Impact of seasonal and geographical differences on breast cancer survival

Hyun Wook Kwon¹, Jung Won Lee², Hee Jeong Kim¹, Beom Seok Koh¹, Jong Han Yu¹, Jong Won Lee¹, Byung Ho Son¹, Sei Hyun Ahn¹

¹Division of Breast and Endocrine Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul; ²Breast and Thyroid Center, Cheon-An Chung-Mu Hospital, Cheonan, Korea

Purpose: Seasonal and geographic variations in ultraviolet B intensities (UVB) impact the vitamin D status, and these differences might significantly affect cancer prognosis. This study evaluates the association between seasonal and geographic differences in UVB exposure and breast cancer survival.

Methods: We divided Korea into two regions according to erythemally weighted annual UVB exposure as follows: Seoul and the southern region. Recurrence and death were also grouped into two seasons: spring/summer and autumn/winter.

Results: The survival and relapse rates, when stratified by season of diagnosis, demonstrated no significant differences between spring/summer and autumn/winter. Among the 1,488 breast cancer patients in our cohort who demonstrated recurrence, 775 cases (52.1%) relapsed during the spring/summer and 594 patients (52.6%) died during the autumn/winter. In total, 6,178 patients (89.1%) and 3,909 patients (91.3%) in Seoul and the southern region survived (P = 0.005). The relapse rate in the Seoul group (13.7%) was higher than the southern group (11.9%). By Kaplan-Meier analysis, there were no statistical differences between the Seoul and southern groups in terms of disease-free (P = 0.43) and cancer-specific survival (P = 0.18). In the Cox analysis, after the adjustment of all the other factors, season of diagnosis and residential area have no statistical significance.

Conclusion: We conclude from our findings that death from breast cancer occurs more frequently in the autumn/winter, and that patients in the southern area of Korea demonstrate better survival. However, we find no significant relationship between geographic and seasonal variations in breast cancer survival.

Keywords: Breast cancer, Season, Geography, Vitamin D

INTRODUCTION

Vitamin D refers to a group of fat-soluble prohormones that are mainly synthesized following exposure to ultraviolet B (UVB) light (280-315 nm in wavelength). The two major forms of vitamin D are D₃ (calciferol) and D₂ (cholecalciferol). The photochemical synthesis of vitamin D₃ occurs cutaneously, whereas provitamin D₃ (7-dehydrocholesterol) is converted to previtamin D₃ (pre-D₃). Vitamin D₃ is hydroxylated by liver 25-hydroxylases (25-OHase) to form 25-hydroxycholecalciferol (25(OH)D₃), which is subsequently 1α-hydroxylated in the kidneys by 25-hydroxyvitamin D₃-1α-hydroxylase (1α-OHase). This yields the active secosteroid 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃; calcitriol), the hormonal form of vitamin D [1-3].

1,25(OH)₂D₃ exerts various biological effects in cells that possess the vitamin D3 receptor (VDR), including the enhancement of cell differentiation and the inhibition of cell proliferation and angiogenesis [4]. Some preclinical studies have established that calcitriol induces growth arrest, differentiation, and apoptosis in vitro in transformed cell lines derived from breast, prostate, colon, and other tissues, and that these effects are mediated by VDR. VDR is also expressed in 80% of human breast cancers. These results have provided background evidence for use in epidemiologic studies [5,6].
The protective role of sunlight against cancer incidence was first hypothesized by Garland and Grand [7] in 1980 and published in their ecological study on colon cancer mortality rates and annual sunlight levels. Support for this theory has also been published in ecological, case control, and cohort studies [8-11]. In a study from the United Kingdom, Lim et al. [12] reported that patients diagnosed in the summer and autumn demonstrate increased survival compared with patients diagnosed in the winter, especially among breast and lung cancer patients. In a Norwegian study, Porojnicu et al. [13] also reported that male lung cancer patients diagnosed in the summer or autumn and also reside in high-UV regions demonstrate a 15% reduced risk of mortality. Freedman et al. [14] have reported that residential exposure to sunlight is associated with reduced mortality from breast, ovarian, prostate, and colon cancers.

