Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia

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Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia

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Article Focus

- Burn injury not only affects the skin but also has other systemic effects
- Inflammatory and immune response to burns may mediate cancer risk
- Gender differences in cancer risk after burn injury may be related to the immune response

Key messages

- Burn injury can have impacts on longer term health
- Increased risk of some cancers post-burn injury is greater in females than males

Strengths and Limitations

- Population-level linked administrative data minimises issues of selection and reporting bias, and loss to follow-up
- Consistency of results using population-level data from two patient populations provides greater support for link between burn injury and some cancers
- Unable to examine impact of burn severity on cancer risk due to lack of available data

Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia

Abstract

Objective: To investigate risk of cancer and potential gender effects in persons hospitalised with burn injury.

Design: Population-based retrospective cohort study using record-linkage systems in Scotland and Western Australia

Subjects: Records of 37,890 and 23,450 persons admitted with a burn injury in Scotland and Western Australia, respectively, from 1983 to 2008. De-identified extraction of all linked hospital morbidity records, mortality and cancer records were provided by the Information Service Division Scotland and the Western Australian Data Linkage Service.

Main outcome measures: Total and gender specific numbers of observed and expected cases of all-cause and site-specific cancers and standardised incidence ratios.

Results: From 1983-2008, for female burn survivors there was a greater number of observed versus expected notifications of all-cause cancer with 1011 (standardised incidence ratio (SIR), 95% confidence interval (CI): 1.3, 1.2 to 1.4) and 244 (SIR, 95%CI: 1.12, 1.05 to 1.30), respectively, for Scotland and Western Australia. No statistically significant difference in all-cause cancer risk was found for males. Significant excesses in observed cancers amongst burn survivors (combined gender) in Scotland and Western Australian were found for buccal cavity, liver, larynx and respiratory tract, and for cancers of the female genital tract.

Conclusions: Results from the Scotland data confirmed the increased risk of 'all-cause' cancer previously observed amongst female burn survivors in Western Australia. The gender dimorphism observed in this study may be related to the role of gender in the immune response to burn injury. More research is required to understand the underlying mechanism(s) that may link burn injury with an increased risk of some cancers.

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1. Introduction

The burden of burn injury is a significant issue, not only in terms of the acute care perspective but also the chronic health effects resulting from both the injury event and the subsequent treatments. While burns predominantly affect the skin, burns are associated with significant systemic effects [1-3], depressed immune functioning[4-8] and prolonged periods of systemic catabolism and hypermetabolism.[9] Prompted by a clinical scenario of a diagnosis of hepatocellular carcinoma in a young male burn patient,[10] and the potential for malignancy after burn, an initial study of burn injury and all-cause cancer risk was undertaken.[11] Results of this study demonstrated a gender effect with female burn survivors having an increased risk of all-cause cancer.

This previous study of burn injury and cancer risk used population-based data linked by the Western Australian Data Linkage System (WADLS). [12] Data linkage in Western Australia provides one of only a handful of information-rich environments worldwide that have been constructed from the linkage of multiple, large, population-based, administrative datasets. The WADLS meets international best practice standards, determined by experiences from the Oxford Record Linkage Study, Scottish Record Linkage System, Rochester Epidemiology Project and the Manitoba Centre for Health Policy.[12] Western Australia has a population of approximately 2.2 million, and as such, did not support detailed gender and site-specific cancer incidence assessments with adequate statistical power. While the WADLS has systematically linked datasets of Western Australians since the 1970s, other Australian States and Territories have only recently established record linkage systems and were not able to support this study. To extend the population-base and enable further detailed examination of the observed gender effect and site specific cancer incidence, approval was sought to access the Scottish population-based record linkage system, the Information Service Division (ISD) Scotland,[13] that has routinely linked health data since the 1980s.

This paper reports a retrospective longitudinal study to explore cancer risk after burn injury using linked hospital morbidity, cancer and death data of persons hospitalised for burn injury in both Western Australia and Scotland. The study aimed to, firstly, confirm the increased risk of 'all-cause' cancer observed in the preliminary Western Australian study of female burn survivors using the Scottish data; and, secondly, examine site-specific cancer risk amongst survivors of burn injury.

2. Methods

Study data were obtained from the Western Australian Data Linkage Service (WADLS) [12] and the Information and Services Division (ISD Scotland) of the National Health Service National Services

Scotland[13] with approval from Curtin University, the Western Australia Department of Health Human Research Ethics Committees and the NHS National Services Scotland Privacy Advisory Committee. The WADLS and ISD Scotland are validated record linkage systems that routinely link administrative health data from core datasets for the entire population of Western Australia and Scotland, respectively.

An index burn injury was defined as the first hospital admission with a burn injury using primary and additional diagnosis International Classification of Diseases (ICD) codes 940-949 (ICD9) and T20-T31 (ICD10). A de-identified extraction of all linked hospital morbidity records (Hospital Morbidity Data System (HMDS), mortality (Death Register, Western Australia) and cancer records (Western Australia Cancer Registry (WACR)) for all persons admitted to hospital with an index burn injury in Western Australia, for the period 1 January 1983 to 31 December 2008, was performed by WADLS [14]. A corresponding de-identified extraction of all linked hospital morbidity records (Scottish Morbidity Records (SMR) 01), cancer registrations (SMR06) and death records (General Register Office for Scotland (GROS)) using the same burn cohort definition was undertaken by ISD Scotland. Hospital admissions data items included age at admission, gender, admission date, separation date, principal and additional diagnoses and external cause of injury.

The Western Australia Cancer Registry (WACR) was established in 1981 and is a population-based cancer registry based on mandatory notification of cancers from pathologists, haematologists and radiation oncologist, and cancer information from death records.[15] Amendments to the Health (Notification of Cancer) Regulations in 1996 required from that time, notifications of all in situ, non-melanoma skin cancers other than basal cell and squamous cell carcinomas, and, all other invasive malignancies and benign Central Nervous System tumours. [15] Malignant cancers are coded according to a modified Australian version of the International Classification of Diseases, Tenth Revision (ICD10-AM) and International Classification of Diseases for Oncology (ICD-O-3).

The Scotland Cancer Registry (SMR06) has recorded all incident cancers in Scotland from 1958, and since 1997 registration has been centralised at ISD Scotland.[16] The registry is responsible for the collection of information on all new cases of primary malignant neoplasms, carcinoma in situ (including grade III intra-epithelial neoplasia), neoplasms of uncertain behaviour and (since 1 January 2000) benign brain and spinal cord tumours arising in residents of Scotland. Data quality is monitored using routine indicators, computer validation and ad hoc studies of data accuracy and completeness of ascertainment.[17] [18] The Scottish cancer notifications are coded using the International Classification of Diseases (ICD) and the International Classification of Diseases for Oncology (ICD-O).

Methods for analysis have been previously published. [11] An incident cancer was defined as a cancer diagnosis notification (C00-C96, excluding C44) after hospital admission for index burn injury. Analysis was restricted to malignant neoplasm notifications (C00-C96, excluding C44) for which all-cause and site-specific cancer incident rates were provided by WACR and ISD Scotland for respective populations. Records were excluded from the analysis if the date of cancer diagnosis was prior to date of discharge for index burn hospitalisation. When a record was identified as having more than one malignant neoplasm notification, each neoplasm was counted as an individual record, however, if multiple tumours of the skin (C43) with identical morphological characteristics (that is, the first three digits ICD-O-3 morphology code) were identified, they were recorded only once. Gender and age-specific cancer (total C00-C96, excluding C44) incident rates for the Western Australian and Scottish populations were pooled for the calendar periods 1983-1988, 1989-1993, 1994-1998, 1999-2003 and 2004-2008 to allow for changes in population cancer incidence during the study period.

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 cancer diagnosis, death, or 31st December 2008, whichever occurred first. 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. [19 20] The 95% confidence intervals (95%CI) were defined under the assumption that the observed number of cancers followed the Poisson distribution. [21]

Separate SIR analyses for all-cause and site-specific cancers were conducted using country specific data for respective burn patient cohorts (all burn depth) for cohorts hospitalised from 1983-2008; all-cause SIRs repeated for sub-cohorts of burn admissions from 1983-1987, with optimum follow-up time. To further explore the gender impact of burn injury on cancer risk, all-cause cancer SIR analyses were repeated on age-restricted sub-cohorts classified to reflect reproductive age at admission for burn injury: <15 years; 15-49 years; and, ≥50 years. All statistical analyses were performed using Stata statistical software V 11 (StataCorp LP, College Station, Tex).

3. Results

As previously reported, in Western Australia from 1983 to 2008, there were 23,450 hospital index admissions for burn-related injury.[14] After exclusion of records with a history of cancer prior to

separation date or death during hospital admission for burn, a total of 22,705 patient records were included in the analysis.[11] There were 673 patients with a first cancer notification after date of separation for burn injury hospitalisation, and with inclusion of multiple malignancies, 759 cancer notifications were included in the standardised incident ratio analyses as independent observations.

In Scotland from 1983-2008, there were a total of 37,890 persons hospitalised for an index burn-related injury. After exclusion of those with a history of cancer prior to separation date or death during hospital admission for burn, a total of 37,506 patients were included in the analysis. There were 2,005 patients with a first cancer notification after date of separation for burn injury hospitalisation, and with inclusion of multiple malignancies, 2,260 cancer notifications were included in the standardised incident ratio analyses as independent observations. Characteristics of the Western Australia and Scotland cohorts are presented in Table 1.

The Western Australia cohort (1983-2008; combined gender) was followed for a total of 283,306 person-years, with mean follow-up time of 12.3 years (range: >0 – 25.9 years). Mean follow-up time for those with a cancer notification was 9.4 years (range: >0 – 25.4) and for those with no cancer notification, 12.4 years (range: >0 – 25.9). The Scotland cohort (1983-2008; combined gender) was followed for a total of 474,489 person-years, with mean follow-up time of 12.6 years (range: 0 -26.0 years). Mean follow-up time for those with a cancer notification was 9.4 years (range: >0-25.8) and for those with no cancer notification, 12.7 years (range: >0-26.0).

