

# Effects of War Aggression in Croatia on Some Forms and Manifestations of Breast Cancer

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## ABSTRACT

*The aim of this study was to determine the differences in epidemiological and clinical manifestations of breast cancer in time of war in Croatia and in peacetime before and after the war, in the defined population of Požeško-Slavonska County. The methods used in this study were the evaluation of relative predictive value of variables by means of  $\chi^2$ -test and the analysis of variance, while the survival studies were tested by Long Rank test according to Kaplan-Meier analysis of survival. This work encompasses 660 patients who had breast cancer. The differences between three time periods were evaluated: the war period (1991–1995), and two control periods: before the war (1981–1990) and after the war (1996–2000). The patients were grouped by age, localization of tumor and survival. During the war period the patients were, on the average, 4.2 years younger than those who acquired the disease in control periods, and the mean age of patients was between 50 and 59 years (36.5% of patients). Although the difference in tumor distribution by sides (left or right breast) and quadrants was statistically significant (war period vs. control periods;  $p < 0.001$ ), there was no statistically significant difference in the survival of patients according to the results of Kaplan-Meier analysis of localization of tumor ( $p > 0.05$ ). The length of survival in terms of age of patients in time of surgical procedure was significantly different ( $p < 0.001$ ). This study confirms the effects of war on some epidemiological and clinical manifestation of breast cancer in the defined population of Požeško-Slavonska County.*

**Key words:** breast cancer, forms and manifestations, war, Croatia

## Introduction

The efforts to define a correlation between psycho-traumatic effects on the body and different malignant diseases are not new in scientific publications. Until now, the connection between ionizing radiation and malignant diseases of different localizations in the body has clearly been documented<sup>1–3</sup>, and likewise, the influence of war on the occurrence of other diseases and conditions<sup>4–6</sup>. The group of Japanese women born between 1940 and 1949 has a significantly higher risk of developing breast cancer, due to irradiation as a carcinogenic influence<sup>7,8</sup>.

Lecompte (1979) tried to describe cancer as a somatic result of deep emotional frustrations, and he concluded that stress might activate previously »peaceful« malignant cells<sup>9</sup>.

All efforts to establish a connection between stress and cancer are based on this balance of organism homeostasis, as well as affected immunoreactivity. It appears that the consequences of war aggression on epidemiological and clinical properties of breast cancer, as well as the survival of such patients, are not thoroughly described in scientific literature<sup>10,11</sup>.

## Patients and Methods

In the defined population of Požeško-Slavonska County 660 patients with breast cancer were monitored through three time periods:

1. War (tested) period: 1991–1995 (156 patients);
2. Period preceding the war (first control): 1981–1990 (281 patients);
3. Period following the war (second control): 1996–2000 (223 patients).

Due to specific war circumstances (restricted traffic communication) 119 patients were forced to start treatment in other institutions. Differences between

patients were recorded through periods with respect to: age, localization of the disease, and length of survival of the patients.

Relative predictive value of tumors and patients variables were evaluated using  $\chi^2$ -test and analysis of variance, and survival was evaluated with Long Rank, Kaplan-Meier test.

## Results

As shown in Figure 1, we can see the distribution of breast cancer by periods. The average age in the war group was 52.2 years. The relations of breast cancer patients' average age by five-year periods were 56.8, 56.2, 52.2, 56.3. This means that the patients from the war period were on the average 4.2 years younger than the control groups, which was statistically significant, according to the analysis of variance ( $F = 5.72$ ) ( $p < 0.0001$ ).

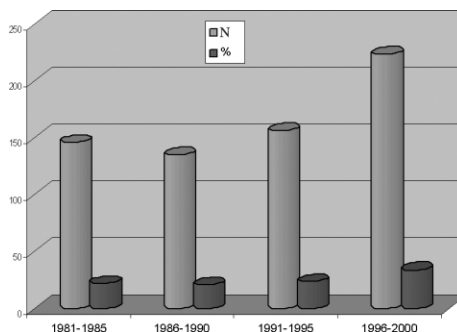


Fig. 1. Distribution of breast cancer by periods.

In the tested period most common were the patients who were 50–59 years old (36.5%), while in the control (peace) periods, the most common age of patients was 60–69 years. A statistically significant difference between age groups was established ( $p < 0.001$ ).

