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Consulting and prescribing behaviour for anxiety and depression in long-term survivors of cancer in the UK

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ABSTRACT

Introduction: Cancer survivors may experience long-term depression or anxiety, however, there is little previous research on the use of services in this area. We explored consultation and prescribing behaviour for depression and anxiety amongst cancer survivors in British primary health care.

Methods: This study uses data on 26,213 survivors of breast, colorectal and prostate cancer at least 5 years post-diagnosis, matched to four controls without cancer, from the UK General Practice Research Database. We compared consultations for depression and anxiety, and prescribing for anti-depressants and anxiolytics between cancer survivors and controls.

Results: Multivariate, matched regression models showed no difference in consulting for depression or anxiety between any cancer survivors and matched controls. However, breast cancer (odds ratio (OR) 1.16, 95% confidence interval (CI) 1.10–1.22) and prostate cancer survivors (OR 1.31, 95% CI 1.16–1.47) were more likely to receive a prescription for an antidepressant. Breast cancer survivors (IRR 2.49, 95% CI 1.82–3.42) and prostate cancer survivors (IRR 2.84, 95% CI 1.94–4.17) who died received significantly more antidepressants than controls who died. There were no differences in anxiolytic prescribing for colorectal and prostate cancer survivors compared to controls. However, breast cancer survivors nearing the end of life received a greater number of anxiolytic prescriptions compared to controls (IRR 1.84, 95% CI 1.36–2.49).

Conclusions: In this cohort of cancer survivors, there were no differences in consultation behaviour for depression and anxiety compared to controls. However, breast and prostate cancer survivors access more antidepressants, and those nearing the end of life received the highest volume of prescriptions. Breast cancer survivors at the end of life also receive more anxiolytics.

1. Introduction

1.1. Context

Survival rates for cancer have been improving over the last 20 years due to improvements in diagnosis and treatment. Once perceived as a fatal condition, cancer has become a treatable disease, with half of all British cancer patients living for at least 5 years past a diagnosis.[1] Until recently, cancer care and research has focused on the acute physical needs associated with a life threatening disease. However, as survival rates for many of the common cancers have improved, cancer

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is increasingly viewed as a chronic illness. This paradigm shift has refocused cancer survivorship research from the acute phase to a long-term disease model covering physical, social and psychological health.[2,3]

It has been suggested that ongoing medical and psychosocial effects of cancer and its treatment can lead to long-term psychological morbidity in cancer survivors.[2] Surveys of long-term breast and prostate cancer survivors have highlighted ongoing depression, anxiety and need for psychological support.[4–6] A recent systematic review considering the long-term psychological consequences of cancer survivorship suggested that while levels of psychological distress are similar to the general population in most cancer survivors, a proportion of cancer survivors consistently report long-term depression and anxiety.[7] Cancer survivors at risk of long-term psychological distress may include those with multiple comorbid diseases or advanced disease, and individuals receiving cancer treatments with long-term side effects.[8]

Psychological care is an important component of health provision immediately following a cancer diagnosis. However, there has been little research on the use of services amongst long-term survivors of cancer. In the UK, primary care is the first point of contact for cancer survivors seeking medical care following discharge from routine follow-up. The purpose of this work is to explore the use of primary care psychological services amongst long-term survivors of cancer, and to compare their consultation behaviour and prescribing behaviours with a non-cancer control population. Specifically, we aimed to investigate whether cancer survivors were more likely to consult for depression and anxiety-related problems and receive prescriptions for antidepressants or anxiolytics. We also considered the effect of comorbidity and proximity to end of life on consultations and prescribing for psychological problems.

