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FAST TRACK

Cancer survival is dependent on season of diagnosis and sunlight exposure

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Sunlight is essential for the production of vitamin D in the body. Evidence exists to suggest that vitamin D metabolites may have a role in tumor growth suppression. In this large study, involving over a million cancer patients from the United Kingdom, we have analyzed the role of season of diagnosis and sunlight exposure in cancer survival for cancers of the breast, colorectum, lung, prostate and at all sites combined. We used population-based data from the Thames Cancer Registry to analyze cancer survival in periods 0–1 and 0–5 years after diagnosis. The analysis was performed using Cox proportional regression analysis adjusting for age and period at diagnosis and including season of diagnosis and sunlight exposure in the preceding months as factors in the analysis. We found evidence of substantial seasonality in cancer survival, with diagnosis in summer and autumn associated with improved survival compared with that in winter, especially in female breast cancer patients and both male and female lung cancer patients (hazard ratios 0.86 [95% CI 0.83–0.89], 0.95 [95% CI 0.92–0.97] and 0.95 [95% CI 0.93–0.98] respectively). Cumulative sunlight exposure in the months preceding diagnosis was also a predictor of subsequent survival, although season of diagnosis was a stronger predictor than cumulative sunlight exposure. We found seasonality in cancer survival to be stronger in women than in men. Our results add to a growing body of evidence that vitamin D metabolites play an important role in cancer survival.

Key words: season; sunlight; cancer; survival; vitamin D

Sunlight is essential for the cutaneous production of vitamin D in the body: ultraviolet B photons are absorbed by 7-dehydrocholesterol within the skin to form cholecalciferol (vitamin D_3). This then undergoes hydroxylation within the liver to form the prohormone, calcidiol (25-hydroxycholecalciferol; 25(OH)D). A second hydroxylation by 1α-hydroxylase occurs within renal tissues, forming the biologically active hormone calcitriol (1,25-dihydroxycholecalciferol; $1,25(OH)_2D$). There are further contributions from dietary intake of both cholecalciferol and ergocalciferol (vitamin D_2) synthesized by plants.

Sunlight is thought to contribute about 90% of serum vitamin D levels.[1,2] In northwestern Europe, including within the United Kingdom, levels of vitamin D are highly dependent on sunlight, compared with populations in the rest of Europe and the United States.[3–5] International comparison studies have shown that dietary vitamin D levels are low in Europe, especially in areas of high latitude (from 40°N to 64°N), including the United Kingdom.[6] Additionally, European populations are thought to be at risk of hypovitaminosis D due specifically to large seasonal variations in sunlight.[7,8]

A protective role of sunlight in cancer incidence was first suggested by observation of an inverse association between cancer incidence rates and sun exposure.[9] It was later proposed that this protective role might be attributed to a mechanism involving vitamin D metabolites in the risk of colon cancer.[10–12]

Most epidemiological studies investigating the relationship between sunlight and cancer have focused on latitudinal associations. For example, Hanchette and Schwartz reported an inverse correlation between the geographic distribution of solar UV radiation intensity and prostate cancer mortality in North America, with lower mortality in the South.[13]

Such correlational observations have been supported by numerous analytic epidemiological investigations: A cohort study conducted by John *et al*. reported substantial reductions in prostate cancer risk to be associated with residence in the south of the United States.[14] Freedman *et al*. found residential exposure to sunlight to be associated with reduced mortality from breast, ovarian, prostate and colon cancers.[15] Another innovative case–control study by John *et al*. reported that sun exposure, as measured by the difference between constitutive skin pigmentation in the axillary fossa and facultative pigmentation on the forehead, was associated with reduced risk of prostate cancer.[16]

In Norway, Robsahm *et al*. found that breast, colon and prostate cancer patients diagnosed in the summer and autumn months showed much better survival than those diagnosed in winter and spring.[17] Moan *et al*. also reported a strong seasonal variation in cancer survival, with better survival in colon cancer patients diagnosed in the summer and autumn.[18] Porojnicu *et al*. similarly demonstrated a seasonal variation in the prognosis of Hodgkin's lymphoma patients.[19]

These recent findings support the hypothesis that the season of diagnosis and treatment affects cancer survival, perhaps through variation in the cutaneous production of vitamin D_3.

Within the United Kingdom, there is large seasonal variation in sunlight, and vitamin D deficiency (hypovitaminosis D) is relatively common during the winter season.[20] In this study, we have investigated whether seasonal variation in cancer survival exists in the United Kingdom, and have attempted to associate this directly to sunlight exposure.

Material and methods

Cancer patients

The Thames Cancer Registry (TCR) is a population-based registry which collects data on cancer in residents of South East England, including London (currently a population of 14 million). The patients registered at the TCR represent a cohort of individuals followed up from diagnosis to death, and the database currently contains over 1.5 million incident cancers. All cases of primary malignant cancer diagnosed during the period from December 1, 1971 to November 30, 2002 were extracted. Cases with an unknown month of diagnosis were excluded from the analysis. In total 588,435 men and 606,127 women were included in the analysis. Of these, colorectal, lung, female breast and prostate cancer

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patients were analyzed separately. As a result, 71,723 men and 76,266 women with colorectal cancer, 131,770 men and 60,353 women with lung cancer, 182,895 women with breast cancer and 92,312 men with prostate cancer were analyzed. Cancer patients were followed up until June 2005 and all-cause mortality data were calculated for periods 0–1 and 0–5 years after diagnosis.

