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Effects of War Aggression in Croatia on Histopathological Manifestations of Breast Cancer in Defined Population of One County

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A B S T R A C T

The aim of the present study was to determine the differences in epidemiological and clinical manifestations of breast cancer during the war in Croatia and in peacetime. 660 consecutive patients were recorded (656 female and 4 male patients) from Požeško -Slavonska County. The changes in histopathological features were recorded in war period (1991–1995, 156 patients) and through two control periods, before the war (1981–1990, 282 patients) and after the war (1995–2000, first five months, 223 patients). The relative predictive value was calculated using χ^2-test. The survival was calculated according to Kaplan-Meier analysis of survival. The histopathological analysis showed an equal distribution of noninvasive cancer (in situ cancer) across periods. In the war period, the level of the most common invasive cancer, ductal breast cancer, was lower (57.7%), compared to control periods (71.2% : 63.7% : 68.2%). Opposite to that, invasive lobular cancer was more common in the war period (3.2%), compared to control periods (0.7%–1.3%). Furthermore, mixed cancer was also increased in the war period (7.1%) compared to control periods (0.7%–2.2%), as was medullar cancer (10.9% vs. 5.5%–5.9%). The study showed statistically significant differences in the survival of patients with different histopathological diagnoses (Log Rank= 47.49, df=7, p<0.0001), while the histological grade of tumor, as a predictive factor was not proved to be statistically significant (p>0.05). This study confirmed the influence of war on histopathological incidence of some forms of breast cancer.

***Key words**: breast cancer, histopathology, war, Croatia*

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Introduction

In the first part of the last century we encountered the hypothesis that cancer, in some individuals, was a somatic presentation of psychic and emotional conflicts. In these persons there is an increased possibility of activation of malignant, until then »peaceful« cells[1].

The correlation between war aggression and carcinogenesis, and between war aggression and other pathological conditions is clearly documented in many publications[2–10]. In most of these publications dominates the pathology which is a direct consequence of ionizing radiation[7,11,12].

In spite of that, the repercussions of direct war events on epidemiological and some clinical and pathohistological forms of breast cancer are not thoroughly described in literature. The influence of war -stress on breast cancer in woman during aggression in Croatia has so far been recorded in only two papers[13–15].

Patients and Methods

In this study, 660 consecutive patients were recorded (656 female and 4 male patients) from the territory of Požeško-Slavonska County. The changes in histopathological features were recorded in war (test) period (1991–1995, 156 patients) and through two control periods, before war (1981–1990, 282 patients) and after the war (1995–2000, first five months, 223 patients). The greatest number of patients (541) was treated in General Hospital in Požega, while a smaller number of residents of our county, due to specific war circumstances, had started treatment in other medical facilities (119 patients). The relative predictive value was calculated by means of χ^2-test. The analysis of survival was calculated by means of to Kaplan-Meier analysis of survival.

Results

This study analyzes the influence of war on the histopathological incidence of breast cancer in the residents of Požeško -Slavonska county. Two basic groups have been analyzed, noninvasive and invasive cancer in all their forms. The histopathological presentation shows an equal distribution of noninvasive cancer by periods (4.1%–5.2%) (Table 1).

We have recorded a slightly lower level of the most common form of invasive cancer, invasive ductal cancer, in the tested period (57.7%) compared to other periods (71.2% : 63.7% : 68.2%). But, in the war period we encountered a more common occurrence of invasive lobular cancer (3.2%), compared to other periods (0.7%–1.3%), and mixed form of breast cancer (7.1%), compared to other periods (0.7%–2.2%). Finally we discovered a significantly higher frequency of medullar breast cancer in the period between 1991–1995 (10.5%), compared to control periods (5.5 –5.9%). The distribution of frequency of some histopathological types of invasive cancer by periods was statistically significant ($\chi^2 = 34.079$, df = 21, $p < 0.001$).

Since the determination of histopathological grade started later in our hospital, the number of analyzed samples is 424 (Figure 1).

In such a restricted sample, well differentiated tumors (G1) were equally distributed in war and control periods (23.4% : 26.0%), moderately differentiated tumors (G2) were equally distributed in war and second-postwar five-year period (53.1% : 53.5%), and poorly differentiated tumors (G3), by means of Bloom Richardson classification, in the after -war period 1995–2000 in 29.3%. We have not found a statistically significant difference between the distribution of histological grade through all three, although incomplete periods ($\chi^2 = 3.56$, df = 4, $p > 0.05$).

