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Published in:
Psychological Medicine

Publication date:
2003

Document Version
Publisher's PDF, also known as Version of record

Psychological Medicine, 2003, **33**, 1111–1117. © 2003 Cambridge University Press
DOI: 10.1017/S0033291703007499 Printed in the United Kingdom

BRIEF COMMUNICATION

Depression and the lower risk for breast cancer development in middle-aged women: a prospective study

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ABSTRACT

Background. Depression has been hypothesized to be potentially linked to an increased risk of breast cancer. Few studies have addressed this question using population-based cohorts and prospective designs, adjusting for known biomedical risk factors. This has been done in the present investigation.

Method. Participants were 5191 women from a cohort of women born between 1941 and 1947 and living in the city of Eindhoven, The Netherlands. All women completed questionnaires regarding the presence of depressive symptoms (Edinburgh Depression Scale) and background (demographic, medical and lifestyle) variables. The questionnaire data were linked with the records of the Eindhoven Cancer Registry. These records provided data on breast cancer diagnoses, which took place up to 5 years after the questionnaire screening.

Results. Fifty-eight women (1·1%) were found to have developed breast cancer at least 2 years after the questionnaire screening. After controlling for 15 potential risk factors, of which family history of breast cancer, hypothyroidism and unilateral oophorectomy were significant predictors of breast cancer development, women with depressive symptoms had a lower risk of subsequent breast cancer (OR = 0·29, 95% CI = 0·09–0·92, $P = 0·04$).

Conclusions. Depressive complaints may be associated with a protective factor involved in the development of breast cancer. Some of the possible candidates for this factor are discussed.

INTRODUCTION

One out of every ten women in the Netherlands develops breast-cancer during her lifetime, which is the major cause of death from cancer in women between the ages 40 to 60 (Coebergh *et al*. 2001; Netherlands Cancer Registry, 2001). A number of conditions have been found to be related to an increased risk of breast cancer: a family history of breast cancer, nulliparity, first pregnancy at late age, early age at menarche and menopause, obesity in post-menopausal women, previous breast disease and a genetic susceptibility to breast cancer (Kampert *et al*. 1988; Claus *et al*. 1991; Kelsey, 1993; Miki *et al*. 1994). However, the total attributable risk of these factors is rather modest and more than 50% of all women who develop breast cancer do not carry any identifiable risk factor (Kelsey, 1993; Netherlands Cancer Registry, 2001).

Depression has been studied in relation to cancer in general, yielding inconsistent results.

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Although some reports showed an increased risk of cancer morbidity and mortality associated with self-reported symptoms of depression (Shekelle *et al.* 1981; Persky *et al.* 1987; Penninx *et al.* 1998), others reported only weak associations (Linkins & Comstock, 1990; Friedman, 1994), or no association at all (Kaplan & Reynolds, 1988; Zonderman *et al.* 1989). A meta-analysis of psycho-oncology studies could not find compelling evidence to support a relation between depression and cancer (McGee *et al.* 1994). However, most earlier studies were flawed by methodological shortcomings, such as a retrospective or only quasi-prospective design, no population-based samples, and insufficient control for known risk factors. A recent methodologically well-conducted prospective study among elderly individuals showed depression to be associated with an elevated risk for subsequent cancer development at most sites (Penninx *et al.* 1998). However, for breast cancer a weak tendency toward a reduced risk seemed to exist, as none of the new breast cancer cases had been chronically depressed before the diagnosis.

A large mental health survey reported that the annual prevalence of major depression of the population between 18 and 65 years of age in the Netherlands is 5–6% or 800 000 persons (NEMESIS; Bijl *et al.* 1998*a*, *b*). Women were at twofold risk for depression compared to men, and women at the age of 45–55 years of age seem to be particularly at risk (prevalence rate of depression up to 12%) (Kessler *et al.* 1994). The high prevalence of depression in the population, together with the fact that the aetiology of a large proportion of breast cancer cases remains unexplained, thus warrants further prospective investigations to be conducted on the relationship between depression and subsequent breast cancer incidence. Moreover, since the menopause is a vulnerable age for having depressive episodes (Kessler *et al.* 1994; Becht *et al.* 2001), this age group may be particularly relevant for investigation. In the present study, therefore, the association between depression and subsequent risk for breast cancer was investigated prospectively, using a well-validated questionnaire for measuring depression in a large population-based cohort of women around menopausal age.

