PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Suicide, other externally caused injuries, and cardiovascular death following a cancer diagnosis: study protocol for a nationwide population-based study in Japan
AUTHORS	Harashima, Saki; Fujimori, Maiko; Akechi, Tatsuo; Matsuda, Tomohiro; Saika, Kumiko; Hasegawa, Takaaki; Inoue, Keisuke; Yoshiuchi, Kazuhiro; Miyashiro, Isao; Uchitomi, Yosuke; Matsuoka, Yutaka

VERSION 1 - REVIEW

REVIEWER	Katherine Henson Principal Cancer Analyst. Public Health England, England
REVIEW RETURNED	09-Apr-2019

GENERAL COMMENTS	Summary: The study protocol describes a population-based study of suicide and cardiovascular mortality risk following cancer diagnosis. This has the potential to be an important study, however clarifications are required throughout the protocol. In the introduction, the authors state that suicide deaths may be misclassified as other externally caused injuries. Did the authors consider combining these into one category, due to these misclassification issues? If not, could the authors hypothesize the potential impact of presenting the categories separately. Methods: The authors have specified that cancer cases will be identified from 2016, but do not specify an end date. Please can this be specified. The authors state that SMRs and EARs will be calculated separately for each factor. Will a multivariable regression analysis be performed? This would be important to assess whether any associations remain after adjustment for the recorded factors. The use of different duration and follow-up times for each analysis has the potential to be challenging to interpret. The different groups were not clearly described in the protocol. How do the authors intend to make the distinctions clear during dissemination of the findings of these analyses? There is limited information on the planned analysis of suicide methods. This needs to be carefully considered, and further described in the study protocol.

	It is not clear how time since diagnosis will be presented, and whether different groupings will be considered. Please can this be described. Will tests for trend and / or heterogeneity performed? If yes, please provide details. Please can the authors provide further detail on the cancer registration process. As a reader with no knowledge of the healthcare system in Japan, I am currently not able to assess the potential impact of the matching processes used in both the mortality and cancer incidence data on the findings of this study. Regarding the identification of the general population mortality rates. Will the same ICD-10 codes be used to identify the mortality rates? In addition, will the coded underlying cause of death be considered, or will free text be reviewed? It is important that the same methodology is used for both the cancer population and general population mortality rates. Please can this be clarified in the manuscript. In the discussion section, the authors mention limitations due to incomplete and/or unstable data in the first few years of the Registry. Please can the authors hypothesize what impact this may have on the findings. Can the authors indicate the completeness of the cancer fields such as behaviour, and whether they will likely impact the findings? Page 7, line 121: Please can the authors define “targeted cancer cases”. Page 9, line 153: Are the authors able to provide a reference for the identification of the “most definitive diagnostic test”? Page 12, line 211: Please can you provide a reference for excluding CNS tumours in the cardiovascular causes analysis?

REVIEWER	Fang Fang Karolinska Institutet
REVIEW RETURNED	14-Apr-2019

GENERAL COMMENTS	Harashima S et al proposed a study to examine the risk of suicide, other externally caused injuries, and cardiovascular death following a cancer diagnosis, using the National Cancer Registry in Japan. I think the proposal is clearly written and its methodology well described. I have a few comments listed below to share with the authors. The authors stated that “Information such as race, educational status, marital status, income, insurance status, and comorbidity is not registered in the NCR database.” As a result, it is difficult to control for these variables as potential confounders. I wonder whether it is possible to perform alternative analysis, such as cross-over analysis, to assess the impact of such uncontrolled factors? The authors stated “For individuals with multiple cancers, the start of the at-risk period will be defined as the date of the most recent cancer diagnosis.” I wonder whether it would be possible to start the follow-up from the diagnosis of first cancer instead, and then

	separately assess the risk of outcomes after the 1st, 2nd, etc. diagnosis? It would be interesting to see whether the risk of outcomes differs between the 1st cancer diagnosis and a 2nd or 3rd? The authors state that “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.” Could you please provide the rationale of studying “month of death”? Also, most of the other variables concern conditions at the time of cancer diagnosis, whereas this variable is different. Caution should also be given when studying surgery because only patients that survived until surgery undergo surgery. The authors stated that “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.” I wonder whether it would make better sense to define 2) as the primary outcomes, whereas 1) and 3) as secondary outcomes of this analysis? Finally, I wonder whether the authors would find discussions about the quality of registrations (for both cancer and causes of death) relevant?

