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ORIGINAL RESEARCH ARTICLE

Treatment of Major Depressive Disorder in Japanese Patients with Cancer: A Matched Cohort Study Using Employer-Based Health Insurance Claims Data

Tatsuo Akechi[1] · Shinji Fujimoto[2] · Izumi Mishiro[2] · Katsuhito Murase[2]

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Abstract

Background and Objective Patients with cancer are at high risk of major depressive disorder (MDD), but little is known about their MDD treatment. We investigated the use of antidepressants and other drugs for MDD after cancer diagnosis, and patient characteristics associated with their use.

Methods Adults with a new cancer diagnosis were matched to cancer-free patients using a Japanese employee health insurance database (JMDC); this exploratory analysis included only cohort patients diagnosed with MDD between 6 months before and 12 months after the cancer diagnosis index month. Initial prescription frequencies of antidepressants and other MDD medications were compared between cancer and cancer-free groups and analyzed according to age, sex, and hospital characteristics.

Results Compared with the cancer-free group ($n = 4097$), significantly fewer patients in the cancer group ($n = 1199$) were prescribed antidepressants {622 (51.9%) [95% CI 49.0–54.7] vs 2385 (58.2%) [95% CI 56.7–59.7]}, particularly selective serotonin reuptake inhibitors. In contrast, prescription of other medications, especially antipsychotics and anxiolytics (tandospirone, hydroxyzine), was more frequent in the cancer group than in the cancer-free group. In the cancer group, women were prescribed antidepressants (mostly selective serotonin reuptake inhibitors) and other medications (mostly benzodiazepines) more than men. Antidepressant prescription decreased with age; patients aged < 40 years had the highest selective serotonin reuptake inhibitor and the lowest conventional antidepressant prescription rate compared with patients aged 40–64 years and ≥ 65 years. Lower selective serotonin reuptake inhibitor and benzodiazepine prescription rates were seen in large (≥ 100 beds) hospitals and in hospitals where patients received their cancer diagnosis.

Conclusions These results suggest Japanese patients with cancer may be undertreated for MDD compared with cancer-free patients. However, when prescribed, medications may be chosen according to patient needs, including avoiding adverse effects and drug–drug interactions.

1 Introduction

A growing body of evidence indicates that depression is common in people who have recently been diagnosed with cancer [1, 2]. A large meta-analysis reported that, among patients with cancer outside palliative care, the prevalence of major depression (as defined by *Diagnostic and Statistical Manual of Mental Disorders* criteria) was 14.9% and that of *Diagnostic and Statistical Manual of Mental Disorders*-defined minor depression was 19.2% [2]. The risk of developing a mental disorder, including depression, in patients with cancer is highest in the months following diagnosis, particularly in those who are working age (approximately 40–64 years old) [3], excluding if the cancer recurs [4]. Indeed, current patients with cancer and survivors of cancer aged < 65 years have worse mental health, poorer quality of

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✉ Tatsuo Akechi
takechi@med.nagoya-cu.ac.jp

[1] Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan

[2] Japan Medical Office, Takeda Pharmaceutical Company Limited, Tokyo, Japan

Key Points

Patients with cancer are at high risk of developing depression in the year after receiving their cancer diagnosis.

This study used a Japanese database of employer-based health insurance claims to determine whether drug prescriptions for depression are similar in primarily working-age patients with cancer compared with cancer-free patients with depression.

We found that patients with cancer were less likely to be prescribed antidepressants than cancer-free patients, suggesting that depression in Japanese patients with cancer may be undertreated, possibly because of concerns about side effects.

life, and higher symptom distress than older patients [5–7]. Many factors are likely to contribute to higher levels of stress in younger patients with cancer, including the effects of diagnosis on work, family, social interactions, and financial problems [8, 9]. Depression is associated with reduced adherence to cancer treatment [10, 11], increased frequency and severity of subjective side effects of cancer drugs [12], and an increased risk of death from cancer, cardiovascular disease, external injury, and suicide [13–15]. In Japan, the risk of suicide among patients with cancer during the first year after diagnosis is almost 24-fold higher than in the general Japanese population and is higher among patients aged 40–64 years than in those aged ≥ 65 years [15]. Therefore, treatment of depression in patients with cancer is vital to minimize the potential harmful consequences, particularly in those aged < 65 years.

Despite its prevalence, depression in patients with cancer often goes unrecognized and untreated [16, 17]. Compared with other high-income countries, Japan has a low rate of treatment of mood disorders, including depression (e.g., 29.6% in Japan during the first year of onset, compared with 35.4% in the USA, 41.4% in New Zealand, and > 40% in most European countries [18]). This may be partly due to a reluctance of patients to seek help, mainly because of low perceived need and a desire to handle the problem themselves [19, 20]. Pharmacotherapy for the treatment of depression is recommended by most guidelines [21–23], and a broad range of drugs is available for treating depression in real-world clinical practice. The Japanese guidelines for depression recommend prescription of antidepressants for moderate and severe depression, but not for mild depression [24]. However, a recent meta-analysis of individual participant data demonstrated that antidepressants are equally effective regardless of the initial depression severity, with no significant interaction between baseline severity and treatment effect (best-fitting mixed-effects model coefficient = − 0.04 [95% confidence interval (CI) − 0.16 to 0.08], $p = 0.49$) [25]. This suggests that even patients with mild depression can benefit from medical treatment [25]. Undertreatment of depression in patients with cancer may also result from concerns regarding drug–drug interactions between antidepressants and cancer medications [26, 27]. Given the prevalence of depression, including mild depression, in patients with cancer in Japan, it is important to determine whether these patients are being treated adequately and appropriately.

