Recent Studies & Advances in Breast Cancer

Chapter 3

Depression in Female Breast Cancer Patients

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1. Introduction

The knowledge of the diagnosis of cancer often leads to anxiety and depression in the affected person. A pessimistic interpretation of one's disease and perspectives on life in the future is almost always present even in those who seeminly continue with their professional and other everyday activities. The studies in the area of psychooncology have shown that five years after the mastectomy in female breast cancer patients the disease outcome depends on the mode of mental reaction in the first three postoperative months.

Visits to one's oncologist tend to focus primarily on the treatment of bodily disease and its adverse effects, and secondarily on the management of pain and other symptoms. Emotional symptoms can be underestimated and even completely overlooked and neglected as an expected companion of cancer. It is quite logical that a psychiatrist should be involved in the treatment of a cancer patient, especially the women with breast cancer. It is a fact that such a treatment approach is not institutionally introduced and therapeutic teams in the management of breast cancer patients do not have psychiatrists.

The patients themselves are reluctant to ask their doctors for help regarding emotional complaints, fearing it could draw the doctor's attention away from cancer treatment, or they are afraid of negative cultural attitudes towards depression [1].

The emotional response of an individual with cancer is determined by the following three factors:

a) attitude towards the diagnosis (eg. as a challenge or a threat);

b) perception of control (partial or none), and

c) view of prognosis (good or poor) [2].

A holistic orientation itself requires that the approach in the treatment of individuals with most serious malignant diseases should be multidisciplinary, involving a collaboration of experts in different areas (various medical specialists, nurses, technicians, psychologists, psychotherapists, spiritual counselors, ethicists, physical therapists, and volunteers) [3].

The success of treatment in oncology is influenced not only by the disease stage, tumor histology, degree of malignancy, and mode of treatment, but also by numerous psychic factors. All the theories concerning psychosomatic background of malignant diseases can be categorized into permissive and causal ones [4].

The permissive theory is a more moderate one and assumes that psychogenic factors involved do not act as direct cancerogens, but that other immediate causal agents make possible that malignant injuries to the tissues and organs appear openly.

The causal theories are numerous, but the one should be mentioned that claims that unconscious unresolved conflicts find their expression in the somatic plane.

Psychological factors that could possibly influence the onset of a cancer would be as follows [5]:

1) stressful life events

2) social relationships and support by the environment

3) personal traits (personas)

4) facing the disease

5) negative emotional reactions

6) psychiatric disorders

7) suppression of emotions

1) Stressful life events

The research efforts concerning this factor are mostly associated with breast tumors and elements preceding the disease onset linked to frequent stressful events (twice as prevalent compared to controls); these investigations lack prospectiveness.

2) Social relationships and support

The most relevant study followed 224 women with breast cancer for 7 years, showing significantly poorer survival rates in those without any social support in their immediate social environment, compared to those who clearly received and felt such support in their families and social environment.

3) Personal traits

Numerous authors have been concerned with the question whether oncologic patients share a similar psychic structure; many of them have concluded that cancer patients often have difficulties in expressing their emotions, inability to express aggression openly, and suppression of depressive moods; in short, these individuals are well adapted to others, but they are alienated from themselves.

4) Facing the disease

It has always been known that an active stance against the disease significantly improves treatment success; an active stance in facing the tumor means better survival.

5) Negative emotional reactions

Anxiety, grief, and depression are significant psychiatric symptoms associated with the onset of cancer, but the studies have failed to demonstrate any causal relationship between the malignancy and these symptoms, but it has been shown that they markedly influence the treatment outcome.

6) Psychiatric diseases

Studies investigating the association of psychiatric diseases with the onset of oncological diseases have not been consistent-only one such study showed that a psychiatric disease was the protective factor in cancer survival; a negative relationship was found in four studies, and five studies were not able to find any association between the two.

7) Suppression

It has been found that cancer patients often have difficulties in expressing their emotions, which has been confirmed in the studies measuring the degree of suppression and length of survival – the more a person shows emotions, the better the chance of longer survival.

In all the phases of breast cancer treatment various psychiatric problems can be present.

Posttraumatic disorders can be associated with the diagnosis of cancer, mastectomy, or chemotherapy. Depressive disorders are commonly linked to the development of metastases.

The use of adjuvant chemotherapy is associated with possible development of psychiatric disorders, and such a treatment is used in even 80% of affected women. Around 20-38% of women with breast cancer diagnosis have a high level of psychological distress in the first year after the diagnosis [6].

In some women, a high level of intrusive symptoms and avoidance coping can last for years after the initial diagnosis. The prevalence rate of depression in women with breast cancer varies from 1.4% to 46%, depending on a number of factors, including stage and size of the tumor, patient age, availability of social support, socioeconomic background, type of surgery, ability to make one's own choices and to be involved in one's treatment, type of therapy (radiation therapy, chemotherapy), and familial and personal history of depression [7].

The treatment and cancer itself have an impact on the anxiety, sexual satisfaction, sleeping, quality of life, perception of one's own body (body image) and self-confidence. Some patients feel traumatized and mutilated, and may have the reactions of grief after surgical interventions, especially after prophylactic bilateral mastectomy. The psychological impact of breast cancer is present too in the spouse, partner, children, and parents of women with breast cancer.

In an analysis of the possible conditions preceding psychological distress, the importance of avoidance coping has been suggested, although possible positive effects of such a behavior have been considered as well, especially in the active treatment phase.

Numerous adverse treatment effects produce some long-lasting consequences, from the distorted body image (mutilation surgery, radiation therapy) to disturbed self-esteem, and inflict significant sexual problems as well. Psychiatric diseases that may accompany this phase of the disease are also an important problem; this particularly refers to the onset of posttraumatic stress disorder, full-blown in as high as 10% of survivors, and in over 48% of patients reflected in some other elements, primarily in the symptoms of reliving the trauma and in avoidance coping [8].

With active palliative management in recent years a step forward has been made from the hospital to out-patient framework, reflected especially in the control of symptoms (pain) in home environments. More adequate supporting psychosocial elements have thus been provided, assuring better quality of life, shifting the disease management burden towards the family, but assuring instead better family relationships with appropriate support from well trained associates in the process.

