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Complete List of Authors:	Harashima, Saki; National Cancer Center Japan, Division of Health Care Research, Behavioral Science and Survivorship Research Group, Center for Public Health Sciences; University of Tokyo Graduate School of Medicine Faculty of Medicine, Department of Stress Sciences and Psychosomatic Medicine Fujimori, Maiko; National Cancer Center Japan, Division of Health Care Research, Behavioral Science and Survivorship Research Group, Center for Public Health Sciences Akechi, Tatsuo; Nagoya City University Graduate School of Medical Sciences and Medical School, Department of Psychiatry and Cognitive-Behavioral Medicine Matsuda, Tomohiro; National Cancer Center Japan, Center for Cancer Registries, Center for Cancer Control and Information Services Saika, Kumiko; National Cancer Center Japan, Center for Cancer Registries, Center for Cancer Control and Information Services Hasegawa, Takaaki; Nagoya City University Hospital, Division of Psycho-oncology and Palliative Care Inoue, Keisuke; National Cancer Center Japan, Division of Health Care Research, Behavioral Science and Survivorship Research Group, Center for Public Health Sciences; Yokohama City University School of Medicine Graduate School of Medicine, Department of Psychiatry Yoshiuchi, Kazuhiro; University of Tokyo Graduate School of Medicine Faculty of Medicine, Department of Stress Sciences and Psychosomatic Medicine Miyashiro, Isao; Osaka International Cancer Institute, Cancer Control Center Uchitomi , Yosuke; National Cancer Center Hospital, Innovation Center for Supportive, Palliative and Psychosocial Care Matsuoka, Yutaka; National Cancer Center Japan, Division of Health Care Research, Behavioral Science and Survivorship Research Group, Center for Public Health Sciences
Keywords:	neoplasms, suicide, cardiovascular diseases, registries, standardized mortality ratio

Title

Suicide, other externally caused injuries, and cardiovascular death following a cancer diagnosis: study protocol for a nationwide population-based study in Japan

Saki Harashima[1, 2], Maiko Fujimori[1], Tatsuo Akechi[3], Tomohiro Matsuda[4], Kumiko Saika[4], Takaaki Hasegawa[5], Keisuke Inoue[1, 6], Kazuhiro Yoshiuchi[2], Isao Miyashiro[7], Yosuke Uchitomi[8], Yutaka J. Matsuoka[1].

Author affiliations

1) Division of Health Care Research, Behavioral Science and Survivorship Research Group, Center for Public Health Sciences, National Cancer Center Japan, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.

2) Department of Stress Sciences and Psychosomatic Medicine, University of Tokyo Graduate School of Medicine Faculty of Medicine, Tokyo, Japan.

3) Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences and Medical School, Nagoya, Japan.

4) Center for Cancer Registries, Center for Cancer Control and Information Services, National Cancer Center Japan, Tokyo, Japan.

5) Division of Psycho-oncology and Palliative Care, Nagoya City University Hospital, Nagoya, Japan.

6) Department of Psychiatry, Yokohama City University School of Medicine Graduate School of Medicine, Yokohama, Japan.

7) Cancer Control Center, Osaka International Cancer Institute, Osaka, Japan.

8) Innovation Center for Supportive, Palliative and Psychosocial Care, National Cancer Center Hospital, Tokyo, Japan.

Corresponding author: Maiko Fujimori, postal address: Division of Health Care Research, Behavioral Science and Survivorship Research Group, Center for Public Health Sciences, National Cancer Center Japan, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. e-mail address: mfujimor@ncc.go.jp, telephone number: +81-3-3547-5201.

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Abstract

Introduction: A growing body of literature has demonstrated that cancer patients have a higher risk of suicide and cardiovascular mortality compared with the general population, especially immediately after diagnosis. Using data from the National Cancer Registry (NCR) in Japan launched in January 2016, we will conduct the first nationwide population-based study in Japan to compare incidence of death from suicide, other externally caused injuries (ECIs), and cardiovascular disease following a cancer diagnosis with that of the general population in Japan. We will also aim to identify the patient subgroups and time periods associated with particularly high risk.

Methods and analysis: Our study cohort will consist of all cancer cases diagnosed in Japan from 1 January 2016 onward and registered in the NCR. We are planning a series of analyses according to data availability from the NCR; the duration of patient inclusion and follow-up will be different for each analysis. We will calculate standardized mortality ratios (SMRs) and excess absolute risks (EARs) for suicide, other ECIs, and cardiovascular death compared with the general population in Japan, after adjustment for sex, age, and prefecture. SMRs and EARs will be calculated separately in relation to a number of factors: sex; age at diagnosis; time since cancer diagnosis; prefecture of residence at diagnosis; primary tumor site; behavior code of tumor; extension of tumor;

whether definitive surgery of the primary site was performed; and month of death. We will conduct the first analysis using cancer incidence and death information from year 2016 cases, which will become available in 2019.

Ethics and dissemination: The study protocol was approved by the institutional review board and ethics committee of the National Cancer Center Japan and Nagoya City University Graduate School of Medical Sciences. The findings will be disseminated through peer-reviewed publications and conference presentations.

