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EPIDEMIOLOGY

Prevalence and risk of depressive symptoms 3–4 months post-surgery in a nationwide cohort study of Danish women treated for early stage breast-cancer

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Abstract *Background* Elevated levels of depressive symptoms are generally found among cancer patients, but results from existing studies vary considerably with respect to prevalence and proposed risk factors. *Purpose* To study the prevalence of depressive symptoms and major depression 3–4 months following surgery for breast cancer, and to identify clinical risk factors while adjusting for pre-cancer sociodemographic factors, comorbidity, and psychiatric history. *Patients and methods* The study cohort consists of 4917 Danish women, aged 18–70 years, receiving standardized treatment for early stage invasive breast cancer during the 2 1/2 year study period. Of these, 3343 women (68%) participated in a questionnaire study 12–16 weeks following surgery. Depressive symptoms (Beck's Depression Inventory II) and health-related behaviors were assessed by questionnaire. The Danish Breast Cancer Cooperative Group (DBCG) and the surgical departments provided disease-, treatment-, and comorbidity data for the study cohort. Information concerning sociodemographics and psychiatric history were obtained from national longitudinal registries. *Results* The results indicated an increased prevalence of depressive symptoms and major depression (13.7%) compared to population-based samples. The pre-cancer variables: Social status, net-wealth, ethnicity, comorbidity, psychiatric history, and age were all independent risk factors for depressive symptoms. Of the clinical variables, only nodal status carried additional prognostic information. Physical functioning, smoking, alcohol use, and BMI were also independently associated with depressive symptoms. *Conclusion* Risk factors for depressive symptoms were primarily restricted to pre-cancer conditions rather than disease-specific conditions. Special attention should be given to socio-economically deprived women with a history of somatic- and psychiatric disease and poor health behaviors.

Keywords Age · Alcohol consumption · Body-mass index · Breast-cancer · Breast neoplasms psychology · Chemotherapy · Cohort studies · Comorbidity · Depression · Epidemiology · Health behavior · Major mastectomy · Neoplasms psychology · Physical function · Prevalence · Prospective studies · Psychiatry · Psychosocial · Radiotherapy · Risk-factors · Smoking · Socioeconomic factors · Stage

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Introduction

While depressive disorders are generally believed to be more prevalent in breast cancer patients than in the general

population, the literature indicates considerable variability [1], with rates from 0–2% [2, 3] up to 55% [4]. Previous studies have generally used relatively small samples of convenience with varying demographic characteristics. The variability of the results could also stem from methodological differences between studies, including the criteria used to define depression, the timing of assessment, disease stage, and treatment status of the women.

Older age is generally associated with reduced emotional expressivity [5, 6], and older women with breast cancer experience report fewer depressive symptoms [7]. Other age-related differences in health status, treatment, and social support may also play a role together with socio-demographic factors such as marital status [8, 9], number of children [10], and socio-economic status [11].

Several studies have used structured psychiatric interviews to assess depression according to diagnostic criteria, primarily as defined in DSM-III [12] or DSM-IV [13], while others have measured depressive symptoms using rating scales such as the Center for Epidemiological Studies Depression Scale (CES-D) [14], the Hospital Anxiety and Depression Scale (HADS) [15], or the Beck Depression Inventory (BDI), [16, 17]. These instruments generally compare well [18, 19] and seem suitable for assessing depression in cancer patients [19, 20]. The HADS, however, may be less suitable than other measures [21–24].

There is considerable variation in the timing of assessment both between- and within studies, with recently diagnosed patients being assessed over time-spans of several months [25, 26], and disease-free breast cancer survivors being assessed from a few months to 18 years after diagnosis [2, 27–29]. The available data indicate that cancer-related distress generally diminishes with time after diagnosis [10, 30–32], increasing again after a possible recurrence [33, 34].

There are also considerable within- and between study differences with respect to the disease and treatment characteristics. Some studies only include patients with early stages of breast cancer [35, 36], while others have investigated more advanced breast cancer [11, 23, 37]. Stage of disease and tumor grade have been reported inconsistently related to psychological problems in cancer and is generally uncorrelated with depression in breast-cancer [38–41]. While breast conserving surgery has been found associated with better body image [42] and lower prevalence of depression [27], there is no clear indication that depression is associated with type of surgery [32, 43, 44]. Radiotherapy [45] and tamoxifen [46, 47] has previously been linked to depression in breast-cancer, but more recent studies have not confirmed these findings [41, 48–50]. There are conflicting results concerning the possible role of chemotherapy [48, 50] and estrogen receptor status [39, 50, 51]. More consistent associations have been found with physical function [41, 52, 53] and overweight [54], whereas the role of poor health behaviors are less frequently investigated [41].

In an ageing population the prevalence of coexisting medical diseases in addition to cancer becomes increasingly important [55, 56]. Depression is common not only among cancer patients but also in other medical illnesses such as diabetes and cardiovascular diseases [57, 58], these being the most common coexisting illnesses in cancer patients [59]. Comorbidity may thus confound possible associations between depression and factors such as treatment or age.

Finally, the generalizability of results may suffer from unknown differences between participants and non-participants, introducing potential confounding by factors such as socio-economic status, comorbidity and psychiatric history. However, in the available studies, these factors are rarely explored.

Aim of the study

While the literature suggests that women treated for breast cancer may be at increased risk of depression, there is considerable variability in the results and proposed risk factors, which may stem from methodological between-study differences, and studies using large population-based samples are needed. In the present study, we present data, collected at baseline, from a large prospective nation-wide cohort study of Danish women recently treated for early stage breast cancer, with the aim of assessing the prevalence of depressive symptoms and investigating the role of potential risk factors, including disease- and treatment-related factors, demographic- and socio-economic factors, psychiatric history, and medical comorbidity.

Methods

Study design

The present study is designed as a nationwide prospective cohort study and consists of 4917 women surgically treated for early stage invasive breast cancer in Denmark between October 2001 and March 2004. The study is conducted in collaboration with The Danish Breast Cancer Cooperative Group (DBCG) and the 24 largest surgical departments responsible for treating breast cancer in Denmark during the inclusion period. Data concerning eligibility, comorbidity, histopathology, and treatment-related variables were obtained from the DBCG registry as well as from the surgical departments. Demographics, psychiatric history and socio-economic variables were obtained from the

unique Danish longitudinal registries. At baseline, 12–16 weeks post-surgery, 3343 (68.0%) women from the cohort also provided extensive information regarding health behaviors, health status, and psychosocial variables through a mail-out questionnaire.

Eligibility

Eligible patients were aged 18–70 years, Danish residents with histologically confirmed stage I or II breast cancer T1-3, N0-3, and M0 according to the TNM classification [60] and no history of other cancers except non-melanoma skin cancer or carcinoma in situ of the cervix uteri. The ability to read Danish, being physically/mentally capable of completing a questionnaire, and allocation to one of the five existing standard DBCG treatment protocols was also required. The protocols were: (A) No adjuvant therapy; (B) Seven courses of chemotherapy (CEF) followed by endocrine treatment for 5 years; (C) Endocrine treatment for 5 years, and (D or E) Seven courses of chemotherapy with CEF or CMF. Women treated with lumpectomy, or who had tumor positive lymph nodes in the axillae and/or non-radical surgery and/or tumors with a diameter >50mm were also allocated to radiotherapy.

Procedure

Eligible women were informed orally and in writing about the study at the surgical departments. The Charlson Comorbidity Index [61] was completed by a physician together with a form indicating the date of surgery, each patient's unique personal identification number (CPR-number), and information regarding eligibility for each woman. Data were sent to the Study Secretariat at the Psychooncology Research Unit at Aarhus University Hospital on a monthly basis. Addresses of eligible women were obtained from the DBCG registry on a monthly basis during the study period, or directly from The Danish Civil Registration System (DCRS), using the CPR-numbers on the Charlson forms. Eligible women were mailed an informed consent form, additional information, a questionnaire package, and a prepaid return envelope, and invited to participate in the study 12–16 weeks after surgery. A hotline telephone and e-mail service was offered to answer questions regarding the study and the questionnaire. If the questionnaires and the written consent form were not returned within 3 weeks, a single reminder was sent. The questionnaires were designed, processed and verified using optical scanning and software (Teleform 7.1; Cardiff). Approval of the study was obtained from The Regional Science-Ethical Committees and The Danish Data Protection Agency.

