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Influence of War Circumstances on Tumor Morphological Characteristics in Patients with Breast Cancer

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ABSTRACT

The influence of war circumstances on tumor morphological characteristics in patients with breast cancer has not been studied up to now. The aim of this study is to investigate if war circumstances have influenced breast cancer incidence. The study covered both the patients in which during a period of observation a breast cancer was diagnosed as well as those who died of the same disease in the same period. Three sources of data were used: 1) The archives of the Oncology and Radiotherapy Center of the University Hospital »Split« (UHS): hospital data of 768 patients were reviewed. The war sample consisted of 380 patients aged 59.4 ± 12.1 (31 to 86) (including 5 males), whereas the pre-war sample was made up of 388 patients aged 58.4 ± 12.7 (19 to 88) (including 3 males); 2) Register of death of the Pathology Department of UHS with 162 analyzed persons whose death was caused by breast cancer in the six-year period between 1988 and 1993. The list of 162 dead patients included 79 people who died from breast cancer diagnosed in that period (1988–1993) and another 83 people that had been diagnosed before that period; 3) The biopsy register of the Pathology Department of UHS with 851 breast biopsies performed between 1988 and 1993. Breast cancer is predominantly a female illness (99.1%). The war circumstances influenced the of T, N and M rate. The rate of N2, N3, M1 were conspicuously higher in the war period. There were significantly more malignant histological diagnoses found in new patients and also significantly more patients died due to breast cancer. Stress and other war circumstances undoubtedly have a negative impact on the numerous markers of breast cancer which we have proved in this study.

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Introduction

Breast cancer is the most common malignant tumor in women that will develop in 1 out of 9 women, or in about 11% of females. It is also the leading cause of cancer death in women. One death caused by breast cancer occurs every 15 minutes¹. 2619 new cases are annually discovered in Croatia and a crude incidence rate was 110.7 in 1999². The influence of war events on the morphological characteristics in patients has not been studied until now (Medline: 1966–2002).

The aim was to find out if the circumstances during the War for the Homeland had influenced the spreading of breast cancer, the histological type of the tumor and the death rate of the patients with breast cancer.

Patients and Methods

The study covered the period between 1988 and 1993. The tested group consisted of patients from the three war years (1991–1993) while the control group consisted of patients from the three-year period preceding the war.

In order to take into consideration all the problems connected with breast cancer the study analyzed the patients in which the existence of breast cancer was confirmed during that period, those that died of breast cancer as well as the patients with biopsies performed in the same period.

Three sources of data were used:

1. The archives of the Oncology and Radiotherapy Center of the University Hospital »Split« (UHS) containing 768 patients. The examined sample consisted of 380 patients (5 males), aged 59.4 ± 12.1 (31–86), whereas the controls were 388 patients (3 males), aged 58.4 ± 12.7 (19 to 88).
2. The death register of the Pathology Department of UHS with 162 analyzed

persons whose death was caused by breast cancer in the six-year period between 1988 and 1993. Out of 162 deaths 79 died from breast cancer diagnosed in that period (1988–1993), whereas 83 of them had been diagnosed before that time.

3. The biopsy register of the Pathology Department of UHS with 851 breast biopsies performed between 1988 and 1993.

Refugees and displaced persons were excluded from the tested group and there were no such patients in the control group either. All the tumors were operated in the Surgical Department of UHS and the bioptic material was analyzed in the Pathology Department of UHS. The bioptic material was fixed in 10% puffed formaldehyde colored with hemalau-eosin and analyzed by means of *Opton* microscope. In the course of the analysis of the bioptic material the pathological type was established and divided according to the criteria of the World Health Organization. All the patients were called back after six and twelve months to have their illness monitored.

Results

Table 1 shows the incidence of the breast cancer patients in the observed period. There were fewest new diagnosed patients in 1990 (14.33%), and most in 1992 (18.75%). During the war years there were fewer newly diagnosed patients compared to the period before the war (49.47%: 50.53%), but the difference is not statistically significant ($p > 0.05$).

