RESEARCH COMMUNICATION

Relationships Between Epidemiological Features and Tumor Characteristics of Breast Cancer

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Abstract

Objectives. Breast cancer is a histological, morphological and molecular heterogenous disease. Like clinical outcomes and prognoses of different subtypes, etiologies might also be different. Therefore, epidemiologic risk factors like sociologic, demographic, antropometric, reproductive, and menstrual factors can be considered as an entity reflected in tumor features. This study was planned to explore the relation between well known risk factors of breast cancer and histological and molecular features of the tumor. Materials and Methods. Epidemiologic data for 250 breast cancer patients followed-up by our clinic and 250 healthy individuals without any diagnosis of malignancy were obtained. The data displaying a relation to breast cancer are age, height, weight, body mass index (BMI), place of birth and province, educational level, menstrual status, age of menarche and menopause, number of births, age at first childbirth, family history of breast cancer, history of smoking and hormone treatment, mammographic screening, and presence of benign lesions. The tumor characteristics of patients in the breast cancer group were recorded. Results. Advanced age, nulliparity, low educational level, irregular mammographic screening, early menarche and late menopause, and high BMI in postmenopausal period were found to be related to increased breast cancer risk. Striking results in terms of the relation between epidemiological factors and tumor features were the early diagnosis of breast cancer in patients with regular mammographic screening. Tumor size was decreased with increased age and increased with increased BMI. Advanced age, prolonged lactation, increased number of births, and high education level were found to decrease axillary involvement. Conclusions. Multiparity still continues to be the strongest protective factor against breast cancer in our society. The decrease in menarche age may be an early sign of the increased breast cancer incidence. Women should be informed about the relation between postmenopausal obesity and breast cancer and encouraged to attend physical activity and exercise programmes. Regular physical examination and mammographic screening are protective against breast cancer.

Keywords: Breast cancer- epidemiological features - tumor characteristics

Asian Pacific J Cancer Prev, **12**, 3375-3380

Introduction

Breast cancer is a histological, morphological and molecular heterogenous disease. Like clinical outcomes and prognosis of different subtypes, etiologies might also be different. With the determination of the age, related incidence changes with histological type (Anderson et al., 2004), stage and grade (Anderson et al., 2005) and receptor status (Yasui et al., 1999; Anderson et al., 2002) and with the introduction of incidence changes of molecular subtypes of breast cancer according to race differences (Ihemelandu et al., 2007), the thought that molecular and histological subtypes are also different entities in etiological aspects gained dominance. Epidemiological risk factors might designate tumor characteristics and the prognosis of breast cancer is a heterogenous disease with respect to etiology. There is a relation between histological and molecular features of breast cancer in a society and sociological, demographical, antropometric, reproductive, menstrual factors and breast cancer-related other customs (like lactation, smoking). As these factors are considered to be considerably different between communities, correct display of these factors for each community may be the basis for correct screening and prevention programmes.

Life style and cultural customs are changing rapidly in our country. Parallel to this, epidemiological factors, proven to be related to breast cancer, like number of births, age at first birth, and lactation are also changing. The knowledge about the effect of impetuous changes in life style and cultural customs on tumor characteristics will be helpful to anticipate the behaviour pattern of breast cancer. This study is planned to explore the relation between well known risk factors of breast cancer and histological and molecular features of the tumor.

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Materials and Methods

The epidemologic data of 250 breast cancer patients followed-up by our clinic and 250 healthy individuals without any diagnosis of malignancy were obtained. The data are collected from women who agreed to attend the study with face-to-face questions and answers.

The data displaying a relation to breast cancer are age, height, weight, body mass index (BMI), place of birth and province, educational level, menstrual status, age of menarche and menopause, number of births, age at first childbirth, family history of breast cancer, history of smoking and hormone treatment, mammographic screening and presence of benign lesions.

BMI was calculated as kg/m^2. Six different geographical areas of Turkey are predicated on the place of birth and province. Education level is classified as analphabet, primary, secondary, high school, and university. Women with no menstruation for more than one year and less than one year were accepted as menopausal and perimenopausal, respectively. Premenopausal women are also classified into two as regular and irregular menstruation periods. Lactation period is calculated as the sum of lactation periods of all children. Family history is defined as the presence of breast cancer in first and second degree relatives or breast cancer in more than one person in the family. Hormone replacement therapy is grouped as estrogen containing, progesteron containing and combined drugs, and the duration of usage is recorded. Smoking is calculated as package/year. The frequency of mammography in screened women is also recorded.

