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

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6 **Title**
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10 2 Suicide, other externally caused injuries, and cardiovascular death following a cancer
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12 3 diagnosis: study protocol for a nationwide population-based study in Japan
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18 5 Saki Harashima^{1, 2}, Maiko Fujimori¹, Tatsuo Akechi³, Tomohiro Matsuda⁴, Kumiko
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21 6 Saika⁴, Takaaki Hasegawa⁵, Keisuke Inoue^{1, 6}, Kazuhiro Yoshiuchi², Isao Miyashiro⁷,
22
23
24 7 Yosuke Uchitomi⁸, Yutaka J. Matsuoka¹.
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27
28
29
30 **Author affiliations**
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32
33 10 1) Division of Health Care Research, Behavioral Science and Survivorship Research
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35
36 11 Group, Center for Public Health Sciences, National Cancer Center Japan, 5-1-1 Tsukiji,
37
38
39 12 Chuo-ku, Tokyo 104-0045, Japan.
40
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42
43 13 2) Department of Stress Sciences and Psychosomatic Medicine, University of Tokyo
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45
46 14 Graduate School of Medicine Faculty of Medicine, Tokyo, Japan.
47

48
49 15 3) Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City
50
51
52 16 University Graduate School of Medical Sciences and Medical School, Nagoya, Japan.
53

54
55 17 4) Center for Cancer Registries, Center for Cancer Control and Information Services,
56
57
58 18 National Cancer Center Japan, Tokyo, Japan.
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6 19 5) Division of Psycho-oncology and Palliative Care, Nagoya City University Hospital,
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8
9 20 Nagoya, Japan.

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12 21 6) Department of Psychiatry, Yokohama City University School of Medicine Graduate
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14
15 22 School of Medicine, Yokohama, Japan.

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18 23 7) Cancer Control Center, Osaka International Cancer Institute, Osaka, Japan.

19
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21 24 8) Innovation Center for Supportive, Palliative and Psychosocial Care, National Cancer
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23
24 25 Center Hospital, Tokyo, Japan.

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27
28
29
30 27 Corresponding author: Maiko Fujimori, postal address: Division of Health Care
31
32
33 28 Research, Behavioral Science and Survivorship Research Group, Center for Public
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35
36 29 Health Sciences, National Cancer Center Japan, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-
37
38
39 30 0045, Japan. e-mail address: mfujimor@ncc.go.jp, telephone number: +81-3-3547-
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48 33 Keywords: neoplasms, suicide, cardiovascular diseases, registries, standardized mortality
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6 **Abstract**
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9 **Introduction:** A growing body of literature has demonstrated that cancer patients have a
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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;

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6 54 whether definitive surgery of the primary site was performed; and month of death. We
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9 55 will conduct the first analysis using cancer incidence and death information from year
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12 56 2016 cases, which will become available in 2019.

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15 57 **Ethics and dissemination:** The study protocol was approved by the institutional review
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18 58 board and ethics committee of the National Cancer Center Japan and Nagoya City
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21 59 University Graduate School of Medical Sciences. The findings will be disseminated
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24 60 through peer-reviewed publications and conference presentations.

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27 61 **Registration number:** UMIN000035118
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32 33 63 **Strengths and limitations of this study**

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36 64 • This will be the first nationwide population-based study in Japan to investigate the
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39 65 impact of a cancer diagnosis on subsequent death by suicide, other externally caused
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42 66 injuries, and cardiovascular events.
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45 67 • Our study will cover virtually all cancer incidence and subsequent fatal outcomes in
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48 68 Japan.
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51 69 • Our study will not be able to control for potential confounding factors for cancer,
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54 70 suicide, and cardiovascular events, such as smoking history and alcohol use,
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57 71 sociodemographic status, and pre-existing medical and psychiatric conditions.
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7 72 • Incidence and survival data in the NCR may be incomplete and/or unstable for the
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9 73 first few years after its launch.
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15 75 **Introduction**

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18 76 In Japan, it is estimated that approximately 1 million people have been newly diagnosed
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21 77 with cancer annually in recent years, and about 1 in 2 Japanese will receive a cancer
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24 78 diagnosis during their lifetime.¹

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27 79 Receiving a cancer diagnosis and undergoing diagnostic workup leading to a definite
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30 80 cancer diagnosis are highly stressful experiences for cancer patients, and a high
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33 81 prevalence of psychiatric symptoms and disorders has been observed around the time of
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36 82 cancer diagnosis.^{2,3} A number of population-based studies have consistently
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39 83 demonstrated that patients with cancer are at increased risk for suicide,⁴⁻¹⁵ especially in
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42 84 the weeks after their cancer diagnosis.¹⁶⁻¹⁹ A high incidence of other externally caused
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45 85 injuries (ECIs), including accidental death and death due to events of undetermined intent,
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48 86 has also been reported among cancer patients.²⁰⁻²² Some suicide deaths may be
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51 87 misclassified as other ECIs,^{23,24} and physical, psychological, and social impairment due
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54 88 to cancer itself or adverse effects of cancer treatment could increase the risk of accidental
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57 89 death.²⁵
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6 90 Furthermore, a few population-based studies have demonstrated that the period
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9 91 immediately after a cancer diagnosis is related to elevated mortality from cardiovascular
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12 92 causes among patients with prostate cancer^{26,27} and those with other cancer types as
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15 93 well.¹⁷ Acute psychological stressors, such as earthquakes, war, and the death of a loved
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18 94 one, are known to trigger cardiovascular events.²⁸⁻³¹ Acute emotional distress induced by
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21 95 a cancer diagnosis may also affect cardiovascular functioning and cause critical outcomes
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24 96 beyond the influence of cancer itself or cancer treatment. Possible mechanisms linking
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27 97 acute psychological stressors to cardiovascular events include pathophysiological
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30 98 pathways that have the potential to cause rupture of vulnerable plaque, thrombosis
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33 99 formation, or fatal arrhythmias (e.g., increased sympathetic tone, blood pressure, shear
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36 100 stress, and blood viscosity; endothelial dysfunction; and hypercoagulability), and health-
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39 101 impairing behaviors related to emotional distress.^{28,29}

