Seasonality pattern of breast, colorectal, and prostate cancer is dependent on latitude

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Background: The season of diagnosis of several forms of cancer has been observed to impact survival, supporting the hypothesis that vitamin D_3 has a protective role in cancer survival. All previous studies demonstrating this seasonality were performed in European populations residing at latitudes upwards of 50°N. This study investigated whether seasonality of prognosis persists in populations residing in the lower latitudes of the contiguous United States (Latitude 21°N to 48°N).

Material/Methods: The 5-year survival data of 19 204 female breast cancer, 6740 colorectal cancer, and 1644 prostate cancer cases was analyzed.

Results: Female breast cancer patients exhibited improved survival when diagnosed in the summer as compared to the winter at all latitudes (Hazard Ratio [HR]: 0.940, 95%; Confidence Interval [CI]: 0.938 to 0.941, P=0.002). Colorectal cancer and prostate cancer also exhibited a similar seasonal pattern (HR: 0.978, 95% CI: 0.975 to 0.980, P=0.008 and HR: 0.935, 95%, CI 0.929 to 0.943, P=0.006), respectively, when the analysis was restricted to northern regions.

Conclusions: These observations contribute to the mounting evidence that vitamin D_3 may affect the progression of cancer. Data also suggest that vitamin D_3 status at the onset of treatment may synergistically improve the prognosis of several cancer types.

MeSH Keywords: Latitude • Vitamin D • Breast Neoplasms • Prostatic Neoplasms • Colonic Neoplasms

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Background

Vitamin D is involved in a number of processes that are essential for healthy body functions. It helps to improve muscle strength and immune function and reduces many of the inflammatory processes within our bodies. Vitamin D is also known to promote the absorption of calcium from the gastrointestinal tract and to maintain adequate blood levels of calcium and phosphate needed for bone formation, mineralization, growth, and repair. Evidence supporting the protective function of vitamin D_3 against many forms of cancer is mounting. A large number of ecological studies have observed that cancer incidence and mortality rates correlate inversely with vitamin D status [1–8]. A recent review by Grant comprehensively outlines the work, to date, that has been completed in the field [9].

Although the cancer-protective mechanism of vitamin D_3 is not fully understood, its actions are likely to involve the activation of the vitamin D receptors (VDR). It has been well established that activated VDR modifies cell function both genomically and non-genomically [10]. VDR has been shown to exhibit tumor-suppressing and differentiation-inducing activities [11]. Promotion of apoptosis as well as inhibition of angiogenesis and metastatic potential has also been attributed to VDR [10,11]. In addition, Vitamin D_3 has been observed to act synergistically with several chemotherapeutic agents [12–17]. VDR expression is known to increase during the development of breast, colon, and prostate cancers, suggesting that these cancer types may be particularly susceptible to vitamin D treatment [18].

Most people get the vitamin D they need through sunlight exposure. It can also be obtained through the diet, but very few foods naturally contain vitamin D. Previous studies have demonstrated that for several forms of cancer, the season of diagnosis may influence cancer survival rates [19–21]. Individuals diagnosed in the summer or autumn months, where most individuals are outdoors during the longer days, were found to have a survival advantage over those diagnosed in the winter or spring months. Many of the studies linking cancer survival and season of diagnosis were performed in European populations residing at latitudes above 50°N [19–21]. To our knowledge, no studies have demonstrated the same seasonal pattern of cancer survival in the lower latitudes of the contiguous United States (24°N to 49°N). Using the National Cancer Institute's SEER*Stat SEER 17 database, this study investigated any association between seasonality and prognosis in cancers of the female breast, colon, rectum, and prostate.

