General Hospital Psychiatry 60 (2019) 98–110

Contents lists available at ScienceDirect

General Hospital Psychiatry

journal homepage: www.elsevier.com/locate/genhospsych

Review article

Interventions to prevent suicidal behavior and ideation for patients with cancer: A systematic review

Yoshitaka Kawashima[a,b,*], Naohiro Yonemoto[a,c], Masatoshi Inagaki[d], Keisuke Inoue[e], Chiaki Kawanishi[f], Mitsuhiko Yamada[a]

[a] Department of Neuropsychopharmacology, National Institute of Mental Health, National Center of Neurology and Psychiatry, 4-1-1, Ogawahigashimachi, Kodaira, Tokyo 187-8553, Japan
[b] Clinical Psychology Course, Department of Psycho-Social Studies, School of Arts and Letters, Meiji University, 1-1, Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8301, Japan
[c] Department of Biostatistics, School of Public Health, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan
[d] Department of Psychiatry, Faculty of Medicine, Shimane University, 89-1, Enyacho, Izumo City, Shimane 693-8501, Japan
[e] Psychiatric Center, Yokohama City University Medical Center, 4-57, Urafune-cho, Minami-ku, Yokohama 232-0024, Japan
[f] Department of Neuropsychiatry, Sapporo Medical University Graduate School of Medicine, S1 W17, Chuo-ku, Sapporo 060-8556, Japan

ARTICLE INFO

Keywords:
Cancer
Intervention
Oncology
Self-harm
Suicide
Systematic review

ABSTRACT

Objective: This study aimed to summarize interventions for suicide prevention in patients with cancer and highlight any methodological issues.
Methods: We searched PubMed, PsycINFO, CINAHL, and the Cochrane database from their inception until July 2018. Additionally, we manually searched the references of included studies and recent systematic reviews of psychotherapy, antidepressants, and collaborative care for cancer patients with depression.
Results: Of the 1365 retrieved articles, 11 randomized controlled trials and 11 intervention studies met the inclusion criteria. These were categorized by type of intervention: psychotherapy, pharmacotherapy, integrated collaborative care, muscle relaxation and therapeutic walking, and cancer treatment. The trials showed little evidence to confirm the effects of suicide prevention strategies. Seven trials were designed to assess the efficacy of interventions treating depression. In all studies, suicidal behavior or ideation was reported as one of the secondary outcomes. Three trials did not report information about suicidal ideation, despite assessing depressive symptoms using scales that contained suicidal ideation items. Most trials demonstrated inadequate study quality.
Conclusions: Our review summarized interventions for suicide prevention in patients with cancer and revealed methodological issues. The findings highlighted a need to explore new treatment strategies that focus on unique suicide risk factors among patients with cancer.

1. Introduction

Patients with cancer are at an increased risk of death from suicide. Previous population-based cancer registry studies have demonstrated that the incidence of suicide among cancer patients is approximately double (standardized mortality ratio [SMR] = 1.8–2.6), compared with the general population [1–4]. In particular, cancer patients within the first three months of diagnosis have a higher suicide rate, relative to patients having a diagnosis of cancer for over three months, with a SMR of 5.75 [5]. A large cohort study in the United States reported that suicide rates were higher among patients with lung and bronchus or stomach cancers than in the general population, with SMRs of 5.74 and 4.68, respectively [4]. One study found that 8.6% of cancer outpatients registered with a palliative care unit had suicidal ideation [6]. Thus, cancer presents a risk for suicide, and prevention of suicide in cancer patients is a very important task.

It is well known that patients with cancer may have depressive disorder; however, the prevalence of depressive disorder appears to be much less common that expected among patients with cancer. A meta-analysis of interview-based studies revealed that the same combination of mood disorders occurred in 30%–40% of patients with cancer in hospital settings [7]. A psychological autopsy study reported 80% of patients with cancer that died by suicide had any depressive symptoms, which suggests depression is related to suicide in this patient

* Corresponding author.
E-mail addresses: ykawashima@meiji.ac.jp (Y. Kawashima), minagaki@med.shimane-u.ac.jp (M. Inagaki), kinoue@yokohama-cu.ac.jp (K. Inoue), mitsuhiko_yamada@ncnp.go.jp (M. Yamada).

https://doi.org/10.1016/j.genhosppsych.2019.07.003
Received 29 March 2018; Received in revised form 5 June 2019; Accepted 3 July 2019

population [8]. In addition, a retrospective hospital study showed that approximately 60% of patients with cancer who were referred to the psychiatry division because of risk for suicide were diagnosed with mood disorder [9].

A recent meta-analysis suggested that there is insufficient evidence for treatment for depressive symptoms among patients with cancer, and the effect of antidepressants for patients with cancer suffering from depression was unclear [10]. Additionally, there is no sufficient high-quality evidence that psychotherapy is effective for reducing depressive symptoms among patients with cancer [11]. A collaborative care intervention for depressive patients with cancer was effective in reducing depressive symptoms compared with treatment as usual [12]. However, an issue with that intervention was that the joint participation of general practitioners and specialist care physicians in collaborative care management for depression was promoted, but not actually achieved in cancer care [13].

Patients with cancer also show a greater frequency of some psychiatric disorders and other dysfunction than individuals without cancer. A recent systematic review reported that the prevalence of substance use was 2%–35% among patients with cancer [14]. In addition, a meta-analysis of interview-based studies showed the prevalence of adjustment disorder was 15%–19% among patients with cancer, and that of anxiety disorders was about 10% [7]. A cohort study demonstrated that compared with women without cancer, breast cancer survivors had more neurocognitive dysfunction, sexual dysfunction, and psychiatric disorders (e.g., sleep, stress-related/post-traumatic stress, somatization, bipolar, and obsessive-compulsive disorders) [15]. Unfortunately, there was insufficient high-quality evidence for effective interventions for traumatic stress symptoms [16] and substance use [14].

Patients with cancer are a unique population, and we cannot simply apply what we know from other groups to this population. Suicide risk factors among patients with cancer also differ from those of individuals without cancer and patients with cancer who are depressive. When considering suicide prevention for patients with cancer, it may be necessary to use new strategies that focus on unique suicide risk factors for this population. Previous suicide attempts, psychiatric disorders, financial loss, chronic pain, and a family history of suicide are generic risk factors for suicide [17]. Among patients with depression, previous attempted suicide, more severe depression, hopelessness, misuse of alcohol and drugs, and male sex were reported to be major suicide risk factors [18]. However, patients with cancer have risk factors, such as time since cancer diagnosis disclosure [5,19], types of cancer with high fatality [20], and advanced stage of cancer [21].

Some practice guidelines for cancer patients recommend assessment of suicidal ideation using a depression rating scale. The guideline published by the American Society of Clinical Oncology recommends periodic screening of depressive symptoms throughout the care period using the Patient Health Questionnaire-9 (PHQ-9) [22]. One item on the PHQ-9 assesses possible suicidal ideation and suicidal behavior. Also, a recent Canadian clinical practice guideline for the management of depression in adult cancer patients recommends assessment of suicidal ideation and suicidal intent using depression rating scales such as the PHQ-9 and Beck Depression Inventory II, and referral to specialty mental health services for cancer patients with depression [23]. However, the recommendation of assessment of suicidal ideation found in the above mentioned two guidelines were developed by the expert consensus process, and it is unclear whether these recommended interventions are effective in reducing suicidality among cancer patients.

Some systematic and literature reviews for suicide in cancer patients have been published [24–26] and others are still works in progress [27]. These previous reviews have reported the prevalence of suicide and the risk factors of suicide among cancer populations. Additionally, there have been several reviews of suicide risk reduction interventions in various populations [28–30]. However, no review has yet reported the effects of a suicide prevention specifically in a cancer population. Although adequate care for patients with cancer is critical to prevent suicide, there is little evidence to support a rationale for the development of suicide prevention interventions for these patients.

The objective of the present study was to summarize interventions for suicide prevention for patients with cancer and identify methodological issues.