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1.

Thank you very much for your insightful comments. We revised the manuscript according to your suggestions, and our responses are as follows:

#1. In the introduction, the authors state that suicide deaths may be misclassified as other externally caused injuries. Did the authors consider combining these into one category, due to these misclassification issues? If not, could the authors hypothesize the potential impact of presenting the categories separately.

Answer: Thank you very much for your comment. Although definition of suicide varies between studies, we will define suicide by ICD-10 codes of X60-X84 and Y87.0 in order to investigate risk of definitely diagnosed suicide and use our results as evidence for proposing suicide prevention strategies in cancer patients, and to compare results with the findings from the previous cohort study in Japan (Yamauchi T, et al. Psychooncology 2014;23:1034-1041). When we evaluate risk of suicide and other ECIs separately, some deaths classified as other ECIs deaths may be misclassification of deaths due to suicide 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. We revised this issue in the Discussion section (revised manuscript, page 15-16, lines 266-271).

#2. The authors have specified that cancer cases will be identified from 2016, but do not specify an end date. Please can this be specified.

Answer: Thank you very much for your comment. Our study subjects will consist of cancer cases diagnosed between 1 January 2016 and 31 December 2016 and they will be observed from the date of a cancer diagnosis to 31 December 2018 . A total of 995,132 malignant cancer cases (defined by C00-C96 according to ICD-10) were diagnosed in Japan in 2016 (Ministry of Health, Labour and Welfare, Japan. Cancer incidence in Japan in 2016. https://www.mhlw.go.jp/content/10900000/000468976.pdf (in Japanese)), and about 1 million cancer patients will be included in our study. We revised this issue in the Abstract and Method section (revised manuscript, page 3, lines 45-47, and page 10, lines 170-172, 175-178).

#3. The authors state that SMRs and EARs will be calculated separately for each factor. Will a multivariable regression analysis be performed? This would be important to assess whether any associations remain after adjustment for the recorded factors.

Answer: Thank you very much for your comment. As you suggested, we will 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. Attained age, and year of diagnosis will not be included in the multivariable models because of short inclusion and follow-up period in our study. We revised this issue in the Method section (revised manuscript, page 13-14, lines 234-238).

#4. The use of different duration and follow-up times for each analysis has the potential to be challenging to interpret. The different groups were not clearly described in the protocol. How do the authors intend to make the distinctions clear during dissemination of the findings of these analyses?

Answer: Thank you very much for your comment. As mentioned in comment to #2, our study subjects will consist of cancer cases diagnosed between 1 January 2016 and 31 December 2016 and they will be observed from the date of a cancer diagnosis to 31 December 2018. We revised this issue in the Abstract and Method section (revised manuscript, page 3, lines 45-47, and page 10, lines 170-172, 175-178).

#5. There is limited information on the planned analysis of suicide methods. This needs to be carefully considered, and further described in the study protocol.

Answer: Thank you very much for your comment. We will describe distribution of characteristics of cases (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)) within an extent in which an individual cannot be identified. We will not perform statistical tests for intergroup comparison because the number of patients died by each suicide method is expected to be small. We revised this issue in the Method section (revised manuscript, page 14, lines 239-243).

#6. It is not clear how time since diagnosis will be presented, and whether different groupings will be considered. Please can this be described.

Answer: Thank you very much for your comment. 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. We revised this issue in the Method section (revised manuscript, page 13, lines 220-224).

#7. Will tests for trend and / or heterogeneity performed? If yes, please provide details.

Answer: Thank you very much for your comment. 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 revised this issue in the Method section (revised manuscript, page 13-14, lines 231-234).

#8. Please can the authors provide further detail on the cancer registration process. As a reader with no knowledge of the healthcare system in Japan, I am currently not able to assess the potential impact of the matching processes used in both the mortality and cancer incidence data on the findings of this study.

