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ORIGINAL ARTICLE

Correlation of educational status and clinicopathological characteristics of breast cancer: a single center experience

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Summary

Purpose: *Educational status may be an important parameter in assessing breast cancer risk and prognosis. The purpose of this study was to investigate the correlation between the level of education and clinicopathological characteristics of breast cancer, including tumor grade, HER-2 and estrogen receptor (ER) status, tumor size, axillary lymph node involvement and metastasis.*

Methods: *The study included 1800 women who were diagnosed with invasive breast cancer during 2005-2013 at Hacettepe University Cancer Institute. Patients were divided into three groups according to their educational status at the time of diagnosis as follows: low (illiterate and elementary school, 5 years or less of education), medium (secondary school and upper secondary school, 6-12 years of education) and high (university level, more than 12 years of education). The associations between educational status and clinicopathologic features of breast cancer at the time of diagnosis were evaluated.*

Results: *In all patient, a significant relationship was found between educational status and T stages (p<0.0001). Patients with higher educational levels were reported to have smaller tumor size regardless to their age and were less likely to have axillary lymph node involvement (p=0.001) or metastasis (p=0.001). A significant correlation was found between educational status and ER positivity in patients over 50 years of age (p=0.03). When the patients of all ages were evaluated, no statistically significant correlation was shown (p=0.27) between educational status and ER positivity. A significant relationship was found between educational status and HER-2 status (p=0.003), regardless of the patients' age. HER-2 positivity increased in patients with low educational status, however this significance was lost in patients over the age of 50 (p=0.1).*

Conclusion: *The relationship between educational status and biological factors in breast cancer are not conclusive as yet, but this particular study revealed that educational status played a major influence in each of the five breast cancer prognostic factors: ER status, HER-2 status, tumor size, lymph node status and metastasis.*

Key words: *biological factors, breast cancer, educational status*

Introduction

Breast cancer is the most frequently seen form of cancer that affects women worldwide. In addition to several other risk factors, high socioeconomic status (SES) is known to increase the incidence of breast cancer [1]. SES consists of factors such as low annual family income, low education level and limited health care access. Education is of paramount importance among these factors because it seems to affect biological and reproductive behaviors, as well as other factors such as age at first birth, parity, physical activity, diet and participation in cancer screening pro-

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grams [2-5]. In conjunction with having an effect on breast cancer development, education may also affect cancer survival by influencing the stage of cancer at the time of diagnosis, the type of cancer treatment being offered, compliance to treatment, psychosocial support and postmenopausal hormone therapy [6-9].

In several studies investigating the relationship between SES and breast cancer, a strong correlation between the level of education and breast cancer has been shown. Patients with low SES are generally considered to have low educational levels, be relatively poor, live in rural areas and have poor prognosis [10-12]. Up until now, there have only been a few epidemiological studies that have investigated the relationship between educational level and susceptibility to breast cancer [6,13,14].

Previous studies from the United States, Canada and Israel demonstrated a correlation between a high level of education and breast cancer by showing a significant increase in breast cancer risk in women with an education of 12 years or more [15,16]. Various other studies have indicated that there is a positive correlation between educational status and breast cancer survival as well [14,17]. However, inconsistent results from these studies made it obvious that the correlation is more multi-factorial than meets the eye [18,19]. That being said, the level of education may still be an important parameter to assess breast cancer risk and mortality. The correlation between clinical and biological features of breast cancer and educational level has been investigated by only a few studies thus far, which is why the main purpose of this study was to investigate the correlation between the level of education and the histological subtype of breast cancer, grade, tumor size, axillary lymph node involvement, metastasis, HER-2 and ER status.

Methods

Study and subjects

This study was conducted at the Hacettepe Cancer Institute and included 1800 women diagnosed with invasive breast cancer during 2005–2014. A retrospective cross-sectional study was done, collecting patient information from 2013 to 2014. The association between educational status and clinicopathologic features of breast cancer at the time of diagnosis were evaluated during this time. Patients whose information was not adequate in regards to educational status and clinicopatologic characteristics were excluded from the present analysis. Educational information was collected by trained medical social workers at the time of patient registration at the institute (the information was provided by the patients). Staging information was obtained from the patient' case records. The patients were divided into three groups according to their educational status at the time of diagnosis as follows: low (illiterate patients and elementary school, 5 years or less), medium (secondary school and upper secondary school, 5-12 years), and high (university level, more than 12 years).