2. Methods

We registered the study protocol with PROSPERO (CRD: 42016047371) [31]. The systematic review was conducted and reported in accordance with the published protocol and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [32].

2.1. Search strategy

We conducted a search of PubMed (from 1949), PsycINFO (from 1887), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (from 1981), and the Cochrane database (from 1993) from their inception until July 2018. The search terms were (cancer* OR carcinoma* OR sarcoma* OR oncolog* OR malignancy OR malignant-tumor OR malignant-neoplasm OR malignant-growth OR vicious-tumor or palliative-care) AND (suicid* OR self-harm* OR selfharm* OR self-poison* OR selfpoison* OR overdose* OR over-dose* OR self-injur* OR selfinjur* OR self-mutilation* OR selfmutilation* OR automutilation* OR auto-mutilation* OR self-destructive* OR selfdestructive*) AND (trial* OR interven* OR randomiz*). In addition, we manually searched the reference lists of included studies and of four recent systematic reviews of antidepressant [10], psychotherapy [11,33], and collaborative care [12] interventions for cancer patients with depression.

2.2. Study eligibility

2.2.1. Inclusion criteria

Studies were included if they met the following criteria. (1) The study population was patients with cancer; this study included articles in which the study population was patients with cancer because our objective was to examine the effect of interventions for this patient population. (2) The study was a randomized controlled trial (RCT) or another intervention study that prospectively examined the effect of intervention, such as single-arm trials or quasi-experimental studies; we included designs such as RCTs, intervention studies (prospective single-arm trials, nonrandomized studies, and quasi-experimental studies) because these designs were well-controlled studies compared with observational studies. Therefore, retrospective observational studies, case series, and case reports were excluded. (3) Suicide death, suicide attempt, self-harm, suicidal ideation were reported in the manuscript as the primary, secondary, or other outcome. We collected information about the definitions of outcomes in the included studies, because these definitions would be operationalized for each outcome.

We included studies that were solely focused on cancer treatment (e.g., chemotherapy or radiation therapy) because cancer treatment could lead to decreased suicide risk, even if suicide risk was not the main focus of treatment.

2.3. Review process

All records identified from searches of the electronic databases and manual searches were loaded into ENDNOTE version X6 (Thomson Reuters, USA). We then removed duplicate records and screened the titles and abstracts to remove records that met the exclusion criteria. Full-text articles of potentially eligible studies were reviewed and identified according to the inclusion and exclusion criteria. The record screening and assessment of full-text articles were independently conducted by at least two of the authors. Any disagreements were discussed

with a third author and resolved by consensus.

2.4. Data extraction

Data extraction was carried out independently by at least two authors. We extracted from identified studies basic bibliographic data and information about study location, study design, inclusion criteria, exclusion criteria, participant characteristics (age, type and severity of cancer), number of participants, type of intervention, trial setting, follow-up period, primary and secondary outcomes, adverse events, and the effect of the intervention.

2.5. Assessment of bias

We assessed the risk of bias of the included studies according to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [34]. At least two authors made independent judgments about random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other types of bias. Disagreements were discussed with a third author and resolved by consensus.

3. Results

3.1. Searches and article selection

The search strategy identified 1563 records through database searches and other searches (Fig. 1): PubMed (n = 1094), PsycINFO (n = 232), CINAHL (n = 167), the Cochrane database (n = 3), and manual searches (n = 67). Of these 1563 records, 1365 articles were

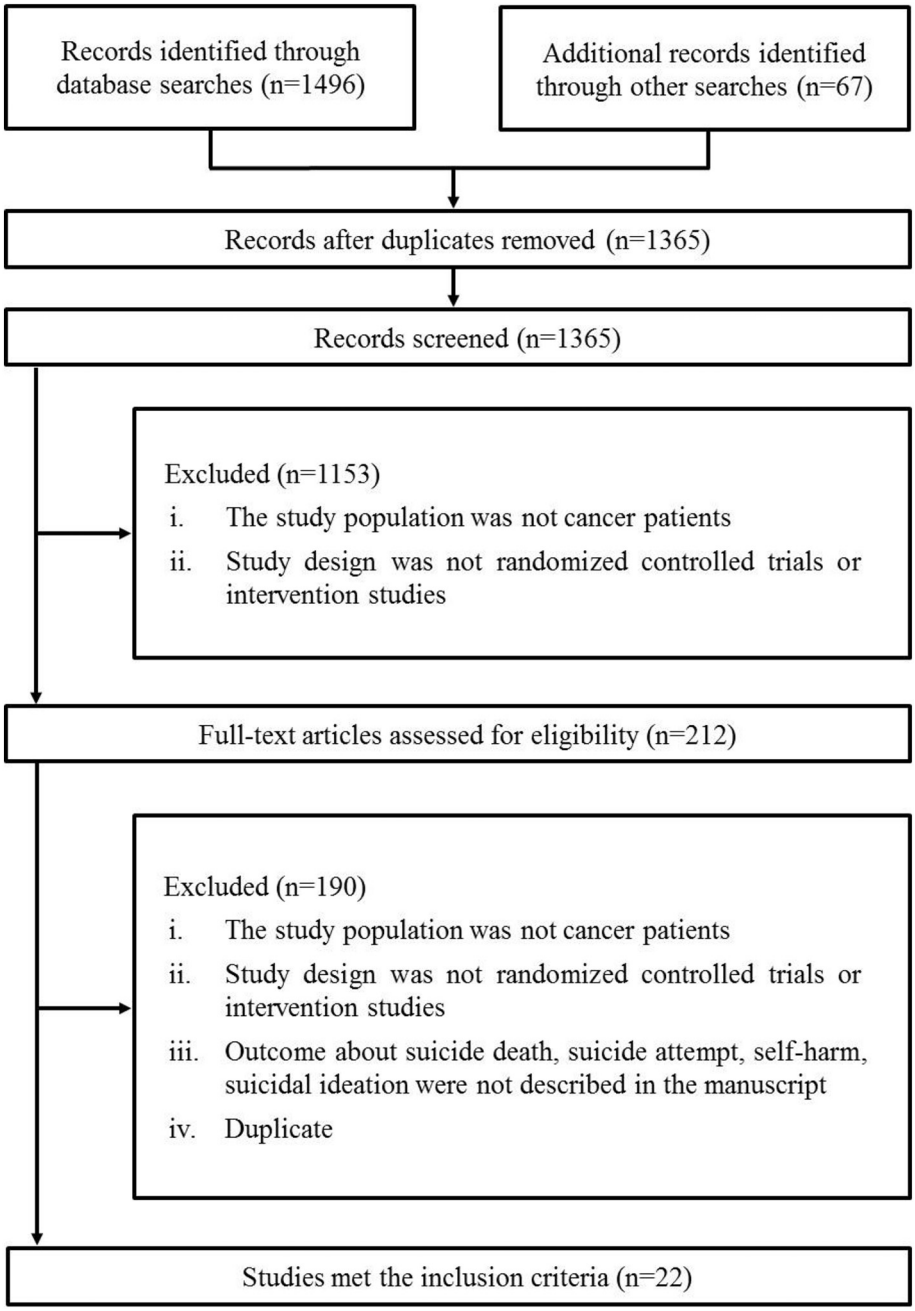

Fig. 1. Study selection process.

Table 1
Characteristics of study participants in 8 randomized controlled trials.