For the Scottish cohort of burn injury patients (combined gender) there was marginal but significant difference (SIR, 95%CI: 1.09, 1.05-1.10) in the overall risk of cancer for persons with a burn injury hospitalisation for the period 1983 to 2008, compared with the general population of Scotland. While a significant increase of 30% in cancer risk was estimated for females there was no difference in cancer risk for males, when compared with the general population of Scotland (refer to Table 2). For the sub-cohort of burn injury patients 1983-1988, the total observed number of cases of cancer (n=838) was statistically significantly lower than expected (n=953.4) with SIR (95%CI) of 0.88 (0.82 to 0.94), with males having a statistically significantly lower number of cases observed than expected. Refer to Table 2 for gender specific SIRs for all-cause cancer for Scotland and Western Australian burn patients, hospitalised during 1983-1988 and 1983-2008.[11]

Female genital cancers were grouped due to the small numbers of observed cancers in sub-groups in the Western Australian data and unstable SIR results. Statistically significant increases in observed genital (combined) cancers for female burn patients in both Western Australia and Scotland were found. The increased breast cancer incidence was statistically significant amongst female burn survivors in Scotland. Statistically significant increases in cancer incidence for combined gender for

both Western Australia and Scottish data were observed for cancers of the buccal cavity, liver and respiratory tract. Refer to Table 3 for gender and site-specific cancer SIRs. For each of these cancers, female burn survivors in both Western Australia and Scotland had higher incidence than males when compared with respective general population data. For the majority of site-specific cancers selected, female burn survivors in both Western Australia and Scotland had higher numbers of observed cancers than expected, with SIRs of similar magnitude. However, SIR results for Scottish data reached statistical significance, reflecting the larger population-base and respective higher number of cancer notifications.

Table 4 presents an SIR analyses of all-cause cancer risk repeated on age-restricted sub-cohorts, classified to reflect reproductive age (<15 years; 15-49 years; and, ≥50 years) at admission for burn injury. For males in both WA and Scotland, no statistically significant differences were found across the three age groups. For female burn survivors in Scotland, the observed numbers of cancers (all-cause) exceeded that expected for each of the three age groups, with statistically significant results observed for the age groups 15-49, and 50 years and older. In the Western Australia data, excess cancers were observed for those younger than 15 years and for those 50 years and older, with statistically significance reached for the older age group; for females 15-49 years at burn injury, no difference in observed and expected all-cause cancer was found.

4. Discussion

4.1 Methodological Issues

Data linkage is a technique which creates links within and between data sources, identifying all the information that relates to the same person, place or event. In addition, when population-level administrative data are used, data linkage minimises issues of selection and reporting bias, as well as loss to follow-up. Data quality of the Western Australia and Scottish Cancer Registers[15 17 18] and hospital morbidity datasets[22 23] are assessed continually for both accuracy and quality; however, potential for misclassification bias may exist. The coding system changed from ICD-9 to ICD-10 in both Western Australia and Scotland during the study period for death and hospital admissions data.

Data of all index burn hospitalisations in Western Australia and Scotland from 1983 to 2008 were analysed with follow-up time from discharge date, allowing for exclusion of prevalent cancers to support temporality of burn exposure and incident cancer. Cancer diagnoses from cancer registries in Western Australia and Scotland were independent of the record of burn injury in the respective hospital morbidity datasets. Minor burns treated in emergency departments were not included in the study. The burn patient cohorts under study are part of the respective reference populations, and as such, this may have a small diluting effect in the standardised incidence ratios. Western

Australia has a population of approximately 2.2 million, and as such, did not support detailed gender and site-specific cancer incidence assessments. Using parallel datasets from Scotland, of population approximately 5.5 million, allowed examination of the consistency of results and trends across the populations.

The Western Australia hospital morbidity data records the principal diagnosis and up to 20 additional diagnosis fields, whereas, the Scottish morbidity data includes the principal diagnosis and 5 additional diagnosis fields. The effects of this reduction in the number of available additional diagnosis fields included the more frequent use in the Scottish data of ICD codes for burns to multiple regions of the body (ICD9 946; ICD10 T29) rather than recording of multiple individual anatomic burn sites, reflected in Table 1; and, an absence of consistently recorded supplementary ICD (ICD9 946; ICD10 T31) data to describe total body surface area burned (TBSA%). This limited our capacity to undertake both SIR analyses restricted to more severe burns of TBSA 20% or greater and incident rate ratio analysis to examine the effects of severity of burn injury (burn depth and TBSA%) using the least exposed group as reference (instead of the general population of Scotland) and confirm previous results. Approximately 90% of persons hospitalised in Western Australia had non-severe burn injury (TBSA<20%).[14] Previous SIR analyses of all-cause cancer risk in Western Australia showed similar trends in results for all burn patients (severe and non-severe) and those hospitalised for severe burn; however, for females hospitalised with severe burn there was a statistically significant increase of 31% in all-cause cancer notifications.[11]

The data analysed in this study are based on linked data from population registers to compare observed cancer incidence in burn patient cohorts with that expected using general population cancer rates adjusting for gender, age and calendar period population changes. Although this study had a follow-up period of up to 26 years from the date of separation for admission for burn injury, the follow up period for many patients may not have provided sufficient observation time to enable identification of all potential malignancies, given the long latency period for many cancers. Further burn injury research is planned with comparison cohorts (non-burn trauma, no injury), using incidence rate ratio analyses to explore injury and patient factors associated with the observed cancer risk.

4.2 Findings

Analysis of ISD Scotland data confirmed the results of our previous study: a statistically significant increase in all-cause cancer risk for female burn survivors with males experiencing no difference. The site specific analyses clearly showed statistically significant increases in the number of observed cancers for combined gender in both the Western Australia and Scottish data for the buccal cavity,

larynx, liver, respiratory tract and oesophagus. There was also a general trend for increased cancer risk for most of the selected types of cancers for females and statistically significant increases in female genital cancers. Sub group analyses, defined crudely by reproductive age, did not elucidate any clear patterns of the influence of oestrogen on cancer incidence, with female burn survivors in Scotland showing increased risk across all age groups. For female burn survivors in WA, an increased risk for all-cause cancer was found for those younger than 15 years (pre-pubescent) and 50 years and older (post-menopausal).

The site-specific analyses showed that whilst statistically significant increases in female genital cancers were found, there was also a general trend for increased cancer risk for most of the selected types of cancers for females. 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, respiratory tract and oesophagus. These results are similar to those found in a Danish study [24] 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. Interestingly, the results of no increase in skin melanoma risk after burn injury in this study support findings of other population-based studies.[24 25]

An alternative explanation for this increased incidence in cancer post-burn may lie in the significant impact a burn injury has on the immune system, or the sustained oxidative and metabolic stress that are integral to the injury response. While burn injury predominantly affects the skin, it has been shown to cause significant depression of both humoral and cell-mediated immunity (CMI), [7 26 27] sustained elevated levels of oxidative stress [28 29] and prolonged elevation of hyper-metabolic and stress hormone levels. [30 31] These effects have been demonstrated to persist for up to 3 years post-injury and can lead to long-term systemic impacts on other organs of the body.[1 2 32-36] Severe burn injury has been demonstrated to induce endoplasmic reticulum (ER) stress, in particular, in the liver.[37] ER stress is a stress-response that initially facilitates cell survival but can switch to a pro-apoptotic signal with prolonged stress.[37 38] However, it has also been shown that the ER stress response can become maladaptive, facilitating adaptation to hypoxic environments and promoting tumour growth. [38 39] It is plausible that the array of host responses combined with the impact of the injury, therefore, creates an environment of increased susceptibility to cancer.

In addition to the observed increase in some of the selected site-specific cancers, the data support evidence for a gender dimorphism (a systematic difference between individuals of different sex in the same species) in the response to burn injury. After burn injury, gender has been shown to be an

important factor with respect to poorer outcomes for mortality[40-43] and improved prognosis for multiple organ dysfunction syndrome,[44] and sepsis,[45] for females compared to males. Similar gender-based differences have also been reported in animal studies of burn injury.[46-50]

The impact of gender with respect to outcomes after burn injury is largely thought to stem from well-established differences in immune biology. There is a substantial volume of published literature to support a gender dimorphism in the immune response[51-54] and sepsis[45] following injury that have impacts on health and mortality.[41 42] The majority of these studies support a more efficient and effective innate and adaptive immune responses in females, leading to more rapid clearance of infectious organisms driven by tissue resident cell populations.[55] This 'advantageous' response reduces the risk of infection in females compared to males [55 56] but leads to elevated risk of autoimmune disease.[57] This dimorphism was thought to arise largely due to the impact of oestrogen on immune function.[58 59] However, recent papers have demonstrated these differences are not completely ablated by ovariectomy (in animal models) [55] and others have shown that oestrogen can be deleterious to the immune response.[60] This suggests a role of other mediators, most likely expressed on the X-chromosome, in the maintenance of the differential immune response. [61 62] The evidence for gender differences in the immune response, both to thermal and other trauma, and its impact on outcomes is substantial. Here, the evidence of increased cancer incidence in selected types of cancer after burn injury, with a greater effect in females, suggests the systemic immune response to burn injury may be a mediator of cancer susceptibility.

5. Conclusion

Using population-based linked data of all burn patients in both Western Australia and Scotland, consistent trends were found in excesses in cancer notifications for a range of selected site specific cancers with an elevated and more widespread increase in female burn patients. Overall, however, the increased cancer risk affected small proportions of the respective burn patient cohorts. More research is required to understand the underlying mechanism(s) that may link burn injury to an increased risk of some cancers and why this is elevated in females, which may in turn enable identification of possible sites for intervention.

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Table 1 **Characteristics of burn injury patients included in analyses with no record of cancer prior to separation date of index burn admission, 1983-2008, by country.**

Characteristics	Western Australia N (%)	Scotland N (%)
Total number burn admissions*	22,705	37,506
Gender: Male	15,481 (68.2)	23,896 (63.7)
Age at index admission (Years)		
<15	8,135 (35.8)	14,579 (38.9)
15-24	4,364 (19.2)	4,495 (12.0)
25-49	7,147 (31.5)	9,554 (25.5)
50-64	1,736 (7.7)	4,080 (10.9)
65+	1,323 (5.8)	4,798 (12.8)
Site of burn**		
Head and neck	6,784 (15.4)	7,592 (16.1)
Trunk	7,553 (17.2)	8,815 (21.0)
Hand, wrist, upper limb	15,801 (35.9)	6,984 (14.8)
Hip , lower limb	11,798 (26.8)	9,531 (3.4)
Eye	379 (0.9)	1,087 (2.3)
Respiratory tract	212 (0.5)	163 (0.3)
Other internal organs	124 (0.3)	165 (0.3)
Multiple regions	656 (1.5)	3,677 (7.8)
Unspecified region	694 (1.6)	858 (1.8)
Burn site depth**		
Erythema	8,929 (20.9)	4,815 (11.5)
Partial thickness	18,449 (41.9)	6,302 (15.0)
Full thickness	7,095 (16.1)	4,924 (11.7)
Unspecified	9,528 (21.7)	25,869 (61.7)
Calendar period of admission		
1983-1988	5,431 (23.9)	11,507 (30.7)
1989-1993	4,200 (18.5)	7,876 (21.0)
1994-1998	4,755 (20.9)	7,130 (19.0)
1999-2003	4,265 (18.9)	5,980 (15.9)
2004-2008	4,054 (17.9)	5,013 (13.4)
Any co-morbidity at index burn		
Yes	2,798 (12.3)	7,679 (20.5)