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42 102 Suicide risk among persons with cancer has been suggested to differ between different
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45 103 ethnic and cultural groups.³² Two previous studies have reported risk of suicide among
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48 104 Japanese patients with cancer compared with the general population.^{22,33} The first, a
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51 105 single-institution study demonstrated that suicide risk among patients newly diagnosed
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54 106 with cancer was significantly elevated within the first year after diagnosis.³³ The second,
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57 107 a population-based prospective study investigating Japanese residents and including over
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6 108 10,000 cancer patients, showed that risk of death by suicide and other ECIs was about 24
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9 109 and 19 times higher, respectively, among those with cancer within the first year after
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12 110 cancer diagnosis than among those without cancer.²² There has been no nationwide study
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15 111 examining the risk of suicide among cancer patients in Japan, and cardiovascular
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18 112 mortality risk following a cancer diagnosis has not been investigated in countries other
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21 113 than Sweden and the United States. As Japan is aging faster than any other country in the
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24 114 world and the number of patients with newly diagnosed cancer is expected to keep
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27 115 increasing,³⁴ the impact of a cancer diagnosis on subsequent stress-related outcomes is a
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30 116 serious public health issue. It is necessary to identify vulnerable patients and the window
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33 117 of maximum risk in order to implement appropriate supportive and preventive
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36 118 intervention.

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39 119 The Act on Promotion of Cancer Registries was enacted in Japan in 2013 and the
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42 120 National Cancer Registry (NCR) in Japan was launched on 1 January 2016.^{35,36}
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45 121 According to the Act, hospitals in Japan have a legal duty to report all targeted cancer
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48 122 cases to the NCR. The NCR has enabled hospitals to calculate accurate cancer incidences
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51 123 and survival rates, and it is expected that the NCR database will contribute to planning
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54 124 and assessment of evidence-based cancer control policies and promote research in such
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57 125 areas as evaluation of cancer care quality and follow-up surveys in nationwide cohort
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6 126 studies. The first NCR data will become available for research purposes in 2019.
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9 127 Using data from the NCR, we will conduct the first nationwide population-based study
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12 128 in Japan to characterize the incidence of death by suicide, ECIs, and cardiovascular
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15 129 disease among patients with a cancer diagnosis compared with the general population in
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18 130 Japan. We will also aim to identify higher-risk patients and time periods that may require
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21 131 more attention. We hypothesize that the risk of suicide, other ECIs, and cardiovascular
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24 132 death is significantly higher within the first year after a cancer diagnosis and that the
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27 133 period soon after a cancer diagnosis is associated with the greatest risk.
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32 33 135 **Methods**

34 35 136 **Data sources**

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39 137 Cancer patients will be identified from the NCR database in Japan. The NCR covers the
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42 138 total population in Japan, and hospitals are required to report all targeted cancer cases
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45 139 newly diagnosed in their institutions from 1 January 2016 onward, irrespective of patient
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48 140 nationality. Data from cancer care hospitals are submitted annually and matched inter-
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51 141 prefecturally, and mortality data submitted by municipalities are matched with the
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54 142 incidence data in the NCR database. The data collection deadline for each year's cases is
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57 143 the end of the following year, and the data will become available for research purposes
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6 144 the year after that. The unit of registration is tumor, duplications of the same cancer case
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9 145 are corrected, and each cancer is registered separately for cases in which a patient is
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12 146 judged to have multiple primary cancers based on pathology.
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15 147 The targeted neoplasms for the NCR include intraepithelial and malignant tumors
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18 148 corresponding to a behavioral code of 2 or 3 in the International Classification of Diseases
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21 149 for Oncology, Third Edition (ICD-O-3); benign and uncertain whether benign or
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24 150 malignant central nervous system (CNS) neoplasms and gastrointestinal stromal tumors;
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27 151 and some types of ovarian borderline malignant tumors. The standard items submitted to
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30 152 the NCR by cancer care hospitals are presented in Table 1. The date of cancer diagnosis
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33 153 is defined as the date of the most definitive diagnostic test before initiation of treatment.
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36 154 Information such as race, educational status, marital status, income, insurance status, and
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39 155 comorbidity is not registered in the NCR database.
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42 156 Details of the NCR system have been described previously.^{35,36}
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48 158 **Study population and inclusion criteria**

