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Influence of stress related to war on biological and morphological characteristics of breast cancer in a defined population

Fajdic J[1], Gotovac N[2], Hrgovic Z[3*], Fassbender WJ[4]

1 Department of Surgery, County Hospital, Pozega, Croatia
2 Department of Radiology, County Hospital, Pozega, Croatia
3 Department of Obstetrics and Gynecology, J.J. Strossmayer University, Clinical Hospital Osijek, Croatia
4 Department of Internal Medicine, Hospital zum Hl. Geist Kempen, Teaching Hospital of the Heinrich Heine University Duesseldorf, Kempen, Germany

* CORRESPONDING AUTHOR:
Kaiserstrasse 15,
60311 Frankfurt, Germany
tel: +4969 293000, fax:+4969 291697
email: info@hrgovic.de (Zlatko Hrgovic)

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ABSTRACT

Purpose: To assess differences between patients with breast cancer before, during and after the 1991-1995 war in Croatia.
Material and Methods: We analyzed 660 patients of Pozesko-Slavonska County, during the three periods. Relative predictive values of patient's characteristics and stage of tumor were assessed using the X^2-test, and survival with Kaplan-Meier analysis.
Results: Tumors were significantly more often of higher stages (IIA and IIB) and with axillary lymph node metastases (N1) during the war, than in pre-war and post-war period.
Breast cancer was significantly more frequent in patients who previously experienced death in the family (35,3%). The Kaplan-Meier analysis showed correlation between survival, T and N stages of tumor and clinical stage of tumor.
Conclusion: The war aggression towards Croatia with its impact on our patients, contributed to modification of characteristics of breast cancer in the analyzed period.

Key words: breast cancer; life change events; stress; survival analysis; war

INTRODUCTION

Around 1930 the hypothesis was developed of cancer being a somatic derivative of deep emotional conflicts and psychogenetic frustrations, i.e. the result of activation of malignant cells after coexisting in apparent harmony with the body for years [1]. During the last three decades, many publications focus on the role of psychological trauma in the development of cancer Siegrist [2], LeShan [3], LeShan [4], and Beck et al. [5], Greer and Morris [6], Muslin et al.[7], Katz et al.[8], Edwards et al.[9], Hilakivi-Clarke et al. [10], Meyerowitz [11], Freidenbergs et al. [12], Greer and Silberfarb [13] and Derogatis et al. [14]. Some publications focused specifically on the correlation between stress and breast cancer, which was first found by Galen, who claimed that melancholic and depressed women have breast cancer more often than those without psychological disorders [3]. The correlation between war aggression and carcinogenesis was most extensively studied in epidemiological studies of radiation and carcinogenesis in the survived population of Hiroshima and Nagasaki [15]. In Croatia, the 1991-1995 Homeland War can be viewed as a source of stress, which caused changes in the immune reactivity of women as well as men. Such changes reflect as the state of disrupted homeostasis, whereas the stimuli causing the change are the stressors. Stressors are physical or psychological, and exogenous or endogenous [16].

The basis of our study is the psychosomatic theory, which is based on the fact that the psychological trauma of losing "the object" (death of a family member) causes the so-called "amputation effect" in the integral part of a "psychobiological whole" [4,5]. Our aim was to study the role of psychological stress related to war, specifically the strong intrinsic stressor of death in the family, on

characteristics of breast cancer in the Pozesko-Slavonska County, Croatia, which was directly exposed to war operations.

MATERIAL AND METHODS

Sample

We analyzed 660 patients (656 women and 4 men) with breast cancer in the Pozesko-Slavonska County, Croatia. The County's population in 1991 was 134,548 inhabitants, of which 69,219 were women. In 1995, one town (Nasice) and its surroundings administratively left our county to join the neighboring one. This diminished our analyzed population by 35,124 inhabitants. However, this administrative change did not influence the habits of inhabitants in regards to attending our department, which specializes in breast diseases. This study was carried out without approval of Institutional Review Board since at that time such board did not exist.

Setting

We analyzed three periods of time: the pre-war period (1981 - 1990), divided into two five-year periods with a total of 281 patients with breast cancer; the war period (1991 - 1995), with 156 patients; and the post-war period (1996 - 2000), with 223 patients. The pre-war and post-war periods served as control groups. Due to the war-related circumstances, 119 patients were diagnosed and started their treatment in other institutions.

