PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia
AUTHORS	Duke, Janine; Bauer, Jacqui; Fear, Mark; Rea, Suzanne; Wood, Fiona; Boyd, James

VERSION 1 - REVIEW

REVIEWER	Lene Mellemkjær Danish Cancer Society Research Center Copenhagen, Denmark
REVIEW RETURNED	23-Sep-2013

GENERAL COMMENTS	Overall comment: This study presents results from follow-up of patients with burn injuries from Scotland and Western Australia with regards to cancer incidence. The results for the cohort from Western Australia, however, have already been published in a previous paper; nevertheless they are repeated here. The present study would benefit from focusing on the new results – the follow-up of patients from Scotland – with a substantial shortening of the description of the Western Australia cohort and results. Abstract: The gender difference in overall cancer incidence is reported but the site specific results are for combined gender. Thus, site specific results underlying the overall results are not mentioned. Introduction: Second paragraph is a detailed description of the material and should be moved in a much shorter version to this section of the paper. Instead the evidence from previous studies regarding cancer risk after burn injuries should be described. Currently only the study from Western Australia is referenced – and results from this study are included as part of the present study. Methods: Page 8, lines 1-2: It is mentioned that an incident cancer was defined as cancer coded by C00-C96 excluding C44. However, C44 is actually included in Table 3? Are these ICD-10 or ICD-O3 topography codes?

	Page 8, first paragraph: It appears that multiple cancers in one person are counted in the analyses yet by excluding patients with cancer prior to the burn injury and ending follow-up at date of cancer diagnosis this is combined with a first cancer approach. If multiple cancers are counted during follow-up, those with cancer prior to the burn should not have been excluded as persons, the cancer should just not be counted and date of cancer should not have been used as an end date. Thus, it seems that a mix of first and multiple cancer approach has been used. Results: How do the authors explain the lack of gender difference in Scottish patients included in the early period (Table 2)? Discussion: First section on Methodological issues should be shortened substantially. The authors do not comment on findings for lymphomas - these malignancies are usually associated with suppression of the immune system. Minor issues: Page 7, last sentence in second paragraph: What is meant by separation date? The term “all cause” is used throughout the paper in connection with cancer, i.e., “all cause cancer” but is usually applied in connection with mortality studies not cancer incidence studies.

REVIEWER	Gerald McGwin and Nicole Safiano Department of Epidemiology and Surgery, University of Alabama at Birmingham, Birmingham, Alabama
REVIEW RETURNED	09-Oct-2013

GENERAL COMMENTS	The authors have performed a retrospective cohort study to examine increased cancer risk in patients with a history of burn injury in Scotland and Western Australia using linked databases and cancer registries. The authors found an increased risk of certain cancers for both genders. For many cancers, there was a higher risk for females than for males. This manuscript is interesting and examines a relationship between an important exposure and outcome. Strengths of this study include two large sample sizes using detailed and well-kept records with longitudinal data. The statistical methods are clearly discussed and appropriate. The discussion contains interesting possible biological reasons for the findings. Specific comments and questions follow below. - Table 1 shows some significant differences between the Scotland and WA cohorts but these are not discussed in regards to their

	potential contribution to differences in the risks between the two cohorts. Also, is there a relationship between site and depth of the burn and the type of cancer? - Why was the sub-cohort for 1983-1988 analyzed and compared to the entire cohort in Table 2? - The finding of a statistically significant increase in esophageal cancer is borderline as the CI for WA contains 1. (see page 12 line 3) Though this can happen it would be useful to have the actual p-values for comparisons if "statistically significant" is going to be used. - It may be a stretch to conclude that there was a significant increase in most types of cancer for females. Only about half reached statistical significance. (pg 12 lines 3-6) - The lack of available data on alcohol and tobacco use warrants further discussion as this may be a significant effect modifier. - In future studies, it may be interesting to study time until first cancer diagnosis.

VERSION 1 – AUTHOR RESPONSE

1) Reviewer Name Lene Mellemkjær
Institution and Country Danish Cancer Society Research Center
Copenhagen, Denmark
Please state any competing interests or state 'None declared': None declared

Overall comment:
This study presents results from follow-up of patients with burn injuries from Scotland and Western Australia with regards to cancer incidence. The results for the cohort from Western Australia, however, have already been published in a previous paper; nevertheless they are repeated here. The present study would benefit from focusing on the new results – the follow-up of patients from Scotland – with a substantial shortening of the description of the Western Australia cohort and results.

Abstract:
The gender difference in overall cancer incidence is reported but the site specific results are for combined gender. Thus, site specific results underlying the overall results are not mentioned.