Registration number: UMIN000035118

Strengths and limitations of this study

- This will be the first nationwide population-based study in Japan to investigate the impact of a cancer diagnosis on subsequent death by suicide, other externally caused injuries, and cardiovascular events.
- Our study will cover virtually all cancer incidence and subsequent fatal outcomes in Japan.
- Our study will not be able to control for potential confounding factors for cancer, suicide, and cardiovascular events, such as smoking history and alcohol use, sociodemographic status, and pre-existing medical and psychiatric conditions.

- Incidence and survival data in the NCR may be incomplete and/or unstable for the first few years after its launch.

Introduction

In Japan, it is estimated that approximately 1 million people have been newly diagnosed with cancer annually in recent years, and about 1 in 2 Japanese will receive a cancer diagnosis during their lifetime.[1]

Receiving a cancer diagnosis and undergoing diagnostic workup leading to a definite cancer diagnosis are highly stressful experiences for cancer patients, and a high prevalence of psychiatric symptoms and disorders has been observed around the time of cancer diagnosis.[2,3] A number of population-based studies have consistently demonstrated that patients with cancer are at increased risk for suicide,[4-15] especially in the weeks after their cancer diagnosis.[16-19] A high incidence of other externally caused injuries (ECIs), including accidental death and death due to events of undetermined intent, has also been reported among cancer patients.[20-22] Some suicide deaths may be misclassified as other ECIs,[23,24] and physical, psychological, and social impairment due to cancer itself or adverse effects of cancer treatment could increase the risk of accidental death.[25]

Furthermore, a few population-based studies have demonstrated that the period immediately after a cancer diagnosis is related to elevated mortality from cardiovascular causes among patients with prostate cancer[26,27] and those with other cancer types as well.[17] Acute psychological stressors, such as earthquakes, war, and the death of a loved one, are known to trigger cardiovascular events.[28-31] Acute emotional distress induced by a cancer diagnosis may also affect cardiovascular functioning and cause critical outcomes beyond the influence of cancer itself or cancer treatment. Possible mechanisms linking acute psychological stressors to cardiovascular events include pathophysiological pathways that have the potential to cause rupture of vulnerable plaque, thrombosis formation, or fatal arrhythmias (e.g., increased sympathetic tone, blood pressure, shear stress, and blood viscosity; endothelial dysfunction; and hypercoagulability), and health-impairing behaviors related to emotional distress.[28,29]

Suicide risk among persons with cancer has been suggested to differ between different ethnic and cultural groups.[32] Two previous studies have reported risk of suicide among Japanese patients with cancer compared with the general population.[22,33] The first, a single-institution study demonstrated that suicide risk among patients newly diagnosed with cancer was significantly elevated within the first year after diagnosis.[33] The second, a population-based prospective study investigating Japanese residents and including over

10,000 cancer patients, showed that risk of death by suicide and other ECIs was about 24 and 19 times higher, respectively, among those with cancer within the first year after cancer diagnosis than among those without cancer.[22] There has been no nationwide study examining the risk of suicide among cancer patients in Japan, and cardiovascular mortality risk following a cancer diagnosis has not been investigated in countries other than Sweden and the United States. As Japan is aging faster than any other country in the world and the number of patients with newly diagnosed cancer is expected to keep increasing,[34] the impact of a cancer diagnosis on subsequent stress-related outcomes is a serious public health issue. It is necessary to identify vulnerable patients and the window of maximum risk in order to implement appropriate supportive and preventive intervention.

The Act on Promotion of Cancer Registries was enacted in Japan in 2013 and the National Cancer Registry (NCR) in Japan was launched on 1 January 2016.[35,36] According to the Act, hospitals in Japan have a legal duty to report all targeted cancer cases to the NCR. The NCR has enabled hospitals to calculate accurate cancer incidences and survival rates, and it is expected that the NCR database will contribute to planning and assessment of evidence-based cancer control policies and promote research in such areas as evaluation of cancer care quality and follow-up surveys in nationwide cohort

studies. The first NCR data will become available for research purposes in 2019.

Using data from the NCR, we will conduct the first nationwide population-based study in Japan to characterize the incidence of death by suicide, ECIs, and cardiovascular disease among patients with a cancer diagnosis compared with the general population in Japan. We will also aim to identify higher-risk patients and time periods that may require more attention. We hypothesize that the risk of suicide, other ECIs, and cardiovascular death is significantly higher within the first year after a cancer diagnosis and that the period soon after a cancer diagnosis is associated with the greatest risk.

Methods

Data sources

Cancer patients will be identified from the NCR database in Japan. The NCR covers the total population in Japan, and hospitals are required to report all targeted cancer cases newly diagnosed in their institutions from 1 January 2016 onward, irrespective of patient nationality. Data from cancer care hospitals are submitted annually and matched inter-prefecturally, and mortality data submitted by municipalities are matched with the incidence data in the NCR database. The data collection deadline for each year's cases is the end of the following year, and the data will become available for research purposes

the year after that. The unit of registration is tumor, duplications of the same cancer case are corrected, and each cancer is registered separately for cases in which a patient is judged to have multiple primary cancers based on pathology.

The targeted neoplasms for the NCR include intraepithelial and malignant tumors corresponding to a behavioral code of 2 or 3 in the International Classification of Diseases for Oncology, Third Edition (ICD-O-3); benign and uncertain whether benign or malignant central nervous system (CNS) neoplasms and gastrointestinal stromal tumors; and some types of ovarian borderline malignant tumors. The standard items submitted to the NCR by cancer care hospitals are presented in Table 1. The date of cancer diagnosis is defined as the date of the most definitive diagnostic test before initiation of treatment. Information such as race, educational status, marital status, income, insurance status, and comorbidity is not registered in the NCR database.

