, if the association is found to be causal, improving vitamin D status may improve ovarian cancer survival rates. *Am J Clin Nutr* 2015;102:109–14.

Keywords: ovarian cancer, overall survival, serum 25-hydroxyvitamin D, progression-free survival, vitamin D status

INTRODUCTION

Vitamin D plays an important role in bone health. It also affects neuromuscular function and inflammation and influences the action of many genes that regulate the proliferation, differentiation, and apoptosis of cells (1). A link with cancer etiology and/or survival is thus plausible. With respect to etiology, colorectal cancer is the only cancer for which there is consistent evidence for an association with circulating 25-hydroxyvitamin D [25(OH)D,¹⁰ used as a marker of vitamin D status] (2, 3). Although ovarian cancer cells express high concentrations of the vitamin D receptor (4), ovarian cancer rates are generally higher in countries at higher latitudes (5), and vitamin D has been shown to inhibit cell proliferation and induce apoptosis in ovarian cancer cell lines (4, 6), a pooled analysis of data from 7 cohort studies (7), as well as a subsequent meta-analysis that included these data and 3 additional studies (8), found little convincing evidence for

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² Supplemental Tables 1 and 2 are available from the “Supplemental data” link in the online posting of the article and from the same link in the online table of contents at <http://ajcn.nutrition.org>.

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¹⁰ Abbreviations used: FIGO, International Federation of Obstetricians and Gynecologists; OS, overall survival; PFS, progression-free survival; 25(OH)D, 25-hydroxyvitamin D.

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an association between 25(OH)D and the risk of developing ovarian cancer.

There are fewer data relating directly to cancer survival, but in 2 recent meta-analyses of data from 4 and 5 studies, respectively, vitamin D deficiency was significantly associated with a higher risk of recurrence (9) and shorter survival after a diagnosis of breast cancer (9, 10). Results from individual studies of other types of cancer have been mixed (3), but these studies have often included relatively small and heterogeneous groups of patients with serum 25(OH)D measured at differing time points relative to diagnosis and treatment and variable control for other potentially important confounders. A recent meta-analysis concluded that 25(OH)D may be associated with breast and colorectal cancer prognosis but that there is a paucity of data for other cancer sites, and further studies are required (11). Only one small study (72 cases) has evaluated ovarian cancer, suggesting that median survival was lower among women with low circulating 25(OH)D before surgery (12).

Ovarian cancer survival is poor. Five-year survival rates are <45%, and as a result, it is the fifth leading cause of cancer mortality among women in the United States, causing more than 14,000 deaths every year (13). A potential lifestyle intervention that could improve survival would thus be of great value. Our aim was to examine the association between circulating 25(OH)D and progression-free survival (PFS) and overall survival (OS) among a large population-based cohort of women with ovarian cancer.

METHODS

The Australian Ovarian Cancer Study is a population-based case-control study, and the methods have been described in detail elsewhere (14). Briefly, 1631 women aged 18–79 years newly diagnosed with invasive or borderline epithelial ovarian, fallopian tube, or primary peritoneal cancer between 2002 and June 2006 were recruited through the major treatment centers and state-based cancer registries across Australia. The study was approved by the human research ethics committees at the QIMR Berghofer Medical Research Institute, and all participating institutions and all participants provided informed consent.

Sociodemographic, medical, and lifestyle data were available from questionnaires completed by the women when they were recruited for the Australian Ovarian Cancer Study. Blood samples were collected at or as soon as possible after diagnosis and shipped overnight, at ambient temperature, to the processing laboratory, where they were separated, and serum samples were aliquoted and stored at -80°C . Clinical data, including histologic subtype, disease stage and grade at diagnosis, and amount of residual disease after surgery, were abstracted from women's medical and pathology records. Trained research nurses abstracted information about treatment, disease progression, and vital status from medical records at 6- to 12-mo intervals. To supplement these data, we linked the cohort to the Australian National Death Index by using probabilistic record linkage software to identify likely matches based on full name, date of birth, date of last contact, and, if applicable, date, cause, and state of residence at the time of death. We estimate mortality follow-up to be complete to 31 October 2011. For women with blood samples collected at diagnosis, survival time was calculated from the date of diagnosis to the date of death or 31 Oc-

tober 2011; for those with samples collected after completion of primary treatment, survival time was calculated from the end of treatment to death or 31 October 2011. PFS was calculated from the date of diagnosis/end of treatment to the date of first progression (or date of death for 12 women who died of ovarian cancer with no reported progression) or the date the woman was last known to be disease free.