Material and Methods

Cancer survival data

The National Cancer Institute compiles data covering 26% of the US population. The Surveillance Epidemiology and End Result (SEER) database, a subset of the National Cancer Institute, contains cancer incidence and survival data from 17 geographic regions reporting between the years 1973 to 2008 [22]. The Kaplan-Meier method was used to calculate observed survival for female breast, colorectal, and prostate cancers using the National Cancer Institute's SEER*Stat version 7.0.5. Inclusion criteria included all malignant cases diagnosed in Atlanta (Metropolitan), Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland SMSA, Seattle, and Utah between 1973 and 2002. Cases were included only if the cancer of diagnosis was also the cause of death. Skin vitamin D_3 production decreases with age [23]; therefore, individuals 50 and older are less able to convert vitamin D to its active form; therefore, the subject age range was limited to 50–64 years of age for colorectal and prostate cancer. Menopausal status was an additional consideration for the breast cancer age selection. Since the SEER*Stat database does not collect menopausal status data, a post-menopausal population was approximated by selecting for females 50 to 64 years of age, as per SEER*Stat recommendations [23]. All non-white races were excluded as well as SEER regions that began data collection between 1992 and 2000.

UVB data

The most populous city within the each SEER region was used to estimate average UVB irradiation in that region. The only exception is for SEER region "*Connecticut - 1973+*" because UV Index (UVI) data could not be obtained for the city of Bridgeport, CT. For "*Connecticut – 1973+*", Hartford, CT, was used instead for both UVB. UVI data was obtained for each region for the year 1995 (the earliest year for which complete annual data was available) from the National Ocean and Atmospheric Administration (NOAA) [24]. NOAA computes UVI using forecasted ozone data, a radioactive transfer model, forecasted cloud amounts, climatological aerosol loading, variable snow and bare earth albedo, as well as elevation [24]. UVB irradiation, ranging from 280 to 315 nm, was calculated from UVI data using the following relationship:

$$UVB_{280–315} \ (W \cdot m^{-2}) = 18.9 \times UVI \ [25].$$

Daily UVB irradiation data was used to calculate summer and winter irradiation averages for each SEER region. Summer was defined as June 1 to July 31 and winter was defined as December 1 to February 28. The peak seasonal irradiation

Table 1. Breast cancer 5 year mortality hazard ratio by season of diagnosis.

Included latitudes (°N)	Summer: Winter ratio of UVB irradiance	Season	HR	Lower	Upper	P-Value
21.3 to 47.6	1.8 to 8.1	Winter	1.000	1.000	1.000	–
		Spring	0.993	0.990	0.995	0.70
		Summer	0.940	0.938	0.941	0.002
		Fall	0.992	0.989	0.994	0.70

95% CI for hazard ratio.

averages were used to calculate summer-to-winter ratios of UVB irradiation (S: W ratios).

Latitude data

Latitude of the most populous city in each SEER region was obtained from the US Census Bureau [26]. For SEER region "*Connecticut – 1973*+", Hartford, CT, was used in lieu of Bridgeport due to the absence of UVI data for Bridgeport.

Statistical analysis

A log rank test was performed on the Kaplan-Meier observed survival data. Cox proportional hazards model was used to analyze each cancer type for variation in 5-year survival, stratified by season of diagnosis. Seasons were defined as follows: winter is December 1 to February 28; spring is March 1 to May 31; summer is June 1 to July 31; and fall is September 1 to November 30. Survival of each season was compared to that of winter. All aforementioned SEER regions were included in the primary analysis of each cancer. For cancer types that did not exhibit seasonality, secondary analyses were performed after controlling for latitude.

A series of intermediate analyses were performed in which minimum latitude was progressively elevated in a step-wise fashion. The minimum latitude was initially set at 37°N. For each analysis in the series, only SEER regions located at or above the minimum latitude would be included in the sample. For the final analysis of colorectal cancer, SEER regions located at 42.2°N latitude and above were included for analysis. Prostate cancer regions were restricted to those located at 47.6°N.