2. Investigation

The investigation described here took place at the Clinic of Oncology, Clinical Cen-

ter Niš, in the period from May 6, 2014 to December 2016. Two groups of examinees were formed for the purpose of the study. The first group consisted of 120 women with the diagnosis of breast cancer, actively treated, aged 27 to 65 years. In the period of 6 months four patients died and were excluded from the analysis. There were 13 patients over 65 years of age. The patients were tested on the day of their enrollment in the study and again after 6 months of treatment. The second group consisted of 50 depresion women no breast cancer aged 22 to 65 years, accompanying breast cancer patients to the oncology clinic. The sample was stratified (the studied and control groups) to a degree by the factor of age of the examinees.

The socio-demographic questionnaire, designed for the purpose of this study, involved questions related to the patient age, marital status, level of education, employment and economic status, high risk behaviors and habits, and the disease, breast cancer.

The rights of the examinees were not in any way compromised during the study. The data obtained was protected and accessible only to the researcher. The examinees were first informed in detail about the study itself, its purpose and scientific rationale, confidentiality of the collected data, and were asked to sign their informed consent to participate in the study.

The study was approved by the Decision of the Ethics Committee of the Clinical Center Niš, No. 12613/57 of May 6, 2014.

The study enrolled 153 examinees, among which 103 (67.3%) breast cancer patients comprising the study group, and 50 (32%) healthy women – patient companions – comprising the control group. The average age of the whole studied population was 48.5±11.4 years (ranging from 22 to 65 years). Age structure of the examinees in different groups was not statistically significantly different, i.e. the groups were homogenous (studied group: 49.4±10.8 vs. control group: 46.5±11.5 years; t=1.471; p=0.143).

Table 1: Socio-demographic characteristics, by groups

		Studied group n (%)	Control group n (%)	$\chi 2$ / t*	p
Employment status	**Unemployed**	39(37,9)	16(32,0)		
	Employed	41(39,8)	25(50,0)		
	Retired	23(22,3)	8(18,0)	1,435	0,488
Educational status	**Incomplete primary school**	3(2,9)	6(12,0)	24,671	<0,001
	Primary school	12(11,7)	12(24,0)		
	High school	17(16,5)	17(34,0)		
	College	22(21,4)	9(18,0)		
	Higher education	49(47,6)	6(12,0)		
Marital status	**Married**	11(10,7)	12(24,0)	7,685	0,104

	Common-law marriage	14(13,6)	7(14,0)		
	Single	67(65,0)	25(50,0)		
	Widow	5(4,9)	5(10,0)		
	Divorced	6(5,8)	1(2,0)		
Children	**Yes**	74(71,8)	46(92,0)	8,083*	0,004
	No	29(28,2)	4(8,0)		
Age at birth of the first child	**±SD**				
25,1 ± 3,0	**23,8 ± 6,9**	1,286	0,201		
Number of children	**Without children[a]**	29(28,2)	6(12,0)	9,959	0,007
	One child	16(15,5)	1(2,0)		
	Two children	56(54,4)	43(86,0)		
	Three and more	2(1,9)	0(0,0)		

Educational status was statistically significantly different between the two groups ($\chi2=24.671$; $p<0.001$). It was further established that a significantly larger number of control group examinees had incomplete primary school ($\chi2=26.184$; $p<0.001$), completed primary school ($\chi2=5.960$; $p=0.014$), and high school ($\chi2=3.881$; $p=0.048$). Higher education was significantly more common among the women with breast cancer ($\chi2=18.986$; $p<0.001$).

Table 2: Personal and family history, by groups

		Studied group n (%)	**Control group n (%)**	**χ2**	**p**
Psychic complaints before the disease	**yes**	4(3,8)	45(91,8)	0,887	0,346
	no	100(96,2)	4(8,2)		
Stressful life events	**yes**	102(99,0)	13(26,0)	96,163	<0,001
	no	1(1,0)	37(74,0)		
Psychiatric drugs	**yes**	8(7,8)	5(10,0)	0,216	0,642
	no	95(92,2)	45(90,0)		
Tumors in the family	**yes**	24(23,3)	3(6,0)	6,933	0,008
	no	79(76,6)	47(94,0)		
Psychiatric diseases in the family	**yes**	7(6,8)	1(2,0)	1,563	0,211
	no	96(93,2)	49(98,0)		

The presence of psychic complaints did not differ significantly between the examined populations ($\chi2=0.887$; $p=0.346$). Stress was present at a high percentage in the patients before the onset of their disease ($\chi2=96.163$; $p<0.001$). Use of psychiatric drugs ($\chi2=0.216$; $p=0.642$), as well as the familial presence of psychiatric diseases ($\chi2=1.563$; $p=0.211$) did not differ sig-

nificantly between the groups. There were significantly more diagnosed tumors in the family histories of breast cancer patients ($\chi2=6.933$; $p=0.008$).

Table 3: Personal habits and needs in the studied groups

		Studied group n (%)	Control group n (%)	χ2	p
Alcohol intake	**yes**	11(10,7)	10(20,0)	2,469	0,116
	no	92(89,3)	40(80,0)		
Cigarette smoking	**yes**	39(37,9)	45(90,0)	36,953	<0,001
	no	64(62,1)	5(10,0)		
Communication avoidance	**yes**	82(79,6)	38(76,0)	0,260	0,610
	no	21(20,4)	12(24,0)		
Sexual desire	**yes**	80(77,7)	49(98,0)		
	no	23(22,3)	1(2,0)	10,219	0,001

Alcohol intake did not differ significantly between the studied groups ($\chi2=2.469$; $p=0.116$), while cigarette smoking was significantly more common in control group women ($\chi2=36.953$; $p<0.001$).

The number of friends and acquaintances did not differ significantly between the cancer patients and healthy women ($\chi2=0.260$; $p=0.610$). Sexual desire was significantly less common in breast cancer patients ($\chi2=10.219$; $p=0.001$).

Table 4: Depression score according to the HAMD scale by groups at the beginning of the study

	$\bar{x}$	SD	Med	Iq	Min	Max	Z	p
Studied group	16,03	5,16	17,00	7,00	5,00	37,00	8,508	<0,001
Control group	7,42	2,86	7,00	4,00	2,00	17,00		

Table 5: Depression score according to the HAMD scale by groups after 6 months

	$\bar{x}$	SD	Med	Iq	Min	Max	Z	p
Studied group	14,43	4,48	16,00	4,00	5,00	33,00	1,363	0,173
Control group	15,36	2,99	16,00	14,0	7,00	21,00		

Statistically significant changes in the score values were found in both groups: in the group of patients the score value decreased significantly after 6 months ($Z=5.031$; $p<0.001$), while the score values in controls increased significantly after the same period of time ($Z=6.058$; $p<0.001$).