Due to the limited word count site-specific results were not included in the original abstract. Reference has now been made in the 'Results' section of the Abstract to allude to the site specific gender results:
Consistent significant trends were found which showed an excess of cancer notifications for a range of selected site specific cancers, including buccal cavity, liver, larynx and respiratory tract, with an elevated and more widespread increase amongst female burn patients.

Introduction:

Second paragraph is a detailed description of the material and should be moved in a much shorter version to this section of the paper. Instead the evidence from previous studies regarding cancer risk after burn injuries should be described. Currently only the study from Western Australia is referenced – and results from this study are included as part of the present study.

Discussion on WADLS in second paragraph has been shortened (and moved to 3rd paragraph) and evidence of previous population-based studies from Denmark and Sweden previously presented in the Discussion section, have now been included in both the Introduction (2nd paragraph) and the Discussion sections.

2nd paragraph

Results of our initial study demonstrated no significant risk of developing any form of (all-site) cancer (combined gender) after burn injury; however, a gender effect with female burn survivors having an increased risk of any form of cancer was found.11 In contrast to our results, a Swedish population-based study 12 of linked burn patient hospitalisation records and cancer registrations reported the risk of developing any form of cancer, for combined gender, was increased (SIR, 95%CI: 1.11, 1.06-1.16), with the risk of lung cancer also significantly increased (SIR, 95%CI: 1.39, 1.21-1.59). However, a Danish study of burn patients 13 found no significant increases in cancer (combined gender) for all malignant neoplasms including all skin cancers (SIR, 95%CI: 0.99, 0.93-1.06).

Methods:

Page 8, lines 1-2: It is mentioned that an incident cancer was defined as cancer coded by C00-C96 excluding C44. However, C44 is actually included in Table 3? Are these ICD-10 or ICD-O3 topography codes?

ICD 10 codes have been used to define the cancer sites as per incidence rates supplied by the cancer registries.

Thank you for identifying this typing error in Table 3 – this has now been corrected: Skin – malignant melanoma C43

Page 8, first paragraph: It appears that multiple cancers in one person are counted in the analyses yet by excluding patients with cancer prior to the burn injury and ending follow-up at date of cancer diagnosis this is combined with a first cancer approach. If multiple cancers are counted during follow-up, those with cancer prior to the burn should not have been excluded as persons, the cancer should just not be counted and date of cancer should not have been used as an end date. Thus, it seems that a mix of first and multiple cancer approach has been used.

For this study, a methodological decision was made to exclude those patients hospitalised for an index burn injury with prevalent cases of cancer from the standardised incidence ratio. This was done, such that the temporality of burn exposure to record of cancer notification could be clearly established and multiple records of cancer per individual after burn injury were included for this clearly defined burn patient population. Previous record of cancer and / or treatment before burn injury hospitalisation may have impacted the immune response and further complicated the interpretation of the results.

In our future research we will be using population-based comparison cohorts (non-burn trauma, no injury) and will be able to examine effects on survival and increased cancer risk after burn injury, for those patients with a previous diagnosis of cancer.

Results:

How do the authors explain the lack of gender difference in Scottish patients included in the early period (Table 2)?

It is difficult to explain the lack of gender difference for the sub-cohort of burn patients in Scotland 1983-88. Some possible suggestions include: for the sub-cohort 1983-88, had less comorbidities and / or had better lifestyle factors than females hospitalised for burns during the remainder of the study period. The following sentence has been included in Discussion Findings 4.2:

The lack of gender difference for the sub-cohort of burn patients hospitalised in Scotland 1983-88 for total (all-sites) cancer risk is difficult to explain. Possible reasons may include that female burn patients had less comorbidity and / or had better lifestyle factors than females hospitalised for burns during the remainder of the study period.

Discussion:

First section on Methodological issues should be shortened substantially.

This section has been shortened from 589 to 411 words as requested. Please refer to Discussion, Methodological issues 4.1

The authors do not comment on findings for lymphomas - these malignancies are usually associated with suppression of the immune system.

A sentence has now been included in Discussion Findings 4.2:

Whilst lymphomas have also been reported in association with immunosuppression,26 27 statistically significant results were found for Western Australian female burn patients only.

Minor issues:

Page 7, last sentence in second paragraph: What is meant by separation date?

Separation date refers to the administrative process / date by which a hospital records the cessation of an episode of care for a patient within the one hospital stay. Authors have included in Methods section, 2nd paragraph: separation (or discharge)…

The term “all cause” is used throughout the paper in connection with cancer, i.e., “all cause cancer” but is usually applied in connection with mortality studies not cancer incidence studies.

All references to “all-cause” have been changed to total (“all-sites”) of cancer and amendments have been underlined in the manuscript text and in relevant Table headings.

