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ORIGINAL ARTICLE

Mood disorder and cancer onset: evidence from a population-based sample of Australian women

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Objective: The role of mood disorders in cancer onset is unclear. The aim of this study was to investigate the association between mood disorder and incident cancer in a population-based sample of women.

Methods: Data were derived from women aged 28-94 years participating in the Geelong Osteoporosis Study. Mood disorder was identified via Clinical Interview (SCID-I/NP). Cancer data was obtained following linkage with the Victorian Cancer Registry. Demographic and lifestyle factors were self-reported. Nested case-control and retrospective study designs were utilized.

Results: In the case-control study (n=807), mood disorder was documented for 18 of the 75 (9.3%) cancer cases and among 288 controls (24.0% vs. 39.3%, p = 0.009). Prior exposure to mood disorder was associated with reduced cancer incidence (OR 0.49, 95%CI 0.28-0.84); this was sustained following adjustment for confounders (OR_{adj} 0.52, 95%CI 0.30-0.90). In the retrospective cohort study (n=655), among 154 women with a history of mood disorder at baseline, 13 (8.5%) developed incident cancer during follow-up, whereas among 501 women with no history of mood disorder, 54 (10.8%) developed incident cancer. Exposure to mood disorder was not associated with incident cancer over the follow-up period (HR 0.58, 95%CI 0.31-1.08, p = 0.09).

Conclusion: Mood disorder was associated with reduced odds of cancer onset. However, this finding was not supported in the retrospective cohort study. Larger studies able to investigate specific cancers and mood disorders as well as underlying mechanisms in both men and women are warranted.

Keywords: Cancer incidence; mood disorder; cancer risk; women

Introduction

Mood disorders pose a substantial health and economic burden across the globe.¹ Due to their chronic, often recurrent nature and common pathophysiological pathways,^{2,3} mood disorders have been associated with a host of physical conditions and illnesses, including cardiovascular disease, diabetes, gastroesophageal reflux disease, asthma, arthritis, and bone fracture.⁴⁻⁷ Moreover, mortality rates among those with mood disorders have been estimated to be 35% greater than in the general population, with the majority of these deaths due to comorbid chronic physical conditions.⁸

The association between psychological distress and poorer survival/increased mortality in populations with established cancer is well documented.⁹⁻¹⁵ The prevalence of elevated psychological distress among adult

patients with cancer is reported to be approximately 30-35% at the time of diagnosis and up to 45% upon disease recurrence.^{16,17} Thus, a diagnosis of cancer generates adjustment reactions with moderate to high levels of psychological distress that can, over time, develop into a depressive or anxiety disorder.¹⁸ The area of psycho-oncology goes beyond medical treatment to integrate psychological and social aspects of cancer.¹⁹ Established in the mid-1970s, this relatively new field covers many areas on the cancer continuum, including changing lifestyle habits to reduce risk of cancer onset, managing symptoms during active treatment and survivorship, and palliative and end-of-life care.¹⁹ Onset of mood and anxiety disorders after cancer diagnosis is well recognized within the health sector; its solidification is best exemplified by the inclusion of mandatory distress screening (i.e., the Distress Thermometer scale) for all

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newly diagnosed cancer patients in Victoria, Australia.²⁰ However, links between psychiatric disorders and cancer onset and risk are still largely unclear.¹⁹

Mood disorders are associated with immune and neuroendocrine dysregulation, as well as with behavioral changes, such as smoking, physical inactivity, and poor diet/excess calorie intake, which have been implicated in the etiology of many cancers.^{21,22} However, longitudinal studies assessing the association between mood disorder and cancer onset have not been conclusive, with some reporting positive associations,²³⁻²⁸ others reporting no association,²⁹⁻³³ and others still reporting negative associations.³⁴⁻³⁶ Possibly adding to the mixed findings, these studies have varied in population type and size, assessment of mood disorder, follow-up period, and cancer type.

Women are more likely than men to experience a mood disorder within their lifetime,^{37,38} which may place them at increased risk for development of cancer due to the associated increase in lifestyle (smoking, sedentary behavior, poor diet) and non-lifestyle cancer risk factors compared to the general population. Thus, investigation of whether women with established mood disorders are indeed at increased risk of subsequent cancer development is warranted. Therefore, in this epidemiological study we aimed to investigate the association between mood disorder and cancer onset in a population-based cohort of Australian women spanning the adult age range.