Table 6: Components of the HAMD score by groups at the beginning of the study

HAMD components	Studied group		Control group		
	$\bar{x}$	SD	$\bar{x}$	SD	p
H1 DEPRESSIVE MOOD	0,10	0,37	0,26	0,44	0,006
H2 FEELING OF GUILT	0,18	0,46	0,28	0,45	0,090
H3 SUICIDE	0,05	0,21	0,26	0,44	<0,001
H4 INSOMNIA EARLY	1,08	0,47	0,32	0,47	<0,001
H5 DIFFICULTIES STAYING ASLEEP	1,34	0,67	0,38	0,49	<0,001
H6 INSOMNIA LATE	1,09	0,65	0,46	0,50	<0,001
H7 WORK AND ACTIVITIES	1,42	0,98	0,42	0,53	<0,001
H8 RETARDATION	0,66	0,57	0,48	0,50	0,076
H9 AGITATION	0,92	0,52	0,26	0,44	<0,001
H10 ANXIETY	1,24	0,68	0,50	0,51	<0,001
H11 ANXIETY, SOMATIC	1,02	0,60	0,34	0,49	<0,001
H12 GASTROINTESTINAL SOMATIC SYMPTOMS	0,77	0,48	0,48	0,50	0,001
H13 GENERAL SOMATIC SYMPTOMS	0,87	0,41	0,38	0,53	<0,001
H14 GENITAL SYMPTOMS	0,83	0,56	0,38	0,53	<0,001
H15 HYPOCHONDRIA	0,83	0,48	0,64	0,48	0,019
H16 LOSS OF WEIGHT	0,72	0,49	0,46	0,50	0,003
H17 INSIGHT INTO THE DISEASE	0,89	0,56	0,24	0,43	<0,001
H18 DIURNAL MOOD VARIATION	0,94	0,34	0,20	0,40	<0,001
H19 DEPERSONALIZATION AND DEREALIZATION	0,46	0,54	0,44	0,50	0,950
H20 PARANOID SYMTOMS	0,30	0,46	0,24	0,43	0,433
H21 OBSESSIVE-COMPULSIVE SYMPTOMS	0,25	0,46	0,18	0,39	0,370

The comparison of individual 21 components of the HAMD score measured at the beginning of the study between the examined groups are shown in Table 6. Statistically significant differences between the groups were established for 16 HAMD score components as follows: depressive mood ($Z=2.759$; $p=0.006$), suicide ($Z=3.795$; $p<0.001$), insomnia early ($Z=7.744$; $p<0.001$), difficulty staying asleep ($Z=7.310$; $p<0.001$), late insomnia ($Z=5.492$; $p<0.001$), work and activities ($Z=6.058$; $p<0.001$), agitation ($Z=6.771$; $p<0.001$), anxiety ($Z=6.051$; $p<0.001$), somatic anxiety ($Z=6.29$; $p<0.001$), somatic gastrointestinal symptoms ($Z=3.376$; $p=0.001$),

general somatic symptoms (Z=5.839; p<0.001), genital symptoms (Z=4.601; p<0.001), hypochondria (Z=2.341; p=0.019), loss of weight (Z=2.925; p=0.003), insight into the disease (Z=6.465; p<0.001), diurnal mood variation (Z=8.730; p<0.001).

Table 7: HAMD score components by groups after 6 months of study

HAMD components	Studied group		Control group		p*
	$\bar{x}$	SD	$\bar{x}$	SD	
H1 DEPRESSIVE MOOD	0,04	0,24	0,00	0,00	0,224
H2 FEELING OF GUILT	0,02	0,14	0,00	0,00	0,323
H3 SUICIDE	0,02	0,14	0,02	0,14	0,981
H4 INSOMNIA EARLY	1,16	0,54	0,94	0,42	0,010
H5 DIFFICULTIES STAYING ASLEEP	1,11	0,49	1,08	0,34	0,575
H6 INSOMNIA LATE	1,00	0,39	1,08	0,44	0,258
H7 WORK AND ACTIVITIES	1,14	0,74	0,96	0,19	0,336
H8 RETARDATION	0,79	0,62	1,00	0,35	0,010
H9 AGITATION	0,66	0,53	0,96	0,35	<0,001
H10 ANXIETY	1,16	0,65	1,12	0,39	0,626
H11 ANXIETY, SOMATIC	1,08	0,59	1,06	0,24	0,734
H12 GASTROINTESTINAL SOMATIC SYMPTOMS	0,64	0,50	0,98	0,25	<0,001
H13 GENERAL SOMATIC SYMPTOMS	0,89	0,34	0,94	0,24	0,371
H14 GENITAL SYMPTOMS	0,60	0,49	0,90	0,30	<0,001
H15 HYPOCHONDRIA	0,78	0,42	0,92	0,27	0,030
H16 LOSS OF WEIGHT	0,61	0,49	0,92	0,27	<0,001
H17 INSIGHT INTO THE DISEASE	1,14	1,77	0,90	0,30	0,408
H18 DIURNAL MOOD VARIATION	0,84	0,37	0,88	0,34	0,466
H19 DEPERSONALIZATION AND DEREALIZATION	0,58	0,49	0,60	0,49	0,750
H20 PARANOID SYMTOMS	0,12	0,32	0,04	0,19	0,125
H21 OBSESSIVE-COMPULSIVE SYMPTOMS	0,08	0,30	0,00	0,00	0,060

After 6 months, comparing the individual components of the HAMD score between the studied and control groups, it was found that there was a statistically significant difference in 6 HAMD components: insomnia early (Z=2.570; p=0.010), retardation (Z=2.590; p=0.010), agitation (Z=3.597; p<0.001), somatic gastrointestinal symptoms (Z=3.579; p=0.019), geni-

tal symptoms (Z=3.759; p<0.001), hypochondria (Z=2.174; p=0.030), and loss of weight (Z=3.939; p<0.001).