***** No previous record of cancer

** Patients may have multiple burn sites per anatomical region per depth

Table 2 **Standardised incidence ratios and 95% confidence intervals and observed and expected numbers for all-cause cancer in persons hospitalised for burn injury in Western Australia and Scotland, during the periods 1983-2008 and 1983-1988.**

	Western Australia††			Scotland		
	Combined SIR 95%CI* O:E**	Male† SIR 95%CI O:E	Female† SIR 95%CI O:E	Combined SIR 95%CI O:E	Male† SIR 95%CI O:E	Female† SIR 95%CI O:E
Total cohort 1983-2008	0.97 (0.9 to 1.0) 759: 785.5	0.9 (0.8 to 1.0) 515: 569.5	1.1 (1.0 to 1.3) 244: 216.0	1.09 (1.05 to 1.10) 2260: 2075.9	0.96 (0.90 to 1.0) 1249: 1303.2	1.3 (1.2 to 1.4) 1011: 772.6
Sub-cohort 1983-1988	1.0 (0.9 to 1.1) 294:294.9	0.9 (0.8 to 1.0) 190:220.3	1.4 (1.1 to 1.7) 104: 74.6	0.9 (0.8 to 0.9) 838: 953.4	0.8 (0.7 to 0.9) 491: 614.3	1.0 (0.9 to 1.2) 347: 339.1

*SIR (95%CI): Standardised Incidence Ratio (95% confidence interval) adjusted for age and gender
** O: E: Observed: Expected
†SIR (95%CI): Standardised Incidence Ratio (95% confidence interval) adjusted for age
†† Western Australian comparison data Duke et al. Burns 2011; 38:340-47.

Table 3 **Standardised incidence ratios and 95% confidence intervals and observed and expected numbers for selected types of cancer in persons hospitalised for burns Western Australia and Scotland, 1983-2008.**

Cancer Site	Western Australia			Scotland		
	Combined SIR 95%CI* O:E**	Male SIR 95%CI† O:E	Female SIR 95%CI† O:E	Combined SIR 95%CI* O:E	Male SIR 95%CI† O:E	Female SIR 95%CI† O:E
Buccal cavity C00 to C14	1.4 (1.03 to 1.9) 45: 32.6	1.4 (1.0 to 1.9) 38:28.1	1.5 (0.7 to 3.2) 7: 4.6	2.6 (2.2 to 3.1) 117: 45.0	2.4 (1.9 to 2.9) 83: 35.1	3.4 (2.5 to 4.8) 34:9.9
Oesophagus C15	1.4 (0.9 to 2.4) 15:10.50	1.5 (0.9 to 2.6) 13: 8.7	1.1 (0.3 to 4.5) 2: 1.8	1.6 (1.3 to 2.0) 82: 51.4	1.5 (1.1 to 1.9) 53:36.1	1.9 (1.3 to 2.7) 29:15.3
Stomach C16	0.6 (0.3 to 1.1) 10:17.0	0.5 (0.2 to 1.1) 7: 13.4	0.8 (0.3 to 2.6) 3: 3.6	1.2 (0.9 to 1.5) 73:63.2	1.1 (0.8 to 1.5) 1.2 5: 2.8	1.3 (0.9 to 1.9) 25:19.5
Colorectal C18 to C20	0.7 (0.6 to 0.9) 69: 96.3	0.7 (0.5 to 0.9) 45: 69.1	0.9 (0.6 to 1.3) 24: 27.2	1.2 (1.1 to 1.4) 268:221.8	1.0 (0.9 to 1.2) 142:140.5	1.4 (1.3 to 1.8) 125: 81.3
Liver C22	2.6 (1.6 to 4.0) 19: 7.4	2.2 (1.3 to 3.7) 14: 6.3	4.7 (2.0 to 11.4) 5: 1.1	1.7 (1.2 to 2.5) 31:18.0	1.5 (1.1 to 2.5) 22: 13.3	1.9 (1.0 to 3.7) 9: 4.7
Pancreas C25	0.7 (0.4 to 1.3) 11: 15.3	0.9 (0.5 to 1.7) 9: 10.4	0.4 (0.1 to 1.6) 2: 5.0	1.1 (0.8 to 1.5) 44:39.6	1.5 (1.03 to 2.0) 34: 23.4	0.6 (0.3 to 1.2) 10: 16.2
Larynx C32	5.7 (0.9 to 3.3) 10: 5.7	1.5 (0.7 to 3.0) 8: 5.4	6.0 (1.5 to 24.1) 2: 0.3	1.9 (1.4 to 2.5) 39: 21.1	1.5 (1.1 to 2.2) 28: 18.5	4.2(2.3 to 7.7) 11:2.6
Respiratory tract C33 to C34	1.4 (1.1 to 1.6) 101: 74.8	1.3 (1.1 to 1.7) 79:59.3	1.4 (0.9 to 2.2) 22:15.4	1.5 (1.4 to 1.7) 448:298.1	1.3 (1.2 to 1.5) 279:210.4	1.9 (1.7 to 2.2) 169:87.7
Skin –melanoma C44	0.7 (0.6 to 0.9) 72: 102.0	0.7 (0.6 to 1.0) 57: 77.9	0.6 (0.4 to 1.0) 15: 24.1	0.8 (0.6 to 1.1) 38:48.5	0.7 (0.4 to 1.1) 19:28.4	1.0 (0.4 to 1.1) 19:20.0
Breast C50	1.0 (0.8 to 1.3) 65: 62.4	1.3 (0.2 to 9.2) 1: 0.8	1.0 (0.8 to 1.3) 64:61.7	1.7 (1.5 to 1.9) 271:161.4	0.7 (0.1 to 4.8) 1:1.5	1.6 (1.5 to 1.9) 270: 160.0
Female genital tract (combined) C51 to C57			1.4 (1.0 to 2.0) 31:26.7			1.7 (1.4 to 2.0) 114: 67.2
Male genital tract (combined) C60 to C63		0.9 (0.8 to 1.1) 141: 150.7			1.1 (1.0 to 1.3) 210: 192.6	
Prostate C61		0.8 (0.6 to 0.9) 102: 135.9			1.1 (0.9 to 1.2) 177: 165.5	
Kidney, Bladder, UT C64 to C68	0.5 (0.3 to 0.7) 17: 37.9	0.4 (0.2 to 0.7) 12: 30.9	0.7 (0.3 to 1.7) 5: 7.0	1.2 (1.0 to 1.4) 135: 110.9	1.2 (1.0 to 1.4) 96: 82.8	1.4 (1.0 to 1.9) 39: 28.0
Brain C71	1.2 (0.7 to 1.9) 16: 13.9	1.0 (0.5 to 1.8) 10: 10.5	1.7 (0.8 to 3.9) 6: 3.5	1.5 (1.1 to 2.0) 39:27.0	1.4 (0.9 to 2.0) 26:19.2	1.7 (1.0 to 2.9) 13:7.8
Lymphomas to all	1.0 (0.7 to 1.4) 36: 35.5	0.8 (0.5 to 1.2) 20: 26.0	1.7 (1.03 to 2.7) 16:9.6	1.1 (0.9 to 1.4) 75:68.0	1.1 (0.8 to 1.4) 48:45.0	1.2 (0.8 to 1.7) 27:23.0
Myeloma/ plasma	1.3 (0.7 to 2.3) 11: 8.6	1.3 (0.7 to 2.6) 8:6.1	1.2 (0.4 to 3.7) 3: 2.49	1.1 (0.7 to 1.6) 22:21.0	1.0 (0.6 to 1.7) 13:13.2	1.2 (0.6 to 2.2) 9: 7.8
Leukaemia's to all	1.1 (0.8 to 1.7) 26: 22.9	1.1 (0.7 to 1.8) 19: 17.0	1.2 (0.6 to 2.5) 7: 6.0	1.3 (1.01 to 1.7) 63:48.6	1.0 (0.73 to 1.4) 34:33.1	1.8 (1.3 to 2.7) 29: 15.5

*SIR (95%CI): Standardised Incidence Ratio adjusted for age and gender (95% confidence interval)

** O: E: Observed: Expected

†SIR (95%CI): Standardised Incidence Ratio adjusted for age (95% confidence interval)

Table 4 **Standardised incidence ratios and 95% confidence intervals and observed and expected numbers for all-cause cancer incidence, for persons hospitalised for burns Western Australia and Scotland, by age group, 1983 to 1988.**

Age at first burn years	SIR (95%CI) (observed: expected)		
	combined gender*	Male†	Female†
<15			
WA	1.17 (0.82 to 1.68) (30:25)	1.19 (0.77 to 1.84) (20:16)	1.15 (0.62 to 2.14) (10:8.6)
Scotland	0.94 (0.69 to 1.28) (41:43.69)	0.72 (0.47 to 1.12) (20:27.77)	1.32 (0.86 to 2.02) (21:15.92)
15 to 49			
WA	0.87 (0.77 to 0.99) (273: 313)	0.87 (0.75 to 1.00) (197: 226)	0.86 (0.69 to 1.1) (76: 87)
Scotland	1.21 (1.12 to 1.31) (617: 509.16)	1.04 (0.94 to 1.16) (345: 331.68)	1.53 (1.36 to 1.73) (272: 177.48)
≥ 50			
WA	1.02 (0.93 to 1.12) (456: 446)	0.91 (0.82 to 1.02) (298: 326)	1.32 (1.13 to 1.54) (158: 120)
Scotland	1.05 (1.00 to 1.11) (1602: 1523)	0.94 (0.88 to 1.00) (884: 943.75)	1.23 (1.15 to 1.33) (718:579.25)

*SIR (95%CI): Standardised Incidence Ratio adjusted for age and gender (95% confidence interval)
†SIR (95%CI): Standardised Incidence Ratio adjusted for age (95% confidence interval)

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

Page numbers in this checklist – relate to page numbers of the final pdf version of uploaded manuscript file

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract *Population-based retrospective cohort record linkage study – in abstract* *Title: Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia. (Pages 1, 5)*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found *Abstract - Page 5*
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported *While burns predominantly affect the skin, burns are associated with significant systemic effects, depressed immune functioning and prolonged periods of systemic catabolism and hypermetabolism, that may increase a person's risk of cancer. (Page 6)*
Objectives	3	State specific objectives, including any prespecified hypotheses *Done: Firstly, confirm the increased risk of 'all-cause' cancer observed in the preliminary Western Australian study of female burn survivors using the Scottish data; and, secondly, examine site-specific cancer risk amongst survivors of burn injury (Page 6)*
Methods		
Study design	4	Present key elements of study design early in the paper *Clearly presented in Introduction and Methods sections (Pages 5- 8)*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection *Clearly presented in Methods section (Pages 6 - 8)*
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Population-based study of linked health administrative datasets: whole of population data are used. (Pages 6-8)* *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable *Burn exposure (Page 7) and cancer outcomes (Page 8) clearly defined.*