2. Methods

2.1. Source of the data

We used data from the General Practice Research Database (GPRD), which contains information on 4.5 million actively consulting patients from 450 general practices in the United Kingdom (UK).[9] The GPRD includes records on individual level clinical diagnoses, test results and prescriptions from primary care. Each consultation is coded using a Read or OXMIS code for each episode of illness or new occurrence of a symptom.[10] Several validation studies have shown a high level of data completeness within the GPRD.[11]

2.2. Description of participants

This study focuses on a cohort of adult survivors of breast, colorectal and prostate cancer. The three cancers were selected because they are the three most prevalent cancers in the UK and represent a significant proportion of all long-term survivors in primary health care. We defined cancer survivors (cases) as those aged 30 or over at the time of diagnosis, with at least 5 years of survival post-diagnosis. Controls were patients with no record of breast, colorectal or prostate cancer at the start of the analysis period. For each case, up to four controls were selected from the same primary care practice and matched on the basis of age (within 1 year) and gender. Survivors and matched control patients were censored from follow-up if the cancer survivor died, was diagnosed with a second cancer, or transferred out of the GPRD primary care practice.

2.3. Antidepressant and anxiolytic prescription definition

We defined antidepressant drugs as tricyclics, selective serotonin re-uptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs), and anxiolytics as benzodiazepines and busipirone, respectively, listed in Sections 4.3 and 4.1.2 of the British National Formulary.[12] See Appendix 1 for further details.

2.4. Statistical analyses

We compared consultation behaviour for depression, anxiety and prescribing for antidepressants and anxiolytics between cancer survivors and their matched controls over a 3 year period from 1 September 2003 to 31 August 2006. A full list of codes used to identify consultations can be provided upon request.

We firstly compared the percentage of cancer survivors and controls consulting for the first time for depression or anxiety, or receiving prescriptions for antidepressants or anxiolytics between 1 September 2003 and 31 August 2006. Secondly, we used conditional logistic regression to determine whether or not cancer survivors were more likely than their matched controls to have a consultation for depression or anxiety, or receive at least one prescription for an antidepressant or anxiolytic during the same analysis period. Thirdly, we compared the volume of prescribing for antidepressants and anxiolytics using World Health Organization defined daily doses to assign each of the prescribed drugs in the GPRD, a defined daily dose (DDD).[13] We used conditional fixed-effects negative binomial regression, offset by follow- up time for each individual, to compare the number of defined daily doses for antidepressants and anxiolytics between cancer survivors and matched controls. This method accounts for the matching by firstly making comparisons within each matched set and then averaging across all the matched sets. All analyses were carried out using Stata MP, version 10.1.

2.5. Explanatory variables used in the regression analyses

We assigned each patient a Charlson comorbidity score based on their clinical history.[14] We did not count cancer as a comorbid disease.[15] We included history of depression and anxiety (defined as a previous consultation for depression or anxiety prior to the start of the analysis period, not as depression prior to cancer in the survivors), respectively, in the corresponding analyses for depression and anxiety consultation behaviour. The number of overall consultations over the 3 year period was also included in the prescribing analysis, as patients consulting more frequently are more likely to receive pharmacological interventions. Because patients nearing the end of their life can be treated differently in primary care, we included a variable indicating whether or not the patient died during the analysis period, and tested for interactions between death and all outcomes.

3. Results

The final dataset included data on 16,938 breast cancer survivors, 5068 colorectal cancer survivors, 4207 prostate cancer survivors, and 104,486 control patients (total $n = 130,699$ patients, see Table 1). Most cancer survivors and controls were elderly, and correspondingly many had at least one comorbid disease. A substantially higher proportion of cancer survivors died within the analysis period.

3.1. Clinical consultations for depression

The majority of patients in this cohort did not consult for depression during the 3 year period (Table 2).

After adjusting for comorbidity score, history of depression and death, there were no significant differences between any cancer survivors and matched controls in terms of consultations for depression over the analysis period (Table 2). Previous history of depression and increasing Charlson comorbidity score were the strongest predictors of consultations for depression in all patients. Full multivariate models are provided in Appendix 2.

3.2. Clinical consultations for anxiety

Only a small proportion of cancer survivors and controls saw their GP for anxiety-related reasons between 2003 and 2006 (Table 2). The univariate, matched analysis for anxiety consulting behaviour suggested an increase in the likelihood of having at least one primary care visit for anxiety amongst breast and prostate cancer survivors compared to controls. However, after adjusting for Charlson score, history of anxiety and death, there was no significant increase in the odds of consulting for an anxiety amongst any of the long-term cancer survivors compared to the control population (Table 2).