Table 8: Changes in the HAMD score components by groups after 6 months of study

HAMD components	Studied group		Control group	
	Z	p	Z	p
H1 DEPRESSIVE MOOD	1,748	0,080	3,606	<0,001
H2 FEELING OF GUILT	3,900	<0,001	3,742	0,001
H3 SUICIDE	1,342	0,180	3,207	<0,001
H4 INSOMNIA EARLY	0,956	0,339	5,240	<0,001
H5 DIFFICULTIES STAYING ASLEEP	3,101	0,002	5,296	<0,001
H6 INSOMNIA LATE	1,508	0,132	4,943	<0,001
H7 WORK AND ACTIVITIES	2,997	0,003	5,014	<0,001
H8 RETARDATION	1,899	0,058	4,747	<0,001
H9 AGITATION	3,856	<0,001	5,596	<0,001
H10 ANXIETY	1,192	0,233	4,625	<0,001
H11 ANXIETY, SOMATIC	0,732	0,464	5,684	<0,001
H12 GASTROINTESTINAL SOMATIC SYMPTOMS	2,271	0,023	4,642	<0,001
H13 GENERAL SOMATIC SYMPTOMS	0,447	0,655	5,292	<0,001
H14 GENITAL SYMPTOMS	3,333	0,001	4,459	<0,001
H15 HYPOCHONDRIA	1,177	0,239	3,300	0,001
H16 LOSS OF WEIGHT	1,808	0,071	4,796	<0,001
H17 INSIGHT INTO THE DISEASE	1,470	0,142	5,578	<0,001
H18 DIURNAL MOOD VARIATION	2,294	0,022	5,516	<0,001
H19 DEPERSONALIZATION AND DEREALIZATION	1,852	0,064	1,789	0,074
H20 PARANOID SYMTOMS	3,212	0,001	2,887	0,004
H21 OBSESSIVE-COMPULSIVE SYMPTOMS	3,402	0,001	3,000	0,003

Table 9: Univariate linear regression analysis of the factors related to the degree of depression according to the Hamilton scale at the beginning of the study

	Beta	95% CI		p
		lower limit	upper limit	
Age	0,010	-0,080	0,090	0,904
Groups	-0,667	-10,165	-7,072	<0,001
Employment status	-0,092	-2,065	0,560	0,259
Educational status	0,230	0,351	1,844	0,004
Marital status	0,028	-0,845	1,199	0,733
Children	0,227	1,042	5,655	0,005
Age at birth of the 1st child	0,098	-0,127	0,386	0,318
Number of children	-0,307	-3,260	-1,090	<0,001
Psychic complaints before the disease	-0,258	8,680	-2,152	0,001
Stressful life events	-0,526	-9,286	-5,450	<0,001
Psychiatric drugs	-0,070	-5,007	1,962	0,389
Tumors in the family	-0,218	-5,957	-0,969	0,007
Psychiatric diseases in the family	-0,219	-10,234	-1,696	0,006
Alcohol intake	-0,235	-3,234	2,425	0,778
Cigarette smoking	0,236	0,966	4,774	0,003
Communication avoidance	0,025	-1,994	2,741	0,756
Sexual desire	0,207	0,822	6,063	0,010

Table 9 presents the results of univariate linear regression analysis of individual socio-demographic factors, factors in personal and family histories, habits and needs, related to the onset of depression according to the Hamilton scale measured at the beginning of the study. Statistically significant risk factors for depression were as follows: women with breast cancer (Beta=-0.667; p<0.001), higher educational status (Beta=0.230; p=0.004), childlessness (Beta=0.227; p=0.005), as well as a lower number of children (Beta=-0.307; p<0.001), presence of psychic complaints before the disease (Beta=-0.258; p=0.001), stress before the disease (Beta=-0.526; p=0.004), tumors in the family (Beta=-0.218; p=0.007), presence of psychiatric diseases in the family (Beta=-0.219; p=0.006), absence of smoking (Beta=0.236; p=0.003), and lack of sexual desire (Beta=0.207 p=0.010).

Table 10: Multivariate linear regression analysis of the factors related to the degree of depression according to the Hamilton scale at the beginning of the study

	Beta	95% CI		p
		lower limit	upper limit	
Groups	-0,678	-11,339	-6,167	<0,001
Educational status	-0,021	-0,684	0,489	0,742
Children	0,224	-6,996	0,399	0,080
Number of children	-0,389	-4,527	-0,980	0,003
Psychic complaints before the disease	-0,171	-6,017	-1,157	0,004
Stress before the disease	0,041	-2,120	3,264	0,675
Tumors in the family	-0,079	-3,139	0,615	0,186
Psychiatric diseases in the family	-0,093	-5,732	0,693	0,123
Cigarette use	-0,144	-3,406	-0,099	0,038
Sexual desire	0,074	-0,793	3,243	0,232

Multivariate linear regression analysis was performed to evaluate depression according to the Hamilton scale in relation to the individual factors that stood out as statistically most significant. Ten factors could be included into the multivariate model: groups, educational status, children and number of children, psychic complaints before the disease, stress, tumors and psychiatric diseases in the family, cigarette use, and sexual desire. The model as a whole was highly statistically significant – $F(10, n=103) = 17.878$, $p<0.001$. The model as a whole explains 52.6% of variance of depression score according to the Hamilton scale. The following factors gave a statistically significant contribution to the model: patient group (Beta=-0.678; $p<0.001$), number of children (Beta=-0.389; $p=0.003$), psychic complaints before the disease (Beta=-0.171; $p=0.004$), and cigarette use (Beta=-0.144; $p=0.038$).

