ASSOCIATION OF BREAST CANCER SYMPTOMS WITH PATIENTS' QUALITY OF LIFE AND DEPRESSION; A CROATIAN CROSS-SECTIONAL STUDY

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SUMMARY

Aim: To find out which symptoms are the most associated with a breast cancer patients' quality of life (QoL) and depression.

Subjects and methods: We performed this cross-sectional study from February to April 2015 at the Department of Medical Oncology, University Hospital for Tumors, Zagreb University Hospital Center "Sestre milosrdnice", Zagreb, Croatia on the sample of 147 breast cancer patients. Primary outcomes were EORTC QLQ-C30 version 3.0 Global QoL scale and Beck Depression Inventory II.

Results: After the adjustment for other symptoms, sociodemographic and clinical variables, fatigue (β=-0.47, P<0.001), pain (β=-0.24, P=0.023), and appetite loss (β=-0.18, P=0.037) were statistically significantly correlated with QoL. Fatigue was the only symptom significantly associated with depression (β=0.39, P=0.006).

Conclusion: Fatigue, pain, appetite loss contributes the most to the overall breast cancer patients QoL. Although correlated, fatigue and pain contribution to lower QoL is independent from each other. Future studies should investigate whether there is an interaction between fatigue and pain changes over course of treatment. Fatigue and number of children are positively, while age and treatment in daily hospital are negatively associated with depression measured by BDI-II.

Key words: *breast cancer - quality of life - depression - fatigue - pain - appetite*

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INTRODUCTION

Depression is often under-detected and under-treated in breast cancer patients (Reich et al. 2008, Vin-Raviv et al. 2015) The co-occurrence of breast cancer and depression leads to questions regarding how these disorders compare in terms of their effects on the overall individual health and how they affect each other (Moussavi & Chatterji 2007). Studies have shown that when depression occurs with breast cancer, the consequences may be decreased motivation and reduced compliance with treatment such as chemotherapy, and may have a detrimental effect on outcome in breast cancer patient and even higher mortality (Nunes et al. 2002, Watson et al. 1999). The cancer diagnosis and treatment may increase psychological distress and have significant influence on the patients' quality of life (QoL) (Groenvold 2010). It is very well known that chemotherapy has a short-term negative impact on QoL due to treatment itself, and induced anxiety and depression. In patients with early breast cancer QoL rebounds after completion of adjuvant treatment (Jeffe et al. 2016). Furthermore, QoL can be impaired by the numerus stressful life events, body image and sexual problems, anxious preoccupations and of course depression (Andritsch et al. 2007, Meyerowitz 1980).

Depression burden may influences severity and number of adverse events from medical treatment (surgery, chemotherapy, radiotherapy, hormonotherapy) by increasing nausea and fatigue which can lower the QoL. Depression and lower quality of life share many risk factors, and both may mediate each other. Studies have shown that breast cancer patients health-related QoL may predict the treatment outcomes and survival (Kypriotakis et al. 2016, Montazeri 2008). Lower level of fatigue may be predictor of recurrence-free survival independently of biological factors (Groenvold et al. 2007). Breast cancer related symptoms may affect patients QoL (Janz et al. 2007). The aim of our study was to find out which symptoms are most associated with the breast cancer patients' QoL and depression. Our hypothesis was that fatigue would be the most important predictor of both QoL and depression.

SUBJECTS AND METHODS

Study setting

We performed this cross-sectional study from February to April 2015 at Department of Medical Oncology, University Hospital for Tumors, Zagreb University Hospital Center "Sestre milosrdnice", Zagreb, Croatia on the sample of 153 patients. Study protocol was

approved by the institution Ethics Committee and all patients signed the Informed consent for participation. The study was performed in accordance with the World Health Organization Declaration of Helsinki ("World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects" 2013).

