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Original Article

The determination of breast cancer risk factors: A single centre experience

Meme kanseri risk faktörleri belirlenmesi: Tek merkez deneyimi

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Abstract

Aim: In developing countries like our country, the frequency of breast cancer is gradually increasing. There are several risk factors of breast cancer. Besides that there can be some unrevealed risk factors. The aim of our study is to reveal demographic data of patients with breast cancer followed up in our hospital and the risk factors of breast cancer.

Material and Methods: 237 female patients treated with the diagnosis of breast cancer between 2005 and 2015 were included in the study. Demographic information, familial features, type of breast cancer, histology, stage-grade, hormone receptor and human epidermal growth factor receptor 2 status of the patients were recorded from the files of the patients. The patients diagnosed with breast cancer were grouped in terms of risk factors, prognostic factors, and characteristics of breast cancer.

Results: A significant correlation was detected between early menarche and PR+ (p=0.034). It was observed that the disease occurred earlier in patients with early menarche (p=0.004). A high positive correlation was detected between triple negative breast cancer and tumor size (p=0.019 r=0.581). Breast cancer was occuring in early ages in nulliparous patients and there was a moderate positive correlation between them (p=0.024 r=0.284).

Conclusion: We revealed that breast cancer might occur in early ages in females with early menarche or both with early menarche and nulliparity. Understanding the etiopathogenesis of this common disease is necessary to determine the content of early diagnosis, treatment, and screening programs. Each society should have their unique screening programmes as distinct from Western societies.

Keywords: breast cancer; epidemiology; risk factors

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Öz

Amaç: Ülkemiz gibi gelişmekte olan ülkelerde ise meme kanseri sıklığı giderek artmaktadır. Meme kanserinin ortaya konulan birçok risk faktörleri bulunmakla birlikte, ortaya konmamış risk faktörleri de olabilir. Çalışmamızın amacı, merkezimizde takip ve tedavi edilen meme kanserli hastaların demografik verileri ve meme kanserine ait risk faktörlerini ortaya koymaktır.

Gereç ve Yöntemler: Çalışmaya 2005-2015 tarihleri arasında meme kanseri nedeni ile takip ve tedavi edilen 237 kadın hasta alındı. Hastaların demografik bilgileri, ailesel özellikleri, meme kanseri tipi, histolojisi, evresi ve derecesi, hormon reseptör ve epidermal büyüme faktör reseptör 2 durumu dosyalarından elde edilerek kaydedildi. Meme kanseri tanısı olan hastalar, kendi içinde risk faktörleri, prognostik faktörler ve meme kanseri özellikleri açısından gruplandırarak değerlendirildi.

Bulgular: Erken menarş ile progesteron reseptör pozitifliği arasında anlamlı bir ilişki bulundu (p=0,034). Erken menarş olanlarda, hastalığın daha erken ortaya çıktığı saptandı (p=0,004). TNBC ile tümör çapı ile pozitif yönde yüksek dereceli bir ilişki saptandı (p=0,019 r=0,581). Hiç doğum yapmayan hastalarda, meme kanseri daha erken yaşta ortaya çıkmaktaydı ve aralarında pozitif yönlü orta dereceli bir ilişki mevcuttu (p=0.024 r=0,284).

Sonuç: Çalışmamızda, erken menarş olan veya erken menarş olup hiç doğum yapmayan kadınlarda meme kanserinin daha erken ortaya çıkabileceği saptanmıştır. Yaygın görülen bu hastalığın etiyopatogenezini anlamak, erken teşhis, tedavi ve tarama programlarının içeriğinin belirlenmesi için gereklidir. Toplumumuzda, meme kanseri gelişiminde etkili risk faktörlerinin, batı toplumlarında olan risk faktörlerinden ne gibi farklılıklar gösterdiğini anlayabilmek ve ülkemize özgü tarama programlarını geliştirebilmek için daha büyük çaplı çalışmalara ihtiyaç vardır.