The tumor features of patients in the breast cancer group are recorded. These are histologic type, tumor size, stage, nuclear grade, axillary lymph node involvement and hormone and Her2 neu receptor status. TNM staging is used for grouping and tumor size is grouped as T1 to T4 and axillary involvement as N0 to N3. ER (+) and/or PR(+), HER2(-) tumors were included in Luminal A group, ER (+) and/or PR(+), HER2(+) tumors in Luminal B group, ER (-), PR(-), HER2(-) tumors in basal-like group, ER (-), PR(-), HER2(+) tumors in Her2 over expressing tumors group. None of the women with proven other types of cancer was included in the control group. The women with cancer other than breast cancer and the ones with *in situ* breast carcinoma were not included in the breast cancer group. The women with incomplete questionnaires and/or pathological information were excluded during evaluation.

Statistical analysis

Binary logistic regression was used to estimate adjusted odds ratios (ORs) and corresponding 95% confidence intervals as well as p values based on the case-control data. The model considered all the risk factors simultaneously. The model included continuous variables for age at menarche, duration of breastfeeding, number of full-term births, age at first full-term birth, BMI, and age at menopause and dummy variables for HRT use (any use of HRT versus never), family history (first degree, second degree, none), nulliparity, mammography screening, and menopausal status. The model also included dummy variables for the confounding factors of education and geographical region of birth. The risk factors that are significantly associated with the breast cancer occurence in the Turkish population were identified through this analysis.

Polytomous logistic regression was used to estimate adjusted odds ratios and corresponding 95% confidence intervals as well as p values based on the case-only data. This analysis was carried out to determine the association between the risk factors and each individual tumor characteristic. The continuous and dummy variables considered above are used to represent the risk factors in the polytomous models. This method allowed us to determine the effect of the risk factors on different specific tumor characteristics.

A two-stage polytomous logistic regression model was used to estimate the adjusted ORs, 95% confidence intervals, and p values for the risk factors while taking into account the interrelation between different tumor characteristics. This analysis allowed us to explain the etiologic heterogeneity of one tumor characteristic holding the other characteristics constant.

Table 1. Reproductive Characteristics of Patient and Control Groups

	Breast cancer (n:250)	Control (n:250)	P value
Age	51.7	46.3	<0.0001
Menarche age	13.1	13.9	0.042
Age at first birth	21.9	21.6	0.613
Lactation duration	27.5	23.1	0.114
Number of births	2.6	2.1	0.0206
Age at menapouse	47.7	45.7	0.0432
BMI (premenapousal)	27.1	26.5	0.122
BMI (postmenapousal)	29.2	27.2	0.002

Results

General characteristics of patients and control groups

The mean age of patients with breast cancer and control group is 51.7 and 46.3, respectively. While mean menarche age is 13.1, age at first birth is 21.9, menopause age is 47.7 in the breast cancer group, these numbers in the control group are 13.9, 21.6 and 45.7, respectively. While the duration of lactation in the breast cancer group is 27.5 months, it is 23.1 months in the control group. The mean number of births in the breast cancer and control groups is 2.6 and 2.1, respectively (Tables 1 and 2).

Factors increasing breast cancer risk

Age was found as a risk factor for breast cancer. Breast cancer risk was increasing with increased age. The risk of breast cancer was higher in women not screened and examined regularly. Regular mammographic screening was found as a protective factor for breast cancer. In accordance with this, the breast cancer risk was decreased with high educational level. The probability of breast cancer for a woman who gave a birth to a child in comparison to a nulliporous woman is decreased 80% approximately. The age at menarche and menopause were also other factors affecting the incidence of breast cancer. The incidence of

Table 2. Specific Characteristics of Patient and Control Groups

		Breast cancer	Control	P value
HRT	Yes	19%	21%	0.19
	No	81%	79%	0.17
Family history	No	76%	78%	0.96
	First degree	11%	10%	0.75
	Second degree	3%	2%	0.4
Mammography	No	62%	39%	0.01
	Regular	14%	33%	0.01
	Irregular	24%	28%	0.11
Education	No	15.6%	6%	0.008
	Primary	44.8%	40%	0.865
	Secondary	12.4%	12.8%	0.651
	High	11.6%	23.2%	0.006
	University	15.2%	18.4%	0.4
Region	Inner Anatolia	58.4%	66%	0.122
	East/Southeast Anatolia	13.6%	10.4%	0.319
	Blacksea	17.2%	14%	0.36
	Aegean/Mediterannean	10,4%	10%	0.34

HRT, Hormone replacement therapy

breast cancer was increasing with early menarche and late menopause. High BMI in postmenopausal women was a factor increasing the incidence of breast cancer. The relation between the incidence of breast cancer and BMI could not be demonstrated in premenopausal women.

