

RESEARCH ARTICLE

Is Season a Prognostic Factor in Breast Cancer?

Hasan Mutlu^{1*}, Zeki Akca², Yasemin Benderli Cihan³, Fatih Kurnaz⁴, Tuncay Aslan⁵, Abdülsamet Erden⁵, Hediye Ugur⁵, Arzu Akşahin⁵, Abdullah Büyükçelik⁶

Abstract

Background: Some studies have indicated an inverse relationship between cancer risk and sunlight exposure. Others have reported that the prognosis of some cancers such as prostate, colon, ovarian and non melanoma skin cancer, were affected by the season in which the cancer was diagnosed. In our study, we evaluated whether season is prognostic in Turkish patients with breast cancer. **Materials and Methods:** A total of 517 patients from Kayseri Training and Research Hospital were analysed retrospectively. Patients were divided into 4 groups according to season of cancer diagnosis: winter, spring, summer and autumn. The prognostic factors for disease free survival and overall survival were investigated. **Results:** No significant differences were found among groups regarding prognostic factors overall. Only estrogen receptor status and lymphovascular invasion were independent prognostic factors ($p=0.001$ and $p=0.001$ respectively). We found significant differences for mean disease free survival among groups ($p=0.019$). Winter group had better mean DFS while summer group had worse DFS. Mean overall survival was similar in the four groups ($p=0.637$). **Conclusions:** The season is not an independent predictive factor. However, due to interaction with other factors, we think that the season of cancer diagnosis is important for cancer prognosis.

Keywords: Breast cancer - season - prognostic factors - survival

Asian Pacific J Cancer Prev, 14 (2), 743-746

Introduction

There have been many epidemiological studies of the relationship between sunlight and cancer. Some of those reported that there were inverse relationship between cancer risk and sunlight exposure (Apperly, 1941; Hanchette et al., 1992; John et al., 2004). Several studies showed that the prognosis of some cancer is related to season of diagnosis and cancer patients diagnosed on summer have a good prognosis (Lim et al., 2006; Porojnicu et al., 2007). Reduced cancer risk and mortality have been reported in prostate, colon, ovarian and non-melanoma skin cancer diagnosed in summer (Hanchette et al., 1992; Freedman et al., 2002; John et al., 2004; 2005; Porojnicu et al., 2005; 2007). The patients with cancer diagnosed in the summer and autumn have better survival when compared to those diagnosed in winter (Robsahm et al., 2004; Moan et al., 2005; Porojnicu et al., 2005). Some studies investigated relationship between prognosis and season in breast cancer patients reported significant differences. A study that evaluated breast cancer patients in two different climate region showed that patients with breast cancer living in cold climate had more estrogen and progesterone receptor expression and more high grade tumour than those living in hot and warm climate (Mutlu et

al., 2011). In according to the season of cancer diagnosis, mortality reduction was reported among breast cancer patients that were diagnosed in the autumn in England (Roychoudhuri et al., 2009). In another study reported that breast cancer patients diagnosed in July to September had poorer prognosis however that study found that the season of breast cancer diagnosis was not an independent prognostic factor in multivariate analysis (Joensuu et al., 1991). For cases diagnosed in 1980-1986, with of 12 years follow, it was reported that cumulative probability of death from breast cancer was the highest in cases diagnosed in winter and the lowest in those diagnosed in autumn and spring (Stajner, 2010). Nonetheless, for cases diagnosed other 2 periods (1973-1979 and 1987-1993), it was found that cumulative probability of death from breast cancer was similar in different seasons.

In this study, we aimed whether the season of cancer diagnosis is an independent prognostic factor and effect the disease free or overall survival in patients with breast cancer.