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51 159 Our study cohort will consist of all cancer cases diagnosed in Japan and registered in the
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54 160 NCR from 1 January 2016 onward. We will exclude cancer cases that are diagnosed
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57 161 incidentally at autopsy, reported only on a death certificate, or missing a diagnosis date.
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6 162 For individuals with multiple cancers, the start of the at-risk period will be defined as the
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9 163 date of the most recent cancer diagnosis. It is estimated that about 1 million cancer
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12 164 patients have been diagnosed annually in recent years in Japan.¹ We are planning a series
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15 165 of analyses according to NCR data availability, and the duration of patient inclusion and
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18 166 follow-up will be different for each analysis. We will conduct the first analysis in 2019,
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21 167 using cancer incidence and death information from year 2016 cases.
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27 169 **Study variables**

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30 170 We will identify cancer patients who died by suicide, ECIs, and cardiovascular causes
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33 171 based on cause of death registered in the NCR database. Outcomes will be classified
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36 172 according to the International Classification of Diseases, 10th Edition (ICD-10) as
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39 173 follows: suicide (X60-X84 and Y87.0), other ECIs (V01-X59 and Y10-Y34), and
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42 174 cardiovascular diseases (I00-I99). Cardiovascular death will be further subcategorized as
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45 175 myocardial infarction (I21-I24), other disease of the heart (I10-I13, I71, and I72),
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48 176 embolism or thrombosis (I26, I74, I80.1, I81, I82, and I85.0), stroke (I60-I64),
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51 177 hemorrhagic stroke (I60-I62), ischemic stroke (I63), and others.
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54 178 Other information we will obtain from the NCR includes sex, age at diagnosis,
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57 179 prefecture of residence at diagnosis, presence/absence of multiple primary tumors,
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6 180 primary site of tumor according to ICD-10 codes, basis of diagnosis, date of diagnosis,
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9 181 extension of tumor, presence/absence of each treatment, presence/absence of definitive
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12 182 surgery of the primary site, hospital region, survival status, and survival time..
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17 18 184 **Statistical analysis**

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21 185 Standardized mortality ratios (SMRs) will be calculated as the observed numbers of
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24 186 targeted events (i.e., suicide, other ECIs, or cardiovascular death) among cancer patients
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27 187 divided by the expected numbers of events in the general population. Excess absolute
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30 188 risks (EARs) will be calculated by subtracting the expected numbers of events from the
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33 189 observed numbers of events; the difference will be then divided by person-years of cancer
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36 190 patients, and the number of events in excess will be expressed per 10,000 person-years.
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39 191 The expected numbers of events will be obtained by multiplying the number of person-
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42 192 years at risk, stratified by sex, age group (0-4, 5-9, ..., 80-84, ≥ 85 years), prefecture, and
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45 193 calendar year, by mortality rates from targeted events in each year in the general
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48 194 population in Japan in each corresponding stratum. We will calculate mortality rates by
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51 195 sex, age, and prefecture in each year in the general population by dividing the numbers
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54 196 of death from each event occurring in Japan (based on datasets from Vital Statics Japan,
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57 197 provided by the Ministry of Health, Labour and Welfare) by the estimated total population
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6 198 in Japan based on Population Estimates.³⁷ We will calculate 95% confidence intervals
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9 199 (CIs) of SMRs and EARs by assuming that the observed numbers of events follow a
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12 200 Poisson distribution. All analyses will be performed using SPSS Statistics for Windows,
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15 201 Version 25.0 (Armonk, NY: IBM Corp).

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18 202 SMRs and EARs will be calculated separately in relation to a number of factors: sex,
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21 203 age at diagnosis, time since cancer diagnosis, prefecture of residence at diagnosis, primary
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24 204 tumor site, behavioral code of tumor, extension of tumor, whether definitive surgery of the
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27 205 primary site was performed, and month of death. Age at diagnosis will be stratified into
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30 206 the following groups: 0-39, 40-49, 50-59, 60-69, 70-79, and ≥ 80 years. Primary tumor
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33 207 site will be based on the classifications used in the Monitoring of Cancer Incidence in
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36 208 Japan (MCIJ) project (Table 2).³⁸ The extension of tumor will be classified into localized
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39 209 (confined to the original organ), regional (spread to regional lymph nodes and/or adjacent
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42 210 tissue), metastatic (metastasized to distant organ), and unknown. Stroke will be excluded
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45 211 from cardiovascular mortality in the analysis of CNS tumors, and CNS tumors will be
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48 212 excluded from “any cancer” in the analysis of death from cardiovascular causes. Cases of
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51 213 hematologic disease will be excluded in the analysis of presence/absence of definitive
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54 214 surgery. We will also explore the suicide methods used by cancer patients and the factors
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57 215 affecting their choice of method.
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6 216 We will also divide cancer patients who die during the observation period into 3
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9 217 groups according to the main cause of death: (1) cancer, (2) suicide, other ECIs, and
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12 218 cardiovascular diseases, and (3) others. Characteristics of patients and tumors will be
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15 219 compared among these groups.
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21 221 **Discussion**