3.3. Prescribing for antidepressants

The proportion of cancer survivors and controls receiving at least one prescription for an antidepressant from 2003 to 2006 is shown in Table 3.

After adjusting for Charlson score, death, number of consultations and stratifying on matched groups, both breast cancer survivors (OR = 1.16, 95% CI 1.11–1.22) and prostate cancer survivors (OR = 1.38, 95% CI 1.25–1.54) were more likely to receive at least one prescription for an antidepressant compared to matched controls (Table 3).

There were no differences in the number of defined daily doses of antidepressants amongst colorectal survivors and controls during the 2003–2006 period, conversely, there were significant differences amongst breast and prostate cancer survivors and controls. Breast cancer survivors were prescribed 76.1 defined daily doses (95% CI 72.3–79.8), compared to 71.3 DDDs (95% CI 69.4–73.2 DDDs) prescribed to breast cancer controls. Prostate cancer survivors were prescribed 41.8 DDDs (95% CI 36.9–46.7) versus 29.1 DDDs (95% CI 26.9–31.4) prescribed to controls.

There was evidence for an interaction between increased defined daily doses and death; cancer survivors who died had substantially more doses of antidepressants than cancer survivors who did not die. Therefore, we conducted a subgroup analysis which showed that both breast cancer survivors who survived past 2006 (IRR = 1.15, 95% CI 1.10–1.19), and breast cancer survivors who died (IRR = 2.00, 95% CI 1.61–2.48) received significantly more doses of antidepressants (as defined by DDDs) than their respectively matched controls. Similarly, prostate cancer survivors who remained alive throughout the analysis period (IRR = 1.29, 95% CI 1.16–1.43) and prostate cancer survivors who died before 2006 (IRR = 2.80, 95% CI 2.07–3.78) received more antidepressants than matched controls.

Differences in defined daily doses amongst cancer survivors may be due to increased dosage. We considered prescribing for fluoxetine (Prozac) and tested whether cancer survivors received more pills compared to controls as a proxy for differences in dosage. There were significant differences between the number of pills prescribed to breast cancer survivors compared to controls (31 pills versus 28, $p < 0.0001$) and between prostate survivors and controls (28 pills versus 25, $p < 0.0001$) within patients who received a monthly prescription.

3.4. Prescribing for anxiolytics

The majority of cancer survivors and controls did not receive an anxiolytic between 2003 and 2006 (Table 3). After adjusting for matching and covariates, there was no evidence for a difference in anxiolytic prescribing between colorectal or prostate cancer survivors and their matched controls. In contrast, breast cancer survivors were slightly more likely to receive a prescription for an anxiolytic (OR = 1.08, 95% CI 1.01–1.15) than matched controls. There was no evidence for interactions between the receipt of anxiolytics and death. The strongest predictor of receipt of anxiolytics was an increasing number of consultations.

Table 1 – Patient characteristics.

	Breast		Colon		Prostate	
	Survivor	Control	Survivor	Control	Survivor	Control
Male	–	–	2569	10,178	4207	16,709
Female	16,938	67,649	2499	9950	–	–
Mean age in 2003 (SD)	66.9 (12.3)		74.1 (10.9)		76.1 (8.1)	
Number of patients with Charlson score > 0	7551 (44.6%)	27,999 (41.4%)	2942 (58.1%)	10,343 (51.4%)	2693 (64.0%)	9345 (55.9%)
Number of patients who died	1964 (11.6%)	1242 (1.8%)	798 (15.7%)	658 (3.3%)	958 (22.8%)	794 (4.8%)

Table 2 – Depression and anxiety consultation behaviour and multivariate models, 2003–2006.