Participants

Targeted population were the patients diagnosed with breast cancer, with ECOG performance status at the time of diagnosis 0, 1 or 2, treated in tertiary health-care institution during the late Winter and early Spring months and able to speak Croatian. Exclusion criteria were: ECOG status 3 or 4, patient's inability to answer the questionnaire by her/himself. We included the consecutive sample of all eligible patients admitted to the oncology ward or treated at the outpatient systemic therapy unit during the study period. The needed sample size was calculated before the start of the data collection. Targeted statistical power was set to 0.80, level of statistical significance to 0.05. Planned statistical test was multiple linear regression with 13 independent variables. Minimal standardized effect size that we planned to assess statistically significantly was determined at $f^2=0.15$. Under these conditions the final sample size of n=131 was needed. Anticipating up to 10% of missing data and incorrectly fulfilled questionnaires, the initially needed sample size was determined to be n=146. Power analysis was done by PASS 14 Power Analysis and Sample Size Software (2015). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

Primary outcome

The primary outcomes were EORTC QLQ - C30 version 3.0 Global QoL scale (Aaronson et al. 1993), and Beck Depression Inventory (BDI-II) (Beck et al. 1996). The European Organization for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire (EORTC QLQ-C30) is one of the most frequently and the best validated instruments to access the breast cancer patients QoL. It was first released in 1993 and it has been validated and improved ever since (Aaronson et al. 1993). EORTS QLQ - C30 Global QoL scale consists of two items: "29. How would you rate your overall health during the past week?", and "30. How would you rate your overall quality of life during the past week?" Patients self-fulfilled the questionnaire and answered the questions on the ordinal level rating scale ranging from 1 which was described as "very poor" to 7 which was described as "Excellent" quality of overall health/life. Rating scale levels between these two extremes were not described by words, but only by numbers. BDI-II contain 21 items for patient self-administration (Beck et al. 1996). It measures severity of depression symptoms as they were defined in American

Psychiatric association's Diagnostic and statistical manual of mental disorders 4th edition (DSM-IV). BDI-II items are scored on the four-point scale ranging from 0 which indicate lack of particular symptom, to 4 which indicate the most severe expression of particular symptom. Total BDI-II result is scored by summing results on particular items. The theoretical range of the total result is from 0 to 63. Score from 0 to 13 is considered normal. Score from 14 to 19 indicates a mild depression, from 20 to 28 a moderate and from 29 to 63 a severe depression.

Independent variables (predictors)

Our independent variables were EORTC QLQ-C30 version 3.0 symptoms scales and items. The symptoms prevalence and severity during the past week was measured on the ordinal level by answer options: 1 - not at all, 2 - a little, 3 - quite a bit, 4 - very much. Fatigue was measured by three items: "10. Did you need to rest"?, "12. Have you felt weak?", "18. Were you tired?". Pain was measured by two items: "9. Have you had pain?", "19. Did pain interfere with your daily activities?". Nausea and vomiting were measured by two items: "14. have you felt nauseated?", "15. Have you vomited?". All other symptoms were measured by single item each: Insomnia "11. Have you had trouble sleeping?"; Dyspnoea "8. Were you short of breath?"; Appetite loss "13. have you lacked appetite?"; Constipation "16. Have you been constipated?"; Diarrhea "17. Have you had diarrhea?". Before the analysis Global QoL scale and all symptoms scales were transformed in accordance with EORTC manual (Aaronson et al. 1993) so that all take the same range of values from 0 to 100. Transformation was done in two steps. In the first step, raw scores were calculated by estimating the average of the items included into particular scale: RawScore = (item1+item2+…+itemn)/n, where "n" is the number of respondents. In the second step raw scores were standardized by linear transformation: Scale = {(RawScore-1)/ range of values}x100, where the range of values is the difference between the maximum possible value of the raw score and the minimum possible value. Higher result of the final symptom scales represented a high level of symptomatology. Higher result of the final Global QoL scale represented higher QoL.

Possible confounders

Additionally to QoL, depression, and symptom indicators we have collected data on possible confounding factors: patients' age and education, marital status and number of children, tumor stage, ECOG performance status, HER2 status, existence of distant metastasis, treatment in outpatient unit or on oncology ward, type of surgery: lumpectomy or mastectomy, and menopausal status. Data on possible confounders were collected by the researcher from each patient medical record.