Anahtar kelimeler: meme kanseri; epidemiyoloji; risk faktörleri

Introduction

Breast cancer is the most common type of cancer among females in the world and comes after lung cancer in cancer-related deaths in females. It is the most frequent reason of cancer-related deaths in females between the ages of 15 and 49[1]. Breast cancer takes the lead at the rate of 45.9% within the type of cancer seen in females in our country. How women's health is affected in a society can be well comprehended when these rates are taken into consideration [2].

The frequency of breast cancer varies geographically worldwide. The incidence of breast cancer is greater in developed and industrialized countries. Food habits, industrialized modern life, early menarche, late delivery of a baby, oral contraceptive and hormone replacement therapy, late menopause, long life expectancy can be regarded as the reason of this situation [3]. We aimed to reveal demographic data of patients with breast cancer followed up in our hospital and the risk factors of breast cancer in our study.

Material and Methods

This study was designed as a retrospective, cross-sectional study. The Ethics Committee of our institute approved this study regarding the principles of the Declaration of Helsinki. Written informed consent was taken from subjects before taking part in the study.

The data of female patients followed up in Yildirim Beyazit Diskapi Training and Research Hospital Oncology Clinic between 2005 and 2015 were recorded retrospectively. Demographic information, familial features, type of breast cancer, histology, stage and grade, HR and HER2 status of the patients were recorded. Male patients and the patients with the diagnosis of carcinoma in situ were excluded from the study.

Data analysis was made in SPSS for Windows 21 Packet Programme. While descriptive statistics were stated as medium (min-max), categorical variables were stated as the number of case and in percentages (%) and frequency analyses were made. Whether potential risk factors have a statistically significant effect on breast cancer or not was evaluated by means of independent samples-T test, Chi-square test, and Bivariate method. 95% confidence interval of the effect of each risk factor on the development of breast cancer was calculated. The results for $p < 0.05$ were accepted as statistically significant.

Results

The data of 237 patients were recorded. 13.3±1.5 for menarche age, 48.5±4.4 for menopause age, 20.6 (±4.1) for maternal age at first delivery, 2.9±1.8 for parity, and 29.7±26.6 month for breast-feeding duration were detected. 209 (88.1%) patients gave birth but 27 (11.3%) patients. Early menarche was detected in 63 (26%) patients (age<12). Other demographic features of the patients with breast cancer were demonstrated in Table-1.

The most common histopathologic type was invasive ductal carcinoma observed in 162 (68.4%) patients. 78 (32.9%) of the cases were in Luminal A, 27 (11.4%) were in Luminal B, 84 (35.4%) were in human epidermal growth factor receptor 2 (HER2), and 48 (20.3%) were in triple-negative breast cancer (TNBC). Receptor distribution was as below: Estrogen receptor-positive (ER+) was 150 (63.3%), progesterone receptor-positive (PR+) was 114 (48.1%) and HER2+ was 85 (35.8%). Other histopathologic and hormone receptor features of the patients with breast cancer were demonstrated in Table-2.

The stages of breast cancer, operation types and other histopathologic features of the patients with breast cancer were demonstrated Table-3.

Table-1: Demographic features of the patients with breast cancer

Number	237
Age, year	54.95±13.1
Family history, n (%)	45 (19)
Breast cancer	42 (17.7)
Unknown	3 (1.3)
Menarche age, year	13.3±1.5
Maternal age at first delivery, year	20.6±4.1
Breastfeeding duration, month	29.7±26.6
Menopause age, year	48.5±4.4
Premenopausal, n (%)	89 (37.6)
Postmenopausal, n (%)	147 (62)
Menarche age, year	13.3±1.5
Early menarche, n (%)	63 (26)
Early menopause (age<40) , n (%)	5 (3.4)
Late menopause (age>55) , n (%)	11 (7.4)

Table- 3: The stages of breast cancer, operation types and histopathologic features of the patients with breast cancer