Subjects

DBCG and/or the collaborating surgical departments initially identified a total of 5441 women as being potentially eligible for the study. Of these, 237 women (4.4%) received treatment at one of the 11 minor surgical departments not participating in the study and were hence excluded. Information from the surgical departments showed that 68 women had a previous cancer disease unknown to the DBCG at the time and that an additional 24 women did not receive standard treatment (typically neo-adjuvant chemotherapy). Furthermore, 99 women were considered unable to read Danish sufficiently well by the surgical departments or as being physically/mentally incapable to fill in a questionnaire. Three women had distant metastases diagnosed within 12 weeks post-surgery, and two women who had left the country within the same time period were also excluded. One woman was reported by her relatives to be hospitalized due to psychiatric illness, and one woman was shown to have had surgery prior to the study period.

In all, 5,006 women were thus eligible for the study. Subsequently seven women who had chosen to block scientific access to their addresses through their CPR-number, and two women who withdrew their consent were deleted from the database. Finally, 80 women were excluded in order to minimize zero-time bias, because their data and addresses were not available within 28 weeks post-surgery.

A total of 4,917 women thus constituted the study cohort. Of these, 3343 women (68.0%) returned a valid questionnaire. The majority of the questionnaires (91%) were mailed out 12–16 weeks after primary surgery. The remaining questionnaires were mailed out during the following three months.

Measures

Depressive symptoms

The 21-item Beck Depression Inventory – Second Edition (BDI-II) is a widely used questionnaire developed for the assessment of symptoms corresponding to criteria for diagnosing depressive disorder listed in The American Psychiatric Associations Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV). According to the manual, a cut score of 17 has yielded a 93% true-positive rate and 18% false-positive rate for the presence of major depression [17]. Its two factor-analytically derived subscales measuring somatic- and cognitive/affective depressive symptoms respectively, makes it particularly useful in medical ill populations in terms of identifying the potentially disease-, and treatment-related symptoms of depression. Internal consistency (Chronbach's Alpha) was

satisfactory (Total: 0.90; Somatic symptoms: 0.75; Cognitive/Affective symptoms: 0.89).

Physical function (PF)

The SF-36 PF 10 item subscale was used to measure physical functioning. The SF-36 is a widely used measure of health related quality of life and PF measures limitations chiefly in basic daily physical activities such as lifting or carrying groceries, climbing stairs etc. There are three response types: "Yes limited a lot" (=1), "Yes limited a little" (=2) and, "No not limited at all" (=3). Individual scores were calculated as outlined in the manual: 100 × ((Sum score – lowest possible score (i.e. 10)) / (Highest possible raw score (i.e. 30) – lowest possible score (i.e. 10))). This transformation yields a score range from 0 (lowest PF) to 100 (best PF) [62, 63]. Internal consistency was satisfactory (Chronbach's alpha = 0.86).

Health behaviors and BMI

Data on health behaviors and BMI were obtained by questionnaire. BMI was calculated as: current weight (Kg)/Height (m^2) and categorized according to WHO guidelines [64]: Underweight (BMI $\leq$ 18.5); Normal weight (>18.5 and <25); Overweight ($\geq$25 and <30); Obese and severely obese ($\geq$30) were collapsed due to few observations (<3%) among severely obese. Alcohol intake was measured as total self-reported consumption during the past seven days and is presented in units per day (beers, glasses of wine or drinks). Ex-drinkers were defined as previous users who had stopped drinking. Never smokers and ex-smokers were categorized separately.

Comorbidity

The Charlson Comorbidity Index (CCI) [61] is a widely used measure of nineteen comorbid conditions that can alter the risk of mortality in longitudinal studies. CCI has been validated among breast cancer patients and the weighted index score takes into account the number and the seriousness of comorbid disease [55, 65]. Cancer specific conditions are not included in the present study since patients with previous malign cancers or metastatic tumors were not eligible. Missing data identified through a linkage with the DBCG registry were requested from the departments every third month.

Clinical variables and treatment

Data on histopathology and treatment-related variables from all eligible patients were obtained through a linkage with the DBCG registry. DBCG was established in 1976 with the aim of ensuring optimal diagnostics and treatment of operable primary breast cancer on a nation-wide basis. DBCG has worked out uniform national guidelines and the participants include all departments of surgery, pathology, radiotherapy, and oncology involved in the treatment of breast cancer in Denmark. The departments provide data to the DBCG on a regularly basis. A previous study [66] has shown that only 3% of all eligible patients fulfilling the criteria's of enrollment in a DBCG protocol between 1978 and 1994 where missing when validating the DBCG registry against The Danish Cancer Registry. Less than one percent was registered by the DBCG but missing in the Danish Cancer Registry. It was also shown that the completeness of the DBCG registry was improving through the study period. The data provided by the DBCG in the present study can therefore be considered as nearly complete.

Sociodemographics

Since 1968, all Danish residents have been assigned a 10-digit personal identification number (CPR-number) by the DCRS, which is used across all public registration systems, making linkages with a large number of registry-based data sources possible. Data were collected through a linkage with six of the nationwide Danish longitudinal registers available for researchers. All registries are administered by the central government agency of statistics in Denmark (Statistics Denmark) [67] except the Danish Psychiatric Central Research Registry, which is administered by the Department of Psychiatric Demography at Aarhus University Hospital. The linkage of all registries was serviced by Statistics Denmark. Age at the time of surgery was calculated on the basis of the CPR-number and time of surgery. All sociodemographic variables refer to pre-cancer conditions either in the year prior to the date of surgery minus one month or, when appropriate, at the date of surgery minus one month. The following registries were used:

The Registry of Income Statistics: (Personal income, net-wealth). The registry is based on the information that banks, employers and others who pay out wages and salaries, remunerations, pensions etc. are required to report to the tax authority. Income was adjusted for the yearly wage-increases for women in Denmark by a weighted average of the three indices of the average earnings in the private-, and public sector (local- and central government) published by Statistics Denmark. The weights were calculated on the basis of the occupational distribution in the 2002 indices for women, also published by Statistics Denmark. Due to the significant fluctuations on the financial markets in the study period and a low Danish core inflation rate in the study period net-wealth was left unadjusted. A mean household net-wealth variable (excluding principal shareholder positions

and value of privately held enterprises) was calculated by using the mean total net-wealth for cohabiting couples. The amounts in Danish kroner (Kr.) were subsequently converted into US dollars ($) on the basis of the exchange rates published by Danmarks Nationalbank (Basis: 12/31 2003).

The Registry-based labor-force statistics (RAS): (Social status). RAS Statistics provides a description of the Danish populations attachment to the labor market and follows the guidelines set by the International Labour Organisation (ILO). RAS Employee skill level acquired through education or learning in praxis is defined on the basis of the Danish version of the European Unions official nomenclature for occupations, ISCO-88 (International Standard Classification of Occupations).

The Registry for Education of the Population (BUE): (Level of Education). Level of education was coded according to UNESCO's International Standard Classification of Education (ISCED-97) nomenclature [68]. Because a significant proportion of the women had 7 years of education, the Lower secondary general category was divided into two categories: 7 years (mandatory for the elderly in the cohort) and 8–10 years. At the tertiary level, data are categorized as pre-, and post master degree. The approximate corresponding years of schooling are indicated in the tables.

Integrated Database for Labor Market Research (IDA): (Marital status, ethnicity and urbanicity). The group of immigrants/descendants is defined by Statistics Denmark as persons for whom neither of their parents are Danish citizens born in Denmark. Women were defined as cohabiting when registered at the same address as one non-related male adult and no other adults. Married, but not cohabiting women were categorized as separated. The urbanicity variable was categorized on the basis of municipality sizes in the year 2002.

The Fertility Database: (Number of children). The database includes information on date of birth and death of children of Danish residents. We calculated the number of children alive at the time of surgery.

The Danish Psychiatric Central Research Registry (DPCR). DPCR is a nationwide administrative registry to which psychiatric inpatients treated in Denmark has been reported since 1969. Since 1995, outpatients have been registered as well [69]. In the present study, psychiatric history was coded as positive in case of psychiatric hospitalization for any reason until one month pre-surgery. From 1995, outpatient history was also coded as positive.

Missing values

Participants were specifically instructed to check for missing answers before returning the questionnaire. The following procedure was applied: Subscale totals with more than 50% missing values were coded as missing and no total score was calculated. Missing values on subscales with an alpha > 0.7 were substituted with the mean of the remaining filled items on the subscale. This procedure is identical to the procedure described in the manual of SF-36 and is regarded as adequate and preferable to procedures such as list-wise deleting or scale mean-substitution of scale-scores when one or more values are missing [62, 70].

Statistical analysis

Response rates were computed in categories of each variable and the unadjusted association with non-response was assessed by Chi^2-test. Subsequently the associations were evaluated simultaneously by a logistic regression analysis with response to the questionnaire (yes or no) as the dependent variable. The results of the logistic regression were presented as adjusted odds ratios (OR).