The average age of both groups was 58.9 ± 12.4 years. The youngest patient was 19 and the oldest 88 years old. In the examined group the average age was 59.37 ± 12.1 (31–86). The average age of the control group was 58.38 ± 12.7 (19–88). That means that the patients from

the tested group were generally one year older than the controls, but the difference is not statistically significant ($p > 0.05$).

In the observed period out of the total number of new patients there were 768 (99.1%) women and 8 (0.9%) men ($p < 0.01$). Most males patients were noted in

1991–4 (0.5%). The difference between men and women in the analyzed periods was not significant ($\chi^2 = 0.55$; $p > 0.05$).

The number of patients with T4-type tumor in the pre-war period decreased between 1988 and 1990, but it increased again during the war. There were more patients with T2 tumor during the period preceding the war (21.8%) compared to the war period (16.6%). The difference between these two groups is significant ($p < 0.05$) (Table 2).

The number of the patients with a lower N rate of tumor (N0 and N1) was higher during the period preceding the war, while the number of patients with a higher N rate of tumor (N2 and N3) was higher in the war period ($p < 0.01$) (Table 3 and Figure 1).

TABLE 1
FREQUENCY OF BREAST CANCER PATIENTS ACCORDING TO YEARS

Year	N	%
1988	142	18.50
1989	136	17.72
1990	110	14.33
1991	124	16.14
1992	144	18.75
1993	112	14.58

TABLE 2
T STAGES OF BREAST CANCER ACCORDING TO YEARS

Year	T1		T2		T3		T4		Total		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
1988	42	5.5	53	6.9	9	1.2	38	4.9	142	18.5		
1989	32	4.2	62	8.1	15	2.0	27	3.5	136	17.7	388	50.5
1990	31	4.0	52	6.8	4	0.5	23	3.0	110	14.3		
1991	44	5.7	34	4.4	8	1.0	38	4.9	124	16.1		
1992	43	5.6	57	7.4	10	1.3	34	4.4	144	18.8	380	49.5
1993	38	4.9	37	4.8	5	0.7	32	4.2	112	14.6		
Total	230	29.9	295	38.4	51	6.7	192	24.9	768	100	768	100

TABLE 3
DISTRIBUTION OF THE N STAGES OF BREAST CANCER ACCORDING TO YEARS

Year	N0		N1		N2		N3		Total		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
1988	58	7.6	74	9.6	10	1.3	0	0.0	142	18.5		
1989	52	6.8	78	10.2	4	0.5	2	0.3	136	17.7	388	50.5
1990	54	7.0	49	6.4	7	0.9	0	0.0	110	14.3		
1991	47	6.1	58	7.6	16	2.1	3	0.4	124	16.1		
1992	48	6.3	66	8.6	21	2.7	9	1.2	144	18.8	380	49.5
1993	48	6.3	45	5.9	15	2.0	4	0.5	112	14.6		
Total	307	40.1	370	48.3	73	9.5	18	2.4	768	100	768	100

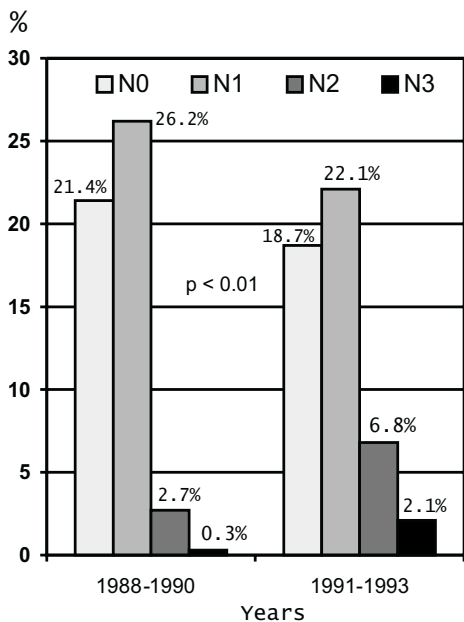


Fig. 1. Graphic image of the distribution of the N stages of breast cancer during the pre-war and war period.