Using the date of diagnosis, the season of diagnosis was defined, as follows: Winter (December 1–February 28 or 29), Spring (March 1–May 31), Summer (June 1–August 31) and Autumn (September 30–November 30). To assess cancer survival, we defined 2 survival periods: 0–1 years and 0–5 years after diagnosis.

Exposure to sunlight

We obtained data on sunlight from the British Meteorological Office which has maintained monthly total sunlight hours data since 1959 at 26 meteorological stations located within the United Kingdom.[21] In this study, we used monthly data collected at Greenwich (located within the TCR catchment area) over the entire study period, 1971–2002. Sunlight data were merged by year and month with incident cancer data by using the date of diagnosis. Cumulative sunlight hours in periods 1, 3, 6 and 9 months before diagnosis were calculated for each month of diagnosis since 1971 and adjusted into a monthly mean figure over those periods which were then divided by 100. Thus, measures of mean cumulative sunlight exposure over periods of 1, 3, 6 and 9 months before diagnosis were established for each month of diagnosis such that 1 unit represents 100 mean sunlight hours per month.

Statistical analysis

A Cox proportional hazards regression model was used to assess the role of exposure to sunlight before diagnosis and season of diagnosis as factors affecting cancer survival. Age and period of diagnosis were grouped into 5 and 4 yearly intervals respectively.

All analyses were adjusted for age and period at diagnosis. Concerning the seasonal comparison, winter was the reference group. First, the season of diagnosis and the 4 monthly cumulative mean measures of sunlight before diagnosis were analyzed separately. Then, these separate analyses were extended to mutual adjustment, such that the analysis of seasonal variation in survival was adjusted for mean cumulative sunlight exposure and *vice versa*. Analysis was performed using SAS version 8.2 (SAS Institute, Cary, NC).

Results

From 1971 to 2002, mean monthly sunlight exposure was highest in the month of August (194.3 ± 31.9 hr [mean ± SD]) and lowest in December (35.8 ± 10.5 hr). Figure 1 shows the distribution of cumulative sunlight hours for each month of diagnosis averaged over 32 years, which was highest in the summer and autumn months. As the intervals over which cumulative sunlight exposure was calculated increased from 1 month to 9 months, the seasonal variation was reduced and the maximum moved from August to November.

Tables I–IV show mortality hazard ratios (HRs) within either 1 or 5 years of diagnosis by season of diagnosis for cancers of the breast, colorectum, lung and at all sites combined. Results are given without adjustment for sunlight hours, or adjusted for mean cumulative sunlight hours over 4 different time periods (1, 3, 6 and 9 months) before diagnosis.

The results for women are presented in Tables I and II. Significantly reduced mortality HRs were observed in the summer for cancers of the breast (0.86), colorectum (0.94), lung (0.95) and all sites combined (0.94) at 0–1 years after diagnosis and without adjustment for sunlight exposure. Adjusting for sunlight hours did not substantially change the observed reduction in mortality HRs in the summer.

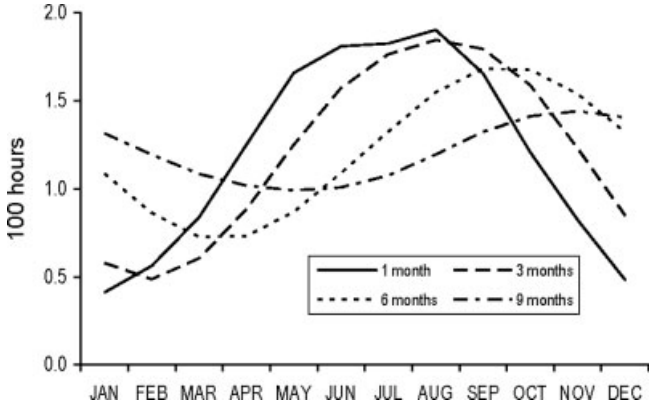

Figure 1 – The distribution of cumulative sunlight hours over the preceding 1, 3, 6 and 9 months for each month of diagnosis averaged over 32 years (1971–2002) recorded at Greenwich.

A reduction in the mortality HR similar to that seen in the summer was also observed in patients diagnosed in the autumn months, but the reduction was slightly lower and not statistically significant in colorectal cancer. As for the summer effect, the reduction in the HR in the autumn was not sensitive to adjustment for the actual sunlight hours (Table I).

Overall, the HRs for 0–5 year survival in women were slightly higher compared with the 0–1 year survival but the general pattern was the same. Regardless of adjustment for cumulative sunlight hours, consistently lower HRs in summer and autumn were observed for breast, colorectal and lung cancer, and at all sites combined (Table II).

Tables III and IV show the results in men. The mortality HRs 0–1 years after diagnosis in men showed little or no seasonal variation at most cancer sites apart from in the case of lung cancer which showed a significantly lower mortality HR (0.94) in the summer. Adjusting for sunlight exposure in the preceding 3 months yielded lower summer HRs: prostate (0.92), colorectum (0.93), lung (0.91), and all sites combined (0.95) (Table III).

In the 0–5 year interval, there was a lack of seasonal variation as in the 0–1 year interval in men except with lung cancer. When adjustment was made for sunlight hours, the seasonal effect was weaker than that at 0–1 years (Table IV).