Answer: Thank you very much for your comment. Incidence data from cancer care hospitals are submitted annually 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. Data aggregation is based on name, birth date, and address of patients. We revised this issue in the Method section (revised manuscript, page 8-9, lines 142-153) and added Figure 1 describing the NCR system in the manuscript.

#9. Regarding the identification of the general population mortality rates. Will the same ICD-10 codes be used to identify the mortality rates? In addition, will the coded underlying cause of death be considered, or will free text be reviewed? It is important that the same methodology is used for both the cancer population and general population mortality rates. Please can this be clarified in the manuscript.

Answer: Thank you very much for your comment. Underlying cause of death is coded using ICD-10 in both the NCR and death certificate. We will identify death from targeted causes using the same definitions according to ICD-10 for both the cancer population and the general population. We revised this issue in the Method section (revised manuscript, page 11, lines 181-182, and page 12, lines 211-213).

#10. In the discussion section, the authors mention limitations due to incomplete and/or unstable data in the first few years of the Registry. Please can the authors hypothesize what impact this may have

on the findings. Can the authors indicate the completeness of the cancer fields such as behaviour, and whether they will likely impact the findings?

Answer: Thank you very much for your comment. Data quality of the NCR for year 2016 cases has recently 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% (Ministry of Health, Labour and Welfare, Japan. Cancer incidence in Japan in 2016. https://www.mhlw.go.jp/content/10900000/000468976.pdf (in Japanese)). We revised this issue in the Method section (revised manuscript, page 9, lines 155-158). If death ascertainment in the NCR system is incomplete, risk of deaths by targeted causes among cancer patients in our study can be underestimated. We revised this issue in the Discussion section (revised manuscript, page 16, lines 274-277).

Data on the completeness of each item in the NCR has not been available yet, the proportion of patients with missing information with birth date, sex, diagnosis date, primary tumor site, and extension of tumor was low in the prefecture-based cancer registries according to the MCIJ 2015 survey (Center for Cancer Control and Information Services, National Cancer Center, Japan. Monitoring of Cancer Incidence in Japan, 2015. https://ganjoho.jp/data/reg_stat/statistics/brochure/mcij2015_report.pdf (in Japanese)). Registration of each item in the NCR is required by law and will be expected to be sufficient for analysis and less likely to impact our findings. We will report this issue in our subsequent paper.

#11. Page 7, line 121: Please can the authors define “targeted cancer cases”.

Answer: Thank you very much for your comment. As mentioned in the Method section in our previous manuscript, “targeted cancer cases” 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. We moved this issue from the Method section to the Introduction section (revised manuscript, page 7, lines 117-122).

#12. Page 9, line 153: Are the authors able to provide a reference for the identification of the “most definitive diagnostic test”?

Answer: Thank you very much for your comment. The most definitive diagnostic tests are arranged hierarchically by levels of definitiveness; histopathologic testing of primary tumor, histopathologic testing of metastatic tumor, cytology, certain kind of tumor specific markers, other clinical testing, and clinical diagnosis (Center for Cancer Control and Information Services, National Cancer Center. Manual for the National Cancer Registry 2016 (2017 revised version. https://ganjoho.jp/data/reg_stat/cancer_reg/national/hospital/ncr_manual_2017rev_201901.pdf (in Japanese)). We revised this issue and provided this reference in the Method section (revised manuscript, page 9-10, lines 160-164).

#13. Page 12, line 211: Please can you provide a reference for excluding CNS tumours in the cardiovascular causes analysis?

Answer: Thank you very much for your comment. We will exclude central nervous system tumors (CNS) in the cardiovascular causes analysis to preclude potential misdiagnosis between stroke look-alike symptom by CNS tumors and stroke, based on the similar study by Fang F (Fang F, et al. N Engl J Med 2012;366:1310-1318). We provided this reference in the Method section (revised manuscript, page 13, lines 230).