Relationship between tumor characteristics and epidemiological factors

Tumor size: The tumor was able to be diagnosed at earlier stages in women screened with regular mammography. While the tumor size decreased with advanced age, it was increased with increased BMI.

Grade: While low grade tumors (G1) were more frequent in women screened with regular mammography, high grade tumors (G2-3) were more frequent in women not screened with mammography.

Tumor type: The incidence of invasive lobular carcinoma was higher in women taking hormone replacement theraphy (HRT). The incidence of invasive ductal carcinoma (IDC) was decreasing with prolonged lactation. Lobular and tubular type carcinomas were higher in older women and in women living in the eastern and south-eastern parts of Anatolia.

Axillary nodal involvement: Advanced age, prolonged lactation, high number of births and high education level were found to be the factors decreasing axillary involvement.

These factors are also increasing N1 chance of axillary involvement against N2 and N3 in women with axillary involvement. The chance of axillary involvement was greater in women with high BMI.

ER / PR: ER positivity was higher in women taking HRT, with early menarche and with high BMI in the postmenopausal period. ER positivity was less frequent in women with breast cancer history in their families. The incidence of ER and PR-positive tumors was decreasing with early menopause.

Her2: Her2 positivity was more frequent in women with high BMI in the postmenopausal period, with prolonged lactation and taking HRT.

Table 3. Relationships Between Tumor Characteristics and Epidemiological Factors

	Odds ratio	95% CI	P value
Tumor size			
Age	0.942	0.903-0.982	0.0050
Regular MG	0.396	0.142-0.905	0.0468
BMI	1.096	0.858-0.989	0.0411
Grade			
Regular MG	0.296	0.126-0.693	0.0050
IDC			
Lactation	0.267	0.782-0.986	0.0457
ILC			
HRT	1.134	1.243-2.223	0.0032
ILC-ITC			
Age	1.027	1.032-1.864	0.05
East-S.East	1.021	1.028-1.654	0.05
Age	0.957	0.924-0.992	0.0159
Lactation	0.974	0.921-0.967	0.0457
Axillary Involvement			
Number of births	0.714	0.529-0.962	0.027
Education	0.688	0.52-0.91	0.087
BMI	1.141	1.001-1.244	0.0497
HRT	1.009	1.273-1.446	0.047
Age at menarche	0.633	0.289-0.765	0.035
ER(+)			
BMI (postmenapousal)	1.144	1.0631.746	0.016
Family history	0.288	0.354-0.916	0.024
Age at menapouse	1.263	1.032-1.456	0.0456
PR(+)			
Age at menapouse	1.132	1.784-1.998	0.0398
BMI (postmenapousal)	1.053	1.095-1.756	0.0432
Her2(+)			
HRT	2.309	1.017-5.243	0.0456
Lactation	1.016	1.099-1.344	0.0486
Luminal B			
BMI (postmenapousal)	1.245	1.023-1.456	0.036
Lactation	1.233	1.383-1.965	0.0465
Triple (-)			
Age at menapouse	0.334	0.323-0.932	0.021
Age at menarche	1.29	1.023-1.589	0.003
Age	0.027	0.032-0.879	0.002

HRT, Hormone replacement theraphy; MG, Mammograhy; IDC, Invasive ductal carcinoma; ILC, Invasive lobular carcinoma; ITC, Invasive tubular carcinoma

Molecular subtype: Luminal B subtype was more frequent in women with prolonged lactation and high BMI in the postmenopausal period. Basal-like (triple negative) type was more frequent in younger women with delayed menarche and early menopause (Table 3).

Discussion

Prognostic factors are described as the tumor and patient-related measurable data gathering information about expected results in a population with similar descriptive features.

Risk factors affect prognostic factors and some of the risk factors are preventable factors. Diversity and frequency of preventable risk factors change from country to country. The introduction of their own results for each country provides both a correct direction for that

population and makes a contribution to describe small-risk groups for prognostic purposes.