Statistical analysis

We set the level of statistical significance at P<0.05 and all confidence intervals at 95% level. The association of QoL, depression, symptoms and possible confounding variables was analyzed by multiple robust regression and iteratively reweighted least squares on all variables used simultaneously. We used Huber's method for robust influence function with Huber's tuning constant of 1.345, and a default median absolute deviation of residuals' scale factor of 0.6745. The criterion for stopping the iteration procedure was set at percent change of 0.001. Regression coefficients and tests of statistical significance were calculated assuming that the robust weights were random, calculated from the sample residuals, and not fixed. In all instances we used two-tail statistical tests. Normality of distributions was analyzed by Shapiro–Wilk and D'Agostino's omnibus K^2 tests. The model fit to the data was expressed by coefficient of determination (R^2) after robust weighting. Cases with missing values were excluded from the analysis. No correction for multiple testing was done, as all analyses were pre-planned, and only two multivariate analysis was interpreted. Statistical data analysis was done by NCSS 10 Statistical Software (2015) (NCSS, LLC. Kaysville, Utah, USA).

RESULTS

Total of 167 patients diagnosed with breast cancer, with ECOG performance status ≤ 2 were assessed for eligibility (Figure 1). Two (1.2%) patients were excluded because of their inability to self-fulfill the questionnaire, and 17 (10.3%) refused to participate. Data on Global QoL was not answered correctly by one patient. Finally, we included 147 breast cancer patients with mean (standard deviation, SD) age of 56 (11.7) years (Table 1). Total age range was 25 to 81 years. Fatigue was the most prevalent symptom followed by insomnia, dyspnea and pain (Table 2).
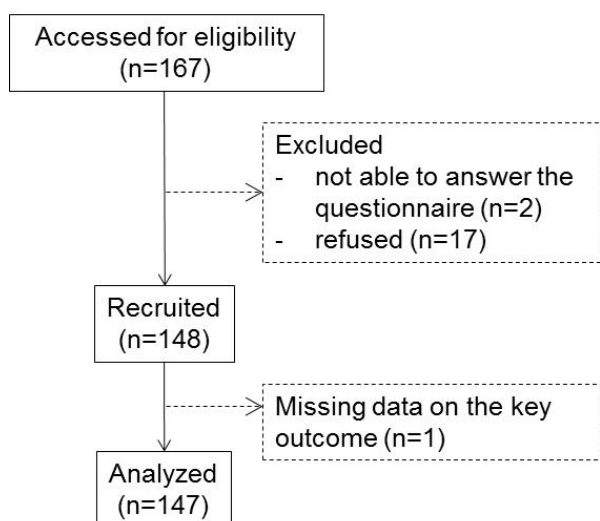
Figure 1. Participants flow diagram

Table 1. Patients sociodemographic and clinical characteristics (n=147)

	Mean	SD
Age (years)	56.1	11.71
Age (years), n (%)		
<50	39	26.5
50-59	44	29.9
60-69	47	32.0
≥70	17	11.6
Education, n (%)		
primary	21	13.7
secondary	92	60.1
university	40	26.1
Stage, n (%)*		
I-II	68	48.2
III-IV	73	51.8
ECOG, n (%)*		
fully active (grade 0)	111	81.6
restricted (grades 1-2)[†]	25	18.4
HER2		
negative	111	81.6
positive	25	18.4
Distant metastasis, n (%)*		
no	72	50.0
yes	72	50.0
Surgery, n (%)		
lumpectomy	80	54.8
mastectomy	66	45.2
Menopausal, n (%)		
no	43	28.1
yes	110	71.9
Relationships, n (%)		
being alone	47	32.6
being in a relationship	97	67.4
Having children, n (%)		
none	22	14.4
one	45	29.4
two	71	46.4
three or more	15	9.8
Patients, n (%)		
hospitalized	30	20.4
outpatients	117	79.6
Quality of life[‡]	60.8	24.08
Beck Depression Inventory II	11.7	8.00
Beck Depression Inventory II, n (%)		
no or minimal	106	69.3
mild	25	16.3
moderate	13	8.5
severe	9	5.9
Symptoms EORTC QLQ-C30		
fatigue	40.9	25.01
insomnia	39.8	31.85
pain	28.0	27.12
dyspnea	30.3	31.16
nausea and vomiting	11.9	17.17
appetite loss	18.2	27.49
constipation	17.8	27.73
diarrhea	10.7	20.69