Author, year	Country	Inclusion criteria	Exclusion criteria	N of participants	Age, mean (SD)	Type of cancer, n (%)	Severity of cancer, n (%)
Psychotherapy							
Chochinov et al., 2011 [35]	Canada, USA, Australia	Aged ≥18 years, terminal prognosis with a life expectancy of 6 months or less, receiving palliative care, willing to commit to three or four contacts over about 7–10 days	Delirious or otherwise cognitively impaired, too ill to complete the requirements of the protocol, unable to speak and read English	Dignity therapy = 165 Standard palliative care = 140 Client-centered care = 136	Dignity therapy = 64.2(14.6), Standard palliative care = 66.7(14.2), Client-centered care = 64.3(14.3)	Gastrointestinal = 108(33%), Genitourinary = 26(8%), Lung = 48(15%), Breast = 29(9%), Gynaecological = 11(3%), Miscellaneous solid tumours = 67(21%), Haematological = 14(4%), Brain = 9(3%), Other = 67(21%)	All participants had a terminal prognosis
Hopko et al., 2013 [36]	USA	Aged ≥18 years, diagnosis of breast cancer, a principal consensus diagnosis of major depression of moderate severity	Bipolar disorder, psychosis, mental retardation, current alcohol or drug dependence, a principal diagnosis other than major depression	Behavioral activation therapy = 42 Problem solving therapy = 38	55.4(11.9)[b]	Breast = 80(100%)	Stage 0 = –[a] (26%), Stage I = –[a] (28%), Stage II = –[a] (32%), Stage III = –[a] (11%), Stage IV = –[a] (3%)
Psychiatric pharmacotherapy							
Musselman et al., 2006 [37]	USA	Aged 18–75 years, female outpatient, diagnosis of breast cancer, major depression or adjustment disorder with depressed mood for at least 2 months, HAM-D score ≥ 14, cancer treatment within the last 5 years	Pregnant and lactating women, serious suicidal risk, history of urinary retention or any serious cardiac disease, intracranial metastases, other serious illness, psychiatric disorder including organic mental disorder, alcohol/substance use disorder, paranoid/psychotic symptoms, bipolar disorder	Paroxetine = 13 Desipramine = 11 Placebo = 11	Paroxetine = 54.6(12.7), Desipramine = 47.7(9.0), Placebo = 58.6(12.8)	Breast = 35(100%)	Stage I = 10(29%), Stage II = 17(49%), Stage III = 2(6%), Stage IV = 6(17%)
Lydiatt et al., 2008 [38]	USA	Aged ≥19 years, newly diagnosed or recurrent cancers of the oral cavity, larynx, pharynx, neck, and paranasal sinuses requiring more than limited excision	MMSE score of < 24, having suicidal risk, major depressive disorder, psychosis, schizophrenia; currently taking an antidepressant medication, having a contraindication to taking citalopram	Citalopram = 15 Placebo = 13	61.0(10.6)[b]	Oral cavity = 6(24%), Oropharynx = 6(24%), Larynx = 7(28%), Hypopharynx = 1(4%), Unknown primary = 4(16%), Ear = 1(4%)	Stage II = 3(12%), Stage III–IV = 22(88%)
Fan et al., 2017 [39]	China	Aged 18–70 years, first diagnosis of cancer within 3 months, basic communication capability	Cardiorespiratory diseases, drug addiction history or sedative–hypnotic drug use, neuropsychiatric or cognitive diseases or a related treatment history, suicidal	Ketamine = 20 Midazolam = 19	Ketamine = 46.8(14.0) Midazolam = 44.7(15.1)	Lung cancer = 7(19%) Gastric cancer = 12(32%) Bone cancer = 7(19%)	All participants were first diagnosis of cancer within 3 months.

(*continued on next page*)

Table 1 (*continued*)

Author, year	Country	Inclusion criteria	Exclusion criteria	N of participants	Age, mean (SD)	Type of cancer, n (%)	Severity of cancer, n (%)
			attempts or ideation before cancer diagnosis, family history of psychiatric history			Pancreas cancer = 11(30%)	
Integrated collaborative care							
Strong et al., 2008 [40]	UK	Cancer prognosis of at least 6 months, major depressive disorder	Unlikely to be able to adhere to the intervention, major communication difficulties, concurrent intensive anticancer treatment, another poorly controlled medical disorder, receiving or needing to a specialist psychiatric care (e.g., having suicidal risk, comorbid severe psychiatric disorder)	Integrated collaborative care = 101 TAU = 99	Integrated collaborative care = 56.6(11.4), TAU = 56.6(12.3)	Breast = 87(44%), Gynaecological = 31(16%), Colorectal = 13(7%), Others = 69(35%)	Disease-free = 132(66%), Local disease = 42(21%), Metastatic disease = 26(13%)
Sharpe et al., 2014 [41]	UK	Aged ≥18 years, diagnosis of cancer, a good cancer prognosis (predicted survival ≥12 months), major depression	Substantial cognitive, communication difficulties, unable to attend regular sessions, continuous depression for ≥2 years, a psychiatric or medical condition requiring alternative treatment, cerebral metastases, already regularly seeing a mental health specialist	Integrated collaborative care = 253 TAU = 247	Integrated collaborative care = 56.6(10.0), TAU = 56.1(10.2)	Breast = 271(54%), Gynaecological = 121(24%), Genitourinary = 27(5%), Others = 8(16%)	Non-active disease =396(79%), Active disease = 104(21%)
Muscle relaxation and therapeutic walking							
Sun et al., 2017 [42]	Taiwan	Aged ≥20 years, female, diagnosis of breast cancer, receiving intravenous chemotherapy because of having higher tendency of depression and suicidal ideation, not currently doing muscle relaxation and therapeutic walking	Too week to engage in muscle relaxation and therapeutic walking or to respond in writing to the questionnaires	Muscle relaxation and therapeutic walking = 44 Standard breast cancer education = 43	Muscle relaxation and therapeutic walking = 54.7(7.5) Standard breast cancer education = 54.4(8.3)	Breast = 87(100%)	Stage I = 17(20%), Stage II = 42(48%), Over Stage III = 28(32%)

Abbreviations

TAU: Treatment as usual, MMSE: Mini-Mental State Examination, HAM-D: Hamilton Rating Scale for Depression.

Note:

[a] The number of participants was not specified in the manuscript.

[b] Mean age in each group was not described.

Table 2
Intervention and findings.

Author, year	Group 1 (n) [duration of intervention]	Group 2 (n) [duration of intervention]	Group 3 (n) [duration of intervention]	Setting	Follow up period (max)	Findings related with suicidal behavior, ideation [result of analysis]
Psychotherapy						
Chochinov et al., 2011 [35]	Dignity therapy (n = 165) [7-10 days]	Standard palliative care (n = 140) [7-10 days]	Client-centered care (n = 136) [7-10 days]	Hospital and home	10 days	No information about suicide death No information about suicide attempt Suicidality in SISC, mean(maximum score): At baseline, 0.29(0.72) in Dignity therapy(n = 108) vs 0.21(0.66) in Standard palliative care(n = 111) vs 0.38(0.86) in Client-centered care(n = 107) At study completion, 0.27(0.73) in Dignity therapy(n = 108) vs 0.30(1.02) in Standard palliative care(n = 111) vs 0.32(0.96) in Client-centered care(n = 107) [No information about the analysis result for the intervention effect over the entire study period]
Hopko et al., 2013 [36]	Behavioral activation therapy (n = 42) [8 weeks]	Problem solving therapy (n = 38) [8 weeks]	-	Hospital	Approximately 2 years	Suicide death, number: 0/76 in both Behavioral activation therapy and Problem solving therapy at approximately 2 years No information about suicide attempt Suicidal ideation item in BDI-II, mean(SD): [a] At pre-treatment, 0.29(0.39) in Behavioral activation therapy vs 0.34(0.53) in Problem solving therapy At post-treatment, 0.09(0.21) in Behavioral activation therapy vs 0.11(0.28) in Problem solving therapy At 3 months, 0.07(0.16) in Behavioral activation therapy vs 0.05(0.17) in Problem solving therapy At 6 months, 0.12(0.19) in Behavioral activation therapy vs 0.13(0.25) in Problem solving therapy At 9 months, 0.13(0.17) in Behavioral activation therapy vs 0.12(0.17) in Problem solving therapy At 12 months, 0.00(0.00) in Behavioral activation therapy vs 0.02(0.16) in Problem solving therapy [A significant main effect of treatment condition was not demonstrated over the entire study period (B = -0.01, 95%CI = [-0.05, 0.04], p = 0.81)] Suicide item in HAM-D, mean(SD): [a] At pre-treatment, 0.38(0.85) in Behavioral activation therapy vs 0.42(0.72) in Problem solving therapy At post-treatment, 0.06(0.16) in Behavioral activation therapy vs 0.01(0.04) in Problem solving therapy At 3 months, 0.14(0.23) in Behavioral activation therapy vs 0.15(0.37) in Problem solving therapy At 6 months, 0.11(0.17) in Behavioral activation therapy vs 0.14(0.36) in Problem solving therapy At 9 months, 0.14(0.16) in Behavioral activation therapy vs 0.16(0.26) in Problem solving therapy At 12 months, 0.01(0.04) in Behavioral activation therapy vs 0.01(0.04) in Problem solving therapy [A significant main effect of treatment condition was not demonstrated over the entire study period (B = 0.24, 95%CI = [-3.31, 3.79], p = 0.89)]
Psychiatric pharmacotherapy				Hospital	6 weeks	

