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A concise and informative title

Anxiety and depression and health service use in cancer survivors

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Declarations

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Conflicts of interest/Competing interests

There are no conflicts of interest nor competing interests.

Availability of data and material

Data was made available through the PROFILES group based at Tilburg University and Department of Research and Development, Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands.

Code availability

Statistical analysis was conducted using STATA version 15.

Authors' contributions

Jackie Yim conducted the analysis and wrote up the results for publications.

Joanne Shaw, Rosalie Viney, Sheena Arora and Alison Pearce provided psycho-oncology and health economics expertise advice to Jackie Yim.

Nicole Ezendam works with the PROFILES team and provided Jackie Yim with the context required to interpret the results with clarity.

All co-authors assisted in the written material.

Ethics approval

Ethics approval was granted by the UTS Human Research Ethics Committee (UTS HREC REF NO. 2015000135). Project approval was granted by the PROFILES research committee.

Consent to participate

Not applicable

Consent for publication

All authors agree and consent for this work to be published.

Abstract

Background

Anxiety and depression have higher prevalence in cancer survivors than the general population and are associated with lower quality of life, poorer survival and an increased risk of suicide. Anxiety and depression are also highly comorbid among cancer survivors and associated with increased health service use. As such, it is important to consider both anxiety and depression and health service use in cancer survivors.

Aim

To explore the association between anxiety and depression and health service utilisation, both cancer-specific and general doctor visits, in cancer survivors.

Methods

Data from a Dutch cancer registry were analysed to determine the association between anxiety and depression, measured using the Hospital Anxiety and Depression Scale, and health service use. Negative binomial regression models, controlling for patient demographics, comorbidities and cancer-related variables were estimated.

Results

Cancer survivors (n=2,538), mean of 61.1 years and between 0.7-10.9 years since diagnosis were included in the analysis. Increasing levels of anxiety and depression were associated with increased health service use. Having severe levels of anxiety was associated with more frequent visits to the GP ($p<0.001$). Severe depression in cancer survivors was associated with more frequent visits to the specialist ($p<0.001$).

Conclusion

Anxiety and depression in cancer survivors, particularly severe anxiety and depression, were associated with increased health service use. Treatment of anxiety and depression in cancer survivors has the potential to reduce overall health service use and the associated costs, as well as improving health outcomes for cancer survivors.

Investigating the association between self-reported comorbid anxiety and depression and health service use in cancer survivors

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Key points for decision makers

- Anxiety and depression in the cancer population is associated with increased health service use and, ultimately, costs to the health system
- Increasing levels of anxiety and depression are associated with more frequent visits to the doctor; up to 6 times more frequent for severe levels of anxiety for cancer-related GP visits
- Identification and treatment of anxiety and depression in cancer survivors may reduce overall health service use and the associated costs, or redirect them to more relevant psycho-oncology professionals.

Introduction

Anxiety and depression are major causes of morbidity internationally. In the United States, nearly one in five adults live with a mental illness [1], and each year one in four people across Europe [2] and one in five people in Australia will experience a mental health disorder [3].

People with a diagnosis of cancer frequently experience comorbid anxiety and depression at rates higher than in the general population; 10% vs 7% for anxiety and 20% vs 5% for depression [4]. This increased prevalence has been observed across demographic backgrounds, cancer types and stages [5, 6]. In a large Canadian study (n=10,153), almost a quarter of all cancer patients had either clinical or sub-clinical levels of anxiety, and 16.5% had either clinical or sub-clinical levels of depression [6]. Anxiety and depression experienced by cancer patients are strongly associated with lower quality of life [7], poorer survival [8] and an increased risk of suicide [9]. Similar prevalence of anxiety-depression are reported among cancer survivors [10-12] although fewer studies have focused on the specific impact of this psychological comorbidity.

Comorbid anxiety and depression among cancer survivors are associated with increased health service use [13, 14] and, ultimately, increased health care costs. It has been reported that depression in cancer survivors is

associated with increased health service use [15-18]. In a retrospective cohort study (n=50,147), depression among prostate cancer patients was associated with increased health service use; higher odds of emergency room visits, hospitalisations and outpatient visits compared with those without depression during their treatment period, and those with depression continued to use more health services post-treatment [15]. A cohort study by Fox et al. [19] found breast cancer patients with comorbid psychopathology was associated with increased complications, prolonged hospitalisations and higher average medical costs than those without a mental illness. Although anxiety was among a number of disorders identified, pooling of psychiatric data precluded individual reporting of the association between health service use and anxiety. Arts et al. [20] found that psychologically distressed (anxiety and depression) survivors of lymphoma and chronic lymphocytic leukemia were associated with increased self-reported health service use. The evidence around the association between anxiety and health service utilisation is more limited.