At the moment of establishing the diagnosis, 80 (10.4%) patients had a metastasis. The number of patients with metastases (6.2%) was higher in the tested group than in the control group (4.2%), while the number of patients without metastases at the moment of diagnosis was higher in the control group (46.3%)

than in the tested group (43,3%) and the difference was statistically significant ($p < 0.05$) (Table 4).

A fibrocystic hyperplasia from the bioptic material was nearly the same (14–22 per year). In all analyzed years fibroadenoma appeared 8 times more often during the war period than in the period preceding the war. Invasive ductal carcinoma occurred 2.56 times more often during the war than before the war. Ca lobulare was 4.5 times more frequent in the war period (Table 5).

A lethal outcome of breast cancer is significantly higher (16%; $p < 0.05$) in war years (94), compared to pre-war years (68).

Discussion

The influence of stress on cancer development has been of great medical interest for a long time. Both Hippocrates and later Galen thought that melancholic people developed cancer more often than other persons³⁻⁶. Other authors later pointed to the possibility of psychological factors influencing the development of cancer. In 16th century the great surgeon Ambrose Pere was certain that mental problems, pressure and anxiety could influence a malignant process⁷. Groddek in 1928 set the hypothesis that cancer was a

TABLE 4
DISTRIBUTION OF THE M STAGES OF BREAST CANCER ACCORDING TO YEARS

Year	M0		M1		Total		Total	
	N	%	N	%	N	%	N	%
1988	127	16.5	15	2.0	142	18.5	388	50.5
1989	129	16.8	7	0.9	136	17.7		
1990	100	13.0	10	1.3	110	14.3		
1991	111	14.5	13	1.7	124	16.1	380	49.5
1992	126	16.4	18	2.3	144	18.8		
1993	95	12.4	17	2.2	112	14.6		
Total	688	89.6	80	10.4	768	100	768	100

TABLE 5
DISTRIBUTION OF THE MOST FREQUENT HISTOLOGICAL FINDINGS ACCORDING TO YEARS

Year	Hyperplasia fibrosa cystica		Fibro-adenoma		Ca lobulare		Ca ductale invasivum		Total	
	N	%	N	%	N	%	N	%	N	%
1988	14	2.9	3	0.6	0	0.0	2	0.4	19	3.9
1989	21	4.3	1	0.2	2	0.4	35	7.2	59	12.2
1990	21	4.3	4	0.8	2	0.4	43	8.9	70	14.5
1991	19	3.9	13	2.7	1	0.2	33	6.8	66	13.7
1992	22	4.6	20	4.1	9	1.9	82	17.0	133	27.5
1993	12	2.5	31	6.4	7	1.4	86	17.8	136	28.2
Total	109	22.5	72	14.8	21	4.3	281	58.1	483	100

somatic disorder resulting from deep psychological frustrations⁸. Foque in 1931 concluded that emotional conflicts could activate malignant cells that otherwise rested in situations of health and peace⁸. Freude Aleksander and other dynamic psychiatrists, who described the human organism as a very complicated energy system with a constant transformation of mental into body energy and reversely, have contributed to a psychosomatic orientation in medicine and to better understanding of numerous functional and pathological processes in the human organism. Psychosomatic approaches to illness imply a continuous interaction of the somatic and mental processes, which leads to the conclusion that human organism is an indivisible whole. In keeping with that position there is no sick organ or isolated system, but a sick man as an individual in constant interaction with his/her environment. That means that all functions are somatic and mental at the same time and dependent on each other⁹.

