RESEARCH ARTICLE

Is Season a Prognostic Factor in Breast Cancer?

Hasan Mutlu[1]*, Zeki Akca[2], Yasemin Benderli Cihan[3], Fatih Kurnaz[4], Tuncay Aslan[5], Abdülsamet Erden[5], Hediye Ugur[5], Arzu Akşahin[5], Abdullah Büyükçelik[6]

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 significantly 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

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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 ssowed that patients with breast cancer living in cold climate had more ostrogen and progesteron 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

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

collected from archieve. 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 survial (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

Table 1. Prognostic Factors

Parameters		Groups				
		Winter (n:127)	Spring (n:126)	Summer (n:130)	Autumn (n:134)	p value
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%	
	Perimenopausal	11.4%	10.3%	12.3%	6.7%	0.373
	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%	
	2	47.2%	42.8%	40.0%	37.3%	
	3	30.7%	36.5%	37.6%	41.0%	0.113
	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%	
	Negative	34.6%	42.8%	30.0%	35.8%	0.172
	Unknown	5.6%	4.1%	3.1%	2.3%	
PR Status	Positive	61.4%	64.2%	63.0%	70.8%	
	Negative	33.0%	31.7%	33.8%	26.8%	0.532
	Unknown	5.6%	4.1%	3.2%	2.4%	
CerbB2 Status	Positive	25.1%	18.2%	20.0%	20.0%	
	Negative	67.7%	77.7%	75.3%	77.6%	0.446
	Unknown	7.2%	4.1%	4.7%	2.4%	
Grade	1	9.4%	13.4%	6.9%	17.1%	
	2	33.0%	36.5%	47.6%	38.8%	0.133
	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%	
	Negative	58.2%	59.5%	57.6%	50.0%	0.208
	Unknown	15.1%	15.2%	13.2%	13.5%	
PNI	Positive	16.5%	19.0%	13.0%	18.6%	
	Negative	66.9%	65.8%	73.0%	67.1%	0.523
	Unknown	25.5%	15.2%	14.0%	14.3%	

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

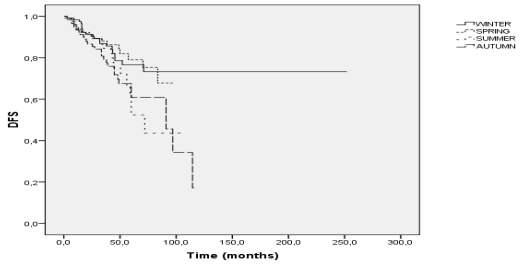

Figure 1. Disease Free Survival Curves

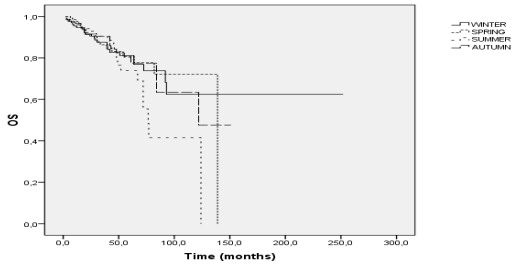

Figure 2. Overall Survival Curves

Table 2. Disease Free Survival and Overall Survival Results

Groups	Disease Free Survival Mean	Disease Free Survival Median	Overall Survival Mean	Overall Survival 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			0.037			
1	0.936	0.32	0.911	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			0.07			
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			0.007			
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 resposible 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 1 α 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; Kizildağ 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 approximetely 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 occurence 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 occured by season, the season can effect breast cancer prognosis.

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