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24 222 This will be the first nationwide study in Japan to investigate the impact of a cancer
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27 223 diagnosis on subsequent death by suicide, other ECIs, and cardiovascular events. The
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30 224 main strength of this study is that it will cover virtually all cancer incidence and
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33 225 subsequent fatal outcomes in Japan using information registered in the NCR. SMRs and
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36 226 EARs of stress-related outcomes after a cancer diagnosis will help to identify higher-risk
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39 227 patients and time periods, and will provide useful evidence for considering the priority of
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42 228 preventive strategies.
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45 229 Several limitations inherent in this study should be acknowledged. First, our study will
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48 230 not be able to control for potential confounding factors for cancer, suicide, and
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51 231 cardiovascular events, such as smoking history and alcohol use, sociodemographic status,
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54 232 and pre-existing medical and psychiatric conditions. These data are not collected in the
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57 233 NCR and we cannot link anonymous cancer registry information to other medical and
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6 234 socioeconomic databases. Second, our study will explore mortality outcomes alone and
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9 235 we cannot capture nonfatal outcomes, such as suicidal ideation, attempted suicide, and
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12 236 nonlethal cardiovascular events. Our findings will represent only a small portion of the
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15 237 psychological burden associated with a cancer diagnosis. Finally, although we will use
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18 238 data from the NCR, which covers the total population in Japan, it is anticipated that
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21 239 incidence and survival data in the NCR may be incomplete and/or unstable for the first
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24 240 few years after its 2016 launch.
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30 242 **Article Summary**

31 243 **Patient and public involvement**

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34 244 Patients and/or public were not involved.
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42 246 **Ethics and dissemination**

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45 247 The study protocol was approved by the institutional review board and ethics committee
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48 248 of the National Cancer Center Japan and Nagoya City University Graduate School of
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51 249 Medical Sciences. The Act on Promotion of Cancer Registries does not require informed
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54 250 consent for the provision of anonymous information, and the requirement for opt-out will
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57 251 be waived because no personal identifiable information will be accessed. The findings
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6 252 will be disseminated through peer-reviewed publications and conference presentations.
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11 254 **Acknowledgement**

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15 255 This study is reviewed and supported by the Japan Supportive, Palliative and
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18 256 Psychosocial Oncology Group (J-SUPPORT) in terms of the adequacy of the research
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21 257 involved, and approved as J-SUPPORT 1902.
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26 259 **Footnotes**

27 260 **Author Contributions**

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31 261 SH and MF wrote the first draft of the manuscript and subsequently incorporated the
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34 262 suggested revisions. All authors contributed to the study conception and design. TM and
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37 263 KS advised on statistical analysis and management of the database. TA and YU
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40 264 supervised the project. All authors contributed to revision of the protocol and have
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43 265 approved the final version of the manuscript.
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271 data collection and analysis, decision to publish, or preparation of the manuscript.

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273 **Competing interests**

274 None declared.

For peer review only

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375 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

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377 Table 2. Primary tumor site according to International Classification of Diseases, 10th
 378 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)

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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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	9
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

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60**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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —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.

BMJ Open

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

Journal:	<i>BMJ Open</i>
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Complete List of Authors:	<p>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</p> <p>Fujimori, Maiko; National Cancer Center Japan, Division of Health Care Research, Behavioral Science and Survivorship Research Group, Center for Public Health Sciences</p> <p>Akechi, Tatsuo; Nagoya City University Graduate School of Medical Sciences, Department of Psychiatry and Cognitive-Behavioral Medicine</p> <p>Matsuda, Tomohiro; National Cancer Center Japan, Center for Cancer Registries, Center for Cancer Control and Information Services</p> <p>Saika, Kumiko; National Cancer Center Japan, Center for Cancer Registries, Center for Cancer Control and Information Services</p> <p>Hasegawa, Takaaki; Nagoya City University Hospital, Division of Psycho-oncology and Palliative Care</p> <p>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</p> <p>Yoshiuchi, Kazuhiro; The University of Tokyo Graduate School of Medicine, Department of Stress Sciences and Psychosomatic Medicine</p> <p>Miyashiro, Isao; Osaka International Cancer Institute, Cancer Control Center</p> <p>Uchitomi, Yosuke; National Cancer Center Hospital, Innovation Center for Supportive, Palliative and Psychosocial Care</p> <p>Matsuoka, Yutaka; National Cancer Center Japan, Division of Health Care Research, Behavioral Science and Survivorship Research Group, Center for Public Health Sciences</p>
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Epidemiology, Mental health, Cardiovascular medicine
Keywords:	neoplasms, suicide, cardiovascular diseases, registries, standardized mortality ratio

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18 5 Saki Harashima^{1, 2}, Maiko Fujimori¹, Tatsuo Akechi³, Tomohiro Matsuda⁴, Kumiko
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21 6 Saika⁴, Takaaki Hasegawa⁵, Keisuke Inoue^{1, 6}, Kazuhiro Yoshiuchi², Isao Miyashiro⁷,
22
23
24 7 Yosuke Uchitomi⁸, Yutaka J. Matsuoka¹.
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26

27
28
29
30 **Author affiliations**
31

32
33 10 1) Division of Health Care Research, Behavioral Science and Survivorship Research
34
35
36 11 Group, Center for Public Health Sciences, National Cancer Center Japan, 5-1-1 Tsukiji,
37
38
39 12 Chuo-ku, Tokyo 104-0045, Japan.
40

41
42 13 2) Department of Stress Sciences and Psychosomatic Medicine, The University of
43
44
45 14 Tokyo Graduate School of Medicine, Tokyo, Japan.
46
47

48
49 15 3) Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City
50
51
52 16 University Graduate School of Medical Sciences, Nagoya, Japan.
53