Age is a well known and the most important risk factor for breast cancer and breast cancer is accepted as a disease of advanced age. It has been shown in Surveillance, Epidemiology and End Results (SEER) data of the National Cancer Institute that, while the incidence of tumors with poor prognostic features increases till age 50 and stands still, the tumors with good prognostic features increase with age (Anderson et al., 2005). The tumors diagnosed in advanced age with no reproductive functions can be expected to have good prognostic features. Axillary nodal involvement gives correct information about interaction between tumor aggressiveness and host defence and is the most important prognostic indicator.

Tumor size is the most important parameter for recurrence risk in women with no axillary involvement. Small tumors with no axillary involvement can be expected in breast cancers diagnosed in advanced ages. Anderson et al. show that the incidence of lobular and tubular carcinomas increases rapidly until 50 years of age and then decreases slowly (Anderson et al., 2004).

Early menarche gives rise to increased hormone levels and early proliferation of breast ductus cells. Therefore, early menarche is a risk factor for breast cancer (Bernstein et al., 1998; Key et al., 2001; Li et al., 2003). The age of menarche is especially important for breast cancer cases diagnosed in the premenopousal period and cancer risk decreases 7% with every one year increase of menarche age (Clavel-Chapelon et al., 2002). The tumors are diagnosed at earlier ages and the chance of hormone positivity is increased with high endogenous estrogen and progesteron levels for a long period of time (Enger et al., 2000; Althuis et al., 2004). In our series the mean age of menarche was 13.5 years. We observed that the age of menarche is decreased when compared to a series of patients by Kuru et al (Kuru et al., 2002), in 2002. This may be explained with changed nutritional practise and decreased physical activity. Decreased menarche age might be the early sign of an increase in breast cancer incidence in the future. Like early menarche, delayed menopause also brings high endogenous estrogen and progesteron levels for a longer period of time. But at this time, as there is no early proliferation of breast ductus cells, the increase of breast cancer risk is not as high as with early menarche.

It is well known that basal-like cancers are more frequent in patients under the age of 35. The second peak of these tumors is in between 51 and 65 years of age (Ihemelandu et al., 2007). The factors increasing the risk factors for hormone receptor negativity might also increease the risk of triple negativity. The most risky group of patients for triple negative tumors can be described as young patients with early menarche and late menopause.

The differentiation of breast cancer cells during gestation makes these cells more insensitive to carcinogenic insults. The risk of breast cancer decreases with early age at first birth. Therefore, while young age at first birth decreases breast cancer risk both in early and advanced ages, the preventive effect of the number of births is seen in breast cancers diagnosed in advanced ages. Every birth decreases the risk of breast cancer both in early and advanced ages by 3% and 12% respectively (Clavel-Chapelon et al., 2002). Beaber et al. (2008) reported that the risk of breast cancer in porous women is 50% less in comparison to nulliporous women. It has been shown that five or more births are more protective than one to two births (Kuru et al., 2002). The protective effect of multiparity and young age at first birth might increase the chance of having tumors with better prognostic features. The direct relationship between the age at first birth and tumor size has been described (García-Closas et al., 2006). In our study, multiparity is shown to be the most powerful protective factor against breast cancer with better tumor characteristics.

Like pregnancy, lactation regulates differentiation of breast epithelium and prevents breast epithelium against carcinogenic insults. At the same time, ovarian functions are supressed and endogenous estrogen and progesteron levels stay decreased during lactation (Bernstein et al., 1998; Key et al., 2001). The studies about the preventive effect of lactation against breast cancer have shown that a longer lactation period is needed for this preventive effect (Ramon et al.,1996; Kuru et al., 2002; García-Closas et al., 2006). Li et al. reported that less than 2-3 years of lactation is not protective (Li et al., 2003). It has been shown in many studies that while endogenous estrogen and progesterone levels are related to IDC, exogenous hormones are related to ILC (Li et al., 2003; Li et al., 2006; Beaber et al., 2008). Lactation and parity are protective for IDC by altering endogenous hormone levels, but are not effective on ILC risk. In our study, lactation is not found to be effective on the incidence of breast carcinoma. This issue of fact might be related to the decrease of lactation periods in our country. Although there is a need for longer periods of lactation for its preventive effect on breast cancer, like parity, lactation is also encountered as a factor increasing the chance of axillary negative breast cancer.