Materials and Methods

Totally 517 patients from Kayseri Training and Research Hospital were analysed retrospectively

¹Department of Medical Oncology, Acibadem Kayseri Hospital, ³Department of Radiation Oncology, ⁵Department of Internal Medicine, Kayseri Training And Research Hospital, ⁴Department of Hematology, Erciyes University, Kayseri, ²Department of Radiation Oncology, Mersin Government Hospital, Mersin, ⁶Department of Internal Medicine, Acibadem University, School of Medicine, Istanbul, Turkey *For correspondence: doktorhasanmutlu@gmail.com

collected from archive. The patients were divided into 4 groups according to the season of cancer diagnosis as winter (December, January, February), spring (March, April, May), summer (June, July, August) and autumn (September, October, November). The prognostic factors such as age, menopausal status, stage, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor (HER 2 or cerb B2) receptor 2 status, grade, lymphovascular invasion (LVI) and perineural invasion (PNI), disease free survival (DFS) and overall survival (OS) were investigated using Statistical Package for the Social Sciences 16.0 (SPSS16.0) statistical software.

To determine patients characteristics, descriptive statistics methods was performed. To evaluate prognostic factors between groups, chi-square tests was performed. The DFS and OS were estimated using Kaplan-Meier methods and were compared using the log-rank test. Univariate analysis was performed using Cox proportional hazards regression modeling. The parameters those their p values <0.250 were included in multivariate analysis. P <0.05 was considered to be statistically significant.

Results

Patients characteristics was given Table 1. It was not found any stastically significant differences among groups regarding age (p=0,863), menopause (p=0.373), stage (p=0.113), ER (p=0.172), PR (p=0.532), Cerb B2 (p=0.446), grade (p=0.133), LVI (p=0.208) and

PNI (p=0.523). When mean disease free survival was evaluated, we found significantly differences between groups (p=0.019). Patients whose were diagnosed in winter had best mean DFS while summer group had worst DFS. When we evaluated mean OS, we did not find any differences (p=0.637). DFS and OS were given Table 2. DFS and OS curve were shown in Figure 1 and Figure 2, respectively. After univariate analysis was performed (univariate analysis results were depicted on Table 3), season (p=0.037), stage (p=0.070), ER (p=0.000), PR