Methods

Participants

Data from women participating in the Geelong Osteoporosis Study (GOS) were utilized. The GOS is a large population-based cohort study. Participants were randomly selected from electoral rolls for the Barwon Statistical Division (BSD) in south-eastern Australia. Between 1994 and 1997, 1494 women (aged 20-94 years) were recruited, with a participation of 77.1%. These women have since returned for follow-up every 2-5 years. Further details have been published elsewhere.³⁹ From a potential pool of 849 women who participated in the most recent female follow-up (2011-2014), those for whom psychiatric data were not available (n=35) were excluded. This resulted in a sample of 814 women aged 28-94 years eligible for inclusion.

Two study designs were utilized, as described below.

Nested case-control

Adult-onset cancer cases and cancer-free controls were selected. For cases, exposures to a mood disorder prior to cancer onset were identified. One case was excluded due to having a childhood cancer and a further six excluded as they had self-reported cancer prior to 1982. Thus, 807 women (75 cases and 732 controls) were included in the analyses. Exposure data for the cases pertained to the scheduled follow-up assessment which most closely preceded the date of cancer onset; for controls, the latest follow-up (2011-2014) data were used.

Retrospective cohort study

Over 20 years of data were available for 666 of the 814 women who underwent a structured psychiatric interview at the most recent assessment in 2011-2014. Those who had a diagnosis of cancer prior to baseline were excluded (n=11), resulting in 655 eligible participants. Participants were then classified as having a history of mood disorder if they had experienced an episode prior to or at the time of their baseline appointment (n=154); otherwise, they were classified as free of a mood disorder (n=501). These participants were followed until the onset of cancer, death, or until the end of the study in 2014. Exposure data for the participants was taken from the baseline assessment (1993-1997).

Data

Cancer

Cancer onset was determined following data linkage with the Victorian Cancer Registry (VCR). Cancer reporting to the registry by hospitals, pathology centers, and screening registers and centers is mandated by law. The VCR records all invasive cancers, in-situ carcinomas, benign tumors, and tumors of uncertain behavior. Nonmelanoma basal and squamous cell skin carcinomas (BCC and SCC respectively) are not recorded. For every cancer case, a minimum amount of information is collected, including patient demographics such as name, date of birth, and residential address, as well as tumor-specific details including (but not limited to) date of diagnosis, site, type, and overall grade.⁴⁰ All malignant neoplasms with ICD-10 codes ranging from C000.0-C96 were included in the analyses.

Information on self-reported cancer was obtained via GOS questionnaires. Participants were required to tick yes if they had ever had the following cancer(s): lung, bowel, breast, uterus, cervix, throat, brain tumor, melanoma, nonmelanoma skin cancer (BCC or SCC), leukemia, myeloma or other (asked to specify type); and indicate their age at onset (years). As the VCR established mandatory reporting from 1982, all participants in the analyses were cross-checked for a self-reported cancer occurring prior to this date.

Mood disorder

The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Non-patient edition (SCID-I/NP), is a validated semi-structured clinical interview to assess DSM-IV Axis I disorders.⁴¹ This tool enables identification of major depressive disorder, dysthymic disorder, minor depressive disorder, bipolar disorder (I, II, or other), mood disorder due to a general medical condition and/or substance induced mood disorders, and depressive disorder not otherwise specified, as well as the age of onset. In the present study, classification as having a lifetime history of mood disorder was contingent on meeting past and/or current diagnostic criteria for any mood disorder. The SCID-I/NP was administered at the most recent follow-up

(2011-2014) by trained clinical researchers who had a minimum postgraduate qualification in psychology and had completed subsequent training including live interviews under supervision.⁴²

Other data

Demographic, clinical, and lifestyle data were self-reported at baseline and follow-up appointments. Education (highest level completed) was self-reported and grouped as (i) primary/part secondary, (ii) completed secondary, and (iii) post-secondary (university/other). Height was measured using a wall-mounted stadiometer to the nearest 0.1 cm and weight was recorded to the nearest 0.1 kg using an electronic scale. Body mass index (BMI) was calculated as kg/m². Current tobacco smoking status (manufactured or hand-rolled cigarette, cigar, or pipe) was self-reported and dichotomized into current smoker versus non-smoker. Habitual physical activity was measured on a 7-point scale ranging from very active to bedfast³⁹ and classified as active if mobility was identified as very active or active; otherwise, participants were classified as sedentary. The number of standard drinks per week was documented and converted to grams per day (g/d), based on the assumption that one standard drink is equivalent to 10 g of alcohol. Mortality was obtained via data linkage with the Australian National Deaths Index (ANDI).

