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Ethnic disparities in breast cancer between Central Europe Caucasian women of Slavic origin and Middle East Turkish subjects

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The biological, cultural, behavioral and sociodemographic differences across populations modulate breast cancer profile among races or ethnics. Following this, we aimed to identify differences in breast cancer epidemiology, histopathology, and clinical presentation from representatives of central Europe (Slovakia) and Middle-East countries (Turkey) to point on ethnic disparities in cancer biology.

The population based cross-sectional study analyzing 414 cases of primary breast carcinomas where 214 represented Caucasian and 200 Turkish subjects.

The differences were found for age at the time of diagnosis (<0.0001), education, menopausal status (<0.001), tumor localization (<0.01), size (<0.0001), grade (<0.05) and axillary lymph node status (<0.001) between groups. Although carcinomas in Slovak subjects were of higher grade, negative axillary nodal status was more frequent finding compared to Turkish patients (50.0 vs. 41.0%). The Slovak group showed carcinomas to be more often ER positive (72.4 vs. 54.0%; <0.001), ER/PgR positive (54.6 vs. 49.0%; <0.001), of better Nottingham prognostic index (<0.001), and less frequent Her-2 positive (21.2 vs. 28.5%). Slovak population expressed significantly higher risk of non-sentinel lymph node metastases with increased tumor size, grade, vascular invasion and Her-2 positivity compared to Turkey population. The tumor size >2 cm and high tumor grade (G3) bears a risk of OR=7.62 and OR=3.10 in Slovak compared to OR=3.94 and OR=1.79 in Turkish cases, respectively.

There are wide demographic and biological disparities in breast cancer between observed ethnics providing unique information for clinicians working at the level of screening or therapy in these populations.

Key words: breast cancer, ethnic, race, disparity, cancer biology

Breast cancer is the most frequent women malignancy worldwide [1]. All women regardless of race, ethnicity or heritage are at risk of developing this pathology. Variations in disease incidence among multicultural populations suggest that etiologic factors differ in their biologic expression and impact on disease outcome [2,3]. Key factors that affect disease development are genetic, environment, reproductive history, endogenous and exogenous hormones, immunity, and host vulnerability. Culture, sociodemographic differences, and behavioral characteristics across populations modulate biology of disease expression among different races and ethnic groups [4]. Previous research found differences in breast cancer features (e.g. grade, size, nodal status) or survival based on geographical region of residence, race/ethnicity, and socioeconomic factors [5-7]. Thus, research considering ethnicity is becoming particularly important giving the level of ethnic diversity in biological profile of carcinoma, age on onset and extent of differences among minor/major ethnic groups across Europe in closer view.

Cancer prevalence in central Europe is increasing [8] and we live the great socio-economic-political changes of limitless international migration and forming one pan-European region. Migration within Europe is on-going social phenomenon of large scale, which affects the health of individual migrants, as well as populations [9]. At this time, except West-European or US studies, data reporting differences in biological features

of breast carcinomas for women from other European/Asian (racial/ethnic) populations/groups are scarce [10]. Thus, we decided to conduct a comparative study including two (frequently overlook) populations of which large communities in several European countries are established, (e.g. 1.7 million Turkish population in Germany forming the largest group /25.8%/ among non-German residents, and over 0.8 millions Slovak people in central European countries) [11,12].

The aim of this study was to identify differences between breast cancer epidemiology, histopathology, aggressiveness and clinical presentation from representatives of central Europe and Middle-East countries (Slovakia and Turkey), in effort to point on ethnic disparities in cancer biology among female populations. A study has also an ambition to help health care providers in planning preventive activities and determining individual therapy, when patient of such ethnicity/race is managed on background of different domestic population.