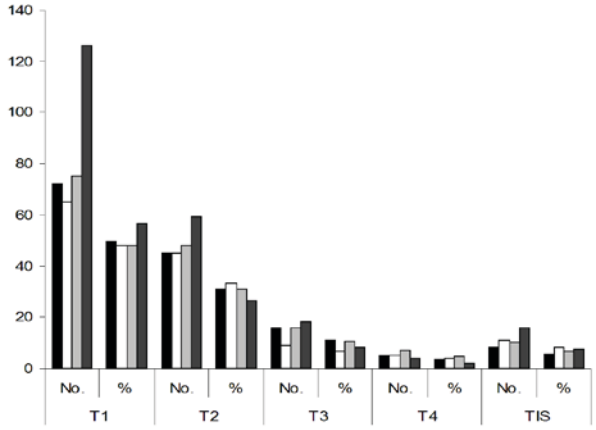
Outcome Measures

For each patient, we studied data on sex, age, age at which they were diagnosed with breast cancer, TNM and clinical stage of tumor, death in the family, and survival [17]. We questioned all patients with a short questionnaire to obtain data on possible deaths in the family during the peace- and war-time periods. It consisted of basic personal data and a simple question about a possible death in the family, including the date at which the death occurred. Other possible stress factors, such as divorce and loss of property or employment, were not analyzed. The response rate was only 27% for patients in the pre-war period (many of these patients died by the time the study was conducted), but was much higher in the war and the post-war periods (76% and 81%, respectively).

Statistics

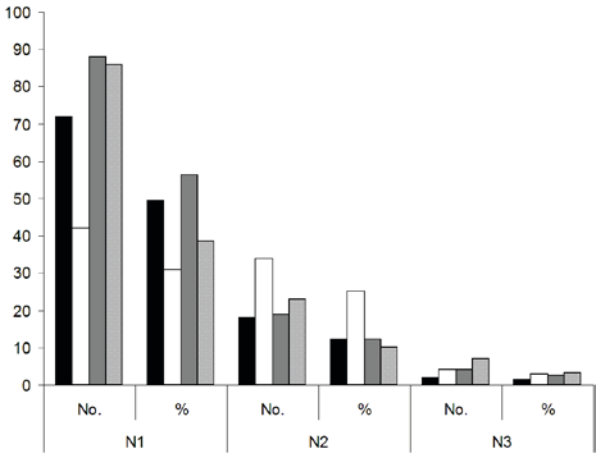
We assessed relative predictive values of patients' characteristics and stages of tumor (TNM) using the X^2-test, and survival by Kaplan-Meier analysis.

Figure 1. **Frequency of the T staging of breast cancer in Pozesko-Slavonska County.**



Legend:
black bars – 1981 - 1985 period
white bars – 1986 - 1990 period
light grey bars – 1991 - 1995 period
dark grey bars – 1996 - 2000 period

Figure 2. **Frequency of the N staging of breast cancer in Pozesko-Slavonska County.**



Legend:
black bars – 1981 - 1985 period
white bars – 1986 - 1990 period
dark grey bars – 1991 - 1995 period
light grey bars – 1996 - 2000 period

RESULTS

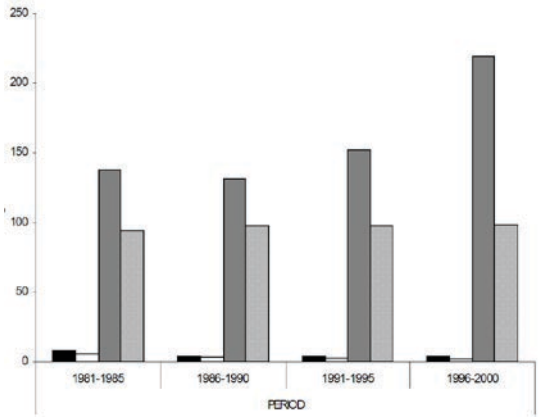
The difference between the observed and expected frequencies of tumors in regards to T and M staging was not statistically significant between the war group and two control groups ($p>0.05$). However, the difference in N staging between the groups was significant ($X^2=37.686$, df=9, $p<0.001$). The war group had the largest proportion of patients with axillary metastases (56.4%) *(Fig. 1,2,3)*. We also found the statistically significant difference ($p<0.001$) between groups in terms of the observed and expected frequencies of particular clinical

Table 1. **Distribution of the clinical staging of breast cancer in Pozesko-Slavonska County.**