Although anxiety and depression have been considered as two distinct entities according to the diagnostic criteria, there is increasing evidence in the context of cancer that depression and anxiety often co-occur [10. The prevalence of co-occurring anxiety and depression among cancer survivors has been estimated to be 9% at six and twelve months post-treatment [10], although other studies have reported higher rates (12%) among some tumour groups [21]. Increasingly, transdiagnostic treatments designed to treat anxiety and depression symptoms simultaneously are being implemented in cancer care. As such, it is important to consider health service use in cancer in the context of increased psychiatric morbidity more broadly.

This study aims to add to the literature by exploring the association between comorbid anxiety and depression and health service use (self-reported general or cancer-specific doctor visits) in Dutch cancer survivors.

Methods

Data source

Data were obtained from The Patient Reported Outcomes Following Initial treatment Long term Evaluation of Survivorship (PROFILES) registry [22].

The PROFILES registry is linked with the population-based Netherlands Cancer Registry (NCR), which registers all newly diagnosed cancer patients within six months of diagnosis [22]. This facilitates the identification of cancer survivors, and previous survivorship studies have shown that patient selection via the NCR works well for long-term survivors (5–15 years after diagnosis) who often are no longer in clinical follow-up [23]. PROFILES is a web-based registry which can be used to facilitate data collection on patient-reported outcomes from cancer survivors. The linkage between the NCR and the PROFILES registry is valuable as it allows researchers to interpret psychosocial outcomes alongside medical and demographic characteristics [22]. All patients who are registered into the NCR are considered potential participants for the PROFILES registry.

For each study conducted within the PROFILES registry, a selection of cancer patients was invited (via post or email) [24]. Each study included survivors with a specific tumour type and diagnosed in specific years (total sample ranging from 2004-2014; colon, rectal, melanoma, thyroid, endometrial, prostate, non-Hodgkin and Hodgkin lymphoma). Cancer survivors were asked to complete a set of patient reported outcomes measures, such as EORTC-QLQ-C30, Fatigue Assessment Scale and the Hospital Anxiety and Depression Scale. More

details about how PROFILE studies are managed and delivered can be found in the PROFILES registry protocol paper [22]. Results and data of each PROFILES study is made available for researchers via the PROFILES registry website (www.profilesregistry.nl).

This paper is a registry-based study and only included PROFILES studies that contained questionnaires for anxiety, depression, cancer and extra care for this analysis: Endometrial 2008, Multiple myeloma 2009, Colorectal 2009 and Thyroid 2010.

Study sample

The four datasets were appended using STATA 15 for analysis (n=3,553). The final data set excluded any participants who were non-respondents (n=627) or who had unverifiable addresses[1] (n=388). Only respondents with verifiable addresses were included in the analysis (n=2,538).

Each PROFILES study collected data from participants on their self-reported anxiety and depression health service utilisation, cancer-related information and other socio-demographic information. Clinical data such as cancer staging and cancer type were collected by the NCR. Participants were asked to answer the survey questions according to their health at the time of completion. Health service utilisation was measured from the date of survey completion as the number of doctor visits made in the past 12 months and whether those visits were cancer-related or not

Each PROFILES study assessed anxiety and depression using the Hospital Anxiety and Depression Scale (HADS). The HADS is a validated self-report measure that assesses the current severity of depression and anxiety symptoms in clinical populations where physical symptoms may complicate the diagnosis of comorbid emotional issues. The scale includes 2 subscales, one for depression and one for anxiety (Cronbach's α HADS_D = 0.82, HADS_A = 0.83) [25]. The HADs has been extensively used in cancer populations [26]. The HADS is a self-report questionnaire and consists of 14 questions (7 for anxiety and 7 for depression) that ask participants to rate how they have been feeling in the past week on a scale from 0-3, with higher scores indicating higher psychological morbidity. Participants are scored using the HADS scoring criteria and scores ranged from 0-21. For this study, the HADS score was recoded as a categorical variable to reflect clinical cut-offs [27] and for ease of interpretation: normal (without anxiety and depression) 0-7, mild ≥8, moderate ≥ 11 & severe ≥15.