Details of the NCR system have been described previously.[35,36]

Study population and inclusion criteria

Our study cohort will consist of all cancer cases diagnosed in Japan and registered in the NCR from 1 January 2016 onward. We will exclude cancer cases that are diagnosed incidentally at autopsy, reported only on a death certificate, or missing a diagnosis date.

For individuals with multiple cancers, the start of the at-risk period will be defined as the date of the most recent cancer diagnosis. It is estimated that about 1 million cancer patients have been diagnosed annually in recent years in Japan.[1] We are planning a series of analyses according to NCR data availability, and the duration of patient inclusion and follow-up will be different for each analysis. We will conduct the first analysis in 2019, using cancer incidence and death information from year 2016 cases.

Study variables

We will identify cancer patients who died by suicide, ECIs, and cardiovascular causes based on cause of death registered in the NCR database. Outcomes will be classified according to the International Classification of Diseases, 10th Edition (ICD-10) as follows: suicide (X60-X84 and Y87.0), other ECIs (V01-X59 and Y10-Y34), and cardiovascular diseases (I00-I99). Cardiovascular death will be further subcategorized as myocardial infarction (I21-I24), other disease of the heart (I10-I13, I71, and I72), embolism or thrombosis (I26, I74, I80.1, I81, I82, and I85.0), stroke (I60-I64), hemorrhagic stroke (I60-I62), ischemic stroke (I63), and others.

Other information we will obtain from the NCR includes sex, age at diagnosis, prefecture of residence at diagnosis, presence/absence of multiple primary tumors,

primary site of tumor according to ICD-10 codes, basis of diagnosis, date of diagnosis, extension of tumor, presence/absence of each treatment, presence/absence of definitive surgery of the primary site, hospital region, survival status, and survival time..

Statistical analysis

Standardized mortality ratios (SMRs) will be calculated as the observed numbers of targeted events (i.e., suicide, other ECIs, or cardiovascular death) among cancer patients divided by the expected numbers of events in the general population. Excess absolute risks (EARs) will be calculated by subtracting the expected numbers of events from the observed numbers of events; the difference will be then divided by person-years of cancer patients, and the number of events in excess will be expressed per 10,000 person-years. The expected numbers of events will be obtained by multiplying the number of person-years at risk, stratified by sex, age group (0-4, 5-9, …, 80-84, ≥ 85 years), prefecture, and calendar year, by mortality rates from targeted events in each year in the general population in Japan in each corresponding stratum. We will calculate mortality rates by sex, age, and prefecture in each year in the general population by dividing the numbers of death from each event occurring in Japan (based on datasets from Vital Statics Japan, provided by the Ministry of Health, Labour and Welfare) by the estimated total population

in Japan based on Population Estimates.[37] We will calculate 95% confidence intervals (CIs) of SMRs and EARs by assuming that the observed numbers of events follow a Poisson distribution. All analyses will be performed using SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp).

SMRs and EARs will be calculated separately in relation to a number of factors: sex, age at diagnosis, time since cancer diagnosis, prefecture of residence at diagnosis, primary tumor site, behavioral code of tumor, extension of tumor, whether definitive surgery of the primary site was performed, and month of death. Age at diagnosis will be stratified into the following groups: 0-39, 40-49, 50-59, 60-69, 70-79, and ≥ 80 years. Primary tumor site will be based on the classifications used in the Monitoring of Cancer Incidence in Japan (MCIJ) project (Table 2).[38] The extension of tumor will be classified into localized (confined to the original organ), regional (spread to regional lymph nodes and/or adjacent tissue), metastatic (metastasized to distant organ), and unknown. Stroke will be excluded from cardiovascular mortality in the analysis of CNS tumors, and CNS tumors will be excluded from "any cancer" in the analysis of death from cardiovascular causes. Cases of hematologic disease will be excluded in the analysis of presence/absence of definitive surgery. We will also explore the suicide methods used by cancer patients and the factors affecting their choice of method.

We will also divide cancer patients who die during the observation period into 3 groups according to the main cause of death: (1) cancer, (2) suicide, other ECIs, and cardiovascular diseases, and (3) others. Characteristics of patients and tumors will be compared among these groups.

Discussion

This will be the first nationwide study in Japan to investigate the impact of a cancer diagnosis on subsequent death by suicide, other ECIs, and cardiovascular events. The main strength of this study is that it will cover virtually all cancer incidence and subsequent fatal outcomes in Japan using information registered in the NCR. SMRs and EARs of stress-related outcomes after a cancer diagnosis will help to identify higher-risk patients and time periods, and will provide useful evidence for considering the priority of preventive strategies.

Several limitations inherent in this study should be acknowledged. First, our study will not be able to control for potential confounding factors for cancer, suicide, and cardiovascular events, such as smoking history and alcohol use, sociodemographic status, and pre-existing medical and psychiatric conditions. These data are not collected in the NCR and we cannot link anonymous cancer registry information to other medical and

socioeconomic databases. Second, our study will explore mortality outcomes alone and we cannot capture nonfatal outcomes, such as suicidal ideation, attempted suicide, and nonlethal cardiovascular events. Our findings will represent only a small portion of the psychological burden associated with a cancer diagnosis. Finally, although we will use data from the NCR, which covers the total population in Japan, it is anticipated that incidence and survival data in the NCR may be incomplete and/or unstable for the first few years after its 2016 launch.