METHOD

Participants

Between September 1994 and October 1995, all 8503 women born between 1941 and 1947, living in the city of Eindhoven, The Netherlands, were invited to take part in a screening study of osteoporosis (the Eindhoven Perimenopausal Osteoporosis Study (EPOS); Smeets-Goevaers *et al.* 1998). A total of 6846 women responded (response rate, 81%) by completing a questionnaire containing demographic, gynaecological and health behaviour items (see below). Subsequently, respondents were asked to complete a depression self-rating scale at home and to return it within 1 week of screening. The questionnaire was completed and returned by 6116 women (89%). Only data from Dutch Caucasian women (96%; to avoid potential language problems) who had never been diagnosed with any form of cancer before the screening (95% of all women, $N = 5596$) were considered for linkage with the cancer registry data. After having received consent for linkage from 95% of these women, 5191 Dutch Caucasian women were identified, who had complete data on both depressive symptoms and subsequent cancer incidence (see below). Response rate was therefore 81% (first response) * 89% (returned depression questionnaire) * 95% (consent for linkage) = 68%. Previous data have demonstrated that Eindhoven is a representative city, showing depression and breast cancer rates closely similar to the rates of rest of the Netherlands (Bijl *et al.* 1998*a*, *b*; Becht *et al.* 2001; Coebergh *et al.* 2001; Netherlands Cancer Registry, 2001).

Measurements

Depressive symptomatology

Depressive symptoms were assessed using the Edinburgh Depression Scale (EDS) (Cox *et al.* 1996), a ten-item self-rating scale originally designed to assess post-natal depression (Edinburgh Post-natal Depression Scale; Cox *et al.* 1987). It has been validated in women from different age strata, including menopausal women (Cox *et al.* 1996; Murray & Carothers, 1990; Becht *et al.* 2001). Items are scored on four-point rating scales. Total scores can range between 0 and 30, with cut-off scores usually between 11 and 13 (Murray & Carothers, 1990;

Pop *et al.* 1992), above which the score is regarded as indicating the presence of depressive symptoms. With a clinical diagnosis of depression as the validity criterion, the sensitivity is 85%, specificity 88%, and positive predictive value (PPV) 44% at cut-off point 13 in a sample of women around menopause (Becht *et al.* 2001).

Control variables

Based on previous research findings, from the questionnaire the following 15 demographic, gynaecological and lifestyle features were obtained to control for confounding in the analyses, all categorical: family history of breast cancer, parity, age at first parity above 30, age at menarche before 13, menopausal age above 52, body mass index $\geqslant 27{\cdot}5$ kg/m², menopausal status, education lower than high school, a history of breastfeeding, oophorectomy, hysterectomy and hypothyroidism, use of oestrogens in any form, current physical exercise (0, 1–3·5, or $>3{\cdot}5$ hours per week), and current alcohol consumption (0, 1–3, >3 glasses per day). Hypothyroidism has been included as a control variable, since some studies have suggested it to be a potential risk factor, although the results have not always been consistent (see Smyth, 1993, for a review). The medical questions have been stated as much as possible in terms reflecting a physician's view in order to minimize self-report biases (e.g. 'Has a physician ever told you that your thyroid gland is working too slowly?'). Since the age range was very small (51–60 years), age was not included as a control variable.

Breast cancer incidence

Data were obtained regarding incidence of breast cancer (excluding carcinoma *in situ*) between 20 years before to 5 years after the questionnaire screening from the regional cancer registry centre (Comprehensive Cancer Center South; IKZ). The population-based Eindhoven Cancer Registry has collected data on new cancer patients since 1955 according to international guidelines (Parkin *et al.* 1997). Since 1988 the registry covers an area in the Southeast Netherlands with a population of $>2\,000\,000$ inhabitants.

Statistical analysis

All statistical analyses were performed using SPSS statistical software.