Although vitamin D can be obtained by consuming vitamin D-rich foods or vitamin supplements, vitamin D levels are most heavily influenced by solar radiation. Korea occupies a wide latitudinal area (33°-39°N) and thus experiences four very distinct seasons. Geographic and seasonal variations in UVB impact the vitamin D status, and these differences might be of prognostic significance to breast cancer. Our group has previously reported that vitamin D deficiency is correlated with poor clinical outcomes in breast cancer patients [15]. In our present study, we explored whether geographic and seasonal variations in Korea are correlated with breast cancer survival.

**METHODS**

**Patients**

Data collected between 1989 and 2010 in the Asan Medical Center Breast Cancer Database were analyzed. A total of 11,698 breast cancer patients listed on this database were included in this study. Patient age (<50 years vs. ≥50 years), tumor size (<2 cm vs. ≥2 cm), lymph node involvement, hormone receptor and HER2-neu status, and adjuvant treatment status were analyzed. Pathological staging was based on the staging criteria of the seventh edition of the American Joint Committee on Cancer. Immunohistochemical staining was performed for the biomarkers of estrogen receptor (ER), progesteron receptor (PR), and human epidermal growth factor receptor 2 (HER2). ER and PR were scored according to the modified allred score. Tumor were considered ER or PR positive when the score was over 5. Tumor were considered HER2 positive only if they were either scored 3+ by immunohistochemistry (IHC) or if they were 2+ by IHC and also HER2 amplified (ratio >2.0) on the basis of fluorescence in situ hybridization (FISH). In the absence of positive FISH data, tumors scored 2+ by IHC were excluded in this study. Using data from the Korea Meteorological Administration collected by the season of diagnosis

**Table 1.** Patient demographics and clinical characteristics stratified by the season of diagnosis

| Variable                  | Spring, summer (n=5,575) | Autumn, winter (n=5,554) | P-value |
|---------------------------|--------------------------|--------------------------|---------|
| Age at operation (yr), mean | 55.9                     | 55.2                     | <0.01   |
| < 50                      | 1,402 (24.5)             | 1,528 (26.8)             |         |
| ≥ 50                      | 4,328 (75.5)             | 4,167 (73.2)             |         |
| Tumor size (cm)           |                          |                          | 0.50    |
| < 2                       | 3,261 (58.5)             | 3,214 (57.9)             |         |
| ≥ 2                       | 2,314 (41.5)             | 2,340 (42.1)             |         |
| Lymph node metastasis     |                          |                          | 0.82    |
| Negative                  | 3,436 (60.0)             | 3,427 (60.2)             |         |
| Positive                  | 2,294 (40.0)             | 2,268 (39.8)             |         |
| ER status                 |                          |                          | 0.32    |
| Negative                  | 2,560 (44.7)             | 2,492 (34.8)             |         |
| Positive                  | 3,170 (55.3)             | 3,203 (65.2)             |         |
| PR status                 |                          |                          | 0.40    |
| Negative                  | 2,927 (21.1)             | 2,864 (21.1)             |         |
| Positive                  | 2,803 (49.7)             | 2,831 (49.7)             |         |
| HER2                      |                          |                          | 0.02    |
| Negative                  | 4,543 (79.3)             | 4,414 (77.5)             |         |
| Positive                  | 1,187 (20.7)             | 1,281 (22.5)             |         |

Values are presented as number (%). ER, estrogen receptor; PR, progesteron receptor; HER2, human epidermal growth factor receptor 2.