Staging and biological factors

Pathological and clinical staging at diagnosis was defined according to the American Joint Committee on Cancer (7th edition) [20]. Tumor grade was defined based on the Bloom-Richardson criteria as I, II, III and other/unknown [21]. ER status was recorded by immunohistochemistry (IHC) (positive when at least 1% of tumor cells showed positive nucleus staining of any intensity and otherwise negative). Due to 1% threshold for ER positivity used in this study, we did not anlyze progesterone receptor (PR) status separately. Assessments for the HER-2 score were recorded based on IHC score (negative: 0 and 1+, positive: 3+) and the ratio of HER-2 to chromosome 17 signaling, in accordance with the American Society of Clinical Oncology-College of American Pathologists (ASCO-CEP) guidelines. Specimens scored 2+ were further evaluated by fluorescence in situ hybridization (FISH) technique. HER-2 amplification was defined as a ratio of HER-2 to chromosome 17, signaling a score that was more than 2.2 [22)]

Statistics

All analyses were performed with two-sided p values. Differences between categorical variables were analyzed by Pearson's x^2 test, and differences between continuous variables were analyzed by using independent T-test or one-way ANOVA test where suitable. Statistical differences between groups were analyzed with log-rank test. Analyses were conducted using the Statistical Package for the Social Sciences (SPSS, version 22) software. Differences at $p<0.05$ were considered significant.

Results

In all patient groups significant relationship was found between educational status and T stage ($p<0.0001$). In this study patients with higher educational levels have smaller tumor size. Patients >50 and <50 years had similar results. The strong association between educational status and T status was maintained even in patients less than 40 years of age (Table 1). All graduate breast cancer patients were less

Table 1. Demographic features and results of all patients

	Educatıonal level			
Features	*None or primary (%)*	*Secondary (%)*	*University (%)*	*p value*
Her2 positivity	27.5	21.5	20.0	0.003
Metastasis at diagnosis	12.9	9.3	6.5	0.001
ER (+) positivity	80.0	81.5	83.6	0.275
Grade 1	12.4	13.5	9.2	0.129
Grade 2	45.5	46.7	51.9	0.129
Grade 3	42.0	39.8	39.0	0.129
T1 stage	24.0	29.3	38.1	<0.0001
T2 stage	55.6	57.0	46.8	<0.0001
T3 stage	14.7	12.1	12.4	<0.0001
T4 stage	5.7	1.6	2.7	<0.0001
N0 stage	39.8	50.9	50.2	0.001
N1 stage	32.1	28.3	28.0	0.001
N2 stage	18.0	14.7	13.9	0.001
N3 stage	10.1	6.0	7.8	0.001

Table 2. Demographic features and results of patients with a cut-off age of 50 years

	Educatıonal level			
	None or primary %	*Secondary %*	*University %*	*p value*
Her2 (+) in pts > 50 years	23.5	21.8	16.4	0.111
Her2 (+) in pts <50 years	32.8	22.2	23.3	0.006
Metastasis at diagnosis in pts. >50 years	13.3	8.5	3.5	<0.0001
Metastasis at diagnosis in pts. <50 years	11.8	9.8	8.8	0.465
ER (+) in pts >50 years	78.2	77.3	86.2	0.034
ER (+) in pts < 50 years	82.5	86.4	81.1	0.335
Grade 1 in pts>50 years	14.1	16.3	12.6	0.091
Grade 2 in pts>50 years	47.2	48.1	35.6	0.091
Grade 3 in pts>50 years	38.6	58.1	29.3	0.001
Grade 1 in pts<50 years	10.1	43.0	46.9	0.403
Grade 2 in pts<50 years	11.0	44.5	44.5	0.403
Grade 3 in pts<50 years	6.1	47.0	47.0	0.403
T1 in pts >50 years	28.0	37.6	44.0	<0.0001
T2 in pts >50 years	57.5	53.2	39.8	<0.0001
T3 in pts >50 years	10.7	6.8	13.6	<0.0001
T4 in pts >50 years	3.8	2.4	2.6	<0.0001
T1 in pts <50 years	18.3	19.6	33.2	<0.0001
T2 in pts <50 years	52.7	63.2	52.5	<0.0001
T3 in pts <50 years	20.6	17.2	11.5	<0.0001
T4 in pts <50 years	8.3	0.0	2.8	<0.0001
N0 in pts >50 years	44.1	51.0	57.1	0.062
N1 in pts >50 years	30.2	28.6	25.4	0.062
N2 in pts >50 years	16.1	12.1	9.5	0.062
N3 in pts.>50 years	9.6	8.3	7.9	0.062
N0 in pts <50 years	33.0	51.2	43.8	0.002
N1 in pts <50 years	34.8	28.0	30.4	0.002
N2 in pts <50 years	21.4	17.1	18.0	0.002
N3 in pts <50 years	10.8	3.7	7.8	0.002