Using a database of insured medical services for Japanese workers and their families, we recently conducted a matched cohort study that found that patients with newly diagnosed cancer have a nearly three-fold higher risk of developing major depressive disorder (MDD) compared with cancer-free individuals [28]. More than 85% of the patients in the study were aged younger than 65 years, allowing us to focus on the risk of depression in a cohort of mainly working-age patients with cancer. The aim of this exploratory analysis of that study was to investigate the use of antidepressants and other drugs to treat depression in those patients with cancer and cancer-free patients from the matched cohort who developed MDD, and to evaluate patient characteristics associated with the use of specific medications.

2 Methods

2.1 Study Design

The primary matched cohort study investigated the risk of MDD after a cancer diagnosis using data derived from the JMDC Inc. (Tokyo, Japan) database of insured medical services and prescriptions in Japan [28]. The JMDC database encompasses employer-based health insurance schemes and, therefore, covers employees and their dependents. This exploratory analysis used data on patient demographics, cancer and MDD diagnoses based on International Statistical Classification of Diseases and Related Health Problems, 10th revision codes [29], and prescriptions for MDD for individuals who met the inclusion criteria described below. The investigators could only access anonymized information from the JMDC database; therefore, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan [30], institutional ethics approval and informed consent were not required.

2.2 Study Population

The matched cohort included adult (aged 18–74 years) patients who were newly diagnosed with cancer

(International Statistical Classification of Diseases and Related Health Problems, 10th revision codes C00–C95) during the enrollment period (January 2012 to September 2017), had no MDD diagnosis (International Statistical Classification of Diseases and Related Health Problems, 10th revision codes F32 ["Depressive episode"] or F33 ["Major depressive disorder, recurrent"]) between 6 and 12 months before the month of cancer diagnosis (index month), and had continuous health insurance enrollment for ≥ 12 months before and ≥ 12 months after the index month. Cancer-free patients in the cohort included individuals with no cancer diagnosis who were matched to patients with cancer (random sampling, with a cancer-free to cancer ratio of 10:1) according to age, sex, and insurance membership category (insured worker vs dependent of a worker), and who had no MDD diagnosis between 6 and 12 months before the index month of their matched patient with cancer and continuous insurance enrollment for ≥ 12 months after the index month.

This exploratory analysis included only those patients with cancer and cancer-free patients from the matched cohort who were diagnosed with MDD during the 18-month observation period (between 6 months before and 12 months after the index month). The observation period started 6 months before cancer diagnosis to capture MDD resulting from stress related to patient concerns with their health, uncertainty of cancer, and/or diagnostic testing. Results from the primary analysis indicate a small, but significant, difference between the cancer and cancer-free groups in the rate of MDD diagnosis during the 6 months before the index month (0.8% vs 0.5% of patients, respectively; unpublished data).

2.3 Outcome Measures

The prescription pattern of treatment of MDD in the cancer group compared with the cancer-free group was an exploratory endpoint of the study. The initial prescription at the time of MDD diagnosis was derived from the JMDC database. Prescribed drugs were identified by Anatomical Therapeutic Chemical codes and categorized according to general class (antidepressants vs other medications) and specific class (e.g., selective serotonin reuptake inhibitor [SSRI]), as listed in Table 1 of the Electronic Supplementary Material [ESM]. Antidepressants included SSRIs, serotonin and noradrenaline reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), conventional antidepressants (including tricyclic antidepressants), sulpiride (an antidepressant at low doses that is certified for the treatment of depression in Japan [31]), and alprazolam (recommended for mild depression with anxiety or agitation [32, 33] and included in the pharmacological treatment algorithm for MDD in patients with advanced cancer [32]). Other medication classes included benzodiazepines (BZDs), non-BZDs, other sleep medication, other non-barbiturates (single agent), barbiturates (single agent), other anxiolytics (tandospirone, hydroxyzine), typical antipsychotics, atypical antipsychotics, herbal hypnotics/sedatives, and mood stabilizers. When more than one drug type was prescribed in combination, each drug type was counted separately.

2.4 Statistical Analysis

The prescription frequency and 95% CIs were calculated for each drug class in the cancer and cancer-free groups. Prescription frequencies and 95% CIs were also calculated for the cancer group according to sex (men, women), age (< 40 years, 40–64 years, ≥ 65 years), number of beds in the hospital that prescribed medication for MDD (< 100 beds, ≥ 100 beds), and whether MDD treatment was provided by the same hospital in which the patient was first diagnosed with cancer (yes, no). Because no specific hypotheses were tested, *p*-values were not calculated; however, if 95% CIs between groups did not overlap, the difference in prescription frequencies was considered to be "significant." Missing prescription dates were imputed as the year and month of medical consultation, with the day as "99" (fictitious date). No inferential statistics were conducted. Netezza N2002-010 7.1.0.4.P2 (IBM, Armonk, NY, USA) was used as the data warehouse platform. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

3 Results

3.1 Demographic Characteristics

The matched cohort included 30,372 patients with cancer, of whom 1199 were diagnosed with MDD within the 18-month observation period and constituted the cancer group in this analysis (Fig. 1). The cancer group included 44.7% men and 55.3% women, with a mean age of 50.5 years; 91.2% of patients were aged < 65 years (Table 1). Patients were diagnosed with a broad range of cancers, with the numbers of patients with each cancer type ranging from two (larynx) to 230 (breast); 132 patients had cancer at multiple sites (Table 2). Of the 303,720 cancer-free individuals in the matched cohort, 4097 were diagnosed with MDD and constituted the cancer-free group (Fig. 1). The characteristics of the cancer-free group were very similar to the cancer group (47.2% men, 52.8% women; mean age 50.4 years, 90.8% aged < 65 years; Table 1), except that the proportion of insured workers was higher and the proportion of dependents was lower compared with the cancer group.