	At least one consultation for depression during 2003–2006		Odds of consulting for depression[a]	At least one consultation for anxiety during 2003–2006		Odds of consulting for anxiety[a]
	Yes	No		Yes	No	
Breast						
Survivor	1617 (9.6%)	15,321 (90.5%)	1.06, 95% CI 1.00–1.14	908 (5.4%)	16,030 (94.6%)	1.06, 95% CI 0.97–1.16
Control	5985 (8.9%)	61,664 (91.2%)	Reference	3383 (5.0%)	64,266 (95.0%)	Reference
Colorectal						
Survivor	416 (8.2%)	4652 (91.8%)	1.07, 95% CI 0.94–1.22	178 (3.5%)	4890 (96.5%)	0.90, 95% CI 0.74–1.10
Control	1596 (7.9%)	18,532 (92.1%)	Reference	718 (3.6%)	19,410 (96.4%)	Reference
Prostate						
Survivor	393 (9.3%)	3814 (90.7%)	1.12, 95% CI 0.98–1.34	133 (3.2%)	4074 (96.8%)	1.25, 95% CI 0.98–1.59
Control	1356 (8.1%)	15,353 (91.9%)	Reference	399 (2.4%)	16,310 (97.6%)	Reference
	11,363	119,336		5719	124,980	

[a] Adjusted for Charlson comorbidity score, previous history of depression or anxiety, respectively, and death. Cases and controls were matched on the basis of age, gender and primary care practice.

Table 3 – Antidepressant and anxiolytics prescribing behaviour and multivariate models, 2003–2006.

	Prescribed an antidepressant least once between 2003 and 2006		Odds of being prescribed an antidepressant[a]	Prescribed an anxiolytic at least once between 2003 and 2006		Odds of being prescribed an anxiolytic[a]
	Yes	No		Yes	No	
Breast						
Survivor	4007 (23.7%)	12,931 (76.3%)	1.16, 95% CI 1.11–1.22	1531 (9.0%)	15,407 (91.0%)	1.08, 95% CI 1.01–1.15
Control	13,681 (20.2%)	53,968 (79.8%)	Reference	5194 (7.7%)	62,455 (92.3%)	Reference
Colorectal						
Survivor	874 (17.3%)	4194 (82.8%)	1.06, 95% CI 0.96–1.17	333 (6.6%)	4735 (93.4%)	0.96, 95% CI 0.81 – 1.12
Control	3166 (15.7%)	16,962 (84.3%)	Reference	1122 (5.6%)	19,066 (94.4%)	Reference
Prostate						
Survivor	757 (18.0%)	3450 (82.0%)	1.38, 95% CI 1.25 – 1.54	235 (5.6%)	3972 (94.4%)	0.87, 95% CI 0.72 – 1.05
Control	1823 (10.9%)	14,866 (89.1%)	Reference	713 (4.3%)	15,996 (95.7%)	Reference

[a] Adjusted for Charlson comorbidity score, number of consultations, and death. Cases and controls were matched on the basis of age, gender and primary care practice.

There was a small but significant difference between the number of defined daily doses for anxiolytics between breast cancer survivors and their matched controls (IRR = 1.09, 95% CI 1.02–1.16) and strong evidence for effect modification by death. While breast cancer survivors who survived past the end of the analysis period in 2006 had the same anxiolytic prescribing behaviours as matched controls (IRR = 1.04, 95% CI 0.97–1.12), breast cancer survivors who died had an 84% increase in prescribed defined daily doses (IRR = 1.84, 95% 1.36–2.49).

4. Discussion

4.1. *Statement of principal findings*

This study examined primary care consultation and prescribing behaviours in a large cohort of long-term cancer survivors in the UK. Long-term survivors of cancer were no more likely to consult for depression or anxiety related reasons compared to a control population. The main predictor for a primary care consultation for depression was not history of cancer, but other comorbid diseases and history of depression.

In terms of pharmacological interventions, long-term breast and prostate cancer survivors were more likely to receive at least one prescription for an antidepressant during the analysis period. Those nearing the end of life received significantly more doses of antidepressants, and proximity to death also influenced prescribing for anxiolytics in breast cancer survivors. Colorectal cancer survivors used all psychological services and pharmacological interventions at the same rate as their corresponding matched control population.