likely to have axillary lymph node involvement (p=0.001) or metastasis (p=0.001) (Table 1). In patients over the age of 50 years no significant association between educational status and axillary node involvement was noted. The strong association between educational status and N status was also maintained in patients less than 40 years of age. Patients who were over 50 years old showed a significant relationship between metastasis and educational status (p<0.0001), however this relationship was not significant in patients under the age of 50 years (p=0.46) (Table 2). A significant correlation was found between educational status and ER levels in patients over 50 years of age (p=0.03) (Table 2). This study also revealed that patients with low educational levels were more likely to have positive ER. When the patients of all ages were evaluated, no statistically significant correlation was shown between educational status and ER positivity (p=0.27) (Table 1). Similarly, no significant correlation between educational status and tumor grade was determined. A significant relationship was found between educational status and HER-2 status in all patient groups (p=0.003; Table 1). HER-2 status increased in patients with low educational status, but the significant increase was lost in patients over >50 years (p=0.1; Table 2).

Discussion

This retrospective study showed that the educational status is independently and strongly associated with each of the five breast cancer prognostic factors: ER status, HER-2 status, tumor size, lymph node status and metastasis. This is the first study to reveal the correlation between HER-2 status and the level of education in breast cancer patients. It seems evident this study occupies an important position by being only the second study of its kind to uncover the correlation between educational level and clinical /pathological features of breast cancer.

Within the pertaining literature, it can be seen that breast cancer patients with low SES or low educational status have poor prognosis. Low-level education patients showed more axillary involvement, had larger tumor sizes, higher stages of cancer and shorter survival time [10-12,14,17]. Previous studies failed to show this association. DeSantis et al. [13], demonstrated an effect of insurance status and area-level educational attainment in regards to breast tumor characteristics: excess risk of metastasis, large tumor growth and positive lymph nodes were evident among women who resided in low-level education areas. In another study done on breast cancer patients residing in Stockholm (year of diagnosis between 1977 and 1997) Rutqvist et al. revealed that patients with higher income, higher level of education and who worked in skilled trades had tumors with better prognostic features, and therefore better clinical outcomes and overall survival rates [6]. Dalton et al. [23] investigated the relationship between socioeconomic position and tumor progression as measured by high-risk vs low-risk breast cancers at the time of diagnosis. This study was stratified by status in a large nation-wide population-based breast cancer cohort in Denmark between 1983 and 1999. The study provided empirical data, which showed that the risk for being diagnosed with a high-risk breast cancer was reduced with an increasing length of education and with an increasing disposable income. In that study, women with higher education levels exhibited 12% less odds ratio (OR) as compared to women with only a basic/high school education, whereas the OR was 22% higher among women in the lowest income group compared to women in the highest income group.

In a retrospective study from India, Krishnatreya et al. [24] showed that there was a significant difference of having stage I breast cancer at the time of diagnosis between a group of literate and illiterate women and a group of qualified and highly educated patients. This study suggested that only when women are educated, specifically on screening and diagnostic methods, it was easier to detect breast cancer in its earlier stages. However, another similar study from Denmark failed to show the same correlation between educational status and tumor size [25].