Analysis

Regression analyses were conducted to examine the association between anxiety and depression and the number of doctor visits in the past 12 months. The Poisson regression model is often used to analyse count data. However, when the data is over-dispersed, a negative binomial regression model is more appropriate [28]. To test whether the negative binomial regression model was more appropriate, an analysis was conducted using the *nbreg* command in STATA. The *nbreg* command includes a likelihood ratio test, which is a test of the overdispersion parameter alpha. When alpha is assumed to be zero, the negative binomial distribution equates to

[1] Patients with unverifiable addresses had incorrect/insufficient information regarding their address in the system for the invitation letter to be sent to them.

a Poisson distribution [29]. A negative binomial distribution is more appropriate than a Poisson model if alpha is significantly different from zero. The likelihood ratio test was conducted for all 4 types of doctor visits, and all p values were statistically significant and reinforce that negative binomial distribution models were more appropriate for these analyses. In addition, the negative binomial regression model was tested against zero-inflated models (Poisson and negative binomial) models using the *countfit* command in STATA. Compared to zero-inflated models, the *countfit* demonstrated that the negative binomial model is a better fit for all 4 types of doctor visits (all $p<0.001$).

Four negative binomial regression regressions were undertaken for different definitions of doctor visits as the dependent variable:

1. Number of visits to a general practitioner (GP) in the last 12 months
2. Number of visits to a specialist doctor in the last 12 months
3. Number of visits to a GP regarding cancer in the last 12 months
4. Number of visits to a specialist doctor regarding cancer in the last 12 months

Variables describing participants' socio-demographic and clinical characteristics were included as controls in the regressions. This included gender, age at cancer diagnosis, marital status, level of education, number of comorbidities, number of comorbidities that interfere with daily activities and socioeconomic status.

Cancer-related variables were also included as control variables: cancer type (colon, rectum, endometrial, multiple myeloma, thyroid), years since diagnosis (< 2 yrs, 2-5 yrs, 5-10 yrs, 5-10 yrs, >10 yrs), the receipt of care from a health professional post-cancer treatment (no, yes), cancer treatments received (all dummy coded); surgery, radiation treatment (radiotherapy & nuclear medicine iodine treatment), chemotherapy, wait and see (for multiple myeloma), and other therapies (not specified by the NCR). The type of cancer treatments received were dummy coded to capture the individual effects of each cancer treatment on medical practitioner visits.

A post-estimation command, *margins*, was used after each negative binomial regression model to predict the number of visits to a medical practitioner. The *margins* command calculates an average predicted count of events based on the previously fit model [30].

Results were reported as incidence rate ratios (IRRs). An IRR greater than one indicates more frequent visits to the doctor, and an IRR less than one indicates less frequent visits to the doctor. Statistical analysis was conducted using STATA version 15 (StataCorp LLC, College Station, Texas).

Participants with a missing response for any of the covariates controlled for within the model were removed via listwise deletion in STATA. Ethics approval was granted by the UTS Human Research Ethics Committee (UTS HREC REF NO. 2015000135).

Results

Sample characteristics

Table 1 presents the sample characteristics. The study sample (n=2,538) was primarily female (64.0%; n= 1,624), with the majority over the age of 55 years (74.4%). Most respondents were married/cohabiting (72.1%)

and received secondary/vocational education (61.8%). The sample mostly consisted of people diagnosed with early-stage (T1) cancers (49.84%). The most common cancer types were colon (35.8%), rectum (18.3%), and endometrial (29.3%). The mean number of years since a cancer diagnosis was 4.25 years. The majority of the study sample did not meet the criteria for clinical levels of anxiety and depression, with 20.21% reporting mild, moderate or severe anxiety and 18.6% reporting mild, moderate or severe depression.

On average, participants in the sample saw a GP 4 times in the previous year and a specialist 4.50 times in the previous year, see Table 1. For cancer-related visits, participants in the sample, on average, saw a GP 1.28 times in the previous year and a specialist 3.41 times in the previous year.

GP and Specialist visits

Table 2 presents the results of the negative binomial regression analysis for anxiety and depression and the number of GP and specialist visits in the past 12 months. Refer to Table 3 in the appendix for the full regression results.

Having clinical levels of anxiety (mild, moderate and severe) is associated with more frequent GP visits in the past 12 months; mild (IRR=1.21, P<0.01), moderate (IRR=1.42, p<0.001) and severe (IRR=1.89, p<0.001). Clinical levels of anxiety are not statistically significantly associated with more frequent specialist visits. Compared to those without depression, those with severe depression have more frequent visits to the GP and specialist in the past 12 months; IRR=1.557, p<0.01 and IRR=2.131, p<0.001, respectively.