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 *Data sources clearly defined in Methods: Information Service Division (ISD) Scotland Western Australia Data Linkage System (Page 7) and reference population-based age and gender cancer incidence rates (Page 7-8)*
Bias	9	Describe any efforts to address potential sources of bias *Population-level linked administrative data minimises issues of selection and reporting bias, and loss to follow-up.*
Study size	10	Explain how the study size was arrived at *Whole of population study undertaken (Scotland and Western Australia) stated in Methods (Page 6-8).*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why *Groupings described / defined in Methods (Page 8)*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding *All analyses clearly presented in Methods for each cohort of burn patients hospitalised in both Scotland and Western Australia: 1) from 1983 to 2008; 2) sub-group 1983-1988; and 3) by grouped age at admission (<15; ≥15 and <50; ≥ 50 years) (Page 8)* *Whole of population examination of observed versus expected cancer cases using Standardised Incidence Ratios, adjusting for 5-year age group and gender, and calendar period from 1983-2008.*
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Whole of population based study using linked data (Page 6-8)* *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed *Numbers of patient records included in study clearly stated in Results (Pages 8-9)*
		(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 *Data presented in Table 1(Page 15)*
		(b) Indicate number of participants with missing data for each variable of interest *N/A*
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) *Average follow up time presented for each patient cohort in Results (Page9)*

Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time *Presented in Results (Page 9) and Table 2 (Page 16), Table 3 (Page 17) and Table 4 (Page 18)*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included *Standardised Incidence Ratio (SIR) and 95% Confidence Intervals clearly presented in text and Tables with appropriate labelling of variables standardised for (e.g. 5-year age groups, gender). Presented in Results (Page 9) and Table 2 (Page 16), Table 3 (Page 17) and Table 4 (Page 18)*
		(*b*) Report category boundaries when continuous variables were categorized Age boundaries clearly reported
		(*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 *All results of sub-group analyses presented. (Tables 2-4 – Pages 16-18)*
Discussion		
Key results	18	Summarise key results with reference to study objectives *Page 12*
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 *Strengths and limitations of the study have been presented in the Discussion 4.2 Methodological Issues (Pages 10-11).* *The burn patient cohorts under study are part of the respective reference populations, and as such, this may have a diluting effect in the standardised incidence ratios. The results presented are for the total burn patient cohorts including both severe and non-severe burns; the results are therefore, conservative.*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. *The results are conservative and results have been interpreted in light of current literature on the impacts of burn injury on the immune system and other systemic effects. (Pages 10 – 13)*
Generalisability	21	Discuss the generalisability (external validity) of the study results *Expected that the sex dimorphic effects on cancer post-burn are generalisable.* *The evidence of increased cancer incidence after burn injury, with a greater effect in females, suggests the systemic immune response to burn injury may be a mediator of cancer susceptibility. (Page 13)*
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 *Funding sources disclosed (Pages 3, 14)*

*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.

Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia

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Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia

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Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia

Abstract

Objective: To investigate risk of cancer and potential gender effects in persons hospitalised with burn injury.

Design: Population-based retrospective cohort study using record-linkage systems in Scotland and Western Australia

Subjects: Records of 37,890 and 23,450 persons admitted with a burn injury in Scotland and Western Australia, respectively, from 1983 to 2008. De-identified extraction of all linked hospital morbidity records, mortality and cancer records were provided by the Information Service Division Scotland and the Western Australian Data Linkage Service.

Main outcome measures: Total and gender specific numbers of observed and expected cases of all-cause and site-specific cancers and standardised incidence ratios.

Results: From 1983-2008, for female burn survivors there was a greater number of observed versus expected notifications of all-cause cancer with 1011 (standardised incidence ratio (SIR), 95% confidence interval (CI): 1.3, 1.2 to 1.4) and 244 (SIR, 95%CI: 1.12, 1.05 to 1.30), respectively, for Scotland and Western Australia. No statistically significant difference in all-cause cancer risk was found for males. Significant excesses in observed cancers amongst burn survivors (combined gender) in Scotland and Western Australian were found for buccal cavity, liver, larynx and respiratory tract, and for cancers of the female genital tract.

Conclusions: Results from the Scotland data confirmed the increased risk of 'all-cause' cancer previously observed amongst female burn survivors in Western Australia. The gender dimorphism observed in this study may be related to the role of gender in the immune response to burn injury. More research is required to understand the underlying mechanism(s) that may link burn injury with an increased risk of some cancers.

Article Focus

- Burn injury not only affects the skin but also has other systemic effects
- Inflammatory and immune response to burns may mediate cancer risk
- Gender differences in cancer risk after burn injury may be related to the immune response

Key messages

- Burn injury can have impacts on longer term health
- Increased risk of some cancers post-burn injury is greater in females than males

Strengths and Limitations

- Population-level linked administrative data minimises issues of selection and reporting bias, and loss to follow-up
- Consistency of results using population-level data from two patient populations provides greater support for link between burn injury and some cancers
- Unable to examine impact of burn severity on cancer risk due to lack of available data

Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia

1. Introduction

The burden of burn injury is a significant issue, not only in terms of the acute care perspective but also the chronic health effects resulting from both the injury event and the subsequent treatments. While burns predominantly affect the skin, burns are associated with significant systemic effects [1-3], depressed immune functioning[4-8] and prolonged periods of systemic catabolism and hypermetabolism.[9] Prompted by a clinical scenario of a diagnosis of hepatocellular carcinoma in a young male burn patient,[10] and the potential for malignancy after burn, an initial study of burn injury and all-cause cancer risk was undertaken.[11] Results of this study demonstrated a gender effect with female burn survivors having an increased risk of all-cause cancer.

This previous study of burn injury and cancer risk used population-based data linked by the Western Australian Data Linkage System (WADLS). [12] Data linkage in Western Australia provides one of only a handful of information-rich environments worldwide that have been constructed from the linkage of multiple, large, population-based, administrative datasets. The WADLS meets international best practice standards, determined by experiences from the Oxford Record Linkage Study, Scottish Record Linkage System, Rochester Epidemiology Project and the Manitoba Centre for Health Policy.[12] Western Australia has a population of approximately 2.2 million, and as such, did not support detailed gender and site-specific cancer incidence assessments with adequate statistical power. While the WADLS has systematically linked datasets of Western Australians since the 1970s, other Australian States and Territories have only recently established record linkage systems and were not able to support this study. To extend the population-base and enable further detailed examination of the observed gender effect and site specific cancer incidence, approval was sought to access the Scottish population-based record linkage system, the Information Service Division (ISD) Scotland,[13] that has routinely linked health data since the 1980s.

This paper reports a retrospective longitudinal study to explore cancer risk after burn injury using linked hospital morbidity, cancer and death data of persons hospitalised for burn injury in both Western Australia and Scotland. The study aimed to, firstly, confirm the increased risk of 'all-cause' cancer observed in the preliminary Western Australian study of female burn survivors using the Scottish data; and, secondly, examine site-specific cancer risk amongst survivors of burn injury.

2. Methods

Study data were obtained from the Western Australian Data Linkage Service (WADLS) [12] and the Information and Services Division (ISD Scotland) of the National Health Service National Services

Scotland[13] with approval from Curtin University, the Western Australia Department of Health Human Research Ethics Committees and the NHS National Services Scotland Privacy Advisory Committee. The WADLS and ISD Scotland are validated record linkage systems that routinely link administrative health data from core datasets for the entire population of Western Australia and Scotland, respectively.

An index burn injury was defined as the first hospital admission with a burn injury using primary and additional diagnosis International Classification of Diseases (ICD) codes 940-949 (ICD9) and T20-T31 (ICD10). A de-identified extraction of all linked hospital morbidity records (Hospital Morbidity Data System (HMDS), mortality (Death Register, Western Australia) and cancer records (Western Australia Cancer Registry (WACR)) for all persons admitted to hospital with an index burn injury in Western Australia, for the period 1 January 1983 to 31 December 2008, was performed by WADLS [14]. A corresponding de-identified extraction of all linked hospital morbidity records (Scottish Morbidity Records (SMR) 01), cancer registrations (SMR06) and death records (General Register Office for Scotland (GROS)) using the same burn cohort definition was undertaken by ISD Scotland. Hospital admissions data items included age at admission, gender, admission date, separation date, principal and additional diagnoses and external cause of injury.

The Western Australia Cancer Registry (WACR) was established in 1981 and is a population-based cancer registry based on mandatory notification of cancers from pathologists, haematologists and radiation oncologist, and cancer information from death records.[15] Amendments to the Health (Notification of Cancer) Regulations in 1996 required from that time, notifications of all in situ, non-melanoma skin cancers other than basal cell and squamous cell carcinomas, and, all other invasive malignancies and benign Central Nervous System tumours. [15] Malignant cancers are coded according to a modified Australian version of the International Classification of Diseases, Tenth Revision (ICD10-AM) and International Classification of Diseases for Oncology (ICD-O-3).

The Scotland Cancer Registry (SMR06) has recorded all incident cancers in Scotland from 1958, and since 1997 registration has been centralised at ISD Scotland.[16] The registry is responsible for the collection of information on all new cases of primary malignant neoplasms, carcinoma in situ (including grade III intra-epithelial neoplasia), neoplasms of uncertain behaviour and (since 1 January 2000) benign brain and spinal cord tumours arising in residents of Scotland. Data quality is monitored using routine indicators, computer validation and ad hoc studies of data accuracy and completeness of ascertainment.[17] [18] The Scottish cancer notifications are coded using the International Classification of Diseases (ICD) and the International Classification of Diseases for Oncology (ICD-O).

Methods for analysis have been previously published. [11] An incident cancer was defined as a cancer diagnosis notification (C00-C96, excluding C44) after hospital admission for index burn injury. Analysis was restricted to malignant neoplasm notifications (C00-C96, excluding C44) for which all-cause and site-specific cancer incident rates were provided by WACR and ISD Scotland for respective populations. Records were excluded from the analysis if the date of cancer diagnosis was prior to date of discharge for index burn hospitalisation. When a record was identified as having more than one malignant neoplasm notification, each neoplasm was counted as an individual record, however, if multiple tumours of the skin (C43) with identical morphological characteristics (that is, the first three digits ICD-O-3 morphology code) were identified, they were recorded only once. Gender and age-specific cancer (total C00-C96, excluding C44) incident rates for the Western Australian and Scottish populations were pooled for the calendar periods 1983-1988, 1989-1993, 1994-1998, 1999-2003 and 2004-2008 to allow for changes in population cancer incidence during the study period.