Stage, n (%)	
1 A	39 (16.5)
1 B	20 (8.4)
2 A	57 (24.1)
2 B	40 (16.9)
3 A	35 (14.8)
3 B	7 (3)
3 C	22 (9.3)
4	17 (7.2)
Metastasis Location, n (%)	
Bone	10 (4.2)
Lung	3 (1.3)
Liver	0 (0)
Others	2 (0.8)
Operation Type, n (%)	
Non-operated	6 (2.5)
MRM	203 (85.7)
BCS	28 (11.8)
Tumor size, mm	29.3±28.2
Number of removed lymph node, n	17.6±9.5
Number of metastatic lymph node, n	3.1±6.1
Perinodal involvement, n (%)	
Unknown	6 (2.5)
None available	179 (75.5)
Available	52 (21.9)
Perineural involvement, n (%)	
Unknown	5 (2.1)
None available	189 (79.7)
Available	43 (18.1)
Perivascular involvement, n (%)	
None available	176 (74.3)
Available	61 (25.7)
Grade, n (%)	
Grade 1	68 (28.7)
Grade 2	95 (40.1)
Grade 3	74 (31.2)

MRM: Modified Radical Mastectomy, BCS: Breast-conserving surgery

Table- 2: Histopathologic and hormone receptor features of the patients with breast cancer

Histology, n (%)	
Unknown	9 (3.8)
Ductal	162 (68.4)
Lobular	22 (9.3)
Medullar	8 (3.4)
Papillary	10 (4.2)
Others	26 (11)
Estrogen receptor, n (%)	
Negative	85 (35.9)
Positive	150 (63.3)
Unknown	2 (0.8)
Progesterone receptor, n (%)	
Negative	113 (47.7)
Positive	113 (47.7)
Unknown	11 (4.6)
HER2, n (%)	
Negative	146 (61.6)
Positive	82 (34.6)
FISH positive	4 (1.7)
Unknown	5 (2.1)
Surrogate definitions of intrinsic subtypes of breast cancer , n (%)	
Luminal A	78 (32.9)
Luminal B	27 (11.4)
HER2 +	84 (35.4)
TNBC	48 (20.3)

FISH: Fluorescence in situ hybridization HER2: human epidermal growth factor receptor 2 TNBC: triple-negative breast cancer

The patients were separated into two groups as below and above age 40. There were 34 patients under the age of 40 (age<40). The distribution for the patients under and above age 40 was as below respectively: 32.4% (11) / 33.0% (67) in Luminal A, 11.8% (4) / 11.3% (23) in Luminal B, and 26.5% (9) / 36.9% (75) in HER2+. TNBC was found as 29.4% (10) / 18.7% (48) respectively. Receptor positivity was found as ER+ 64.7% (22) /63.1% (128), PR+ 38.2% (13) /47.3% (101), HER2+ 26.5% (9) / 36.9% (76), TNBC 29.4% (10) / 16.7% (44). While perinodal involvement was found as 36.7% (11) / 21.7% (41), perivascular involvement was found as 38.2% (13) / 21.7% (44) respectively for the patients below and above age 40. A significant dominance was observed in ER+ and PR+ above age 40 (p=0.046, r=0.211). Histologic grade was found out worse with increasing age. There was not a significant difference between two groups in terms of family history and histologic grade (p=0.976). The rate of incidence of TNBC under age 40 was high.

A positive high correlation was observed between smoking and tumor size (p=0.0444, r=0.518).

A statistically significant difference was not found out in terms of tumor stage when compared the patients with a family history and not. Tumor size of the patients with a family history was found out bigger (p=0.004, r=0.694). HER2 showed an increase negatively (70.3%). TNBC was more common (r=0.132).

No statistically significant correlation was found out among early menarch and tumor stage, tumor size and grade, perinodal, perineural, and perivascular involvement, ER+ and HER2+. A significant correlation was detected in PR+ (p=0.034). The occurence of the disease was early in patients with early menarche with a 95% confidence level (p=0.004).

A statistically significant correlation was not found out in terms of tumor stage, tumor type, tumor grade, perinodal, perineural, and perivascular involvement when compared the patients giving birth to the nulliparous ones. No correlation was detected between nulliparity and HR+ and HER2+. A positive high correlation was detected between nulliparous patients and tumor size (r=0.492). Breast cancer was occuring in early ages in nulliparous patients and there was a moderate positive correlation between them (p=0.024 r=0.284).