**Table 2.** Patient demographics and clinical characteristics stratified by residential groups

| Variable                  | Seoul (n=7,077) | Southern (n=4,348) | P-value |
|---------------------------|----------------|-------------------|---------|
| Age at operation (yr), mean | 56.9           | 55.3              | <0.01   |
| < 50                      | 1,720 (24.3)   | 1,210 (27.8)      |         |
| ≥ 50                      | 5,357 (75.7)   | 3,138 (72.2)      |         |
| Tumor size (cm)           |                |                   | 0.45    |
| < 2                       | 3,938 (57.9)   | 2,492 (58.6)      |         |
| ≥ 2                       | 2,896 (42.1)   | 1,758 (41.4)      |         |
| Lymph node metastasis     |                |                   | 0.81    |
| Negative                  | 4,245 (60.0)   | 2,618 (60.2)      |         |
| Positive                  | 2,832 (40.0)   | 1,730 (39.8)      |         |
| ER status                 |                |                   | <0.01   |
| Negative                  | 3,201 (45.2)   | 1,851 (42.6)      |         |
| Positive                  | 3,876 (54.8)   | 2,497 (57.4)      |         |
| PR status                 |                |                   | 0.02    |
| Negative                  | 3,649 (51.6)   | 2,142 (49.3)      |         |
| Positive                  | 3,428 (48.4)   | 2,206 (50.7)      |         |
| HER2                      |                |                   | <0.01   |
| Negative                  | 5,624 (79.5)   | 3,333 (76.7)      |         |
| Positive                  | 1,453 (20.5)   | 1,015 (23.3)      |         |

Values are presented as number (%). ER, estrogen receptor; PR, progesteron receptor; HER2, human epidermal growth factor receptor 2.
over the last 22 years, we divided Korea into two residential regions according to erythemally weighted annual UVB exposure (MJ/m²) (Fig. 1): Seoul (Seoul and surround areas) and the southern region (all other areas). We chose 4,550 MJ/m² as the cut-off value for the amount of daily solar radiation. Recurrence and death were classified as occurring in the spring/summer (March-August) or in autumn/winter (September-February).

**Statistical analysis**

The demographic and clinical characteristics of the patients stratified by two residential regions (Table 1) and the season of diagnosis (Table 2) were analyzed using the chi-square test. The frequencies of death and relapse were estimated during each season. Survival and relapse rates according to the area of residence and the season were estimated using the chi-square test. Disease-free survival (DFS; until recurrence or death) and cancer-specific survival (CSS; until death from breast cancer) were calculated using the Kaplan-Meier product-limit method (Figs. 2, 3). Hazard ratio of DFS and CSS for patients with each residential region and season of diagnosis evaluated considering the potential confounding factors: age, tumor size, hormone receptor status, HER2-neu status (Table 3). All other statistical analyses were performed using SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA). In this study, P < 0.05 were considered statistically significant.

**RESULTS**

This study included 7,077 and 4,348 patients residing in Seoul or

---

**Fig. 1.** Annual erythemally-weighted ultraviolet-B exposure (MJ/m²) Obtained from http://minwon.kma.go.kr.

**Fig. 2.** Kaplan-Meier estimates of (A) disease-free survival and (B) cancer-specific survival are shown stratified by season of diagnosis.
the southern region, respectively. The two groups, according to season of diagnosis, were similar in terms of patient characteristics, except for age (P < 0.01), HER2 status (P = 0.02) (Table 1). The demographic and clinical characteristics of the study patients stratified by residential region and season of diagnosis are shown in Table 1.

Table 3. Multivariate Cox proportional hazards model for cancer-specific survival and disease-free survival