A ratio of the average summer time to winter time peak irradiances was calculated (S: W ratio). Simple linear regression was performed between S: W ratio and latitudes of SEER regions were included in the analysis. All data was analyzed using GraphPad Prism Version 5.01 (GraphPad Software Inc, 2012, La Jolla, CA).
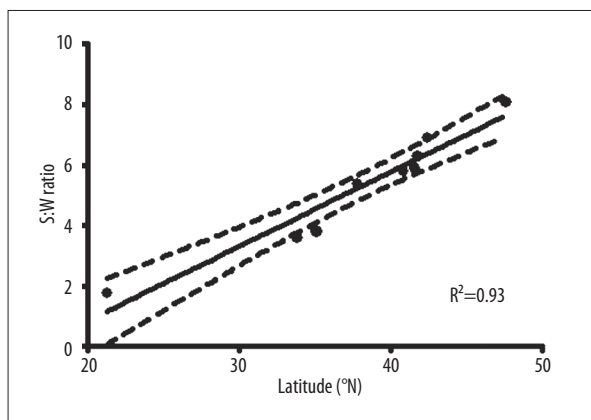

Figure 1. Simple linear regression analysis of S: W ratio *vs.* latitude.

Results

For breast cancer analysis, when all SEER regions were included, 19 204 cases met our inclusion criteria with 24.15% (4638) cases diagnosed in the winter, 25.69% (4934) cases diagnosed in the spring, 25.49% (4895) cases diagnosed in the summer, and 24.67% (4737) cases diagnosed in the fall. Hazard ratios for each season of diagnosis are displayed in Table 1. Female breast cancer cases diagnosed in the summer (HR: 0.940, 95% CI: 0.938 to 0.941, P=0.002) showed a significant survival advantage over those diagnosed in the winter. No difference in survival was observed between cases diagnosed in the winter compared to spring (HR: 0.993, 95% CI: 0.990 to 0.995, P=0.70) nor winter compared to fall (HR: 0.992, 95% CI: 0.989 to 0.994, P=0.70). When similar analyses were performed for colorectal cancer and prostate cancer, a seasonality pattern of cancer survival was not observed.

Simple linear regression demonstrated that S: W ratio and latitude are positively correlated (slope: 0.25, 95% CI: 0.19 to 0.31, R^2: 0.93) (Figure 1). Puget Sound (Seattle), located at the highest latitude of all SEER regions (47.62°N), exhibited the greatest summer-to-winter differential (S: W ratio 8.07). Hawaii, located at the lowest latitude (21.32°N), was calculated to have

Table 2. Latitude and S: W ratio by SEER region.

SEER region	Latitude (°N)	Summer: Winter ratio of UVB Irradiance
Seattle (Puget Sound) – 1974+	47.6	8.1
Detroit (Metropolitan) – 1973+	42.4	6.9
Connecticut – 1973+	41.8	6.3
Iowa – 1973+	41.6	5.9
Utah – 1973+	40.8	5.8
San Francisco-Oakland SMSA – 1973+	37.8	5.4
New Mexico – 1973+	35.1	3.8
Atlanta (Metropolitan) – 1975+	33.8	3.6
Hawaii – 1973+	21.3	1.8

the lowest S: W ratio (S: W ratio 1.83). All calculated S: W ratios are shown in Table 2.

A total of 6740 patients met the inclusion criteria for the colorectal cancer analysis. Of this total, 24.70% (1665) were diagnosed in the winter, 25.83% (1741) in the spring, 25.27% (1703) in the summer, and 24.20% (1631) in the fall. The colorectal cancer subjects from regions between 42.2°N and 47.6°N exhibited improved survival when diagnosed in the summer as compared to the winter (HR: 0.978, 95% CI: 0.975 to 0.980, P=0.008) (Table 3). In addition, significant improvements in survival were also observed in the spring and fall groups as

compared to the winter (HR: 0.984, 95% CI: 0.980 to 0.987, P=0.004; HR: 0.991, 95% CI: 0.987 to 0.993, P<0.0001, respectively). Hazard ratios for each season of diagnosis for colorectal cancer analyses are summarized in Table 3. The S: W ratio in the regions analyzed ranged from 6.9 to 8.1.