No significant correlation was found out among advanced maternal age at first delivery (age >30) and tumor stage, perineural - perivascular involvement, histologic grade, type of breast cancer, HR+ and HER2+. A significant correlation was detected between advanced maternal age at first delivery and tumor size (p=0.0442 r=0.509). Tumor size was increasing in direct proportion to advanced maternal age at first delivery (p=0.016 r=0.163).

There was also no significant correlation detected between breastfeeding duration and tumor stage. Perivascular involvement rates were (48/193) 21.8% and (9/27) 33.3% respectively when compared the mothers who did not breast-feed to the breastfeeding ones. A low positive correlation with a 90% confidence level was observed between perinodal involvement and the patients who did not breast-feed. No significant correlation was detected between two groups in terms of tumor type, histologic grade, HR+ and HER2+. A moderate positive correlation was observed between the patients who did not breast-feed and show HER2 over expression (r=0.156).

Based on 50 as age limit, 61 patients within 147 patients diagnosed with postmenopausal went through menopause after the age of 50. A moderate positive correlation between these patients and tumor stage, and a positive correlation with a 90% confidence level between these patients and perinodal involvement were also detected. A moderate positive correlation was also observed between them and ER+ and PR+, which were 48.4% and 35.9% respectively (p=0.049 r=0.190, p=0.040 r=0.187) significant correlation was not detected among tumor type, histologic grade, perivascular involvement, tumor size, and HER2+.

We analysed TNBCs between each other due to the fact that they differ from the other types and 48 (20.3%) patients were with TNBC. While a significant correlation was not detected among tumor stage and perineural, perinodal and perivascular involvement and histologic grade, a high positive correlation was found out with tumor size (p=0.019 r=0.581).

Discussion

In our study, we revealed that breast cancer might occur in early ages in females with early menarche or both with early menarche and nulliparity. Demographic data of the patients diagnosed with breast cancer in our hospital were substantially compatible with literature.

That having a family history is one of the factors in the development of breast cancer [4]. A meta-analysis in which 52 epidemiologic studies were analysed revealed that 12% of the patients had one and 1% of the patients had one or more fam-

ily member with breast cancer [5]. We revealed in our study that 42 patients (17.7%) had a first degree relative with breast cancer. On the other hand, we detected that tumor size was bigger in the patients with a family history. A low positive correlation between family history and grade distribution was also detected and HER2 showed an increase negatively (70.3%). This correlation may depend on genetic differences but there is no knowledge related to this finding in literature.

That exposing to endogenous, estrogen and progesterone substantially increases breast cancer risk [5, 6]. Menarche age was 13.1±1.09 in 13,665 healthy females in a study conducted by Vicdan et al [7]. In accordance with the literature, mean menarche age was 13.3±1.5. While there was no significant correlation among early menarche and tumor stage, tumor size, perinodal, perineural and perivascular involvement, tumor grade, ER+ and HER2+, a significant correlation was found with PR+. A meta-analysis conducted by Abdulkareem, 10 studies within 19 showed that there was a positive correlation between early menarche and HR+ breast cancer [8]. We revealed a significant correlation between early menarche and PR+ not ER+ in our study. We detected that breast cancer occurs earlier in patients with early menarche. The correlation between early menarche and breast cancer, particularly HR+, is high but there is no information in literature in this direction. As a consequence, the screening programmes of the patients with breast cancer should be initiated earlier.

Compared the nulliparous patients to the ones giving birth, there was no significant correlation among tumor stage, perinodal, perineural and perivascular involvement, tumor grade, HR+ and HER2+. In the analysis of 36 studies conducted by Anderson et al., a high positive correlation was detected between nulliparity and HR+ breast cancer [9]. The reason why we did not acquire any data in this direction can be derived from the limited nulliparous patients in our study within the whole population. A high positive correlation was observed between nulliparity and tumor size. We found out that breast cancer occurs in early ages in the nulliparous patients and the ones with early menarche. There is no data in this direction in the studies. This situation can be related to the long-term estrogen exposition derived from early menarche and nulliparity.