These results suggest that while long-term survivors of three common cancers do not consult with their GPs for depression and anxiety more than the general population, those patients who do see their GPs may access more pharmacological interventions. This was an unexpected finding, and we explored several hypotheses to explain the results. It is possible that cancer survivors are more likely to receive long-term and persistent treatment for depression. However, there were no clear differences in the rates of repeat

prescribing for antidepressants between any of the cancer survivors and control groups. Secondly, it is possible that cancer survivors were receiving certain tricyclic drugs for neuropathic pain relief. We conducted a sensitivity analyses to determine whether removing tricyclic drugs from the analyses would affect these findings, however, the results were similar whether or not tricyclic prescriptions were included or excluded. Our third hypothesis was that long-term cancer survivors receive higher dosages of pharmacological interventions for depression and anxiety due to increased severity of depression. When we considered prescribing for fluoxetine, which is administered at a single strength, we found that cancer survivors received a greater number of doses compared to controls, which supports this final hypothesis but is not definitive. With increased use and scoring of the Hospital Anxiety and Depression score (HADS) in primary care, our hypothesis that depression is more severe in some cancer survivors can be tested in GPRD datasets with more recent follow-up.

4.2. *Comparison with existing literature and meaning of the study: possible mechanisms and implications for clinicians or policy makers*

Depression is a commonly recognised disorder in the acute phase of cancer following diagnosis and treatment.[16] Although rates of major disorder vary by population and diagnostic criteria, depressive disorder may be up to four times higher in cancer patients compared to the general population.[17] However, people closer to diagnosis may experience higher levels of depression and anxiety, compared to people who are further from a diagnosis. This study suggests that while most longer-term cancer survivors do not access their GP for depression or anxiety related services at higher rates compared to a control population, those nearing the end of life require increased pharmacological support to manage depression and anxiety. Depression is a widely recognised problem in palliative care.[18] Previous research has shown that breast cancer patients at the end of life were more likely to receive prescribed antidepressants than other palliative patients, which corresponds to our research.[19,20] Depression and anxiety at the end of life are treatable, and primary care is well placed to offer pharmacological interventions to this population.

4.3. *Strengths and weaknesses of this study*

The results from this research should be considered within the context of several limitations. Firstly, the GPRD is a collection of primary care records used primarily for clinical use rather than for research. Although the pharmacological data in the GPRD is highly accurate as all prescriptions issued are automatically entered onto the computer system, GPs and nurses may not record all symptoms or diagnoses. However, the analyses in this study have all been conducted as comparisons between matched cases and controls, and it is unlikely that clinicians would record depression or anxiety differently in either group.

It is difficult to judge the severity of psychological disease amongst patients in this cohort. The Read/OXMIS coding system does not always distinguish whether patients who consulted for depression had clinically significant depression, which is either defined as an elevated DSM-IV or HAD score. Nonetheless, it is important that these patients have consulted with their GP for these issues, regardless of clinical definitions of depression or anxiety.

Lastly, although the GPRD provides high quality clinical and prescribing data from primary care, use of secondary or tertiary care is not consistently recorded. Cancer survivors, but not their controls, may have access to other services outside of primary care for psychological health issues, however, this analysis does not include these services.

4.4. *Unanswered questions and future research*

As part of this project, we received data from the National Cancer Intelligence Network, which provided data on the stage of cancer at diagnosis and treatment. However, the additional data from the GPRD-NCIN linkage wereas limited in this cohort; only half of all primary care practices in the GPRD participate in the linkage scheme and not all cancer registries collect data on treatment and stage. Our original hypothesis was that stage and treatment at the time of diagnosis may influence depression and anxiety outcomes in long-term cancer survivors. The limited data meant that we could not determine whether certain subgroups of patients with later stage disease or intensive treatment access psychological services differently in primary care.

5. Conclusions

Consulting behaviour for depression and anxiety was not increased in this cohort of long-term cancer survivors. Although we could not explore the effects of stage or treatment, our analysis shows that cancer survivors nearing the end of life access a higher volume of pharmaceutical interventions for anxiety and depression. While most long-term cancer survivors likely do not require screening for depression and anxiety, a subset of patients will continue to access pharmacological interventions in the long-term.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2010.07.035.

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