| Variable                   | Cancer-specific survival |     |     | Disease-free survival |     |     |
|----------------------------|--------------------------|-----|-----|-----------------------|-----|-----|
|                            | 95% CI                   | HR  | P-value | 95% CI                   | HR  | P-value |
| Tumor size (cm)            | 1.58-2.10                | 1.00| <0.01    | 1.55-1.95                | 1.00| <0.01    |
| <2                         |                          |     |         |                        |     |         |
| ≥2                         | 1.82                     |     |         | 1.74                   |     |         |
| Lymph node metastasis      | 3.91-5.32                | 4.56| <0.01    | 2.40-3.02                | 2.67| <0.01    |
| Negative                   | 1.00                     |     |         | 1.00                   |     |         |
| Positive                   | 4.56                     |     |         | 2.67                   |     |         |
| ER status                  | 0.47-0.65                |     | <0.01    | 0.71-0.93                |     | <0.01    |
| Negative                   | 1.00                     |     |         | 1.00                   |     |         |
| Positive                   | 0.55                     |     |         | 0.81                   |     |         |
| PR status                  | 0.51-0.73                |     | <0.01    | 0.61-0.81                |     | <0.01    |
| Negative                   | 1.00                     |     |         | 1.00                   |     |         |
| Positive                   | 0.61                     |     |         | 0.70                   |     |         |
| HER2                       | 0.68-0.94                |     | <0.01    | 0.94-1.21                |     | 0.35     |
| Negative                   | 1.00                     |     |         | 1.00                   |     |         |
| Positive                   | 0.80                     |     |         | 1.06                   |     |         |
| Residential region         | 0.08-1.26                |     | 0.12     | 0.87-1.08                |     | 0.62     |
| Seoul                      | 1.00                     |     |         | 1.00                   |     |         |
| Southern                   | 1.11                     |     |         | 0.96                   |     |         |
| Season of diagnosis        | 0.84-1.09                |     | 0.51     | 0.90-1.10                |     | 0.98     |
| Spring, summer             | 1.00                     |     |         | 1.00                   |     |         |
| Autumn, winter             | 0.96                     |     |         | 1.00                   |     |         |

HR, hazard ratio; CI, confidence interval; ER, estrogen receptor; PR, progesteron receptor; HER2, human epidermal growth factor receptor 2.
fied by residential groups are summarized in Table 2. Patients in Seoul were statistically older than patients in the southern area (P < 0.001), and the ER expression level was statistically higher in the southern group (P = 0.005). HER2 expression was lower in patients in Seoul (P < 0.001). There were no differences in terms of tumor size or lymph node metastasis between the two groups.

Relationship between season, recurrence, and death
The survival and relapse rates, when stratified by season of diagnosis, demonstrated no significant differences between spring/summer and autumn/winter. Kaplan-Meier estimates of DFS and CSS also demonstrated no differences based on the season of diagnosis (Fig. 2). Among the 1,488 breast cancer patients in our cohort who demonstrated recurrence, 775 cases (52.1%) relapsed during the spring/summer and 594 patients (52.6%) died during the autumn/winter. In the Cox analysis, after the adjustment of all the other factors (age, tumor size, lymph node metastasis, ER, PR, and HER2 status), there were no significant differences with season of diagnosis (Table 3).

Relationship between geography, recurrence, and death
In total, 6,178 patients (89.1%) and 3,909 patients (91.3%) in Seoul and the southern region survived (P = 0.005). The relapse rate in the Seoul group (13.7%) was higher than the southern group (11.9%). By Kaplan-Meier analysis, the southern group demonstrated a better overall prognosis, but there were no statistical differences between the Seoul and southern groups in terms of DFS (P = 0.43) and CSS (P = 0.18) (Fig. 3). In the Cox analysis, we also could not find significant differences with regard to the risk of DFS and CSS between Seoul and Southern group (Table 3).

DISCUSSION
Our present findings show that breast cancer patients in Seoul, who receive less sunlight exposure, demonstrate a higher risk of recurrence and death compared with patients in the southern region. After adjustment for potential confounders, however, both season of diagnosis and residential area have no statistical significance. Kaplan-Meier estimates also demonstrated no significant differences between our two study groups stratified by region. Moreover, we found no relationship between season of diagnosis and breast cancer recurrence or death in our analysis. This is the first study to report an association between seasonal and geographic variation, recurrence, and death in Korean breast cancer patients. Because race and skin pigmentation also play considerable roles in vitamin D synthesis [16], we compared our study results with those reported from neighboring nations. Fukuda et al. [17] reported the preventive effects of solar radiation on several types of cancer in Japan, most notably gastrointestinal cancer, but found no relationship with female breast cancer and socioeconomic variables were considered to be potential confounders. Cancer mortality rates in China have been inversely associated with UVB exposure for most types of cancer, including breast cancer [18].