TABLE 1
DISTRIBUTION OF FREQUENCY OF SOME HISTOPATHOLOGICAL TYPES BY PERIODS

PHD		Period				Total
		1981-1985	1986-1990	1991-1995	1996-2000/V	
NIR	N	6	7	8	11	32
	%	4.1	5.2	5.1	4.9	4.8
IDR	N	104	86	90	152	432
	%	71.2	63.7	57.7	68.2	65.5
ILR	N	1	1	5	3	10
	%	0.7	0.7	**3.2**	1.3	1.5
MIJ	N	3	1	11	5	20
	%	2.1	0.7	7.1	2.2	3.0
MED	N	8	8	17	13	46
	%	5.5	5.9	**10.9**	5.8	7.0
KOL	N	8	4	10	11	33
	%	5.5	3.0	6.4	4.9	5.0
PAG	N	1	2	2	4	9
	%	0.7	1.5	1.3	1.8	1.4
NDR	N	15	26	13	24	78
	%	10.3	19.3	8.3	10.8	11.8
Total	N	146	135	156	223	660
	%	100.0	100.0	100.0	100.0	100.0

NIR – non-invasive cancer; IDR – invasive ductal cancer; ILR – invasive lobular cancer; MIJ – mixed cancer; MED – medullar cancer; KOL – coloid cancer; PAG – Mb. Paget; NDR – non-differentiated cancer

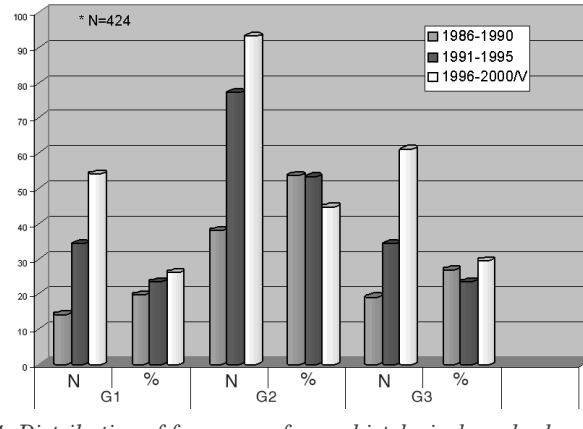

Fig. 1. Distribution of frequency of some histological grades by periods.

The histopathological diagnosis was a significant predictive factor of survival, resulting in a statistically significant difference in survival of patients with different histopathological diagnoses (Log Rank = 47.49, df = 7, $p < 0.001$) (Figure 2).

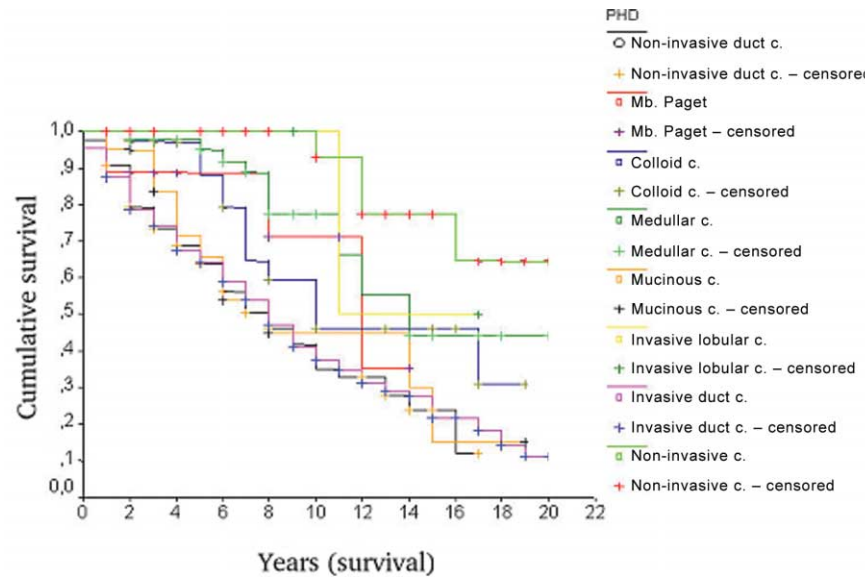

Fig. 2. Histopathological diagnosis as predictor of survival.

The percentage of survival was markedly high in patients with noninvasive breast cancer (87.5%), while it was much smaller in patients with invasive ductal cancer (47.45%), and non-identified breast cancer (41.03%). The histological grade of tumor as predictor of survival did not show a statistical significance in this study (Long Rank = 0.05, df = 3, $p > 0.05$) Figure 3.