Statistical analyses

Statistical analyses were performed using Minitab version 16 and SPSS for Windows version 22. Differences in characteristics between groups were determined using *t* tests for continuous parametric variables, the Kruskal-Wallis test for nonparametric continuous variables and for discrete variables, and chi-square tests or Fisher's exact test when expected cell counts were less than five.

In the nested case-control study, logistic regression was used to calculate odds ratios (OR) with 95% confidence intervals (95% CIs) to determine the association between mood disorder and cancer. Potential covariates including age, education, BMI, smoking status, alcohol consumption, and physical activity level were tested sequentially and retained if significant. In the retrospective cohort study, the relationship between mood disorder

and de-novo cancer onset was examined using Cox proportional hazards models to calculate hazards ratios (HR) with 95% CIs. A *p*-value < 0.05 was considered significant.

Ethics statement

The GOS was approved by the human research ethics committees of Barwon Health (project 92/01) and Deakin University (project 2013-116). Written informed consent was obtained from all participants.

Results

Nested case-control study

There were 75 women with a confirmed diagnosis of cancer: one (1.3%) respiratory, two (2.7%) lip/oral cavity/pharynx, four (5.3%) thyroid, seven (9.3%) lymphoid/hematopoietic, nine (12%) melanoma/other neoplasms of skin, nine (12%) female genital organs, 20 (26.7%) digestive organs, and 23 (30.7%) breast. Characteristics of the women with and without cancer are shown in Table 1. Those with cancer were older, less likely to be physically active, and less likely to have completed secondary or postsecondary education; otherwise, no further differences were detected between the groups. A prior history of mood disorder was documented for 18 of the 75 cancer cases and 288 of 732 controls (24.0% vs. 39.3%, *p* = 0.009). Mood disorder was associated with a reduced odds of cancer (OR 0.49, 95%CI 0.28-0.84, *p*=0.007). After adjustment for education, the relationship between mood disorder and cancer onset was sustained (OR_{adj} 0.52, 95% CI 0.30-0.90, *p* = 0.016). Further adjustments for age, BMI, current smoking, physical activity level, and alcohol consumption did not contribute to the final model.

Retrospective cohort study

Women (*n*=655) were followed from baseline over a period of 9,798 person-years (*p*-yr). Those with a history of mood disorder had a longer follow-up time in years compared to those with no history of mood disorder; otherwise, the groups were similar regarding education,

Table 1 Participant characteristics in the nested case-control study (*n*=807)

	Cancer cases <i>n</i> =75	Controls <i>n</i> =732	<i>p</i> -value
Mood disorder (prior to cancer)	18 (24.0)	288 (39.3)	0.009
Age (years)	61.8 (51.7-71.7)	54.7 (41.1-68.0)	0.004
BMI (kg/m ²)	27.3 (24.3-32.6)	27.1 (23.7-31.9)	0.454
Smoking (current)	4 (5.3)	86 (11.8)	0.093
Physically active	9 (12.2)	176 (24.7)	0.016
Alcohol (g/d)	1.43 (0.0-8.5)	2.9 (0.0-8.6)	0.168
Education (highest level completed)			< 0.001
Primary/part secondary	46 (62.2)	286 (39.7)	
Completed secondary	11 (14.9)	116 (16.1)	
Postsecondary (university/other)	17 (23.0)	318 (44.2)	

Data presented as median (interquartile range) or *n* (%).
BMI = body mass index.

Table 2 Participant characteristics in the retrospective cohort study (n=655)

	Mood disorder (prior to baseline) n=154	No mood disorder n=501	p-value
Age (years)	43.6 (34.9-52.7)	44.0 (33.4-56.2)	0.630
Follow-up (years)	16.5 (15.8-17.1)	16.0 (14.5-16.8)	< 0.001
BMI (kg/m ²)	25.9 (22.6-29.4)	25.3 (22.5-29.5)	0.383
Smoking (current)	30 (19.5)	66 (13.2)	0.053
Physically active	20 (13.0)	78 (15.6)	0.432
Alcohol (g/d)	2.9 (0.0-7.3)	2.9 (0.0-7.1)	0.364
Education			0.202
Primary/part secondary	77 (50.0)	267 (53.3)	
Completed secondary	32 (20.8)	122 (24.4)	
Postsecondary (university/other)	45 (29.2)	112 (22.4)	

Data presented as median (interquartile range) or n (%).
BMI = body mass index.