3.2 Treatment of MDD in the Cancer and Cancer-Free Groups

Compared with cancer-free patients, a significantly lower percentage of patients with cancer were treated with antidepressants (51.9% [95% CI 49.0–54.7] vs 58.2% [56.7–59.7]; Table 3). In particular, the frequency of SSRI prescription was significantly lower in the cancer group (16.7% [14.6–18.9]) than in the cancer-free group (27.4% [26.1–28.8]). Conversely, the frequency of NaSSA prescription was significantly higher in the cancer group (10.5% [8.8–12.4]) than in the cancer-free group (5.8% [5.1–6.6]). Prescription of other medications was generally more frequent in patients with cancer than in cancer-free patients. In particular, compared with cancer-free patients, patients with cancer were more frequently prescribed typical antipsychotics (6.3% [5.0–7.8] vs 0.9% [0.7–1.3]), atypical antipsychotics (7.1% [5.7–8.7] vs 4.3% [3.7–5.0]), and other anxiolytics (3.4% [2.5–4.6] vs 1.2% [0.9–1.6]). In contrast, BZDs were prescribed to patients with cancer at a significantly lower rate than cancer-free patients (37.9% [35.1–40.7] vs 47.1% [45.6–48.7]).

Table 1 Patient demographics in the adult cancer and cancer-free groups who developed major depressive disorder

Variable	Cancer group $N = 1199$	Cancer-free group $N = 4097$
Sex		
Male	536 (44.7) [41.9–47.6]	1934 (47.2) [45.7–48.7]
Female	663 (55.3) [52.4–58.1]	2163 (52.8) [51.3–54.3]
Age, years		
Mean (SD)	50.5 (10.9)	50.4 (10.6)
Median (min., max.)	51 (18, 74)	51 (18, 74)
< 40	171 (14.3) [12.3–16.4]	593 (14.5) [13.4–15.6]
40–64	922 (76.9) [74.4–79.3]	3128 (76.3) [75.0–77.6]
≥ 65	106 (8.8) (7.3–10.6)	376 (9.2) [8.3–10.1]
Membership		
Insured worker	687 (57.3) [54.4–60.1][a]	2574 (62.8) [61.3–64.3][a]
Dependent	512 (42.7) [39.9–45.6][a]	1523 (37.2) [35.7–38.7][a]

Values are expressed as *n* (%) [95% CI] unless mentioned otherwise

CI confidence interval, *max.* maximum, *min.* minimum, *SD* standard deviation

[a]Indicates significant difference between cancer and cancer-free groups based on non-overlapping 95% CIs

3.3 Effect of Sex on Treatment of MDD in Patients with Cancer

Among patients with cancer, women were more frequently prescribed antidepressants than men (Table 4). Selective serotonin reuptake inhibitors, NaSSAs, and alprazolam were more frequently prescribed to women than to men, although the difference was significant only for alprazolam (8.3% [6.3–10.7] vs 3.7% [2.3–5.7]). Conversely, SNRIs and conventional antidepressants were more frequently prescribed to men than to women, with the difference for conventional antidepressants being significant (12.7% [10.0–15.8] vs 7.4% [5.5–9.7]). Women were also more frequently prescribed other types of medication than men, although none of the differences reached statistical significance (Table 4). In the cancer-free group, men were prescribed antidepressants, particularly SNRIs and NaSSAs, and non-BZDs more frequently, and atypical antipsychotics less frequently, than women (Table 2 of the ESM).

3.4 Effect of Age on the Treatment of MDD in Patients with Cancer

Among patients with cancer, the prescription frequency of antidepressants decreased with increasing patient age (Table 5). Prescription of SSRIs was highest in younger patients (aged < 40 years), whereas prescription of conventional antidepressants was highest in older (aged ≥ 65 years) patients. Other medications were more commonly prescribed to middle-aged (40–64 years) patients than to older or younger patients, with a significant difference between middle-aged and younger subgroups (62.3% [59.0–65.4] vs 49.1% [41.4–56.9]). In particular, middle-aged patients were prescribed BZDs and non-BZDs at a higher frequency than older and younger patients, although these differences were not significant. Similar results were also seen in the cancer-free group (Table 2 of the ESM).

3.5 Effect of Hospital Characteristics on Treatment of MDD in Patients with Cancer

Larger hospitals (≥ 100 beds) prescribed SSRIs and BZDs at a significantly lower frequency than smaller hospitals (SSRIs: 15.4% [12.0–19.3] vs 35.4% [30.6–40.3]; BZDs: 28.5% [24.1–33.3] vs 43.5% [38.5–48.6]) (Table 6). Similar results were also seen in the cancer-free group (Table 2 of the ESM). In the cancer group, SSRIs and BZDs were prescribed significantly less frequently when the MDD treatment occurred at the same hospital as the cancer diagnosis (SSRIs: 15.0% [11.3–19.4] vs 32.4% [28.2–36.9]; BZDs: 24.1% [19.5–29.1] vs 44.1% [39.6–48.8]) (Table 7).