Abbreviations: SD = standard deviation;   ECOG = Eastern Cooperative Oncology Group Performance Status;
IQR = interquartile range; BDI-II = Beck Depression Inventory;
* Data were not properly collected for stage 6 (4.1%), ECOG status 11 (7.5%); distant metastasis 3 (2.0%) of participants
[†] No patients with ECOG performance status 3 or 4 were included
[‡] EORTC QLQ-C30 version 3.0 Global Quality of Life scale

Table 2. Symptoms raw scores (n=147)

	Not at all		A Little		Quite a Bit		Very Much		Total		Mean	SD
	n	%	n	%	n	%	n	%	n	%		
Fatigue												
Did you need to rest?	23	15.9	59	40.7	52	35.9	11	7.6	145	100	2.35	0.84
Have you been tired?	23	15.9	65	44.8	47	32.4	10	6.9	145	100	2.30	0.82
Have you felt weak?	42	29.8	62	44.0	32	22.7	5	3.5	141	100	2.00	0.82
Insomnia												
Have you had trouble sleeping?	42	29.2	44	30.6	46	31.9	12	8.3	144	100	2.19	0.96
Pain												
Have you had pain?	61	42.1	51	35.2	26	17.9	7	4.8	145	100	1.86	0.88
Did pain interfere with your daily activities?	68	46.9	45	31.0	22	15.2	10	6.9	145	100	1.82	0.93
Dyspnea												
Were you short of breath?	61	42.1	45	31.0	30	20.7	9	6.2	145	100	1.91	0.94
Nausea and vomiting												
Have you felt nauseated?	85	58.2	41	28.1	17	11.6	3	2.1	146	100	1.58	0.78
Have you vomited?	130	89.0	13	8.9	2	1.4	1	0.7	146	100	1.14	0.43
Appetite loss												
Have you lacked appetite?	92	63.4	32	22.1	16	11.0	5	3.4	145	100	1.54	0.83
Constipation												
Have you been constipated?	96	65.8	26	17.8	20	13.7	4	2.7	146	100	1.53	0.83
Diarrhea												
Have you had diarrhea?	111	76.0	23	15.8	12	8.2	0	0.0	146	100	1.32	0.62

Data are presented as number (percentage) of patients;   SD = standard deviation

The multivariate model with all symptoms, socio-demographic and clinical variables included, statistically significantly predicted the QoL and depression (P<0.001 in both cases). Multiple coefficients of determination were R^2=0.73 and R^2=0.68 respectively. Distribution of unstandardized residuals for QoL was not significantly different from the normal one (Shapiro-Wilk test, P=0.053; D'Agostino Omnibus test, P=0.079), but it was in case of BDI-II (Shapiro-Wilk test, P<0.001; D'Agostino Omnibus test, P<0.001). However, distribution of residuals was symmetric.

After the adjustment for all variables by multivariable robust regression analysis, significant positive association with QoL was detected in cases of education and diarrhea and significant negative association in cases of fatigue, pain and appetite loss (Table 3). Significant positive association with depression was found in the cases of number of children and fatigue. Significant negative association was found in the cases of age and treatment in daily hospital. After the adjustment for all other symptoms, sociodemographic and clinical variables, interaction of fatigue and pain was not significantly associated with QoL or depression. Their effect on QoL was independent of each other although fatigue and pain were correlated (r=0.64; P<0.001). Age was significantly negatively correlated with QoL scale result, and significantly positively with BDI-II result (Figure 2). Univariately depression and QoL were significantly negatively correlated (r=-0.50; P<0.001). But after the adjustment for all planned sociodemographic, and clinical variables their correlation was not significant (r=-0.14; P=0.167).

DISCUSSION

Our study shown the negative association of fatigue, pain, appetite loss, and the positive association of education and diarrhea with breast cancer patients' QoL. Fatigue and number of children were positively, and age and treatment in daily hospital were negatively associated with depression measured by BDI-II.

The mean Global QoL score revealed by this study was significantly higher than in one previous Croatian study (Murgić et al. 2012). This difference probably reflects the fact of negative correlation of age and QoL found in both studies and the fact that previous Croatian study was done on the sample of patients whose mean age was significantly higher than in our study. Both Croatian studies found the significant correlation between age and global QoL. Previous Croatian study has found significant correlation of constipation and Global QoL while in our study constipation was single the least important predictor of QoL and their partial correlation was not statistically significant. This difference should probably be explained by age differences between two studies as well, as the prevalence of constipation increasing significantly after the age of 70. Our results on Global QoL, pain, nausea and vomiting, appetite loss, and constipation scale were almost identical to International reference pre-treatment values (Scott et al. 2008). We found more severe fatigue, insomnia and dyspnoea what should probably be explained by the different targeted populations. In our study majority of patients were already treated, so higher fatigue, insomnia and dyspnoea may be associated with that fact.