Our current hypothesis was based on the fact that sun-induced vitamin D levels are affected by geographic and seasonal variation. As reported previously, this difference in vitamin D levels impacts the risk of breast cancer. Freedman et al. [14] reported that residential exposure to sunlight is negatively and significantly associated with breast cancer mortality. However, many factors must be considered when associating geographic location with vitamin D synthesis. Lifestyle, latitude, seasonal variation, cloud and ozone coverage, and socioeconomic status all influence solar exposure [19]. Millen et al. [20] reported that the region of residence and solar radiation are not significantly related to breast cancer risk, but that time spent outside is associated with this risk.

Several ecological studies have reported significant variation in clinical prognosis according to season of diagnosis [12,21]. In a previous Norwegian study, diagnoses during the summer and fall (the seasons with the highest levels of vitamin D) demonstrated the lowest risk of breast cancer death [22]. Lim et al. [12] suggested in their study that female breast cancer patients diagnosed in the summer and autumn demonstrate prolonged survival compared with patients diagnosed in the winter and that sunlight exposure in the months preceding diagnosis is a predictor of survival. Both human and animal studies support this finding [23]. In our present study, we found that more Korean breast cancer patients died in the autumn/winter than in the spring/summer, but we could not determine any prognostic variations that depended on the season of diagnosis.

Old age has been suggested as a risk factor for vitamin D insufficiency because the cutaneous synthesis of vitamin D₃ declines with age. One of the possible causes for increased cancer risk is that aging decreases the capacity of the skin to produce vitamin D. MacLaughlin et al. [24] suggested that epidermal concentrations of 7-dehydrocholesterol demonstrate age-dependent decreases. In addition, age-related decreases in VDR and the renal production of 1,25(OH)₂D have been reported in aging kidneys [25]. It must be considered also that older generations may tend to stay indoors more prevalently, especially in the winter. Interestingly in this regard, the Korea National Health and Nutrition Examination Survey (KNHANES) has reported that a vitamin D insufficiency is a greater threat to younger generations in Korea because they have settled in urban areas in increasing proportions and thus spend more time indoors [26].