Tables V and VI show mortality HRs in relation to mean cumulative sunlight exposure during periods 1, 3, 6 and 9 months before diagnosis for women and men respectively. Results are given both without and with adjustment for season of diagnosis.

When season of analysis was not considered, cumulative sunlight exposure was associated with reduced mortality HRs, with values down to 0.92 per 100 sunlight hours for breast cancer in the 0–1 year period of analysis when 3-month cumulative sunlight exposure was used. In women, all estimates derived from cumulative sunlight hours 1, 3 and 6 months before diagnosis were lower than 1.00 and the majority were statistically significant (Table V).

In men, the pattern was less clear but a reduction was evident for lung cancer (Table VI). For both men and women, the apparent association with sunlight disappeared completely when adjustment was made for season.

Figure 2 summarizes the seasonal variation in mortality HRs, adjusting only for age and period at diagnosis.

Discussion

In this study, we have examined the effect of season and sunlight on cancer survival. Our results can be summarized as follows: for breast cancer in females, as well as lung cancer and cancers at all sites combined in both sexes, patients diagnosed in

TABLE I – MORTALITY HAZARD RATIOS BY SEASON OF DIAGNOSIS IN THE PERIOD 0–1 YEARS AFTER DIAGNOSIS IN WOMEN[1]

Cancer site	Season of diagnosis	Unadjusted	Adjusted for sunlight hours			
		HR[2]	HR[3]	HR[4]	HR[5]	HR[6]
Breast	Winter	1.00	1.00	1.00	1.00	1.00
	Spring	0.95 (0.91–0.98)	0.95 (0.90–1.00)	0.94 (0.90–0.98)	0.97 (0.93–1.02)	0.97 (0.93–1.02)
	Summer	0.86 (0.83–0.89)	0.87 (0.81–0.93)	0.84 (0.78–0.90)	0.84 (0.81–0.88)	0.88 (0.84–0.92)
	Autumn	0.91 (0.88–0.95)	0.91 (0.87–0.96)	0.89 (0.84–0.95)	0.86 (0.82–0.91)	0.90 (0.87–0.94)
Colorectum	Winter	1.00	1.00	1.00	1.00	1.00
	Spring	0.99 (0.96–1.02)	0.98 (0.94–1.03)	0.99 (0.96–1.02)	0.99 (0.95–1.03)	1.00 (0.96–1.05)
	Summer	0.94 (0.91–0.97)	0.93 (0.88–0.98)	0.94 (0.89–1.00)	0.94 (0.91–0.97)	0.95 (0.91–0.99)
	Autumn	0.98 (0.95–1.01)	0.97 (0.93–1.01)	0.98 (0.93–1.03)	0.98 (0.93–1.02)	0.97 (0.94–1.00)
Lung	Winter	1.00	1.00	1.00	1.00	1.00
	Spring	0.97 (0.95–1.00)	0.96 (0.93–0.99)	0.96 (0.94–0.99)	0.98 (0.95–1.01)	0.98 (0.95–1.01)
	Summer	0.95 (0.92–0.97)	0.92 (0.88–0.97)	0.92 (0.87–0.96)	0.94 (0.91–0.97)	0.95 (0.92–0.98)
	Autumn	0.96 (0.93–0.98)	0.94 (0.91–0.98)	0.93 (0.89–0.97)	0.94 (0.90–0.97)	0.96 (0.93–0.98)
All sites	Winter	1.00	1.00	1.00	1.00	1.00
	Spring	0.98 (0.97–0.99)	0.97 (0.95–0.98)	0.97 (0.96–0.98)	0.99 (0.98–1.01)	0.98 (0.97–1.00)
	Summer	0.94 (0.93–0.95)	0.92 (0.90–0.93)	0.91 (0.89–0.93)	0.93 (0.92–0.94)	0.94 (0.93–0.95)
	Autumn	0.95 (0.94–0.96)	0.93 (0.92–0.95)	0.92 (0.90–0.94)	0.93 (0.91–0.94)	0.95 (0.94–0.96)

[1]Values in parentheses indicate 95% confidence intervals.–[2]Mortality hazard ratios adjusted for age and period of diagnosis.–[3]Mortality hazard ratios also adjusted for cumulative mean sunlight hours during 1 month before diagnosis.–[4]Mortality hazard ratios also adjusted for cumulative mean sunlight hours during 3 months before diagnosis.–[5]Mortality hazard ratios also adjusted for cumulative mean sunlight hours during 6 months before diagnosis.–[6]Mortality hazard ratios also adjusted for cumulative mean sunlight hours during 9 months before diagnosis.