	Number (percentage) of patients				
Clinical	1981-1985	1986-1990	1991-1995*	1996-2000	Total
0	8 (5.5)	11 (8.1)	10 (6.4)	16 (7.2)	45 (6.8)
I	43 (29.5)	41 (30.4)	27 (17.3)	83 (37.2)	194 (29.4)
II A	23 (15.8)	20 (14.8)	49 (31.4)**	51 (22.9)	143 (21.7)
II B	26 (17.8)	19 (14.1)	42 (26.9)**	32 (14.3)	119 (18.0)
III A	24 (16.4)	32 (23.7)	15 (9.6)	30 (13.5)	101 (15.3)
III B	14 (9.6)	8 (5.9)	9 (5.8)	7 (3.1)	38 (5.8)
IV	8 (5.5)	4 (3.0)	4 (2.6)	4 (1.8)	20 (3.0)
Total	146 (100.0)	135 (100.0)	156 (100.0)	223 (100.0)	660 (100.0)

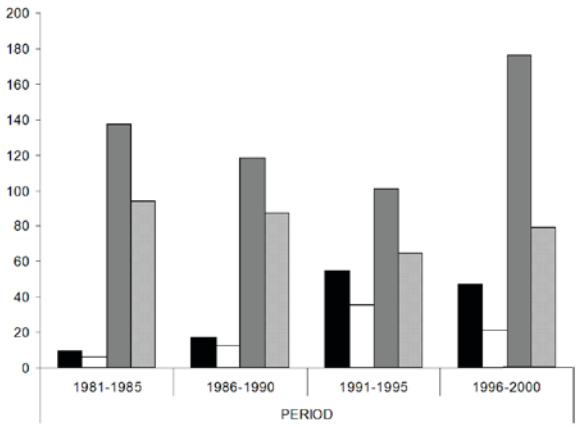
* war period
** statistically significant (p<0.050) diferrence (X^2-test)

Figure 3. **Distribution of the M staging of breast cancer in Pozesko-Slavonska County.**



Legend:
black bars – number of patients with M1
white bars – percentage of patients with M1
dark grey bars – number of patients with M0
light grey bars – percentage of patients with M0

Figure 4. **Frequency of patients with breast cancer in Pozesko-Slavonska County in regard to having a war-related death in the family.**



Legend:
black bars – number of patients who had a death in the family
white bars – percentage of patients who had a death in the family
dark grey bars – number of patients who did not have a death in the family
light grey bars – percentage of patients who did not have a death in the family

stages of tumors, with significantly higher prevalence of breast cancer stage IIA (31.4%) and IIB (26.9%) in the war group *(Tab. 1)*.

As much as 35.3% of our patients had a close family member killed in war *(Fig. 4)*. There was a significant difference (X^2=45.854, df=3, p<0.001) between patients with breast cancer who had previously had a death in the family (19.4%) and those who had not (80.6%), tested in regards to the pre-war, war, and post-war periods.

The T staging of tumors had a significant influence on the length of survival, which differed according to particular grades of the T staging (Log Rank=373.18, df=4, p<0.001). The highest rate of survival was in the lower grades of T staging, e.g., TIS and T1 (91.1% and 69.2%, respectively), whereas not one patient with highest T stage survived *(Fig. 5)*. Similarly, the N staging of tumors also proved to be a predictor of survival, when analyzed with the Log Rank test (p<0.001) *(Fig. 6)*. The highest proportion of survived patients was in the N_0 group (82.0%). Also, there was a statistically significant difference between clinical stages of tumors at the time of operation, when analyzed for the length of survival (Log Rank=1108.65, df=6, p<0.001).

The proportion of patients who survived decreased rapidly with the increase in the clinical stage of the disease *(Fig. 7)*. On the other hand, the proportion of patients who had a member of the family dying in the war was extremely high (91.4%) among the survived patients, and the difference when compared with Log Rank test to those who did not was statistically significant (Log Rank=72.99, df=1, p<0,0001) *(Fig. 8)*.