Estrogen and progesterone induce proliferation of breast epithelium cells and show a promoter effect on carcinogenesis. Estrogen receptor is a nuclear receptor and when connected to estrogen, cell division occurs with DNA and protein synthesis. Progesterone receptor also binds to progesterone in a similar fashion (King et al., 1984; Wittliff et al., 1984; Rayter et al., 1991).

Her2 accelerates tumor growth by aromatase upregulation, activation of growth factor pathways, and mutual interaction of hormonal mechanisms (Howe et al., 2005). The primary source of endogenous estrogen in premenopausal women is ovaries. Endogenous hormone levels of the obese premenopousal women are less than the levels of women with normal BMI (Potischman et al., 1996). The transformation of androstenodion to estron by aromatases in fat tissue is high in obese postmenopausal women. Therefore, endogenous estrogen levels stay high for a longer period of time. This issue of fact may explain the effect of postmenopausal obesity on cancer incidence.

Cumulative (relative) low endogenous hormone levels in premenopausal obese women may give rise to upregulation of ER and PR levels in normal breast epithelium (Sherman et al., 2007). In these women, an inadequate decrease of endogenous hormone levels in the

postmenopausal period may explain the high frequency of HR positive tumors. There are many studies displaying the interaction between obesity in the postmenopausal period and HR positive breast tumors (Potter et al., 1995; Mannisto et al., 1996; Honda et al., 1999; Enger et al., 2000). What is still uncertain is whether high standing endogenous estrogen levels induce estrogen receptors or progression of HR positive lesions.

Postmenopausal obesity also increases Her2 positivity (Sherman et al., 2007). Therefore, the risk of Luminal B (Her2 (+)/ HR(+)) type tumors is high in these patients.

The difficulty of assessment of the lesions with physical and radiological examinations in obese women may give rise to the diagnosis of greater tumors with advanced stages. BMI is one of the patient-related and amendable risk factors of breast cancer. Physical activity might be preventive for breast cancer by both regulating ovulatory cycles in the premenopausal period (Gammon et al., 1998) and decreasing BMI in the postmenopausal period (Friedenreich et al., 1998).

Hormone replacement therapy (HRT) is the most easily preventable risk factor among the risk factors of breast cancer and therefore many studies on this subject have been published (Li et al., 2000; Daling et al., 2002; Newcomb et al., 2002). The increased incidence of ILC in comparison with IDC in the last 30 years is explained with increased use of HRT (Levi et al., 2003; Li et al., 2003). It is well known that lobular cancer is more hormone sensitive than ductal carcinoma. Exogenous estrogen and progesteron have the potential for acceleration of cell cycle and induction of uneuploidy with genotoxic potential (Yang et al., 2007). In general, combined preparations are found to be more risky for breast carcinoma (Rosenberg et al., 2006). It has been shown that oral contraceptives (OC) should be used for at least 5 years in order to have an increased lobular carcinoma risk (Ahmed et al., 1996; Newcomer et al., 2003). Family and benign breast disease history are the other proven risk factors for ILC (Rosenberg et al., 2006). It is known that tendency for bilaterality of ILC is high and genetics play an important role for its etiopathogenesis. The family history is more important for premenopausal women. The prevalence of HRT and OC use is not high in our country and their relationship with breast cancer incidence could not be displayed in our study. Further studies are needed to explore the relation between Her2 and endogenous and exogenous hormones.

Epidemiological studies from Europe and the U.S.A. have shown that breast cancer is more prevalent among women with a high education level (Sherman et al., 2007). This occurence is explained with racial and familial predisposition. Still, there is a direct relation between mammographic screening and breast cancer incidence. This direct relation is linked to an increased number of mammographies used for high risk lesions and educated women. This situation seems to be completely different in our country. High educational level and regular mammographic screening are found to be protective against breast cancer. In our opinion, the awareness about breast cancer is higher among educated women. These women adhere to screening programmes more closely, know self- examination procedures, and reach medical services more easily. In recent years, with increased and simplified percutaneous biopsy techniques, atypical high-risk lesions are diagnosed and treated before they are transformed into cancer in women screened with regular mammography.

In conclusion, multiparity still continues to be the strongest potective factor against breast cancer in our society. The decrease in menarche age may be an early sign of the increased breast cancer incidence in the future. Women should be informed about the relation between postmenopausal obesity and breast cancer and encouraged to attend physical activity and exercise programmes. Regular physical examination and mammographic screening are protective against breast cancer. Education campaigns and disclosure about breast cancer should be

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