TABLE II – MORTALITY HAZARD RATIOS BY SEASON OF DIAGNOSIS IN THE PERIOD 0–5 YEARS AFTER DIAGNOSIS IN WOMEN[1]

Cancer site	Season of diagnosis	Unadjusted	Adjusted for sunlight hours			
		HR[2]	HR[3]	HR[4]	HR[5]	HR[6]
Breast	Winter	1.00	1.00	1.00	1.00	1.00
	Spring	0.99 (0.97–1.01)	1.00 (0.97–1.03)	0.99 (0.97–1.01)	1.00 (0.97–1.02)	0.99 (0.97–1.02)
	Summer	0.93 (0.91–0.95)	0.94 (0.90–0.98)	0.93 (0.89–0.96)	0.93 (0.90–0.95)	0.93 (0.91–0.96)
	Autumn	0.94 (0.92–0.96)	0.95 (0.92–0.97)	0.94 (0.90–0.97)	0.93 (0.90–0.96)	0.94 (0.92–0.96)
Colorectum	Winter	1.00	1.00	1.00	1.00	1.00
	Spring	0.99 (0.97–1.02)	0.98 (0.95–1.01)	0.99 (0.96–1.01)	0.99 (0.96–1.02)	0.99 (0.96–1.03)
	Summer	0.96 (0.94–0.99)	0.94 (0.90–0.98)	0.95 (0.91–0.99)	0.96 (0.94–0.99)	0.96 (0.94–0.99)
	Autumn	0.98 (0.96–1.01)	0.97 (0.94–1.00)	0.97 (0.94–1.02)	0.98 (0.95–1.02)	0.98 (0.96–1.01)
Lung	Winter	1.00	1.00	1.00	1.00	1.00
	Spring	0.98 (0.95–1.00)	0.96 (0.93–0.99)	0.97 (0.95–1.00)	0.99 (0.96–1.01)	0.98 (0.95–1.01)
	Summer	0.95 (0.93–0.98)	0.93 (0.89–0.97)	0.93 (0.89–0.97)	0.95 (0.92–0.97)	0.96 (0.93–0.98)
	Autumn	0.97 (0.94–0.99)	0.95 (0.92–0.98)	0.95 (0.91–0.98)	0.95 (0.92–0.98)	0.96 (0.94–0.99)
All sites	Winter	1.00	1.00	1.00	1.00	1.00
	Spring	0.99 (0.98–1.00)	0.98 (0.96–0.99)	0.98 (0.97–0.99)	1.00 (0.98–1.01)	0.98 (0.97–1.00)
	Summer	0.96 (0.95–0.97)	0.93 (0.92–0.95)	0.93 (0.92–0.95)	0.95 (0.94–0.96)	0.95 (0.94–0.96)
	Autumn	0.95 (0.95–0.96)	0.94 (0.93–0.95)	0.93 (0.92–0.95)	0.94 (0.93–0.96)	0.96 (0.95–0.97)

[1]Values in parentheses indicate 95% confidence intervals.–[2]Mortality hazard ratios adjusted for age and period of diagnosis.–[3]Mortality hazard ratios also adjusted for cumulative mean sunlight hours during 1 month before diagnosis.–[4]Mortality hazard ratios also adjusted for cumulative mean sunlight hours during 3 months before diagnosis.–[5]Mortality hazard ratios also adjusted for cumulative mean sunlight hours during 6 months before diagnosis.–[6]Mortality hazard ratios also adjusted for cumulative mean sunlight hours during 9 months before diagnosis.

summer and autumn showed increased survival compared with those diagnosed in the winter. In addition, sunlight exposure in the months preceding diagnosis was found to be a predictor of survival, though it did not contribute to this increased survival as an independent factor when season of diagnosis was considered.

The main question then is why season of diagnosis is a better predictor of cancer survival than cumulative sunlight hours before diagnosis, which show not only seasonal but yearly variation.

We found that when adjusting only for age and period of diagnosis, both season of diagnosis and sunlight exposure showed an association with cancer survival. In contrast, when season of diagnosis and cumulative sunlight hours were mutually adjusted, the seasonal effect persisted without attenuation, but the sunlight effect was eliminated. Although seasonal variation in cancer survival has been demonstrated already in recent Norwegian studies for colon, breast and prostate cancer, and Hodgkin's lymphoma,[17–19] our result that sunlight was not an independent factor was unexpected and requires careful interpretation. Our *a priori* expectation would have been that sunlight hours would prevail as an independent predictor of survival, and that its inclusion in the model would eliminate the apparent effect of season. This result could have been interpreted as supporting the hypothesis that variation in vitamin D levels, through sunlight exposure, lies behind the observed seasonal variation in survival. In the light of the present results, it is important to consider the possibility that the seasonal effect might be due to other factors than sunlight and vitamin D, such as a relatively higher diagnosis rate in summer, modulation of behavior and the prevalence of infections in winter leading to early cancer death.

We investigated relative incidence by month of diagnosis and found little variation except 2 months with low incidence: August and December, which probably reflect the summer and Christmas vacations. Robsahm *et al.* made the same analysis and also found that the seasonal variation in survival did not coincide with seasonal variation in incidence.[17]

It is recognized that the winter season is associated with an increased mortality rate due to influenza and other infections. We have calculated mortality HRs for both the first year and the first 5 years after diagnosis. Especially in the first year, survival tended to be higher in patients diagnosed in summer and autumn. Since the excess mortality in cancer patients is highest in the first months after diagnosis, it is unlikely that the higher cancer mortality in the

TABLE III – MORTALITY HAZARD RATIOS BY SEASON OF DIAGNOSIS IN THE PERIOD 0–1 YEARS AFTER DIAGNOSIS IN MEN[1]