Women were eligible for the current analyses if they were diagnosed with invasive ovarian cancer, had completed the baseline study questionnaire, and provided a blood sample either at the time of diagnosis or after completion of primary treatment and before recurrence ($n = 1006$). Ten women with cancers of unknown stage were excluded. Women with blood samples collected at diagnosis ($n = 670$) did not differ significantly from excluded participants with invasive cancer ($n = 625$) with respect to their mean age at diagnosis or other clinical prognostic factors [International Federation of Obstetricians and Gynecologists (FIGO) stage, histologic grade of disease, or residual disease after primary surgery, all $P > 0.1$]. In contrast, those with samples collected after treatment ($n = 336$) were significantly less likely to have high-grade, advanced disease or macroscopic residual disease after primary surgery (all $P \leq 0.01$).

Analysis for 25(OH)D was performed at the Queensland University of Technology (Brisbane, Australia) by using a commercial chemiluminescent immunoassay [LIAISON 25(OH)D Vitamin D TOTAL Assay; DiaSorin Inc.]. This assay measures both 25(OH)D₂ (ergocalciferol) and 25(OH)D₃ (cholecalciferol), and the laboratory that performed the testing is a participant in the Vitamin D External Quality Assessment Scheme. Intra- and interassay variability was 3% and 8%, respectively. There is no clear consensus about the optimum 25(OH)D concentration, with some recommending a minimum of 50 nmol/L (equivalent to 20 ng/mL) and others 75 nmol/L or even higher, but concentrations <25 nmol/L (10 ng/mL) are generally considered deficient. We therefore classified women into 4 groups for analysis: <25, 25–49.9, 50.0–74.9, and ≥ 75 nmol 25(OH)D/L.

We used generalized linear models and ANOVA to assess the relation between sociodemographic, clinical, and lifestyle variables and 25(OH)D concentrations and Cox proportional hazards models to evaluate the relation between serum 25(OH)D and OS, ovarian cancer-specific survival, and PFS. All models were adjusted for age at diagnosis. We also present HRs and 95% CIs adjusted for state of residence, BMI (in kg/m^2 ; <18.5, 18.5–24.9, 25–29.9, 30+, unknown), and smoking status at diagnosis (current smoker yes/no) because causal diagrams (directed acyclic graphs) constructed by using the DAGitty program v2.0 (www.dagitty.net) (15) suggested that inclusion of these variables was sufficient to control for potential confounding by other variables related to serum 25(OH)D (season of blood collection, time spent outside, physical activity, and diet) and/or survival (histology, grade of disease, and residual disease after surgery). Survival models were left-truncated at the date of blood collection because women had to survive to this point to be eligible for inclusion. Analyses were performed for the entire study group and also stratified by timing of blood collection (at diagnosis or after the end of treatment and before recurrence). Because the outcome for women with advanced disease at diagnosis and/or who do not respond to primary treatment is very poor and thus potentially less likely to be influenced by aspects



of lifestyle, we conducted additional analyses stratified by these variables.

Proportional hazards assumptions were tested by including interactions between each variable and log survival time. This suggested that the association between age and OS varied slightly over time ($P = 0.047$), but inclusion of an interaction term for age \times time did not alter the magnitude of the associations between vitamin D status and survival, and this was therefore omitted from final models. All analyses were performed by using SAS version 9.2 (SAS Institute).