GP and specialist visits – cancer-related

Table 4 presents the results of the negative binomial regression analysis for the number of cancer-related GP and specialist visits in the past 12 months. Refer to Table 5 in the appendix for the full regression results.

For cancer survivors having moderate levels of anxiety is associated with more frequent cancer-related visits to the GP (IRR=2.366, p<0.001) and specialist (IRR=1.235, p<0.05). Severe anxiety is associated with the largest increase in frequency to the GP; 6.284 times more frequent than those without anxiety. While for depression, mild levels are associated with more frequent visits to both the GP (IRR=1.672, p<0.05) and the specialist (IRR= 1.252, p<0.01). The largest increase in the frequency of specialist visits is associated with severe levels of depression (IRR=1.951, p<0.001) when compared to those without depression.

Predicted number of doctor visits

Figure 1 presents the predicted number of doctor visits in a year by clinical levels of anxiety and depression. For clinical levels of anxiety, regardless of whether a GP visit is cancer-related or not, an upward trend is seen in the number of visits, whereas the number of specialist visits remains stable.

Severe levels of anxiety and depression predict the highest number of visits within any type of doctor visit (GP or specialist). The number of visits to a GP (specialist) is ordered and increasing when levels of anxiety (depression) becomes more severe; the higher the level of mental distress predicts for higher numbers of doctor visits. For severe levels of anxiety, the predicted mean number of GP visits is 6.8 and 4.6 specialist visits in the past 12 months. For severe levels of depression, the predicted mean number of GP visits was 5.9 and 8.5 specialist visits in the past 12 months. Except for depression in cancer-related GP visits, severe levels of anxiety

and depression predict the highest number of visits for either GP or specialist visits. For severe levels of anxiety, the predicted mean number of cancer-related GP visits is 5.9 and 4.1 specialist visits in the past 12 months. For severe levels of depression, the predicted mean number of GP visits was 5.9 and 8.5 specialist visits in the past 12 months.

Discussion

Our results demonstrate an association between anxiety, depression and health service use in cancer survivors; the higher the level of anxiety or depression experienced, the more frequent patients attend doctor visits, leading to increased costs to the health system. These findings are consistent with and add to the existing literature [13, 14] that demonstrate the association between both anxiety and depression and health service use. Given that almost a quarter of all cancer patients and survivors experience anxiety and depression [12] and many cancer patients report unmet needs for psychosocial care [31], routine identification and treatment of comorbid anxiety and depression will improve patient outcomes. It is therefore imperative for health services and policy-makers to ensure psycho-oncology services are available to provide timely care to cancer survivors. This has the potential to mitigate increased health service use related to psychological symptoms and lead to reduced costs to the health system overall.

For those with severe anxiety, the most significant increase is in the frequency of cancer-related GP visits, 6.2 times more frequent than those without anxiety. Higher utilisation of health services has been observed in primary care, where patients with anxiety or depression had almost double the health care costs of those who did not have anxiety or depression [32]. Mackenzie et al. [33] found that cancer patients prefer talking to their GP rather than their specialist about anxiety and depression symptoms because they felt they had more pressing issues to discuss with their specialist. In survivorship, the limited number of specialist visits is likely to increase preference for primary care management. This could explain more frequent GP visits presented in the results. More frequent GP visits could also be attributed to the fact that mental health is typically managed by GPs rather than a specialist.

For those with severe depression, the largest increase in the number of doctor visits is seen for specialist visits; 2.13 times more frequent than those without depression. Increased specialist visits observed in the depression cohort could be explained by referrals to a psychiatrist for review, treatment and ongoing follow-up, although this is speculative given the types of specialist visits were not differentiated within the PROFILES dataset.

Although the proportion of our sample with comorbid anxiety (20.21%) and depression (18.56%) is comparable with estimates in the existing literature; 22.6% for anxiety and 16.5% for depression [6], the relatively low numbers of participants with severe A&D means interpretation of results should be considered in the light of this. In this study, a clear gradient can be seen for visits to the GP and specialist, whereby increasing levels of A&D is associated with more frequent doctor visits. This association is less apparent for cancer-related doctor visits; only moderate anxiety, mild depression, and severe depression were statistically significant. We do not believe that this is a clinical issue but rather a result of smaller proportions of cancer survivors reporting cancer-related visits, contributing to a smaller effect size to reach statistical significance.