First, univariate cross-tabulation analyses including the χ^2 test for the distribution of categorical variables were performed with occurrence of breast cancer at least 2 years after the initial depression screening being the outcome variable. Subsequently, multiple predictors of this outcome variable, that showed (nearly) significant results in the univariate analyses, were entered stepwise into a multiple logistic regression analysis. In this analysis, all effects were controlled for the effects of all the other variables. The 2 year interval between initial screening and breast cancer diagnosis was applied in order to exclude possible cases with depressive symptoms as a result of the presence of a pre-diagnostic cancer and at the same time to allow for sufficient time for tumour development after the screening (Netherlands Cancer Registry, 2001).

Depression scores were used both continuously and dichotomized in the regression analyses. For the dichotomization, a cut-off score of 14 was used, which is slightly higher than the more frequently applied cut-points ranging between 11 and 13 (Cox *et al.* 1987, 1996; Murray & Carothers, 1990; Pop *et al.* 1992) in order to obtain a higher PPV (51%) for identifying depressed cases (Becht *et al.* 2001).

RESULTS

Of the 5191 respondents with both complete EDS and cancer incidence data, who had never been diagnosed with cancer before the initial screening, 58 (1·1%) were diagnosed as having developed breast cancer at least 2 years after the initial screening (24 women who developed breast cancer during this 2 year interval were excluded from the analyses, as indicated above).

Of those 5191 respondents, 1189 (22·9%) women may be considered depressed when using a cut-off of 12, and 840 (16·2%) would be labelled as being depressed when using a cut-off score of 14.

In univariate analyses, the following variables were (borderline) significant predictors of cancer development (see Table 1): breast cancer in the family (either in the first or second degree, since the figures did not differ between these categories; $\chi^2_{(1)} = 13{\cdot}35$, $P < 0{\cdot}001$); unilateral

Table 1. *Number of breast cancer cases per risk/protective factor*

Risk factor	Risk factor absent *N* (%)	Risk factor present *N* (%)	*P*
Family history†	23 (0·8)	17 (2·3)	***
Oophorectomy			
Unilateral	48 (1·0)	9 (3·2)	**
Bilateral		1 (1·2)	NS
Hypothyroidism	51 (1·0)	5 (4·4)	**
Alcohol			
1–3 glasses	8 (0·7)	42 (1·1)	NS
>3 glasses		8 (1·4)	NS
First parity >30	49 (1·1)	1 (0·3)	NS
Oestrogens	5 (0·6)	53 (1·1)	NS
Late menopause	54 (1·1)	3 (0·6)	NS
Obesity	44 (1·1)	13 (0·9)	NS
Education (at least high school)	42 (1·1)	11 (0·9)	NS
Nulliparity	50 (1·1)	8 (1·2)	NS
No history of breastfeeding	36 (1·1)	14 (1·0)	NS
Early menarche	39 (1·1)	19 (1·0)	NS
Protective factor	**Protective factor absent *N* (%)**	**Protective factor present *N* (%)**	***P***
Physical exercise	32 (1·1)		
1–3·5 h/week		15 (1·0)	NS
>3·5 h/week		10 (1·5)	NS
Hysterectomy	44 (1·0)	14 (1·5)	NS
Menopause	36 (1·3)	22 (0·8)	NS
Depressed	54 (1·2)	3 (0·4)	*

† Family history had 1499 missing values, which formed an additional category, of whom 18 (1·0%) developed breast cancer.
* $P<0·05$; ** $P<0·01$; *** $P<0·001$; NS, not significant.