This study has several limitations to note. First, we were unable...
to investigate confounding factors such as dietary vitamin D intake, socioeconomic status, and lifestyle. Geography may also be closely related with socioeconomic status. However, we do report for the first time that a relationship exists between sunlight exposure and breast cancer recurrence and mortality. In conclusion, our present retrospective analyses of a Korean cohort indicate that breast cancer deaths occur more often in the winter and less frequently in patients who live in the southern region of Korea. However, geographic and seasonal variations do not appear to affect breast cancer survival. To determine if this relationship is caused by differences in UVB exposure, future prospective studies that examine the associations between individual levels of sunlight exposure and breast cancer survival need to be performed.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Deeb KK, Trump DL, Johnson CS. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. Nat Rev Cancer 2007;7:684–700.
2. Ali MM, Vaidya V. Vitamin D and cancer. J Cancer Res Ther 2007;3:225–30.
3. Stroud ML, Stilgoe S, Stott VE, Alhabian O, Salman K. Vitamin D: a review. Aust Fam Physician 2008;37:1002–5.
4. Majewski S, Skopinska M, Marczak M, Szmurlo A, Bollag W, Jablonska S. Vitamin D3 is a potent inhibitor of tumor cell-induced angiogenesis. J Investig Dermatol Symp Proc 1996;1:97–101.
5. de Lyra EC, da Silva IA, Katayama ML, Brentani MM, Nonogaki S, Goes JC, et al. 25(OH)D3 and 1,25(OH)2D3 serum concentration and breast tissue expression of 1alpha-hydroxylase, 24-hydroxylase and Vitamin D receptor in women with and without breast cancer. J Steroid Biochem Mol Biol 2006;100:184–92.
6. Valrance ME, Brunet AH, Welsh J. Vitamin D receptor-dependent inhibition of mammary tumor growth by EB1089 and ultraviolet radiation in vivo. Endocrinology 2007;148:4887–94.
7. Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? Int J Epidemiol 1980;9:227–31.
8. 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(4A):2687–99.
9. Grant WB. How strong is the evidence that solar ultraviolet B and vitamin D reduce the risk of cancer? An examination using Hill’s criteria for causality. Dermatoendocrinol 2009;1:17–24.
10. Grant WB. An ecological study of cancer incidence and mortality rates in France with respect to latitude, an index for vitamin D production. Dermatoendocrinol 2010;2:62–7.
11. Grant WB. Update on evidence that support a role of solar ultraviolet-B irradiance in reducing cancer risk. Anticancer Agents Med Chem 2013;13:140–6.
12. Lim HS, Roychoudhuri R, Peto J, Schwartz G, Baade P, Moller H. Cancer survival is dependent on season of diagnosis and sunlight exposure. Int J Cancer 2006;119:1530–6.
13. Porojnicu AC, Robsahm TE, Dahlback A, Berg JP, Christiani D, Bruland OS, et al. Seasonal and geographical variations in lung cancer prognosis in Norway: does vitamin D from the sun play a role? Lung Cancer 2007;55:263–70.
14. 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.
15. Kim HJ, Lee YM, Ko BS, Lee JW, Yu JH, Son BH, et al. Vitamin D deficiency is correlated with poor outcomes in patients with luminal-type breast cancer. Ann Surg Oncol 2011;18:1830–6.
16. John EM, Schwartz GG, Koo J, Wang W, Ingles SA. Sun exposure, vitamin D receptor gene polymorphisms, and breast cancer risk in a multiethnic population. Am J Epidemiol 2007;166:1409–19.
17. Fukuda Y, Nakaya T, Nakao H, Yahata Y, Imai H. Multilevel analysis of solar radiation and cancer mortality using ecological data in Japan. Biosci Trends 2008;2:235–40.
18. Chen W, Clements M, Rahman B, Zhang S, Qiao Y, Armstrong BK. Relationship between cancer mortality/incidence and ambient ultraviolet B irradiance in China. Cancer Causes Control 2010;21:1701–9.
19. Kimlin MG. Geographic location and vitamin D synthesis. Mol Aspects Med 2008;29:453–61.
20. Milen AE, Pettinger M, Freudenheim JL, Langer RD, Rosenberg CA, Mossavar-Rahmani Y, et al. Incidental invasive breast cancer, geographic location of residence, and reported average time spent outside. Cancer Epidemiol Biomarkers Prev 2009;18:495–507.
21. Mutlu H, Colak T, Ozdogan M, Altunor Torun Y, Akca Z. The effect of seasonal differences on prognostic factors in Turkish patients with breast cancer. Eur J Cancer Prev 2011;20:475–7.
22. Robsahm TE, 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.
23. Welsh J. Vitamin D and breast cancer: insights from animal models. Am J Clin Nutr 2004;80(6 Suppl):1721S–45.
24. Maclaurhin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. J Clin Invest 1985;76:1536–8.
25. Gallagher JC. Vitamin D and aging. Endocrinol Metab Clin North
26. Choi HS, Oh HJ, Choi H, Choi WH, Kim JG, Kim KM, et al. Vitamin D insufficiency in Korea—a greater threat to younger generation: the Korea National Health and Nutrition Examination Survey (KN-HANES) 2008. J Clin Endocrinol Metab 2011;96:643-51.