No significant correlation was found out between advanced maternal age at first delivery, HR+ and HER2+. We detected that the tumor size of the patients having advanced maternal age was bigger and it increased in proportion to the age. We also determined that there is a correlation between advanced maternal age and perinodal involvement. According to a study of Bao et al., advanced maternal age was associated with both ER+/PR+ and ER-/PR- [10]. Besides, another study revealed that there was a positive correlation between advanced maternal age and HER2 breast cancer [11]. In accordance with literature, there was no correlation between advanced maternal age and HR+ and HER2 in our study. Perhaps this was because we had a small extent patient population. We could also add ethnic and genetic factors.

A significant correlation was not detected between the patients who did not breast-feed and HR+ and HER2+. The rate of the patients not showing HER2 over expression within the patients who did not breast-feed was 82.1%. According to a study conducted in China, a negative correlation was detected between breastfeeding duration and HER2 breast cancer [12]. In consequence of our study, similarly, we determined a moderate negative correlation between breastfeeding duration and HER2+. In spite of the data revealing that long-term breastfeeding decreases the development of breast cancer, it is not obvious whether breastfeeding duration has an effect on the development of breast cancer.

Mean menopause age was 48.5±4.4. It was 51 in western societies [13]. A study conducted by Sahin et al. revealed that mean menopause age for 729 females was 47±4.8 [14]. We revealed similar results in our study. It indicates that females in our society go through early menopause compared to the western societies. Due to the fact that the number of the patients in our study who were above 55 years of age was limited, we separated our patients into two groups considering late menopause age as above 50 (age>50), which was above 55 in western societies (age>55). A positive correlation between the patients going through late menopause and tumor stage and perinodal involvement was detected. ER+ in 48.4% and PR+ in 35.9% of the patients were determined and a significant correlation was found out. But there was no significant correlation with HER2+. Each one-year delay in menopause age causes an increase in breast cancer up to 3% [15]. In most of the studies, a positive correlation was determined between HER2 breast cancer and late menopause age. Similar results were detected

in 3 studies in literature review conducted by Anderson et al. [9]. We detected a significant correlation between related variables in a similar manner to literature. We also determined a significant correlation between perinodal involvement and tumor stage. This situation indicates that patients with late menopause are diagnosed at an advanced stage.

We also analysed TNBC because of the fact that it differs from the other types and detected that 48 (20.3%) patients were with TNBC. The mean age was 55.7±15.4 and 26 (54%) patients were under the age of 60. Between 10% and 20% of patients with breast cancer were with triple negative phenotype (TNBC) in different studies [16, 17]. TNBC was detected in 29.3% patients with family history of breast cancer and 16.2% patients without a family history. That detecting a high rate in patients with family history was also accordant with literature [18]. Besides that a significant correlation was detected between TNBC and tumor size. In a study conducted by Bauer et al., 92,358 patients were analysed in terms of TNBC and 6370 (12.5%) of them were detected with it. Median tumor size was 22 mm in the group of TNBC and 17 mm in the other group. The cancer cells were poorly differentiated or undifferentiated in 76% of TNBC cases and 28% in the other group. The stages of breast cancer differed in two groups based on the time of diagnosis. The patients in TNBC group were diagnosed at the advanced stage compared to the other one [19]. TNBC was at the rate of 20.3% in our patient group in accordance with literature and the mean age for TNBC was 55. Median tumor size of the patients with TNBC in our study was 34 mm in the first group and 28 mm in the other one. There was no significant correlation between histologic grade and TNBC. This situation may be derived from the limited patient included our study and/or multiple risk factors, which are effective on the development of breast cancer.

We revealed that breast cancer might occur in early ages in females with early menarche or both with early menarche and nulliparity. Understanding the etiopathogenesis of this common disease is necessary to determine the content of early diagnosis, treatment, and screening programs. Breast cancer screening for the patients with early menarche should be initiated in early ages for the diagnosis and treatment of the disease. Extended studies are required to comprehend how risk factors of breast cancer in our society differentiate from the others in western societies and to develop screening programmes.

Declaration of conflict of interest

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