oophorectomy ($\chi^2_{(2)}=12·64$, $P=0·003$); hypothyroidism ($\chi^2_{(1)}=12·20$, $P=0·007$); menopause ($\chi^2_{(1)}=2·96$, $P=0·09$); and absence of depression ($\chi^2_{(1)}=5·05$, $P=0·02$). Within those classified as depressed, only three women (0·4%) were diagnosed with breast cancer, whereas within the non-depressed group, 54 (1·2%) had developed breast cancer, OR = 0·29, 95% CI = 0·09–0·91. When cut-off scores 11 to 15 were applied, the results were similar to the one obtained for cut-point 14, all except the analysis for cut-point 12 being significant. In order to explore the possibility of a dose–response relationship, we made four groups based on the depressive symptoms scores: (*i*) scores below all cut-off points used in the literature (<11; Cox *et al*. 1987, 1996; Murray & Carothers, 1990; Pop *et al*. 1992); (*ii*) mildly elevated scores (11, 12, or 13; 10% of the sample); (*iii*) moderately elevated depression scores (14, 15, or 16; 8% of the sample); and (*iv*) highest scores (⩾17; 9% of the sample). The respective numbers of women who developed cancer were 49 (1·3%), five (0·9%), two (0·4%) and one (0·2%). Because of the small numbers in the highest two classes, this trend did not reach statistical significance ($\chi^2_{(3)}=5·59$, $P=0·13$).

Table 2. *Predictors of breast cancer incidence in the multivariate logistic regression analysis*

Predictor	OR	95% CI	*P*
Family history	3·12	1·61–6·03	***
Oophorectomy			
Unilateral	2·81	1·24–6·36	*
Bilateral	1·38	0·19–10·21	NS
Hypothyroidism	4·11	1·58–10·71	**
Depression	0·29	0·09–0·92	*

* $P<0·05$; ** $P<0·01$; *** $P<0·001$; NS, not significant.

The result of the multivariate logistic regression analysis is shown in Table 2. Three control variables remained significant predictors in the model, which was highly significant ($\chi^2_{(4)}=29·69$, $P<0·001$): breast cancer in the family (OR = 3·12, 95% CI = 1·61–6·03, $P=0·001$); unilateral oophorectomy (OR = 2·81,

95% CI = 1·24–6·36, $P = 0·01$); and hypothyroidism (OR = 4·11, 95% CI = 1·58–10·71, $P = 0·004$). Menopause was not a significant predictor ($P = 0·244$). The reduced risk associated with depression remained significant in this multivariate analysis (OR = 0·29, 95% CI = 0·09–0·92, $P = 0·04$). When depression scores were entered as a continuous variable in this multiple logistic regression analysis, this also yielded a significant negative association: the higher the depression score, the lower the cancer risk (OR = 0·95, 95% CI = 0·90–1·00, $P = 0·049$).

DISCUSSION

In the present prospective population-based investigation among middle-aged women, we found no evidence for an elevated risk of breast cancer for depressed women. On the contrary, high depression scores were significantly associated with diminished breast cancer incidence rates at least 2 years after the questionnaire screening, the risk being only 29% of the risk of the remaining women. In addition, when depressive symptoms scores were entered as a continuous variable, a significant negative association emerged, suggesting a dose–response effect: the higher the depression score, the lower the probability of cancer development. These effects remained significant in a multivariate analysis, in which the significant effects found for family history of breast cancer, early menarche, oophorectomy and hypothyroidism were controlled.

A potential explanation for the inverse association found may be emotional inhibition, which has been suggested to be a potential risk marker or risk factor for breast cancer in a recent review (Butow *et al*. 2000). However, in the present investigation, women reporting a low number of depressive symptoms (a subgroup of whom may consist of emotional inhibitors) did not have elevated risks (1·3% were diagnosed as having breast cancer, compared to 1·1% in the whole sample). Rather, the depressed group showed a reduced-risk: only 0·4% of the depressed group (three persons) were diagnosed with breast cancer. One may speculate that expression of negative feelings may somehow be protective, rather than suppression of negative feelings being a risk factor. This speculation is in line with studies on emotional disclosure, showing beneficial effects of writing expressively about personally relevant and emotionally taxing topics, with reported beneficial effects ranging from better mood to immunological improvements (see, for reviews Pennebaker, 1997; Smyth, 1998). The main mechanisms for those health benefits seem to be linked with cognitive rearrangement (e.g. finding meaning) of emotionally upsetting events, which may have various beneficial effects, including an improved immune function (Pennebaker, 1997; Smyth, 1998). If this mechanism would account for the effects in the present study, it is expected that the depressive episodes of our subjects were just temporary stages, which would be left behind cognitively rearranged.