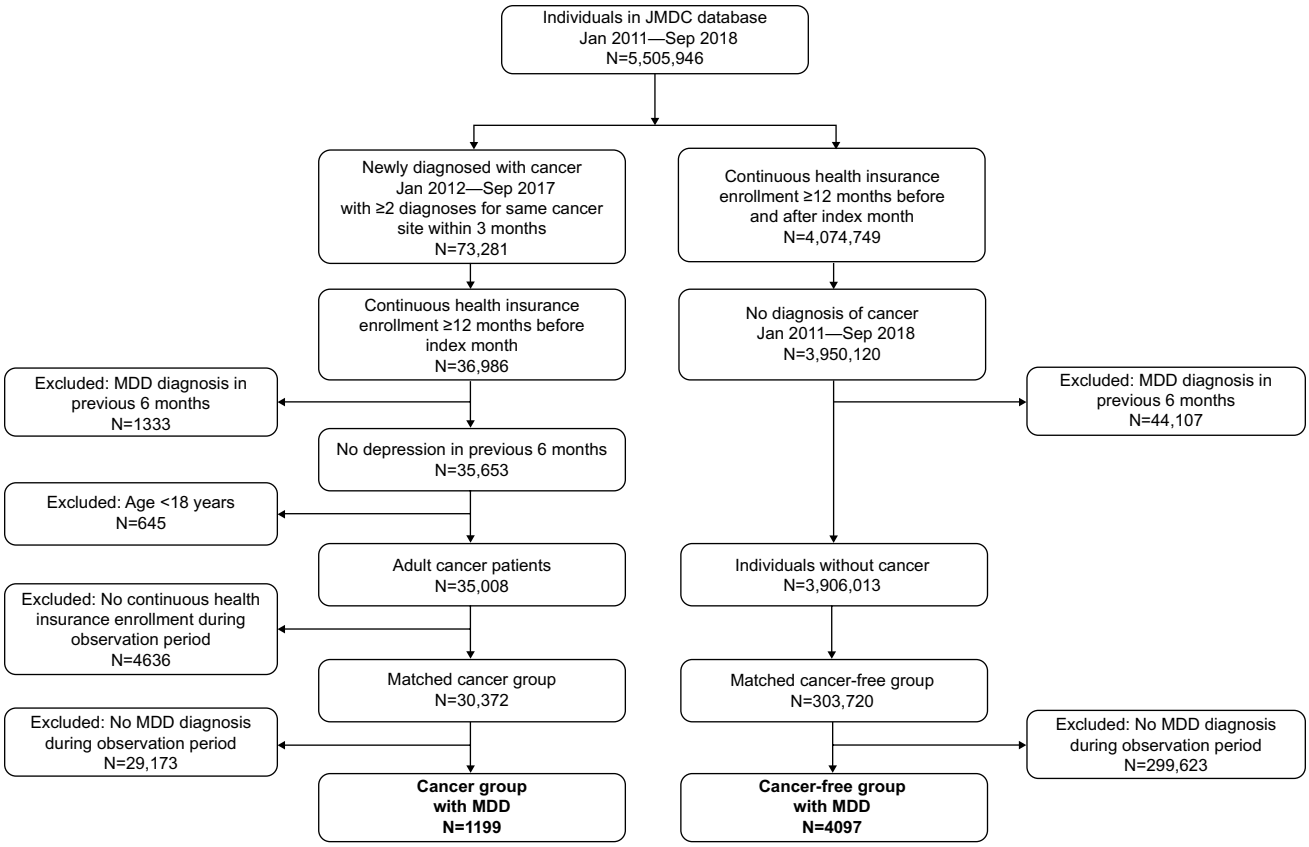

Fig. 1 Flow diagram of cancer and cancer-free groups. *MDD* major depressive disorder

4 Discussion

In this large Japanese database study, patients with cancer were treated for MDD with antidepressants at a significantly lower rate than cancer-free patients (51.9% [49.0–54.7] vs 58.2% [56.7–59.7]). The prescription of SSRIs was particularly low in patients with cancer compared with cancer-free patients, which may reflect clinicians' concerns about drug–drug interactions of SSRIs with certain cancer drugs [26] and worsening of adverse events of chemotherapy, especially nausea and appetite loss [34]. In contrast, NaSSAs were prescribed at a higher rate in patients with cancer, possibly because of their anti-nausea and sleep-inducing effects [35]. Instead of receiving antidepressants, patients with cancer tended to be prescribed other medications when diagnosed with MDD. Of these other medications, antipsychotics and other anxiolytics were prescribed to patients with cancer at higher rates than to cancer-free patients, possibly because some of these drugs have positive effects on nausea and insomnia [36, 37]. These results suggest that depression in Japanese patients with cancer may be undertreated; however, when medications are prescribed, they may be specifically chosen to address the particular needs of patients with cancer.