Material and methods

Specimen collection. This was a retrospective study including primary invasive female breast carcinomas (n=452) operated at co-worked institutions both randomly selected from the hospital registers. The cases with known disease stage, histological grade, hormonal receptor and Her-2 status were included. Patients after neoadjuvant therapy, carcinomas in situ, medullary and lobular carcinomas were excluded from correlations due to inability of histological grading [13]. Subsequently a total of 414 cases entered final analyses of which 214 cases represented Slovak and 200 Turkish subjects. Based on retrospective analysis of clinical outcomes, no specific written informed consent was required. However, the process of data collection was conducted in compliance with ethical requirements of each of participating institutions (IRB 423/2008).

Histologic examination. Histological assessments were performed on 4-5 μm thick hematoxylin and eosin stained sections of formalin-fixed, paraffin-embedded tumors. Typing was evaluated according to the WHO Classification of Tumours [14], and histological grading as presented by Elston and Ellis [15].

Immunohistochemical analysis. Tissue sections (4-5μm thick) from paraffin blocks were used for immunohistochemical analyses. For detection of estrogen receptors (ER) we used anti-ER (clone ER1D5, Immunotech) and for detection of progesterone receptors (PR) we used anti-PR (clone 1A6, Immunotech). The ER and PR status was interpreted semiquantitatively as positive when >10% of tumor cells showed positive nuclear staining. Her-2 immunohistochemical status was initially analyzed by HercepTest (DakoCytomation, Glostrup). The results were interpreted as follows: 0 = no membrane staining (MS); 1+ = faint, partial MS; 2+ = weak complete MS in more than 10% of invasive cancer cells; 3+ = intense complete MS in more than 10% of invasive cancer cells. Patients with 2+ results were re-examined by FISH.

Fluorescence in situ hybridization (FISH). For FISH study 4-μm thick sections of formalin-fixed paraffin-embedded tissue mounted on silanized slides were used. The ONCOR HER-2/neu Gene Detection System (Ventana Medical System) was used. FISH methodology and results interpretation was used as described previously [16]. For scoring of signals was epifluorescence microscope was used. Signals from 40 randomly selected cancer nuclei from two distinct areas were enumerated. A mean signal of >4 indicated Her-2 amplification, whereas signal ≤4 indicated that Her-2 gene amplification was not identified.

Statistical analysis. The chi-square (two-tailed) statistic was used to examine categorical variables and associations between clinico-pathological characteristics in univariate analysis. An independent sample t-test was used to compare the mean of two samples, and the Mann-Whitney test was used to test the difference between two independent samples. For assessment of probability of non-sentinel lymph node involvement we applied the Odds ratio (OR) and a 95% confidence interval (95%CI) obtained from unconditional logistic regression. The P value < 0.05 was considered significant. All statistics were performed with MedCalc 12.1.4 (MedCalc® Inc., Mariakerke, Belgium) software.

Results

The study population consisted of 414 women with verified histology of breast carcinoma divided in two groups. 214 cases represented sample of Caucasian (Slovak) women ranging in age from 33 to 98 years (mean 59.3) and 200 patients belonged to Turkish population in age from 30 to 80 years (mean 53.9) at the time of diagnosis, respectively. The significant differences were found for age at the diagnosis (<0.0001), education level, menopausal status (<0.001), and tumor localization (<0.01). The majority of Slovak patients were of middle education level (62.2%), postmenopausal status (72.9%) and older than 50 years (75.7%) compared to Turkish patients. Here contrary up to 12.0% (3-times more than Slovak) women had university education and carcinoma occurred more often in premenopausal (27.5%; 2-times more) and young women before 50 years of age (45.5%; nearly 2-times more). In both groups carcinoma most often occurred in upper outer quadrant (Table 1).

Concerning the disease stage, we have revealed significant differences in tumor size (<0.0001), grade (<0.05) and axillary lymph node status (<0.001), whereas difference in tumor type and peritumoral vascular invasion (PVI) was insignificant. In Turkish patients, the majority of carcinomas were >2 cm (74.0%) and only 2.0% of women has tumor smaller than 1 cm compared to Slovak patients (43.9% and 30.0%), respectively. Although carcinomas in Slovak subjects were in majority of higher grade, negative axillary lymph node status was more frequent finding compared to Turkish patients (50.0% versus 41.0%), Table 2.