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 cancer diagnosis, death, or 31st December 2008, whichever occurred first. 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. [19 20] The 95% confidence intervals (95%CI) were defined under the assumption that the observed number of cancers followed the Poisson distribution. [21]

Separate SIR analyses for all-cause and site-specific cancers were conducted using country specific data for respective burn patient cohorts (all burn depth) for cohorts hospitalised from 1983-2008; all-cause SIRs repeated for sub-cohorts of burn admissions from 1983-1987, with optimum follow-up time. To further explore the gender impact of burn injury on cancer risk, all-cause cancer SIR analyses were repeated on age-restricted sub-cohorts classified to reflect reproductive age at admission for burn injury: <15 years; 15-49 years; and, ≥50 years. All statistical analyses were performed using Stata statistical software V 11 (StataCorp LP, College Station, Tex).

3. Results

As previously reported, in Western Australia from 1983 to 2008, there were 23,450 hospital index admissions for burn-related injury.[14] After exclusion of records with a history of cancer prior to

separation date or death during hospital admission for burn, a total of 22,705 patient records were included in the analysis.[11] There were 673 patients with a first cancer notification after date of separation for burn injury hospitalisation, and with inclusion of multiple malignancies, 759 cancer notifications were included in the standardised incident ratio analyses as independent observations.

In Scotland from 1983-2008, there were a total of 37,890 persons hospitalised for an index burn-related injury. After exclusion of those with a history of cancer prior to separation date or death during hospital admission for burn, a total of 37,506 patients were included in the analysis. There were 2,005 patients with a first cancer notification after date of separation for burn injury hospitalisation, and with inclusion of multiple malignancies, 2,260 cancer notifications were included in the standardised incident ratio analyses as independent observations. Characteristics of the Western Australia and Scotland cohorts are presented in Table 1.

The Western Australia cohort (1983-2008; combined gender) was followed for a total of 283,306 person-years, with mean follow-up time of 12.3 years (range: >0 – 25.9 years). Mean follow-up time for those with a cancer notification was 9.4 years (range: >0 – 25.4) and for those with no cancer notification, 12.4 years (range: >0 – 25.9). The Scotland cohort (1983-2008; combined gender) was followed for a total of 474,489 person-years, with mean follow-up time of 12.6 years (range: 0 -26.0 years). Mean follow-up time for those with a cancer notification was 9.4 years (range: >0-25.8) and for those with no cancer notification, 12.7 years (range: >0-26.0).

For the Scottish cohort of burn injury patients (combined gender) there was marginal but significant difference (SIR, 95%CI: 1.09, 1.05-1.10) in the overall risk of cancer for persons with a burn injury hospitalisation for the period 1983 to 2008, compared with the general population of Scotland. While a significant increase of 30% in cancer risk was estimated for females there was no difference in cancer risk for males, when compared with the general population of Scotland (refer to Table 2). For the sub-cohort of burn injury patients 1983-1988, the total observed number of cases of cancer (n=838) was statistically significantly lower than expected (n=953.4) with SIR (95%CI) of 0.88 (0.82 to 0.94), with males having a statistically significantly lower number of cases observed than expected. Refer to Table 2 for gender specific SIRs for all-cause cancer for Scotland and Western Australian burn patients, hospitalised during 1983-1988 and 1983-2008.[11]

Female genital cancers were grouped due to the small numbers of observed cancers in sub-groups in the Western Australian data and unstable SIR results. Statistically significant increases in observed genital (combined) cancers for female burn patients in both Western Australia and Scotland were found. The increased breast cancer incidence was statistically significant amongst female burn survivors in Scotland. Statistically significant increases in cancer incidence for combined gender for

both Western Australia and Scottish data were observed for cancers of the buccal cavity, liver and respiratory tract. Refer to Table 3 for gender and site-specific cancer SIRs. For each of these cancers, female burn survivors in both Western Australia and Scotland had higher incidence than males when compared with respective general population data. For the majority of site-specific cancers selected, female burn survivors in both Western Australia and Scotland had higher numbers of observed cancers than expected, with SIRs of similar magnitude. However, SIR results for Scottish data reached statistical significance, reflecting the larger population-base and respective higher number of cancer notifications.

Table 4 presents an SIR analyses of all-cause cancer risk repeated on age-restricted sub-cohorts, classified to reflect reproductive age (<15 years; 15-49 years; and, ≥50 years) at admission for burn injury. For males in both WA and Scotland, no statistically significant differences were found across the three age groups. For female burn survivors in Scotland, the observed numbers of cancers (all-cause) exceeded that expected for each of the three age groups, with statistically significant results observed for the age groups 15-49, and 50 years and older. In the Western Australia data, excess cancers were observed for those younger than 15 years and for those 50 years and older, with statistically significance reached for the older age group; for females 15-49 years at burn injury, no difference in observed and expected all-cause cancer was found.

4. Discussion

4.1 Methodological Issues

Data linkage is a technique which creates links within and between data sources, identifying all the information that relates to the same person, place or event. In addition, when population-level administrative data are used, data linkage minimises issues of selection and reporting bias, as well as loss to follow-up. Data quality of the Western Australia and Scottish Cancer Registers[15 17 18] and hospital morbidity datasets[22 23] are assessed continually for both accuracy and quality; however, potential for misclassification bias may exist. The coding system changed from ICD-9 to ICD-10 in both Western Australia and Scotland during the study period for death and hospital admissions data.

Data of all index burn hospitalisations in Western Australia and Scotland from 1983 to 2008 were analysed with follow-up time from discharge date, allowing for exclusion of prevalent cancers to support temporality of burn exposure and incident cancer. Cancer diagnoses from cancer registries in Western Australia and Scotland were independent of the record of burn injury in the respective hospital morbidity datasets. Minor burns treated in emergency departments were not included in the study. The burn patient cohorts under study are part of the respective reference populations, and as such, this may have a small diluting effect in the standardised incidence ratios. Western

Australia has a population of approximately 2.2 million, and as such, did not support detailed gender and site-specific cancer incidence assessments. Using parallel datasets from Scotland, of population approximately 5.5 million, allowed examination of the consistency of results and trends across the populations.

The Western Australia hospital morbidity data records the principal diagnosis and up to 20 additional diagnosis fields, whereas, the Scottish morbidity data includes the principal diagnosis and 5 additional diagnosis fields. The effects of this reduction in the number of available additional diagnosis fields included the more frequent use in the Scottish data of ICD codes for burns to multiple regions of the body (ICD9 946; ICD10 T29) rather than recording of multiple individual anatomic burn sites, reflected in Table 1; and, an absence of consistently recorded supplementary ICD (ICD9 946; ICD10 T31) data to describe total body surface area burned (TBSA%). This limited our capacity to undertake both SIR analyses restricted to more severe burns of TBSA 20% or greater and incident rate ratio analysis to examine the effects of severity of burn injury (burn depth and TBSA%) using the least exposed group as reference (instead of the general population of Scotland) and confirm previous results. Approximately 90% of persons hospitalised in Western Australia had non-severe burn injury (TBSA<20%).[14] Previous SIR analyses of all-cause cancer risk in Western Australia showed similar trends in results for all burn patients (severe and non-severe) and those hospitalised for severe burn; however, for females hospitalised with severe burn there was a statistically significant increase of 31% in all-cause cancer notifications.[11]

The data analysed in this study are based on linked data from population registers to compare observed cancer incidence in burn patient cohorts with that expected using general population cancer rates adjusting for gender, age and calendar period population changes. Although this study had a follow-up period of up to 26 years from the date of separation for admission for burn injury, the follow up period for many patients may not have provided sufficient observation time to enable identification of all potential malignancies, given the long latency period for many cancers. Further burn injury research is planned with comparison cohorts (non-burn trauma, no injury), using incidence rate ratio analyses to explore injury and patient factors associated with the observed cancer risk.

4.2 Findings

Analysis of ISD Scotland data confirmed the results of our previous study: a statistically significant increase in all-cause cancer risk for female burn survivors with males experiencing no difference. The site specific analyses clearly showed statistically significant increases in the number of observed cancers for combined gender in both the Western Australia and Scottish data for the buccal cavity,

larynx, liver, respiratory tract and oesophagus. There was also a general trend for increased cancer risk for most of the selected types of cancers for females and statistically significant increases in female genital cancers. Sub group analyses, defined crudely by reproductive age, did not elucidate any clear patterns of the influence of oestrogen on cancer incidence, with female burn survivors in Scotland showing increased risk across all age groups. For female burn survivors in WA, an increased risk for all-cause cancer was found for those younger than 15 years (pre-pubescent) and 50 years and older (post-menopausal).

The site-specific analyses showed that whilst statistically significant increases in female genital cancers were found, there was also a general trend for increased cancer risk for most of the selected types of cancers for females. 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, respiratory tract and oesophagus. These results are similar to those found in a Danish study [24] 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. Interestingly, the results of no increase in skin melanoma risk after burn injury in this study support findings of other population-based studies.[24 25]

An alternative explanation for this increased incidence in cancer post-burn may lie in the significant impact a burn injury has on the immune system, or the sustained oxidative and metabolic stress that are integral to the injury response. While burn injury predominantly affects the skin, it has been shown to cause significant depression of both humoral and cell-mediated immunity (CMI), [7 26 27] sustained elevated levels of oxidative stress [28 29] and prolonged elevation of hyper-metabolic and stress hormone levels. [30 31] These effects have been demonstrated to persist for up to 3 years post-injury and can lead to long-term systemic impacts on other organs of the body.[1 2 32-36] Severe burn injury has been demonstrated to induce endoplasmic reticulum (ER) stress, in particular, in the liver.[37] ER stress is a stress-response that initially facilitates cell survival but can switch to a pro-apoptotic signal with prolonged stress.[37 38] However, it has also been shown that the ER stress response can become maladaptive, facilitating adaptation to hypoxic environments and promoting tumour growth. [38 39] It is plausible that the array of host responses combined with the impact of the injury, therefore, creates an environment of increased susceptibility to cancer.

In addition to the observed increase in some of the selected site-specific cancers, the data support evidence for a gender dimorphism (a systematic difference between individuals of different sex in the same species) in the response to burn injury. After burn injury, gender has been shown to be an

important factor with respect to poorer outcomes for mortality[40-43] and improved prognosis for multiple organ dysfunction syndrome,[44] and sepsis,[45] for females compared to males. Similar gender-based differences have also been reported in animal studies of burn injury.[46-50]

The impact of gender with respect to outcomes after burn injury is largely thought to stem from well-established differences in immune biology. There is a substantial volume of published literature to support a gender dimorphism in the immune response[51-54] and sepsis[45] following injury that have impacts on health and mortality.[41 42] The majority of these studies support a more efficient and effective innate and adaptive immune responses in females, leading to more rapid clearance of infectious organisms driven by tissue resident cell populations.[55] This 'advantageous' response reduces the risk of infection in females compared to males [55 56] but leads to elevated risk of autoimmune disease.[57] This dimorphism was thought to arise largely due to the impact of oestrogen on immune function.[58 59] However, recent papers have demonstrated these differences are not completely ablated by ovariectomy (in animal models) [55] and others have shown that oestrogen can be deleterious to the immune response.[60] This suggests a role of other mediators, most likely expressed on the X-chromosome, in the maintenance of the differential immune response. [61 62] The evidence for gender differences in the immune response, both to thermal and other trauma, and its impact on outcomes is substantial. Here, the evidence of increased cancer incidence in selected types of cancer after burn injury, with a greater effect in females, suggests the systemic immune response to burn injury may be a mediator of cancer susceptibility.