Article Summary

Patient and public involvement

Patients and/or public were not involved.

Ethics and dissemination

The study protocol was approved by the institutional review board and ethics committee of the National Cancer Center Japan and Nagoya City University Graduate School of Medical Sciences. The Act on Promotion of Cancer Registries does not require informed consent for the provision of anonymous information, and the requirement for opt-out will be waived because no personal identifiable information will be accessed. The findings

will be disseminated through peer-reviewed publications and conference presentations.

Acknowledgement

This study is reviewed and supported by the Japan Supportive, Palliative and Psychosocial Oncology Group (J-SUPPORT) in terms of the adequacy of the research involved, and approved as J-SUPPORT 1902.

Footnotes

Author Contributions

SH and MF wrote the first draft of the manuscript and subsequently incorporated the suggested revisions. All authors contributed to the study conception and design. TM and KS advised on statistical analysis and management of the database. TA and YU supervised the project. All authors contributed to revision of the protocol and have approved the final version of the manuscript.

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Competing interests

None declared.

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Table 1. Items submitted to the National Cancer Registry in Japan by cancer care hospitals.

1. Name of hospital	14. Date of diagnosis
2. Patient's ID	15. Circumstance of cancer detection
3. Name (Hiragana)	16. Extension of disease (clinical)
4. Name (Kanji)	17. Extension of disease (pathological)
5. Sex	18. Surgery of primary site
6. Birth date	19. Laparo/thoracoscopic surgery
7. Address of patients	20. Endoscopic surgery
8. Laterality	21. Result of surgery
9. Diagnosis (primary site)	22. Radiation therapy
10. Diagnosis (morphology)	23. Chemotherapy
11. Diagnosis facility	24. Endocrinotherapy
12. Treatment facility	25. Other treatment
13. Basis of diagnosis	26. Date of death

Table 2. Primary tumor site according to International Classification of Diseases, 10th Edition code used in the Monitoring of Cancer Incidence in Japan (MCIJ) project.[38]

Any cancer (C00-C96, D00-D09)	Breast (C50, D05)
Oral cavity and pharynx (C00-C14)	Uterus (C53-C55, D06)
Esophagus (C15, D001)	Cervix uteri (C53, D06)
Stomach (C16)	Corpus uteri (C54)
Colon and rectum (C18-C20, D010-D012)	Ovary (C56)
Colon (C18 and D010)	Prostate (C61)
Rectum (C19-C20, D011-D012)	Bladder (C67, D090)
Liver and intrahepatic bile ducts (C22)	Kidney and urinary organs (except bladder) (C64-C66, C68)
Gallbladder and other parts of biliary tract (C23-C24)	Brain and other parts of central nervous system (C70-C72)
Pancreas (C25)	Thyroid (C73)
Larynx (C32)	Malignant lymphoma (C81-C85, C96)
Lung and bronchus (C33-C34, D021-D022)	Multiple myeloma (C88, C90)
Skin (C43-C44, D030-D049)	Leukemia (C91-C95)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-10
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	9
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-10
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-12
		(*b*) Describe any methods used to examine subgroups and interactions	11-12
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,	

		multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Suicide, other externally caused injuries, and cardiovascular death following a cancer diagnosis: study protocol for a nationwide population-based study in Japan

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Complete List of Authors:	Harashima, Saki; National Cancer Center Japan, Division of Health Care Research, Behavioral Science and Survivorship Research Group, Center for Public Health Sciences; The University of Tokyo Graduate School of Medicine, Department of Stress Sciences and Psychosomatic Medicine Fujimori, Maiko; National Cancer Center Japan, Division of Health Care Research, Behavioral Science and Survivorship Research Group, Center for Public Health Sciences Akechi, Tatsuo; Nagoya City University Graduate School of Medical Sciences, Department of Psychiatry and Cognitive-Behavioral Medicine Matsuda, Tomohiro; National Cancer Center Japan, Center for Cancer Registries, Center for Cancer Control and Information Services Saika, Kumiko; National Cancer Center Japan, Center for Cancer Registries, Center for Cancer Control and Information Services Hasegawa, Takaaki; Nagoya City University Hospital, Division of Psycho-oncology and Palliative Care Inoue, Keisuke; National Cancer Center Japan, Division of Health Care Research, Behavioral Science and Survivorship Research Group, Center for Public Health Sciences; Yokohama City University School of Medicine, Department of Psychiatry Yoshiuchi, Kazuhiro; The University of Tokyo Graduate School of Medicine, Departmnt of Stress Sciences and Psychosomatic Medicine Miyashiro, Isao; Osaka International Cancer Institute, Cancer Control Center Uchitomi , Yosuke; National Cancer Center Hospital, Innovation Center for Supportive, Palliative and Psychosocial Care Matsuoka, Yutaka; National Cancer Center Japan, Division of Health Care Research, Behavioral Science and Survivorship Research Group, Center for Public Health Sciences
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Keywords:	neoplasms, suicide, cardiovascular diseases, registries, standardized mortality ratio

Title

Suicide, other externally caused injuries, and cardiovascular death following a cancer diagnosis: study protocol for a nationwide population-based study in Japan

Saki Harashima[1, 2], Maiko Fujimori[1], Tatsuo Akechi[3], Tomohiro Matsuda[4], Kumiko Saika[4], Takaaki Hasegawa[5], Keisuke Inoue[1, 6], Kazuhiro Yoshiuchi[2], Isao Miyashiro[7], Yosuke Uchitomi[8], Yutaka J. Matsuoka[1].

