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Cancer and suicidal ideation and behaviours: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Prevalence of suicidal ideation (SI) and behaviours are higher among patients with cancer than general population. No systematic review/meta-analysis investigated this topic; therefore, our aim will be to assess the relationship between cancer and SI and behaviours.

Methods We will search PubMed/MEDLINE, EMBASE, SCOPUS, Web of Science, PsycINFO and Cochrane Library databases from their inception until 30 June 2018. Case–control and cohort studies focused on the association between cancer (any type) and suicidal outcomes (suicide, suicide attempt and SI) will be included. Two team members will independently: (A) perform the selection of the included studies and data extraction, with the supervision of a third member in case of discrepancies and (B) assess each study with: (1) Newcastle-Ottawa Scale (NOS); (2) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement; (3) Grading of Recommendations Assessment, Development and Evaluation (GRADE). We will conduct a random-effects meta-analysis. Individual and pooled ORs and associated 95% CIs will be calculated as well as between-study heterogeneity. We will examine the potential for publication bias. If possible, we will explore reasons for potential between-study heterogeneity.

Ethics and dissemination This study does not require ethical approval. The study will be submitted to a peer-reviewed journal, will be publicly disseminated and will be the topic of research presentations.

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Strengths and limitations of this study

- This will be the first systematic review and meta-analysis on the topic.
- Implications of our future findings might provide evidence to the improvement of policies on suicidal symptom screening by healthcare professionals working in oncology.
- The findings could be limited to determine the timing of suicide risk after a cancer diagnosis and the specific cancer sites associated with suicide due to the less investigation from previous studies.

INTRODUCTION

In 2015, cancer was the second leading cause of death worldwide,[1] and suicide was the 17th cause of death and the second among 15–29 year olds.[2] Cancer might also lead to suicide: prior studies have shown that suicide incidence among patients with cancer is almost double compared with the general population.[3–5] Moreover, patients with cancer were found to be particularly prone to suicidal ideation (SI), especially in the case of advanced cancer,[4 5] and suicide attempts (SAs)[5 6] as well. However, little is known about: (1) the timing of suicide risk following a cancer diagnosis; (2) whether findings are consistent across different populations and (3) the shared risk factors.

1. Concerning the timing of risk following the cancer diagnosis, one study reported that standardised mortality ratio (SMR: the ratio of observed deaths in the study group to expected deaths in the general population) was 3.09 for men and 2.18 for women within the first 5 months after diagnosis; during 12–23 months after cancer diagnosis, SMR decreased but remained elevated to 1.57 and 1.72, respectively.[7] In another study, risk of suicide was highest during the first 3 months for men, while highest from 3 to 12 months for women.[8] Such difference can be explained by different prognosis, in particular to poor prognosis in the first peak (3 months) and to moderate–good prognosis in the second risk increase (12–14 months)[9]; the last peak of risk elevation has been explained by the possible cancer recurrence after the failure of treatment. Moreover, patients with prostate cancer seem to be particularly at risk of suicide after 15 years since the cancer diagnosis.[10 11] This finding has been tentatively interpreted with late-onset metastases and/or symptoms, long-term urinary incontinence and erectile dysfunctions.[11] Hence, suicide risk

may shift, from being related to psychological effects linked to the diagnosis in the short term, to being associated to cancer-related sequelae, side effects of cancer treatment, fear of cancer recurrence and further ageing-related factors in the long term.[10]

2. Concerning consistency across populations, gender, age, income and regional differences have been reported. Male patients with cancer seem to have a higher suicide risk than females.[5] The highest suicide risk was reported among people aged 40–46 and over 60 years.[5] Among patients with cancer, higher income was associated with less SI.[12] Regional differences were also found: the association between cancer and suicide was found to be stronger in Eastern European nations.[13] Authors hypothesised that this association could be related to indicators of social disintegration (such as divorce, abortion and illegitimacy rates, and urbanicity) but only in less developed regions (eg, Ukraine vs USA).[14 15] Accordingly, living alone, further indicator of social disintegration, is associated with suicide.[16]
3. Pertaining risk factors, SI and behaviours seem to be linked to the same risk factors in patients with cancer and in the general population: male gender, older age, depression, hopelessness, pain and poor physical functioning. In particular, depressive disorders (including major depression, minor depression and other forms of depressive conditions, such as demoralisation) affect up to 60% of patients with cancer.[17] However, depression in these patients could not be recognised because it could be hard to distinguish depressive symptoms from some cancer treatment-related and cancer disease-related symptoms, such as fatigue.[18] Further risk factors for suicide among individuals diagnosed with cancer include the already described time since diagnosis, cancer site, advanced stage of cancer at diagnosis and poor prognosis.[4 5] The majority of studies did not examine specific cancer types and some pooled together more severe forms of cancer, such as oesophagus, liver, pancreas and lung cancers.[3] Although disease with advanced stage and poor prognosis seem to be linked to higher suicide risk, increased suicide risk was also observed in patients with low-risk prostate cancer.[19] In particular, shared risk factors (eg, smoking, alcohol consume and air pollution) might lead to spurious associations between cancer and suicide conditions.[20–23] The evaluation of other factors, such as pain[24–26] and social support,[27 28] may also help in the identification of new targeted prevention strategies.