RESULTS

Women had a mean age of 60 y at diagnosis, and most had serous (63%), high-grade (71%), and/or FIGO stage III or IV (71%) cancers (**Table 1**). Among those with data available, 46% had no residual disease after surgery, and 25% had one or more comorbidities. Overall, 90% were treated with chemother-

apy, with 80% commencing on carboplatin plus taxol, 9% on carboplatin alone, and <2% on other drug combinations. Approximately two-thirds of blood samples ($n = 670$) were collected at diagnosis, with the remaining 336 collected after completion of primary treatment and before recurrence (median 9 mo after diagnosis). Compared with women with samples collected at diagnosis, those with samples collected after treatment were significantly less likely to have serous, advanced-stage or high-grade cancers, or residual disease after surgery, and as a result, they were significantly less likely to be treated with chemotherapy or experience progression of their disease or death during follow-up (all $P < 0.05$). They also had significantly higher serum 25(OH)D concentrations (mean 48 vs. 42 nmol/L, $P < 0.0001$). Overall, 682 women experienced progression of their disease, and 595 died during follow-up (mean 59, maximum 118 mo), with 564 (95%) of the deaths resulting from ovarian cancer.

TABLE 1
Characteristics of the cohort, overall and by timing of blood collection¹

	Timing of blood collection		
	At diagnosis ($n = 670$)	Postdiagnosis ($n = 336$)	Total ($n = 1006$)
Age, y	60.0 \pm 10.2 ²	59.1 \pm 10.9	59.7 \pm 10.5
25(OH)D, nmol/L	41.9 \pm 18.7	47.8 \pm 18.8	43.9 \pm 19.0
Histology, n (%)			
Serous	449 (67.9)	186 (55.4) ³	635 (63.1)
Mucinous	12 (1.8)	26 (7.7)	38 (3.8)
Endometrioid	73 (10.9)	47 (14.0)	120 (11.9)
Clear cell	41 (6.1)	26 (7.7)	67 (6.7)
Mixed/other	95 (14.2)	51 (15.2)	146 (14.5)
FIGO stage at diagnosis, n (%)			
I	96 (14.3)	101 (30.1) ³	197 (19.6)
II	57 (8.5)	36 (10.7)	93 (9.2)
III	446 (66.6)	167 (49.7)	613 (60.9)
IV	71 (10.6)	32 (9.5)	103 (10.2)
Grade of disease at diagnosis, n (%)			
1	53 (8.3)	34 (11.2) ³	87 (9.2)
2	111 (17.4)	73 (24.0)	184 (19.6)
3	473 (74.3)	197 (64.8)	670 (71.2)
Unknown	33	32	65
Amount of residual disease after surgery, n (%)			
None	244 (38.4)	174 (62.1) ³	418 (45.7)
≤ 1 cm	181 (28.5)	61 (21.8)	242 (26.5)
> 1 cm	210 (33.1)	45 (16.1)	255 (27.9)
Unknown	35	56	91
Adjuvant treatment, ⁴ n (%)			
None	42 (6.3)	55 (16.4) ³	97 (9.6)
Carbo/taxol	553 (82.5)	247 (73.5)	800 (79.5)
Carboplatin	66 (9.9)	26 (7.7)	92 (9.1)
Other	9 (1.3)	8 (2.4)	17 (1.7)
Other comorbidities, n (%)			
0	408 (75.7)	245 (74.9)	653 (75.4)
1	112 (20.8)	78 (23.9)	190 (21.9)
≥ 2	19 (3.5)	4 (1.2)	23 (2.7)
Unknown	131	9	140
Progression during follow-up, n (%)	491 (73.3)	191 (56.9) ³	682 (67.8)
Died during follow-up, n (%)	435 (64.9)	160 (47.6) ³	595 (59.2)

¹FIGO, International Federation of Obstetricians and Gynecologists; 25(OH)D, 25-hydroxyvitamin D.

²Mean \pm SD (all such values).

³ $P < 0.05$ compared with women with samples collected at diagnosis.

⁴Carbo/taxol: women commenced on carboplatin and taxol. Carboplatin: women commenced on carboplatin alone.

Other: women commenced on another drug with or without carboplatin.