Some limitations of this study should be noted. Self-reported data is susceptible to recall bias, where participants may not remember and accurately report health service utilisation (the number of doctor visits made in a year). It has been reported that a 16% inflation to the number of self-reported GP visits should be applied as a sensitivity analysis [34]. This sensitivity analysis was conducted, and no major differences were found in the estimated IRRs, and statistical significance remained identical. This study does not demonstrate causality but can only demonstrate associations between anxiety and depression and health service use. Caution should be applied in interpreting a causal relationship because there may be endogeneity bias if omitted variables are correlated with any of the independent variables in the model [35]. Anxiety and depression may be correlated with other health factors, which can also be correlated with health service utilisation. The inclusion of the number of comorbidities and the number of comorbidities interfering with daily activities attempts to account for such correlation, however, is still unable to fully control for general health.

The PROFILES sample may not be representative of all Dutch people living with cancer because (1) the registry will only cover those registered in the NCR in the southern Netherlands, and (2) participation in PROFILES studies is voluntary (selection bias) and not all cancer types are represented. Therefore, the generalisability of these results may only apply to the cancer types explored in this analysis. Furthermore, the findings from this study may only be compared with other countries that have a similar population and health care system as the Netherlands.

Cancer is the second leading cause of death internationally [36], and the cost of cancer is significant [36]; approximately US $1.16 trillion annually [37]. Comorbid anxiety and depression in cancer survivors are associated with decreased quality of life [38-40], worse cancer treatment side effects [41] and increased health service use (costs) [15, 16, 42, 43]. More recently, Gu et al. [44] demonstrated that depression in an elderly cancer population was associated with 43.8% higher expenditure to the health system but also 32.9% higher patient expenditure when compared with those without depression. Anxiety and depression are often undetected in busy cancer services [45]. Early identification and treatment of anxiety and depression typically lead to improved outcomes, including greater cancer treatment adherence, improved doctor-patient communication and fewer clinic calls and visits [46]. Psychological interventions have been shown to reduce the prolonged use of health services among cancer patients [47, 48]. Routine identification and treatment of comorbid anxiety and depression may reduce overall health service use (costs) or redirect them to relevant psycho-oncology professionals. By doing so, there is potential to improve the allocation of scarce health resources and alleviate the economic burden placed on the health system.

Conclusion

Comorbid anxiety and depression in cancer survivors are associated with increased health service use. Clinical levels of anxiety in cancer survivors are associated with more frequent visits to the GP, whereas clinical levels of depression are associated with more frequent specialist visits. Treatment of anxiety and depression in cancer survivors may reduce overall health service use and the associated costs or, redirect them to more relevant psycho-oncology professionals. Health services need to identify and treat anxiety and depression in cancer survivors routinely. By doing so, there is potential to improve clinical outcomes for cancer survivors with

anxiety and depression, improve the allocation of scarce health resources and alleviate the economic burden placed on the health system.

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Table 1 - Sample characteristics

	Frequency (n=2,538)	Percentage
Gender		
Male	914	36.01
Female	1,624	63.99
Age at cancer diagnosis		
≤25 years	19	0.75
26-35	72	2.84
36-45	130	5.12
46-55	429	16.90
56-65	840	33.10
66-75	793	31.25
76-85	255	10.05
85+	0	0
Socio-economic status		
Low	544	21.89
Medium	1017	40.93
High	861	34.65
Living in care institutions	63	2.54
Missing	53	2.08
Marital status		
Married/cohabiting	1830	72.10
Divorced/Separated	131	5.16
Widowed	401	15.80
Never married/cohabited	104	4.1
Missing	72	2.84
Education		
High (tertiary)	428	17.53
Medium (secondary/vocational)	1508	61.75
Low (no/primary school)	506	20.72
Missing	96	3.78
Employment status		
Yes, in a paid job	473	18.64
No	1959	77.19
Missing	106	4.18
In general, how would you say your health is?		
Excellent	155	6.11
Very good	314	12.37
Good	1282	50.51
Fair	537	21.16
Poor	64	2.52
Missing	186	7.33

	Frequency (n=2,538)	Percentage
Years since diagnosis		
<2 years	458	18.05
2-5 years	1141	44.96
5-10 years	762	30.02
>10 years	177	6.97
Cancer type		
Colon	908	35.78
Rectum	463	18.24
Endometrial	744	29.31
Multiple Myeloma	120	4.73
Thyroid	303	11.94
Cancer stage (TNM staging)		
T1	1265	49.84
T2	654	25.77
T3	473	18.64
T4	90	3.55
Missing	56	2.21
Cancer treatments received		
Surgery	2404	94.72
Radiation	783	30.85
Chemotherapy	457	18.01
Other therapies	4	0.16
Wait and see	20	0.79
Level of anxiety (HADS)		
Normal (0-7)	1858	73.21
Mild (8-10)	294	11.58
Moderate (11-14)	168	6.62
Severe (≥15)	51	2.01
Missing	33	1.30
Level of depression (HADS)		
Normal (0-7)	1885	74.27
Mild (8-10)	290	11.43
Moderate (11-14)	151	5.95
Severe (≥15)	30	1.18
Missing	182	7.17
Number of general visits in the past 12 months		
GP	4.010	
Specialist	4.461	
Number of cancer-related visits in the past 12 months		
GP	1.288	
Specialist	3.415	