Cancer site	Season of diagnosis	Unadjusted	Adjusted for sunlight hours			
		HR[2]	HR[3]	HR[4]	HR[5]	HR[6]
Prostate	Winter	1.00	1.00	1.00	1.00	1.00
	Spring	1.01 (0.97–1.05)	0.99 (0.94–1.04)	1.00 (0.96–1.04)	1.03 (0.99–1.08)	1.05 (0.99–1.10)
	Summer	0.96 (0.92–1.00)	0.92 (0.86–0.99)	0.92 (0.85–0.98)	0.95 (0.91–0.99)	0.98 (0.94–1.03)
	Autumn	0.97 (0.94–1.01)	0.95 (0.90–1.00)	0.94 (0.88–1.00)	0.94 (0.89–1.00)	0.96 (0.92–1.00)
Colorectum	Winter	1.00	1.00	1.00	1.00	1.00
	Spring	1.03 (0.99–1.06)	1.00 (0.96–1.05)	1.01 (0.98–1.05)	1.07 (1.03–1.11)	1.06 (1.02–1.11)
	Summer	0.99 (0.95–1.02)	0.94 (0.89–1.00)	0.93 (0.87–0.98)	0.96 (0.93–1.00)	1.01 (0.97–1.05)
	Autumn	1.02 (0.98–1.05)	0.99 (0.95–1.04)	0.97 (0.92–1.02)	0.95 (0.91–1.00)	1.01 (0.97–1.04)
Lung	Winter	1.00	1.00	1.00	1.00	1.00
	Spring	0.98 (0.96–1.00)	0.97 (0.95–0.99)	0.97 (0.95–0.99)	0.99 (0.97–1.01)	0.99 (0.97–1.02)
	Summer	0.94 (0.92–0.95)	0.92 (0.89–0.95)	0.91 (0.88–0.94)	0.93 (0.91–0.94)	0.95 (0.93–0.97)
	Autumn	0.98 (0.96–0.99)	0.97 (0.95–0.99)	0.96 (0.93–0.98)	0.95 (0.93–0.98)	0.97 (0.95–0.99)
All sites	Winter	1.00	1.00	1.00	1.00	1.00
	Spring	1.01 (1.00–1.02)	0.99 (0.98–1.01)	1.00 (0.99–1.01)	1.02 (1.01–1.04)	1.02 (1.01–1.03)
	Summer	0.99 (0.98–1.00)	0.95 (0.93–0.97)	0.95 (0.93–0.97)	0.98 (0.97–0.99)	0.99 (0.98–1.00)
	Autumn	0.98 (0.97–0.99)	0.96 (0.95–0.97)	0.95 (0.93–0.97)	0.96 (0.94–0.97)	0.98 (0.97–0.99)

[1]Values in parentheses indicate 95% confidence intervals.–[2]Mortality hazard ratios adjusted for age and period of diagnosis.–[3]Mortality hazard ratios also adjusted for cumulative mean sunlight hours during 1 month before diagnosis.–[4]Mortality hazard ratios also adjusted for cumulative mean sunlight hours during 3 months before diagnosis.–[5]Mortality hazard ratios also adjusted for cumulative mean sunlight hours during 6 months before diagnosis.–[6]Mortality hazard ratios also adjusted for cumulative mean sunlight hours during 9 months before diagnosis.

TABLE IV – MORTALITY HAZARD RATIOS BY SEASON OF DIAGNOSIS IN THE PERIOD 0–5 YEARS AFTER DIAGNOSIS IN MEN[1]

Cancer site	Season of diagnosis	Unadjusted	Adjusted for sunlight hours			
		HR[2]	HR[3]	HR[4]	HR[5]	HR[6]
Prostate	Winter	1.00	1.00	1.00	1.00	1.00
	Spring	1.01 (0.99–1.04)	0.99 (0.95–1.02)	1.00 (0.98–1.03)	1.02 (0.99–1.06)	1.02 (0.99–1.06)
	Summer	0.98 (0.96–1.01)	0.94 (0.89–0.98)	0.95 (0.91–1.00)	0.98 (0.95–1.00)	0.99 (0.96–1.02)
	Autumn	1.00 (0.97–1.02)	0.97 (0.94–1.00)	0.97 (0.93–1.01)	0.98 (0.94–1.01)	0.99 (0.97–1.02)
Colorectum	Winter	1.00	1.00	1.00	1.00	1.00
	Spring	1.02 (1.00–1.05)	1.00 (0.97–1.04)	1.01 (0.99–1.04)	1.04 (1.01–1.07)	1.04 (1.01–1.08)
	Summer	1.00 (0.97–1.02)	0.96 (0.92–1.01)	0.96 (0.92–1.01)	0.98 (0.96–1.01)	1.01 (0.98–1.04)
	Autumn	1.01 (0.98–1.04)	0.99 (0.96–1.03)	0.98 (0.94–1.02)	0.98 (0.94–1.01)	1.00 (0.97–1.03)
Lung	Winter	1.00	1.00	1.00	1.00	1.00
	Spring	0.98 (0.97–1.00)	0.98 (0.96–1.00)	0.99 (0.98–1.01)	0.99 (0.98–1.01)	0.99 (0.97–1.01)
	Summer	0.94 (0.92–0.95)	0.92 (0.89–0.95)	0.93 (0.92–0.95)	0.93 (0.92–0.95)	0.94 (0.93–0.96)
	Autumn	0.97 (0.96–0.99)	0.96 (0.93–0.98)	0.96 (0.93–0.98)	0.96 (0.93–0.98)	0.97 (0.96–0.99)
All sites	Winter	1.00	1.00	1.00	1.00	1.00
	Spring	1.01 (1.00–1.02)	0.99 (0.98–1.01)	1.00 (0.99–1.01)	1.02 (1.01–1.03)	1.02 (1.00–1.03)
	Summer	0.99 (0.98–1.00)	0.96 (0.95–0.98)	0.96 (0.95–0.98)	0.99 (0.98–1.00)	1.00 (0.99–1.01)
	Autumn	0.98 (0.97–0.99)	0.96 (0.95–0.97)	0.95 (0.94–0.97)	0.96 (0.95–0.98)	0.98 (0.97–0.99)