Response to Reviewer 2

Thank you very much for your insightful comments. We revised the manuscript according to your suggestions, and our responses are as follows:

#1. The authors stated that “Information such as race, educational status, marital status, income, insurance status, and comorbidity is not registered in the NCR database.” As a result, it is difficult to control for these variables as potential confounders. I wonder whether it is possible to perform alternative analysis, such as cross-over analysis, to assess the impact of such uncontrolled factors?

Answer: Thank you very much for your comment. As we revised the manuscript, our study subjects will consist of cancer cases diagnosed between 1 January 2016 and 31 December 2016 and they will be observed from the date of a cancer diagnosis to 31 December 2018 (revised manuscript, page 10, lines 170-172). As you suggested, case-crossover analysis is useful for assessing the impact of uncontrolled factor, but we cannot conduct case-crossover analysis because cancer incidence data before 2016 had not been registered in the NCR and we cannot set control periods.

#2. The authors stated “For individuals with multiple cancers, the start of the at-risk period will be defined as the date of the most recent cancer diagnosis.” I wonder whether it would be possible to start the follow-up from the diagnosis of first cancer instead, and then separately assess the risk of outcomes after the 1st, 2nd, etc. diagnosis? It would be interesting to see whether the risk of outcomes differs between the 1st cancer diagnosis and a 2nd or 3rd?

Answer: Thank you very much for your comment. We will investigate impact of the most recent cancer diagnosis because cancer incidence data before 2016 had not been registered in the NCR and we can only identify the first cancer diagnosis after 2016. As you pointed out, it is important to examine impact of multiple cancer diagnosis on suicidality and we will calculate SMRs and EARs by presence/absence of multiple tumors. We revised this issue in the Abstract and Method section (revised manuscript, page 3, lines 49-53 and page 12-13, lines 215-218).

#3. The authors state that “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.” Could you please provide the rationale of studying “month of death”? Also, most of the other variables concern conditions at the time of cancer diagnosis, whereas this variable is different. Caution should also be given when studying surgery because only patients that survived until surgery undergo surgery.

Answer: Thank you very much for your comment. In Japan, seasonal changes in mortality rates from suicide and cardiovascular have been reported (Nakaji S, et al. Eur J Epidemiol 2004;19:905-913)

and we intended to examine whether seasonal variation of risk of suicide and cardiovascular death is also observed in cancer patients. As you pointed out, it is inappropriate to conduct stratified analysis using the variable at the time of death and follow-up duration in our study will be too short to investigate impact of seasonality. We will investigate this matter in another study when adequate data are accumulated in the NCR. We deleted this issue in the Abstract and Method section (revised manuscript, page 3, lines 49-53 and page 12-13, lines 215-218).

As you pointed out, outcomes regarding presence/absence of surgery should be interpreted with caution because only patients that survived until surgery undergo surgery. We revised this issue in the Discussion section (revised manuscript, page 16, lines 271-273).

#4. The authors stated that “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.” I wonder whether it would make better sense to define 2) as the primary outcomes, whereas 1) and 3) as secondary outcomes of this analysis?

Answer: Thank you very much for your comment. As you pointed out, it is reasonable that (1) and (3) should be combined together and we will compare characteristics of patients and tumors between the two groups: (1) death due to targeted causes (suicide, other ECIs, and cardiovascular disease) and (2) death due to other causes. We revised this issue in the Method section (revised manuscript, page 14, lines 244-247).

#5. Finally, I wonder whether the authors would find discussions about the quality of registrations (for both cancer and causes of death) relevant?

Answer: Thank you very much for your comment. 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% (Ministry of Health, Labour and Welfare, Japan. Cancer incidence in Japan in 2016. https://www.mhlw.go.jp/content/10900000/000468976.pdf (in Japanese)). Quality of cause of death information in Japan has been also reported to be high (Mathers CD, et al. Bull World Health Organ 2005;83:171-177). We revised this issue in the Method section (revised manuscript, page 9, lines 155-158 and page 11, lines 188).

VERSION 2 – REVIEW

REVIEWER	Fang Fang Karolinska Institutet
REVIEW RETURNED	07-Jun-2019

GENERAL COMMENTS	Thank you for your responses.