For each variable an unadjusted comparison of BDI scores across categories was carried out by a Kruskal-Wallis test. Next, a negative binomial regression model was used to evaluate the association of each variable with total BDI score adjusted for the influence of other variables. Results of these analyses were presented as a Ratios of Means (RM), which gives the expected BDI score in a category relative to the expected BDI score in the reference category.

The independent variables considered in the regression models referred to three phases of the woman's cancer history: Pre-cancer, peri-surgery and post-surgery, and data were analyzed accordingly. Demographics and health status data were analyzed in the first step, since these data refer to pre-cancer conditions and therefore are unbiased by the cancer experience. Information and experiences related to the disease and its treatment had been known to the women for more than 2 months, when the questionnaire was completed. Clinical variables were therefore analyzed in the second step. Post-cancer health behaviors and other health-related variables might be moderated by the cancer diagnosis and treatment, and were therefore analyzed in the third step. At each step, we report the unadjusted stratified mean values and the prevalence of major depression as percentages. At step 2 and 3, we also report RM adjusted for all variables included at the previous steps in the analysis as well as age-adjusted RM. Finally, we considered a total risk-model for the prevalence of depressive symptoms 3–4 month post-surgery using backward negative binomial regression analysis. Supplementary analyses of the somatic and the cognitive/affective subscales of BDI were also performed. In order to validate and elaborate our findings, we also applied logistic regression analysis to calculate the odds ratios for major depression for the

identified risk factors. Age was treated as a continuous variable in all multivariate analyses.

The nbreg procedure in STATA 9.2 for UNIX was used for the negative binomial regression analyses; all other analyses were conducted with SPSS 14.0.1 for Windows 2000.

Results

Non-responders

Data on psychiatric history, co-morbidity, socio-demographics, and histopathology and treatment for each variable were obtained for at least 98.5% of all eligible women, allowing a nearly complete comparison of questionnaire responders with non-responders (Table 1). When adjusting for age, neither histopathology nor treatment-related variables were significantly related to response rate (all P-values >.21). Also, there were no differences in participation related to DBCG's five standard treatment protocols (P = .38, data not shown). In contrast, psychiatric history, comorbidity and all the sociodemographic variables, except having children (P = .06), were found to be significantly associated to response rate when controlling for age (Table 1). Responders were generally younger, better educated, had higher incomes, higher mean net-wealth, higher social status (employed in jobs requiring medium to high skill levels, excluding self-employed or assisting spouses), and were more likely to be married or cohabiting. Lower participation was found for women having a psychiatric history, serious comorbid disease, for immigrants/descendants, and residents of the center of Copenhagen.

Depression

Total BDI-II scores could be calculated for all but 22 women (n = 3321) and only 46 respondents had more than one missing item on the BDI. Median age was 55.7 years (range: 26–70 years) and mean BDI Total score was 8.85 (SD = 7.44). Mean scores on the somatic-, and cognitive/affective subscales were 3.59 (SD = 2.38) and 4.48 (SD = 5.25) respectively. In all, 13.7% had a BDI score above or equal to 17 and could thus be classified as suffering from major depression. BDI scores of responders who returned the reminder questionnaire (n = 444) did not differ significantly from scores of the remaining responders (P = .26). Time from surgery to the first questionnaire was mailed out was not associated to the BDI score (Rho = −.008; P = .64). For major depression, the overall proportion of users of prescribed anti-depressive medications or anxiolytica for more than 3 days the previous month was 35%. When adding women who had consulted a psychiatrist or psychologist more than once since diagnosis, the percentage was 51% (data not shown).

Sociodemographic- and health-related risk factors for depressive symptoms

A significant negative correlation was found between age and BDI total scores (Rho = − .17; P < .001), with fewer depressive symptoms found among the 50–69 year old women compared to the 18–35 year old women. Nearly a third of the patients with a psychiatric history (33%) or with a score above one point on the Charlson Comorbidity Index (30%) were classified as suffering from major depression. In the age-adjusted analyses, risk factors for depressive symptoms were: Younger age, low income (≤20.000$), negative net-wealth, low social status (being outside the workforce, i.e. old age pensioners, unemployed etc. and recipients of early retirement pension etc.), less education, being divorced/separated, and having a history of somatic- or psychiatric disease (Table 2). When entering all the sociodemographic variables into a regression analysis with additional adjustment for psychiatric history and comorbidity, the independent pre-cancer risk factors for depressive symptoms were: Younger age, psychiatric history, comorbidity, being a recipient of early retirement pension, rehabilitation- or sickness benefits, and having a negative mean household net-wealth. In addition, an increased prevalence of depressive symptoms among immigrants and descendants was observed (P = .05) (Table 2).

Clinical risk factors for depressive symptoms

In the unadjusted analyses, higher levels of depressive symptoms were predicted by axillary lymph node involvement, pre-menopausal status, and treatment with chemotherapy (Table 3). After adjustment for age, only axillary lymph node involvement (>3) was a risk factor (RM = 1.11, 95% CI = 1.03–1.20). The age-adjusted analyses revealed no further influence of disease- and treatment-related factors (all P > .11), including the five standard DBCG treatment protocols (P = .10, data not shown). Additional adjustment for sociodemographics-, psychiatric history and comorbidity resulted only in minor and insignificant changes (Table 3).

Analyses of the subscale scores on the BDI while adjusting for age, pre-cancer health status, and sociodemographic variables revealed that the observed effects for both lymph node involvement was driven by an association with the somatic subscale of the BDI (P < .001), while there were no associations with scores on the cognitive/affective subscale (P = .38).

Table 1 Characteristics of the study cohort and questionnaire response-rate[a]

	Study cohort	Questionnaire responders	Questionnaire response-rate	
	N (%)	*N*	%	OR (Age-adj.)
Socio-demographics and health status				
Age			$P < .001$	
18–35	136 (2.8)	95	69.9	
36–49	1209 (24.6)	902	74.6	
50–59	1852 (37.7)	1288	69.5	
60–69	1720 (35.0)	1058	61.5	
Marital status			$P < .001$	$P < .001$
Married or cohabiting	3656 (74.4)	2556	70.0	1.00
Divorced, separated or married—single	644 (13.1)	412	64.0	**0.77**
Widow—single	317 (6.4)	181	57.1	**0.71**
Unmarried—single	287 (5.8)	188	65.5	**0.74**
Children			$P = .15$	$P = .06$
No	589 (12.0)	385	65.4	1.00
Yes	4328 (88.0)	2958	68.3	1.20
Education			$P < .001$	$P < .001$
Lower secondary general (7 years)	988 (20.1)	551	55.8	1.00
Lower secondary general (8–10 years)	733 (14.9)	470	64.1	1.20
Upper secondary (11–13 years)	1893 (38.5)	1324	69.9	**1.62**
Tertiary < master degree (14–17 years)	1021 (20.8)	799	78.3	**2.42**
Tertiary ≥ master degree (≥18 years)	210 (4.3)	160	76.2	**2.09**
Missing	72 (1.5)	39		
Urbanicity			$P = .01$	$P = .008$
<10.000 inhabitants	831 (16.9)	570	68.6	1.00
10.000–50.000	1729 (35.2)	1208	69.9	1.08
50.000–300.000	1068 (21.7)	726	68.0	0.98
Copenhagen-suburbs	776 (15.8)	524	67.5	0.97
Copenhagen-center	500 (10.2)	309	61.8	**0.72**
Social status			$P < .001$	$P < .001$
Top manager or employee–upper level	471 (9.6)	383	81.3	1.00
Employee–medium level	682 (13.9)	560	82.1	1.05
Employee–basic level	1122 (22.8)	821	73.2	**0.63**
Employee–others or in education	521 (10.6)	335	64.3	**0.42**
Self-employed or assisting spouse	198 (4.0)	125	63.1	**0.40**
Unemployed, recipient of temporary allowance-, cash- or pre-retirement benefits etc	1028 (20.9)	627	61.0	**0.37**
Old age pension	321 (6.5)	170	53.0	**0.28**
Recipients of early retirement pension, rehabilitation- or sickness benefits	559 (11.4)	315	56.4	**0.31**
Personal income			$P < .001$	$P < .001$
≤20.000$	919 (18.7)	509	55.4	1.00
>20.000 $ & ≤30.000 $	1034 (21.0)	625	60.4	**1.20**
>30.000 $ & ≤40.000 $	991 (20.2)	690	69.6	**1.69**
>40.000 $ & ≤55.000 $	1164 (23.7)	883	75.9	**2.28**
>55.000 $	794 (16.1)	629	79.2	**2.77**
Household net-wealth per person			$P = .03$	$P < .001$
<0 $	1046 (21.3)	683	65.3	1.00
≥0 $ & <20.000 $	909 (18.5)	603	66.3	**1.23**