Discussion

The consequences of war aggression on morphological and histopathological characteristics of tumors and on the survival of patients are not clear so far. In many publications the investigators tried to determine the relation between stress, war and breast cancer[4–6,13,16–20].

The history of medical science has recorded efforts to determine the quality and quantity of stress that would correlate with the emergence of the disease[21].

Today's management of diseases takes into account the continuous and interconnected reactions of somatic and psychic processes as inseparable parts[22].

Riley (1975) was successful in proving the effects of stress on rats in an experiment in which he implanted breast-cancer tumor cells into rats, in 90% cases, in a situation when the rats were under stress[23,24]. Despite the difficulties in measuring stress as a subjective quality, it has been presented in this study as a probable modifier of histopathological forms of breast cancer which is statistically simply measured.

The war aggression on Croatia was not, unfortunately, followed by scientific and other publications that would clarify this problem. Precisely, only a couple of authors are involved in the problem of war-stress in Croatia and its correlation with the development of different diseases[13,14,25,26]. Compared to some other wars, in the war in Croatia, women were not victims of ionizing radiation. This is-

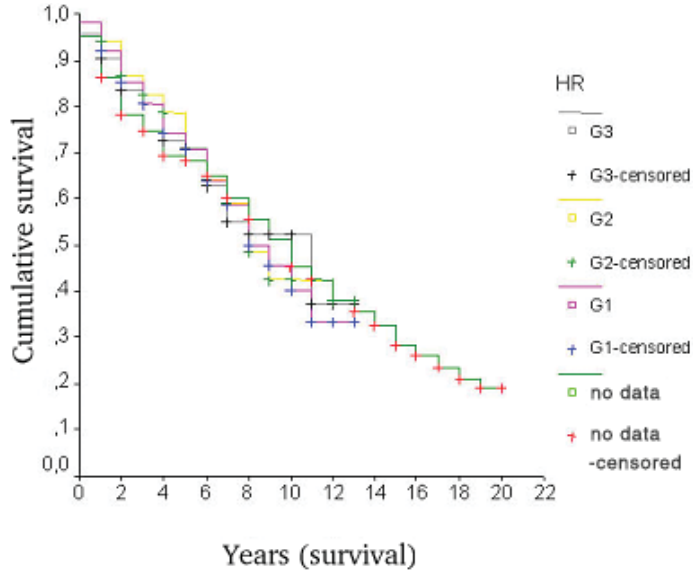

Fig. 3. Histological grade of tumor as predictor of survival.

sue is well covered in world literature[27–29]. Japanese authors claim that the exposure of breast tissue to ionizing radiation involves a much higher risk in the first four decades of life than in later periods[29].

The changes of health in women that were victims of aggression on Croatia can be viewed in the light of the psychosomatic theory of development of cancer, which is based on the research of psycho-neuro-immunological disorders[30].

Although there is no direct evidence, it is highly probable that the weakened immunological system, due to chronic stress, can lead to increased morbidity and mortality[31].

According to data of the Croatian Institute for Public Health and State Cancer Register, Bulletin No. 25/2000, the incidence and mortality of breast cancer in Croatia is continuously increasing, irrespective of the fact whether it was a war or peace-time period[32].

Histopathological findings in this study were an exceptionally significant factor for the prognosis of breast cancer. The prevalence of invasive ductal cancer is higher in all periods (71.2% : 63.7% : 57.7% : 68.2%) compared to all other forms.

Similar frequencies of invasive ductal carcinoma are usual in almost all pathohistological records in peaceful times. The tested distribution of frequencies of some histopathological types of breast cancer by periods was statistically significant ($p<0.001$). One of the important factors in this study was the fact that war -stress was an obvious inducer of increased frequency of:

– invasive lobular cancer (3.2%);

– mixed type cancer (7.1%);

– medullar breast cancer (10.9%).

In addition let us say that the frequencies of non-differentiated breast cancer in the same period are to some extent lower than expected (8.3%).

Lobular cancer in literature is described as a clinically heterogeneous group with a prognostically less favorable outcome[33,34]. Despite the data in literature describing a high percentage of bilateral and multilateral occurrences of this cancer[35], we could not confirm such findings in our patients.

In literature are also found descriptions of increased incidence of lobular breast cancer in correlation with hormonal therapy in menopausal woman[36–38], but in this study, the increase of invasive lobular cancer should be taken with reserve, because our questionnaire did not provide adequate data concerning the hormonal therapy of population under war stress.