In the current analysis, antidepressants were prescribed to patients with cancer who developed MDD at a significantly lower rate than to cancer-free patients (51.9% vs 58.2%). Previous studies have examined the prescription of antidepressants and other psychotropic medications to patients with cancer [6, 38, 39], including a study using the JMDC database [39]. In that previous JMDC analysis, 45% of newly diagnosed patients with cancer in Japan were prescribed any type of psychotropic within 13 months of cancer diagnosis, most commonly BZDs; only 3.4% of patients were prescribed antidepressants [39]. However, the study did not analyze whether patients were diagnosed with depression or other mental disorders [39]. In other studies, a cross-sectional analysis of routine clinical data from multiple centers in Scotland reported that antidepressants were prescribed to 24% of patients with cancer who had *Diagnostic and Statistical Manual of Mental Disorders*-defined major depression and younger patients were more likely to receive treatment than older patients [6]. Similarly, in a multicenter study in the USA, 25% of patients with cancer who had depressive symptoms were prescribed SSRIs or SNRIs, with higher rates of prescription among patients aged < 55 years [38]. The variation in prescription frequency reported in these studies likely reflects differences in patient characteristics,

Table 2 Cancer site in the cancer group ($N = 1199$)

Cancer site	Value
Breast	230 (19.2)
Multiple categories	132 (11.0)
Colorectum	128 (10.7)
Stomach	87 (7.3)
Lung	80 (6.7)
Malignant lymphoma	50 (4.2)
Leukemia	46 (3.8)
Prostate gland	41 (3.4)
Pancreas	39 (3.3)
Thyroid gland	38 (3.2)
Ovary	35 (2.9)
Uterine cervix	33 (2.8)
Bladder	27 (2.3)
Other malignant neoplasm	27 (2.3)
Kidney, urinary tract (except bladder)	24 (2.0)
Oral cavity, pharynx	24 (2.0)
Brain, central nervous system	22 (1.8)
Skin	22 (1.8)
Uterine corpus	22 (1.8)
Esophagus	18 (1.5)
Liver	18 (1.5)
Other male genitalia	10 (0.8)
Multiple myeloma	10 (0.8)
Bone and articular cartilage	7 (0.6)
Gallbladder, bile duct	7 (0.6)
Mesothelium and soft tissue	7 (0.6)
Other intrathoracic organ	4 (0.3)
Nasal cavity, paranasal sinus, and middle ear	3 (0.3)
Other endocrine gland	3 (0.3)
Other female genitalia	3 (0.3)
Larynx	2 (0.2)
Eye	0 (0)
Small intestine	0 (0)
Other digestive organ	0 (0)

Data are *n* (%)

data sources, definitions of depression, and analysis methods. Our study is unique in that we identified patients from a matched cohort who developed MDD in the months leading up to or after cancer diagnosis to examine how depression is treated in patients with cancer compared with cancer-free patients. Use of a matched cohort as the data source minimizes the confounding effect of factors other than cancer that might influence prescription patterns, such as age.

Consistent with previous studies [6, 38–40], we found that women with cancer were more likely than men to be prescribed antidepressants or other medications. The type of medication prescribed to women may be selected to avoid pharmacokinetic interactions with anticancer drugs such as tamoxifen for breast cancer [26], or to help counteract chemotherapy side effects such as nausea that are more common in women [41]. We also found that the prescription of antidepressants decreased as patients aged, again consistent with previous findings [6, 38]. The lower rates of prescription to older patients may result from concerns regarding polypharmacy for comorbidities in addition to cancer [42] or from the understanding that antidepressants may be less efficacious in patients aged older than 65 years [43]. The higher prescription rate of conventional antidepressants (which includes tricyclic antidepressants) among older patients may reflect their successful use during a previous depressive episode that occurred more than a year before cancer diagnosis (and, therefore, outside the exclusion period for this study). Prescription of conventional antidepressants was also high in older patients in the cancer-free group (data not shown), perhaps because tricyclic antidepressants are a well-characterized class of drug used for depression before newer antidepressants such as SSRIs and SNRIs became available and are generally considered effective for pain management in elderly patients [44]. Selective serotonin reuptake inhibitors and BZDs were prescribed less frequently when the patient was treated for MDD at a large hospital or at the same hospital where they received their cancer diagnosis. Compared with smaller hospitals or clinics, large hospitals are likely to have both cancer and psychiatry and/or psychology facilities and, therefore, may be better placed to consider the patient's overall treatment needs for both cancer and MDD when prescribing medication. Our results also suggest that physicians in smaller hospitals, which may include mental health clinics, may treat MDD similarly in both patients with cancer and patients without cancer, perhaps because they are less likely to consider the patients' full medical background. In addition, there is limited evidence to guide the choice of treatment for MDD in patients with cancer [45].

The results of this study are strengthened by the use of a matched cohort of patients with cancer and cancer-free patients identified from a nationwide health insurance database of primarily working-age individuals. The relatively large sample size of the cancer group with MDD allowed analysis of the effects of age, sex, and hospital type on the choice of medication. The study also included a broad range of antidepressants and other medications commonly prescribed to patients with depression.