As for the histology, data from Slovak group showed carcinomas to be significantly more often ER positive (72.4%

Table 1. Demographic characteristic of patients

Parameter	Population	
	Slovak	Turkey
n	214	200
Mean age (years)	59	54
SD	11.6	12.3
Age range (years)	33 – 98	30 – 80
P value †‡		< 0.001† < 0.0001‡
Education	Value (n [%])	Value (n [%])
Elementary	72 (33.6)	84 (42.0)
Middle	133 (62.2)	92 (46.0)
University	9 (4.2)	24 (12.0)
P value *		< 0.001
Menopausal status		
Premenopause	28 (13.1)	55 (27.5)
Perimenopause	30 (14.0)	28 (14.0)
Postmenopause	156 (72.9)	117 (58.5)
P value *		< 0.001
Tumor localization		
C50.0	1 (0.5)	0 (0.0)
C50.1	29 (13.6)	20 (10.0)
C50.2	42 (19.6)	23 (11.5)
C50.3	25 (11.7)	12 (6.0)
C50.4	85 (39.7)	120 (60.0)
C50.5	31 (14.4)	23 (11.5)
C50.6	1 (0.5)	2 (1.0)
C50.7	0 (0.0)	0 (0.0)
P value *		< 0.01

† P value obtained from unpaired Student-*t* test
‡ P value obtained from Mann-Whitney test
* P value obtained from Chi-square test for trend (two-tailed)
Abbreviations: SD = standard deviation

Table 2. Clinico-pathological characteristic of patients

Parameter	Value (n [%])	
Population	Slovak	Turkey
n	214	200
Age at diagnosis (years)		
≤ 50	52 (24.3)	91 (45.5)
> 50	162 (75.7)	109 (54.5)
≤ 30	3 (1.4)	14 (7.0)
P value *		< 0.0001
Tumor size (cm)		
≤ 1 cm	64 (30.0)	4 (2.00)
1 – 2 cm	56 (26.1)	48 (24.0)
> 2 cm	94 (43.9)	148 (74.0)
P value *		< 0.0001
Tumor type		
Invasive ductal	156 (72.9)	156 (78.0)
Invasive lobular	26 (12.1)	23 (11.5)
Other	32 (15.0)	21 (10.5)
P value *		NS
Tumor grade†		
1	36 (19.1)	45 (25.4)
2	58 (30.9)	62 (35.0)
3	94 (50.0)	70 (39.6)
P value *		< 0.05
Lymph nodes status		
0	107 (50.0)	82 (41.0)
1	62 (29.0)	39 (19.5)
2	32 (14.9)	52 (26.0)
3	13 (6.10)	27 (13.5)
P value *		< 0.001
Peritumoral vascular invasion		
Absent	104 (48.6)	111 (55.5)
Present	110 (51.4)	89 (44.5)
P value *		NS

* P value obtained from Chi-square test for trend (two-tailed)
† Except lobular breast cancer
Abbreviations: NS = not significant

versus 54.0%; <0.01), ER/PgR positive (54.6% versus 49.0%; <0.0001), of better prognosis expressed by Nottingham prognostic index (<0.001), and insignificantly less frequent Her-2 positive (21.2% versus 28.5%) compared to Turkish patients, respectively. The intraductal component and PgR status showed no differences, table 3. The most prominent differences were noted for Her-2 and ER status. In Slovak group a significant positive correlations between Her-2 and negative correlations between ER status and increased tumor size, tumor grade and axillary lymph node involvement were observed, whereas only ER status showed this trend in Turkish cases. Her-2 status did not show significant associations with above mentioned parameters (Table 4). Striking differences were found in univariate risk assessment of non-sentinel lymph node metastases (NSLNM) after adjustment for tumor size, grade and PVI. Slovak population expressed significantly higher risk of NSLNM with increased tumor size, grade, PVI and Her-2 positivity compared to Turkey population. For example, tumor size in cases >2 cm and high tumor grade bears a risk with an OR=7.62 (95%CI=3.66-15.90) and OR=3.10 (95%CI=1.40-6.87) in Slovak women compared to OR=3.94 (95%CI=2.02-7.67) and OR=1.79 (95%CI=0.83-2.86) in Turkish cases, respectively. The risk of NSLNM expressed for PVI and Her-2 positivity was more than two-fold higher in Slovak compared to Turkey subjects (OR_{PVI}=6.03 versus OR=2.26 and $OR_{Her\text{-}2}$=2.45 versus OR=1.5, respectively), Table 5.