Disproportional increase of lobular breast cancer disregarding the age and localization of tumor during peace periods in Geneva is described by some authors[39], while Japanese authors report also an increase of this particular form of cancer (5.8%)[40]. Changes in incidence of invasive lobular breast cancer have also been recently described in some papers[41,42], as well as some interesting comparisons in other papers[43].

Medullar cancer as subgroup of low -risk cancer, with a lower tendency towards metastatic spreading, constitutes about 5–7% of breast carcinoma[35,44–46]. In war period their incidence is 10.9%.

According to results of Kaplan-Meier analysis of survival, the difference in survival with different histopathological presentations was statistically significant. Invasive ductal cancer had poorest survival rate (47.5%) in contrast to noninvasive breast cancer, which is found to have a survival rate of up to 87.5%.

Histological grade according to Bloom Richardson is in practice a variable of exceedingly high prognostic value. Therefore, patients with tumors of higher grade or poorer differentiation have a 53% survival rate in a ten-year period, opposed to 90% survival rate of patients with well differentiated tumors (G1)[47].

According to Figure 1, the commonest tumor recorded is of grade G2, through three incomplete periods. The difference in grades by time periods was not statistically significant.

It appears that the prevalence of lower-grade tumors (G1) in patients from the war period (76.5% total) is, in part, a cause of lower mortality in the same period.

Despite the high prognostic significance of histological grade, the analysis of survival (Kaplan-Meier analysis) showed that that variable did not have an important predictive value.

Fajdić (2003) finds that the length of survival according to age of patients in time of surgical procedure was significantly different ($p<0.001$)[48].

This study confirms the hypothesis about the significant effect of war-stress on the biological behavior of breast cancer, which eventually, to some extent, did modify the histopathological incidence of breast cancer, the commonest malignant disease of women today.

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UTJECAJ RATNE AGRESIJE U HRVATSKOJ NA HISTOPATOLOŠKU PREZENTACIJU RAKA DOJKE U DEFINIRANOJ POPULACIJI JEDNE ŽUPANIJE

S A Ž E T A K

Cilj ove studije bio je utvrditi rizik u histopatološkoj prezentaciji pojedinih vrsta raka dojke u bolesnica zahvaćenih ratnim nedaćama za vrijeme Domovinskog rata u Hrvatskoj u periodu od 1991. do 1995. godine kao i u kontrolnim mirnodopskim petogodišnjim periodima: prijeratnom (1981.–1985.), (1986.–1990.) i poslijeratnom (1996.– 2000., prvih pet mjeseci). Ispitivan je uzorak od 660 bolesnika (656 žena i 4 muškarca) s područja Županije požeško-slavonske. Promjene u histopatološkoj prezentaciji su praćene kroz ratno ispitno razdoblje (1991.–1995.) (156 bolesnika) i kroz dva kontrolna mirnodopska razdoblja, prijeratnom (1981.–1990.) i poslijeratnom (1995.–2000., prvih 5 mjeseci) (223 bolesnika). Najveći dio bolesnika (541) je liječen u požeškoj bolnici, dok je kod manjeg dijela oboljelih žitelja županije zbog specifičnih ratnih okolnosti liječenje započeto u drugim ustanovama (119). Relativna prediktivna vrijednost ispitanika i tumora ocijenjena je χ^2-testom. Analiza preživljenja računata je prema Kaplan-Meierovoj analizi duljine preživljenja. Histopatološka prezentacija raka dojke pokazuje podjednaku distribuciju neinvazivnog raka dojke prema periodima. Uočena je niža razina najčešćeg oblika invazivnog raka, duktalnog raka dojke u ratnom periodu (57,7%) u odnosu na ostala razdoblja praćenja (71,2% : 63,7% : 68,2%). Međutim, u ratnom je periodu zapažena češće prisustvo invazivnog lobularnog raka (3,2%), u usporedbi s ostalim periodima (0,7%–1,3%). Zatim i miješanog oblika raka dojke (7,1%) u usporedbi s ostalim periodima (0,7%–2,2%), te medularnog raka dojke (10,9%), u usporedbi s ostalim periodima (5,5%–5,9%). U studiji su se pokazale statistički značajnima razlike u preživljenju kod bolesnika s različitim histopatološkim dijagnozama (Log Rank= 47.49, df=7, $p<0.0001$), dok histološki gradus tumora kao prediktor preživljenja nije u ovoj studiji pokazao statističku značajnost ($p>0,05$). U ovom istraživanju je statistički potvrđen utjecaj ratnih stradanja na histopatološku prezentaciju pojedinih oblika raka dojke po periodima u definiranoj populaciji jedne županije.