To our knowledge, no previous systematic review and meta-analysis investigated the association between a cancer diagnosis and suicide risk. Thus, the aim of this study is to assess the risk of SIs and behaviours after a cancer diagnosis. Secondary aim of this study will be to specifically address the knowledge gaps in the previous literature, focusing on the timing of suicide risk and controlling for all the possible confounding factors. We will focus not only on suicide but also on SI and SAs since they are risk factors for suicide.[29] Our future findings might shed further light on the improvement of on-time suicidal symptom screening among patients with cancer. For instance, healthcare professionals working in oncology should receive specific training to identify and treat depression and SI and behaviours.

OBJECTIVES

To investigate the association between cancer diagnosis and

1a. Suicide,
1b. SA,
1c. SI.

These analyses will be performed controlling for confounding factors when possible.

METHODS

The present protocol has been registered in PROSPERO and is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement.[30]

The meta-analysis will be reported in accordance with the reporting checklist proposed by the Meta-analysis of Observational Studies in Epidemiology group.[31]

Types of studies

Studies will be included if: they are case–control and both prospective and retrospective cohort studies of any length of follow-up; they investigate the association between cancer diagnosis and subsequent SI and behaviours; they report data on cancer diagnoses and suicidal outcomes; they focus on any type of study population. If available, we will use estimates of the association (ORs, risk ratios or rate ratios) and 95% CIs that have accounted for potential confounders; otherwise, we will include data on the number of cases and non-cases with and without cancer diagnoses to calculate crude estimates of the association, and we will conduct sensitivity analyses restricted to adjusted estimates.

Studies will be excluded if: they are not written in English; they focus on patients with cancer only or suicidal patients only; they pool different suicidal outcomes together (eg, suicide and SA) and separate data are not available after having contacted the authors; they rely on self-reported cancer diagnoses only; they are randomised controlled trials, because we aimed to exclude the potential bias of treatment interventions; they are cross-sectional studies, because we focus on suicide risk after cancer diagnosis.

Types of participants

We will include studies of subjects regardless of age, sex or ethnicity who were participants in observational studies (case–control and cohort) from inpatient, outpatient or mixed community settings with any cancer diagnosis.

Cancer

We will include studies that examine the impact of a diagnosis of any malignant neoplasm (International

Classification of Diseases (ICD)-9: 140–209; ICD-10: C00–C97). In sensitivity analyses, we will consider site-specific cancers if sufficient data are available.

Suicidal outcomes

We will refer to established nomenclature.[29] We will separately consider all the suicidal events as reported by the original study authors: suicide (self-inflicted death), SA (self-inflicted potentially injurious behaviour with a non-fatal outcome and with the intention to die) and SI (thinking of dying of suicide). If possible, we will consider the distinction between passive SI (eg, thoughts of being better off dead) and active SI as well. We will include deliberate self-harm only if it is possible to distinguish non-suicidal self-injury (NSSI) and SA (NSSI refers to an intentional act of causing physical injury to oneself without wanting to die). As outcomes, we will consider the number of events (suicide and SA) and any standardised rating scale for assessing the presence of SI; it could be an item as for Montgomery–Åsberg Depression Rating Scale[32] or Hamilton Rating Scale for Depression,[33] or a specific scale about suicide, like the Columbia-Suicide Severity Rating Scale.[34] We will consider SI as presence versus absence. If only mean score measures of SI are shown in an article, we will contact the authors.

Search methods for the identification of studies

Electronic searches

We will search PubMed/MEDLINE, EMBASE, SCOPUS, Web of Science, PsycINFO and Cochrane Library, from their inception until 30 June 2018, to identify cohort and case–control studies reporting the association between cancer and suicidal outcomes. Combinations of Medical Subject Headings terms will be: [cancer* OR tumor* OR carcinoma* OR neoplas* OR oncolog* OR metastas* OR malign*] AND [suicid* OR self-harm* OR self harm OR self-poisoning OR self poisoning] (see online supplementary document 1).

Reference lists

The reference lists of all the included studies, relevant papers and previous systematic reviews will be also handsearched for the identification of additional studies.

Data collection

Selection of studies

Two authors (RC and QS) will independently check the titles and abstracts of all the references generated by the search strategies to decide if they meet the inclusion criteria. All studies potentially eligible for inclusion will be added to the preliminary list, and their full-text articles will be retrieved. The two authors will then assess all full-texts to verify if they meet the inclusion criteria. If the authors disagree, the final decision will be made by consensus with the involvement of FF, EM or AC.