(*continued on next page*)

Table 2 (*continued*)

Author, year	Group 1 (n) [duration of intervention]	Group 2 (n) [duration of intervention]	Group 3 (n) [duration of intervention]	Setting	Follow up period (max)	Findings related with suicidal behavior, ideation [result of analysis]
Musselman et al., 2006 [37]	Paroxetine (n = 13) [6 weeks]	Desipramine (n = 11) [6 weeks]	Placebo (n = 11) [6 weeks]			No information about suicide death No information about suicide attempt Suicide item in HAM-D, mean: At baseline, 0.08 in Paroxetine(n = 13) vs 0.73 in Desipramine(n = 11) vs 0.55 in Placebo(n = 11) At 4 weeks, 0 in Paroxetine(n = 13) vs 0.27 in Desipramine(n = 11) vs 0.55 in Placebo(n = 11) At 6 weeks, 0 in Paroxetine(n = 13) vs 0.27 in Desipramine(n = 11) vs 0.27 in Placebo(n = 11) [A significant main effect of treatment condition was not demonstrated over the entire study period (p = 0.46)]
Lydiatt et al., 2008 [38]	Citalopram (n = 15) [12 weeks]	Placebo (n = 13) [12 weeks]	-	Hospital	16 weeks	No information about suicide death No information about suicide attempt Number of participants with suicidal ideation using MINI: 0/15 in Citalopram vs 2/10 in Placebo during the 16 weeks
Fan et al., 2017 [39]	Ketamine (n = 20) [40 min]	Midazolam (n = 19) [40 min]	-	Hospital	7 days	No information about suicide death No information about suicide attempt Suicidal ideation item by BSI, mean(SD): At baseline, 17.06(1.82) in Ketamine(n = 20) vs 16.6(2.14) in Midazolam(n = 17) At 1 day, 9.53(9.53) in Ketamine(n = 20) vs 16.79(7.07) in Midazolam(n = 17) At 3 days, 9.07(8.21) in Ketamine(n = 20) vs 16.93(8.27) in Midazolam(n = 17) At 7 days, BSI scores were not described in a manuscript. [A significant effect on reducing BSI score was demonstrated in Ketamine at 1 day (p = 0.05) and 3 days(p = 0.03), compared to Midazoram, however this effect was no longer significant at 7 days(p = 0.26)] Suicidal ideation item in MADRS, mean(SD): At baseline, 3.65(1.17) in Ketamine(n = 20) vs 3.65(1.27) in Midazolam(n = 17) At 1 day, 1.69(1.93) in Ketamine(n = 20) vs 3.42(1.75) in Midazolam(n = 17) At 3 days, 1.77(1.84) in Ketamine(n = 20) vs 3.52(1.89) in Midazolam(n = 17) At 7 days, BSI scores were not described in a manuscript. [A significant effect on reducing MADRS-SI score was demonstrated in Ketamine at 1 day (p = 0.01) and 3 day(p = 0.01), compared to Midazoram, however this effect was no longer significant at 7 days(p = 0.58)]
Integrated collaborative care						
Strong et al., 2008 [40]	Integrated collaborative care (n = 101) [3 months]	Treatment as usual (n = 99) [NA]	-	Hospital	12 months	Number of suicide death: 0/90 in Integrated collaborative care vs 1/82 in Treatment as usual during the 12 months No information about suicide attempt No information about suicidal ideation
Sharpe et al., 2014 [41]	Integrated collaborative care (n = 253) [4 months]	Treatment as usual (n = 247) [NA]	-	Hospital	48 weeks	No information about suicide death Number of participants with suicidal attempt:

(*continued on next page*)

Table 2 (*continued*)

Author, year	Group 1 (n) [duration of intervention]	Group 2 (n) [duration of intervention]	Group 3 (n) [duration of intervention]	Setting	Follow up period (max)	Findings related with suicidal behavior, ideation [result of analysis]
						1/223 in Integrated collaborative care vs 0/224 in Treatment as usual during the 48 weeks No information about suicidal ideation
Muscle relaxation and therapeutic walking						
Sun et al., 2017 [42]	Muscle relaxation and therapeutic walking (n = 44) [12 weeks]	Standard breast cancer education (n = 43) [NA]	-	Hospital	12 weeks	No information about suicide death No information about suicide attempt Suicidal ideation item by BSI, mean rank: At pretest, 45.06 in Muscle relaxation and therapeutic walking(n = 44) vs 42.92 in standard breast cancer education(n = 43) At posttest, 42.57 in Muscle relaxation and therapeutic walking (n = 44) vs 45.47 in standard breast cancer education(n = 43) [A significant effect on reducing BSI score was not demonstrated at posttest in Muscle relaxation and therapeutic walking, compared to standard breast cancer education (p = 0.26)]

Abbreviations:
SD: standard deviation
MINI: Mini-International Neuropsychiatric Interview
SISC: Structured Interview for Symptoms and Concerns
BDI-II: Beck Depression Inventory-II
HAM-D: Hamilton Rating Scale for Depression
BSI: Beck Scale for suicidal ideation
MADRS: Montgomery-Asberg Depression Rating Scale
Note:
[a] The number of participants was not specified in the manuscript.

retained after removing duplicates. After reviewing the titles and abstracts, the full texts of 212 articles were obtained for further assessment of eligibility. Of these 212 articles, 22 studies met our inclusion criteria, including 11 RCTs [35–45] and 11 intervention studies [46–56], which reported data on suicidal behavior or ideation (Tables 1, 2, and Supplementary Table 1). These 22 studies were all individual trials.

3.2. Characteristics of the identified studies

We classified the 22 studies into five categories by type of intervention: two trials in the psychotherapy group [35,36], three trials in the psychiatric pharmacotherapy group [37–39], two trials in the integrated collaborative care group [40,41], one trial in the muscle relaxation and therapeutic walking group [42], and 14 trials in the cancer treatment group [43–56].

We distinguished eight RCTs that conducted psychosocial or psychiatric interventions from 11 studies conducting only cancer treatment. The characteristics of study participants and the intervention programs in the eight RCTs are shown in Tables 1 and 2. The range of the number of participants varied among trials, and was between 28 and 500 individuals per study. For the type of cancer which study participants suffered from, breast cancer was most frequent, and this included six trials [35–37,40–42] of the eight RCTs. Additionally, three trials included only breast cancer patients as the study participants [36,37,42]. In terms of severity of cancer, all trials included a variety of patients with different severities, other than one trial in which participants had a life expectancy of six months or less [35]. The range of duration of the intervention varied among trials, being between 40 min for pharmacotherapy and four months for integrated collaborative care.

3.2.1. Psychotherapy

Effects of the intervention on suicidal outcome are shown in Table 2. No psychotherapy studies showed effectiveness for reducing suicide, as evidenced by the results of the two trials [27,28]. Additionally, the study by Chochinov et al. [35] reported that no significant differences were found for distress levels, the primary outcome, when comparing before versus after completion of the study, for dignity therapy, standard palliative care, or client-centered care. A study by Hopko et al. [36] presented evidence for the effectiveness of behavioral activation therapy and problem-solving therapy in mitigating depressive symptoms, the primary outcome [57].