Nowadays the notion of stress is very fashionable in medical slang and is considered as having a great influence on the development of many psychosomatic illnesses (peptic ulcer, spastic colon, colitis, bronchial asthma, lung tuberculosis, in-

fertility etc.)¹⁰. Stress is considered as an emotional and biological response of the organism to a real stimulant that causes or predicts danger to the same organism. Such a state urges the psychomotor mechanisms to defend themselves with a varying effect⁹. Holmes tried to add up the quality and quantity of stress and study their role in the development of various diseases¹¹. His conclusion was that stress had an influence on the incidence of some diseases, but he pointed out that the lifestyle also influenced the behavior and the reactions of a person. Sacher concluded that establishing a defense mechanism in each individual is more important than the stress itself¹². He was focused on the influence of stress on endocrine disorders and he found that neurosis and psychosis are effective modes of defense and that those patients rarely suffered from endocrine disturbances. Riley and associates found a higher level of plasma corticosteroids five minutes after an induced stress¹³. Immediately after applying the stress the number of circulating T cells are falling down and thymus had tendency of involution. Immunity disorders compromise the organism's ability to control malignant processes, so the malignant cells are able to escape the control that exists in an intact

immune system. Riley 1975 proved experimentally those mice with implanted tumors if exposed to stress situations developed carcinoma in 90% cases in contrast to 10% cases in controls¹⁴. Greene found out that leukemia developed more often in situations when patients had lost a dear person or got separated from him/her with an ensuing state of depression, hopelessness and lack of perspective¹⁵. Shekelle associates monitored 2020 depressed patients during 17 years and found among them twice as many cancerous diseases than in the rest of the population¹⁶.

War influence on tumor morphological markers and breast cancer patients' survival has not been studied up to now. The stress that was brought about makes it difficult to measure the subjective factor but it is also an important breast cancer prognosis modifier. That is why this work focused on the study of factors that could be objectified and analysed^{17–21}.

According to Croatian National Institute of Public Health the incidence and the death rate of breast cancer in Croatia has been in constant growth in the last two decades. We have found nearly the same incidence of newly diagnosed patients with breast cancer in both our groups. If we assumed that war circumstances had a negative influence on breast cancer, we could expect a significantly higher percentage in the war period. The lack of that kind of data could be explained by our failing to diagnose the real number of patients. There were traffic blockades in many parts of the country. During the war many people gave priority to the war instead of their health, and the regional Oncology Departments of UHS, in keeping with the new series of regulations, ceased breast-checking free of charge.

The average age of patients in this study was 58.9. The youngest patient was 19 and the oldest was 88 years of age.

There was no significant age difference between the observed groups. During the war period the average age of breast cancer patients was one year higher, which means that the groups were compatible.

The literature data point that the breast cancer will develop in 1 out of 9 women. The risk for men is a hundred times lower. In this article the ratio between sexes in the incidence of breast cancer is 91 in women to 0.9 in men, which complies with literature data¹.

The difference in T- grade of the breast cancer of the two observed groups was significant. Beside the histological findings, the clinical grade of the tumor according to TNM classification was important for the prognosis and for the choice of treatment methods. T stands for the size of the tumor at the moment of checking. In the pre-war period 5.2% more breast tumors with T2 grade were diagnosed. During the free breast-checking period before the war, a physician was able to palpate the T2 grade (2–5 cm size) tumors, while in the war period the patients often came after they had noticed breast skin changes. That is why in the war period there were 2.1% more T4 grade breast cancers found at the moment of the diagnosis compared to the pre-war period.

The capture of lymph nodes is noted down with N and in this study a significant difference in the lymph node capture of the pre-war patients compared to the war period was found. The breast cancer patients with a lower N grade tumor were more frequent in the pre-war period, whereas in the war period there were more with the higher N grade of the tumor. Such results could be explained by a later diagnosis of breast cancer, causing – because of the advanced grade of cancer – social problems as well as health care problems.

It is known that the survival of the breast cancer patients depends on the prospects of metastases. This work showed significantly more patients with metastases in the war group and more patients without metastases in the pre-war group. This confirms the negative influence of the war circumstances on breast cancer. The histological finding is also important for the prognosis and breast cancer therapy.