54
55 17 4) Center for Cancer Registries, Center for Cancer Control and Information Services,
56
57
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6 19 5) Division of Psycho-oncology and Palliative Care, Nagoya City University Hospital,
7
8

9 20 Nagoya, Japan.
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12 21 6) Department of Psychiatry, Yokohama City University School of Medicine,
13
14

15 22 Yokohama, Japan.
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18 23 7) Cancer Control Center, Osaka International Cancer Institute, Osaka, Japan.
19
20

21 24 8) Innovation Center for Supportive, Palliative and Psychosocial Care, National Cancer
22
23

24 25 Center Hospital, Tokyo, Japan.
25
26

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29

30 27 Corresponding author: Maiko Fujimori, postal address: Division of Health Care
31
32

33 28 Research, Behavioral Science and Survivorship Research Group, Center for Public
34
35

36 29 Health Sciences, National Cancer Center Japan, 5-1-1 Tsukiji, Chuo-ku, Tokyo
37
38

39 30 104-0045, Japan. e-mail address: mfujimor@ncc.go.jp, telephone number:
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45 32 Word Count: 2,587 words
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48 33 Keywords: neoplasms, suicide, cardiovascular diseases, registries, standardized
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36 **Abstract**

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

45 **Methods and analysis:** Our study subjects will consist of cancer cases diagnosed
46 between 1 January 2016 and 31 December 2016 in Japan and they will be observed until
47 31 December 2018. We will calculate standardized mortality ratios (SMRs) and excess
48 absolute risks (EARs) for suicide, other ECIs, and cardiovascular death compared with
49 the general population in Japan, after adjustment for sex, age, and prefecture. SMRs and
50 EARs will be calculated separately in relation to a number of factors: sex; age at
51 diagnosis; time since cancer diagnosis; prefecture of residence at diagnosis; primary
52 tumor site; behavior code of tumor; extension of tumor; whether definitive surgery of
53 the primary site was performed; and presence/absence of multiple primary tumors.

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7 54 **Ethics and dissemination:** The study protocol was approved by the institutional review
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10 55 board and ethics committee of the National Cancer Center Japan and Nagoya City
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12 56 University Graduate School of Medical Sciences. The findings will be disseminated
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18 58 **Registration number:** UMIN000035118
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23 24 60 **Strengths and limitations of this study**

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27 61 • This will be the first nationwide population-based study in Japan to investigate the
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30 62 impact of a cancer diagnosis on subsequent death by suicide, other externally caused
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33 63 injuries, and cardiovascular events.
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36 64 • Our study will cover virtually all cancer incidence and subsequent fatal outcomes in
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39 65 Japan.
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42 66 • Our study will not be able to control for potential confounding factors for cancer,
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45 67 suicide, and cardiovascular events, such as smoking history and alcohol use,
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48 68 sociodemographic status, and pre-existing medical and psychiatric conditions.
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52 53 54 70 **Introduction**

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57 71 In Japan, it is estimated that approximately 1 million people have been newly diagnosed
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6 72 with cancer annually in recent years, and about 1 in 2 Japanese will receive a cancer
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9 73 diagnosis during their lifetime.[1]
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12 74 Receiving a cancer diagnosis and undergoing diagnostic workup leading to a definite
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15 75 cancer diagnosis are highly stressful experiences for cancer patients, and a high
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18 76 prevalence of psychiatric symptoms and disorders has been observed around the time of
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21 77 a cancer diagnosis.[2, 3] A number of population-based studies have consistently
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24 78 demonstrated that patients with cancer are at increased risk for suicide,[4-15] especially
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27 79 in the weeks after their cancer diagnosis.[16-19] A high incidence of other externally
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30 80 caused injuries (ECIs), including accidental death and death due to events of
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33 81 undetermined intent, has also been reported among cancer patients.[20-22] Some
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36 82 suicide deaths may be misclassified as other ECIs,[23, 24] and physical, psychological,
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39 83 and social impairment due to cancer itself or adverse effects of cancer treatment could
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42 84 increase the risk of accidental death.[25]
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45 85 Furthermore, a few population-based studies have demonstrated that the period
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48 86 immediately after a cancer diagnosis is related to elevated mortality from cardiovascular
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51 87 causes among patients with prostate cancer[26, 27] and those with other cancer types as
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54 88 well.[17] Acute psychological stressors, such as earthquakes, war, and the death of a
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57 89 loved one, are known to trigger cardiovascular events.[28-31] Acute emotional distress
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90 induced by a cancer diagnosis may also affect cardiovascular functioning and cause
91 critical outcomes beyond the influence of cancer itself or cancer treatment. Possible
92 mechanisms linking acute psychological stressors to cardiovascular events include
93 pathophysiological pathways that have the potential to cause rupture of vulnerable
94 plaque, thrombosis formation, or fatal arrhythmias (e.g., increased sympathetic tone,
95 blood pressure, shear stress, and blood viscosity; endothelial dysfunction; and
96 hypercoagulability), and health-impairing behaviors related to emotional distress.[28.
97 29]