For the prostate cancer analysis, 1644 subjects met the selection criteria, with 23.26% (384) cases being diagnosed in the winter, 26.28% (432) in the spring, 23.54% (387) in the summer, and 26.82% (441) in the fall. Prostate cancer cases did not exhibit a similar survival seasonality until the latitude was limited to 47.6°N (HR: 0.935, 95% CI 0.929 to 0.943, P=0.006) (Table 3). No significant differences in survival were observed between spring and winter (HR: 1.035, 95% CI: 1.028 to 1.042, P=0.15) or fall and winter (HR: 1.004, 95% CI: 0.997 to 1.011, P=0.87) for prostate cancer diagnoses. Hazard ratios for prostate cancer analyses are shown in Table 3. At the latitude of analysis, the S: W ratio was calculated to be 8.1.

Discussion

Previous studies have shown that abnormal regulation of adhesion proteins such as Wnt/beta-catenin signaling and subsequently increased beta-catenin expression is involved in the proliferation and growth of colon cancer cells. However, many of these studies did not investigate whether the downregulation of beta-catenin in colon cancer may result in compromised invasion and migration *in vitro*. [27]. In this current study, when all SEER regions were taken into account, females diagnosed with breast cancer in the summer exhibited significantly improved 5-year survival compared to females diagnosed in the winter. This finding is consistent with the results of several similar studies undertaken in European populations

Table 3. 5 year cancer mortality hazard ratio by season of diagnosis adjusted for latitude.

Cacner type	Latitude(s) included (°N)	Summer: Winter ratio of UVB irradiance	Season	HR	Lower	Upper	P-Value
Colorectal	42.4 to 47.6	6.9 to 8.1	Winter	1.000	1.000	1.000	1.000
			Spring	0.984	0.080	0.987	0.004
			Summer	0.978	0.975	0.980	0.008
			Fall	0.991	0.987	0.993	<0.0001
Prostate	47.6	8.1	Winter	1.000	1.000	1.000	1.000
			Spring	1.035	1.028	1.042	0.15
			Summer	0.935	0.929	0.942	0.006
			Fall	1.004	0.997	1.011	0.87

95% CI for hazard ratio.

[18,28]. Recent studies have suggested that microRNA-10b (miR-10b) acts as a promoter of metastasis in breast cancer, although the underlying mechanism remains largely unknown. E-cadherin (E-cad) adhesion protein seems to be a potential target of miR-10b. Yong Liu et al. state that the existence of a novel E-cadherin-related mechanism by which miR-10b modulates breast cancer metastasis exists and that miR-10b may be a useful biomarker of advanced progression and metastasis of breast cancer [29].

A recent study, using data extracted from the SEER database, did not show any overall seasonality in cumulative probability of death from breast cancer [30]. Interestingly, a seasonal variation in tumor stage at the time of diagnosis was detected by the authors, with spring having the highest proportion of localized tumors. Cancers such as breast cancer are under hormonal control and therefore highly influenced by fluctuating menstrual hormones in pre-menopausal women [31]. These hormone-positive tumors can be age-specific and are under the control of receptors for estrogen (ER) and progesterone (PgR). In addition to this cyclical variance in menstrual hormones, breast cancer ER and PgR expression has been demonstrated to exhibit circannual rhythmicity [31]. ER and PgR expression reaches a nadir during the spring season [32–36], which explains the localized restriction of tumor growth seen during spring in a previous study [30]. Because 50%-80% of invasive breast cancers are hormone-responsive [37], the complex interactions between rhythmic hormone and hormone receptor levels may have concealed any seasonal survival patterns caused by vitamin D_3 production. Consistent with this hypothesis are observations that breast cancers diagnosed pre-menopausally can exhibit seasonality of prognosis, but only in receptor-negative cancers [38].

Studies have also shown that the capacity for UVB-stimulated cutaneous vitamin D_3 synthesis declines with advancing age [22]. In a study investigating the seasonality of prostate cancer survival, although all age groups exhibited improved survival when cancer was diagnosed in the summer, the greatest improvement was seen in the youngest age group [20]. Thus, failure to adjust for the advanced age of subjects during analysis may obscure the effects of vitamin D_3 on seasonal survival.