The difference in frequency of localization of breast cancer by sides (left breast vs. right breast) between war and control periods, tested by means of  $\chi^2$ -test, was shown to be statistically significant ( $p < 0.001$ ). Tumors localized in left breast

were more common during the war period (58.3%), as shown in Figure 2.

A statistically significant difference between three groups was also found in the distribution of breast cancer by quadrants. Although the most common quad-

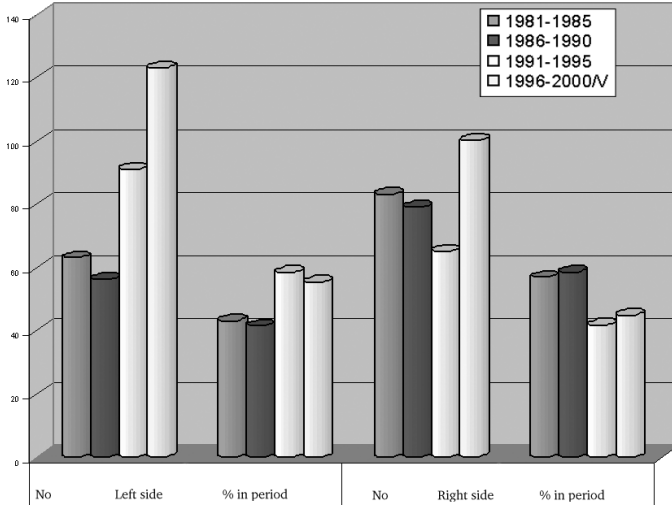


Fig. 2. Frequency of localization of breast cancer by sides.

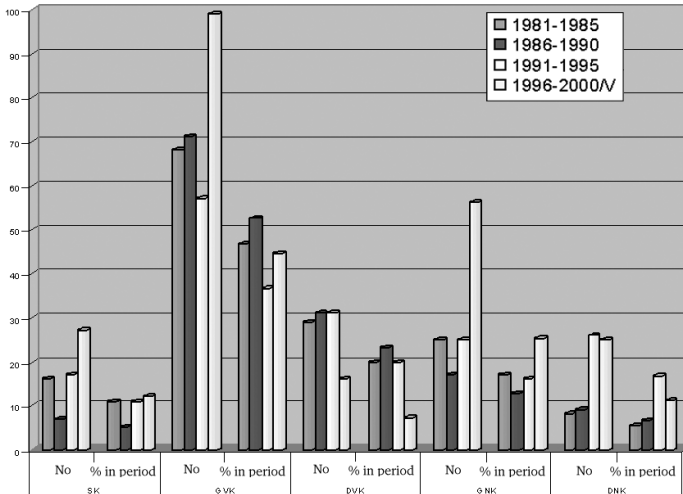


Fig. 3. Distribution of quadrants where breast cancer was found.

rant is upper lateral, it was not so often a site of tumor in the war period. In contrast, the tumors localized in medial lower quadrant were more frequent than expected (16.7%), which is shown in Figure 3.

In this paper there was not a statistically significant difference in survival between the 3 before mentioned periods, as Kaplan-Meier analysis of survival showed (Log Rank = 5.33, df=3,  $p>0.005$ ). These data are shown in Figure 4.

The length of survival in terms of age of patients in time of surgical procedure was significantly different ( $p<0.0001$ ). Figure 5. As shown in Figures 6 and 7 we did not detect a statistically significant difference in the survival of patients with tumors in left or right breast or with localization in different quadrants of the same breast ( $p>0.005$ ).

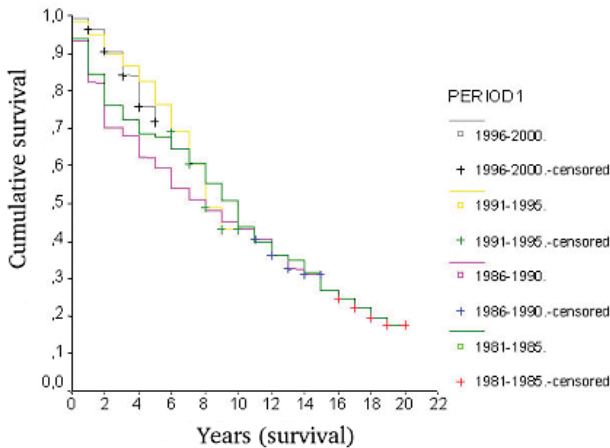


Fig. 4. Difference in survival through periods (Kaplan-Meier analysis of survival).