Although preliminary, our results seem to be in disagreement with those obtained in most of the few prospective studies on depression as a risk factor for breast cancer development (Hahn & Pettiti, 1988; Friedman, 1994; Bleiker *et al*. 1996; Penninx *et al*. 1998; Gallo *et al*. 2000; Jacobs & Bovasso, 2000). Two studies found no significant associations (Hahn & Pettiti, 1988; Bleiker *et al*. 1996), while three reports, of which two were based on the same small cohort of 1213 women, found elevated risks: OR = 1·4, 95% CI = 1·06–1·76 (Friedman, 1994); OR = 3·8, 95% CI = 1·0–4·2 (Gallo *et al*. 2000); and OR = 14·0, 95% CI = 3·76–78·08 (Jacobs & Bovasso, 2000). However, methodological limitations of these studies preclude drawing clear conclusions: (*i*) depression was sometimes assessed using a questionnaire measuring a personality tendency toward depression, rather than depressive symptomatology (Hahn & Pettiti, 1988; Bleiker *et al*. 1996); (*ii*) breast cancer incidences included those immediately after the screening (implying the risk that a subgroup already had undiagnosed breast cancer before the screening and before depression assessment) (Hahn & Pettiti, 1988); and (*iii*) no statistical adjustment was performed for some of the known risk factors for breast cancer (Hahn & Pettiti, 1988; Friedman, 1994; Gallo *et al*. 2000; Jacobs & Bovasso, 2000). In addition, the only cohort in which a substantial elevated risk was reported for depression (Jacobs & Bovasso, 2000) was based on 11 depressed cases only, of whom two developed breast cancer. This finding may have been due to chance. In contrast, in the study by Penninx *et al*. (1998) none of their

breast cancer cases was chronically depressed before the cancer diagnosis, suggesting a potential inverse association. However, again the results were based on a small proportion of cases (31 breast cancers, while only 3% of the total sample was classified as being depressed) and no adequate correction for known risk factors. It can be concluded that the few prospective studies conducted so far on the potential risk of breast cancer associated with depression have been heterogeneous as to the methods employed, with usually no adequate control for known risk factors and/or a too small number of participants, precluding clear conclusions.

Of the control variables in the present study, family history of breast cancer was the strongest predictor, which is consistent with previous findings (Kelsey, 1993; Miki *et al.* 1994). We cannot explain the enhanced risk associated with unilateral oophorectomy, or the lack of protection by bilateral oophorectomy (Rebbeck *et al.* 1999). The effect of unilateral oophorectomy cannot be explained by oestrogen-based medication, because; this is usually applied to women with both ovaries removed; and, medication containing oestrogens was not related to breast cancer risk in the present investigation. However, since only nine breast cancer cases reported a removed ovary, the unilateral oophorectomy effect found may have been due to chance. Finally, the finding that hypothyroidism may be a risk factor has been suggested before, although the few results have not always been consistent (see, for a review, Smyth, 1993).

Limitations

This study was based on a small number of respondents having developed breast cancer, which resulted in limited statistical power and a potential risk of our findings being due to chance. Replications using a larger sample, but preferably a longer follow-up are needed. In addition, although the net response rate was satisfactory (68%), it cannot be excluded that a systematic non-response by depressed women took place and that it has biased the results in an unknown way.

Our depression variable was based on only a single depressive mood assessment by means of a questionnaire. Although the positive predictive value for a diagnosis of major depression when using a cut-off point of 14 on the EDS is 51% (Becht *et al.* 2001), the measurement of depressive symptoms at one point in time is clearly not identical to depression diagnosis or assessment of chronic repression. In a recent study, only repeated assessments of depressive symptoms, indicating a more chronic depression, yielded positive associations with later development of some cancers, in contrast to single measurements (Penninx *et al.* 1998). Although individuals who once have had a depressive episode are claimed frequently to have relapses or even show a development into chronicity (Bijl *et al.* 1998*a*), future research should take into account the potentially differential effects of a single depressive episode and of chronic depression or an interview-based depression diagnosis.

Nevertheless, the present study has presented some provoking data, suggesting that a single depressive episode may indicate a protective factor for breast cancer development 2 to 5 years after an initial questionnaire screening.

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