In the current study, to control for menstruation-related hormonal variance, a post-menopausal population was selected for analysis. The decline and cessation of ovarian hormonal synthesis may cause the effects of other hormones on breast cancer survival to become more apparent [37]. Additionally, by limiting subject age to a maximum of 64 years, we attempted to exclude individuals who may have impaired vitamin D_3 synthesis [20]. The age limits used in the current study may explain the observed seasonal pattern of breast cancer survival that was absent in the Stajner study [30].

Table 4. Latitude ranges analyzed in the current study and recent studies.

Study Region	Latitude range (°N)
United States*	21 to 48
Norway	58 to 71
United Kingdom**	50 to 52

* Latitude range of SEER regions included in analyses;
** Latitude range of South East England [21,40].

Similar analyses based on all combined SEER regions did not demonstrate seasonality of prognosis for colorectal and prostate cancers. Previous studies observed a link between the survival rate of various cancers and season of diagnosis. These studies, however, were performed in regions located at more northerly latitudes than the contiguous United States, such as Norway [19,20] and the United Kingdom [21] (Table 4). The large solar zenith angles (SZA) associated with winter at high latitudes result in an increased amount of UVB absorption by the ozone layer [39]. Cutaneous vitamin D_3 synthesis relies on the conversion of 7-dehydrocholesterol to pre-vitamin D_3 by solar $UVB_{290-315 nm}$ radiation [40]. In regions located above 37°N latitude, during late fall and winter (November to February) UVB irradiation is attenuated by amounts upwards of 80%, limiting the potential for vitamin D_3 synthesis [41]. Conversely, at latitudes below approximately 37°N, vitamin D_3 can be reliably produced throughout the year [39,41]. Because these high latitudes exhibit a large disparity between summer and winter UVB irradiation levels, summer and winter vitamin D_3 levels of residents of those regions are also likely to vary greatly. It follows that the relatively low latitude of the United States would not provide a sufficient difference in UVR and, consequently, vitamin D_3 levels between summer and winter to produce any seasonality patterns for survival for all types of cancers.

To examine regions with the greatest differential between summer and winter UVB irradiation levels, only regions located at higher latitudes (above 37°N) were included in secondary analyses. Significant survival advantages were observed for colorectal and prostate cancers diagnosed during the summer at latitudes above 42.4°N and at 47.6°N, respectively. The S: W ratio of UVB irradiation correlated linearly with latitude. These data are consistent with the hypothesis that vitamin D_3 status at the time of diagnosis may improve cancer survival.

Of the 3 cancer types investigated in the current study, the effects of seasonality were most pronounced in the female breast cancer group. Several other authors have previously commented on this trend [18,21,43,44] but no explanatory hypothesis has been proposed. The tumor-suppressing and

differentiation-inducing actions of VDR have been generalized to many cancer types [11]. Specific mechanisms for the suppressions of breast cancer have also been attributed to VDR [10,45,44]. Activated VDR has been demonstrated to down-regulate ER synthesis and ER activity [10,45]. As previously mentioned, ER and PgR exhibit circannual rhythmicity and a pattern of rhythmicity persists even after menopause [31,36]. Because hormone receptor concentrations are fundamental predictors of breast cancer outcome, the interaction between the rhythmicity of vitamin D_3 and the rhythmicity of ER may be important in recognizing the strength of the relationship between female breast cancer and seasonality of prognosis. After diagnosis and treatment, many women seek breast reconstruction as a means of maintaining aesthetic beauty. The internal mammary artery and vein are often used as sites of anastomoses in microvascular breast reconstruction because this area supports lymphatic drainage of the breast. However, its role in breast cancer metastasis remains unclear. Christoph Andree et al. concluded that the internal mammary lymphatic drainage system is an important and often underappreciated pathway for breast cancer metastasis. Their findings indicate that routine sampling of these lymph nodes at the time of microvascular breast reconstruction is easy to perform and is a useful tool for identifying women who might require additional treatment and to increase cancer-free survival. [46]