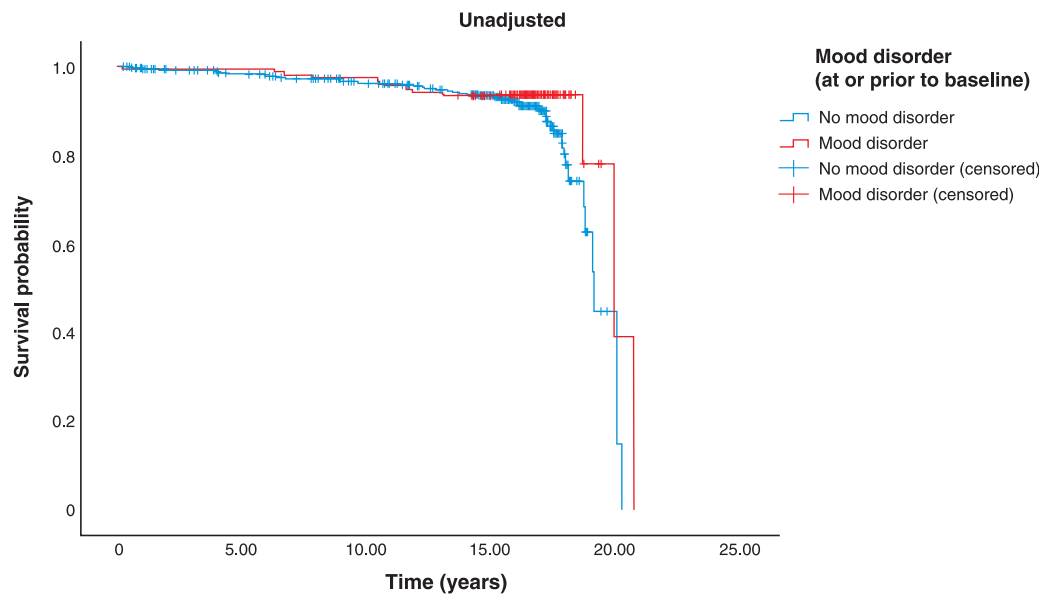


Figure 1 Kaplan-Meier survival curve showing cancer-free time over the 20-year period for women exposed and unexposed to mood disorder at baseline.

age, BMI, smoking status, physical activity level, and alcohol consumption at baseline (Table 2). During the study period, there were 67 (10.2%) incident cancers and 34 (5.2%) deaths. Among 154 women with a history of mood disorder at baseline, 13 (8.5%) developed incident cancer during follow-up, whereas among 501 women with no history of mood disorder, 54 (10.8%) developed incident cancer. Exposure to mood disorder was not associated with incident cancer over the follow-up period (HR 0.58, 95%CI 0.31-1.08, $p = 0.09$; Figure 1).

Discussion

Results from the nested case-control portion of this study indicated that mood disorder is associated with a reduction in the likelihood of cancer onset, independent of education, age, BMI, smoking, physical activity level, and alcohol consumption. However, no significant association between lifetime history of mood disorder and incident cancer was observed in the retrospective cohort study.

Consistent with a recent finding investigating the association between mood disorders and a host of subsequent medical conditions, Momen et al.⁴³ followed 5.9 million members of the Danish population from 2000 to 2016 and assessed a wide range of mental disorders and medical conditions, including cancer. Following adjustment for age, sex, and calendar time, mental disorders were almost universally associated with an increased risk of each of the included medical conditions; however, the inverse was observed between mental conditions and cancer (HR 0.82; 95%CI 0.80-0.84). Similarly, a longitudinal prospective study by Chang et al.⁴⁴ investigated over 600,000 adults (aged 30-64 years) from the Korean population. Over the 19-year study period, depressive symptomology (measured via a questionnaire based on DSM-IV criteria) was associated with a reduced incidence of overall cancer among women (HR 0.90, 95%CI 0.83-0.98). Furthermore, an inverse association between mood disorder and de-novo cancer onset has been reported in studies investigating site-specific cancers, with a reduced risk of cancer noted among breast⁴⁵ and cervical³² sites in women. In

addition, reductions in cancer onset have been noted in prostate (men) and rectal (men and women) cancer sites.^{32,46} Bipolar disorder has also been shown to be associated with a reduced risk of cancer. In another nationwide, population-based, longitudinal study with over 1.7 million participants in Denmark, those with a diagnosis of mania or bipolar disorder had an approximately 40% reduced rate of renal or upper urinary tract tumors, which was sustained after adjustment for age, sex, employment status, psychotropic and other medication use.³⁴ Antipsychotic (but not lithium), anticonvulsant, and antidepressant treatment was also associated with a reduction, albeit small, in the incidence rate of renal or other upper urinary tract tumors.³⁴ These findings are further supported by the findings of Huang et al.,³⁶ who reported that bipolar patients taking lithium had a reduced overall risk of cancer onset.