5. Conclusion

Using population-based linked data of all burn patients in both Western Australia and Scotland, consistent trends were found in excesses in cancer notifications for a range of selected site specific cancers with an elevated and more widespread increase in female burn patients. Overall, however, the increased cancer risk affected small proportions of the respective burn patient cohorts. More research is required to understand the underlying mechanism(s) that may link burn injury to an increased risk of some cancers and why this is elevated in females, which may in turn enable identification of possible sites for intervention.

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Table 1 **Characteristics of burn injury patients included in analyses with no record of cancer prior to separation date of index burn admission, 1983-2008, by country.**

Characteristics	Western Australia N (%)	Scotland N (%)
Total number burn admissions*	22,705	37,506
Gender: Male	15,481 (68.2)	23,896 (63.7)
Age at index admission (Years)		
<15	8,135 (35.8)	14,579 (38.9)
15-24	4,364 (19.2)	4,495 (12.0)
25-49	7,147 (31.5)	9,554 (25.5)
50-64	1,736 (7.7)	4,080 (10.9)
65+	1,323 (5.8)	4,798 (12.8)
Site of burn**		
Head and neck	6,784 (15.4)	7,592 (16.1)
Trunk	7,553 (17.2)	8,815 (21.0)
Hand, wrist, upper limb	15,801 (35.9)	6,984 (14.8)
Hip , lower limb	11,798 (26.8)	9,531 (3.4)
Eye	379 (0.9)	1,087 (2.3)
Respiratory tract	212 (0.5)	163 (0.3)
Other internal organs	124 (0.3)	165 (0.3)
Multiple regions	656 (1.5)	3,677 (7.8)
Unspecified region	694 (1.6)	858 (1.8)
Burn site depth**		
Erythema	8,929 (20.9)	4,815 (11.5)
Partial thickness	18,449 (41.9)	6,302 (15.0)
Full thickness	7,095 (16.1)	4,924 (11.7)
Unspecified	9,528 (21.7)	25,869 (61.7)
Calendar period of admission		
1983-1988	5,431 (23.9)	11,507 (30.7)
1989-1993	4,200 (18.5)	7,876 (21.0)
1994-1998	4,755 (20.9)	7,130 (19.0)
1999-2003	4,265 (18.9)	5,980 (15.9)
2004-2008	4,054 (17.9)	5,013 (13.4)
Any co-morbidity at index burn		
Yes	2,798 (12.3)	7,679 (20.5)

***** No previous record of cancer

** Patients may have multiple burn sites per anatomical region per depth

Table 2 **Standardised incidence ratios and 95% confidence intervals and observed and expected numbers for all-cause cancer in persons hospitalised for burn injury in Western Australia and Scotland, during the periods 1983-2008 and 1983-1988.**

	Western Australia††			Scotland		
	Combined SIR 95%CI* O:E**	Male† SIR 95%CI O:E	Female† SIR 95%CI O:E	Combined SIR 95%CI O:E	Male† SIR 95%CI O:E	Female† SIR 95%CI O:E
Total cohort 1983-2008	0.97 (0.9 to 1.0) 759: 785.5	0.9 (0.8 to 1.0) 515: 569.5	1.1 (1.0 to 1.3) 244: 216.0	1.09 (1.05 to 1.10) 2260: 2075.9	0.96 (0.90 to 1.0) 1249: 1303.2	1.3 (1.2 to 1.4) 1011: 772.6
Sub-cohort 1983-1988	1.0 (0.9 to 1.1) 294:294.9	0.9 (0.8 to 1.0) 190:220.3	1.4 (1.1 to 1.7) 104: 74.6	0.9 (0.8 to 0.9) 838: 953.4	0.8 (0.7 to 0.9) 491: 614.3	1.0 (0.9 to 1.2) 347: 339.1

*SIR (95%CI): Standardised Incidence Ratio (95% confidence interval) adjusted for age and gender
** O: E: Observed: Expected
†SIR (95%CI): Standardised Incidence Ratio (95% confidence interval) adjusted for age
†† Western Australian comparison data Duke et al. Burns 2011; 38:340-47.

Table 3 **Standardised incidence ratios and 95% confidence intervals and observed and expected numbers for selected types of cancer in persons hospitalised for burns Western Australia and Scotland, 1983-2008.**

Cancer Site	Western Australia			Scotland		
	Combined SIR 95%CI* O:E**	Male SIR 95%CI† O:E	Female SIR 95%CI† O:E	Combined SIR 95%CI* O:E	Male SIR 95%CI† O:E	Female SIR 95%CI† O:E
Buccal cavity C00 to C14	1.4 (1.03 to 1.9) 45: 32.6	1.4 (1.0 to 1.9) 38:28.1	1.5 (0.7 to 3.2) 7: 4.6	2.6 (2.2 to 3.1) 117: 45.0	2.4 (1.9 to 2.9) 83: 35.1	3.4 (2.5 to 4.8) 34:9.9
Oesophagus C15	1.4 (0.9 to 2.4) 15:10.50	1.5 (0.9 to 2.6) 13: 8.7	1.1 (0.3 to 4.5) 2: 1.8	1.6 (1.3 to 2.0) 82: 51.4	1.5 (1.1 to 1.9) 53:36.1	1.9 (1.3 to 2.7) 29:15.3
Stomach C16	0.6 (0.3 to 1.1) 10:17.0	0.5 (0.2 to 1.1) 7: 13.4	0.8 (0.3 to 2.6) 3: 3.6	1.2 (0.9 to 1.5) 73:63.2	1.1 (0.8 to 1.5) 1.2 5: 2.8	1.3 (0.9 to 1.9) 25:19.5
Colorectal C18 to C20	0.7 (0.6 to 0.9) 69: 96.3	0.7 (0.5 to 0.9) 45: 69.1	0.9 (0.6 to 1.3) 24: 27.2	1.2 (1.1 to 1.4) 268:221.8	1.0 (0.9 to 1.2) 142:140.5	1.4 (1.3 to 1.8) 125: 81.3
Liver C22	2.6 (1.6 to 4.0) 19: 7.4	2.2 (1.3 to 3.7) 14: 6.3	4.7 (2.0 to 11.4) 5: 1.1	1.7 (1.2 to 2.5) 31:18.0	1.5 (1.1 to 2.5) 22: 13.3	1.9 (1.0 to 3.7) 9: 4.7
Pancreas C25	0.7 (0.4 to 1.3) 11: 15.3	0.9 (0.5 to 1.7) 9: 10.4	0.4 (0.1 to 1.6) 2: 5.0	1.1 (0.8 to 1.5) 44:39.6	1.5 (1.03 to 2.0) 34: 23.4	0.6 (0.3 to 1.2) 10: 16.2
Larynx C32	5.7 (0.9 to 3.3) 10: 5.7	1.5 (0.7 to 3.0) 8: 5.4	6.0 (1.5 to 24.1) 2: 0.3	1.9 (1.4 to 2.5) 39: 21.1	1.5 (1.1 to 2.2) 28: 18.5	4.2(2.3 to 7.7) 11:2.6
Respiratory tract C33 to C34	1.4 (1.1 to 1.6) 101: 74.8	1.3 (1.1 to 1.7) 79:59.3	1.4 (0.9 to 2.2) 22:15.4	1.5 (1.4 to 1.7) 448:298.1	1.3 (1.2 to 1.5) 279:210.4	1.9 (1.7 to 2.2) 169:87.7
Skin –melanoma C44	0.7 (0.6 to 0.9) 72: 102.0	0.7 (0.6 to 1.0) 57: 77.9	0.6 (0.4 to 1.0) 15: 24.1	0.8 (0.6 to 1.1) 38:48.5	0.7 (0.4 to 1.1) 19:28.4	1.0 (0.4 to 1.1) 19:20.0
Breast C50	1.0 (0.8 to 1.3) 65: 62.4	1.3 (0.2 to 9.2) 1: 0.8	1.0 (0.8 to 1.3) 64:61.7	1.7 (1.5 to 1.9) 271:161.4	0.7 (0.1 to 4.8) 1:1.5	1.6 (1.5 to 1.9) 270: 160.0
Female genital tract (combined) C51 to C57			1.4 (1.0 to 2.0) 31:26.7			1.7 (1.4 to 2.0) 114: 67.2
Male genital tract (combined) C60 to C63		0.9 (0.8 to 1.1) 141: 150.7			1.1 (1.0 to 1.3) 210: 192.6	
Prostate C61		0.8 (0.6 to 0.9) 102: 135.9			1.1 (0.9 to 1.2) 177: 165.5	
Kidney, Bladder, UT C64 to C68	0.5 (0.3 to 0.7) 17: 37.9	0.4 (0.2 to 0.7) 12: 30.9	0.7 (0.3 to 1.7) 5: 7.0	1.2 (1.0 to 1.4) 135: 110.9	1.2 (1.0 to 1.4) 96: 82.8	1.4 (1.0 to 1.9) 39: 28.0
Brain C71	1.2 (0.7 to 1.9) 16: 13.9	1.0 (0.5 to 1.8) 10: 10.5	1.7 (0.8 to 3.9) 6: 3.5	1.5 (1.1 to 2.0) 39:27.0	1.4 (0.9 to 2.0) 26:19.2	1.7 (1.0 to 2.9) 13:7.8
Lymphomas to all	1.0 (0.7 to 1.4) 36: 35.5	0.8 (0.5 to 1.2) 20: 26.0	1.7 (1.03 to 2.7) 16:9.6	1.1 (0.9 to 1.4) 75:68.0	1.1 (0.8 to 1.4) 48:45.0	1.2 (0.8 to 1.7) 27:23.0
Myeloma/ plasma	1.3 (0.7 to 2.3) 11: 8.6	1.3 (0.7 to 2.6) 8:6.1	1.2 (0.4 to 3.7) 3: 2.49	1.1 (0.7 to 1.6) 22:21.0	1.0 (0.6 to 1.7) 13:13.2	1.2 (0.6 to 2.2) 9: 7.8
Leukaemia's to all	1.1 (0.8 to 1.7) 26: 22.9	1.1 (0.7 to 1.8) 19: 17.0	1.2 (0.6 to 2.5) 7: 6.0	1.3 (1.01 to 1.7) 63:48.6	1.0 (0.73 to 1.4) 34:33.1	1.8 (1.3 to 2.7) 29: 15.5