4.1 Study Limitations

Limitations of the study include the analysis of drugs by general category, not individually and the fact that medication

Table 3 Frequency of prescription for each drug class after observation start in adult cancer and cancer-free groups

Drug class/name	Adult cancer group $N = 1199$	Cancer-free group $N = 4097$
No treatment	143 (11.9) (10.1–13.9)[a]	640 (15.6) [14.5–16.8][a]
Antidepressants	622 (51.9) [49.0–54.7][a]	2385 (58.2) [56.7–59.7][a]
SSRI	200 (16.7) [14.6–18.9][a]	1124 (27.4) [26.1–28.8][a]
SNRI	162 (13.5) [11.6–15.6]	491 (12.0) [11.0–13.0]
NaSSA	126 (10.5) [8.8–12.4][a]	239 (5.8) [5.1–6.6][a]
Conventional	117 (9.8) [8.1–11.6]	446 (10.9) [9.9–11.9]
Sulpiride	8 (0.7) [0.3–1.3]	40 (1.0) [0.7–1.3]
Alprazolam	75 (6.3) [5.0–7.8]	327 (8.0) [7.2–8.9]
Other medications	715 (59.6) [56.8–62.4]	2371 (57.9) [56.3–59.4]
BZD	454 (37.9) [35.1–40.7][a]	1931 (47.1) [45.6–48.7][a]
Non-BZD	148 (12.3) [10.5–14.3]	461 (11.3) [10.3–12.3]
Other sleep medication	53 (4.4) [3.3–5.7]	124 (3.0) [2.5–3.6]
Other non-barbiturate (single agent)	0 (0.0) [0.0–0.3]	1 (0.0) [0.0–0.1]
Other anxiolytic	41 (3.4) [2.5–4.6][a]	50 (1.2) [0.9–1.6][a]
Atypical antipsychotic	85 (7.1) [5.7–8.7][a]	178 (4.3) [3.7–5.0][a]
Barbiturate (single agent)	1 (0.1) [0.0–0.5]	5 (0.1) [0.0–0.3]
Typical antipsychotic	75 (6.3) [5.0–7.8][a]	38 (0.9) [0.7–1.3][a]
Herbal hypnotics/sedatives	0 (0.0) [0.0–0.3]	0 (0.0) [0.0–0.1]
Mood stabilizers	2 (0.2) [0.0–0.6]	28 (0.7) [0.5–1.0]

Values are expressed as *n* (%) [95% CI]

BZD benzodiazepine, *CI* confidence interval, *NaSSA* noradrenergic and specific serotonergic antidepressant, *SNRI* serotonin noradrenaline reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor

[a]Indicates significant difference between cancer and cancer-free groups based on non-overlapping 95% CIs

combinations (e.g., an SSRI in combination with a BZD) and changes over time were not analyzed. In addition, the possible influence of other patient factors (e.g., severity of depression, history of MDD more than 12 months before the index month, and psychiatric or other comorbidities) or physician factors (e.g., psychiatry or oncology specialty) on medication choice was not assessed or controlled for. Furthermore, although prescriptions were concurrent with MDD diagnosis, it is possible that drugs were prescribed for other conditions. Although the influence of hospital size based on the number of beds was examined, the exact type of hospital (e.g., mental health clinic, breast cancer clinic) could not be determined. Moreover, the study focused on pharmacotherapy, and the role of other treatment modalities such as psychotherapy was not examined. Although the database includes patients aged 18–74 years, cancer and other comorbidities are more common in older adults, and future studies with larger sample sizes of older adults are required to fully examine how depression is treated in elderly patients with cancer.

4.2 Clinical Implications

Depression in patients with cancer is highly prevalent and, if left untreated, can adversely affect patient outcomes. Given that antidepressant treatment is of benefit even in mild depression [25], clinicians should consider individualized medical treatment of patients with cancer and depression.

5 Conclusions

Our study indicates that patients with cancer in Japan may be undertreated for MDD compared with cancer-free patients. However, our results also suggest that medications, when prescribed, are being chosen according to individual patient needs, such as minimizing adverse effects and avoiding drug–drug interactions, made possible by a broad range of drugs for depression with different mechanisms of action. Nevertheless, although antidepressants and other depression treatments are generally effective in patients with cancer, further data on the relative efficacy and safety of specific

Table 4 Frequency of prescription for each drug class after observation start in men and women in the adult cancer group

Drug class/name	Men *N* = 536	Women *N* = 663
No treatment	70 (13.1) [10.3–16.2]	73 (11.0) [8.7–13.6]
Antidepressants	269 (50.2) [45.9–54.5]	353 (53.2) [49.4–57.1]
SSRI	76 (14.2) [11.3–17.4]	124 (18.7) [15.8–21.9]
SNRI	84 (15.7) [12.7–19.0]	78 (11.8) [9.4–14.5]
NaSSA	45 (8.4) [6.2–11.1]	81 (12.2) [9.8–15.0]
Conventional	68 (12.7) [10.0–15.8][a]	49 (7.4) [5.5–9.7][a]
Sulpiride	6 (1.1) [0.4–2.4]	2 (0.3) [0.0–1.1]
Alprazolam	20 (3.7) [2.3–5.7][a]	55 (8.3) [6.3–10.7][a]
Other medications	308 (57.5) [53.2–61.7]	407 (61.4) [57.6–65.1]
BZD	201 (37.5) [33.4–41.8]	253 (38.2) [34.4–42.0]
Non-BZD	64 (11.9) [9.3–15.0]	84 (12.7) [10.2–15.4]
Other sleep medication	28 (5.2) [3.5–7.5]	25 (3.8) [2.5–5.5]
Other non-barbiturate (single agent)	0 (0.0) [0.0–0.7]	0 (0.0) [0.0–0.6]
Other anxiolytic	21 (3.9) [2.4–5.9]	20 (3.0) [1.9–4.6]
Atypical antipsychotic	35 (6.5) [4.6–9.0]	50 (7.5) [5.6–9.8]
Barbiturate (single agent)	0 (0.0) [0.0–0.7]	1 (0.2) [0.0–0.8]
Typical antipsychotic	28 (5.2) [3.5–7.5]	47 (7.1) [5.3–9.3]
Herbal hypnotics/sedatives	0 (0.0) [0.0–0.7]	0 (0.0) [0.0–0.6]
Mood stabilizers	1 (0.2) [0.0–1.0]	1 (0.2) [0.0–0.8]