98 Suicide risk among persons with cancer has been suggested to differ between
99 different ethnic and cultural groups.[32] Two previous studies have reported risk of
100 suicide among Japanese patients with cancer compared with the general population.[22,
101 33] The first, a single-institution study demonstrated that suicide risk among patients
102 newly diagnosed with cancer was significantly elevated within the first year after a
103 diagnosis.[33] The second, a population-based prospective study investigating Japanese
104 residents including over 10,000 cancer patients, showed that risk of death by suicide and
105 other ECIs was about 24 and 19 times higher, respectively, among those with cancer
106 within the first year after a cancer diagnosis than among those without cancer.[22]
107 There has been no nationwide study examining the risk of suicide among cancer

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6 108 patients in Japan, and cardiovascular mortality risk following a cancer diagnosis has not
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9 109 been investigated in countries other than Sweden and the United States. As Japan is
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12 110 aging faster than any other country in the world and the number of patients with newly
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15 111 diagnosed cancer is expected to keep increasing,[34] the impact of a cancer diagnosis on
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18 112 subsequent stress-related outcomes is a serious public health issue. It is necessary to
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21 113 identify vulnerable patients and the window of maximum risk in order to implement
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24 114 appropriate supportive and preventive intervention.
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27 115 The Act on Promotion of Cancer Registries was enacted in Japan in 2013 and the
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30 116 National Cancer Registry (NCR) in Japan was launched on 1 January 2016.[35, 36]
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33 117 According to the Act, hospitals in Japan have a legal duty to report all targeted cancer
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36 118 cases (i.e. intraepithelial and malignant tumors corresponding to a behavioral code of 2
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39 119 or 3 in the International Classification of Diseases for Oncology, Third Edition
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42 120 (ICD-O-3); benign and uncertain whether benign or malignant central nervous system
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45 121 (CNS) neoplasms and gastrointestinal stromal tumors; and some types of ovarian
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48 122 borderline malignant tumors) to the NCR. The NCR has enabled hospitals to calculate
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51 123 accurate cancer incidences and survival rates, and it is expected that the NCR database
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54 124 will contribute to planning and assessment of evidence-based cancer control policies
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57 125 and promote research in such areas as evaluation of cancer care quality and follow-up
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6 126 surveys in nationwide cohort studies. The first NCR data will become available for
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9 127 research purposes in 2019.
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12 128 Using data from the NCR, we will conduct the first nationwide population-based
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15 129 study in Japan to characterize the incidence of death by suicide, ECIs, and
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18 130 cardiovascular disease among patients with a cancer diagnosis compared with the
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21 131 general population in Japan. We will also aim to identify higher-risk patients and time
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24 132 periods that may require more attention. We hypothesize that the risk of suicide, other
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27 133 ECIs, and cardiovascular death is significantly higher within the first year after a cancer
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30 134 diagnosis and that the period soon after a cancer diagnosis is associated with the
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33 135 greatest risk.
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39 137 **Methods**

40 41 42 138 **Data sources**

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45 139 Cancer patients will be identified from the NCR database in Japan. The NCR covers the
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48 140 total population in Japan, and hospitals are required to report all targeted cancer cases
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51 141 newly diagnosed in their institutions from 1 January 2016 onward, irrespective of
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54 142 patient nationality. The NCR system in Japan is described in Figure 1. Incidence data
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57 143 from cancer care hospitals are submitted to prefectural governors and prefectural
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6 144 governors review and match record in their prefecture and enter the data in the NCR
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8
9 145 database in the Ministry of Health, Labour and Welfare (MHLW) (National Cancer
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12 146 Center (NCC)). The MHLW /NCC matches the cancer registry data inter-prefectually
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15 147 and information from death certificate on cancer disease is matched with the incidence
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18 148 data in the NCR. The NCC follows up cancer patients in the NCR database by linking to
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21 149 national death certificate data and registers death information in the NCR. The unit of
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24 150 registration is tumor, duplications of the same cancer case are corrected, and each
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27 151 cancer is registered separately for cases in which a patient is judged to have multiple
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29
30 152 primary cancers based on pathology. Data aggregation is based on name, birth date, and
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33 153 address of patients. The data collection deadline for each year's cases is the end of the
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36 154 following year, and the data will become available for research purposes the year after
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39 155 that. Data quality of the NCR for year 2016 cases has been reported to be very high: the
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42 156 proportion of Death Certificate Notification (DCN) was 4.5%, the proportion of Death
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45 157 Certificate Only (DCO) was 3.2%, the mortality incidence (M/I) ratio was 0.37, and the
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48 158 morphological verification (MV) proportion was 85.4%.[37]

51 159 The standard items submitted to the NCR by cancer care hospitals are presented in
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54 160 Table 1. The date of cancer diagnosis is defined as the date of the most definitive
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57 161 diagnostic test before initiation of treatment and diagnostic tests are arranged
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6 162 hierarchically by levels of definitiveness as follows: histopathologic testing of primary
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9 163 tumor, histopathologic testing of metastatic tumor, cytology, certain kind of tumor
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12 164 specific markers, other clinical testing, and clinical diagnosis.[38] Information such as
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15 165 race, educational status, marital status, income, insurance status, and comorbidity is not
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18 166 registered in the NCR database.