Chochinov et al. [35] compared the effect of dignity therapy with standard palliative care and client-centered care on distress in cancer patients. Participants were 441 cancer patients with a terminal prognosis (a life expectancy of 6 months or less). Dignity therapy is a short-term psychotherapy that was developed for patients and their families living with life-threatening or life-limiting illness, such as cancer. Participants in the standard palliative care group had access to the complete range of palliative care support services that were available to all study participants. Patients in the client-centered care group discussed here-and-now issues with their therapist. The number of contacts for client-centered care was the same as for dignity therapy. In this trial, reductions in scores on several dimensions of distress were measured as the primary outcome. Among them, suicidality was assessed by the Structured Interview for Symptoms and Concerns (SISC) [58]. Score ranges for suicidality in the SISC are from 0 “None” to 6 “Extreme”, and a lower score indicates a lower suicidality. According to assessment of the risk of bias, this study has a high risk of bias related to allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and other potential sources of bias. In addition, there was insufficient information about selective reporting (Table 3).

Hopko et al. [36] reported the effect of behavioral activation therapy and problem-solving therapy on suicidal ideation as a secondary analysis of their previous study [35]. Participants in the 2013

Table 3
Risk of bias.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other biases
Psychotherapy							
Chochinov et al., 2011 [35]	Low	High	High	High	High	Unclear	High
Hopko et al., 2013 [36]	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear
Psychiatric pharmacotherapy							
Musselman et al., 2006 [37]	Unclear	Unclear	Low	Low	Low	Low	High
Lydiatt W et al., 2008 [38]	Low	High	Low	Low	Low	Unclear	High
Fan et al., 2017 [39]	Low	Low	Low	Unclear	Low	High	Unclear
Integrated collaborative care							
Strong et al., 2008 [40]	Low	Low	Unclear	Unclear	Low	Low	High
Sharpe et al., 2014 [41]	Low	Low	Unclear	Low	Low	Low	Low
Muscle relaxation and therapeutic walking							
Sun et al., 2017 [42]	High	High	Low	Low	Low	High	High

study were 80 participants with breast cancer and major depression. Behavioral activation therapy was developed to treat depression. This intervention augments overt behaviors and improves thought, mood, and quality of life. In contrast, the basic premise of problem-solving therapy is to help patients learn to resolve their problems and develop self-efficacy. In this trial, participants completed a suicidal ideation item from the Beck Depression Inventory-II (BDI-II: score ranges from 0 "I don't have any thoughts of killing myself" to 3 "I would kill myself if I had the chance") [59], a suicide item from the Hamilton Rating Scale for Depression (HAM-D: score ranges from 0 "Absence of suicidal ideation" to 4 "Attempts at suicide") [60] and at pre- and post-treatment and 3, 6, 9, and 12 months after the treatment. For these scales, a lower score indicates lower levels of symptoms. Repeated measures analyses were conducted using generalized estimating equations to examine the effects of treatment over time. The effects of these interventions were not compared with a control group. For the risk of bias, this study was assessed as having a high risk of bias related to selective reporting. In addition, the study contained insufficient information about random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and other potential sources of bias (Table 3).

3.2.2. Psychiatric pharmacotherapy

In pharmacotherapy studies, ketamine might be effective for reducing acute suicidal ideation as assessed by two scales among cancer patients, when compared with midazolam [39]. This trial did not describe the primary outcome. However, it did report that ketamine was effective for decreasing depressive symptoms at 1 and 3 days, compared with midazolam. Other trials using paroxetine or desipramine [37] and citalopram [38] reported that there were no significant differences over the entire study period in suicidal outcome, relative to placebo. In terms of primary outcomes, a trial by Musselman et al. [37] reported that the change in depressive symptoms from baseline to the six-week endpoint for paroxetine and desipramine was not significantly different to placebo. A trial by Lydiatt et al. [38] found that there was no significant difference between citalopram and placebo in the number of patients with severe depressive symptoms during 12 weeks of active study, with depressive symptoms being the primary outcome of this study.

Musselman et al. [37] compared the efficacy and safety of the selective serotonin reuptake inhibitor (SSRI) paroxetine and the tricyclic antidepressant desipramine with a placebo to treat depression among women with breast cancer. Participants were 35 breast cancer outpatients with major depression or adjustment disorder with depressed mood. Patients at serious risk of suicide were excluded. The primary outcome of the study was the difference from baseline of HAM-D depressive symptom scores. HAM-D suicide item scores were evaluated at baseline and 4 and 6 weeks later. Repeated measures analysis was applied to assess effect of treatment on the suicidal item in the HAM-D. In assessing the risk of bias, a high risk of bias related to other potential sources of bias was identified. In addition, there was insufficient information about random sequence generation and allocation concealment (Table 3).

Lydiatt et al. [38] conducted a trial to compare the effect of the SSRI citalopram with a placebo to prevent major depressive disorder in cancer patients. Participants were 28 patients with head and neck cancer. Patients at risk of suicide were excluded. The primary outcome of the study was the number of participants who developed depression, as assessed by the HAM-D. The HAM-D was used to measure depressive symptoms, but no information was provided about the HAM-D suicide item scores. For the risk of bias, this study was assessed as having a high risk of bias related to allocation concealment and other potential sources of bias. In addition, there was insufficient information about selective reporting (Table 3).

Fan et al. [39] compared the effect of ketamine with midazolam in decreasing suicidal ideation and depressive symptoms among cancer patients. Participants were 39 patients with newly-diagnosed cancer (within three months of diagnosis). Patients with a history of suicide attempts or suicidal ideation before cancer diagnosis were excluded. The primary outcome was not described in the manuscript. However, suicidal ideation was evaluated using the Beck Scale for suicidal ideation (BSI) [61] and the Montgomery-Asberg Depression Rating Scale (MADRS) [62]. The score range for the BSI is from 0 (e.g., "None", "Has sense of control") to 2 (e.g., "Moderate to strong", "Has no sense of control"). The BSI has 19 items with total scores ranging from 0 to 38, and a lower score indicates lower levels of suicidal ideation. The score range for the suicidal ideation item in the MADRS is rated from 0 "Enjoys life or takes it as it comes" to 6 "Explicit plans for suicide when there is an opportunity. Active preparations for suicide". A lower score indicates a lower severity of suicide. According to the assessment of the risk of bias, this trial has high risk of bias related to selective reporting. Additionally, there was insufficient information about the blinding of outcome assessment and other biases (Table 3).

3.2.3. Integrated collaborative care

No integrated collaborative care studies show effectiveness for reducing the number of suicide deaths [40] or suicide attempts [41] during the study period. However, both these studies provided evidence for the effectiveness of integrated collaborative care in decreasing depressive symptoms, the primary outcome of the trials.

A trial by Strong et al. [40] was the first study in a series of Symptom Management Research Trials in Oncology (SMaRT Oncology). This trial compared the effect of integrated collaborative care with treatment as usual on depressive symptoms in cancer patients with major depressive disorder. Participants were 200 cancer outpatients with a prognosis of at least 6 month's life expectancy and major depressive disorder. Patients at risk of suicide were excluded. The integrated collaborative care intervention comprised a maximum of 10 sessions over 3 months that included coordination of care, education about depression and its treatment, problem-solving therapy and behavioral activation, and monitoring of participants' progress every month using the PHQ-9 depression severity scale. Participants in the usual care group were encouraged to obtain treatment from their primary care physician. A primary outcome of the study was the difference from baseline in depressive symptom scores on the self-report Symptom Checklist-20 (SCL-20) evaluated at 3 months. Although depressive symptoms were evaluated using the PHQ-9, PHQ-9 scores on suicidal ideation were not reported. Numbers of suicide deaths were reported as adverse events. According to the assessment of the risk of bias, this trial was assessed as having a high risk of bias related to other potential sources of bias. In addition, there was insufficient information about blinding of participants and personnel and blinding of outcome assessment (Table 3).