Values are expressed as *n* (%) [95% CI]

BZD benzodiazepine, *CI* confidence interval, *NaSSA* noradrenergic and specific serotonergic antidepressant, *SNRI* serotonin noradrenaline reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor

[a]Indicates significant difference between men and women based on non-overlapping 95% CIs

Table 5 Frequency of prescription for each drug class after observation start by age in the adult cancer group

Drug class/name	< 40 years old *N* = 171	40–64 years old *N* = 922	≥ 65 years old *N* = 106
No treatment	29 (17.0) [11.7–23.4]	102 (11.1) [9.1–13.3]	12 (11.3) [6.0–18.9]
Antidepressants	95 (55.6) [47.8–63.1]	475 (51.5) [48.2–54.8]	52 (49.1) [39.2–59.0]
SSRI	39 (22.8) [16.7–29.8]	148 (16.1) [13.7–18.6]	13 (12.3) [6.7–20.1]
SNRI	21 (12.3) [7.8–18.2]	126 (13.7) [11.5–16.1]	15 (14.2) [8.1–22.3]
NaSSA	18 (10.5) [6.4–16.1]	101 (11.0) [9.0–13.2]	7 (6.6) [2.7–13.1]
Conventional	11 (6.4) [3.3–11.2]	89 (9.7) [7.8–11.7]	17 (16.0) [9.6–24.4]
Sulpiride	2 (1.2) [0.1–4.2]	5 (0.5) [0.2–1.3]	1 (0.9) [0.0–5.1]
Alprazolam	15 (8.8) [5.0–14.1]	56 (6.1) [4.6–7.8]	4 (3.8) [1.0–9.4]
Other medications	84 (49.1) [41.4–56.9][a]	574 (62.3) [59.0–65.4][a]	57 (53.8) [43.8–63.5]
BZD	55 (32.2) [25.2–39.7]	369 (40.0) [36.8–43.3]	30 (28.3) [20.0–37.9]
Non-BZD	14 (8.2) [4.5–13.4]	122 (13.2) [11.1–15.6]	12 (11.3) [6.0–18.9]
Other sleep medication	4 (2.3) [0.6–5.9]	41 (4.4) [3.2–6.0]	8 (7.5) [3.3–14.3]
Other non-barbiturate (single agent)	0 (0.0) [0.0–2.1]	0 (0.0) [0.0–0.4]	0 (0.0) [0.0–3.4]
Other anxiolytic	9 (5.3) [2.4–9.8]	25 (2.7) [1.8–4.0]	7 (6.6) [2.7–13.1]
Atypical antipsychotic	13 (7.6) [4.1–12.6]	65 (7.0) [5.5–8.9]	7 (6.6) [2.7–13.1]
Barbiturate (single agent)	0 (0.0) [0.0–2.1]	1 (0.1) [0.0–0.6]	0 (0.0) [0.0–3.4]
Typical antipsychotic	11 (6.4) [3.3–11.2]	58 (6.3) [4.8–8.1]	6 (5.7) [2.1–11.9]
Herbal hypnotics/sedatives	0 (0.0) [0.0–2.1]	0 (0.0) [0.0–0.4]	0 (0.0) [0.0–3.4]
Mood stabilizers	0 (0.0) [0.0–2.1]	1 (0.1) [0.0–0.6]	1 (0.9) [0.0–5.1]

Values are expressed as *n* (%) [95% CI]

BZD benzodiazepine, *CI* confidence interval, *NaSSA* noradrenergic and specific serotonergic antidepressant, *SNRI* serotonin noradrenaline reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor

[a]Indicates significant difference between age subgroups 40–64 years and < 40 years based on non-overlapping 95% CIs

Table 6 Frequency of prescription for each drug class after observation start by the number of beds in the hospital that provided depression treatment in adult patients with cancer

Drug class/name	< 100 beds *N* = 393	≥ 100 beds *N* = 396
Antidepressants	330 (84.0) [80.0–87.5][a]	292 (73.7) [69.1–78.0][a]
SSRI	139 (35.4) [30.6–40.3][a]	61 (15.4) [12.0–19.3][a]
SNRI	66 (16.8) [13.2–20.9]	96 (24.2) [20.1–28.8]
NaSSA	68 (17.3) [13.7–21.4]	58 (14.6) [11.3–18.5]
Conventional	56 (14.2) [10.9–18.1]	61 (15.4) [12.0–19.3]
Sulpiride	8 (2.0) [0.9–4.0]	0 (0.0) [0.0–0.9]
Alprazolam	40 (10.2) [7.4–13.6]	35 (8.8) [6.2–12.1]
Other medications	235 (59.8) [54.8–64.7]	213 (53.8) [48.7–58.8]
BZD	171 (43.5) [38.5–48.6][a]	113 (28.5) [24.1–33.3][a]
Non-BZD	51 (13.0) [9.8–16.7]	63 (15.9) [12.4–19.9]
Other sleep medication	18 (4.6) [2.7–7.1]	23 (5.8) [3.7–8.6]
Other non-barbiturate (single agent)	0 (0.0) [0.0–0.9]	0 (0.0) [0.0–0.9]
Other anxiolytic	9 (2.3) [1.1–4.3]	13 (3.3) [1.8–5.5]
Atypical antipsychotic	13 (3.3) [1.8–5.6]	26 (6.6) [4.3–9.5]
Barbiturate (single agent)	0 (0.0) [0.0–0.9]	0 (0.0) [0.0–0.9]
Typical antipsychotic	19 (4.8) [2.9–7.4]	21 (5.3) [3.3–8.0]
Herbal hypnotics/sedatives	0 (0.0) [0.0–0.9]	0 (0.0) [0.0–0.9]
Mood stabilizers	1 (0.3) [0.0–1.4]	1 (0.3) [0.0–1.4]