Table 11: Univariate linear regression analysis of the factors related to the degree of depression according to the Hamilton scale after 6 months of study

	Beta	95% CI		p
		lower limit	upper limit	
Age	0,097	-0,092	0,022	0,232
Groups	0,107	-0,459	2,306	0,189
Employment status	-0,039	-1,098	0,666	0,630
Educational status	-0,003	-0,552	0,505	0,974
Marital status	0,178	-1,431	0,084	0,028
Children	0,124	-0,359	2,796	0,127
Age at birth of the 1st child	-0,012	-0,183	0,162	0,902
Number of children	-0,144	-1,437	-0,073	0,076

Psychic complaints before the disease	0,088	-3,485	1,022	0,282
Stress before the disease	0,082	0,737	2,272	0,315
Psychiatric drugs	-0,043	-2,959	1,715	0,600
Tumors in the family	-0,029	-1,398	2,022	0,719
Psychiatric diseases in the family	-0,051	-3,861	-1,991	0,529
Alcohol use	-0,035	-2,308	1,481	0,667
Cigarette use	-0,184	-2,792	-0,215	0,022
Communication avoidance	0,038	-1,213	1,957	0,643
Sexual desire	0,103	-0,634	2,934	0,205

Table 11 presents the results of univariate linear regression analysis of inidividual socio-demographic factors, factors in the personal and familial history, and habits and needs of impact on depression according to the Hamilton scale measured 6 months after the beginning of the study. Statistically significant risk factors for depression were marital status (Beta=0.178; p=0.028) (meaning that a higher risk was established for the divorced, widows and single women), and cigarette use (Beta=0.236; p=0.003).

Table 12: Multivariate linear regression analysis of the factors related to the degree of depression according to the Hamilton scale after 6 months of study

	Beta	**95% CI**		**p**
		lower limit	**upper limit**	
Marital status	0,093	-1,154	0,360	0,302
Cigarette use	-0,180	-2,790	-0,142	0,030
Number of children	-0,123	-1,418	0,250	0,168

The following two factors, shown to be statistically significant, were entered into the multivariate model to evaluate depression according to the Hamilton scale: marital status and cigarette use, as well as the third factor, number of children (fulfilled the requirements to be entered into the model, p<0.010). The whole model was statistically significant – F (3, n=103)= 3.593, p= 0.015. The model as a whole was able to account for 4.9% of variance of depression score according to the Hamilton scale. The factor of cigarette use was the only one with a statistically significant contribution to the model (Beta=-0,180; p=0,030).

Table 13: Univariate linear regression analysis of the type of therapy in relation to the degree of depression according to the Hamilton scale at the beginning of the study

Type of therapy	**Beta**	**95% CI**		**p**
		lower limit	**upper limit**	
Cytostatic therapy	0,057	-8,600	15,705	0,563
Biological therapy	0,228	0,444	5,042	0,020
Radiation therapy	0,008	-2,972	2,752	0,939
Hormonal therapy	-0,260	-6,060	-0,943	0,008

At the beginning of the study, it was found that the patients on biological therapy were exposed to a higher risk for depression (Beta=0.228; p=0.020), while those on hormonal therapy had a lower risk for the onset of depression (Beta=-0.260; p=0.008).

Table 14: Univariate linear regression analysis of the type of therapy in relation to the degree of depression according to the Hamilton scale after 6 months of study

Type of therapy	Beta	95% CI		p
		lower limit	upper limit	
Cytostatic therapy	0,012	-8,410	9,410	0,900
Biological therapy	0,231	0,352	3,780	0,019
Radiation therapy	0,036	-1,724	2,502	0,716
Hormonal therapy	-0,294	-4,783	-1,041	0,003

The type of therapy as a factor of impact in the onset of depression after 6 months of study is presented in Table 14. It was established that the patients on biological therapy were at a higher risk for depression (Beta=0.231; p=0.019), while those on hormonal therapy had a lower risk for depression (Beta=-0.294; p=0.003).

3. Discussion

Impelled by the ample literature material on the topic and a lot of conflicting data, this study was performed aiming to establish the prevalence of depression in women with breast cancer.

The study, as well as the clinical practical experience acquired so far, has indicated that

30-50% of oncologic patients, in addition to their malignant disease, are affected by various psychiatric-psychological disorders that require a timely and appropriate diagnosis and therapy. Numerous predisposing factors could be held responsible for the development of psychiatric disorders in oncologic patients, such as various organic factors, the nature of their disease, treatment-related influences, reduced fertility, prior stress and psychiatric disorders, disturbed communication with the family, etc. [10,11].

Depression is one of the most widespread diseases in the 21st century. Its prevalence is ever increasing, mostly due to modern stressful and hectic lifestyles. It is thought that nowadays one in every ten people is at the risk of developing depression. However, it is not a rare case that depression is accompanied by other somatic or psychic diseases, e.g. various cardiovascular, endocrine, neurological, dermatological, malignant diseases, anxiety, addictions, and others. In most cases, a cause-and-effect relationship can be identified: depression may occur as the consequence of another phenomenon, when it often remains unrecognized or is even willfully neglected as „less important“, which is utterly wrong. There is also the possibility that depression and a comorbid condition have a common cause. In any case, numerous studies have shown that depression and comorbidities reduce quality of life of a patient, especially in

those in terminal phases of their somatic disease. Moreover, there are multifold adverse

effects of depression on the course and prognosis of another disease; it has been demonstrated that depression concurrent with another morbidity increases the risk of fatal outcome. It is therefore extremely important to focus attention on the prevention of depression, its timely recognition, and not to underestimate depression and possible comorbidities, so that adequate therapeutic support can be instituted not only in the form of pharmacological measures, but also as a cognitive-behavioral therapy and other psychotherapeutic approaches.

This study enrolled 103 patients with breast cancer planned to receive some of the anticancer therapies, aged 48.5±11.4 years on the average. Breast cancer incidence rises with advancing age, peaking in the age group from 50 to 60 years. The data in our study agreed with the literature data, where the average age of examinees ranged from 50 to 60 years.

Age distibution of the patients in our group corresponded to the breast cancer age distribution epidemiological information for the countries with high incidence rates of this tumor [12].

In most developed countries the number of breast cancer patients is on a constant rise, with the incidence peak shifting towards younger women, which could perhaps be explained by lifestyle changes. A number of studies have shown that among the breast cancer patients there are only 23% of those below 50 years of age [13].

With advancing age, the frequency of malignant diseases in general rises [14,15]. A number of studies have suggested that the onset of the disease in an advanced age is related to a more favorable biological profile of breast cancer [16]. A study by *Nixon et al.* has confirmed that women below 35 years of age have a poorer prognosis compared to the elderly patients. It has been shown that with advancing age the prevalence of markers of poor prognosis decreases significantly [17].

The women with a larger number of menstrual cycles during their reproductive age due to an earlier menarche (before 12 years of age) or those with late-onset menopause (after their 55 years of life) are exposed to a higher risk due to a prolonged exposure to the action of estrogen and progesteron.