Table 3. Robust regression on QLQ-C30 version 3.0 Global Quality of Life scale, and to Beck Depression Inventory (BDI-II) total result (n=147)

	Global QLQ-C30		BDI-II	
	β_{adj}	p	β_{adj}	p
Age (years)	-0.16	0.119	-0.34	0.007
Education				
primary	referent		referent	
secondary	0.31	0.044	-0.02	0.901
university	0.35	0.018	0.16	0.070
ECOG status				
fully active (grade 0)	referent		referent	
restricted (grades 1-2)[*]	0.01	0.852	0.03	0.728
Stage, n (%)				
I-II	referent		referent	
III-IV	0.11	0.140	0.16	0.070
HER2				
negative	referent		referent	
positive	-0.11	0.106	0.08	0.355
Hormone				
negative	referent		referent	
positive	0.04	0.546	-0.09	0.328
Distant metastasis				
no	referent		referent	
yes	0.04	0.576	-0.10	0.274
Surgery				
lumpectomy	referent		referent	
mastectomy	-0.00	0.968	0.05	0.580
Menopausal				
no	referent		referent	
yes	0.03	0.715	0.21	0.065
Relationships				
being alone	referent		referent	
being in a relationship	0.06	0.402	-0.06	0.504
Having children				
none	referent		referent	
one	-0.03	0.767	0.18	0.202
two	-0.09	0.501	0.24	0.124
three or more	-0.06	0.566	0.29	0.029
Patients, n (%)				
hospitalized	referent		referent	
outpatients	0.06	0.372	-0.21	0.016
Body mass index (kg/m^2)	0.05	0.492	-0.01	0.911
EORTC QLQ - C30 Symptoms scales				
Fatigue	-0.47	<0.001	0.39	0.006
Nausea and vomiting	0.03	0.704	-0.07	0.523
Pain	-0.24	0.023	0.20	0.113
Dyspnea	-0.18	0.076	0.16	0.207
Insomnia	-0.03	0.675	-0.02	0.893
Appetite loss	-0.18	0.037	0.19	0.079
Constipation	0.01	0.860	0.07	0.485
Diarrhea	0.19	0.013	-0.17	0.067

Abbreviation: B = unstandardized multivariate regression coefficient; β_{adj} = standardized multivariate (adjusted) regression coefficient; t = t-test statistic with n-p-1 degrees of freedom where p is total number of parameters in the model; P = two-tailed test statistical significance of multivariate regression coefficient; ECOG = Eastern Cooperative Oncology Group Performance Status;
[*] No patients with ECOG performance status 3 or 4 were included;   * Data were not properly collected for stage 6 (4.1%), ECOG status 11 (7.5%); distant metastasis 3 (2.0%) of participants; cases with missing values were excluded pairwise;
[†] No patients with ECOG performance status 3 or 4 were included
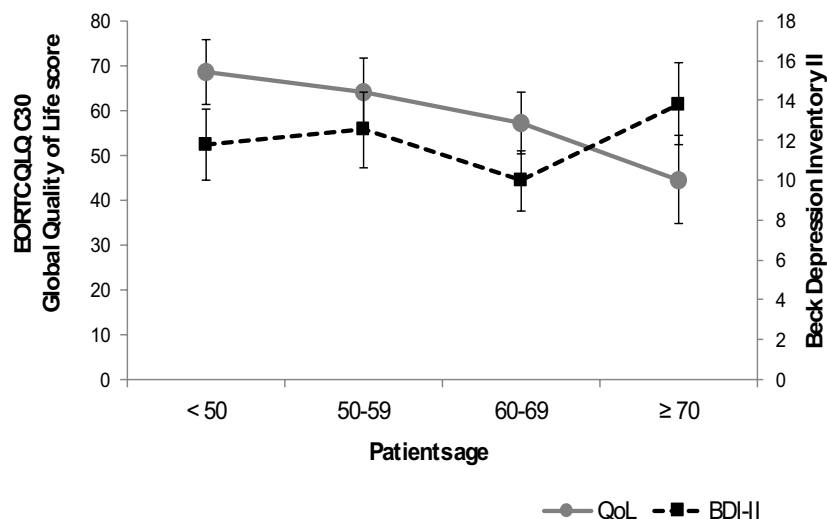
Figure 2. EORTC QLQ C-30 Global Quality of Life score and Beck Depression Inventory II result by patients age;
error bar represents 95% confidence intervals