Values are expressed as *n* (%) [95% CI]

BZD benzodiazepine, *CI* confidence interval, *NaSSA* noradrenergic and specific serotonergic antidepressant, *SNRI* serotonin noradrenaline reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor

[a]Indicates significant difference between < 100 beds and ≥ 100 beds based on non-overlapping 95% CIs

Table 7 Frequency of prescription for each drug class after observation start by whether major depressive disorder (MDD) treatment was provided by the same hospital in which the patient was first diagnosed with cancer

Drug class/name	Same hospital for cancer and MDD diagnoses *N* = 320	Different hospital for cancer and MDD diagnoses *N* = 469
Antidepressants	234 (73.1) [67.9–77.9][a]	388 (82.7) [79.0–86.0][a]
SSRI	48 (15.0) [11.3–19.4][a]	152 (32.4) [28.2–36.9][a]
SNRI	69 (21.6) [17.2–26.5]	93 (19.8) [16.3–23.7]
NaSSA	63 (19.7) [15.5–24.5]	63 (13.4) [10.5–16.9]
Conventional	41 (12.8) [9.4–17.0]	76 (16.2) [13.0–19.9]
Sulpiride	0 (0.0) [0.0–1.1]	8 (1.7) [0.7–3.3]
Alprazolam	26 (8.1) [5.4–11.7]	49 (10.4) [7.8–13.6]
Other medications	180 (56.3) [50.6–61.8]	268 (57.1) [52.5–61.7]
BZD	77 (24.1) [19.5–29.1][a]	207 (44.1) [39.6–48.8][a]
Non-BZD	52 (16.3) [12.4–20.8]	62 (13.2) [10.3–16.6]
Other sleep medication	16 (5.0) [2.9–8.0]	25 (5.3) [3.5–7.8]
Other non-barbiturate (single agent)	0 (0.0) [0.0–1.1]	0 (0.0) [0.0–0.8]
Other anxiolytic	15 (4.7) [2.6–7.6]	7 (1.5) [0.6–3.1]
Atypical antipsychotic	14 (4.4) [2.4–7.2]	25 (5.3) [3.5–7.8]
Barbiturate (single agent)	0 (0.0) [0.0–1.1]	0 (0.0) [0.0–0.8]
Typical antipsychotic	29 (9.1) [6.2–12.8][a]	11 (2.3) [1.2–4.2][a]
Herbal hypnotics/sedatives	0 (0.0) [0.0–1.1]	0 (0.0) [0.0–0.8]
Mood stabilizers	0 (0.0) [0.0–1.1]	2 (0.4) [0.1–1.5]

Values are expressed as *n* (%) [95 % CI]

BZD benzodiazepine, *CI* confidence interval, *MDD* major depressive disorder, *NaSSA* noradrenergic and specific serotonergic antidepressant, *SNRI* serotonin noradrenaline reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor

[a]Indicates significant difference between subgroups based on non-overlapping 95% CIs

drugs in this patient population are needed to help inform the choice of medication [45].

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Declarations

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Conflict of interest Tatsuo Akechi has received lecture fees from Astellas, AstraZeneca, Daiichi-Sankyo, Dainippon-Sumitomo, Eisai, Hisamitsu, Kyowa-hakko Kirin, Kyowa, Eli Lilly, MSD, Meiji-seika Pharma, Mochida, Mundipharma, Otsuka, Pfizer, Shionogi, Terumo, and Tsumura, and has received research funds from Daiichi-Sankyo, Eisai, FUJIFILM RI Pharma, Eli Lilly, MSD, Novartis, Otsuka, Shionogi, and Tanabe-Mitsubishi. Izumi Mishiro, Shinji Fujimoto, and Katsuhito Murase are employees of Takeda Pharmaceutical Company Limited.

Ethics approval This study used anonymized information from the JMDC database; therefore, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan, institutional ethics approval was not required.

Consent to participate This study used anonymized information from the JMDC database; therefore, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan, informed consent was not required.

Consent for publication Not applicable.

Availability of data and material The data that support the findings of this study are available from JMDC Inc. but were used under license for the current study; therefore, restrictions apply and the data are not publicly available. For inquiries about access to the data set used in this study, please contact JMDC (https://www.jmdc.co.jp).

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Author contributions All authors were investigators in the study and participated in the study design, interpretation of the study results, and in the drafting, critical revision, and approval of the final version of the manuscript. IM conducted the statistical analysis.

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