The rates of incidence and mortality of breast cancer increase with advancing age. Approximately 95% of new cases and 97% of cancer deaths are reported in those over 40 years of age [18, 19, 20, 21]. In the USA, in the period 2004-2008, the lowest incidence rates were reported in the age group 20-24 years, and the highest incidence rates in the age group 75-79 years (421/100.000). In Central Serbia, the highest breast cancer incidence rates are reported in the age group 60-69 years [22].

Related to the marital status, most of the examinees in this study were single (65.0%), and in a common-law marriage (13.6%). These are followed by widows (4.9%), married women (10,7%), while the lowest percentage was reported for divorced women (5.8%). The data confirmed the trends present in the current literature on the issue [23,24].

The study by from the Norwegian Cancer Registry has shown that married persons affected by cancer stand a greater chance of defeating their disease than those who are not married. For instance, a married man is 35% less susceptible to cancer-related death compared to a bachelor. Women who have never married are 17% more susceptible to cancer-related death compared to their married counterparts (22%) [25].

Married women have longer overall survival and lower mortality compared to the singles, widows, or divorced women [25].

Some other studies [26] have suggested that the women with a lower educational level, even if married or living with a partner, have a higher risk of developing depression. Studies have shown that the women with a lower educational level have fewer affirmative (positive) social interactions, emotional support, and are therefore more prone to depression [27]. On the other hand, the fact that female patients are married or that they are living with a partner should imply that they have more of the social support compared to the singles, divorced or widows, and therefore are not expected to have more of the depression symptoms.

One of the more important aspects of breast cancer are its physical consequences, i.e. the scars that could impair the physical appearance of women and could therefore produce discontent and problems with their sexual life, having a general adverse influence on their sexual relationship with the partner. In intimate relationships, the issue of the disease is the one with the priority.

The belief that men desert women with breast cancer is not unusual and can be a source of stress for women faced with the disease. The notions such as this can have an adverse impact on the psychic status of women with the diagnosis of breast cancer. In contrast, various studies and partial reports suggest that after the diagnosis of breast cancer a marriage collapses most commonly as the consequence of already present marital problems.

Regarding the level of education, there was a statistically significant difference between the groups. In Turkey, for instance, 36.2% had primary education, 41.9% high school education, and 21.9% had higher education, while in Iran there were slightly more illiterate and women with primary education (47.3%), 33.9% had high school education, and 18.8% had higher education [28]. Compared to these data, the number of examinees in our study with college or higher education was twice as high. It was still considerably below the European standards, but still below the percentage of prevalence of highly educated women reported in some of

the studies. The level of education of women is important in the onset of breast cancer since it possibly influences other risk factors: educated women are better informed about the adverse effects of some of the agents and are able to perform better the proper measures of prevention and abide by the expert advice regarding proper nutrition, alcohol intake, cigarette smoking, and so on. Better education also provides a better socioeconomic background and high quality living conditions (nutrition, dwelling, etc.).

The literature reports a lower percentage of retired women (10-20%), a higher percentage of employed women (30-60%), while the number of housewives ranges from 16% to 60% [29].

Depression among employed women was significantly reduced after the surgical treatment, while the prevalence of depression among retired and unemployed women remained the same. Among married women, the prevalence of depression was significantly reduced, in contrast to widows and divorced women. A week after their operation, the percentage of depression among married women was lower than in widows or divorced women. A similar effect was observed when employed women were compared to unemployed or retired women [29].

It is believed today that a positive family history of breast cancer is an important factor in the onset of the disease. It has been shown in the literature that a patient with breast cancer has at least one first-degree relative with the disease, although the results of numerous studies can hardly be interpreted adequately due to a lack of such cases [30,31]. It is thought that 5-10% of women with breast cancer have an autosomal inherited *BRCA1* mutation, and in a smaller number of cases a *BRCA2* gene mutation.

A woman with a cancer in one portion of the breast is at a 3-4 higher risk of developing cancer in the same breast. Such cancers are not considered a recurrent disease, but as *de novo* lesions.

Introduction of the concept of adjuvant chemotherapy has markedly increased the survival of breast cancer patients [32]. Chemotherapy acts systemically. If distant metastases are present at a site, still clinically silent and diagnostically unconfirmed, the use of adjuvant chemotherapy prevents the development of metastatic foci. With time, the type of chemotherapy has changed and evolved since the middle of the XX century when CMF protocol was administered, to FAC combination regimen in the 1970s with a considerably better therapeutic effect. Nowadays, AC chemotherapy in combination with Taxanes is the treatment administered to breast cancer patients at a higher risk for disease relapse. In the elderly, CMF is still considered a gold standard.

Together with chemotherapy, adjuvant hormonal therapy is used as well. It is used if

the tumor in question is hormone dependent. The use of tamoxifen in the period of five years represents the treatment modality able to prolong survival markedly. In patients with favorable primary tumor-related factors with free lymph nodes, adjuvant chemotherapy is often the only required therapeutic modality. In our study, systemic chemotherapy was used in 51% of women with breast cancer.

In addition to the above, immunotherapy is also used in breast cancer treatment, with some key advantages compared to the above modalities. The effects of targeted therapy depend on specific signaling pathways and oncogene changes in the cells. However, it is known that cells may activate compensatory signaling pathways that could make them resistant to this type of treatment. The studies designed to examine the combination of tyrosine-kinase inhibitors for multiple receptors are under way, but the potential toxicity of such combinations may limit their usefulness [33].

In many countries with different cultural backgrounds, an association of psychological distress with somatic symptoms has been confirmed. In the analysis and understanding of the association of stress with somatic diseases, a multidimensional approach is the one most appropriate. Clinical and research models based on the theoretical assumptions of the biopsychosocial model require ample theoretical knowledge and tolerance of cognitive dissonance, while the researchers and therapists are educated mostly to work with specific methods, and most of the studies assess only inidividual risk factors.

The exciting research in psychoneuroimmunology in the last fifteen years or so has shown that stress-provoked biopsychosocial reaction may be the cause or may trigger numerous psychic and somatic disorders. A significant issue in that regard is whether stress is able to influence health compromising the immune system [34,35]. According to the study, the diseased faced stressful life situations prior to the onset of their disease statistically significantly more often than control examinees.