A trial by Sharpe et al. [41] was the second trial in the SMaRT Oncology series and used more study sites and participants than Strong et al.'s trial [40]. Participants were 500 cancer outpatients with a prognosis of at least 12 month's life expectancy and major depressive disorder. The intervention program was almost the same as Strong et al.'s trial and the PHQ-9 was used to monitor participants' progress in the trial. A primary outcome of the study was the difference from baseline in depressive symptom scores on the SCL-20 evaluated at 24 weeks. Although depressive symptoms were evaluated using the PHQ-9, PHQ-9 scores on suicidal ideation were not reported. Numbers of suicide attempts were reported as adverse events. For the risk of bias, this study had a low risk of bias, except for blinding of participants and personnel (Table 3).

3.2.4. Muscle relaxation and therapeutic walking

One muscle relaxation and therapeutic walking study did not show effectiveness in reducing suicidal ideation [42]. This study did not specify a primary outcome in the manuscript. The effects of muscle relaxation and therapeutic walking on depression and quality of life were unclear compared with standard breast cancer education because

the change in scores from pretest to posttest was not described.

Sun et al. [42] compared the effect of muscle relaxation and therapeutic walking with standard breast cancer education on depression, suicidal ideation, and quality of life in cancer patients. Participants were 87 breast cancer patients receiving chemotherapy with a higher tendency for depression and suicidal ideation (the participants expressed hopelessness and no purpose in life after the diagnosis of cancer). Participants in the muscle relaxation and therapeutic walking group practiced the muscle relaxation techniques (MRTs) at least two times per day using a CD-ROM recording of MRTs applicable to breast cancer patients, and recorded their MRT completion (number/time/day) for 12 weeks. Additionally, they were asked to walk 90–120 min per week or three times per week for at least 30 min per session, and to record their number of steps, walking time per day, and strength for 12 weeks. Standard breast cancer education was the departmental routine for patients. The primary outcome was not described in the manuscript although suicidal ideation was assessed by the MADRS. The Mann-Whitney *U* test was conducted to examine the difference between scores for two groups only at posttest. However, the change in the scores from pretest to posttest was not explored and examination of the effect of the intervention is therefore not reported. Accordingly, the effect of intervention is unclear. For the assessment of bias, this trial was assessed as having a high risk of bias related to random sequence generation, allocation concealment, selective reporting, and other biases (Table 3).

3.2.5. Cancer treatment

In total, 14 studies that focused on cancer treatment were identified (Supplementary Table 1). Of these, seven studies focused on pharmacotherapy (including chemotherapy) [43,46–51], three studies on chemoradiotherapy [44,45,52], two studies on radiotherapy [53,54], one study on bone-marrow transplantation [55], and one study on screening tests [56]. Three studies were RCTs [43–45] and the remaining 11 were other intervention studies (e.g., prospective single-arm trials, nonrandomized studies, and quasi-experimental studies) [46–56]. All 14 studies reported the numbers of individuals with suicide deaths, attempts, or suicidal ideation as adverse events.

3.3. Frequency of suicidal behavior in identified studies

The incidence of suicide attempts or suicide deaths, even in cancer patients, would be too low to produce adequate statistical power. Hopko et al. [36] reported that, over two years, none out of 76 participants attempted suicide. Similarly, Sharpe et al. [41] reported only one suicide attempter (0.2%) out of 447 participants over a one-year follow-up period. More importantly, patients at risk for suicide were excluded from the trials conducted by Musselman et al. [37], Lydiatt et al. [38], and Strong et al. [40]. Additionally, the incidence of suicide attempts or suicide deaths in the 14 cancer treatment studies were reported to have occurred infrequently, with most studies reporting only one incident of suicide outcome.

These studies used various scales to assess suicidality in participating patients; however, the cut-off point, definition of severity for suicidality, and specific definition of suicide were not sufficiently described (Supplementary Table 2).

4. Discussion

Our systematic review summarized interventions for suicide prevention among patients with cancer and revealed their methodological issues. No intervention had been designed to prevent suicide for cancer patients, and suicide was measured only as a secondary outcome in all of the 22 trials. Seven of the eight trials were designed to treat depression [36–42]. From our results, treating depression among cancer patients might be not an effective way to reduce suicide. Although depression is known to be an important risk factor for suicide among patients with cancer [8–9], there are other risk factors, including: substance use [14]; neurocognitive dysfunction, sexual dysfunction, sleep, stress-related/post-traumatic stress, somatization, bipolar, and obsessive-compulsive disorders [15]; pain [63–64]; sense of burden on others [6,65]; and poor social support [66,67]. It is necessary to examine whether other treatments targeted at other modifiable risks for suicidality among cancer patients might be effective in the future.

Several RCTs for cancer patients with depression have been conducted to date, and several systematic reviews and meta-analyses have been carried out to evaluate the effect of interventions for depressive symptoms in these patients. For example, Okuyama et al. identified 13 studies in their systematic review of psychotherapy interventions [11]. Ostuzzi et al. identified 9 studies in their systematic review of antidepressant interventions [10]. In addition, Li et al. identified 9 studies in their systematic review of collaborative care interventions [12]. These systematic reviews demonstrated an effect of interventions on depressive symptom. However, we identified here only two RCTs [36,37] which reported suicidal ideation among cancer patients with depression by our hand-searching of these reviews. Additionally, three trials [38,40,41] identified in our study reported no information about suicidal ideation, although these trials used the PHQ-9 or HAM-D each of which includes one item rating suicidality. Our findings demonstrate that most RCTs conducted for cancer patients with depression have not reported information about suicidal ideation, despite using scales containing suicidal ideation items. The availability of suicidal ideation data is important for future meta-analyses and would help to clarify whether interventions for depression are effective in reducing suicidal ideation among these patients. Subscale information on suicidal information should be reported in future trials. Most importantly, it is necessary to standardize the definition of suicide, assessment methods, and tools for assessment of severity of suicide risk, because variable scales were used in each of the included studies (Supplementary Table 2). Meyer et al. indicated that the introduction of the nonspecific term “suicidality” resulted in definitions in suicide research becoming increasingly complex, because this term lumps together suicidal ideation, self-injurious behavior, suicide attempts, and suicide despite the differing consequences for the patient [68]. Therefore, it is important to state clearly concrete definitions for suicidal behavior or suicidal ideation without using ambiguous terms such as suicidality. To achieve this, it may be desirable for researchers to use the definition of suicide from the Columbia Classification Algorithm of Suicide Assessment [69], which is recommended by the US Food and Drug Administration [68]. The PHQ-9 may be effective for evaluating suicide risk among patients with cancer because this tool is a commonly used, validated screening tool for both psychiatrists and general practitioners [70]. Moreover, this scale is recommended as a useful screening tool for assessing depression by the American Society of Clinical Oncology [22].

The incidence of suicide attempts or deaths by suicide, even in cancer patients, is too low to produce adequate statistical power to examine the effect of interventions on suicidality. In future research, it is necessary to target cancer patients at high risk of suicide.

Suicide rates vary among patients with different type of cancers [4,71]. In the 22 identified trials, breast cancer was the most frequent cancer type. Further examination of suicidal behavior or suicidal ideation in patients with certain types of cancer is warranted.

The identified trials showed insufficient quality (Table 3). RCTs with well-designed methods are needed to develop and select interventions that could substantially improve suicide-related outcomes for cancer patients. Future investigators should follow the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [72] and the Consolidated Standards of Reporting Trials (CONSORT) guidelines [73].

The primary limitation of this study is the low number of studies identified. Most intervention studies for cancer patients with depression have not reported information about suicidal ideation, despite using psychometric scales containing suicidal ideation items. In addition,

other reason for was that patients at high risk of suicide were excluded from the efficacy trials.