The present study has several limitations, including limitations of the data available from the SEER database. Factors that may affect vitamin D status but could not be controlled for in this study include vitamin D dietary intake [2,48], obesity [2,48], physical activity, alcohol consumption [2], smoking [2], and socioeconomic status [2]. These limitations accounted for the inconsistency in results between the findings in the literature because of the challenges of conducting studies observing individual behaviors. Measuring blood levels of vitamin D avoids some of the limitations of assessing dietary intake. However, vitamin D levels in the blood vary by race, with the season (as discussed within this review), and possibly with the activity of genes whose products are involved in vitamin D transport and metabolism. These variations complicate the interpretation of studies that measure the concentration of vitamin D in serum at a single point in time. The use of S: W ratio may also have limited interpretation value. The ratio was a convenient method to calculate a crude estimation of the difference in seasonal UVB irradiation of each region. The actual irradiance experienced by individuals residing in each region is highly influenced by their individual behaviors [20]. Although studies in the past have used SCC as a measure of UV exposure [18,20,29], SCC incidence data was not available. Finally, the limited geographic distribution of SEER regions restricted the population available for sampling when latitude was being controlled for. Seasonality for colorectal cancer survival was observed when the 2 most northerly SEER regions were included for analysis, while prostate cancer survival seasonality was observed in the most northerly SEER region. Because SEER regions are only located in the contiguous US, the maximum latitude for which there is data is 48°N, excluding Alaska.

Conclusions

Vitamin D is involved in a number of processes that are essential for healthy body functions. It helps to improve muscle strength and immune function and reduces many of the inflammatory processes within our bodies. Vitamin D is also known to promote the absorption of calcium from the gastrointestinal tract and to maintain adequate blood levels of the calcium and phosphate needed for bone formation, mineralization, growth, and repair. Many ecological studies have observed that cancer incidence and mortality rates correlate inversely with vitamin D_3 status [1–8]. Individuals living in southern latitudes were found to have lower rates of incidence and death for colorectal, breast, and prostate cancers than those living at northern latitudes. Because sunlight/UV exposure is necessary for the production of vitamin D_3, it was hypothesized that variation in vitamin D levels accounted for the observed relationships. Other investigators have also demonstrated that in several European populations season of diagnosis is a prognostic factor for many cancer types [19–21]. Evidence-based studies done in laboratory settings have shown an association with the possible cancer-protective role for vitamin D. They suggested that vitamin D promoted the differentiation and death of cancer cells, or slowed their proliferation. This study observes seasonality of cancer prognosis in the US using data obtained from the SEER database. The observations from this study suggested that the seasonality of cancer prognosis is latitude-dependent. The findings of this study are consistent with the accumulating evidence supporting the role of vitamin D_3 as a protective agent against several forms of cancer.

References:

1. Grant W: An ecological study of cancer incidence and mortality rates in France with respect to latitude, an index for vitamin D production. Demato-Endocrinology, 2010; 2: 62–67

2. Grant WB, Garland CF: The association of solar ultraviolet B (UVB) with reducing risk of cancer: multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates. Anticancer Res, 2006; 26: 2687–99

3. Boscoe FP, Schymura MJ: Solar ultraviolet-B exposure and cancer incidence and mortality in the United States, 1993–2000. BMC Cancer, 2006; 6: 264

4. Grant WB: Does solar ultraviolet irradiation affect cancer mortality rates in China? Asian Pac J Cancer Prev, 2007; 8: 236–42

5. Chen W, Clements M, Rahman B et al: Relationship between cancer mortality/incidence and ambient ultraviolet B irradiance in China. Cancer Causes Control, 2010; 21: 1701–9

6. Neale RE, Youlden DR, Krnjacki L et al: Latitude variation in pancreatic cancer mortality in Australia. Pancreas, 2009; 38: 387–90