*SIR (95%CI): Standardised Incidence Ratio adjusted for age and gender (95% confidence interval)

** O: E: Observed: Expected

†SIR (95%CI): Standardised Incidence Ratio adjusted for age (95% confidence interval)

Table 4 **Standardised incidence ratios and 95% confidence intervals and observed and expected numbers for all-cause cancer incidence, for persons hospitalised for burns Western Australia and Scotland, by age group, 1983 to 1988.**

Age at first burn years	SIR (95%CI) (observed: expected)		
	combined gender*	Male†	Female†
<15			
WA	1.17 (0.82 to 1.68) (30:25)	1.19 (0.77 to 1.84) (20:16)	1.15 (0.62 to 2.14) (10:8.6)
Scotland	0.94 (0.69 to 1.28) (41:43.69)	0.72 (0.47 to 1.12) (20:27.77)	1.32 (0.86 to 2.02) (21:15.92)
15 to 49			
WA	0.87 (0.77 to 0.99) (273: 313)	0.87 (0.75 to 1.00) (197: 226)	0.86 (0.69 to 1.1) (76: 87)
Scotland	1.21 (1.12 to 1.31) (617: 509.16)	1.04 (0.94 to 1.16) (345: 331.68)	1.53 (1.36 to 1.73) (272: 177.48)
≥ 50			
WA	1.02 (0.93 to 1.12) (456: 446)	0.91 (0.82 to 1.02) (298: 326)	1.32 (1.13 to 1.54) (158: 120)
Scotland	1.05 (1.00 to 1.11) (1602: 1523)	0.94 (0.88 to 1.00) (884: 943.75)	1.23 (1.15 to 1.33) (718:579.25)

*SIR (95%CI): Standardised Incidence Ratio adjusted for age and gender (95% confidence interval)
†SIR (95%CI): Standardised Incidence Ratio adjusted for age (95% confidence interval)

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Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia

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James Boyd: Planning, conduct and reporting

Jacqui Bauer: Conduct and reporting

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Article Focus

- Burn injury not only affects the skin but also has other systemic effects
- Inflammatory and immune response to burns may mediate cancer risk
- Gender differences in cancer risk after burn injury may be related to the immune response

Key messages

- Burn injury can have impacts on longer term health
- Increased risk of some cancers post-burn injury is greater in females than males

Strengths and Limitations

- Population-level linked administrative data minimises issues of selection and reporting bias, and loss to follow-up
- Consistency of results using population-level data from two patient populations provides greater support for link between burn injury and some cancers
- Unable to examine impact of burn severity on cancer risk due to lack of available data

Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia

Abstract

Objective: To investigate risk of cancer and potential gender effects in persons hospitalised with burn injury.

Design: Population-based retrospective cohort study using record-linkage systems in Scotland and Western Australia

Subjects: Records of 37,890 and 23,450 persons admitted with a burn injury in Scotland and Western Australia, respectively, from 1983 to 2008. De-identified extraction of all linked hospital morbidity records, mortality and cancer records were provided by the Information Service Division Scotland and the Western Australian Data Linkage Service.

Main outcome measures: Total and gender specific numbers of observed and expected cases of total (all-sites~~cause~~) and site-specific cancers and standardised incidence ratios.

Results: From 1983-2008, for female burn survivors there was a greater number of observed versus expected notifications of all-cause cancer with 1011 (standardised incidence ratio (SIR), 95% confidence interval (CI): 1.3, 1.2 to 1.4) and 244 (SIR, 95%CI: 1.12, 1.05 to 1.30), respectively, for Scotland and Western Australia. No statistically significant difference in ~~all-cause~~total (all-sites) cancer risk was found for males. ~~Significant excesses in observed cancers amongst burn survivors (combined gender) in Scotland and Western Australian were found for buccal cavity, liver, larynx and respiratory tract, and for cancers of the female genital tract.~~ 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.

Conclusions: Results from the Scotland data confirmed the increased risk of ~~'all-cause'~~ total (all-sites) cancer previously observed amongst female burn survivors in Western Australia. The gender dimorphism observed in this study may be related to the role of gender in the immune response to burn injury. More research is required to understand the underlying mechanism(s) that may link burn injury with an increased risk of some cancers.

Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia

1. Introduction

The burden of burn injury is a significant issue, not only in terms of the acute care perspective but also the chronic health effects resulting from both the injury event and the subsequent treatments. While burns predominantly affect the skin, burns are associated with significant systemic effects [1-3], depressed immune functioning[4-8] and prolonged periods of systemic catabolism and hypermetabolism.[9] Prompted by a clinical scenario of a diagnosis of hepatocellular carcinoma in a young male burn patient,[10] and the potential for malignancy after burn, an initial study of burn injury and total (all-sites) ~~all-cause~~ cancer risk was undertaken.[11] ~~Results of this study demonstrated a gender effect with female burn survivors having an increased risk of all-cause cancer.~~

~~This previous study of burn injury and cancer risk used population based data linked by the Western Australian Data Linkage System (WADLS).~~ [12] ~~Data linkage in Western Australia provides one of only a handful of information-rich environments worldwide that have been constructed from the linkage of multiple, large, population-based, administrative datasets. The WADLS meets international best practice standards, determined by experiences from the Oxford Record Linkage Study, Scottish Record Linkage System, Rochester Epidemiology Project and the Manitoba Centre for Health Policy.~~[12] ~~Western Australia has a population of approximately 2.2 million, and as such, did not support detailed gender and site-specific cancer incidence assessments with adequate statistical power. While the WADLS has systematically linked datasets of Western Australians since the 1970s, other Australian States and Territories have only recently established record linkage systems and were not able to support this study. To extend the population base and enable further detailed examination of the observed gender effect and site specific cancer incidence, approval was sought to access the Scottish population-based record linkage system, the Information Service Division (ISD) Scotland,~~[13] ~~that has routinely linked health data since the 1980s.~~

Results of our initial study demonstrated no significant risk of developing any form (all-sites) of 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).

This previous study of burn injury and cancer risk used population-based data linked by the Western Australian Data Linkage System (WADLS). [14] Western Australia has a population of approximately 2.2 million, and as such, did not support detailed gender and site-specific cancer incidence assessments with adequate statistical power. While the WADLS has linked datasets of Western Australians since the 1970s, other Australian States have only recently established record linkage systems and were not able to support this study. To extend the population-base and enable further detailed examination of the observed gender effect and site specific cancer incidence, approval was sought to access the Scottish population-based record linkage system, the Information Service Division (ISD) Scotland,[15] that has routinely linked health data since the 1980s.

This paper reports a retrospective longitudinal study to explore cancer risk after burn injury using linked hospital morbidity, cancer and death data of persons hospitalised for burn injury in both Western Australia and Scotland. The study aimed to, firstly, confirm the increased risk of ~~'all-cause'~~total (all-sites) cancer observed in the preliminary Western Australian study of female burn survivors using the Scottish data; and, secondly, examine site-specific cancer risk amongst survivors of burn injury.

2. Methods

Study data were obtained from the Western Australian Data Linkage Service (WADLS) ~~[12]~~[14] and the Information and Services Division (ISD Scotland) of the National Health Service National Services Scotland~~[13]~~[15] with approval from Curtin University, the Western Australia Department of Health Human Research Ethics Committees and the NHS National Services Scotland Privacy Advisory Committee. The WADLS and ISD Scotland are validated record linkage systems that routinely link administrative health data from core datasets for the entire population of Western Australia and Scotland, respectively.

An index burn injury was defined as the first hospital admission with a burn injury using primary and additional diagnosis International Classification of Diseases (ICD) codes 940-949 (ICD9) and T20-T31 (ICD10). A de-identified extraction of all linked hospital morbidity records (Hospital Morbidity Data System (HMDS), mortality (Death Register, Western Australia) and cancer records (Western Australia Cancer Registry (WACR)) for all persons admitted to hospital with an index burn injury in Western Australia, for the period 1 January 1983 to 31 December 2008, was performed by WADLS. ~~[14]~~[16] A corresponding de-identified extraction of all linked hospital morbidity records (Scottish Morbidity Records (SMR) 01), cancer registrations (SMR06) and death records (General Register Office for Scotland (GROS)) using the same burn cohort definition was undertaken by ISD Scotland. Hospital

admissions data items included age at admission, gender, admission date, separation (or discharge) date, principal and additional diagnoses and external cause of injury.

The Western Australia Cancer Registry (WACR) was established in 1981 and is a population-based cancer registry based on mandatory notification of cancers from pathologists, haematologists and radiation oncologist, and cancer information from death records.[15,17] ~~Amendments to the Health (Notification of Cancer) Regulations in 1996 required from that time, notifications of all in situ, non-melanoma skin cancers other than basal cell and squamous cell carcinomas, and, all other invasive malignancies and benign Central Nervous System tumours.~~ [15] Malignant cancers are coded according to a modified Australian version of the International Classification of Diseases, Tenth Revision (ICD10-AM) and International Classification of Diseases for Oncology (ICD-O-3).

The Scotland Cancer Registry (SMR06) has recorded all incident cancers in Scotland from 1958, and since 1997 registration has been centralised at ISD Scotland.[16,18] The registry is responsible for the collection of information on all new cases of primary malignant neoplasms, carcinoma in situ (including grade III intra-epithelial neoplasia), neoplasms of uncertain behaviour and (since 1 January 2000) benign brain and spinal cord tumours arising in residents of Scotland. Data quality is monitored using routine indicators, computer validation and ad hoc studies of data accuracy and completeness of ascertainment.[17,18,19,20] The Scottish cancer notifications are coded using the International Classification of Diseases (ICD) and the International Classification of Diseases for Oncology (ICD-O).

Methods for analysis have been previously published. [11] An incident cancer was defined as a cancer diagnosis notification (C00-C96, excluding C44) after hospital admission for index burn injury. Analysis was restricted to malignant neoplasm notifications (C00-C96, excluding C44) for which ~~all-cause~~ total (all-sites) and site-specific cancer incident rates were provided by WACR and ISD Scotland for respective populations. Records were excluded from the analysis if the date of cancer diagnosis was prior to date of discharge for index burn hospitalisation. When a record was identified as having more than one malignant neoplasm notification, each neoplasm was counted as an individual record, however, if multiple tumours of the skin (C43) with identical morphological characteristics (that is, the first three digits ICD-O-3 morphology code) were identified, they were recorded only once. Gender and age-specific cancer (total C00-C96, excluding C44) incident rates for the Western Australian and Scottish populations were pooled for the calendar periods 1983-1988, 1989-1993, 1994-1998, 1999-2003 and 2004-2008 to allow for changes in population cancer incidence during the study period.