Table 1 continued

	Study cohort	Questionnaire responders	Questionnaire response-rate	
	N (%)	*N*	%	OR (Age-adj.)
≥20.000 $ & <55.000 $	923 (18.8)	628	68.0	**1.32**
≥55.000 $ & <120.000 $	1055 (21.5)	744	70.5	**1.59**
≥120.000 $	969 (19.7)	678	70.0	**1.66**
Ethnicity			$P = .006$	$P = .001$
Not Immigrant or descendant	4730 (96.2)	3235	68.4	1.00
Immigrant or descendant	174 (3.5)	102	58.6	**0.59**
Psychiatric history			$P < .001$	$P < .001$
No	4505 (91.6)	3113	69.1	1.00
Yes	412 (8.4)	230	55.8	**0.57**
Charlson comorbidity Index (CCI)			$P < .001$	$P < .001$
No comorbidity	4300 (87.5)	2975	69.2	1.00
CCI score = 1	478 (9.7)	298	62.3	**0.81**
CCI score > 1	123 (2.5)	61	49.6	**0.51**
Clinical variables				
Tumor size			$P = .73$	$P = .52$
≤20 mm	2956 (60.1)	2023	68.4	1.00
>20 mm & ≤50 mm	1775 (36.1)	1198	67.5	0.96
>50 mm	156 (3.2)	101	64.7	0.83
Nodal status			$P = .31$	$P = .28$
0	2464 (50.1)	1645	66.8	1.00
1-3	1565 (31.8)	1087	69.5	1.12
>3	871 (17.7)	599	68.8	1.06
Tumor grade			$P = .85$	$P = .45$
I	1183 (24.1)	794	67.1	1.00
II	1743 (35.4)	1198	68.7	1.06
III	1029 (20.9)	693	67.3	0.94
Non-ductal carcinoma	916 (18.6)	628	68.6	1.07
ER/PR Receptorstatus			$P = .38$	$P = .31$
ER- and PR-negative	924 (18.8)	623	67.4	1.00
ER- and/or PR-positive	3941 (80.2)	2689	68.2	1.08
Missing	52 (1.1)	31		–
Menopausal status			$P < .001$	$P = .36$
Pre-menopausal	1740 (35.4)	1291	74.2	1.00
Post-menopausal	3160 (64.3)	2040	64.6	0.91
Type of Surgery			$P = .71$	$P = .80$
Mastectomy	2664 (54.2)	1813	68.1	1.00
Lumpectomy	2243 (45.6)	1522	67.9	0.98
Chemotherapy			$P < .001$	$P = .68$
No chemotherapy	2885 (58.7)	1886	65.4	1.00
In treatment (CEF or CMF)	2015 (41.0)	1445	71.7	1.03
Radiotherapy			$P < .001$	$P = .86$
No radiotherapy	1018 (20.7)	688	67.6	1.00
To be treated after chemotherapy	1637 (33.3)	1179	72.0	1.03
Has been treated with radiotherapy	2246 (45.7)	1465	65.2	0.98
Hormone therapy			$P < .001$	$P = .22$
No hormone therapy	1843 (37.5)	1233	66.9	1.00

Table 1 continued

	Study cohort	Questionnaire responders	Questionnaire response-rate	
	N (%)	*N*	%	OR (Age-adj.)
To be treated after chemotherapy (TAM)	1093 (22.2)	823	75.3	1.19
In treatment (TAM + FEM)	1939 (39.4)	1256	64.8	1.04

[a] The study cohort comprises of 4,917 women. The questionnaire responders totals 3343 women (68.0%). OR = Odds ratio. Age-adjusted odds ratios in bold differs significantly (95% CI) from the reference group (OR = 1.00). Missing observations are not shown when less than one percent. As a consequence totals differs slightly

When entered into a logistic regression with major depression vs. no major depression as the dependent variable while adjusting for age and sociodemographic factors, nodal status only exhibited a trend towards being a risk factor for major depression ($P = .07$, data not shown). Results of similar analyses of all other clinical variables, including treatment, did not reach statistical significance (all $P > .30$, data not shown).

Health behavior, health status and depressive symptoms

Smoking status: In the age-adjusted analysis more depressive symptoms were found among women smoking more than 9 cigarettes per day compared to never-smokers. After full adjustment, only the consumption of 20 or more cigarettes per day was associated with depressive symptoms (Table 4). The results of the fully adjusted analysis applied to both the somatic ($P < .001$) and the cognitive/affective component ($P < .001$) of the BDI (data not shown).

Alcohol consumption: After adjustment for sociodemographic- and clinical variables, only the consumption of three or more units per day showed to be significantly related to depressive symptoms compared to never drinkers (Table 4). This applied to both the somatic ($P = .01$) and the cognitive/affective subscale ($P = .001$) of the BDI (data not shown).

Body mass: In the age-adjusted analysis, overweight, obese or severely obese women reported significantly more depressive symptoms compared to women with normal weight. This association remained relatively unaffected in the fully adjusted analysis (Table 4). This effect was most pronounced for the somatic subscale of the BDI ($P < .001$) (data not shown).

Physical functioning: A strong association was observed between physical function and the prevalence of depressive symptoms (Table 4). The mean BDI-score of women with a SF-36 score below or equal to 70 was nearly 2.5 fold higher than for women with a score of 100. The corresponding prevalence of major depression was more than five fold higher (30.6% vs. 5.8%). The strength of the association in the age-adjusted analysis of depressive symptoms was only minimally affected in the fully adjusted analysis. The association applied to both the somatic (RM = 2.39, 95% CI = 2.21 to 2.59, $P < .001$) and the cognitive/affective subscale (RM = 2.72, 95% CI = 2.36 to 3.14, $P < .001$) of the BDI (data not shown).

In the fully adjusted analysis, both comorbidity and axillary lymph node involvement ceased to be statistically significant predictors when physical function was added as a covariate, but remained independent predictors, when smoking status, BMI, and alcohol consumption were added separately as covariates.

Independent predictors of depressive symptoms and major depression

The results of a backward regression analysis including all the presented independent variables ($P < .05$) are presented in Table 5. Independent predictors of depressive symptoms 12–16 month post-surgery were: Younger age, being divorced or separated, being immigrant or descendant, having a positive psychiatric history, belonging to an upper-middle household (i.e. having a mean net-wealth of 55–120.000$), smoking more than 20 cigarettes per day, and reporting reduced physical functioning (<100). Moderate alcohol consumption (≥1 and <2 units per day) was an independent predictor of fewer depressive symptoms. When entering all the identified independent predictors of depressive symptoms into a logistic regression with major depression vs. non-depressed as the dependent variable, the results generally supported these findings. The fully adjusted odds ratio of suffering from major depression when having a physical function score below or equal to 70 compared to a score of 100 was 7.38 (95% CI = 4.77–11.41).

Discussion

The present study is, to the best of our knowledge, the first nationwide prospective study of risk factors and the prevalence of depressive symptoms and major depression following breast cancer. Further strengths include: A large sample size; Admission to data on nearly all eligible cases during the study period; Nationwide standardized

Table 2 Sociodemographic and health related risk factors for depressive symptoms[a]