Author affiliations

1) Division of Health Care Research, Behavioral Science and Survivorship Research Group, Center for Public Health Sciences, National Cancer Center Japan, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.

2) Department of Stress Sciences and Psychosomatic Medicine, The University of Tokyo Graduate School of Medicine, Tokyo, Japan.

3) Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

4) Center for Cancer Registries, Center for Cancer Control and Information Services, National Cancer Center Japan, Tokyo, Japan.

5) Division of Psycho-oncology and Palliative Care, Nagoya City University Hospital, Nagoya, Japan.

6) Department of Psychiatry, Yokohama City University School of Medicine, Yokohama, Japan.

7) Cancer Control Center, Osaka International Cancer Institute, Osaka, Japan.

8) Innovation Center for Supportive, Palliative and Psychosocial Care, National Cancer Center Hospital, Tokyo, Japan.

Corresponding author: Maiko Fujimori, postal address: Division of Health Care Research, Behavioral Science and Survivorship Research Group, Center for Public Health Sciences, National Cancer Center Japan, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. e-mail address: mfujimor@ncc.go.jp, telephone number: +81-3-3547-5201.

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Abstract

Introduction: A growing body of literature has demonstrated that cancer patients have a higher risk of suicide and cardiovascular mortality compared with the general population, especially immediately after a cancer diagnosis. Using data from the National Cancer Registry (NCR) in Japan launched in January 2016, we will conduct the first nationwide population-based study in Japan to compare incidence of death by suicide, other externally caused injuries (ECIs), and cardiovascular disease following a cancer diagnosis with that of the general population in Japan. We will also aim to identify the patient subgroups and time periods associated with particularly high risk.

Methods and analysis: Our study subjects will consist of cancer cases diagnosed between 1 January 2016 and 31 December 2016 in Japan and they will be observed until 31 December 2018. We will calculate standardized mortality ratios (SMRs) and excess absolute risks (EARs) for suicide, other ECIs, and cardiovascular death compared with the general population in Japan, after adjustment for sex, age, and prefecture. SMRs and EARs will be calculated separately in relation to a number of factors: sex; age at diagnosis; time since cancer diagnosis; prefecture of residence at diagnosis; primary tumor site; behavior code of tumor; extension of tumor; whether definitive surgery of the primary site was performed; and presence/absence of multiple primary tumors.

Ethics and dissemination: The study protocol was approved by the institutional review board and ethics committee of the National Cancer Center Japan and Nagoya City University Graduate School of Medical Sciences. The findings will be disseminated through peer-reviewed publications and conference presentations.

Registration number: UMIN000035118

Strengths and limitations of this study

- This will be the first nationwide population-based study in Japan to investigate the impact of a cancer diagnosis on subsequent death by suicide, other externally caused injuries, and cardiovascular events.
- Our study will cover virtually all cancer incidence and subsequent fatal outcomes in Japan.
- Our study will not be able to control for potential confounding factors for cancer, suicide, and cardiovascular events, such as smoking history and alcohol use, sociodemographic status, and pre-existing medical and psychiatric conditions.

Introduction

In Japan, it is estimated that approximately 1 million people have been newly diagnosed

with cancer annually in recent years, and about 1 in 2 Japanese will receive a cancer diagnosis during their lifetime.[1]

Receiving a cancer diagnosis and undergoing diagnostic workup leading to a definite cancer diagnosis are highly stressful experiences for cancer patients, and a high prevalence of psychiatric symptoms and disorders has been observed around the time of a cancer diagnosis.[2, 3] A number of population-based studies have consistently demonstrated that patients with cancer are at increased risk for suicide,[4-15] especially in the weeks after their cancer diagnosis.[16-19] A high incidence of other externally caused injuries (ECIs), including accidental death and death due to events of undetermined intent, has also been reported among cancer patients.[20-22] Some suicide deaths may be misclassified as other ECIs,[23, 24] and physical, psychological, and social impairment due to cancer itself or adverse effects of cancer treatment could increase the risk of accidental death.[25]

Furthermore, a few population-based studies have demonstrated that the period immediately after a cancer diagnosis is related to elevated mortality from cardiovascular causes among patients with prostate cancer[26, 27] and those with other cancer types as well.[17] Acute psychological stressors, such as earthquakes, war, and the death of a loved one, are known to trigger cardiovascular events.[28-31] Acute emotional distress

induced by a cancer diagnosis may also affect cardiovascular functioning and cause critical outcomes beyond the influence of cancer itself or cancer treatment. Possible mechanisms linking acute psychological stressors to cardiovascular events include pathophysiological pathways that have the potential to cause rupture of vulnerable plaque, thrombosis formation, or fatal arrhythmias (e.g., increased sympathetic tone, blood pressure, shear stress, and blood viscosity; endothelial dysfunction; and hypercoagulability), and health-impairing behaviors related to emotional distress.[28. 29]