Discussion

Several studies have analyzed mortality and survival between various ethnics/races, and differences have been noted in many of them, as well as in national cancer statistics [2,17]. It was proved that Asian-Americans tend to have lower incidence of breast cancer than Caucasians, and they also have a superior prognosis [18]. On the other side Hispanic women are more

frequently diagnosed at a later stage and exhibit less favorable disease features relative to non-Hispanic Caucasians [19]. As for African-American women it was thought the carcinomas are more often diagnosed at a later stage, have less favorable characteristics, and may suffer barriers to quality care, resulting in higher mortality and poorer survival rates than Caucasian woman. It was suggested this disparity might be caused by unequal access to medical care. However, results from large studies support the theory that equal treatments produce equal outcomes [20,21]. Considering that health care is getting equal in modern medical centers, remaining differences in cancer mortality and survival rates may originate from racial/ethnic disparities in clinical, socioeconomic and biological characteristics of the disease, which suggest racial and geographical differences in the biology of disease [22]. The deeper insight into these associations could bring the molecular classification of carcinomas [23,24], and detection of genes expression profiles that may serve as individual predictors of outcome and response to adjuvant therapy with high accuracy [25,26]. However, these techniques are not accessible for every breast cancer unit as there are still medical institutions that have to rely only on histopathology. It is the basic histological analysis (e.g. ER, PgR, Her-2 status, tumor grading) not complex gene-expression profiling that may primary revealed differences in tumor biology between ethnics/races population or predict disease aggressiveness [27,28].

Despite the evident breast cancer burden worldwide, the information about its epidemiology in different ethnic groups is difficult to obtain. This is because of the difficulty of defining and classifying people into ethnic groups and inconsistent or incomplete way of data monitoring and collection [29]. Breast cancer is the most frequent cancer

Table 3. Clinico-pathological characteristic of patients

Parameter	Value (n [%])	
Population	Slovak	Turkey
n	214	200
Receptor status		
ER positive	155 (72.4)	108 (54.0)
ER negative	59 (27.6)	92 (46.0)
PgR positive	123 (57.5)	112 (56.0)
PgR negative	91 (42.5)	88 (44.0)
P value *		< 0.01
ER + / PgR +	117 (54.6)	98 (49.0)
ER + / PgR -	38 (17.8)	10 (5.0)
ER - / PgR +	6 (2.80)	14 (7.0)
ER - / PgR -	53 (24.8)	78 (39.0)
P value *		< 0.0001
Her-2 status		
Negative	167 (78.8)	133 (71.5)
Positive	45 (21.2)	53 (28.5)
P value *		NS
Nottingham prognostic index		
≤ 3.4	98 (45.8)	54 (27.0)
3.5 – 5.4	74 (34.6)	89 (44.5)
> 5.4	42 (19.6)	57 (28.5)
P value *		< 0.001
Intraductal component		
Low grade	78 (36.4)	85 (42.5)
High grade	46 (21.6)	46 (23.0)
None	90 (42.0)	69 (34.5)
P value *		NS

* P value obtained from Chi-square test (two-tailed)
Abbreviations: NS = not significant; ER = estrogen receptor; PgR = progesterone receptor

Table 4. Correlations between clinico-pathological factors and molecular predictive markers