	MD (%)	Depressive symptoms (BDI II - Total)				
		Mean	Age-adjusted		Fully adjusted[b]	
			RM	(95% CI)	RM	(95% CI)
Age		$P < .001$		$P < .001$[c]		$P < .001$
18–35	17.9	10.48	1.00	(referent)	**0.985**	0.980–0.989
36–49	16.7	9.95	0.95	0.80–1.13		
50–59	13.3	8.82	**0.84**	0.71–0.99		
60–69	11.2	7.78	**0.74**	0.62–0.88		
Marital status		$P = .002$		$P < .001$		$P = .15$
Married or cohabiting	12.7	8.61	1.00	(referent)	1.00	(referent)
Divorced, separated or married—single	18.4	10.17	**1.19**	1.09–1.30	1.10	1.00–1.20
Widow—single	12.8	8.51	1.10	0.97–1.25	1.09	0.96–1.24
Unmarried—single	17.6	9.38	1.05	0.93–1.19	1.00	0.88–1.14
Children		$P = .77$		$P = .40$		$P = .39$
No	14.1	8.75	1.00	(referent)	1.00	(referent)
Yes	13.7	8.86	1.04	0.95–1.14	1.04	0.95–1.14
Education (ISCED 97 based)		$P = .006$		$P = .03$		$P = .53$
Lower secondary general (7 years)	14.5	8.60	1.00	(referent)	1.00	(referent)
Lower secondary general (8–10 years)	16.2	9.48	0.99	0.89–1.11	1.04	0.94–1.16
Upper secondary (11–13 years)	13.2	8.87	0.94	0.86–1.03	1.04	0.95–1.14
Tertiary < master degree (14–17 years)	13.0	8.73	0.91	0.83–1.01	1.04	0.93–1.16
Tertiary master degree (≥18 years)	8.2	7.81	**0.81**	0.69–0.94	0.93	0.78–1.10
Social status (ISCO-88 based)		$P < .001$		$P < .001$		$P = .01$
Top manager or employee—upper level	12.6	8.51	1.00	(referent)	1.00	(referent)
Employee—medium level	10.9	8.69	1.00	0.90–1.11	0.99	0.88–1.11
Employee—basic level	13.1	8.84	1.02	0.93–1.13	0.98	0.87–1.12
Employee—others or in education	14.5	8.52	1.02	0.90–1.15	0.97	0.84–1.12
Self-employed or assisting spouse	11.4	7.90	0.97	0.82–1.15	0.97	0.81–1.16
Unemployed, recipient of temporary allowance-, cash- or pre-retirement benefits etc	12.0	8.34	**1.13**	1.02–1.27	1.06	0.92–1.22
Old age pension	14.9	7.84	**1.23**	1.04–1.45	1.16	0.96–1.41
Recipients of early retirement pension, rehabilitation- or sickness benefits	24.0	11.80	**1.55**	1.36–1.75	**1.29**	1.09–1.53
Personal income		$P = .90$		$P < .001$		$P = .46$
≤20.000 $	16.7	9.43	1.00	(referent)	1.00	(referent)
>20.000 $ & ≤30.000 $	15.5	9.15	0.94	0.85–1.04	1.06	0.95–1.18
>30.000 $ & ≤40.000 $	14.0	8.94	**0.85**	0.77–0.94	1.04	0.92–1.17
>40.000 $ & ≤55.000 $	11.5	8.41	**0.78**	0.71–0.86	0.98	0.87–1.11
>55.000 $	12.0	8.53	**0.80**	0.72–0.88	1.03	0.90–1.18
Household Net-Wealth per person		$P < .001$		$P < .001$		$P = .02$
<0 $	18.6	10.40	1.00	(referent)	1.00	(referent)
≥0 $ & <20.000 $	14.0	9.25	0.92	0.84–1.01	**0.90**	0.82–0.99
≥20.000 $ & <55.000 $	12.0	8.54	**0.85**	0.77–0.93	**0.90**	0.82–0.98
≥55.000 $ & <120.000 $	13.7	8.50	**0.86**	0.79–0.94	0.94	0.86–1.03
≥120.000 $	9.8	7.54	**0.78**	0.71–0.85	**0.85**	0.78–0.94
Urbanicity (municipality size)		$P = .39$		$P = .45$		$P = .41$
<10.000 Inhabitants	13.6	8.76	1.00	(referent)	1.00	(referent)
10.000–50.000	13.7	8.83	1.02	0.94–1.11	1.04	0.95–1.13
50.000–300.000	15.9	9.05	1.04	0.95–1.15	1.04	0.95–1.15

Table 2 continued

	MD (%)	Depressive symptoms (BDI II - Total)				
		Mean	Age-adjusted		Fully adjusted[b]	
			RM	(95% CI)	RM	(95% CI)
Copenhagen—suburbs	12.4	9.01	1.04	0.94–1.15	1.07	0.97–1.18
Copenhagen—center	10.5	8.25	0.94	0.84–1.06	0.96	0.85–1.08
Ethnicity		$P = .03$		$P = .08$		$P = .05$
Not immigrant or descendant	13.5	8.80	1.00	(referent)	1.00	(referent)
Immigrant or descendant	18.6	10.18	1.16	0.98–1.36	1.18	1.00–1.38
Psychiatric history		$P < .001$		$P < .001$		$P < .001$
No	12.3	8.47	1.00	(referent)	1.00	(referent)
Yes	32.9	13.92	**1.65**	1.48–1.84	**1.49**	1.33–1.66
Charlson comorbidity Index (CCI)		$P = .004$		$P < .001$		$P = .005$
No comorbidity	12.9	8.64	1.00	(referent)	1.00	(referent)
CCI score = 1	19.0	10.08	**1.23**	1.11–1.36	**1.12**	1.01–1.23
CCI score > 1	30.0	12.95	**1.67**	1.35–2.05	**1.34**	1.08–1.65

[a] MD = Prevalence of major depression (BDI-II scores $\geq$ 17); CI = Confidence interval; RM = Ratios of means. Age-adjusted RM in bold differs significantly (95% CI) from the reference group (RM = 1.00)

[b] Fully adjusted for all other socio-demographic variables, psychiatric history and comorbidity ($N = 3273$)

[c] Unadjusted

treatment; A prospective design using unbiased measures of pre-cancer demographics; Application of a consecutive inclusion procedure at a well-defined point in time 12–16 weeks following surgery in order to reduce potential zero-point bias; Acceptable questionnaire response rate and highly detailed data on histopathological-, treatment-, sociodemographic- and health related variables for both participants and non-participants.

A mean score of 8.85 on the BDI-II and a point prevalence of major depression (MD) of 13.7% 12–16 weeks after surgery were observed. In a sample of 187 randomly selected Danish women a mean score of 7.1 on the BDI-II [71] and a prevalence of MD of 10.7% was found (unpublished data: Zachariae, R.). In another Danish study also using the BDI-II [72], a MD prevalence of 12.1% in a randomly selected sample of 109 younger women aged 20–35 yrs., and 3.0% among 133 elderly women aged 70–85 years. was found (unpublished data: Zachariae, R.). In the present study, the indicated prevalence of MD among 18–35 year olds was 17.9%, while the prevalence was 11.2% among the eldest (60–69 years). In a study of 616 randomly selected Danish women aged 20–79 years. the point prevalence of MD was 3.6% while using the Major Depression Inventory, corresponding to a prevalence of 8.8% of minor and major depression on the Hamilton Depression Scale [73]. In the US, the 12-month point prevalence for MD was 6.6% according to the National Comorbidity Survey Replication study [74] while prevalence in Europe generally is found to be somewhat lower (3–5%) [73].

Our results thus suggest, that the prevalence of major depression and depressive symptoms is increased following surgery for invasive breast cancer.

Of the cancer- and treatment related variables, only nodal status (>3) was a modest risk factor for increased depressive symptoms and only marginally so for major depression. The generalizeability of this finding is supported by the finding that participation in the questionnaire study, when adjusting for age, was neither biased by histopathological nor treatment related variables. This result can therefore be seen as being in general accordance with the negative findings in a large US-sample, although histopathological- and treatment related variables were specified in less detail and nodal status was not analysed separately in that study [41]. The results raise the question why the level of depressive symptoms following a diagnosis of breast cancer is increased, while generally unpredicted by any of a detailed set of cancer- and treatment related variables? A straightforward answer could be that what matters most to women having early stage breast cancer, is the cancer per se—i.e. the personal-, social- and economic implications of having a potentially life-threatening disease. Our finding that nodal status was the only cancer- and treatment related risk factor for depression may reflect that the prognostic significance of nodal spread may be the only clinical variable commonly perceived by the women as having a negative prognostic influence.

In contrast to treatment- and disease characteristics, sociodemographics, comorbidity, and psychiatric history,

Table 3 Clinical risk factors for depressive symptoms[a]

	MD (%)	Depressive symptoms (BDI–total)				
		Mean	Age-adjusted		Fully adjusted[b]	
			RM	(95% CI)	RM	(95% CI)
Tumor size		$P = .35$		$P = .83$		$P = .75$
≤20 mm	13.4	8.78	1.00	(referent)	1.00	(referent)
>20 mm & ≤50 mm	14.1	8.92	1.01	0.95–1.07	1.00	0.95–1.06
>50 mm	15.8	9.29	1.05	0.89–1.24	1.07	0.90–1.26
Nodal status		$P = .001$		$P = .02$		$P = .02$
0	12.5	8.50	1.00	(referent)	1.00	(referent)
1–3	13.7	8.95	1.05	0.99–1.12	1.05	0.98–1.11
>3	16.9	9.57	**1.11**	1.03–1.20	**1.11**	1.03–1.20
Tumor grade		$P = .07$		$P = .76$		$P = .74$
I	13.0	8.60	1.00	(referent)	1.00	(referent)
II	14.7	9.00	1.04	0.96–1.12	1.03	0.96–1.11
III	12.7	9.07	1.02	0.93–1.11	1.04	0.96–1.14
Non-ductal carcinoma	14.1	8.67	1.01	0.92–1.10	1.01	0.93–1.11
ER/PR Receptorstatus		$P = .12$		$P = .86$		$P = .60$
ER- and PR-negative	12.5	8.98	1.00	(referent)	1.00	(referent)
ER- and/or PR-positive	14.0	8.81	0.99	0.92–1.07	0.98	0.91–1.05
Menopausal status		$P < .001$		$P = .12$		$P = .38$
Pre-menopausal	15.8	9.59	1.00	(referent)	1.00	(referent)
Post-menopausal	12.3	8.37	1.08	0.98–1.19	1.04	0.95–1.15
Type of surgery		$P = .53$		$P = .23$		$P = .67$
Mastectomy	14.3	8.98	1.00	(referent)	1.00	(referent)
Lumpectomy	12.9	8.69	0.97	0.91–1.02	0.99	0.93–1.05
Chemotherapy		$P < .001$		$P = .23$		$P = .09$
No chemotherapy	12.7	8.30	1.00	(referent)	1.00	(referent)
In treatment (CEF or CMF)	15.0	9.56	1.04	0.97–1.12	1.06	0.99–1.13
Radiotherapy		$P < .001$		$P = .73$		$P = .46$
No radiotherapy	13.4	8.62	1.00	(referent)	1.00	(referent)
To be treated after chemotherapy	14.6	9.52	1.03	0.95–1.12	1.05	0.97–1.14
Has been treated with radiotherapy	13.1	8.41	1.02	0.94–1.10	1.02	0.95–1.11
Hormone therapy		$P < .001$		$P = .20$		$P = .33$
No hormone therapy	12.6	8.55	1.00	(referent)	1.00	(referent)
To be treated after chemotherapy (TAM)	16.9	9.99	1.06	0.98–1.15	1.06	0.98–1.15
In treatment (TAM + FEM)	12.8	8.41	1.05	0.98–1.13	1.02	0.95–1.10