Suicide risk among persons with cancer has been suggested to differ between different ethnic and cultural groups.[32] Two previous studies have reported risk of suicide among Japanese patients with cancer compared with the general population.[22, 33] The first, a single-institution study demonstrated that suicide risk among patients newly diagnosed with cancer was significantly elevated within the first year after a diagnosis.[33] The second, a population-based prospective study investigating Japanese residents including over 10,000 cancer patients, showed that risk of death by suicide and other ECIs was about 24 and 19 times higher, respectively, among those with cancer within the first year after a cancer diagnosis than among those without cancer.[22] There has been no nationwide study examining the risk of suicide among cancer

patients in Japan, and cardiovascular mortality risk following a cancer diagnosis has not been investigated in countries other than Sweden and the United States. As Japan is aging faster than any other country in the world and the number of patients with newly diagnosed cancer is expected to keep increasing,[34] the impact of a cancer diagnosis on subsequent stress-related outcomes is a serious public health issue. It is necessary to identify vulnerable patients and the window of maximum risk in order to implement appropriate supportive and preventive intervention.

The Act on Promotion of Cancer Registries was enacted in Japan in 2013 and the National Cancer Registry (NCR) in Japan was launched on 1 January 2016.[35, 36] According to the Act, hospitals in Japan have a legal duty to report all targeted cancer cases (i.e. intraepithelial and malignant tumors corresponding to a behavioral code of 2 or 3 in the International Classification of Diseases for Oncology, Third Edition (ICD-O-3); benign and uncertain whether benign or malignant central nervous system (CNS) neoplasms and gastrointestinal stromal tumors; and some types of ovarian borderline malignant tumors) to the NCR. The NCR has enabled hospitals to calculate accurate cancer incidences and survival rates, and it is expected that the NCR database will contribute to planning and assessment of evidence-based cancer control policies and promote research in such areas as evaluation of cancer care quality and follow-up

surveys in nationwide cohort studies. The first NCR data will become available for research purposes in 2019.

Using data from the NCR, we will conduct the first nationwide population-based study in Japan to characterize the incidence of death by suicide, ECIs, and cardiovascular disease among patients with a cancer diagnosis compared with the general population in Japan. We will also aim to identify higher-risk patients and time periods that may require more attention. We hypothesize that the risk of suicide, other ECIs, and cardiovascular death is significantly higher within the first year after a cancer diagnosis and that the period soon after a cancer diagnosis is associated with the greatest risk.

Methods

Data sources

Cancer patients will be identified from the NCR database in Japan. The NCR covers the total population in Japan, and hospitals are required to report all targeted cancer cases newly diagnosed in their institutions from 1 January 2016 onward, irrespective of patient nationality. The NCR system in Japan is described in Figure 1. Incidence data from cancer care hospitals are submitted to prefectual governors and prefectural

governors review and match record in their prefecture and enter the data in the NCR database in the Ministry of Health, Labour and Welfare (MHLW) (National Cancer Center (NCC)). The MHLW /NCC matches the cancer registry data inter-prefectually and information from death certificate on cancer disease is matched with the incidence data in the NCR. The NCC follows up cancer patients in the NCR database by linking to national death certificate data and registers death information in the NCR. The unit of registration is tumor, duplications of the same cancer case are corrected, and each cancer is registered separately for cases in which a patient is judged to have multiple primary cancers based on pathology. Data aggregation is based on name, birth date, and address of patients. The data collection deadline for each year's cases is the end of the following year, and the data will become available for research purposes the year after that. Data quality of the NCR for year 2016 cases has been reported to be very high: the proportion of Death Certificate Notification (DCN) was 4.5%, the proportion of Death Certificate Only (DCO) was 3.2%, the mortality incidence (M/I) ratio was 0.37, and the morphological verification (MV) proportion was 85.4%.[37]

The standard items submitted to the NCR by cancer care hospitals are presented in Table 1. The date of cancer diagnosis is defined as the date of the most definitive diagnostic test before initiation of treatment and diagnostic tests are arranged

hierarchically by levels of definitiveness as follows: histopathologic testing of primary tumor, histopathologic testing of metastatic tumor, cytology, certain kind of tumor specific markers, other clinical testing, and clinical diagnosis.[38] Information such as race, educational status, marital status, income, insurance status, and comorbidity is not registered in the NCR database.

Details of the NCR system have been described previously.[35, 36]

Study population and inclusion criteria

Our study cohort will consist of all cancer cases diagnosed in Japan between 1 January 2016 and 31 December 2016 and registered in the NCR and they will be followed until 31 December 2018. We will exclude cancer cases that are diagnosed incidentally at autopsy, reported only on a death certificate, or missing a diagnosis date. For individuals with multiple cancers, the start of the at-risk period will be defined as the date of the most recent cancer diagnosis. A total of 995,132 malignant cancer cases (defined by C00-C96 according to International Classification of Diseases, 10th Edition (ICD-10)) were diagnosed in Japan in 2016,[37] and about 1 million cancer patients will be included in our study.