Table 2 - Negative binomial regression of the number of GP and specialist visits in the past 12 months

	GP visits^		Specialist visits^^	
	IRR	**95% CI**	**IRR**	**95% CI**
Anxiety (HADS) (Ref: Normal)				
Mild	1.208**	1.067 - 1.368	0.977	0.865 - 1.104
Moderate	1.421***	1.212 - 1.666	1.054	0.901 - 1.232
Severe	1.893***	1.449 - 2.472	1.098	0.828 - 1.456
Depression (HADS) (Ref: Normal)				
Mild	1.050	0.925 - 1.191	1.237***	1.093 - 1.400
Moderate	1.106	0.932 - 1.312	1.243*	1.048 - 1.474
Severe	1.557**	1.123 - 2.158	2.131***	1.543 - 2.943
Constant	1.298	0.614 - 2.745	11.35***	5.932 - 21.702
Alpha	0.471***	0.426 - 0.522	0.450***	0.408 - 0.497
Observations	1945		1935	

Abbreviation; IRR, Incidence rate ratio, CI, Confidence interval, HADS, Hospital Anxiety and Depression Scale, *, p<0.05, **, p<0.01, *** p<0.001. Covariates included as controls were: gender, age at cancer diagnosis, cancer type, years since diagnosis, socioeconomic status, marital status, education, number of comorbidities (other than cancer), number of comorbidities that interfere with daily activities and the types of cancer treatments received.

^ Statistically significant covariates include cancer type, years since diagnosis, level of education, number of comorbidities and the number of comorbidities that interfere with daily activities

^^ Statistically significant covariates include gender, cancer type, years since diagnosis, number of comorbidities, the number of comorbidities that interfere with daily activities and the type of cancer treatments received

Table 4 - Negative binomial regression of the number of cancer-related GP and specialist visits in the past 12 months

	GP visits – cancer-related		Specialist visits – cancer-related	
	IRR	**95% CI**	**IRR**	**95% CI**
Anxiety (HADS) (Ref: Normal)				
Mild	1.080	0.740 - 1.577	1.056	0.920 - 1.212
Moderate	2.366***	1.496 - 3.742	1.235*	1.037 - 1.471
Severe	6.284***	2.880 - 13.712	1.311	0.955 - 1.801
Depression (HADS) (Ref: Normal)				
Mild	1.672*	1.125 - 2.485	1.252**	1.088 - 1.442
Moderate	1.499	0.910 - 2.470	1.046	0.857 - 1.277
Severe	1.058	0.389 - 2.880	1.951***	1.344 - 2.831
Constant	0.472		16.44***	8.020 - 33.679
Alpha	4.511***	3.957 – 5.143	0.525***	0.471 - 0.585
Observations	1,795		1,868	

Abbreviation; IRR, Incidence rate ratio, CI, Confidence interval, HADS, Hospital Anxiety and Depression Scale, *, p<0.05, **, p<0.01, *** p<0.001

^ Statistically significant covariates include cancer type, years since diagnosis, socioeconomic status, marital status, level of education, number of comorbidities and the type of cancer treatments received

^^ Statistically significant covariates include age at cancer diagnosis, cancer type, years since diagnosis, number of comorbidities and the type of cancer treatments received

Article title

Investigating the association between self-reported comorbid anxiety and depression and health service use in cancer survivors

Journal name

Pharmacoeconomics

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Appendix

Table 1 - Negative binomial regression of the number of GP and specialist visits in the past 12 months