[a] MD = Prevalence of major depression (BDI-II scores ≥ 17); CI = Confidence interval; RM = Ratios of Means. RM in bold differs significantly (95% CI) from the reference group (RM = 1.00)

[b] Fully adjusted for socio-demographic variables (age, marital status, children, education, urbanicity, social status, personal income, household net-wealth and ethnicity), psychiatric history and comorbidity

were consistently found to be risk factors for both depressive symptoms and major depression.

Poor health behaviours (i.e. extensive smoking or drinking), being overweight and low levels of physical functioning were independently associated with higher levels of depressive symptoms in the fully adjusted analysis. Due to the cross-sectional nature of this part of the data set, it may be that physical functioning and extensive drinking and smoking 12–16 weeks following surgery in part could be a consequence of depressive symptomatology following breast cancer, rather than the opposite causal direction. However, with respect to physical functioning, the mean score for women aged 45–54 on the SF-36 PF was 85.5 (SD = 15.3) and thus similar to Danish norms (86.2; SD = 20.1) [62]. For women aged 55–64 the mean score was in fact somehow higher 83.5 (SD = 17.3)

Table 4 Depressive symptoms and self-reported health behaviours, BMI and physical function[a]

	N	MD (%)	Depressive symptoms (BDI II - total)				
			Mean	Age-adjusted		Fully adjusted[b]	
				RM	(95% CI)	RM	(95% CI)
Smoking status			$P < .001$		$P < .001$		$P < .001$
Never smoker	1311	11.4	8.18	1.00	(referent)	1.00	(referent)
Ex-smoker	987	12.0	8.60	1.05	0.98–1.12	1.05	0.98–1.13
1–9 per day	175	11.4	8.09	1.00	0.88–1.14	0.98	0.86–1.12
10–19 per day	459	15.7	9.44	**1.16**	1.06–1.26	1.06	0.97–1.16
≥20 per day	332	26.5	11.92	**1.44**	1.30–1.59	**1.34**	1.21–1.48
Alcohol			$P < .001$		$P < .001$		$P = .001$
Never drinker	331	15.1	9.18	1.00	(referent)	1.00	(referent)
Ex-drinker	177	22.6	11.13	**1.19**	1.03–1.38	1.13	0.97–1.32
<1 drink per day	1340	13.7	8.93	0.95	0.86–1.04	0.99	0.90–1.10
≥1 & <2 drinks per day	803	10.6	7.91	**0.86**	0.78–0.96	0.94	0.85–1.05
≥2 & <3 drinks per day	386	11.7	8.45	0.94	0.83–1.06	1.01	0.89–1.14
≥3 drinks per day	233	19.7	9.94	1.12	0.97–1.28	**1.21**	1.05–1.39
Body Mass Index (BMI)			$P = .02$		$P < .001$		$P = .007$
Normal weight (>18.5 & <25)	1898	12.0	8.43	1.00	(referent)	1.00	(referent)
Underweight (≤18.5)	83	15.7	9.30	1.12	0.93–1.34	1.03	0.86–1.23
Overweight (≥25 & <30)	894	14.5	9.19	**1.12**	1.05–1.19	**1.09**	1.02–1.17
Obese or severely obese (≥30)	380	20.0	10.12	**1.21**	1.11–1.33	**1.15**	1.04–1.26
Physical function (SF-36 PF)			$P < .001$		$P < .001$		$P < .001$
100	535	5.8	5.51	1.00	(referent)	1.00	(referent)
>90 & <100	817	6.2	6.96	**1.26**	1.15–1.38	**1.30**	1.19–1.42
>80 & ≤90	837	12.1	8.91	**1.62**	1.49–1.77	**1.67**	1.53–1.82
>70 & ≤80	542	17.5	10.24	**1.87**	1.70–2.06	**1.90**	1.73–2.09
≥0 & ≤70	566	30.6	13.28	**2.54**	2.32–2.79	**2.51**	2.27–2.77

[a] MD = Prevalence of major depression (BDI-II scores ≥17); CI = Confidence interval; RM = Ratios of means. RM in bold differs significantly (95% CI) from the reference group (RM = 1.00)

[b] Adjusted for all clinical factors (tumor size, nodal status, tumor grade, ER/PR receptor status, menopausal status, surgery, chemotherapy, radiotherapy and hormone therapy) and all socio-demographic variables (age, marital status, children, education, urbanicity, social status, personal income, household net-wealth and ethnicity), psychiatric history and comorbidity

compared to norms 78.0 (SD = 24.8). Physical functioning as measured by the SF-36 may therefore not be a consequence of early breast cancer in any substantial degree but rather a true risk factor for depression as well as major depression. Low physical functioning was strongly associated to both the somatic- and the cognitive/affective BDI subscales, and the question remains whether some women are attributing their low level of physical functioning to a possible recurrence. Ethnicity also emerged as an independent significant predictor in the final model (Table 5). There may exist cultural barriers in the Danish health system adding to the stress of the disease for these women. If so, it is likely that the problems are even more pronounced in ethnic minorities since only those being able to read Danish were included in the study, and those who were not could be even worse off.

In the US 51.6% of all MD cases have been found to receive treatment [74] whereas only 13.2% MD cases were in treatment by a medical doctor for a nervous/mental disease in a Danish population based sample [73]. In the present study we found that 35% were in medical treatment for nervous/mental disease. Compared to Danish norms the treatment rate is therefore higher, but a substantial number of Danish women treated for invasive breast cancer remain untreated for a possible major depression.

When comparing responders with non-responders in the total study cohort, lower participation was generally seen in groups that were at increased risk of depression with the exception of younger women. However, we found no differences in depressive symptoms between women who returned the reminder when compared to those who returned the first questionnaire. Nonetheless, it is likely that

Table 5 Final model: independent predictors of depressive symptoms[a,b]