Data extraction and management

Using a standardised data extraction sheet, RC and QS will independently extract data from the included studies. Any disagreement will be discussed with a third member of the review team (FF, EM or AC), and decisions will be documented. In the case of missing information concerning the outcomes of interest, we will directly contact study authors up to three times to obtain additional information.

The following data will be extracted from all studies meeting the inclusion criteria: country, study design, year, sample size and type, period of assessment, hazard period (ie, the assessed time period after the cancer diagnosis), suicide outcomes, percentage of males, age, ethnicity, cancer type, main results, list of confounders included in design and analysis, crude numbers and measure of association (ORs) and 95% CIs, and data source.

When available, we will consider both raw data and the models adjusted for covariates. If a study conducts one analysis of men and one of women, those will be included as two separate studies.

In the case of studies published on the same data source, we will use the most recently published results or the largest sample size. To avoid the risk of overlapping studies for each study, we will extract: (1) the names of the authors and (2) the names of the databases/studies (data source) and we will check for duplicates; then, in the case of doubts, we will contact the authors.

Assessment of quality, strength of reporting and certainty of evidence in included studies

Two authors (RC and VEDM) will independently assess the quality of the studies using the Newcastle-Ottawa Scale (NOS)[35] and the strength of reporting of studies according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[36] The NOS assesses with eight questions the quality of case–control and cohort studies in three broad categories: (1) patient selection; (2) comparability of study groups; (3) assessment of the outcome. The STROBE statement consists of a 22-item checklist for the assessment of the strengths and weaknesses of each section of a single study (title, abstract, introduction, methods, results and discussion). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology for evaluating the certainty of evidence for each outcome will be used as well.[37] The certainty of evidence will be classified as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) or very low (any estimate of effect is very uncertain).

Data analysis

Main analyses

We will calculate pooled ORs and 95% CIs. We will assess heterogeneity with the χ^2 goodness of fit and I^2 statistics. Concerning I^2, we will consider Cochrane

recommendations.[38] We will consider statistically significant a p value <0.05 (presence of heterogeneity). In the case of the presence of heterogeneity, we will perform sensitivity analyses and metaregressions when possible.

We will use a random-effects model since we hypothesise that the effect will be similar but not identical across studies. A funnel plot will be created to reveal the preferential publication of statistically significant results. Tests for funnel plot asymmetry will be used in the presence of at least 10 studies. The Egger's test will be also used to evaluate the funnel plot asymmetry.[39]

Additional analyses

We would like to calculate the pooled prevalence for each suicidal outcome in subjects with and without cancer. Moreover, if there is a sufficient number of studies for each suicidal outcome, we will investigate potential sources of heterogeneity using metaregression models, and we will perform subgroup analyses by sociodemographic (eg, age, sex, ethnicity, socioeconomic status, social support) and clinical characteristics (eg, smoking and other substance use, physical disorders, pain, cancer type, cancer stage (0, I, II, III and IV), early and late suicide (early suicide: suicide during the first year after the cancer diagnosis)) and by study design (case–control and cohort). If possible, we will also compare subjects died by suicide to subjects died by accidental causes (myocardial infarction, road traffic and motor vehicle accidents, homicide, domestic and industrial accidents or any other external cause) as a secondary outcome. If sufficient data are available, we will perform a subgroup analysis on adult cancer survivors only.

Further potential points of discussion

Even if it might be outside of the scope of this study, considering the constant increase of the number of patients requesting Euthanasia or Assisted Suicide (EAS) in countries where this procedure is allowed[40] is mandatory. So, we will also take into account this issue, trying to differentiate between patients with cancer with a terminal condition and patient with a better prognosis requesting EAS.

Software

All analyses will be conducted in Stata V. 14.

Patient and public involvement

Patients and/or public were not involved.

Strengths and limitations of this study

To our knowledge, this will be the first systematic review and meta-analysis investigating the relationship between cancer and SI and behaviours. The implications of our future findings might provide evidence to the improvement of policies on suicidal symptom screening by healthcare professionals working in oncology.

Limitations mainly included the lack of investigation on specific topics: the number of studies investigating the timing of suicide risk following a cancer diagnosis, and specific cancer sites associated with suicide could be limited; also, it could be difficult to distinguish depressive symptoms from some cancer treatment-related and cancer disease-related symptoms.

Ethics and dissemination

No ethical approval is required to perform this study. We will publish results in a peer-reviewed scientific journal and data set will be made freely available.

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Contributors RC wrote the first draft of the protocol and subsequently incorporated the suggested revisions. FF, EM, QS and AC revised each section of the protocol. VEDM, JG-F and EB-G globally revised the writing. PC supervised the entire project.

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