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21 167 Details of the NCR system have been described previously.[35, 36]
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25 26 27 169 **Study population and inclusion criteria**

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30 170 Our study cohort will consist of all cancer cases diagnosed in Japan between 1 January
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33 171 2016 and 31 December 2016 and registered in the NCR and they will be followed until
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36 172 31 December 2018. We will exclude cancer cases that are diagnosed incidentally at
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39 173 autopsy, reported only on a death certificate, or missing a diagnosis date. For
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42 174 individuals with multiple cancers, the start of the at-risk period will be defined as the
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45 175 date of the most recent cancer diagnosis. A total of 995,132 malignant cancer cases
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48 176 (defined by C00-C96 according to International Classification of Diseases, 10th Edition
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51 177 (ICD-10)) were diagnosed in Japan in 2016,[37] and about 1 million cancer patients will
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54 178 be included in our study.

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180 **Study variables**

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

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195 **Statistical analysis**

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

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6 198 (SMRs) will be calculated as the observed numbers of targeted events (i.e. suicide, other
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9 199 ECIs, or cardiovascular death) among cancer patients divided by the expected numbers
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12 200 of events in the general population. Excess absolute risks (EARs) will be calculated by
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15 201 subtracting the expected numbers of events from the observed numbers of events; the
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18 202 difference will be then divided by person-years of cancer patients, and the number of
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21 203 events in excess will be expressed per 10,000 person-years. The expected numbers of
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24 204 events will be obtained by multiplying the number of person-years at risk, stratified by
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27 205 sex, age group (0-4, 5-9, ..., 80-84, ≥ 85 years), prefecture, and calendar year, by
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29
30 206 mortality rates from targeted events in each year in the general population in Japan in
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32
33 207 each corresponding stratum. We will calculate mortality rates by sex, age, and
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36 208 prefecture in each year in the general population by dividing the numbers of death from
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39 209 each event occurring in Japan (based on datasets from Vital Statics Japan, provided by
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42 210 the MHLW) by the estimated total population in Japan based on Population
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45 211 Estimates.[40] The numbers of death by each targeted event in the general population
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48 212 will be calculated by using the same definition according to ICD-10 codes as those used
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51 213 in the cancer patients. We will calculate 95% confidence intervals (CIs) of SMRs and
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54 214 EARs by assuming that the observed numbers of events follow a Poisson distribution.
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57 215 SMRs and EARs will be calculated separately in relation to a number of factors:
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6 216 sex, age at diagnosis, time since cancer diagnosis, prefecture of residence at diagnosis,
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9 217 primary tumor site, behavioral code of tumor, extension of tumor, whether definitive
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12 218 surgery of the primary site was performed, and presence/absence of multiple tumor. Age
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15 219 at diagnosis will be stratified into the following groups: 0-39, 40-49, 50-59, 60-69,
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18 220 70-79, and ≥ 80 years. Time after a cancer diagnosis will be divided into 0 to 2 months,
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21 221 3 to 5 months, 6 to 11 months, and ≥ 12 months for suicide and other ECIs. Risk of
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24 222 suicide and other ECIs during the first week after diagnosis will be also separately
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27 223 calculated. For cardiovascular death, we will investigate < 1 week, 1 week to < 1 month,
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30 224 1 to 5 months, 6 to 11 months, and ≥ 12 months. Primary tumor site will be based on the
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33 225 classifications used in the MCIJ project (Table 2).[41] The extension of tumor will be
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35
36 226 classified into localized (confined to the original organ), regional (spread to regional
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39 227 lymph nodes and/or adjacent tissue), metastatic (metastasized to distant organ), and
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41
42 228 unknown. Stroke will be excluded from cardiovascular mortality in the analysis of CNS
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45 229 tumors, and CNS tumors will be excluded from “any cancer” in the analysis of death
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48 230 from cardiovascular causes.[17] Cases of hematologic disease will be excluded in the
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51 231 analysis of presence/absence of definitive surgery. Likelihood ratio tests based on
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54 232 Poisson regression models will be conducted to test for heterogeneity. All p -value will
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57 233 be two-sided tests and be considered to be statistically significant at a p -value of less
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6 234 than 0.05. We will also perform multivariable regression analysis based on Poisson
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9 235 regression models to adjust for following factors: sex, age at a cancer diagnosis, primary
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12 236 tumor site, extension of tumor, presence/absence of multiple tumors, and follow-up
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15 237 period. All factors will be included in the multivariable regression model with no
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18 238 interaction terms. We will also test for the heterogeneity from the multivariable models.
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21 239 In order to explore the factors affecting their choice of suicide method by cancer
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24 240 patients we will describe distribution of characteristics of patients and tumors (e.g. sex,
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27 241 age at diagnosis, extension of tumor, and time since diagnosis) by common suicide
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30 242 methods in Japan (e.g. poisoning (X60-X69), hanging (X70), and jumping from heights
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33 243 (X80)).
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36 244 We will also divide cancer patients who die during the observation period into 2
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39 245 groups according to the main cause of death: (1) suicide, other ECIs, and cardiovascular
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42 246 diseases, and (2) others. Characteristics of patients and tumors will be compared
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45 247 between two groups.
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48 248 All analyses will be performed using SPSS Statistics for Windows, Version 25.0
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51 249 (Armonk, NY: IBM Corp).
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57 251 **Discussion**
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6 252 This will be the first nationwide study in Japan to investigate the impact of a cancer
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9 253 diagnosis on subsequent death by suicide, other ECIs, and cardiovascular events. The
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12 254 main strength of this study is that it will cover virtually all cancer incidence and
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15 255 subsequent fatal outcomes in Japan using information registered in the NCR. SMRs and
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18 256 EARs of stress-related outcomes after a cancer diagnosis will help to identify
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21 257 higher-risk patients and time periods, and will provide useful evidence for considering
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24 258 the priority of preventive strategies.