5. Conclusion

Our systematic review summarized interventions for suicide prevention in patients with cancer and revealed their methodological issues. It is necessary to explore new treatment strategies that focus on unique suicide risk factors among patients with cancer, because there is little evidence to confirm the effects of suicide prevention interventions for this population.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2019.07.003.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

We especially thank Ms. Mayumi Matsutani and Ms. Hitomi Muramatsu for their research assistance. This study was supported by the Research and Development Grants for Comprehensive Research for Persons with Disabilities (Mental Disorder Area) from the Japan Agency for Medical Research and Development (17dk0307050h003) and JSPS KAKENHI (Grant Number JP16J11981).

We thank Diane Williams, PhD, and Catherine Deeprose, Phd, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

References

[1] Crocetti E, Arniani S, Acciai S, Barchielli A, Buiatti E. High suicide mortality soon after diagnosis among cancer patients in central Italy. Br J Cancer 1998;77(7):1194–6.
[2] Levi F, Bulliard JL, La Vecchia C. Suicide risk among incident cases of cancer in the Swiss Canton of Vaud. Oncology 1991;48(1):44–7.
[3] Miccinesi G, Crocetti E, Benvenuti A, Paci E. Suicide mortality is decreasing among cancer patients in Central Italy. Eur J Cancer 2004;40(7):1053–7.
[4] Misono S, Weiss NS, Fann JR, Redman M, Yueh B. Incidence of suicide in persons with cancer. J Clin Oncol 2008;26(29):4731–8.
[5] Dormer NR, McCaul KA, Kristjanson LJ. Risk of suicide in cancer patients in Western Australia, 1981–2002. Med J Aust 2008;188(3):140–3.
[6] Akechi T, Okuyama T, Sugawara Y, Nakano T, Shima Y, Uchitomi Y. Suicidality in terminally ill Japanese patients with cancer. Cancer 2004;100(1):183–91.
[7] Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol 2011;12(2):160–74.
[8] Henriksson MM, Isometsa ET, Hietanen PS, Aro HM, Lonnqvist JK. Mental disorders in cancer suicides. J Affect Disord 1995;36(1–2):11–20.
[9] Akechi T, Kugaya A, Okamura H, Nakano T, Okuyama T, Mikami I, et al. Suicidal thoughts in cancer patients: clinical experience in psycho-oncology. Psychiatry Clin Neurosci 1999;53(5):569–73.
[10] Ostuzzi G, Matcham F, Dauchy S, Barbui C, Hotopf M. Antidepressants for the treatment of depression in people with cancer. Cochrane Database Syst Rev 2015;6:CD011006.
[11] Okuyama T, Akechi T, Mackenzie L, Furukawa TA. Psychotherapy for depression among advanced, incurable cancer patients: a systematic review and meta-analysis. Cancer Treat Rev 2017;56:16–27.
[12] Li M, Kennedy EB, Byrne N, Gérin-Lajoie C, Katz MR, Keshavarz H, et al. Systematic review and meta-analysis of collaborative care interventions for depression in patients with cancer. Psychooncology 2017;26(5):573–87.
[13] Shaw J, Sethi S, Vaccaro L, Beatty L, Kirsten L, Kissane D, et al. Is care really shared? A systematic review of collaborative care (shared care) interventions for adult cancer patients with depression. BMC Health Serv Res 2019;19(1):120.
[14] Yusufov M, Braun IM, Pirl WF. A systematic review of substance use and substance use disorders in patients with cancer. Gen Hosp Psychiatry 2019;S0163-8343(18):30527–9.
[15] Carreira H, Williams R, Müller M, Harewood R, Stanway S, Bhaskaran K. Associations between breast cancer survivorship and adverse mental health outcomes: a systematic review. J Natl Cancer Inst 2018;110(12):1311–27.
[16] Dimitrov L, Moschopoulou E, Korszun A. Interventions for the treatment of cancer-related traumatic stress symptoms: a systematic review of the literature. Psychooncology 2019;28(5):970–9.
[17] World Health Organization. Preventing suicide: a global imperative. https://apps.who.int/iris/bitstream/handle/10665/131056/9789241564779_eng.pdf?sequence=1; 2014.
[18] Hawton K, Casañas I Comabella C, Haw C, Saunders K. Risk factors for suicide in individuals with depression: a systematic review. J Affect Disord 2013;147:17–28.
[19] Henson KE, Brock R, Charnock J, Wickramasinghe B, Will O, Pitman A. Risk of suicide after cancer diagnosis in England. JAMA Psychiat 2018;76(1):51–60.
[20] Robinson D, Renshaw C, Okello C, Møller H, Davies EA. Suicide in cancer patients in South East England from 1996 to 2005: a population-based study. Br J Cancer 2009;101(1):198–201.
[21] Yousaf U, Christensen ML, Engholm G, Storm HH. Suicides among Danish cancer patients 1971–1999. Br J Cancer 2005;92(6):995–1000.
[22] Andersen BL, DeRubeis RJ, Berman BS, Gruman J, Champion VL, Massie MJ, et al. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. J Clin Oncol 2014;32(15):1605–19.
[23] Li M, Kennedy EB, Byrne N, Gérin-Lajoie C, Katz MR, Keshavarz H, et al. Management of depression in patients with cancer: a clinical practice guideline. J Oncol Pract 2016;12(8):747–56.
[24] Robson A, Scrutton F, Wilkinson L, MacLeod F. The risk of suicide in cancer patients: a review of the literature. Psychooncology 2010;19(12):1250–8.
[25] Spoletini I, Gianni W, Caltagirone C, Madaio R, Repetto L, Spalletta G. Suicide and cancer: where do we go from here? Crit Rev Oncol Hematol 2011;78(3):206–19.
[26] L1 Anguiano, Mayer DK, Piven ML, Rosenstein D. A literature review of suicide in cancer patients. Cancer Nurs 2012;35(4):E14–26.
[27] Calati R, Fang F, Mostofsky E, Shen Q, Di Mattei VE, Garcia-Foncillas J, et al. Cancer and suicidal ideation and behaviours: protocol for a systematic review and meta-analysis. BMJ Open 2018;8(8):e020463.
[28] Mann JJ, Apter A, Bertolote J, Beautrais A, Currier D, Haas A, et al. Suicide prevention strategies: a systematic review. JAMA 2005;294(16):2064–74.
[29] Bolton JM, Gunnell D, Turecki G. Suicide risk assessment and intervention in people with mental illness. BMJ 2015;351:h4978.
[30] Zalsman G, Hawton K, Wasserman D, van Heeringen K, Arensman E, Sarchiapone M, et al. Suicide prevention strategies revisited: 10-year systematic review. Lancet Psychiatry 2016;3(7):646–59.
[31] Kawashima Y, Yonemoto N, Inagaki M, Inoue K, Kawanishi C, Yamada M. Interventions to prevent suicidal behaviors for patients with cancer: a systematic review. PROSPERO 2016:CRD42016047371 Available from http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID=CRD42016047371.
[32] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
[33] Akechi T, Okuyama T, Onishi J, Morita T, Furukawa TA. Psychotherapy for depression among incurable cancer patients. Cochrane Database Syst Rev 2008;2:CD005537.
[34] Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011.
[35] Chochinov HM, Kristjanson LJ, Breitbart W, McClement S, Hack TF, Hassard T, et al. Effect of dignity therapy on distress and end-of-life experience in terminally ill patients: a randomised controlled trial. Lancet Oncol 2011;12(8):753–62.
[36] Hopko DR, Funderburk JS, Shorey RC, McIndoo CC, Ryba MM, File AA, et al. Behavioral activation and problem-solving therapy for depressed breast cancer patients: preliminary support for decreased suicidal ideation. Behav Modif 2013;37(6):747–67.
[37] Musselman DL, Somerset WI, Guo Y, Manatunga AK, Porter M, Penna S, et al. A double-blind, multicenter, parallel-group study of paroxetine, desipramine, or placebo in breast cancer patients (stages I, II, III, and IV) with major depression. J Clin Psychiatry 2006;67(2):288–96.
[38] Lydiatt WM, Denman D, McNeilly DP, Puumula SE, Burke WJ. A randomized, placebo-controlled trial of citalopram for the prevention of major depression during treatment for head and neck cancer. Arch Otolaryngol Head Neck Surg 2008;134(5):528–35.
[39] Fan W, Yang H, Sun Y, Zhang J, Li G, Zheng Y, et al. Ketamine rapidly relieves acute suicidal ideation in cancer patients: a randomized controlled clinical trial. Oncotarget 2017;8(2):2356–60.
[40] Strong V, Waters R, Hibberd C, Murray G, Wall L, Walker J, et al. Management of depression for people with cancer (SMaRT oncology 1): a randomised trial. Lancet 2008;372(9632):40–8.
[41] Sharpe M, Walker J, Holm Hansen C, Martin P, Symeonides S, Gourley C, et al. Murray G; SMaRT (Symptom Management Research Trials) Oncology-2 Team. Integrated collaborative care for comorbid major depression in patients with cancer (SMaRT Oncology-2): a multicentre randomised controlled effectiveness trial. Lancet 2014;384(9948):1099–108.
[42] Sun FK, Hung CM, Yao Y, Lu CY, Chiang CY. The effects of muscle relaxation and therapeutic walking on depression, suicidal ideation, and quality of life in breast cancer patients receiving chemotherapy. Cancer Nurs 2017;40(6):E39–48.
[43] Antin JH, Lee SJ, Neuberg D, Alyea E, Soiffer RJ, Sonis S, et al. A phase I/II double-blind, placebo-controlled study of recombinant human interleukin-11 for mucositis and acute GVHD prevention in allogeneic stem cell transplantation. Bone Marrow Transplant 2002;29(5):373–7.
[44] Lee AW, Tung SY, Chua DT, Ngan RK, Chappell R, Tung R, et al. Randomized trial of radiotherapy plus concurrent-adjuvant chemotherapy vs radiotherapy alone for regionally advanced nasopharyngeal carcinoma. J Natl Cancer Inst 2010;102(15):1188–98.
[45] Fernandez-Martos C, Aparicio J, Salud A, Alonso V, Massuti B, Vera SafontR M, et al. Multicenter randomized phase II study of chemoradiation (CRT) followed by