Figure 5. **Rate of survival of patients with different T stages of breast cancer in Pozesko-Slavonska County (Kaplan-Meier).**

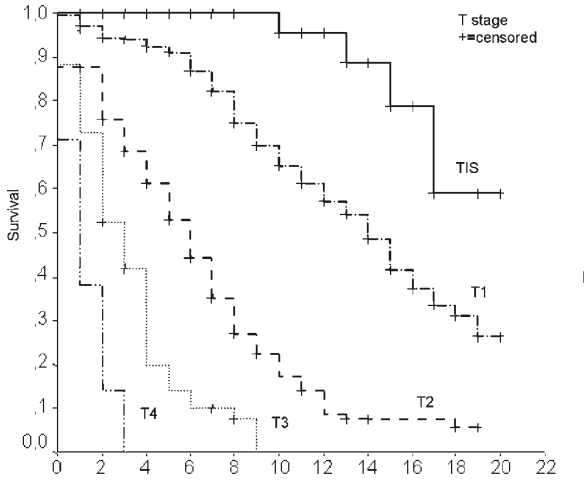


Figure 6. **Rate of survival of patients with different N stages of breast cancer in Pozesko-Slavonska County (Kaplan-Meier).**

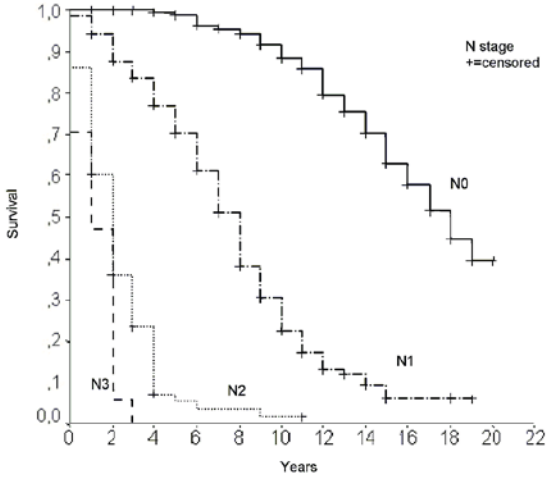


Figure 7. **Rate of survival of patients with different clinical stages of breast cancer in Pozesko-Slavonska County (Kaplan-Meier).**

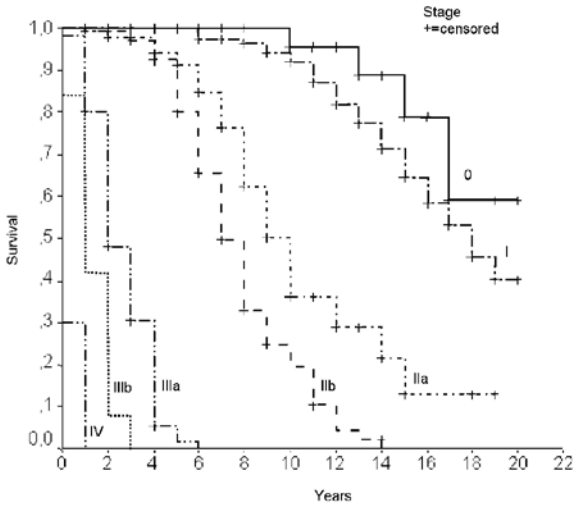
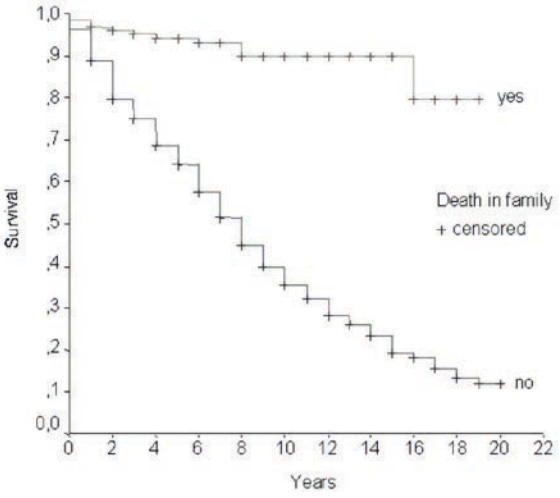


Figure 8. **Rate of survival of patients with breast cancer in Pozesko-Slavonska County according to having had a war-related death in the family (Kaplan-Meier).**



DISCUSSION

We analyzed the role of stress as a potential modifying factor in the clinical course of breast cancer. Although Croatia has a recent history of war (the 1991-1995 Homeland War), only one study in Croatia found the correlation between stress related to war and breast cancer. Belicza et al. [18], analyzed changes in frequency of breast cancer in the hospital's cancer registry in Zagreb during twenty years (1980 – 2000). They found no increased pTNM stage of breast cancer during war-period; conversely pTNM stage was lower in the war and post-war period than in control group. Discrepancies between their results and this study could be attributed to different exposition to war operations between two analyzed groups. Patients encountered in the study of Belicza et al., were mostly from Zagreb and near surroundings where exposition to direct war operation was significantly lower compared to Pozesko-Slavonska County [18]. Correlation analyses found that the disrupted immunological and endocrinological homeostasis due to acute or chronic stress related to war was an important risk factor in pathogenesis of different diseases, including cancer [19-23]. Such studies have a strong background in the so-called psychosomatic theory, which originates from the 1970-ties. This theory was primarily based on studies of connections between the psychological, neurological, and immunological disorders [24]. Cohen and Herbert [25] argued that there are three mechanisms with which an organism reacts to the state of disrupted normality: the hypothalamo-pituitary-adrenal axis; directly connecting the immunological and central nervous system (inducing neurohormonal changes in the central nervous system) [25].