Several studies have recognized fatigue as the most important independent predictor of QoL (Byun & Kim 2012, Dagnelie et al. 2007, Janz et al. 2007) what is consistent with our results. Dagnelie et al. found the overall QoL variance explained by fatigue to be larger than the one explained by combined functional and symptom subscales (Dagnelie et al. 2007). Contrary to our study Dagnelie et al. have not found significant contribution of age or pain to QoL. Our two studies were not completely comparable as they used only EORTC question 30 as criterion, and not the whole Global QoL scale, but they reported that the (not shown) results were very similar when they used the whole Global QoL scale. Additionally, 45% of their sample was patients diagnosed with lung cancer, and the multivariate analysis was not done separately for breast cancer. Although the correlation between fatigue and QoL was identical for lung and breast cancer, and similar for other subscales and symptoms, except for dyspnoea, the difference in tumor types might still have made a difference between our results as the effect of other confounding factors and interactions of other symptoms were not controlled in the same way. The last but not least, prevalence and severity of fatigue, pain, dyspnoea and insomnia was much higher in our sample.

Several studies found that pain is important independent predictor of QoL (Byun & Kim 2012), but in all cases that we are aware of, the importance of pain was significantly lower than in our study. After adjustment for anxiety, fatigue, and depression Byun and Kim (2012) found the linear regression standardized β coefficient for pain to QoL to be -0.18 (P=0.003) what was significantly less important than fatigue (β=-0.42; P<0.001).

Limitation of our study was the non-probability, consecutive instead of random sampling. We did enrollment during the late winter and early spring. If the breast cancer patients' QoL and depression has seasonal variations our study results generalizability to the whole year and the entire targeted population may be questionable. Another threat to generalizability of our results and conclusions is caused by the fact that we recruited patients in only one, highly specialized institution. It is possible that the association of symptoms, QoL and depression of patients treated in different types of institutions is different. Proportion of patients treated in outpatient unit vs patients admitted to the oncology ward is specific for this particular institution, and the enrollment period. So, this variable's effect may be different in different treatment settings where the proportion of patients treated in outpatient unit is different. We may assume that the average QoL would be lower, and the average depression higher in the institutions with the higher proportion of hospitalized patients. Accordingly, our results should be read as the "best-case-scenario".

CONCLUSION

There are many factors influencing quality of life and depression of breast cancer patients, but fatigue, pain, and appetite loss contributes the most to the overall QoL. Although correlated, fatigue and pain contribution to lower QoL is independent from each other. Future studies should investigate whether there is an interaction between fatigue and pain changes over course of treatment. Fatigue and number of children are positively, and age and treatment in daily hospital negatively associated with depression measured by BDI-II.

Contribution of individual authors:

Robert Šeparović designed the study, wrote the first manuscript draft.

Tajana Silovski contributed to the conception of the study, took active part in the data collection and critically revised the first draft of the study.

Ana Tecić Vuger designed the study, collected and analyzed the data and gave critical comments to the first draft of the manuscript.

Žarko Bajić contributed to the design of the study, performed the statistical data analysis and wrote the first draft of the manuscript.

Hrvoje Silovski contributed to the conception of the study, data collection and interpreting the findings.

Andreja Jurić contributed to the conception of the study, data collection and critical reading of the manuscript first draft.