surgery (S) and chemotherapy (CT) versus induction CT followed by CRT and S in high-risk rectal cancer: GCR-3 final efficacy and safety results. J Clin Oncol 2009;27:4103.
[46] Wicki A, Brown N, Xyrafas A, Bize V, Hawle H, Berardi S, et al. First-in human, phase 1, dose-escalation pharmacokinetic and pharmacodynamic study of the oral dual PI3K and mTORC1/2 inhibitor PQR309 in patients with advanced solid tumors (SAKK 67/13). Eur J Cancer 2018;96:6–16.
[47] McKay RR, De Velasco G, Werner L, Bellmunt J, Harshman L, Sweeney C, et al. A phase 1 study of buparlisib and bevacizumab in patients with metastatic renal cell carcinoma progressing on vascular endothelial growth factor-targeted therapies. Cancer 2016;122(15):2389–98.
[48] Gonzalez-Angulo AM, Meric-Bernstam F, Chawla S, Falchook G, Hong D, Akcakanat A, et al. Weekly nab-rapamycin in patients with advanced nonhematologic malignancies: final results of a phase I trial. Clin Cancer Res 2013;19(19):5474–84.
[49] Kattan J, Mahjoubi M, Droz JP, Kramar A, Culine S, Boutan-Laroze A, et al. High failure rate of carboplatin-etoposide combination in good risk non-seminomatous germ cell tumours. Eur J Cancer 1993;29A(11):1504–9.
[50] Droz JP, Pico JL, Ghosn M, Kramar A, Rey A, Ostronoff M, et al. A phase II trial of early intensive chemotherapy with autologous bone marrow transplantation in the treatment of poor prognosis non seminomatous germ cell tumors. Bull Cancer 1992;79(5):497–507.
[51] Philip T, Chauvin F, Armitage J, Bron D, Hagenbeek A, Biron P, et al. Parma international protocol: pilot study of DHAP followed by involved-field radiotherapy and BEAC with autologous bone marrow transplantation. Blood 1991;77(7):1587–92.
[52] Abitbol AA, Schwade JG, Lewin AA, Sridhar K, Brandon AH, Markoe AM, et al. Hyperfractionated radiation therapy and concurrent 5-fluorouracil, cisplatin and mitomycin-C in head and neck carcinoma. A pilot study. Am J Clin Oncol 1992;15(3):250–5.
[53] Bamberg M, Kortmann RD, Calaminus G, Becker G, Meisner C, Harms D, et al. Radiation therapy for intracranial germinoma: results of the German cooperative prospective trials MAKEI 83/86/89. J Clin Oncol 1999;17(8):2585–92.
[54] Oliver RT, Edmonds PM, Ong JY, Ostrowski MJ, Jackson AW, Baille-Johnson H, et al. Pilot studies of 2 and 1 course carboplatin as adjuvant for stage I seminoma: should it be tested in a randomized trial against radiotherapy? Int J Radiat Oncol Biol Phys 1994;29(1):3–8.
[55] Meloni G, Vignetti M, Avvisati G, Capria S, Micozzi A, Giona F, et al. BAVC regimen and autograft for acute myelogenous leukemia in second complete remission. Bone Marrow Transplant 1996;18(4):693–8.
[56] Straus DJ, Jung SH, Pitcher B, Kostakoglu L, Grecula JC, Hsi ED, et al. CALGB 50604: risk-adapted treatment of nonbulky early-stage Hodgkin lymphoma based on interim PET. Blood 2018;132(10):1013–21.
[57] Hopko DR, Armento ME, Robertson SM, Ryba MM, Carvalho JP, Colman LK, et al. Brief behavioral activation and problem-solving therapy for depressed breast cancer patients: randomized trial. J Consult Clin Psychol 2011;79(6):834–49.
[58] Wilson KG, Graham ID, Viola RA, et al. Structured interview assessment of symptoms and concerns in palliative care. Can J Psychiatry 2004;49:350–8.
[59] Beck AT, Steer RA, Brown GK. Manual for Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation; 1996.
[60] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
[61] Beck AT, Steer RA. Manual for the Beck Scale for Suicidal Ideation. San Antonio, TX: Psychological Corporation; 1991.
[62] Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–9.
[63] Akechi T, Okamura H, Nishiwaki Y, Uchitomi Y. Predictive factors for suicidal ideation in patients with unresectable lung carcinoma. Cancer 2002;95(5):1085–93.
[64] Walker J, Waters RA, Murray G, Swanson H, Hibberd CJ, Rush RW, et al. Better off dead: suicidal thoughts in cancer patients. J Clin Oncol 2008;26(29):4725–30.
[65] Filiberti A, Ripamonti C, Totis A, Ventafridda V, De Conno F, Contiero P, et al. Characteristics of terminal cancer patients who committed suicide during a home palliative care program. J Pain Symptom Manage 2001;22(1):544–53.
[66] Noor-Mahomed SB, Schlebusch L, Bosch BA. Suicidal behavior in patients diagnosed with cancer of the cervix. Crisis 2003;24(4):168–72.
[67] Chochinov HM, Wilson KG, Enns M, Mowchun N, Lander S, Levitt M, et al. Desire for death in the terminally ill. Am J Psychiatry 1995;152(8):1185–91.
[68] Meyer RE, Salzman C, Youngstrom EA, Clayton PJ, Goodwin FK, Mann JJ, et al. Suicidality and risk of suicide—definition, drug safety concerns, and a necessary target for drug development: a brief report. J Clin Psychiatry 2010;71(8):1040–6.
[69] Posner K, Oquendo MA, Gould M, et al. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry 2007;164(7):1035–43.
[70] Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. Validity of a brief depression severity measure. J Gen Intern Med 2001;16:606–13.
[71] Hem E, Loge JH, Haldorsen T, Ekeberg Ø. Suicide risk in cancer patients from 1960 to 1999. J Clin Oncol 2004;22(20):4209–16.
[72] Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013;346:e7586.
[73] Schulz KF, Altman DG. Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 2010;152(11):726–32.