[1]Values in parentheses indicate 95% confidence intervals.–[2]Mortality hazard ratios adjusted for age and period of diagnosis.–[3]Mortality hazard ratios also adjusted for cumulative mean sunlight hours during 1 month before diagnosis.–[4]Mortality hazard ratios also adjusted for cumulative mean sunlight hours during 3 months before diagnosis.–[5]Mortality hazard ratios also adjusted for cumulative mean sunlight hours during 6 months before diagnosis.–[6]Mortality hazard ratios also adjusted for cumulative mean sunlight hours during 9 months before diagnosis.

winter months would lead to an apparent better survival in patients diagnosed in summer and autumn. If anything, the effect would be in the opposite direction.

One possible explanation lies in that we used meteorological sunlight hours data as a surrogate for true patient exposure. However, our assumption that sunlight hours data provide a good measure of true sunlight exposure is simplistic for a variety of reasons: sunlight hours only represent the cumulative time over which the sun has shone in a given month, but give no measure of the intensity of that incident light. Adjustment for this factor would serve to increase the difference between exposures in the winter and summer months. In addition, behavioral changes associated with warmer outdoor temperatures and psychosocial associations of the summer months might result in patients spending more time outdoors undergoing exposure to sunlight. Considering these 2 factors alone, it is very probable that our sunlight hours data provide us with a substantially underestimated measure of the true difference in the exposure of patients to sunlight between winter and summer. If this is the case, then sunlight hours provide a dampened and potentially noisier measure of sunlight exposure than season, which could in reality be the better measure of sunlight exposure and vitamin D production. Indeed, the use of more representative measures of sunlight, or more specifically, UVB exposure in large epidemiological studies remains areas for future work.

Laboratory studies support the hypothesis that $1,25(OH)_2D$ exerts antiproliferative effects[22–25] and it is plausible that these underlie the observed seasonality in cancer survival. However, it is well established that while the serum concentration of biologically inert 25(OH)D shows variation with ultraviolet light exposure, active $1,25(OH)_2D$ does not, since its production and thus systemic release requires hydroxylation of 25(OH)D in the kidneys, a conversion that is tightly regulated and not correlated with systemic levels of the 25(OH)D.[26] However, evidence of extrarenal synthesis of $1,25(OH)_2D$ might offer a plausible explanation for the seasonal variation in survival. Recent studies have reported 1α-hydroxylase expression in the prostate, breast and colon and thus the ability of these cells to locally synthesize $1,25(OH)_2D$ which can then exert its antiproliferative and antimetastatic effects in an autocrine or paracrine fashion.[27–31] There is evidence that this extrarenal production is not subject to the tight regulation present in the kidneys.[32]

TABLE V – MORTALITY HAZARD RATIOS IN RELATION TO CUMULATIVE SUNLIGHT EXPOSURE PRECEDING DIAGNOSIS IN THE 0–1 AND 0–5 YEAR PERIODS AFTER DIAGNOSIS IN WOMEN[1]

Cancer Site	Exposure to sunlight (months)	0–1 Years		0–5 Years	
		Unadjusted[2]	Adjusted[3]	Unadjusted[2]	Adjusted[3]
Breast	1	0.93 (0.90–0.95)	1.00 (0.96–1.04)	0.96 (0.95–0.98)	0.99 (0.97–1.02)
	3	0.92 (0.90–0.95)	1.03 (0.97–1.08)	0.95 (0.94–0.97)	1.01 (0.97–1.04)
	6	0.96 (0.93–1.00)	1.11 (1.03–1.19)	0.95 (0.93–0.97)	1.02 (0.98–1.07)
	9	1.11 (1.04–1.19)	1.11 (0.99–1.23)	0.99 (0.95–1.04)	1.01 (0.95–1.08)
Colorectum	1	0.97 (0.95–0.99)	1.01 (0.97–1.04)	0.99 (0.97–1.00)	1.02 (0.99–1.05)
	3	0.96 (0.94–0.99)	1.00 (0.96–1.04)	0.98 (0.96–1.00)	1.01 (0.98–1.05)
	6	0.98 (0.95–1.01)	1.00 (0.94–1.06)	0.99 (0.96–1.01)	1.00 (0.99–1.05)
	9	1.05 (0.99–1.12)	1.05 (0.96–1.16)	1.03 (0.98–1.08)	1.01 (0.94–1.09)
Lung	1	0.98 (0.96–0.99)	1.02 (0.99–1.05)	0.98 (0.97–1.00)	1.02 (0.99–1.05)
	3	0.98 (0.96–0.99)	1.03 (1.00–1.07)	0.98 (0.96–0.99)	1.02 (0.99–1.06)
	6	0.99 (0.96–1.01)	1.04 (0.99–1.09)	0.99 (0.96–1.01)	1.03 (0.98–1.08)
	9	1.03 (0.98–1.08)	1.02 (0.94–1.10)	1.02 (0.98–1.07)	1.01 (0.95–1.09)
All sites	1	0.97 (0.97–0.98)	1.02 (1.01–1.03)	0.98 (0.98–0.99)	1.02 (1.01–1.03)
	3	0.97 (0.96–0.97)	1.03 (1.02–1.05)	0.97 (0.97–0.98)	1.02 (1.00–1.04)
	6	0.97 (0.96–0.98)	1.04 (1.02–1.06)	0.97 (0.96–0.98)	1.02 (1.00–1.04)
	9	1.00 (0.98–1.02)	1.01 (0.97–1.04)	0.98 (0.96–0.99)	0.98 (0.95–1.01)