Study variables

We will identify cancer patients who died by suicide, ECIs, and cardiovascular causes based on underlying cause of death according to ICD-10 registered in the NCR database. Outcomes will be classified as follows: suicide (X60-X84 and Y87.0), other ECIs (V01-X59 and Y10-Y34), and cardiovascular diseases (I00-I99). Cardiovascular death will be further subcategorized as myocardial infarction (I21-I24), other disease of the heart (I10-I13, I71, and I72), embolism or thrombosis (I26, I74, I80.1, I81, I82, and I85.0), stroke (I60-I64), hemorrhagic stroke (I60-I62), ischemic stroke (I63), and others. Quality of cause of death information in Japan has been reported to be high.[39] Other information we will obtain from the NCR includes sex, age at diagnosis, prefecture of residence at diagnosis, presence/absence of multiple primary tumors, primary site of tumor according to ICD-10 codes, basis of diagnosis, date of diagnosis, extension of tumor, presence/absence of each treatment, presence/absence of definitive surgery of the primary site, hospital region, survival status, and survival time.

Statistical analysis

Person-years at risk will be computed from the date of a cancer diagnosis to the date of death, or December 31 2018, whichever comes first. Standardized mortality ratios

(SMRs) will be calculated as the observed numbers of targeted events (i.e. suicide, other ECIs, or cardiovascular death) among cancer patients divided by the expected numbers of events in the general population. Excess absolute risks (EARs) will be calculated by subtracting the expected numbers of events from the observed numbers of events; the difference will be then divided by person-years of cancer patients, and the number of events in excess will be expressed per 10,000 person-years. The expected numbers of events will be obtained by multiplying the number of person-years at risk, stratified by sex, age group (0-4, 5-9, …, 80-84, ≥ 85 years), prefecture, and calendar year, by mortality rates from targeted events in each year in the general population in Japan in each corresponding stratum. We will calculate mortality rates by sex, age, and prefecture in each year in the general population by dividing the numbers of death from each event occurring in Japan (based on datasets from Vital Statics Japan, provided by the MHLW) by the estimated total population in Japan based on Population Estimates.[40] The numbers of death by each targeted event in the general population will be calculated by using the same definition according to ICD-10 codes as those used in the cancer patients. We will calculate 95% confidence intervals (CIs) of SMRs and EARs by assuming that the observed numbers of events follow a Poisson distribution.

SMRs and EARs will be calculated separately in relation to a number of factors:

sex, age at diagnosis, time since cancer diagnosis, prefecture of residence at diagnosis, primary tumor site, behavioral code of tumor, extension of tumor, whether definitive surgery of the primary site was performed, and presence/absence of multiple tumor. Age at diagnosis will be stratified into the following groups: 0-39, 40-49, 50-59, 60-69, 70-79, and ≥ 80 years. Time after a cancer diagnosis will be divided into 0 to 2 months, 3 to 5 months, 6 to 11 months, and ≥ 12 months for suicide and other ECIs. Risk of suicide and other ECIs during the first week after diagnosis will be also separately calculated. For cardiovascular death, we will investigate < 1 week, 1 week to < 1 month, 1 to 5 months, 6 to 11 months, and ≥ 12 months. Primary tumor site will be based on the classifications used in the MCIJ project (Table 2).[41] The extension of tumor will be classified into localized (confined to the original organ), regional (spread to regional lymph nodes and/or adjacent tissue), metastatic (metastasized to distant organ), and unknown. Stroke will be excluded from cardiovascular mortality in the analysis of CNS tumors, and CNS tumors will be excluded from "any cancer" in the analysis of death from cardiovascular causes.[17] Cases of hematologic disease will be excluded in the analysis of presence/absence of definitive surgery. Likelihood ratio tests based on Poisson regression models will be conducted to test for heterogeneity. All *p*-value will be two-sided tests and be considered to be statistically significant at a *p*-value of less

than 0.05. We will also perform multivariable regression analysis based on Poisson regression models to adjust for following factors: sex, age at a cancer diagnosis, primary tumor site, extension of tumor, presence/absence of multiple tumors, and follow-up period. All factors will be included in the multivariable regression model with no interaction terms. We will also test for the heterogeneity from the multivariable models.

In order to explore the factors affecting their choice of suicide method by cancer patients we will describe distribution of characteristics of patients and tumors (e.g. sex, age at diagnosis, extension of tumor, and time since diagnosis) by common suicide methods in Japan (e.g. poisoning (X60-X69), hanging (X70), and jumping from heights (X80)).

We will also divide cancer patients who die during the observation period into 2 groups according to the main cause of death: (1) suicide, other ECIs, and cardiovascular diseases, and (2) others. Characteristics of patients and tumors will be compared between two groups.

All analyses will be performed using SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp).

Discussion

This will be the first nationwide study in Japan to investigate the impact of a cancer diagnosis on subsequent death by suicide, other ECIs, and cardiovascular events. The main strength of this study is that it will cover virtually all cancer incidence and subsequent fatal outcomes in Japan using information registered in the NCR. SMRs and EARs of stress-related outcomes after a cancer diagnosis will help to identify higher-risk patients and time periods, and will provide useful evidence for considering the priority of preventive strategies.