Population	*Slovakian*				*Turkey*			
	Her-2 status		Estrogen Receptor		Her-2 status		Estrogen Receptor	
	Positive/total (%)	*P* value‡	Positive/total (%)	*P* value‡	Positive/total (%)	*P* value‡	Positive/total (%)	*P* value‡
Tumor size (cm)								
≤ 1 cm	9/63 (14.3)	< 0.01	53/64 (82.8)	< 0.01	1/4 (25.0)	NS	1/4 (25.0)	< 0.05
1 – 2 cm	7/56 (12.5)		43/56 (76.8)		11/44 (25.0)		36/48 (75.0)	
> 2 cm	29/93 (31.2)		58/94 (61.7)		40/138 (29.0)		71/148 (48.0)	
Tumor grade#								
1	0/35 (0.00)	< 0.0001	35/36 (97.2)	< 0.0001	11/44 (25.0)	NS	34/45 (75.5)	< 0.0001
2	8/58 (13.8)		52/58 (89.6)		20/60 (33.3)		37/62 (59.7)	
3	35/93 (37.6)		45/94 (47.9)		18/64 (28.1)		24/70 (34.3)	
Lymph nodes status								
0	15/106 (14.2)	< 0.001	86/107 (80.4)	< 0.01	18/76 (23.7)	NS	50/82 (61.0)	< 0.05
1	14/62 (22.6)		42/62 (67.7)		16/38 (42.1)		19/39 (48.7)	
2	9/31 (29.0)		19/32 (59.4)		15/48 (31.2)		23/52 (44.2)	
3	7/13 (53.8)		8/13 (61.5)		3/24 (12.5)		10/27 (37.0)	

‡ P value obtained from Chi-square test for trend (two-tailed)
# Except lobular breast cancer
Abbreviations: NS = not significant

Table 5. Predictor variables for non-sentinel lymph node metastases

Population	*Slovak*				*Turkey*			
			Univariate Analysis				Univariate Analysis	
	No. of patients	NSLNM (n/%)	OR (95%CI) †	*P* value‡	No. of patients	NSLNM (n/%)	OR (95%CI) †	*P* value‡
Tumor size (cm)								
≤ 1 cm	64	14 (21.9)	1.00		4	0 (0.0)		
1 – 2 cm	56	25 (44.6)	2.88 (1.30-6.37)		48	18 (37.5)	1.00	
> 2 cm	94	64 (68.1)	7.62 (3.66-15.9)	< 0.05	148	100 (67.6)	3.94 (2.02-7.67)	< 0.0001
Tumor grade#								
1	36	16 (44.4)	1.00		45	24 (53.3)	1.00	
2	58	24 (41.4)	0.88 (0.38-2.04)		62	36 (58.1)	1.21 (0.56-2.62)	
3	94	67 (71.3)	3.10 (1.40-6.87)	< 0.001	70	47 (67.1)	1.79 (0.83-2.86)	NS
PVI								
Absent	104	29 (27.9)	1.00		111	56 (50.5)	1.00	
Present	110	77 (70.0)	6.03 (3.34-10.9)	< 0.001	89	62 (69.7)	2.26 (1.26-4.05)	< 0.01
Her-2 status								
Negative	167	75 (44.9)	1.00		133	75 (56.4)	1.00	
Positive	45	30 (66.7)	2.45 (1.23-4.90)	NS	53	35 (66.0)	1.50 (0.77-2.92)	NS

† Odds ratios (Ors) and 95% confidence intervals (CIs) obtained from logistic regression model

‡ P value obtained from Chi-square test (two-tailed)

Except lobular breast cancer

Abbreviations: NS = not significant; NSLNM = nonsentinel axillary lymph node metastases; PVI = peritumoral vascular invasion