2) Reviewer Name Gerald McGwin and Nicole Safiano

Institution and Country Department of Epidemiology and Surgery, University of Alabama at Birmingham, Birmingham, Alabama

Please state any competing interests or state ‘None declared’: None declared

The authors have performed a retrospective cohort study to examine increased cancer risk in patients with a history of burn injury in Scotland and Western Australia using linked databases and cancer registries. The authors found an increased risk of certain cancers for both genders. For many cancers, there was a higher risk for females than for males. This manuscript is interesting and

examines a relationship between an important exposure and outcome. Strengths of this study include two large sample sizes using detailed and well-kept records with longitudinal data. The statistical methods are clearly discussed and appropriate. The discussion contains interesting possible biological reasons for the findings.

Specific comments and questions follow below.

- Table 1 shows some significant differences between the Scotland and WA cohorts but these are not discussed in regards to their potential contribution to differences in the risks between the two cohorts. Also, is there a relationship between site and depth of the burn and the type of cancer?

The gender distribution for patients was similar between cohorts. While the age distribution was not too dissimilar, the Scottish data contained 23% of burn patients 50 years and older vs. 14% in WA. It is possible that the higher comorbidity observed amongst Scottish data may be related to this older age distribution. Despite these differences, the method of indirect standardisation determined excesses in observed cancer vs. expected cancers adjusting for age and gender population denominators for each population.

Recording difference between the two hospital data collection i.e. an absence of consistent TBSA% data in the Scottish data, and the use of 'single' ICD codes to represent burns to multiple body regions, made detailed interpretation of the differences in burn sites and depth between the datasets, difficult.

From previous results of multivariate Poisson regression modelling using WA data, we found no significant increase in risk of cancer associated with severity of burn depth (compared with erythema): partial thickness (IRR, 95%CI: 1.02, 0.79-1.31), full thickness (IRR, 95%CI: 0.84, 0.61-1.14) and unspecified burn depth (IRR, 95%CI: 0.82, 0.64-1.06). However, for patients with burns of TBSA 20% or greater (compared to reference TBSA 10% or less), a significant increase in the risk of cancer was estimated (IRR, 95%CI: 1.81, 1.22-2.69). With an absence of consistently recorded TBSA% data and use 'single' ICD codes to represent burns to multiple body regions in the Scottish data, we were not able to examine the effects of these patient injury variables on SIRs for either site specific or 'all sites' cancer.

- Why was the sub-cohort for 1983-1988 analyzed and compared to the entire cohort in Table 2?

The sub-cohort 1983-1988 represents a group of patients with the longest overall opportunity for follow-up, with optimum follow-up time to cancer.

- The finding of a statistically significant increase in esophageal cancer is borderline as the CI for WA contains 1. (see page 12 line 3) Though this can happen it would be useful to have the actual p-values for comparisons if "statistically significant" is going to be used.

Thank you for identifying the incorrect inclusion of oesophageal cancers. While SIRs were > 1 for WA oesophageal cancers, statistical significance was not achieved. This sentence has been amended in text:

Statistically significant increases in the number of observed cancers for combined gender were found in both the Western Australia and Scottish data for the buccal cavity, larynx, liver and respiratory tract.

- It may be a stretch to conclude that there was a significant increase in most types of cancer for

females. Only about half reached statistical significance. (pg 12 lines 3-6)

Authors appreciate this comment and have amended the text: In Discussion Findings 4.2:

There was also a general trend for increased cancer risk for a number of the selected types of cancers for females and statistically significant increases in female genital cancers. (paragraph 1)

The site-specific analyses showed statistically significant increases in female genital cancers. A general trend of excess cancers amongst female burn patients across a number of the site-specific cancers examined was also found; however, these excesses did not always reach statistical significance, possibly due to small numbers. (paragraph 2)

- The lack of available data on alcohol and tobacco use warrants further discussion as this may be a significant effect modifier.
The possible association of the findings with higher exposure levels to alcohol and smoking amongst the burn populations examined are suggested in the Discussion Findings 4.2 paragraph 2:

These results are similar to those found in a Danish study 13 and may be related to tobacco or alcohol use amongst this patient population. However, it would be expected that inhalation injury may also increase the cancer risk of the upper and lower respiratory tract, and in the case of the diagnosis of hepatocellular cancer in a young male (12 years of age) burn patient in Western Australia,10 tobacco or alcohol use would be most unlikely attributable agents.

We agree that lifestyle factors (including alcohol and tobacco) are important; the requirements of further research to examine the effects of and / or adjust for the possible impacts of smoking and alcohol on cancer risk amongst the burn patient cohort are presented in Discussion, Methodological Issues 4.1:

Further burn injury research is planned with comparison cohorts (non-burn trauma, no injury), using incidence rate ratio analyses to explore patient (including lifestyle factors such as smoking and alcohol) and injury factors associated with the observed cancer risk.