	BDI II-total		MD (Major depression)			
	RM	(95% CI)	Age-adjusted		Fully adjusted	
			OR	(95% CI)	OR	(95% CI)
Age		$P < 0.001$		$P < .001$[c]		$P < .001$
Years	**0.984**	0.981–0.988	**0.979**	0.969–0.990	**0.962**	0.949–0.977
Marital status		$P = .02$		$P = .009$		$P = .23$
Married or cohabiting	1.00	(referent)	1.00	(referent)	1.00	(referent)
Divorced, separated or married—single	**1.10**	1.01–1.20	**1.57**	1.19–2.07	1.39	1.02–1.91
Widow—single	1.14	1.00–1.29	1.22	0.77–1.94	1.07	0.63–1.81
Unmarried—single	0.94	0.84–1.06	1.35	0.90–2.00	1.09	0.70–1.70
Ethnicity		$P = .01$		$P = .16$		$P = .09$
Not immigrant or descendant	1.00	(referent)	1.00	(referent)	1.00	(referent)
Immigrant or descendant	**1.23**	1.05–1.43	1.44	0.87–2.40	1.62	0.92–2.83
Psychiatric history		$P < .001$		$P < .001$		$P < .001$
No	1.00	(referent)	1.00	(referent)	1.00	(referent)
Yes	**1.40**	1.26–1.55	**3.51**	2.61–4.73	**2.40**	1.70–3.38
Household net-wealth per person		$P = .02$		$P = .003$		$P = .06$
<0 $	1.00	(referent)	1.00	(referent)	1.00	(referent)
≥0 $ & <20.000 $	0.94	0.86–1.02	0.74	0.55–1.01	0.79	0.57–1.11
≥20.000 $ & <55.000 $	0.95	0.87–1.04	**0.63**	0.46–0.86	0.88	0.63–1.25
≥55.000 $ & <120.000 $	1.06	0.97–1.16	0.76	0.57–1.02	1.29	0.92–1.81
≥120.000 $	0.95	0.87–1.04	**0.53**	0.38–0.75	0.90	0.62–1.31
Smoking status		$P = .002$		$P < .001$		$P < .001$
Never Smoker	1.00	(referent)	1.00	(referent)	1.00	(referent)
Ex-smoker	1.06	1.00–1.13	1.04	0.81–1.35	1.10	0.84–1.45
1–9 per day	0.98	0.86–1.11	1.03	0.63–1.69	1.02	0.61–1.72
10–19 per day	1.06	0.97–1.15	**1.44**	1.06–1.96	1.11	0.79–1.56
≥20 per day	**1.21**	1.10–1.33	**2.02**	2.02–3.66	**2.10**	1.50–2.96
Alcohol		$P = .03$		$P < .001$		$P = .06$
Never drinker	1.00	(referent)	1.00	(referent)	1.00	(referent)
Ex-drinker	1.04	0.90–1.20	1.55	0.97–2.46	1.17	0.70–1.97
<1 per day previous week	0.95	0.86–1.04	0.83	0.59–1.17	0.87	0.60–1.26
≥1 & <2 per day previous week	**0.90**	0.81–1.00	**0.66**	0.45–0.96	0.78	0.52–1.18
≥2 & <3 per day last week	0.97	0.86–1.09	0.76	0.49–1.17	0.80	0.50–1.29
≥3 per day last week	1.07	0.93–1.22	1.42	0.91–2.21	1.42	0.87–2.33
Physical function (SF-36 PF)		$P < .001$		$P < .001$		$P < .001$
100	1.00	(referent)	1.00	(referent)	1.00	(referent)
>90 & <100	**1.31**	1.19–1.43	1.05	0.66–1.67	1.15	0.71–1.85
>80 & ≤90	**1.67**	1.53–1.83	**2.22**	1.46–3.37	**2.28**	1.47–3.53
>70 & ≤80	**1.94**	1.76–2.13	**3.49**	2.28–5.35	**3.57**	2.29–5.58
≥0 & ≤70	**2.52**	2.29–2.78	**8.08**	5.37–12.17	**7.38**	4.77–11.41

[a] MD = Prevalence of major depression (BDI-II scores ≥ 17); CI = Confidence interval; RM = Ratios of Means. OR and RM in bold differs significantly (95% CI) from the reference group (OR = 1.00 or RM = 1.00)

[b] *First column*: Independent predictors of depressive symptoms ($P < .05$), identified by backward regression analysis including all clinical factors (tumor size, nodal status, tumor grade, ER/PR receptor status, menopausal status, surgery, chemotherapy, radiotherapy and hormone therapy), all socio-demographic variables (age, marital status, children, education, urbanicity, social status, personal Income, household net-wealth and ethnicity), psychiatric history, comorbidity and self-reported health behaviors (smoking, use of alcohol), body mass index and physical function. *Second column*: Unadjusted RM and CI. *Third column*: Age-adjusted OR and CI for major depression. *Fourth column*: OR and CI for major depression fully adjusted for all independent predictors identified in the backward regression analysis ($N = 3190$).

[c] Unadjusted

the true level of depression in the study cohort may be somehow underestimated. The finding that women with an indication of major depression were more than 2.5 times likely to be in treatment for nervous/mental disease compared to a population based Danish sample, thereby reducing the "natural" level of depressive symptoms following breast-cancer, may further add to such a bias.

Conclusion

The present study confirms that the prevalence of major depression and depressive symptoms is increased among women treated for early stage breast-cancer. Concerns have been raised with respect to potentially adverse consequences of treatment for breast-cancer, e.g. chemotherapy, radiotherapy, mastectomy, and tamoxifen, but our results suggest that these concerns are unjustified with respect to depression. While cancer-specific variables were of minor importance, socio-economic and general health-related factors seem to play a substantial role as risk factors for depressive symptoms. It is possible that the influence of these risk factors is even more pronounced in countries with greater inequality in public access to adequate health services and treatment. The results calls for considerations about establishing screening procedures for major depression in breast-cancer, in order to provide adequate support and treatment to those who are in need.

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References

1. Massie NJ, Popkin MK (1998) Depressive disorders. In: Holland J (ed) Psycho-oncology. Oxford University Press, New York
2. Al Ghazal SK, Sully L, Fallowfield L et al (2000) The psychological impact of immediate rather than delayed breast reconstruction. Eur J Surg Oncol 26:17–19
3. Maraste R, Brandt L, Olsson H et al (1992) Anxiety and depression in breast-cancer patients at start of adjuvant radiotherapy—relations to age and type of surgery. Acta Oncol 31:641–643
4. Gaston-Johansson F, Fall-Dickson JM, Bakos AB et al (1999) Fatigue, pain, and depression in pre-autotransplant breast cancer patients. Cancer Pract 7:240–247
5. Gross JJ, Carstensen LL, Pasupathi M et al (1997) Emotion and aging: experience, expression, and control. Psychol Aging 12:590–599
6. Charles ST, Reynolds CA, Gatz M (2001) Age-related differences and change in positive and negative affect over 23 years. J Pers Soc Psychol 80:136–151
7. Mosher CE, Danoff-Burg S (2005) A review of age differences in psychological adjustment to breast cancer. J Psychosoc Oncol 23:101–114
8. Dean C (1987) Psychiatric morbidity following mastectomy—preoperative predictors and types of illness. J Psychosom Res 31:385–392
9. Bloom JR (1982) Social support, accommodation to stress and adjustment to breast-cancer. Soc Sci Med 16:1329–1338
10. Deshields T, Tibbs T, Fan MY et al (2006) Differences in patterns of depression after treatment for breast cancer. Psychooncology 15:398–406
11. Pinder KL, Ramirez AJ, Black ME et al (1993) Psychiatric-disorder in patients with advanced breast-cancer—prevalence and associated factors. Eur J Cancer 29A:524–527
12. Spitzer RL, Williams JBW, Gibbon M et al (1992) The structured clinical interview for Dsm-Iii-R (Scid).1. History, rationale, and description. Arch Gen Psychiatry 49:624–629
13. First MB, Gibbon M, Spitzer RL (1996) Structured clinical interview for DSM-IV (IP). New York, Biometrics research department, New York State Psychiatric Institute.
14. Radlof LS (1977) The CES-D Scale: A self-report depression scale for research in the general population. J Applied Psychol Meas 1:385–401
15. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361–370
16. Beck AT, Erbaugh J, Ward CH et al (1961) An inventory for measuring depression. Arch Gen Psychiatry 4:561–571
17. Beck AT, Steer RA, Brown GK (1996) Manual: Beck depression inventory, 2nd edn. The Psychological Corp Hartcourt & Brace, San Antonio, TX
18. Wilcox H, Field T (1998) Correlations between the BDI and CES-D in a sample of adolescent mothers. Adolescence 33:565–574
19. Berard RMF, Boermeester F, Viljoen G (1998) Depressive disorders in an out-patient oncology setting: prevalence, assessment, and management. Psychooncology 7:112–120
20. Hann D, Winter K, Jacobsen P (1999) Measurement of depressive symptoms in cancer patients: Evaluation of the Center for Epidemiological Studies Depression Scale (CES-D). J Psychosom Res 46:437–443
21. Hall A, A'Hern R, Fallowfield L (1999) Are we using appropriate self-report questionnaires for detecting anxiety and depression in women with early breast cancer?. Eur J Cancer 35:79–85
22. Groenvold M, Fayers PM, Sprangers MAG et al (1999) Anxiety and depression in breast cancer patients at low risk of recurrence compared with the general population: A valid comparison? J Clin Epidemiol 52:523–530
23. Love AW, Grabsch B, Clarke DM et al (2004) Screening for depression in women with metastatic breast cancer: a comparison of the Beck depression inventory short form and the hospital anxiety and depression scale. Aust N Z J Psychiatry 38:526–531
24. Love AW, Kissane DW, Bloch S et al (2002) Diagnostic efficiency of the Hospital Anxiety and Depression Scale in women with early stage breast cancer. Aust N Z J Psychiatry 36:246–250