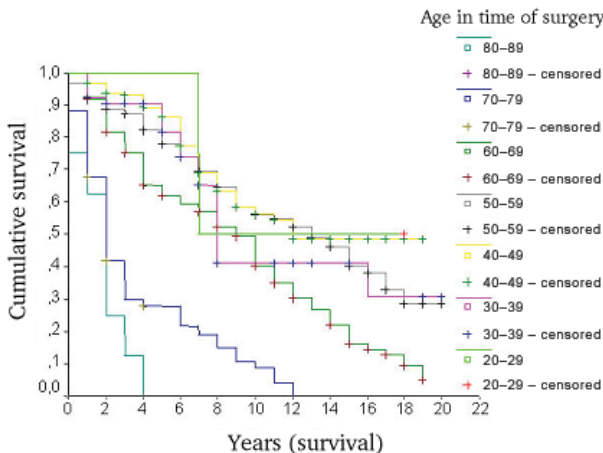


Fig. 5. The length of survival by patient's age.

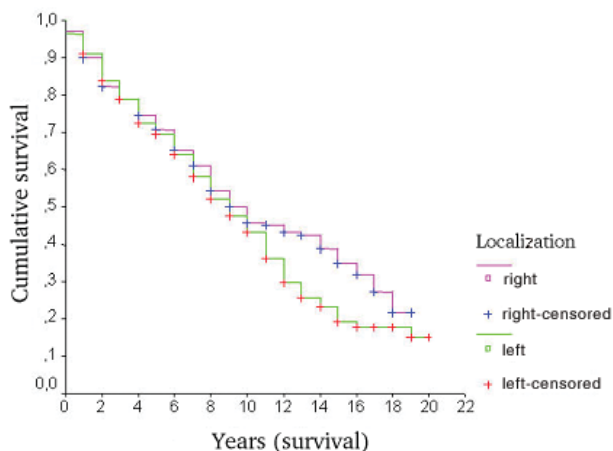


Fig. 6. Survival of patients with different localization of tumors.

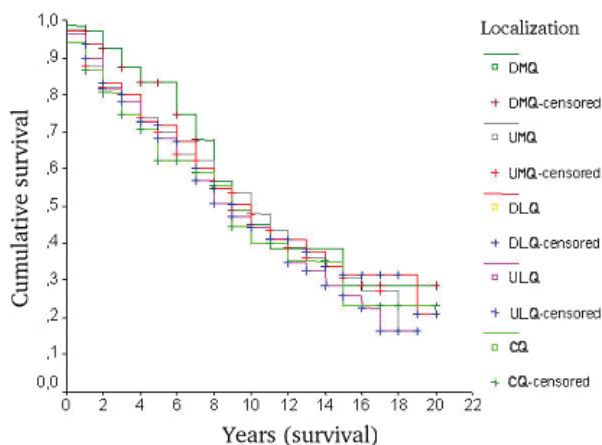


Fig. 7. Survival of patients with localization in different quadrants of the breast.

## Discussion

Modern therapeutic approach of human diseases puts the human activities, and not the organ of the affected system in focus, having in mind that interactions with somatic and psychological processes are interconnected and not separable<sup>12</sup>.

There is no abundance of literature in Croatia that would connect the war and breast cancer, despite the aggression on the country. Publications by Karelović from University Hospital »Split« in 1998, and by a group of authors from University

Hospital. »Sestre milosrdnice«, Zagreb, in 1999<sup>10,11,13</sup> deal with this issue, although with different goals. Both point to the connection between war stress and breast cancer. There are also two recent publications that show a causative connection

between the war in Croatia and a higher incidence of breast cancer, although they are focused on describing the endocrinological and metabolic changes in people who were prisoners during the aggression on Croatia<sup>14,15</sup>.

The key question is: Can we blame war aggression as an inducer of higher incidence of breast cancer, or how much did war stress affect the clinical and epidemiological characteristics of breast cancer in the defined population of a county?