	GP visits		Specialist visits	
	IRR	**95% CI**	**IRR**	**95% CI**
Anxiety (HADS) (Ref: Normal)				
Mild	1.208**	1.067 - 1.368	0.977	0.865 - 1.104
Moderate	1.421***	1.212 - 1.666	1.054	0.901 - 1.232
Severe	1.893***	1.449 - 2.472	1.098	0.828 - 1.456
Depression (HADS) (Ref: Normal)				
Mild	1.050	0.925 - 1.191	1.237***	1.093 - 1.400
Moderate	1.106	0.932 - 1.312	1.243*	1.048 - 1.474
Severe	1.557**	1.123 - 2.158	2.131***	1.543 - 2.943
Gender (Ref: Female)				
Male	0.947	0.853 - 1.051	1.111*	1.003 - 1.230
Age at cancer diagnosis (Ref: ≤ 25 years)				
26-35 years	1.354	0.812 - 2.258	0.934	0.601 - 1.452
36-45 years	1.516	0.924 - 2.487	0.867	0.567 - 1.326
46-55 years	1.310	0.806 - 2.128	0.827	0.548 - 1.249
56-65 years	1.354	0.833 - 2.201	0.825	0.546 - 1.248
66-75 years	1.475	0.904 - 2.408	0.874	0.576 - 1.327
76-85 years	1.437	0.866 - 2.384	0.756	0.489 - 1.170
Cancer type (Ref: Thyroid)				
Colon	0.978	0.808 - 1.184	0.730**	0.604 - 0.883
Rectum	0.976	0.810 - 1.175	0.769**	0.640 - 0.923
Endometrial	0.703***	0.588 - 0.840	0.748**	0.627 - 0.891
Multiple Myeloma	1.912*	1.048 - 3.490	0.881	0.516 - 1.505
Years since diagnosis (Ref: ≤2 years)				
>2-5yr	0.917	0.819 - 1.026	0.677***	0.609 - 0.752
>5-10yr	0.881*	0.779 - 0.996	0.453***	0.402 - 0.510
>10yr	0.630***	0.506 - 0.783	0.404***	0.327 - 0.500
Socioeconomic status (Ref: Low)				
Medium	1.110	0.999 - 1.233	1.048	0.945 - 1.163
High	0.961	0.858 - 1.077	1.033	0.923 - 1.155
Living in care institutions	1.198	0.902 - 1.590	0.961	0.715 - 1.293
Marital status (Ref: Married/cohabiting)				
Divorced/separated	1.106	0.931 - 1.313	0.912	0.769 - 1.082
Widowed	1.027	0.911 - 1.157	1.034	0.919 - 1.163
Never married/never cohabited	1.195	0.979 - 1.457	1.006	0.825 - 1.227
Education (Ref: Tertiary)				
Secondary/vocational	1.216***	1.086 - 1.361	0.956	0.860 - 1.061
No/primary school)	1.453***	1.264 - 1.671	0.906	0.792 - 1.037
Receipt of care from a health professional (other than a doctor) post-cancer treatment (Ref: Yes)				
No	0.983	0.902 - 1.070	0.965	0.888 - 1.049
Number of comorbidities (other than cancer) (Ref: 0)				
1	1.328***	1.187 - 1.486	1.156**	1.037 - 1.288
2	1.392***	1.227 - 1.579	1.272***	1.126 - 1.437
3-4	1.764***	1.522 - 2.044	1.292***	1.120 - 1.491
≥5	1.651***	1.289 - 2.115	1.643***	1.290 - 2.092
Number of comorbidities interfering with daily activities (Ref: 0)				
1	1.218***	1.092 - 1.359	1.136*	1.020 - 1.266
≥2	1.188*	1.034 - 1.365	1.229**	1.072 - 1.410

Cancer treatments received (Dummy coded)				
Surgery	1.354	0.787 - 2.332	0.594*	0.373 - 0.944
Radiation	0.963	0.863 - 1.073	1.000	0.901 - 1.110
Chemotherapy	0.895	0.789 - 1.015	1.365***	1.212 - 1.537
Other Therapies	1.437	0.561 - 3.675	0.512	0.195 - 1.347
Wait & See	0.982	0.613 - 1.576	1.348	0.855 - 2.123
Constant	1.298	0.614 - 2.745	11.35***	5.932 - 21.702
Alpha	0.471***	0.426 - 0.522	0.450***	0.408 - 0.497
Observations	1,945		1,935	
Log-likelihood	-4568		-4641	
Pseudo R2	0.042		0.050	

Abbreviation; IRR, Incidence rate ratio, CI, Confidence interval, HADS, Hospital Anxiety and Depression Scale, *, p<0.05, **, p<0.01, *** p<0.001

Table 2 - Negative binomial regression of the number of cancer-related GP and specialist visits in the past 12 months