Associations between sociodemographic and lifestyle variables and serum 25(OH)D concentrations were as expected (**Supplemental Table 1**) and did not differ by timing of blood collection. Concentrations were significantly higher in samples collected in summer and autumn than those collected in winter and spring, and they were highest in the state of Queensland, where the population center is closest to the equator, and lowest in Tasmania, which is furthest from the equator. They were also significantly higher among those who spent more time outdoors, were more physically active, had greater dietary vitamin D intake, and used dietary supplements containing vitamin D and significantly lower among those with older age and BMI. These associations and the proportion of women with concentrations indicative of deficiency (<25 nmol/L: 20% at diagnosis; 9% posttreatment) were comparable with population data previously reported for Australia using the same assay (16). Aside from age and modest associations with state of residence and BMI, none of these factors was significantly associated with OS in this cohort (**Supplemental Table 1**).

There was little association between serum 25(OH)D and clinical predictors of survival, including histologic subtype, stage and grade of disease, amount of residual disease after surgery, or the presence of other comorbidities (**Supplemental Table 2**). Although women with FIGO stage IV disease at diagnosis or >1 cm residual disease had slightly lower serum 25(OH)D concentrations than those with less advanced or less residual disease, these associations were weakened and nonsignificant after adjusting for age, state of residence, BMI, and season and timing of blood collection.

Overall, 5-y survival in the cohort was 52%, but this varied significantly with serum 25(OH)D concentration, from 44% among those with serum 25(OH)D <25 nmol/L to 52%, 54%, and 67% among those with concentrations of 25–49.9, 50–74.9 and ≥ 75 nmol/L, respectively (log-rank $P = 0.005$). However, this association was seen only among women with samples collected at diagnosis ($P = 0.02$ vs. $P = 0.3$ for samples collected after diagnosis), so given the large differences in both mean serum 25(OH)D and survival by timing of sample collection (**Table 1**), all further analyses were conducted separately for the 2 groups.

Women with very low (<25 nmol/L) and intermediate (25–49.9 nmol/L) serum 25(OH)D concentrations were at significantly greater risk of dying of any cause during follow-up than those with concentrations of 50–74.9 nmol/L (**Table 2**). Overall, there was a 7% (95% CI: 1%, 12%) reduction in risk of dying per 10-nmol/L increment in serum 25(OH)D. Further adjustment for stage of disease at diagnosis or amount of residual disease after surgery, both strong predictors of survival, or exclusion of women with stage IV disease and/or >1 cm residual disease after surgery, who had somewhat lower serum 25(OH)D concentrations than those with less advanced disease, did not materially alter our results (data not shown). Given the high proportion of deaths from ovarian cancer, the results were also unchanged when we considered death from ovarian cancer as the outcome of interest (data not shown). Although statistically significant only for stage III, the magnitude of the association was somewhat greater for women with FIGO stage I disease at diagnosis and progressively weakened with increasing stage of disease, although the differences by stage were not statistically significant ($P = 0.1$) (**Table 3**). We considered whether low serum 25(OH)D concentrations at diagnosis might be a marker of poorer health status, independent of severity of disease, but there was no suggestion that women who reported more comorbidities or symptoms at diagnosis had lower serum 25(OH)D concentrations than did those with fewer comorbidities/symptoms (all $P > 0.7$).

There was no clear association between serum 25(OH)D measured after primary treatment and OS (**Table 2**), although the risk of dying among those with the highest serum 25(OH)D concentrations (only 7% of women) was approximately half that of women with lower concentrations. There was also a nonsignificant association with increasing serum 25(OH)D among women with stage I disease at diagnosis (**Table 3**). Because this was a heterogeneous group with samples collected up to 3 y after diagnosis, we repeated the analyses among women with samples collected within 1 y of diagnosis ($n = 243$). This again suggested that women with serum 25(OH)D concentrations of ≥ 75 nmol/L had significantly better survival than those with concentrations of 50–74.9 nmol/L (adjusted HR: 0.35; 95% CI: 0.14, 0.88), but we also saw improved survival for those with concentrations between