[1]Values in parentheses indicate 95% confidence intervals.–[2]Mortality hazard ratios adjusted for age and period of diagnosis.–[3]Mortality hazard ratios also adjusted for season of diagnosis.

TABLE VI – MORTALITY HAZARD RATIOS IN RELATION TO CUMULATIVE SUNLIGHT EXPOSURE PRECEDING DIAGNOSIS IN THE 0–1 AND 0–5 YEAR PERIODS AFTER DIAGNOSIS IN MEN[1]

Cancer Site	Exposure to sunlight (months)	0–1 Years		0–5 Years	
		Unadjusted[2]	Adjusted[3]	Unadjusted[2]	Adjusted[3]
Prostate	1	0.99 (0.97–1.01)	1.03 (0.99–1.08)	1.00 (0.99–1.02)	1.04 (1.01–1.07)
	3	0.98 (0.95–1.01)	1.05 (0.99–1.10)	0.99 (0.98–1.01)	1.03 (0.99–1.07)
	6	0.97 (0.94–1.01)	1.06 (0.98–1.15)	0.99 (0.97–1.02)	1.04 (1.00–1.09)
	9	1.03 (0.96–1.11)	1.13 (1.01–1.27)	1.01 (0.96–1.06)	1.04 (0.96–1.12)
Colorectum	1	1.00 (0.98–1.03)	1.04 (1.00–1.07)	1.01 (0.99–1.02)	1.02 (1.00–1.05)
	3	1.00 (0.98–1.03)	1.06 (1.01–1.11)	1.00 (0.98–1.02)	1.03 (0.99–1.07)
	6	1.02 (0.99–1.05)	1.13 (1.06–1.21)	1.00 (0.98–1.03)	1.06 (1.01–1.12)
	9	1.06 (0.99–1.12)	1.14 (1.03–1.26)	1.02 (0.97–1.07)	1.07 (1.00–1.16)
Lung	1	0.97 (0.96–0.98)	1.01 (0.99–1.03)	0.97 (0.96–0.98)	1.02 (1.00–1.04)
	3	0.97 (0.96–0.98)	1.03 (1.00–1.05)	0.97 (0.96–0.98)	1.03 (1.00–1.08)
	6	1.00 (0.98–1.01)	1.05 (1.01–1.08)	0.99 (0.97–1.00)	1.03 (1.00–1.07)
	9	1.07 (1.04–1.10)	1.05 (1.00–1.11)	1.05 (1.02–1.08)	1.03 (0.99–1.08)
All sites	1	1.00 (0.99–1.01)	1.03 (1.01–1.04)	1.00 (1.00–1.01)	1.02 (1.01–1.03)
	3	0.99 (0.98–1.00)	1.04 (1.02–1.05)	0.99 (0.99–1.00)	1.03 (1.02–1.04)
	6	0.98 (0.97–0.99)	1.04 (1.02–1.06)	0.98 (0.97–0.99)	1.03 (1.01–1.04)
	9	0.98 (0.96–1.00)	1.03 (1.00–1.06)	0.97 (0.95–0.98)	1.01 (0.99–1.04)

[1]Values in parentheses indicate 95% confidence intervals.–[2]Mortality hazard ratios adjusted for age and period of diagnosis.–[3]Mortality hazard ratios also adjusted for season of diagnosis.

While the vitamin D hypothesis might apply to multiple cancer sites, breast, prostate and colorectal cancers have been the focus of past research.[33] We have extended the analysis to lung cancer and cancers at all sites combined, finding breast, lung and colorectal cancer survival to be associated with season of diagnosis in women. Men showed less seasonal variation in survival, and only in lung cancer did patients have increased survival when diagnosed in the summer and autumn months. That this variation was much stronger in women than in men is noteworthy: it is well established that hypovitaminosis D is more common in women than in men in the winter season.[34–36] Data from previous studies show a similar increased seasonality in women compared with men, although such differences are not commented upon.[15,17,18] These differences merit further investigation.

In the case of colorectal cancer, we found survival to be slightly increased in patients who were diagnosed in the summer months, a result that is consistent with other studies.[18] However, we found the seasonal association to be refractory to adjustment for sunlight exposure.