	GP visits – cancer-related		Specialist visits – cancer-related	
	IRR	**95% CI**	**IRR**	**95% CI**
Anxiety (HADS) (Ref: Normal)				
Mild	1.080	0.740 - 1.577	1.056	0.920 - 1.212
Moderate	2.366***	1.496 - 3.742	1.235*	1.037 - 1.471
Severe	6.284***	2.880 - 13.712	1.311	0.955 - 1.801
Depression (HADS) (Ref: Normal)				
Mild	1.672*	1.125 - 2.485	1.252**	1.088 - 1.442
Moderate	1.499	0.910 - 2.470	1.046	0.857 - 1.277
Severe	1.058	0.389 - 2.880	1.951***	1.344 - 2.831
Gender (Ref: Female)				
Male	0.915	0.660 - 1.269	1.095	0.976 - 1.229
Age at cancer diagnosis (Ref: ≤ 25 years)				
26-35 years	2.050	0.484 - 8.694	0.953	0.582 - 1.561
36-45 years	1.858	0.462 - 7.472	0.747	0.464 - 1.203
46-55 years	1.482	0.386 - 5.693	0.842	0.533 - 1.332
56-65 years	1.367	0.351 - 5.330	0.723	0.456 - 1.145
66-75 years	1.335	0.337 - 5.289	0.696	0.437 - 1.109
76-85 years	0.906	0.218 - 3.769	0.583*	0.357 - 0.950
Cancer type (Ref: Thyroid)				
Colon	0.757	0.416 - 1.376	0.616***	0.494 - 0.768
Rectum	0.892	0.505 - 1.576	0.691***	0.562 - 0.851
Endometrial	0.552*	0.317 - 0.960	0.609***	0.498 - 0.746
Multiple Myeloma	1.295	0.268 - 6.262	0.640	0.354 - 1.157
Years since diagnosis (Ref: ≤2 years)				
>2-5yr	0.506***	0.363 - 0.705	0.598***	0.532 - 0.672
>5-10yr	0.362***	0.249 - 0.524	0.307***	0.267 - 0.352
>10yr	0.206***	0.105 - 0.406	0.266***	0.207 - 0.342
Socioeconomic status (Ref: Low)				
Medium	1.574**	1.128 - 2.197	1.071	0.950 - 1.207
High	1.297	0.913 - 1.842	1.015	0.893 - 1.154
Living in care institutions	2.174	0.863 - 5.473	1.010	0.715 - 1.428
Marital status (Ref: Married/cohabiting)				
Divorced/separated	1.833*	1.089 - 3.083	0.826	0.678 - 1.006
Widowed	0.947	0.648 - 1.382	1.082	0.945 - 1.237
Never married/never cohabited	2.007*	1.074 - 3.751	1.049	0.839 - 1.313
Education (Ref: Tertiary)				
Secondary/vocational	1.568*	1.112 - 2.211	0.925	0.821 - 1.042
No/primary school)	2.005**	1.298 - 3.098	1.022	0.875 - 1.193
Receipt of care from a health professional (other than a doctor) post-cancer treatment (Ref: Yes)				
No	0.966	0.756 - 1.235	1.007	0.917 - 1.106
Number of comorbidities (other than cancer) (Ref: 0)				
1	1.137	0.806 - 1.605	1.132*	1.001 - 1.279
2	1.191	0.812 - 1.748	1.182*	1.027 - 1.361
3-4	1.835**	1.171 - 2.875	1.158	0.980 - 1.368
≥5	1.246	0.582 - 2.669	1.139	0.856 - 1.517
Number of Comorbidities interfering with daily activities (Ref: 0)				
1	1.398	0.995 - 1.964	1.016	0.895 - 1.152
≥2	1.360	0.891 - 2.076	1.008	0.859 - 1.183
Cancer treatments received (Dummy coded)				

Surgery	0.889	0.222 - 3.569	0.461**	0.278 - 0.766
Radiation	1.033	0.742 - 1.439	1.121	0.995 - 1.264
Chemotherapy	1.637**	1.139 - 2.353	1.691***	1.482 - 1.929
Other Therapies	2.378	0.219 - 25.876	0.812	0.262 - 2.518
Wait & See	1.239	0.306 - 5.022	1.440	0.872 - 2.377
Constant	0.472		16.44***	8.020 - 33.679
Alpha	4.511***	3.957 – 5.143	0.525***	0.471 - 0.585
Observations	1,795		1,868	
Log-likelihood	-2066		-3985	
Pseudo R2	0.046		0.074	

Abbreviation; IRR, Incidence rate ratio, CI, Confidence interval, HADS, Hospital Anxiety and Depression Scale, *, p<0.05, **, p<0.01, *** p<0.001