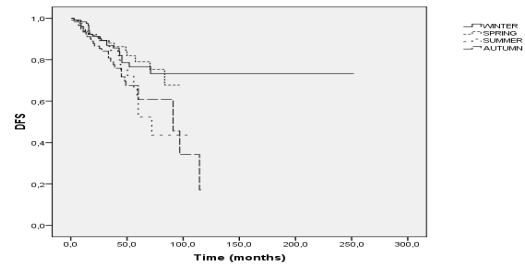


Figure 1. Disease Free Survival Curves

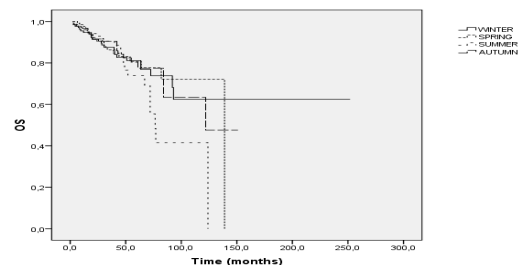


Figure 2. Overall Survival Curves

Table 1. Prognostic Factors

Parameters	Groups				p value	
	Winter (n:127)	Spring (n:126)	Summer (n:130)	Autumn (n:134)		
Age (mean)	54.6±11.6	54.1±10.7	55.4±13.1	53.6±11.6	0.863	
Menopause	Premenopausal	33.4%	30.9%	33.8%	37.3%	0.373
	Perimenopausal	11.4%	10.3%	12.3%	6.7%	
	Postmenopausal	51.0%	57.9%	52.3%	55.2%	
	Unknown	4.2%	0.9%	1.6%	0.8%	
Stage	1	7.8%	10.3%	14.6%	9.7%	0.113
	2	47.2%	42.8%	40.0%	37.3%	
	3	30.7%	36.5%	37.6%	41.0%	
	4	5.5%	0.7%	0.7%	3.7%	
	Unknown	8.8%	9.7%	7.1%	8.3%	
ER Status	Positive	59.8%	53.1%	66.9%	61.9%	0.172
	Negative	34.6%	42.8%	30.0%	35.8%	
	Unknown	5.6%	4.1%	3.1%	2.3%	
PR Status	Positive	61.4%	64.2%	63.0%	70.8%	0.532
	Negative	33.0%	31.7%	33.8%	26.8%	
	Unknown	5.6%	4.1%	3.2%	2.4%	
CerbB2 Status	Positive	25.1%	18.2%	20.0%	20.0%	0.446
	Negative	67.7%	77.7%	75.3%	77.6%	
	Unknown	7.2%	4.1%	4.7%	2.4%	
Grade	1	9.4%	13.4%	6.9%	17.1%	0.133
	2	33.0%	36.5%	47.6%	38.8%	
	3	25.9%	24.6%	23.0%	22.3%	
	Unknown	31.7%	25.5%	22.5%	21.8%	
LVI	Positive	26.7%	25.3%	29.2%	36.5%	0.208
	Negative	58.2%	59.5%	57.6%	50.0%	
	Unknown	15.1%	15.2%	13.2%	13.5%	
PNI	Positive	16.5%	19.0%	13.0%	18.6%	0.523
	Negative	66.9%	65.8%	73.0%	67.1%	
	Unknown	25.5%	15.2%	14.0%	14.3%	

* ER: Eostrogen receptor, PR: Progesteron receptor, LVI: Lymphovascular invasion, PNI: Perineural invasion

Table 2. Disease Free Survival and Overall Survival Results

Groups	Disease Free Survival		Overall Survival	
	Mean	Median	Mean	Median
Winter	89.7±13.0	Not Reached	177.9±15.2	Not Reached
Spring	80.3±3.2	Not Reached	112.6±5.6	139.0±0
Summer	72.3±5.1	72.0± 9.8	84.9±6.5	76.5±4.1
Autumn	77.4±4.8	91.0±15.8	111.4±7.9	122.0±0
P Value	0.019		0.637	

Table 3. Univariate Cox Regression Analysis Results

Parameter	B	SE	p value	Exp(β)	95,0%CI for Exp(β)	
					Lower	Upper
Season						
1	0.936	0.32	0.037	1.037	0.554	1.939
2	0.55	0.301	0.068	1.733	0.961	3.126
3	0.673	0.286	0.018	1.96	1.12	3.432
Histology	-0.056	0.253	0.824	0.945	0.576	1.551
Stage						
1	-1.917	1.1	0.081	0.147	0.017	1.269
2	-1.844	1.029	0.073	0.158	0.021	1.187
3	-1.265	1.024	0.217	0.282	0.038	2.099
Grade						
1	-0.802	0.384	0.037	0.448	0.211	0.951
2	-0.783	0.266	0.003	0.457	0.272	0.77
LVI	0.735	0.222	0.001	2.085	1.35	3.222
PNI	-0.516	0.263	0.05	0.597	0.357	1
ER	0.752	0.209	0	2.122	1.407	3.158
PR	0.663	0.211	0.002	1.941	1.283	2.937
CerBB2	-0.299	0.239	0.21	0.741	0.464	1.184

($p=0.002$), grade ($p=0.210$) and LVI ($p=0.222$) were include in multivariate analysis. In final multivariate analysis, both of ER ($p=0.001$) and LVI ($p=0.001$) were significant. For stage p values was borderline ($p=0.050$).

Discussion

In our study, the season that cancer diagnosed was evaluated whether it was independent prognostic factor in patients with breast cancer. For the others prognostic factors (age, menopausal status, stage, estrogen receptor status, progesteron receptor status, cerb B2 receptor status, grade, lymphovascular invasion and perineural invasion), there were no significant differences between groups. Despite of knowing prognostic factors were not significant different, the season when breast cancer was diagnosed has affected significantly DFS ($p=0.019$). But after univariate and multivariate analysis, the DFS has been affected only by ER and LVI in our study. The season when cancer was diagnosed was important for DFS but was not independent prognostic factor. The season can not affect directly DFS but the other factors such as sunlight exposure and vitamin D intake those effecting by season may be responsible for this reason (Garland et al., 1995; Gorham et al., 1989; John et al., 1999; Shin et al., 2002; Grant et al., 2003; Abbas et al., 2008; Mohr et al., 2008).