We found a substantial seasonal variation in lung cancer mortality that was present in both sexes. Little attention has been given to the effect of season and sunlight on lung cancer survival in the past. However, recently Zhou *et al.* have found both surgery season and dietary vitamin D intake to be predictors of early-stage non-small cell lung cancer mortality in surgical patients, with those treated in the summer experiencing improved survival.[37] That vitamin D metabolites exert an effect on tumor growth is plausible. Indeed, through the identification of vitamin D receptor expression in certain lung cancer cell lines, it has been proposed that a subset of lung cancers may be susceptible to the differentiating effects of vitamin D metabolites.[38] However, little evidence of 1α-hydroxylase activity in lung cells has been found. Recently however, Yokomura *et al.* reported an elevation in 1α-hydroxylase activity in the alveolar macrophages of patients with lung cancer, with expression of this enzyme correlated with levels of $1,25(OH)_2D$ in the serum.[29] This significant source of the active hormone may account for the consistent seasonal variation observed among both men and women.

Breast cancer showed the largest seasonal variation in survival. Both human and animal studies support this finding[39] which confirms and extends previous work by Robsahm *et al.*[17]

In our study, we have not examined the effect of ethnicity on seasonality in cancer survival despite the important effect of skin pigmentation in modulating ultraviolet absorption. Clemens *et al.* have shown that dark-skinned populations may require 10–50 times the

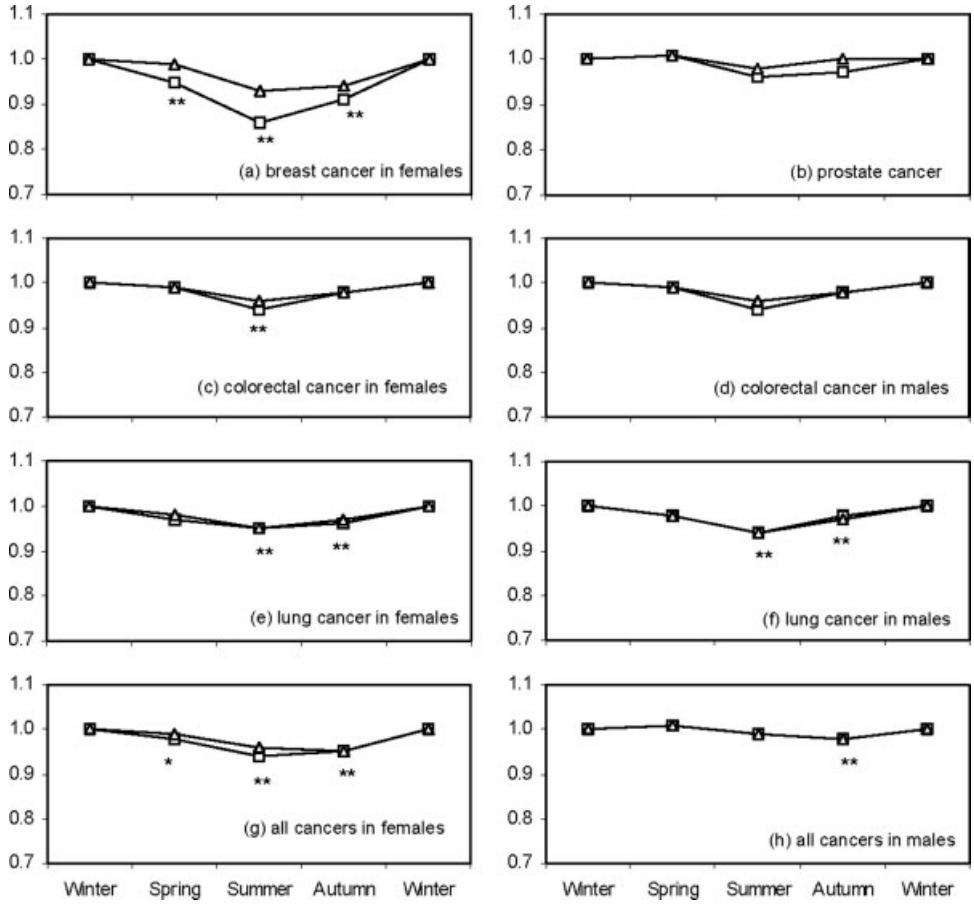

FIGURE 2 – Seasonal variation in mortality both in the 0–1 and 0–5 year periods after diagnosis given by sex and site. (□) Hazard ratio for 0–1 years after diagnosis. (△) Hazard ratio for 0–5 years after diagnosis. All HRs are adjusted for age and period of diagnosis. $p < 0.05$. Winter is the reference category (HR = 1.00).

exposure to ultraviolet B radiation to produce an equivalent amount of vitamin D as do those with lighter skin.[40] Ethnicity also affects diet. Some authors have speculated that the low incidence of breast and prostate cancer in some Asian countries might be due to the increased consumption of phytoestrogens present in soy, which through down regulating expression of CYP enzymes, might lead to an enhancement of local $1,25(OH)_2D$ levels and an increase in its differentiating effects.[27] We have not examined the role of dietary vitamin D intake in attenuating cancer survival and mortality, although other studies have identified such associations.[11,37]

The present study has methodological strengths. We have directly examined the effect of season of diagnosis and sunlight exposure on cancer survival in a cohort of over 1 million cancer patients and yielded results consistent with existing literature. In conclusion, we found substantial seasonality in cancer survival, with diagnosis in the summer and autumn months being associated with improved survival, especially in lung and breast cancer patients. The magnitude of the observed seasonality was smaller than that reported in Norway by Moan *et al.*[18] and dependent on sex and cancer site. We also found sunlight exposure to be a predictor of cancer survival, although season of diagnosis was a stronger predictor than sunlight. Our results add to a growing body of evidence that vitamin D may play an important role in cancer survival.

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