Several limitations inherent in this study should be acknowledged. First, our study will not be able to control for potential confounding factors for cancer, suicide, and cardiovascular events, such as smoking history and alcohol use, sociodemographic status, and pre-existing medical and psychiatric conditions. These data are not collected in the NCR and we cannot link anonymous cancer registry information to other medical and socioeconomic databases. Second, our study will explore mortality outcomes alone and we cannot capture nonfatal outcomes, such as suicidal ideation, attempted suicide, and nonlethal cardiovascular events. Our findings will represent only a small portion of the psychological burden associated with a cancer diagnosis. Third, some deaths classified as other ECIs may be misclassification of deaths due to suicide,[23, 24] and assuming that more under-reporting of suicide occurs in cancer patients than in the

general population, risk of suicide among cancer patients in our study will be potentially underestimated. Fourth, in the analysis of presence/absence of definitive surgery of the primary tumor, the result should be interpreted with caution because only patients who did not die by targeted outcomes and survived until surgery could undergo surgery. Finally, if death ascertainment in the NCR system is incomplete, risk of deaths by targeted causes among cancer patients can be underestimated.

Article Summary

Patient and public involvement

Patients and/or public were not involved.

Ethics and dissemination

The study protocol was approved by the institutional review board and ethics committee of the National Cancer Center Japan and Nagoya City University Graduate School of Medical Sciences. The Act on Promotion of Cancer Registries does not require informed consent for the provision of anonymous information, and the requirement for opt-out will be waived because no personal identifiable information will be accessed. The findings will be disseminated through peer-reviewed publications and conference

presentations.

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Footnotes

Author Contributions

SH, MF, TA, TM, KS, TH, KI, KY, IM, YU, and YM contributed to the study conception and design. TM and KS advised on statistical analysis and management of the database. TA and YU supervised the project. SH and MF will perform the data analysis and all coauthors will be involved in interpretation of the data. SH and MF wrote the first draft of the manuscript and all coauthors reviewed the manuscript and provided critical revisions. All authors have approved the final version of the manuscript.

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310

311 **Competing interests**

312 None declared.

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Table 1. Items submitted to the National Cancer Registry in Japan by cancer care hospitals.

1. Name of hospital	14. Date of diagnosis
2. Patient's ID	15. Circumstance of cancer detection
3. Name (Hiragana)	16. Extension of disease (clinical)
4. Name (Kanji)	17. Extension of disease (pathological)
5. Sex	18. Surgery of primary site
6. Birth date	19. Laparo/thoracoscopic surgery
7. Address of patients	20. Endoscopic surgery
8. Laterality	21. Result of surgery
9. Diagnosis (primary site)	22. Radiation therapy
10. Diagnosis (morphology)	23. Chemotherapy
11. Diagnosis facility	24. Endocrinotherapy
12. Treatment facility	25. Other treatment
13. Basis of diagnosis	26. Date of death

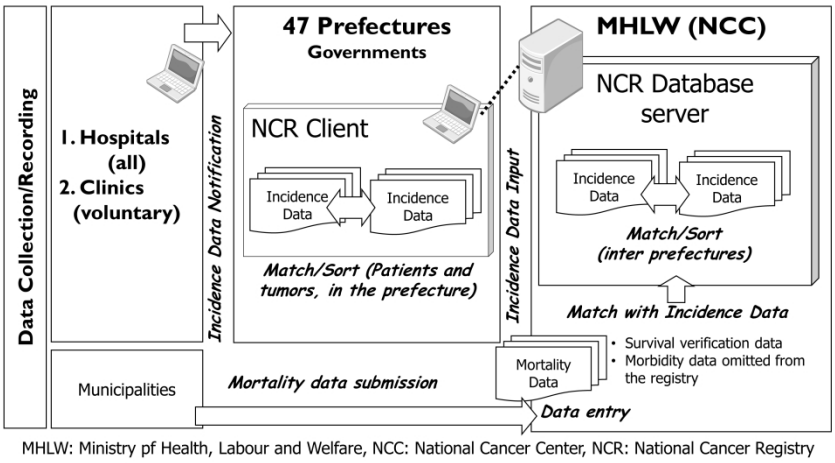
Table 2. Primary tumor site according to International Classification of Diseases, 10th Edition code used in the Monitoring of Cancer Incidence in Japan (MCIJ) project.[41]

Any cancer (C00-C96, D00-D09)	Breast (C50, D05)
Oral cavity and pharynx (C00-C14)	Uterus (C53-C55, D06)
Esophagus (C15, D001)	Cervix uteri (C53, D06)
Stomach (C16)	Corpus uteri (C54)
Colon and rectum (C18-C20, D010-D012)	Ovary (C56)
Colon (C18 and D010)	Prostate (C61)
Rectum (C19-C20, D011-D012)	Bladder (C67, D090)
Liver and intrahepatic bile ducts (C22)	Kidney and urinary organs (except bladder) (C64-C66, C68)
Gallbladder and other parts of biliary tract (C23-C24)	Brain and other parts of central nervous system (C70-C72)
Pancreas (C25)	Thyroid (C73)
Larynx (C32)	Malignant lymphoma (C81-C85, C96)
Lung and bronchus (C33-C34, D021-D022)	Multiple myeloma (C88, C90)
Skin (C43-C44, D030-D049)	Leukemia (C91-C95)

Figure legends

Figure 1. The National Cancer Registry system in Japan.

Reporting of newly diagnosed cancer cases from 1 January 2016 onward has become a legislative duty of hospitals in Japan. Information collected in each prefecture must be registered in the National Cancer Registry (NCR) database and the National Cancer Center follows up patients in the NCR by linking to mortality data based on national death certificate files.



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338x190mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10-11
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	10-11
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-14
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10-11
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-14
		(*b*) Describe any methods used to examine subgroups and interactions	12-14
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,	

		multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17-18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.