One of the generally accepted explanations of the association between socioeconomic factors and tumor size is the variations of access to screening services and timely follow up [13]. A National Health Survey [26] showed that insured women were more likely to have a mammography within the previous 2 years (70%), as compared to uninsured women (33%). The survey also revealed that women residing in low-educational level areas, especially black women, were less likely to have regular screening mammography, and therefore had clinically more advanced tumors at the time of diagnosis. One can deduce from this survey that patients with higher levels of education seem to have a higher awareness of the disease, are more likely to do self breast examinations, and

so are diagnosed with earlier stage of breast cancer.

Much like the previous studies just mentioned, our study demonstrated that patients with higher educational levels had smaller tumor sizes and were less likely to have axillary lymph node involvement or metastasis. Furthermore, our study uncovered the significant association between educational status and metastasis at the time of diagnosis among patients who were over 50 years old. What is more, the strong association between educational status and TN status was maintained in patients who were less than 40 years of age, where the effect of mammography and breast ultrasonography was less. This association can be explained by higher awareness of the disease and a higher rate of self-examination among Turkish patients with higher educational levels.

In regard to patients with a low SES, a poor prognosis was noticed and hence the relationship between tumor biology and SES was investigated. According to studies conducted in the U.K., a direct correlation between SES and ER expression was successfully determined [27]. During a similar study in Scotland, women under the age of 65 with a high SES were shown to be more likely to have ER negative tumors as compared to women with a low SES. However, during this study cancer specific survival was too varied and a correlation could not conduce in regard to the differences in ER status alone (9.2% and 3.7%, respectively). Another such trial study from England conducted by Taylor and Cheng [28], reported that affluent women had more non-invasive carcinoma, less invasive cancers that were ER negative and lower histological grade as compared to deprived women. In yet another study conducted by Bauer et al. [29], a population-based California registry was used and the following conclusion was determined: Women residing in socioeconomically deprived areas are more likely to have triple negative tumors.

In the study that investigated mortality risks of women in the California Cancer Registry between 2000 and 2010 - gauging both ethnicity and SES - patients with the lowest SES were more likely to have triple negative and HER-2 positive subtypes [12]. De Santis et al. [13], used a National Cancer Database to show that uninsured women were more likely to have less differentiated tumors and ER-PR negative breast cancers. A significantly higher percentage of the patients from educationally deprived areas was diagnosed with estrogen and progesterone positive breast tumors or high-grade breast cancer when compared to the patients from educationally advanced areas. In another study done by Sineshaw et al. (2010-2011), using a National Cancer Database, it was shown that women with low SES were more likely to have triple negative and HER-2 positive breast cancers [30]. However, these studies used institutional or state-level cancer registries with area-level SES and did not show educational status or showed results for breast cancer subtypes without including HER-2 status. Furthermore, a correlation between biological factors and educational status was not investigated in these studies.

Our study, however, did investigate the correlation between educational status and biological features of cancer in Turkish breast cancer patients. Our study uncovered a significant correlation between educational status and ER levels in patients over 50 years of age. It became obvious that patients with a low educational level were more likely to have positive ER. When the whole population was evaluated, no statistically significant correlation was shown. Similarly, no significant correlation between educational status and tumor grade was determined. The odds of patients having a positive HER-2 status were higher in those with lower educational levels when compared to patients with higher educational levels. The exact reason for the correlation between breast cancer, and ER levels, PR levels, grade and HER-2 status remains unknown. One possible explanation is that environmental and social factors that are more commonly seen in people with lower educational level may effect primary tumor biology, which may cause unfavorable tumor features.

The present study had several strengths as well as limitations. The lack of data of personal risk factors (e.g., reproductive factors, environmental factors, obesity, breast feeding and hormone use), which might also be effected by the educational status, might influence the interpretation of our study. While the exact relationship between biological factors of breast cancer and educational status still waits to be elucidated, the findings of this study have shown that patients with lower educational levels have larger tumors, more axillary involvement and are more commonly HER-2 positive. Further studies including breast cancer risk factors in larger patient groups are needed to support the findings and the conclusions of this study.

Conflict of interests

The authors declare no confict of interests.

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