The leading researcher, a professor at the Breast Cancer Research Institute in Great Britain, tried to examine whether psychological stress or adverse life events had an impact on breast cancer risk [36]. Most of the examinees enrolled in the period 2003-2010 were asked how often they had experienced some stressful event in the past 5 years. They were also asked if they lost one of the parents till their 20th year of life. The researchers excluded the influence of other risk factors such as obesity, physical activity, alcohol intake, family history of breast cancer, age at menarche, age at menopause, number of children, age of their mothers at birth, length of breast feeding, and so on. The results showed that 34% of women reported frequent stressful events or a continuing stress in the period of 5 years prior to the study, and 74% reported at least one adverse life event, such as grief (loss or disease of a close person) or a divorce. Of 106.612 women, in 1783 breast cancer was diagnosed. After a careful consideration of other-

risk factors, the authors found that there was not any statistically significant association of the frequency of stress with overall breast cancer risk. Further studies are warranted, but other possible factors of risk for breast cancer should be taken into account as well.

A weak association could be found for only one of eight characteristic types of stressful events. A divorce can be associated with negative breast cancer estrogen receptors in premenopausal women, but this occurred in 25 cases only and has only a statistical significance. Such a result was not substantiated by an increased risk with other similar stressful events such as grief.

The results showed that women who often or continuously experienced stressful events had a risk for breast cancer similar to those who never experienced such stresses or experienced them only occasionally.

Dr Minouk Schoemaker reported: "Stressful life events are common and many women will have experienced them in the run-up to being diagnosed with breast cancer, but our results suggest that those stressful events are unlikely to be the cause of the disease."

The analysis showed a sightly higher risk for breast cancer in women who had lost their mothers while still young, but not if they had lost their fathers. Genetic predisposition is a much more probable breast cancer factor of risk than stress.

The Center for the Biology of Chronic Disease (Valley Cottage, New York, USA) performed the research and demonstrated that stress increased cortisol binding by the glucocorticoid receptor (GR) [37]. Glucocorticoid receptor (GR) interacts with GABP-β to produce a *BRCA1* promoter. This in turn activates *BRCA1*. The study also shows that the addition of hydrocortisone, which binds to GR, eliminates the interaction of GR with GABP-β, which induces a lack of GABP transcription factor in BRCA1 gene, decreasing its value and increasing the risk of breast cancer. Another pathway via which stress causes a lack of GABP transcription factor has been suggested, involving the presence of certain latent viruses in the cell. This event was described in 2003 in a book [38].

Many studies have confirmed that our psychic state has an impact on our health. A cancer appears when the defense system is defeated and cannot cope with various threats. A significant accent in the treatment of cancer is put on the human will, eagerness and decision of the affected to be treated.

Our immune system is suppressed by various psychic factors, out of which the most important are long-standing grief, feeling of failing in life, anger, and often mentioned stress. Chronic exposure to conflict situations, especially when there is a conflict between the needs, wishes and opportunities, produces chronic frustration as well. Since the usual de-

fense mechanisms (rationalizations, projections, sublimations) are no longer able to deal-with the problem, a physical disease occurs. Cancer most frequently affects depressive people, too rational, afraid of emotions, with a poor life of imagination, psychically constrained and passive [39,40,41,42].

David Kissen studied the patients with breast cancer and their ability to express emotions. He concluded that poor emotional outlet combined with narcissistic omnipotency of a person with the idea that all of the problems she should and can resolve alone, is the key characteristic of a person with breast malignancy. The study by S. Levi corroborates these findings, reporting that women with breast cancer who clearly show their fear, depression, anger, stand a better chance to survive their disease compared to those who are „good patients“ or „stoics“. The results of these studies show that the probability of survival is higher in patients in whom psychotherapy and chemotherapy is applied, than in those treated with only one of these modalities.

Numerous studies show that stressogenic life events have an impact on the course of depression, quality of remission, and relapse rates [39]. Etiological significance of these facts, however, has not been fully elucidated [43]. For instance, although most of the depressive patients experience stressful life events before the onset of the episode of depression, only a small portion of the individuals exposed to such stressors in fact become depressive.

A prevailing opinion of today's authors is that a wide spectrum of biological, social, and psychological etiological factors have a role in the genesis of depression. They act in variable proportions in each individual person. In addition to stressful life events and genetic factors, the following are also commonly mentioned: abuse in early childhood, premature loss of parents, quality of social support, and others [43,44].

In some of the studied clusters, patients have experienced significantly more stressogenic life events compared to their controls. Regarding the type of stressors preceding the episode of depression our results are mostly in harmony with the literature data [45], with some differences however in their frequency. In our sample, the stressors related to poor socioeconomic situation, unemployment, and worse working conditions were the ones more often encountered, which was expected in view of the ongoing social transition in our country. The frequency of individual stressful life events associated with disturbed partner relationships matched the data from the literature.

It has been suggested that stress and depression produce similar hormonal and immunological effects [45], and that stress that precedes the onset of depression is characterized by some still unexplained pathophysiological mechanisms.

The prevalence of depression after the diagnosis of breast cancer is even up to 33%.

Depression may have some very serious consequences related to the quality of life and increase mortality of the disease.

In a large national study in Denmark involving breast cancer patients, the researchers examined their psychiatric treatment (women in both early and more advances disease stages); it was shown that those with depression have a moderate, but significantly higher risk of death compared to those without depression, dependent both on the disease course and timing of depression.

Breast cancer mortality is also significantly higher in women with other psychiatric diagnoses as well [46].

Studies show that depression reaches its peak soon after the diagnosis, and then gradually decreases in the period of one to two years. Nevertheless, long-term patient follow-up is essential because of the possible development of depression and anxiety disorders even years after the diagnosis. In the diagnosis and treatment of psychiatric disorders an individualized approach is crucial. Although psychiatrists are not oncologists, they too have to be well acquainted with the treatment options and their possible side effects. It is important that the psychiatrist inform other team members about the psychic status of the patient, and to gain insight into all other medical findings available. Breast cancer brings about other important countertransference and transference issues during the treatment. Lots of doctors have family members and friends with the diagnosis, and we have to be fully aware of our feelings while we are helping our patients. Furthermore, patients often idealize or underestimate some of the team members, especially if the diagnosis was delayed or inappropriate. Patients have to change their behaviors, take good care of their nutrition, they should not smoke, they have to reduce their alcohol intake and stress exposure, and to adapt to complicated and demanding treatments, persisting pain (especially with bone metastases), changes at the workplace or at home, and changes in their sexual and social relationships and in their familial interactions.

