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Do depressive symptoms predict cancer incidence? 17-year follow-up of the Whitehall II study

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ABSTRACT

Objective: To explore the association between depressive symptom history and cancer incidence.
Methods: Affective/emotional depressive symptoms were assessed using the General Health Questionnaire (GHQ-30) depression sub-scale across phase 1 (1985–1988), phase 2 (1989–1990), and phase 3 (1991–1994) of the Whitehall II prospective cohort study; 'chronic' = depressive episode at phase 1, 2 and 3; 'new' = depressive episode at phase 3 only. Cancer incidence was obtained from the National Health Service Central Register with an average follow-up of 15.6 years (range 0.08–17.4). The study sample consisted of 6983 participants, aged 35–55 years at baseline. Results were adjusted for age, sex, socio-economic position, health behaviours, health status/conditions, medication, and social support.
Results: Over a 17.4 year follow-up, chronic depressive symptoms did not increase the risk of cancer incidence compared to those who never experienced symptoms (hazard ratio (HR) = 1.03, 95% confidence interval (CI): 0.71–1.49). Participants who experienced new depressive symptoms had an increased risk of cancer incidence in the first 9 years of follow-up (HR = 1.89, 95% CI: 1.23–2.90) but no increased risk in later years (HR = 0.84, 95% CI: 0.52–1.35).
Conclusion: Chronic depressive symptoms were not associated with cancer incidence. In contrast, new-onset symptoms were associated with a substantially increased risk, possibly due to reverse causality.

Introduction

Meta-analyses indicate that depressive symptoms are a risk factor for both cancer incidence and mortality [1–3], although there is large disparity among associations from individual studies. Mixed findings can be attributed to methodological factors, such as failure to adequately control for potential confounders [4–6], differences in study sample characteristics [3], and inadequate measures of depression [4]. There are also potential difficulties surrounding the accuracy of depression diagnosis among those with physical illnesses due to somatic symptom overlap. For example, symptoms such as fatigue, loss of appetite, and general malaise, could be due to depression, or 'sickness behaviour' as a result of cancer or comorbid illness [7–9]. In addition, no study has taken into account a participants' history of depression, which could be an important determinant of cancer incidence. For example, new-onset/recent depressive symptoms have been shown to increase the risk of cardiovascular events [10,11] and all-cause mortality [12].

There are several possible biological and behavioural pathways by which the association between depression and cancer incidence may be explained. Firstly, depression may have a direct effect on the immune system through dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis [4,13–15]. Secondly, depression may indirectly lead to cancer through behavioural pathways, such as smoking, alcohol consumption, and low levels of physical activity [16–19]. Equally, depressed patients may be less likely to attend routine health checks, and have poorer adherence to treatment regimens [20,21]. A third consideration is the possibility of reverse causality whereby sub-clinical cancer may cause depression as a result of an inflammatory response [22–25].

This is the first study known to the authors to use repeated measures of depression to explore the association between depressive symptom history and cancer incidence. It is also the first to isolate the role of affective/emotional depressive symptoms, which are less likely to be confounded by somatic symptoms of poor physical health, such as fatigue or tiredness. A further strength includes data on a wide range of potential confounders and mediators.

Methods

Participants

The target population for the Whitehall II study was all London-based office staff aged 33–55 working in 20 civil service departments, covering a wide range of employment grades from low to high incomes.

Abbreviations: CI, confidence interval; HR, hazard ratio; pyrs, person-years; SD, standard deviation.

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With a response rate of 73%, the study recruited 10,308 participants; 6895 men and 3413 women at phase 1 (1985–1988) [26]. Phase 2 (1989–1990) comprised of 8132 participants (79% of phase 1 responders), and phase 3 (1991–1994) comprised of 8815 participants (86% of phase 1 responders). Mean follow-up for cancer incidence after phase 3 was 15.6 years (range 0.08 to 17.4), with a total 109,209 person-years and 776 incident cancers.

Depressive symptoms

At phases 1, 2 and 3, participants completed the 30-item General Health Questionnaire (GHQ-30) [27,28] which is used to detect minor psychiatric disorders in non-psychiatric populations [29,30]. A four-item depressive symptom sub-scale was derived (Cronbach's α: 0.88) based-on principal components factor analysis [31,32]. The scale has been compared with the validated seven-item depression subscale of the 28-item GHQ [33], and the test–retest reliability was r = 0.78 in a sample of 286 participants who repeated the GHQ depression subscale within 1 month [33]. Participants were asked whether, over the last few weeks, they had: 'been thinking of yourself as a worthless person'; 'felt that life is entirely hopeless'; 'felt that life isn't worth living'; and, 'found at times you couldn't do anything as your nerves were so bad'. These 4-items assess the affective/emotional symptoms of depression only, and do not cover somatic symptoms, such as tiredness, pain, or sleep disturbance. Items were scored on a four-point scale (0 = 'not at all', 1 = 'no more than usual', 2 = 'rather more than usual', 3 = 'much more than usual'), giving a range from 0–12. Participants were defined as experiencing an 'episode of depressive symptoms', if they had a sum score of 4 or more. This cut point, as used in previous studies, results in a prevalence rate similar to that of clinical depression in the general UK population [33–35]. The dichotomised GHQ depression sub-scale was used to create the following two exposure variables: Depression Incidence and Depression History.