7. Kato I, Tajima K, Kuroishi T, Tominaga S: Latitude and pancreatic cancer. Jpn J Clin Oncol, 1985; 15: 403–13

8. Mizoue T: Ecological study of solar radiation and cancer mortality in Japan. Health Phys, 2004; 87: 532–38

9. Grant W: Ecological studies of the UV-Vitamin D-Cancer hypothesis. Anticancer Res, 2012; 32: 223–26

10. Haussler M, Jurutka P, Mizwicki M, Norman A: Vitamin D receptor (VDR)-mediated actions of 1-α, 25 (OH)2 vitamin D3: Genomic and non-genomic mechanisms. Best Pract Res Clin Endocrinol Metab, 2011; 25: 543–59

11. Giovannucci E: The epidemiology of vitamin D and cancer incidence and mortality: A review (United States). Cancer Causes Control, 2005; 16: 83–95

12. Gewirtz DA, Sundaram S, Magnet KJ: Influence of topoisomerase II inhibitors and ionizing radiation on growth arrest and cell death pathways in the breast tumor cell. Cell Biochem Biophys, 2000; 33: 19–31

13. James SY, Mackay AG, Colston KW: Vitamin D derivatives in combination with 9-cis retinoic acid promote active cell death in breast cancer cells. J Mol Endocrinol, 1995; 14: 391–94

14. Ravid A, Rocker D, Machlenkin A et al: 1,25-Dihydroxyvitamin D3 enhances the susceptibility of breast cancer cells to doxorubicin-induced oxidative damage. Cancer Res, 1999; 59: 862–67

15. Vink-van Wijngaarden T, Pols HA, Buurman CJ et al: Inhibition of breast cancer cell growth by combined treatment with vitamin D3 analogues and tamoxifen. Cancer Res, 1994; 54: 5711–17

16. Wang Q, Yang W, Uytingco MS et al: 1,25-Dihydroxyvitamin D3 and all-trans-retinoic acid sensitize breast cancer cells to chemotherapy-induced cell death. Cancer Res, 2000; 60: 2040–48

17. Ma Y, Trump D, Johnson C: Vitamin D in combination cancer treatment. J Cancer, 2010; 1: 101–7

18. Robsahm T, Tretli S, Dahlback A, Moan J: Vitamin D3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway). Cancer Causes Control, 2004; 15: 149–58

19. Porojnicu A, Lagunova Z, Robsahm T et al: Changes in risk of death from breast cancer with season and latitude. Breast Cancer Res Treat, 2007; 102: 323–28

20. Lagunova Z, Porojnicu A, Dahlback A et al: Prostate cancer survival is dependent on season of diagnosis. The Prostate, 2007; 67: 1362–70

21. Lim HS, Roychoudhuri R, Peto J et al: Cancer survival is dependent on season of diagnosis and sunlight exposure. Int J Cancer, 2006; 119: 1530–36

22. MacLaughlin J, Holick MF: Aging decreases the capacity of human skin to produce Vitamin D3. J Clin Invest, 1985; 76: 1536–38

23. SEER [internet]. SEER*Stat Case Listing Exercise 1a [cited 2012 Feb 11]. SEER*Stat tutorial; [about 3 screens]. Available from: http://seer.cancer.gov/seerstat/tutorials/case1a/webprint/

24. National Oceanic and Atmospheric Administration [internet]. Stratosphere: UV Index [cited 2012 Feb 11]. Climate Prediction Center; [about 1 screen]. Available from: http://www.cpc.ncep.noaa.gov/products/stratosphere/uv_index/

25. McKenzie R, Smale D, Kotkamp M: Relationship between UVB and erythemally weighted radiation. Photochem Photobiol Sci, 2004; 3: 252–56

26. US Census Bureau [internet]. Topologically Integrated Geographic Encoding and Referencing system (TIGER Products) [updated 2011 Dec 19, cited 2012 Feb 11] Latitude and Longitude All U.S. Places [about 60 screens]. Available from: http://www.census.gov/geo/www/tiger/latlng.txt