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27 259 Several limitations inherent in this study should be acknowledged. First, our study
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29
30 260 will not be able to control for potential confounding factors for cancer, suicide, and
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33 261 cardiovascular events, such as smoking history and alcohol use, sociodemographic
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36 262 status, and pre-existing medical and psychiatric conditions. These data are not collected
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39 263 in the NCR and we cannot link anonymous cancer registry information to other medical
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42 264 and socioeconomic databases. Second, our study will explore mortality outcomes alone
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44
45 265 and we cannot capture nonfatal outcomes, such as suicidal ideation, attempted suicide,
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48 266 and nonlethal cardiovascular events. Our findings will represent only a small portion of
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51 267 the psychological burden associated with a cancer diagnosis. Third, some deaths
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54 268 classified as other ECIs may be misclassification of deaths due to suicide,[23, 24] and
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57 269 assuming that more under-reporting of suicide occurs in cancer patients than in the
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6 270 general population, risk of suicide among cancer patients in our study will be potentially
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9 271 underestimated. Fourth, in the analysis of presence/absence of definitive surgery of the
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12 272 primary tumor, the result should be interpreted with caution because only patients who
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15 273 did not die by targeted outcomes and survived until surgery could undergo surgery.
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18 274 Finally, if death ascertainment in the NCR system is incomplete, risk of deaths by
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21 275 targeted causes among cancer patients can be underestimated.
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27 277 **Article Summary**

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30 278 **Patient and public involvement**

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33 279 Patients and/or public were not involved.
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39 281 **Ethics and dissemination**

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41
42 282 The study protocol was approved by the institutional review board and ethics committee
43
44
45 283 of the National Cancer Center Japan and Nagoya City University Graduate School of
46
47
48 284 Medical Sciences. The Act on Promotion of Cancer Registries does not require
49
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51 285 informed consent for the provision of anonymous information, and the requirement for
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54 286 opt-out will be waived because no personal identifiable information will be accessed.
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57 287 The findings will be disseminated through peer-reviewed publications and conference
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6 288 presentations.
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16
17
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20
21 293 involved, and approved as J-SUPPORT 1902.
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24 294

25 26 27 295 **Footnotes**

28 29 30 296 **Author Contributions**

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32
33 297 SH, MF, TA, TM, KS, TH, KI, KY, IM, YU, and YM contributed to the study
34
35
36 298 conception and design. TM and KS advised on statistical analysis and management of
37
38
39 299 the database. TA and YU supervised the project. SH and MF will perform the data
40
41
42 300 analysis and all coauthors will be involved in interpretation of the data. SH and MF
43
44
45 301 wrote the first draft of the manuscript and all coauthors reviewed the manuscript and
46
47
48 302 provided critical revisions. All authors have approved the final version of the
49
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51 303 manuscript.
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7
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10
11
12 308 in study design, data collection and analysis, decision to publish, or preparation of the
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15 309 manuscript.

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21 311 **Competing interests**

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24 312 None declared.
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For peer review only

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6 422 Table 1. Items submitted to the National Cancer Registry in Japan by cancer care
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9 423 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/thoroscopic 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

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425 Table 2. Primary tumor site according to International Classification of Diseases, 10th
 426 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)

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428 **Figure legends**

429 Figure 1. The National Cancer Registry system in Japan.

430 Reporting of newly diagnosed cancer cases from 1 January 2016 onward has become a

431 legislative duty of hospitals in Japan. Information collected in each prefecture must be

432 registered in the National Cancer Registry (NCR) database and the National Cancer

433 Center follows up patients in the NCR by linking to mortality data based on national

434 death certificate files.

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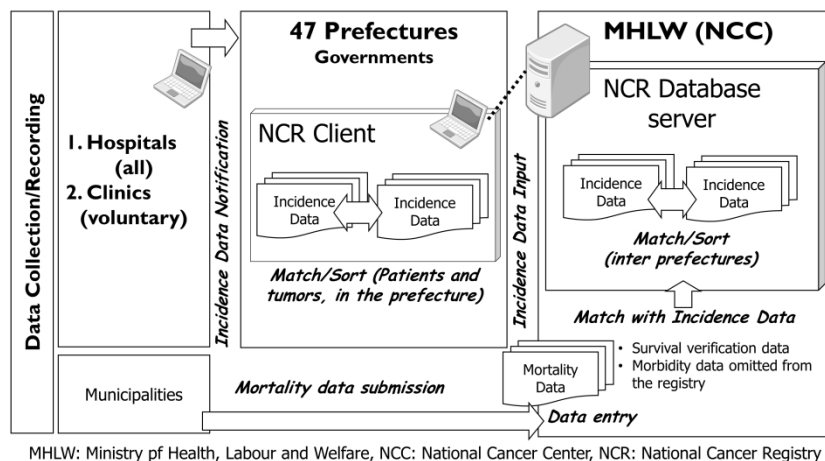


Figure 1. The National Cancer Registry system in Japan. Reporting of newly diagnosed cancer cases from 1 January 2016 onward has become a legislative duty of hospitals in Japan. Information collected in each prefecture must be registered in the National Cancer Registry (NCR) database and the National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

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	10-11
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

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60**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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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.