Furthermore, chronic stress reduces the number of granulocytes and T- and B-lymphocytes, and inhibits cellular immunity [26]. The extent to which these changes will take

place depends on characteristics and intensity of stressors, duration of stress, sex and age, overall health status, genetic material, as well as social and economical factors. In this study, the death in the family is considered as such stressor, possibly influencing certain clinical and biological characteristics of breast cancer. In the framework of the psychosomatic theory, if the immunological status is weakened and personality "rigid". The disintegration of the autonomous nervous system follows, with the occurrence of disease as a possible somatic result [8,27].

We did not find a statistically significant difference between the prevalence of breast cancer during the war, when compared to the control periods. The T_1 stage of cancer, which is well treated and has good prognosis, was comparably represented in all groups, most of all in the post-war group (56.5%). This is probably the result of preventive measures undertaken for the improvement of early detection of breast cancer. Still, there was no significant difference in the frequencies of tumors with regards to their size in the observed periods.

However, the size, number, and location of metastases in involved axillary lymph nodes are directly related to the rate of survival and the probability of the relapse. According to Holland et al. [28], only 40% of patients with breast cancer have malignant cells localized to breast gland. Many authors sought for the connection between the spread and the size of the primary tumor, but there are some differences, probably due to using TNM or pTNM (Carter [29], Belicza et al. [30], Fajdic et al. [31]). We found that 60.5% of our patients had axillary metastases. The highest proportion of patients with N_1 stage was found in the war group (56.4%), whereas in the post-war group 48.0% of patients had no of axillary metastases. This can be explained by the preventive oncological measures undertaken in Croatia after the 1991-1995 war.

The war also influenced the clinical staging of breast cancer. In the war group, we found the significantly higher prevalence of breast cancer stage IIA (31.4%) and IIB (26.9%), whereas the stage I cancer was most frequent in the post-war group (37.2%). This is probably due to better organization of oncological service after the war, introduction of screening programs, and the contemporary diagnostic methods. The clinical stages of cancer are at the same time the important factor in length of survival (Kaplan-Meier test, $p<0.001$). At the same time, there was no difference in terms of survival between the analyzed periods (Kaplan-Meier test, $p>0.05$).

Stress resulting from the loss of a family member became prominent in the 1991-1995 period, when 35.3% of patients had the death in the family before the onset of the disease. The question is: is the stress of losing a family member a coincidence, or the cause of the disease? Our findings not only confirm the correlation between the stress and breast cancer, but also show the correlation between stress and several clinical and biological characteristics of cancer, such as the T and N stage according to the TNM classification, and the clinical staging.

The extremely high (91.4%) frequency of patients who had a member of the family dying in the war among the survived patients is probably due to three factors. First, most of these patients had cancer of clinical stage I or IIA (43.0% and 26.6%, respectively); second, these patients had low stage of tumor according to T and N classification; and the third, the time of follow-up for these patients was much shorter than for patients in the other groups.

We found that the survival of patients with breast cancer correlated with the TNM staging, clinical staging, and death of a family member in the patients' personal history. These findings support the idea that people under stress are at high risk for breast cancer, in terms of prevalence and prognosis, and need to be diagnosed and treated properly.

CONCLUSIONS

We have found that war and death in family have had effect on several clinical, biological and patohistological characteristics of breast cancer. We can argue that such patients had reduced immunologic potential. During war period (1991-1995) patients were, on average, 4.2 years younger. Detected tumors were of higher stage (IIA and IIB) and had positive axillary lymph nodes (N1), low expression of hormonal receptors, and medium histological grade (G2). During war period prevailed following types of cancer: invasive lobular cancer, mixed type, and medullar breast cancer. Kaplan-Meier analysis showed that TNM and stage of cancer, patohistological diagnosis, as well as age and death in the family had influence on survival.

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