References

1. *Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC: The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85:365–76. https://doi.org/10.1093/jnci/85.5.365*

2. *Andritsch E, Dietmaier G, Hofmann G, Zloklikovits S, Samonigg H: Global quality of life and its potential predictors in breast cancer patients: an exploratory study. Support. Care Cancer 2007; 15:21–30. https://doi.org/10.1007/s00520-006-0089-7*

3. *Beck A, Steer R, Brown G: Manual for Beck Depression Inventory-II. Psycholoical Corporation, San Antonio, TX, 1996*

4. *Byun HS, Kim GD: Impacts of Fatigue, Pain, Anxiety, and Depression on the Quality of Life in Patients with Breast Cancer. Asian Oncol Nurs 2012; 12:27–34. https://doi.org/10.1016/S0378-5122(12)70123-8*

5. *Dagnelie PC, Pijls-Johannesma MCG, Lambin P, Beijer S, De Ruysscher D, Kempen GIJM: Impact of fatigue on overall quality of life in lung and breast cancer patients selected for high-dose radiotherapy. Ann Oncol 2007; 18:940–4. https://doi.org/10.1093/annonc/mdm057*

6. *Groenvold M: Health-related quality of life in early breast cancer. Dan Med Bull 2010; 57:B4184*

7. *Groenvold M, Petersen MA, Idler E, Bjorner JB, Fayers PM, Mouridsen HT: Psychological distress and fatigue predicted recurrence and survival in primary breast cancer patients. Breast Cancer Res Treat 2007; 105:209–19. https://doi.org/10.1007/s10549-006-9447-x*

8. *Janz NK, Mujahid M, Chung LK, Lantz PM, Hawley ST, Morrow M, Schwartz K, Katz SJ: Symptom experience and quality of life of women following breast cancer treatment. J Womens Health (Larchmt) 2007; 16:1348–61 https://doi.org/10.1089/jwh.2006.0255*

9. *Jeffe DB, Pérez M, Cole EF, Liu Y, Schootman M: The Effects of Surgery Type and Chemotherapy on Early-Stage Breast Cancer Patients' Quality of Life Over 2-Year Follow-up. Ann Surg Oncol 2016; 23:735–43. https://doi.org/10.1245/s10434-015-4926-0*

10. *Kypriotakis G, Vidrine DJ, Francis LE, Rose JH: The longitudinal relationship between quality of life and survival in advanced stage cancer. Psychooncology 2016; 25:225–31. https://doi.org/10.1002/pon.3846*

11. *Meyerowitz BE: Psychosocial correlates of breast cancer and its treatments. Psychol Bull 1980; 87:108–31*

12. *Montazeri A: Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. J Exp Clin Cancer Res 2008; 27:32. https://doi.org/10.1186/1756-9966-27-32*

13. *Moussavi S, Chatterji S: Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet 2007; 370:851–858. https://doi.org/10.1016/S0140-6736(07)61415-9*

14. *Murgić J, Soldić Z, Vrljić D, Samija I, Kirac I, Bolanca A., Kusić Z: Quality of life of Croatian breast cancer patients receiving adjuvant treatment--comparison to long-term breast cancer survivors. Coll Antropol 2012; 36:1335-41*

15. *Nunes SOV, Reiche EMV, Morimoto HK, Matsuo T, Itano EN, Xavier ECD, Yamashita CM, Vieira VR, Menoli AV, Silva SS, Costa FB, Reiche FV, Silva FLV, Kaminami MS: Immune and hormonal activity in adults suffering from depression. Brazilian J Med Biol Res = Rev Bras Pesqui medicas e Biol 2002; 35:581–7*

16. *Reich M, Lesur A, Perdrizet-Chevallier C: Depression, quality of life and breast cancer: a review of the literature. Breast Cancer Res Treat 2008; 110:9–17. https://doi.org/10.1007/s10549-007-9706-5*

17. *Scott N, Fayers PNA, Bottomley A, Graeff D, Sprangers M, Al E: EORTC QLQ-C30 Reference Values, 2008*

18. *Vin-Raviv N, Akinyemiju TF, Galea S, Bovbjerg DH: Depression and Anxiety Disorders among Hospitalized Women with Breast Cancer. PLoS One 2015; 10: e0129169. https://doi.org/10.1371/journal.pone.0129169*

19. *Watson M, Haviland J, Greer S, Davidson J, Bliss J: Influence of psychological response on survival in breast cancer: a population-based cohort study. Lancet 1999; 354:1331–1336. https://doi.org/10.1016/S0140-6736(98)11392-2*

20. *World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA 2013; 310:2191–4. https://doi.org/10.1001/jama.2013.281053*

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