'Depression Incidence' indicates the number of times a participant experienced an episode of depressive symptoms across phases 1 to 3. Participants who did not experience an episode of depressive symptoms at phase 1, 2 or 3, were classed as having 'never' experienced depressive symptoms. Those who reported an episode at all three phases were classed as experiencing 'chronic' depressive symptoms, as defined previously by Penninx et al. [10].

'Depression History' refers to the temporal arrangement of depressive symptom episodes. Over three-quarters of depressive and anxiety disorders begin prior to age twenty-four, whilst new-onset disorder in adulthood remains relatively rare [36–38]. To ensure the highest probability of capturing emerging depressive symptoms, participants who had a depressive episode at phase 3, but not at phase 1 or 2 were classified as experiencing 'new' depressive symptoms, as previously defined by Penninx et al. [10]. 'Never' and 'chronic' depressive symptoms were defined in the same way as the Depression Incidence variable. All other participants who experienced a depressive symptom episode once or twice across phases 1 to 3 were classified as experiencing a history of 'non-chronic' depressive symptoms.

Cancer incidence

Cancer incidence data for 1971–2008 were obtained from the National Health Service Central Register (NHSCR) for nearly all participants (n = 10,297). Cancer sites in cancer registry data were coded according to International Classification of Diseases revision 9 (ICD-9) in 1971–1994, and revision 10 (ICD-10) from 1995 onwards. Incidence of malignant cancer was defined as ICD-9 codes 140–208 or ICD-10 codes C00–C97. Follow-up time was from phase 3 to first incident cancer, or censored at death or end 2008. Total incident cancer was 776, this included 109 smoking-related, 311 hormone-related, and 356 other. Hormone related cancers were breast (ICD-9 174; ICD-10 C50), cervix (180; C53), corpus uteri (182; C54), ovary (183; C56), and prostate (185; C61). Smoking-related cancers were considered to be oral cavity (ICD9 140–149; ICD-10 C00–C06, C09–C14), oesophagus (150; C15), pancreas (157; C25), respiratory and intrathoracic organs (160–163; C30–C34, C38), and urinary tract (188–189; C64–C68) [39].

Covariates

Variables believed to be associated with both depression and cancer incidence were included as covariates in the analysis, and were obtained at phase 3 unless otherwise indicated.

Demographic data included age and sex. Socio-economic position was indexed by civil service employment grade, ranging from 1 (highest) to 6 (lowest) [26].

Measures of health status obtained from clinical screening included body-mass-index (BMI in kg/m^2, grouped into quintiles) and systolic blood pressure (mm Hg, grouped into quintiles). Self-reported 'health in the last year' was assessed using a 5 point scale (very good, good, average, poor, very poor).

Health conditions included self-reported respiratory illness (yes/no), and presence of longstanding illness (yes/no).

Medication use included self-reported 'antidepressant use in the last 14 days' at phase 1 (yes/no).

Health behaviours were categorised as follows: smoking (non-smoker, ex-smoker, 1–10 per day, 11–20 per day, and 21+ per day); alcohol consumption (units per week, grouped into quintiles); fruit and vegetable consumption (0–2 per week, 3–4 per week, 5–6 per week, daily, and 2+ per day); meat consumption (0–3 per month, 1–2 per week, 3–4 per week, 5–6 per week, and daily); and physical activity (number of hours of mild/moderate/vigorous physical activity per week).

Social support measures were obtained from phase 2, and included 'emotional support' (seven-item scale measuring confiding, boosting self-esteem, sharing interests and reciprocity), 'practical support' (four-item scale measuring the level of practical help received), and 'negative aspects of social support' (four-item scale measuring the inadequacy of the closest person to deliver support [31]. These measures were based on the person nominated as closest in the Close Persons Questionnaire [40], which has been validated against the Self Evaluation and Social Support Interview in a sample of 201 Civil Servants [40]. Social support measures were grouped into tertiles representing low, medium and high support.

Missing data

There were missing data for the following covariates: employment grade (n = 6, 0.1%); smoking (n = 232, 3.3%); alcohol consumption (n = 6, 0.1%); meat consumption (n = 10, 0.1%); body mass index (n = 310, 4.4%); systolic blood pressure (n = 306, 4.4%), fruit and vegetable consumption (n = 7, 0.1%);respiratory illness (n = 5, 0.1%), health in the last year (n = 8, 0.1%); antidepressant use (question introduced only partway through phase 1 data collection, n = 1748, 25.0%); practical support (n = 258, 3.7%); emotional support (n = 277, 4.0%); and negative aspects of social support (n = 278, 4.0%). Overall 12.8% of records had missing covariate data (34.7% if including antidepressant use); therefore, multiple imputation (*mi* command in Stata 12.0) [41,42] was used to impute missing data for covariates. Analysis models were run with ten imputations.

Statistical analysis

All analyses were conducted using Stata 12.0. To assess the characteristics of the study sample, continuous variables were grouped to allow the calculation of rate-ratios using the Mantel–Haenszel method. Kaplan–Meier graphs were produced to show the unadjusted relationship between Depression Incidence/Depression History and cancer incidence over time. Log-rank tests were used to test the equality of survival curves.

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