It is evident in this study that war aggression on our country was not an inducer of a higher incidence of breast cancer, but we have recorded several clinical, epidemiological and pathological changes in our patients.

An answer to the question why we have not found a higher incidence of breast cancer in comparison with peaceful periods lies, to a high extent, in giving priorities to war medicine in that period, while oncological care was in the background. That is confirmed by a higher number of discovered tumors after 1996. Despite that, Kaplan-Meier analysis did not show a statistically significant connection between the period of treatment and the length of survival.

The fact that patients during the war were on the average 4.2 years younger than in control periods is significant and important, along with the fact that the patients who were 50–59 years old had the highest risk of developing breast cancer, which is different from our statistical data from other periods<sup>16</sup>. Kaplan-Meier analysis of survival of age groups shows a statistically significant difference (Figure 5).

A position of tumor is closely connected with lymphatic pathways of spreading of malignant cells. For that reason, it is very important to see how did the local-

ization of breast tumors changed in patients under war stress, which could eventually have an influence on known directions of lymphatic spreading of malignant cells. We found a statistically significant difference in the frequency of localizations with respect to side (left-right) and with respect to breast quadrants.

Despite a statistically significant difference, it appears that the data concerning a higher frequency and a higher incidence of left breast tumors (58.3%) can be taken only as a descriptive indicator of this distribution.

The most common tumor localization through this 20-year long study was the upper lateral quadrant (44.7%), which is to some extent in accordance with other studies<sup>17</sup>. Central tumor localization, in medial quadrants of the breast, due to more frequent lymphatic spreading in retrosternal lymphatic nodes, proved to be less benign<sup>18</sup>, due to direct implication on surgical treatment.

The localization of tumor by sides and quadrants was not a statistically significant predictor of survival in this study, which was shown by Kaplan-Meier analysis.

Fajdić (2003) also confirmed the influence of war on histopathological characteristics of some forms of breast cancer. The author indicated that the incidence of the most common form of breast cancer, invasive ductal cancer, was lower compared to the control period<sup>19</sup>.

As in other studies that indicate a correlation between stress and breast cancer in the broadest sense<sup>20–32</sup>, in this study we have pointed to elements that confirm a strong modifying impact of war aggression on some clinical and epidemiological characteristics of breast cancer.

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## UČINAK RATNE AGRESIJE NA HRVATSKU NA NEKE OBLIKE I OČITOVANJE RAKA DOJKE

### SAŽETAK

Cilj ovog rada bio je odrediti razlike u epidemiološkim i kliničkim očitovanjima raka dojke za vrijeme rata u Hrvatskoj i u mirnodobskim uvjetima prije i nakon rata, na

definiranoj populaciji Požeško-slavonske županije. Metode korištene u ovom istraživanju su  $\chi^2$ -test relativne prediktivne vrijednosti varijabla i analiza razlika, dok je preživljenje testirano Long Rank testom prema Kaplan-Meier analizi preživljenja. U istraživanje su uključene 660 pacijentice koje su imale rak dojke te su procijenjene razlike među njima u odnosu na tri vremenska perioda: ratni period (1991.–1995.) i dva kontrolna perioda: prije rata (1981.–1990.) i nakon rata (1996.–2000.). Pacijentice su grupirane po dobi, lokalizaciji tumora i preživljenju. Tijekom ratnog perioda pacijentice su bile u prosijeku 4.2 godine mlađe nego one kojima je dijagnosticirana bolest u kontrolnim periodima, a srednja dob pacijentica je bila između 50–59 godina (36.5% pacijentica). Iako je razlika u raspodjeli tumora po stranama i kvadrantima dojke bila statistički značajna (ratni period naspram kontrolnih perioda;  $p < 0.001$ ), nije bilo statistički značajne razlike u preživljenju pacijentica prema rezultatima Kaplan-Meier analize lokalizacije tumora. Dužina preživljenja prema dobi kada je pacijentica operirana se statistički značajno razlikovala ( $p < 0.001$ ). Ova studija potvrđuje učinak rata na neke epidemiološke i kliničke značajke raka dojke na definiranoj populaciji Požeško-slavonske županije.