25. Farragher B (1998) Psychiatric morbidity following the diagnosis and treatment of early breast cancer. Ir J Med Sci 167:166–169
26. Pasacreta JV (1997) Depressive phenomena, physical symptom distress, and functional status among women with breast cancer. Nurs Res 46:214–221
27. Al Ghazal SK, Fallowfield L, Blamey RW (2000) Comparison of psychological aspects and patient satisfaction following breast conserving surgery, simple mastectomy and breast reconstruction. Eur J Cancer 36:1938–1943
28. Cordova MJ, Cunningham LLC, Carlson CR et al (2001) Posttraumatic growth following breast cancer: a controlled comparison study. Health Psychol 20:176–185
29. Yeter K, Rock CL, Pakiz B et al (2006) Depressive symptoms, eating psychopathology, and physical activity in obese breast cancer survivors. Psychooncology 15:453–462
30. Burgess C, Cornelius V, Love S et al (2005) Depression and anxiety in women with early breast cancer: five year observational cohort study. Br Med J 330:702–705
31. Goldberg JA, Scott RN, Davidson PM et al (1992) Psychological morbidity in the 1st year after breast surgery. Eur J Surg Oncol 18:327–331
32. Rijken M, de Kruif AT, Komproe IH et al (1995) Depressive symptomatology of post-menopausal breast cancer patients: a comparison of women recently treated by mastectomy or by breast-conserving therapy. Eur J Surg Oncol 21:498–503
33. Andersen BL, Kiecoltglaser JK, Glaser R (1994) A Biobehavioral Model of Cancer Stress and Disease Course. Am Psychol 49:389–404
34. Andersen BL, Shapiro CL, Farrar WB et al (2005) Psychological responses to cancer recurrence—a controlled prospective study. Cancer 104:1540–1547
35. Antoni MH, Lehman JM, Kilbourn KM et al (2001) Cognitive-behavioral stress management intervention decreases the prevalence of depression and enhances benefit finding among women under treatment for early-stage breast cancer. Health Psychol 20:20–32
36. Green BL, Krupnick JL, Rowland JH et al (2000) Trauma history as a predictor of psychologic symptoms in women with breast cancer. J Clin Oncol 18:1084–1093
37. Hopwood P, Howell A, Maguire P (1991) Psychiatric morbidity in patients with advanced cancer of the breast—prevalence measured by 2 self-rating questionnaires. Br J Cancer 64:349–352
38. vantSpijker A, Trijsburg RW, Duivenvoorden HJ (1997) Psychological sequelae of cancer diagnosis: a meta-analytical review of 58 studies after 1980. Psychosom Med 59:280–293
39. Aragona M, Muscatello MRA, Mesiti M (1997) Depressive mood disorders in patients with operable breast cancer. J Exp Clin Canc Res 16:111–118
40. Ell K, Sanchez K, Vourlekis B, Lee PJ et al (2005) Depression, correlates of depression, and receipt of depression care among low-income women with breast or gynecologic cancer. J Clin Oncol 23:3052–3060
41. Bardwell WA, Natarajan L, Dimsdale JE et al (2006) Objective cancer-related variables are not associated with depressive symptoms in women treated for early-stage breast cancer. J Clin Oncol 24:2420–2427
42. Kissane DW, Clarke DM, Ikin J et al (1998) Psychological morbidity and quality of life in Australian women with early-stage breast cancer: a cross-sectional survey. Med J Aust 169:192–196
43. Aukst-Margetic B, Jakovljevic M, Margetic B et al (2005) Religiosity, depression and pain in patients with breast cancer. Gen Hosp Psychiatry 27:250–255
44. Fallowfield LJ, Hall A, Maguire GP et al (1990) Psychological outcomes of different treatment policies in women with early breast-cancer outside a clinical-trial. Br Med J 301:575–580
45. Lasry JCM, Margolese RG, Poisson R et al (1987) Depression and body-image following mastectomy and lumpectomy. J Chronic Dis 40:529–534
46. Duffy LS, Greenberg DB, Younger J et al (1999) Iatrogenic acute estrogen deficiency and psychiatric syndromes in breast cancer patients. Psychosomatics 40:304–308
47. Cathcart CK, Jones SE, Pumroy CS et al (1993) Clinical recognition and management of depression in node-negative breast-cancer patients treated with Tamoxifen. Breast Cancer Res Treat 27:277–281
48. Kissane DW, Grabsch B, Love A et al (2004) Psychiatric disorder in women with early stage and advanced breast cancer: a comparative analysis. Aust N Z J Psychiatry 38:320–326
49. Day R, Ganz PA, Costantino JP (2001) Tamoxifen and depression: More evidence from the National Surgical Adjuvant Breast and Bowel Project's Breast Cancer Prevention (P-1) randomized study. J Natl Cancer Inst 93:1615–1623
50. Lee KC, Ray GT, Hunkeler EM et al (2007) Tamoxifen treatment and new-onset depression in breast cancer patients. Psychosomatics 48:205–210
51. Tjemsland L, Soreide JA, Malt UF (1995) Psychosocial factors in women with operable breast-cancer—an association to estrogen-receptor status. J Psychosom Res 39:875–881
52. Stommel M, Kurtz ME, Kurtz JC et al (2004) A longitudinal analysis of the course of depressive symptomatology in geriatric patients with cancer of the breast, colon, lung, or prostate. Health Psychol 23:564–573
53. Krishnan L, Stanton AL, Collins CA et al (2001) Form or function? Part 2. Objective cosmetic and functional correlates of quality of life in women treated with breast-conserving surgical procedures and radiotherapy. Cancer 91:2282–2287
54. Werrij MQ, Mulkens S, Hospers HJ et al (2006) Overweight and obesity: the significance of a depressed mood. Patient Educ Couns 62:126–131
55. Extermann M (2000) Measurement and impact of comorbidity in older cancer patients. Crit Rev Oncol Hematol 35:181–200
56. Janssen-Heijnen MLG, Houterman S, Lemmens VEPP et al (2005) Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. Crit Rev Oncol Hematol 55:231–240
57. Evans DL, Charney DS, Lewis L et al (2005) Mood disorders in the medically ill: scientific review and recommendations. Biol Psychiatry 58:175–189
58. Krishnan KRR, Delong M, Kraemer H et al (2002) Comorbidity of depression with other medical diseases in the elderly. Biol Psychiatry 52:559–588
59. Louwman WJ, Janssen-Heijnen MLG, Houterman S et al (2005) Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. Eur J Cancer 41:779–785
60. Singletary SE, Allred C, Ashley P et al (2002) Revision of the American joint committee on cancer staging system for breast cancer. J Clin Oncol 20:3628–3636
61. Charlson ME, Pompei P, Ales KL et al (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383
62. Bjørner JB, Damsgaard MT, Watt T et al (1997) Dansk manual for SF-36 (Danish manual for the SF-36), Lægemiddelindustriforeningen, Copenhagen.
63. Ware JE, Sherbourne CD (1992) The Mos 36-item short-form health survey (Sf-36) .1. Conceptual-Framework and Item Selection. Med Care 30:473–483
64. World Health Organization (2000) Obesity. Preventing and managing the global endemic. Technical report series no 894, WHO, Geneva.

65. Extermann M (2000) Measuring comorbidity in older cancer patients. Eur J Cancer 36:453–471
66. Rostgaard K, Holst H, Mouridsen HT et al (2000) Do clinical databases render population-based cancer registers obsolete? The example of breast cancer in Denmark. Cancer Causes Control 11:669–674
67. Statistics Denmark (2005). Statistics Denmark. Numbers on time. http://www.dst.dk/HomeUK/About/introSD.aspx. Cited 23 nov 2007
68. UNESCO (2006) ISCED 1997. International standard classification of education, Re-edition. http://www.uis.unesco.org/TEMPLATE/pdf/isced/ISCED_A.pdf. Cited 11 oct 2007.
69. Munk-Jorgensen P, Mortensen PB (1997) The Danish Psychiatric Central Register. Dan Med Bull 44:82–84
70. Schafer JL, Graham JW (2002) Missing data: our view of the state of the art. Psychol Methods 7:147–177
71. Zachariae R, Zachariae C, Ibsen HHW et al (2004) Psychological symptoms and quality of life of dermatology outpatients and hospitalized dermatology patients. Acta Derm Venereol 84:205–212
72. Thomsen DK, Mehlsen MY, Viidik A et al (2005) Age and gender differences in negative affect—Is there a role for emotion regulation? Personality and Individual Differences 38:1935–1946
73. Olsen LR, Mortensen EL, Bech P (2004) Prevalence of major depression and stress indicators in the Danish general population. Acta Psychiatr Scand 109:96–103
74. Kessler RC, Berglund P, Demler O et al (2003) The Epidemiology of Major Depressive Disorder: Results From the National Comorbidity Survey Replication (NCS-R). JAMA 289:3095–3105