27. Han J, Gao B, Jin X, Xu Z et al: Small interfering RNA-mediated downregulation of beta-catenin inhibits invasion and migration of colon cancer cells in vitro. Med Sci Monit, 2012; 18(2): BR273–80

28. Porojnicu A, Dahlback A, Moan J: Sun Exposure and Cancer Survival in Norway: changes in the risk of death with season of diagnosis and latitude. Adv Exp Med Biol, 2008; 624: 43–54

29. Liu Y, Zhao J, Zhang PY et al: MicroRNA-10b targets E-cadherin and modulates breast cancer metastasis. Med Sci Monit, 2012; 18(3): BR299–308

30. Stajner I: Season of breast cancer diagnosis and probability of death from breast cancer in the United States. Int J Cancer, 2010; 126: 3010–13

31. Oh EY, Ansell C, Nawaz H et al: Global breast cancer seasonality. Breast Cancer Res Treat, 2010; 123: 233–43

32. Hughes A, Jacobson H, Wagner R, Jungblut P: Ovarian independent fluctuations of estradiol receptor levels in mammalian tissues. Mol Cell Endocrinol, 1976; 5: 379–88

33. Martin P, Rolland P, Jacquemier J et al: Multiple steroid receptors in human breast cancer. III. Relationships between steroid receptors and the state of differentiation and the activity of carcinomas throughout the pathologic features. Cancer Chemother Pharmacol, 1979; 2(2): 115–20

34. Cohen P: Host heterogeneity in female breast cancer: possible significance for pathophysiology, therapy, and prevention. Breast Cancer Res Treat, 1990; 15: 205–12

35. Vyzula R, Zaloudik J, Dusek L, Vermousek I: Seasonal variation in estrogen and progesterone receptor levels in breast cancer – a factor in data interpretation. Neoplasia, 2001; 48: 19–25

36. Paradiso A, Fanelli M, Mangia A et al: Predictability of monthly and yearly rhythms of breast cancer features. Breast Cancer Res Treat, 2001; 67: 41–49

37. Mason BH, Holdaway IM, Stewart W, Kay R: Season of initial discovery of tumour as an independent variable predicting survival in breast cancer. Br J Cancer, 1990; 61: 137–41

38. Gonzalez L, Corte M, Vazquez J et al: Androgen receptor expression in breast cancer: Relationship with clinicopathological characteristics of the tumors, prognosis, and expression of metalloproteases and their inhibitors. BMC Cancer, 2008; 8: 149–59

39. Tsiaras W, Weinstock M: Factors influencing vitamin D status. Acta Derm Venereol, 2011; 91: 115–24

40. Holick M: Vitamin D: A millennium perspective. J Cell Biochem, 2003; 88: 296–307

41. Holick M: Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancer, and cardiovascular disease. Am J Clin Nutr, 2004; 80: 1678–88

42. Ordinancesurvey.co.uk [Internet]. UK Ordinance, Crown; c2012 [cited 2012 Feb 11]. Available from: http://www.ordnancesurvey.co.uk/oswebsite/

43. 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

44. Moan J, Porojnicu AC, Robsahm TE et al: Solar radiation, vitamin D and survival rate of colon cancer in Norway. J Photochem Photobiol B, 2005; 78: 189–93

45. Matthews D, Laporta E, Zinser G et al: Genomic vitamin D signaling in breast cancer: insights from animal models and human cells. J Steroid Biochem Mol Biol, 2010; 121: 362–67

46. Christoph Andree et al: Detecting of breast cancer metastasis by means of regional lymph node sampling during autologous breast reconstruction – a screening of 519 consecutive patients. Med Sci Monit, 2012; 18(1): CR605–10

47. Swami S, Krishnan A, Feldman D: 1-α, 25-dihydroxyvitamin D3 down-regulates estrogen receptor abundance and suppresses estrogen actions in CF-7 human breast cancer cells. Clin Cancer Res, 2000; 6: 3371–79

48. Holick M: Vitamin D deficiency. N Engl J Med, 2007; 357: 266–81