TABLE 2
HRs and 95% CIs for the association between circulating 25(OH)D and OS¹

25(OH)D	Deaths/total, <i>n</i>	5-y OS, %	Age-adjusted HR ² (95% CI)	Fully adjusted HR ^{2,3} (95% CI)
At diagnosis (<i>n</i> = 670)				
<25 nmol/L	95/136	39	1.53 (1.15, 2.04)	1.44 (1.07, 1.95)
25–49.9 nmol/L	223/327	45	1.30 (1.02, 1.65)	1.30 (1.01, 1.66)
50–74.9 nmol/L	96/170	51	(referent)	(referent)
≥ 75 nmol/L	21/37	54	1.00 (0.62, 1.60)	0.99 (0.61, 1.59)
Per 10 nmol/L			0.93 (0.88, 0.98)	0.93 (0.88, 0.99)
After treatment (<i>n</i> = 336)				
<25 nmol/L	14/31	68	0.80 (0.45, 1.44)	0.86 (0.47, 1.59)
25–49.9 nmol/L	77/157	65	0.88 (0.63, 1.23)	0.90 (0.64, 1.28)
50–74.9 nmol/L	62/125	59	(referent)	(referent)
≥ 75 nmol/L	7/23	87	0.52 (0.24, 1.13)	0.47 (0.21, 1.04)
Per 10 nmol/L			0.98 (0.91, 1.07)	0.97 (0.89, 1.06)

¹OS, overall survival; 25(OH)D, 25-hydroxyvitamin D.

²From Cox proportional hazards models.

³Adjusted for age (y), state of residence, smoking status at diagnosis (current smoker yes/no), and BMI (in kg/m²; <18.5, 18.5–24.9, 25–29.9, ≥ 30 , unknown).

TABLE 3

Association between circulating 25(OH)D concentrations and overall survival, by stage of disease at diagnosis¹

FIGO stage at diagnosis	Deaths/total, <i>n</i>	HR ² (95% CI) per 10 nmol/L
25(OH)D at diagnosis (<i>n</i> = 670)		
I	13/96	0.79 (0.56, 1.11)
II	24/57	0.87 (0.65, 1.16)
III	341/446	0.93 (0.88, 0.99)
IV	57/71	1.01 (0.83, 1.24)
25(OH)D after treatment (<i>n</i> = 336)		
I	14/101	0.70 (0.44, 1.10)
II	13/36	1.09 (0.81, 1.47)
III	107/167	1.01 (0.91, 1.12)
IV	26/32	1.04 (0.82, 1.32)

¹FIGO, International Federation of Obstetricians and Gynecologists; 25(OH)D, 25-hydroxyvitamin D.

²HRs and 95% CIs from Cox proportional hazards models adjusted for age (y) and state of residence (New South Wales, Queensland, Victoria/South Australia/Tasmania, Western Australia).

25 and 49.9 nmol/L (adjusted HR: 0.62; 95% CI: 0.41, 0.93) and there was no trend with increasing serum 25(OH)D (*P* = 0.7).

There was no significant association between serum 25(OH)D and PFS, although the estimates were in the same direction as those for OS (Table 4).

DISCUSSION

Our data suggest that circulating 25(OH)D at diagnosis is a predictor of survival among women with ovarian cancer, independent of known prognostic factors, including age, stage of disease, and residual disease after surgery. This association was somewhat stronger for women with earlier stage disease and thus an inherently better outcome than for those with more advanced disease. Further adjustment for other factors associated with 25(OH)D or survival did not appreciably alter our estimates, suggesting this association may be real, but we cannot completely exclude the possibility of residual confounding by another un-

measured factor that is associated with both 25(OH)D and survival.

The association is intriguing. Low vitamin D may simply be a marker of poor outcome, but the association remained strong after adjusting for other known prognostic factors, suggesting that serum 25(OH)D measurements could potentially provide additional prognostic information to that currently obtained from standard clinical parameters. It also raises the question of whether supplementing women with vitamin D before and during treatment might improve their outcome, although data from randomized trials are required to answer this question.