- In future studies, it may be interesting to study time until first cancer diagnosis.
We plan to undertake further analysis using WA linked data – using comparison cohorts (no injury, non-burn injury) where we will include in the analyses such variables as time to first cancer, previous history of cancer, and measures of social / economic disadvantage and lifestyle factors.

VERSION 2 – REVIEW

REVIEWER	Lene Mellemkjær Danish Cancer Society Research Center, Copenhagen, Denmark
REVIEW RETURNED	27-Nov-2013

GENERAL COMMENTS	The authors have addressed most of the issues raised, however, the approach for follow-up for cancer has still not be adequately addressed:

	Has the approach been to count person-years until first cancer but still include multiple cancers during follow-up? This would not be compatible. What approach is used for calculating the cancer incidence rates in the background populations? Are these multiple cancer rates or first primary cancer rates? In the response letter, the authors explain that patients with cancer were excluded so that temporality could be clearly established and so that immune responses from a prior cancer and/or the treatment could not affect results. However, it has not been explained why this first cancer approach has not been used during follow-up, instead multiple cancers were counted during follow-up. The mix-up of approaches needs to be addressed. These issues have not been mentioned in the manuscript. Regarding ICD classifications, whenever specific ICD codes are mentioned in the text as well as in Tables (see Table 3), please specify which classification is used.

VERSION 2 – AUTHOR RESPONSE

Reviewer Name Lene Mellemkjær

Has the approach been to count person-years until first cancer but still include multiple cancers during follow-up? This would not be compatible.

Response to reviewer:

Our approach was similar to those presented by cancer registries where site-specific age standardised cancer incidence is used for comparative studies. The analyses counted person-years until first cancer of interest i.e. we calculated site-specific person years for each cancer category.

What approach is used for calculating the cancer incidence rates in the background populations? Are these multiple cancer rates or first primary cancer rates?

Response to reviewer:

The cancer incidence rates in the background population were provided by the cancer registries in both Western Australia and Scotland. The incidence rates (rate at which new cases occur in a population during a specific period) were provided for total (all-sites) and site-specific cancers.
Ref: Chapter 11. Statistical methods for Registries (Boyle and Parkin)
In the response letter, the authors explain that patients with cancer were excluded so that

temporality could be clearly established and so that immune responses from a prior cancer and/or the treatment could not affect results. However, it has not been explained why this first cancer approach has not been used during follow-up, instead multiple cancers were counted during follow-up.

The description of our approach has been expanded in the methods section which follows-up to cancer of interest i.e. individual calculations were conducted for total (all-sites) and site-specific cancers:

For the determination of incident rates, the calculation of person-years began on the day of final hospital discharge for the index burn admission and the study observation period continued until date of defined cancer diagnosis, death, or 31st December 2008, whichever occurred first. Individual calculations were conducted for total (all-sites) and site-specific cancers. The observed numbers of cases of cancer and person-years at risk were calculated by age (5-year age groups), gender and calendar period (1983-1988, 1989-1993, 1994-1998, 1999-2003 and 2004-2008). The expected numbers of cancer cases were estimated by multiplying the specific number of person years per category by the corresponding incidence of cancer in Western Australia, Scotland, and combined cancer incidence rates, provided by WACR and ISD Scotland. The Standardised Incident Ratios (SIRs) were calculated by dividing the observed number of cases by the number expected. 21 22 The 95% confidence intervals (95%CI) were defined under the assumption that the observed number of cancers followed the Poisson distribution. 23

Authors outlined in previous response that patients with cancer prior to burn injury were excluded so that temporality could be clearly established and so that immune responses from a prior cancer and/or the treatment could not affect results. While any immune assaults and / or subsequent treatments impacts after first cancer diagnosis post index burn injury may have influenced subsequent cancer incidence, they were subsequent to an index or first burn injury severe enough to require hospitalisation. A study population that had no prior histories of cancer and burn injury hospitalisations, allowed assessment of a relationship between burn and cancer(s) that were not complicated by a compromised immune system, that may have potentially had an additive effect and increased subsequent cancer risk, that we were not investigating. Whilst for our burn cohort, all subsequent cancers were included in the analysis – we had a clearly defined starting point that included all persons in WA and Scotland with a first burn injury requiring hospitalisation, with no prior history of cancer.

Regarding ICD classifications, whenever specific ICD codes are mentioned in the text as well as in Tables (see Table 3), please specify which classification is used.

Response to reviewer:
The version of ICD in WACR used was specified in Methods para 3. In Methods para 4 the ICD version has now been included for Scottish data:

The Scottish cancer notifications are coded using the International Classification of Diseases (ICD-10) and the International Classification of Diseases for Oncology (ICD-O).

Table 3 has been updated to include International Classification of Disease s (ICD) version 10.