There are several potential mechanisms which may account for an inverse association between mood disorder and cancer. Mood disorders are characterized by increased levels of pro-inflammatory cytokines,⁴⁷⁻⁵¹ possibly as a result of immune-system adaptation to multiple stressors associated with psychiatric disorders, including but not limited to smoking, physical inactivity, and poor diet.⁵² Homeostatic adaptation to exogenous threats by upregulation may come at the cost of increased vulnerability to inflammation and related tissue damage,⁵³ which has been associated with immune dysregulation and development of certain cancers.⁵⁴⁻⁵⁷ However, increased immune activation and surveillance has also been hypothesized to reduce cancer risk via prevention or resolution of infection by viruses associated with cancer development.⁵⁸ In addition, expression of immune mediators, combined with activation of select cells and factors within the tumor microenvironment, may also influence whether inflammation promotes tumor growth or antitumor host immunity.^{59,60} Biological and inflammatory mechanisms were not explored in this study. As such, whether inflammation and associated immune profiles mediate any association(s), positive or negative, between mood disorder and incident cancer remains to be confirmed. Larger population-based studies are required.

Those with a mood disorder can experience sedentary behaviour and social isolation.⁶¹ In turn, these individuals may be less likely to present to health care professionals, which may impact the likelihood of receiving a prompt cancer diagnosis. In addition, the somatic symptoms of depression can overlap with those of cancer, including sleep disturbances, fatigue, and loss of appetite. As such, there is the possibility that symptoms of early-stage cancers may be similarly ascribed to, and potentially interpreted as, depressive symptomology, although it is likely that as cancer progresses and is fully expressed, detection will occur.⁶²⁻⁶⁴ This may reflect why some other studies have found an increased risk of cancer among individuals with depressive symptomology, especially within the first year of diagnosis. On the other hand, potential misclassification may result in a survival bias. Investigating stage at diagnosis for those with and without a history of depression may further clarify this explanation. In addition, findings may have clinical implications

and contribute to understanding the decreased survival observed in cancer patients with depression compared to those patients without.^{65,66}

Mood disorder is associated with increased morbidity and a reduced life expectancy compared to the general population. As such, the negative association may reflect premature mortality from other medical conditions in the mood disorder group, such as cardiovascular conditions and stroke.⁶⁷⁻⁷⁵ Although in the present study women with a history of mood disorder at baseline had a slightly longer follow-up time compared to those with no history of mood disorder, further analyses highlighted no significant differences in deaths recorded during the follow-up period for women with a history of mood disorder at baseline compared to those with no such history ($p = 0.411$).

Strengths of the current study include the comprehensive and longitudinal nature of the data, allowing for temporal investigation, and that participants were selected at random from the electoral roll rather than by disease status. Likewise, use of a structured clinical interview – the gold-standard validated tool for assessing psychopathology – provided information on current and lifetime history of mood disorder as well as age of onset, rather than just psychiatric symptomology. Furthermore, data on cancer diagnoses were obtained objectively from a comprehensive cancer registry. The VCR was initiated in 1982 and is the most comprehensive and reliable cancer registry in the state of Victoria due to mandatory reporting laws; thus, it is unlikely that any cancer diagnoses have been overlooked in this study. As with all observational studies, results could be biased by unrecognized or residual confounding factors, and may not be generalizable to other populations of women, men, or certain cancer subtypes. Furthermore, as case numbers were relatively low in the retrospective cohort study, the study may have been underpowered to detect an association. Moreover, power constraints prevented specific subtype analyses and exploration of mood disorder specifiers, such as specific mood disorders, chronicity, and whether individuals were medicated. Therefore, heterogeneous biological mechanisms may be at play.

In conclusion, this study adds to the evidence base exploring the association between mood disorder and risk of incident cancer in women. While a negative association was observed in the nested case-control study, this finding was not supported in the retrospective cohort study. As such, larger studies able to investigate specific cancers and mood disorders as well as underlying mechanisms, in both men and women, are warranted.

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Disclosure

The authors report no conflicts of interest.

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