We found little evidence that 25(OH)D concentrations measured after completion of treatment were associated with survival. These samples were collected after completion of primary treatment and before recurrence of disease and were selected to represent "usual" postdiagnosis vitamin D status among these women. The lack of association among this group suggests that modification of vitamin D status after completion of treatment may not influence survival. However, this group was very heterogeneous, comprising women with very early stage disease who did not have adjuvant treatment and those with more advanced disease who had responded well to treatment and were in remission, and their samples were collected up to 3 y after diagnosis. When we restricted the analysis to women with samples collected within 1 y of diagnosis, we did see significantly better survival among women with the highest 25(OH)D concentrations, but there was no trend with increasing serum 25(OH)D.

Only one very small study has previously evaluated vitamin D status in relation to ovarian cancer survival, and this also reported a survival advantage for the 41 women with serum 25(OH)D concentrations >10 ng/mL (equivalent to 25 nmol/L) before surgery, compared with the 31 women with lower concentrations (*P* = 0.04) (12). There is, however, increasing evidence that vitamin D status, as measured by circulating 25(OH)D, is associated with outcome for cancers at a number of other sites, including the breast (9), bowel (17), pancreas (18), lung (19), and prostate (20). Some of these studies have included serum 25(OH)D measurements from samples collected up to several months after diagnosis. As in our analysis, those that used samples collected around diagnosis have generally reported the

TABLE 4

HRs and 95% CIs for the association between circulating 25(OH)D and PFS¹

25(OH)D	Progression/total, <i>n</i>	5-y PFS, %	Age-adjusted HR ² (95% CI)	Fully adjusted HR ^{2,3} (95% CI)
At diagnosis (<i>n</i> = 670)				
<25 nmol/L	99/136	25	1.15 (0.88, 1.50)	1.15 (0.87, 1.53)
25–49.9 nmol/L	242/327	26	1.06 (0.85, 1.31)	1.06 (0.85, 1.33)
50–74.9 nmol/L	124/170	27	(referent)	(referent)
≥75 nmol/L	26/37	37	0.95 (0.62, 1.45)	0.90 (0.59, 1.39)
Per 10 nmol/L			0.98 (0.94, 1.03)	0.98 (0.93, 1.03)
After treatment (<i>n</i> = 336)				
<25 nmol/L	14/31	57	0.72 (0.41, 1.27)	0.68 (0.38, 1.24)
25–49.9 nmol/L	90/157	43	0.84 (0.62, 1.14)	0.83 (0.60, 1.14)
50–74.9 nmol/L	76/125	42	(referent)	(referent)
≥75 nmol/L	11/23	54	0.60 (0.32, 1.13)	0.54 (0.28, 1.05)
Per 10 nmol/L			1.00 (0.93, 1.08)	1.00 (0.92, 1.09)

¹PFS, progression-free survival; 25(OH)D, 25-hydroxyvitamin D.

²From Cox proportional hazards models.

³Adjusted for age (y), state of residence, smoking status at diagnosis (current smoker yes/no), and BMI (in kg/m²; <18.5, 18.5–24.9, 25–29.9, ≥30, unknown).



strongest associations (17, 18, 20, 21) with weaker or sometimes no association seen when samples have been collected at varying times after diagnosis (22, 23). This suggests that future studies should pay greater attention to the timing of serum collection for 25(OH)D measurement because this may influence study results. Other strengths of our analysis include the large population-based cohort, the long and essentially complete follow-up, and the detailed clinical information available.

In conclusion, our data show that serum 25(OH)D concentrations at diagnosis were independently associated with survival after a diagnosis of ovarian cancer (adjusted HR: 0.93, 95% CI: 0.88, 0.99 per 10 nmol/L), suggesting that measurement of serum 25(OH)D at diagnosis may provide additional prognostic information for women newly diagnosed with invasive ovarian cancer. They also raise the possibility that vitamin D supplementation may improve outcomes, especially for women diagnosed with less advanced disease, but randomized trials are required to evaluate this.

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