The 1α 25 (OH)2D₃- vitamin D receptor (VDR) complex may play a role in maintaining genomic integrity and facilitating DNA repair. Similarly some studies have shown that vitamin D₃ had a modulatory effects (up-regulation of proapoptotic genes or down-regulation of proantiptotic genes) on apoptosis related genes (Narvaez et al., 2001; Pirianov et al., 2001; Kizildag et al., 2010). In a study, it was mentioned close cooperation between VDR action and p53 tumor suppressor pathway (Patel et al., 2012). Wild type p53 induces apoptosis and mutation rate of p53 in breast cancer is approximately 30% and it was reported that the median level of 25(OH)D was lower in the P53+ group in a borderline trend (Kermani et al., 2011). Also it was previously reported that vitamin D promotes cell differentiation and 1α 25(OH)2 D₃ reduces the invasive potential of cancer cells in experimental studies and it was found that the median level of 25(OH) D was significantly higher in the patients with metastasis (Krishnan et al., 2010; Kermani et al., 2011). As mentioned above, vitamin D₃ may play a important role during occurrence of cancer. Also vitamin D₃ and sunlight exposure may have an effect in determining of prognostic factors in patients with breast cancer.

Unlike the others studies that mentioned in introduction section, we found that cancer patients diagnosed in winter had better disease free survival. When we evaluated the groups as overall survival, although winter groups had longer OS ratio than other groups, the difference did not have a statistical meaning ($p=0,637$). In this case, we need to answer: "Which date is important for prognosis? Date of diagnosis or unknowing initial time at the beginning of tumor?" Because especially sunlight exposure are much more in summer than winter. We can speculated that season at the beginning of tumor (not at the diagnosis of tumor) may be an important factor on prognosis of breast

cancer via sunlight exposure and vitamin D₃ instead of season at the diagnosis of cancer.

We think that the season of cancer diagnosed time is important as cancer prognosis. Duo to the others factors those are occurred by season, the season can effect breast cancer prognosis.