In our study, we used both assessment tools to evaluate depression in breast canceer-patients-the HAMD and MADRS.

We found that there was no correlation between the scales at the beginning of the study; however, the correlation was negative in both groups of examinees after 6 months. This was to be expected, since in general there was a statistically significant correlation in the diagnosis of depression between the scales.

Our results agree with the results of other studies using similar methodology [46].

Regarding the degree of depression, there was a statistically significant difference in the depression degree assessment with HAMD scale at the time of diagnosis and after 6

months.

A comparison of individual 21 components of the HAMD score measured at the beginning of the study between the examined groups is presented in **Table 6**. There were statistically significant differences between the groups in 16 components: depressive mood, suicide, early insomnia, difficulty staying asleep, late insomnia, work and activity, agitation, anxiety, somatic gastrointestinal symptoms, general somatic symptoms, genital symptoms, hypochondria, weight loss, insight into the disease, and daily mood variations.

In addition to stressful events, other psychological factors influence the onset of a malignant disease as well, such as social relations and support of the environment; personality traits and suppression of emotions. Cancer naturally changes the patient's lifestyle, and family can thus offer signifact support in that regard. The severity of depression in a woman with cancer can be influenced by her perception of support by her partner/spouse. Some studies have shown that increased social support, a broader network of contacts, and the perception of support by the partner is associated with a lower level of depression in women with breast cancer. There are diverse results concerning the impact of psychic status of women with cancer on their partners and vice versa. The studies suggest that any avoidance of open discussion about the cancer by the partner is associated with increased patient distress. The level of distress is similar in the patient and her partner.

In addition to the family, professionals can also extend a kind of support (psychologists, psychiatrists, psychotherapists). The fact alone that the patient is able to speak openly about the disease and that there are people interested in her case is a relief of a kind. Professional support can take the form of group or individual activity, and this type of help is essential for those without their families. Psychological therapy can certainly help in the treatment of cancer, especially during chemotherapy or radiation therapy [48].

After chemotherapy, together with depression and cognitive disturbances, other mental disorders are also possible (adjustment disorders, insomnia, anxiety). In 2004 alone, 215.990 women were diagnosed with breast cancer, and more than 80% of them were treated with chemotherapy. Possible side effects of chemotherapy should be known to both the patients and anyone involved in their physical and psychological management.

Although depression after chemotherapy is well known and described, the data about other mental disorders are limited, and cognitive disorders after chemotherapy have been of late increasingly examined. Cognitive dysfunctions may involve consciousness (attention, vigilance), cognition (memory, learning), executive functioning (planning, organization), aphasia, apraxia, agnosia. Studies of the cognitive changes after chemotherapy support the hypothesis that the changes occur after the initiation of chemotherapy, especially in the areas of verbal memory and psychomotor functioning. Studies have shown that younger women with breast

cancer treated with chemotherapy after surgical intervention are at an increased risk of adjustment disorder, and sleep disturbances, fatigue and other problems are also common quality of life issues. Patients should be informed about the potential psychic side effects in their informed consent forms, and mental help should be made available to all women with breast cancer [49].

In women with breast cancer numerous problems related to their body image after the surgery can also occur. Altered body image is also a constant reminder of their disease – the change is abrupt and reconstructive surgery is a commonly used approach in the resolution of this problem. Patients sometimes refuse or delay their treatment because of the altered cosmesis. The disturbances related to the altered body image last about two years after the surgery. Women also commonly have various sensory changes and even difficulties in their adaptation to the breast prosthesis. Chemotherapy, with hair loss, weight gain and similar issues, cause problems in their body image, and radiotherapy can cause dermatological problems as well.

The basic objectives of psychotherapy in the treatment of oncologic patients are as follows: to reduce the patient's resistance to her treatment; to remove possible conflict situations the patient is exposed to (that can markedly influence the processes of diagnosis and treatment); to remove the tendency towards a deeper regression, passivization, and infantilization; to position the patient in an active stance towards the actual (present) and future problems and to motivate her for her treatment and to teach her to live with her disease.

In spite of a high prevalence of psychiatric disorders in oncology patients, there have been few studies elaborating in more detail the use of medicaments in the prevention and treatment of these disorders. However, numerous clinicians' observations suggest the need and justify the use of psychopharmacotherapy (anxiolytics, antidepressants, and antipsychotics, increasing noradrenergic, serotonergic and dopaminergic neurotransmission) in oncology in the treatment of anxiety and depression disorders and for the conditions occurring after using the drugs that may induce or mimic anxiety or depression [50].

In the introduction of psychopharmaceuticals in the treatment of oncologic patients it is necessary to assess disorder severity, comorbid conditions, premorbid personality traits, and take into account organ-involvement with the malignant process, pain intensity, type of oncologic treatment and its adverse effects, and possible development of a metabolic disorder.

Antidepressants in cancer patients can help to alleviate the adverse effects of chemotherapy (e.g., insomnia, loss of appetite), in pain control (due to their analgesic action and effect in increasing the action of narcotics), and in the treatment of depressive disorder (they improve sleeping, appetite and energy) [51]. However, antidepressants may exert their action via prostaglandin as well, known to regulate every component of the cellular microanatomy and physiology [52]. An ideal anticancer drug should inhibit the creation of prostaglandin in a way that

prevents cancer pathogenesis. Some recent studies have indicated that antidepressants have the properties such as these. Their immunostimulating and antimicrobial action can help in the resolution of infections occurring after chemotherapy or irradiation [53,54].

A larger number of examinees would improve the validity and reliability of conslusions in such studies. Furthermore, attention should be focused on genetic/molecular factors of risk as well.

A psychological response to breast cancer and its treatment varies in accordance with the age of the affected woman, personality traits, familial and social relations, and a varying impact of the fertility, body image and treatment side effects on the marital, parental, professional and social roles a woman may have. Psychiatric consultations and supportive psychotherapy are useful in women with breast cancer, offering them a chance to work on their existential, somatic, emotional, social, psychosexual and marital problems. Psychiatric consultations and psychotherapy also present the chance for the patient to express emotions openly, to obtain support and alleviate one's anxiety, fear, and depression.

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