type (24.1% of all cancer), and the most common cause of cancer-related death in Turkish women [30]. Similarly, up to 18% of all cancers among women in Slovak republic belong to breast cancer with incidence rate 52.2/100,000 and mortality 15.4 deaths per 100,000 females [31]. In this cohort of two rarely evaluated ethnics we have found differences in breast cancer demographic and clinico-pathological factors indicating ethnic, racial and geographical differences. Demographic characteristic of Turkish patients showed high disease prevalence in young age, in women of elementary and academic education. This indicates that access to medical care and health education is struggling and needs more effective cancer information and support. Moreover, if low level of cancer knowledge in Turkish population was revealed [32]. Furthermore, Turkish women with breast cancer themselves or in relatives are experiencing a high level of needs, mainly psychological [33] when associated with diagnosis, treatment and follow-up. As cancer screenings and therapy is for people from some ethnically/geographically communities difficult to cope with, and educational level is the major predictive factor influencing the basic knowledge, achieving improvement will required cooperation between official government reforms and voluntary sector staff activity [34]. Therefore public health attention in Turkey needs to be directed towards the risk factors and health care facilities that impact on breast cancer development.

Turkey has been recently in a sociodemographic, cultural, and economic transformation where women living in both rural and urban areas have received little attention related to breast cancer risk. As the obstetric an gynaecological lifestyle and nutritional factors have impact on disease differences in women [35], informing health professionals and social workers about these issues is important for improving awareness in women about breast cancer risk neither in homeland, nor among residents abroad. Moreover, if there was observed high cancer prevalence in central Europe, explained by growing proportion of elderly people, lowering general mortality, early detection rate and increasing expenditures on health care. The increased burden of cancer could be than interpreted as a paradoxical effect of improving treatments and thereby survival.

Ethnical and geographical background in observed groups had an impact on clinic-pathological differences, as well. We have revealed that despite of higher tumor grade in Slovak patients incidence of axillary lymph node involvement was lower than in Turks. The factors to influence this include better ER, PgR or Her-2 profile [36,37], access to screening mammography, and early detection rate in Slovak women. Moreover, the high proportion of ER-negative, PgR-negative, Her-2-positive tumors seen in Turkish women may represent the "Her-2 cancer subtype", which has larger size, higher grade, poorer prognostic index, and higher stage resulting in recurrence, metastatic spread, and poorer outcome [38].

Persistence of wide disparities in socioeconomic status, availability of health insurance, structure of health care facilities, and health care affordability, may affect the cancer statistic in studied populations. Thus for disparities revealed in our study another explanation should be the difference in beginning of screening mammography (MMG). In Turkey, biannual MMG screening is recommended for women older

than 50 years [39], whereas in Slovakia it starts from 40 [40]. Studies showed that MMG after 40 years can reduce mortality [41], thus lowering screening age in Slovak population may have an impact on differences showed in this study.

The last influence that can explain the disparities is a possible impact of significantly different age between the populations and possibility of hereditary breast cancer syndromes in population on cancer prevalence. Even more, if we have revealed five-times increased proportion of carcinomas in women less than 30 years in Turkish population. The results from molecular germline analysis showed that up to 15.1% of families with suspicion of familiar breast cancer demonstrated presence of a germline mutation in breast cancer predisposing genes (BRCA1, BRCA2) in Turkey women [42,43], and similarly approximately 13.3-17.1% in Slovakia [44]. Therefore, based on high difference in cancer prevalence among cases ≤30 years of age revealed in this study, germline mutation profile have to be considered as a part of study protocols when detailed analysis on ethnic/racial breast cancer differences will be investigated in further studies. Moreover, if breast cancer in young women is a unique biologic entity driven by unifying oncogenic signaling pathways, and is characterized by less hormone sensitivity, higher Her-2 expression, what warrants offering this poor-prognosis group of patients better preventative and therapeutic options [45].

Although this study is the first to compare clinic-pathological data between previously unstudied populations, the results can not be generalized as this was a region based recruiting protocol. Thus for further generalization of the findings the results needs to be validated by multi-centric approach.

Conclusions

The results of this study by revealing disparities in age of onset, hormone receptor status, Her-2 expression, higher tumor size, grade, aggressiveness and stage of disease suggest that natural history of the disease is reflecting racial/geographical disparity. Moreover, they provide unique information for clinicians indicating unfavorable breast cancer features/outcome seen among Turks, when working with ethnics residing outside its homeland, and low awareness of breast cancer risk factors and screening in this population.

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