References

- Abbas S, Linseisen J, Slanger T, Kropp S, Mutschelknauss EJ (2008). Serum 25-hydroxy vitamin D and risk of postmenopausal breast cancer-results of a large case control study. *Carcinogenesis*, **29**, 93-9.
- Apperly F (1941). The relation of solar radiation to cancer mortality in North America. *Cancer Res*, **1**, 191-5.
- Freedman DM, Dosemeci M, McGlynn K (2002). Sunlight and mortality from breast, ovarian, colon, prostate, and non-melanoma skin cancer: a composite death certificate based case-control study. *Occup Environ Med*, **59**, 257-62.
- Garland FC, Garland CF, Gorham ED, Young JF (1990). Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. *Prev Med*, **19**, 614-22.
- Gorham E, Garland C, Garland F, Young JF (1989). Acid haze air pollution and breast and colon cancer in 20 Canadian cities. *Can J Public Health*, **80**, 96-100.
- Grant WB (2003). Ecologic studies of solar UV B radiation and cancer mortality rates. *Recent Results Cancer Res*, **164**, 371-7.
- Hanchette CL, Schwartz GG (1992). Geographic patterns of prostate cancer mortality—evidence for a protective effect of ultraviolet radiation. *Cancer*, **70**, 2861-9.
- Joensuu H, Toikkanen S (1991). Association between the month of diagnosis and prognosis in breast carcinoma. *Br J Cancer*, **64**, 753-6.
- John E, Schwartz G, Dreon D, Koo J (1999). Vitamin D and breast cancer risk: the NHANES I epidemiologic follow-up study, 1971-1975 to 1992. *Cancer Epidemiol Biomark Prev*, **8**, 399-406.
- John EM, Dreon DM, Koo J, Schwartz GG (2004). Residential sunlight exposure is associated with a decreased risk of prostate cancer. *J Steroid Biochem Mol Biol*, **89**, 549-52.
- John EM, Schwartz GG, Koo J, Berg JP, Dahlback A (2005). Sun exposure, vitamin D receptor gene polymorphisms, and risk of advanced prostate cancer. *Cancer Res*, **15**, 5470-9.
- Kermani IA, Kojidi HT, Gharamaleki JV, et al (2011). Association of serum level of 25 hydroxy-vitamin D with prognostic factors for breast cancer. *Asian Pac J Cancer Prev*, **12**, 1381-4.
- Kizildag S, Ates H, Kizildag S (2010). Treatment of K562 cells with 1,25-dihydroxyvitamin D₃ induces distinct alterations in the expression of apoptosis-related genes BCL2, BAX, BCLXL, and p21. *Ann Hematol*, **89**, 1-7.
- Krishnan AV, Swami S, Feldman D (2010). Vitamin D and breast cancer: inhibition of estrogen synthesis and signaling. *J Steroid Biochem Mol Biol*, **121**, 343-8.
- Lim HS, Roychoudhuri R, Peto J, et al (2006). Cancer survival is dependent on season of diagnosis and sunlight exposure. *Int J Cancer*, **119**, 1530-6.
- Moan J, Porojnicu AC, Robsahm TE, et al (2005). Solar radiation, vitamin D and survival rate of colon cancer in Norway. *J Photochem Photobiol B*, **78**, 189-93.
- Mohr SB, Garland CF, Gorham ED, Grant WB, Garland FC (2008). Relationship between low ultraviolet B irradiance and higher breast cancer risk in 107 countries. *Breast J*, **14**, 255-60.

- Mutlu H, Colak T, Ozdoğan M, Altuner TY, Akça Z (2011). The effect of seasonal differences on prognostic factors in Turkish patients with breast cancer. *Eur J Cancer Prev*, **20**, 475-7.
- Narvaez CJ, Welsh J (2001). Role of mitochondria and caspases in vitamin D-mediated apoptosis of MCF-7 breast cancer cells. *J Biol Chem*, **276**, 9101-7
- Patel JB, Patel KD, Patel SR, et al (2012). Recent candidate molecular markers: vitamin D signaling and apoptosis specific regulator of p53 (ASPP) in breast cancer. *Asian Pac J Cancer Prev*, **13**, 1727-35.
- Pirianov G, Colston KW (2001). Interaction of vitamin D analogs with signaling pathways leading to active cell death in breast cancer cells. *Steroids*, **66**, 309-18.
- Porojnicu AC, Lagunova Z, Robsahm TE, et al (2007). Changes in risk of death from breast cancer with season and latitude: sun exposure and breast cancer survival in Norway. *Breast Cancer Res Treat*, **102**, 323-8.
- Porojnicu AC, Robsahm TE, Dahlback A, et al (2007). Seasonal and geographical variations in lung cancer prognosis in Norway. Does Vitamin D from the sun play a role? *Lung Cancer*, **55**, 263-70.
- Robsahm TE, Tretli S, Dahlback A, Moan J (2004). Vitamin D3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway). *Cancer Causes Control*, **15**, 149-58
- Roychoudhuri R, Robinson D, Coupland V, Holmberg L, Møller H (2009). Season of cancer diagnosis exerts distinct effects upon short- and long-term survival. *Int J Cancer*, **124**, 2436-41.
- Shin MH, Holmes MD, Hankinson SE, et al (2002). Intake of dairy products, calcium, and vitamin D and risk of breast cancer. *J Natl Cancer Inst*, **94**, 1301-11.
- Stajner I (2010). Season of breast cancer diagnosis and probability of death from breast cancer in the United States. *Int J Cancer*, **126**, 3010-3.