The histological findings in the war period are statistically significantly different compared to the findings of the pre-war period. The finding of the hyperplastic fibrous cysts in the examined biotic material in all observed years was equal. That means that during the three pre-war and the three war years 14 to 22 new cases were discovered annually. Fibrous tumors were 8 times more frequent in war biotic material than in the pre-war, while ductile invasive carcinoma was 2.5 times more frequent in the war compared to the pre-war period. A lobular carcinoma was 4.5 times more often found in the war than in the pre-war period. The significant increment of malignant tumors in the war period cannot be explained by mere geographical isolation due to war circumstances or to economic factors. It is questionable to what extent stress could be held responsible for this situation.

A noticeably lower number of histological findings compared to the number of newly diagnosed patients could be explained by the fact that biopsies and operations were performed in other hospitals, because patients in Split were forwarded to regional oncology centers to undergo radiotherapy.

The death of the breast cancer patients depends on numerous factors among which the grade and the histological findings are most important. In

this work the death rate of the breast cancer patients was found statistically significantly higher in the war period. The reason for that is probably higher TNM grade of breast cancer at the moment of diagnosis. Also, there were more malignant breast tumors diagnosed in the war period compared to the pre-war period. That is the second reason for a higher death rate. The results were not compared to literature data due to the absence of such results in literature. This work confirms the hypothesis that war circumstances significantly influence most breast cancer characteristics.

It cannot be stated for certain what are the specific causes of such statistically relevant changes of breast cancer characteristics at the moment of diagnosis stress or geographic isolation or lack of free breast check-ups or all those together. It can be assumed that war circumstances had their influence on the significant change of biological breast cancer behavior compared to the pre-war period.

Conclusion

Breast cancer is predominantly a women's disease. The war circumstances significantly influenced TNM type of breast cancer grade and the histological findings of new patients. There was a higher death rate from breast cancer during the war. This study confirms the hypothesis that war impact is a significant factor in breast cancer condition. We do not know if the stress or geographic isolation or the ceasing of free breast check-ups or all those factors together are the reasons for detecting higher grades of breast cancer at the moment of diagnosis, but it is certain that war circumstances had a part in that.

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UTJECAJ RATNIH PRILIKA NA TUMORSKA MORFOLOŠKA OBILJEŽJA BOLESNIKA S RAKOM DOJKE

S A Ž E T A K

Utjecaj ratnih prilika na tumorska morfološka obilježja bolesnika s rakom dojke do danas nije proučavan. Cilj je bio ispitati jesu li ratne prilike utjecale na rak dojke. U radu su obrađeni ispitanici kojima je u promatranom periodu dijagnosticiran rak dojke i ispitanici koji su u tom razdoblju umrli od raka dojke. Korištena su tri izvora podataka: 1) Arhiv povijesti bolesti Kliničkog centra za onkologiju i radioterapiju Kliničke bolnice »Split« (KBS), gdje je obrađeno 768 bolesnika. Ratnu skupinu činilo je 380 bolesnika (5 muškaraca), prosječne starosne dobi 59 godina (31–86). Predratnu skupinu činilo je 388 bolesnika (3 muškarca), prosječne starosne dobi 58 godina (19–88); 2) Knjiga prijave smrti Odjela za patologiju KBS, gdje su obrađene 162 osobe koje su u razdoblju od 1988.–1993. godine umrle od raka dojke. Od 162 umrla 79 ih je imalo postavljenu dijagnozu unutar 6 promatranih godina, dok je za preostala 83 ispitanika godina dijagnosticiranja datirana prije ovog perioda; 3) Knjiga biopsija Odjela za patologiju KBS. Obraden je 851 ispitanik kojem je u razdoblju od 1988.–1993. godine izvršena biopsija dojke. Rak dojke je pretežno bolest žena (99,1%). Ratne prilike su značajno (p < 0,05) utjecale na visinu T, N i M stupnja raka dojke. U ratnom periodu bilo je upadljivo više N2, N3 i M1 stupnja raka dojke. Tijekom rata bilo je značajno više malignih patohistoloških nalaza novooboljelih, kao i značajno više umrlih od raka dojke. Stres i druge okolnosti koje rat uvjetuje nesumnjivo značajno nepovoljno utječu na niz tumorskih obilježja raka dojke, što je ovim radom i dokazano.