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 cancer diagnosis, death, or 31st December 2008, whichever occurred first. 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. [~~19~~23]

Separate SIR analyses for total (all-sites) ~~all-cause~~ and site-specific cancers were conducted using country specific data for respective burn patient cohorts (all burn depth) for cohorts hospitalised from 1983-2008; total (all-sites) ~~all-cause~~ SIRs repeated for sub-cohorts of burn admissions from 1983-1987, with optimum follow-up time. To further explore the gender impact of burn injury on cancer risk, total (all-sites) ~~all-cause~~ cancer SIR analyses were repeated on age-restricted sub-cohorts classified to reflect reproductive age at admission for burn injury: <15 years; 15-49 years; and, ≥50 years. All statistical analyses were performed using Stata statistical software V 11 (StataCorp LP, College Station, Tex).

3. Results

In Scotland from 1983-2008, there were a total of 37,890 persons hospitalised for an index burn-related injury. After exclusion of those with a history of cancer prior to separation date or death during hospital admission for burn, a total of 37,506 patients were included in the analysis. There were 2,005 patients with a first cancer notification after date of separation for burn injury hospitalisation, and with inclusion of multiple malignancies, 2,260 cancer notifications were included in the standardised incident ratio analyses as independent observations. Characteristics of the Western Australia and Scotland cohorts are presented in Table 1.

As previously reported, in Western Australia from 1983 to 2008, there were 23,450 hospital index admissions for burn-related injury.[14] After exclusion of records with a history of cancer prior to separation date or death during hospital admission for burn, a total of 22,705 patient records were included in the analysis.[11] There were 673 patients with a first cancer notification after date of separation for burn injury hospitalisation, and with inclusion of multiple malignancies, 759 cancer notifications were included in the standardised incident ratio analyses as independent observations.

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For the Scottish cohort of burn injury patients (combined gender) there was marginal but significant difference (SIR, 95%CI: 1.09, 1.05-1.10) in the overall risk of cancer for persons with a burn injury hospitalisation for the period 1983 to 2008, compared with the general population of Scotland. While a significant increase of 30% in cancer risk was estimated for females there was no difference in cancer risk for males, when compared with the general population of Scotland (refer to Table 2). For the sub-cohort of burn injury patients 1983-1988, the total observed number of cases of cancer (n=838) was statistically significantly lower than expected (n=953.4) with SIR (95%CI) of 0.88 (0.82 to 0.94), with males having a statistically significantly lower number of cases observed than expected. Refer to Table 2 for gender specific SIRs for total (all-sites) cancer for Scotland and Western Australian burn patients, hospitalised during 1983-1988 and 1983-2008.[11]

The Western Australia cohort (1983-2008; combined gender) was followed for a total of 283,306 person-years, with mean follow-up time of 12.3 years (range: >0 – 25.9 years). Mean follow-up time for those with a cancer notification was 9.4 years (range: >0 – 25.4) and for those with no cancer notification, 12.4 years (range: >0 – 25.9). The Scotland cohort (1983-2008; combined gender) was followed for a total of 474,489 person-years, with mean follow-up time of 12.6 years (range: 0 -26.0 years). Mean follow-up time for those with a cancer notification was 9.4 years (range: >0-25.8) and for those with no cancer notification, 12.7 years (range: >0-26.0).

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Female genital cancers were grouped due to the small numbers of observed cancers in sub-groups in the Western Australian data and unstable SIR results. Statistically significant increases in observed genital (combined) cancers for female burn patients in both Western Australia and Scotland were found. The increased breast cancer incidence was statistically significant amongst female burn survivors in Scotland. Statistically significant increases in cancer incidence for combined gender for both Western Australia and Scottish data were observed for cancers of the buccal cavity, liver and respiratory tract. Refer to Table 3 for gender and site-specific cancer SIRs. For each of these cancers, female burn survivors in both Western Australia and Scotland had higher incidence than males when compared with respective general population data. For the majority of site-specific cancers selected, female burn survivors in both Western Australia and Scotland had higher numbers of observed cancers than expected, with SIRs of similar magnitude. However, SIR results for Scottish data reached statistical significance, reflecting the larger population-base and respective higher number of cancer notifications.

Table 4 presents an SIR analyses of total (all-sites) ~~all-cause~~ cancer risk repeated on age-restricted sub-cohorts, classified to reflect reproductive age (<15 years; 15-49 years; and, ≥50 years) at admission for burn injury. For males in both WA and Scotland, no statistically significant differences were found across the three age groups. For female burn survivors in Scotland, the observed numbers of cancers (total all-sites) ~~(all-cause)~~ exceeded that expected for each of the three age groups, with statistically significant results observed for the age groups 15-49, and 50 years and older. In the Western Australia data, excess cancers were observed for those younger than 15 years and for those 50 years and older, with statistically significance reached for the older age group; for females 15-49 years at burn injury, no difference in observed and expected total (all-sites) ~~all-cause~~ cancer was found.

4. Discussion

4.1 Methodological Issues

~~Data linkage is a technique which creates links within and between data sources, identifying all the information that relates to the same person, place or event. In addition, when population-level administrative data are used, data linkage minimises issues of selection and reporting bias, as well as loss to follow-up. Data quality of the Western Australia and Scottish Cancer Registers[15 17 18] and hospital morbidity datasets[20 21] are assessed continually for both accuracy and quality; however, potential for misclassification bias may exist. The coding system changed from ICD-9 to ICD-10 in both Western Australia and Scotland during the study period for death and hospital admissions data.~~

~~Data of all index burn hospitalisations in Western Australia and Scotland from 1983 to 2008 were analysed with follow-up time from discharge date, allowing for exclusion of prevalent cancers to support temporality of burn exposure and incident cancer. Cancer diagnoses from cancer registries in Western Australia and Scotland were independent of the record of burn injury in the respective hospital morbidity datasets. Minor burns treated in emergency departments were not included in the study. The burn patient cohorts under study are part of the respective reference populations, and as such, this may have a small diluting effect in the standardised incidence ratios. Western Australia has a population of approximately 2.2 million, and as such, did not support detailed gender and site specific cancer incidence assessments. Using parallel datasets from Scotland, of population approximately 5.5 million, allowed examination of the consistency of results and trends across the populations.~~

When population-level administrative data are used, data linkage minimises issues of selection and reporting bias, as well as loss to follow-up. Data quality of the Western Australia and Scottish Cancer Registers [17 19 20] and hospital morbidity datasets [24 25] are assessed continually for both accuracy and quality. Data of all index burn hospitalisations in Western Australia and Scotland from 1983 to 2008 were analysed with follow-up time from discharge date, allowing for exclusion of prevalent cancers to support temporality of burn exposure and incident cancer. Cancer diagnoses from cancer registries in Western Australia and Scotland were independent of the record of burn injury in the respective hospital morbidity datasets. Minor burns treated in emergency departments were not included in the study. The burn patient cohorts under study are part of the respective reference populations, and as such, this may have a small diluting effect in the standardised incidence ratios. Using parallel datasets from Western Australia and Scotland, of populations 2.2 million and 5.5 million, respectively, allowed examination of the consistency of results and trends across the populations.

The Western Australia hospital morbidity data records the principal diagnosis and up to 20 additional diagnosis fields, whereas, the Scottish morbidity data includes the principal diagnosis and 5 additional diagnosis fields. Consequent to the reduced number of additional diagnosis fields in the Scottish data, there was an absence of recorded supplementary total body surface area burned (TBSA%) data (ICD9 946; ICD10 T31) and greater use of ICD codes for burns to multiple regions of the body (ICD9 946; ICD10 T29) rather than individual anatomic burn sites, reflected in Table 1. This limited both SIR analyses restricted to more severe burns of TBSA 20% or greater and incident rate ratio analysis to examine the effects of severity of burn injury (burn depth and TBSA %). Previous SIR analyses of total (all-sites) cancer risk in Western Australia showed similar trends in results for all burn patients (severe and non-severe).[11] ~~The effects of this reduction in the number of available~~

additional diagnosis fields included the more frequent use in the Scottish data of ICD codes for burns to multiple regions of the body (ICD9 946; ICD10 T29) rather than recording of multiple individual anatomic burn sites, reflected in Table 1; and, an absence of consistently recorded supplementary ICD (ICD9 946; ICD10 T31) data to describe total body surface area burned (TBSA%). This limited our capacity to undertake both SIR analyses restricted to more severe burns of TBSA 20% or greater and incident rate ratio analysis to examine the effects of severity of burn injury (burn depth and TBSA%) using the least exposed group as reference (instead of the general population of Scotland) and confirm previous results. Approximately 90% of persons hospitalised in Western Australia had non-severe burn injury (TBSA<20%).[14] Previous SIR analyses of all cause cancer risk in Western Australia showed similar trends in results for all burn patients (severe and non severe) and those hospitalised for severe burn; however, for females hospitalised with severe burn there was a statistically significant increase of 31% in all cause cancer notifications.[11]

The data analysed in this study are based on linked data from population registers to compare observed cancer incidence in burn patient cohorts with that expected using general population cancer rates adjusting for gender, age and calendar period population changes. Although this study had a follow-up period of up to 26 years from the date of separation for admission for burn injury, the follow up period for many patients may not have provided sufficient observation time to enable identification of all potential malignancies, given the long latency period for many cancers. Further burn injury research is planned with comparison cohorts (non-burn trauma, no injury), using incidence rate ratio analyses to explore injury and patient (including lifestyle factors such as smoking and alcohol) factors associated with the observed cancer risk.

4.2 Findings

Analysis of ISD Scotland data confirmed the results of our previous study: a statistically significant increase in all-causetotal (all-sites) cancer risk for female burn survivors with males experiencing no difference. The site specific analyses clearly showed statistically significant increases in the number of observed cancers for combined gender in both the Western Australia and Scottish data for the buccal cavity, larynx, liver, respiratory tract and oesophagus. There was also a general trend for increased cancer risk for a number for most of the selected types of cancers for females and statistically significant increases in female genital cancers. Sub group analyses, defined crudely by reproductive age, did not elucidate any clear patterns of the influence of oestrogen on cancer incidence, with female burn survivors in Scotland showing increased risk across all age groups. For female burn survivors in WA, an increased risk for all-causetotal (all-sites) cancer was found for those younger than 15 years (pre-pubescent) and 50 years and older (post-menopausal). 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.

The site-specific analyses showed ~~that whilst~~ statistically significant increases in female genital cancers. ~~were found, there was also a general trend for increased cancer risk for most of the selected types of cancers for females.~~ 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. Whilst lymphomas have also been reported in association with immunosuppression, [26] [27] statistically significant results were found only for Western Australian female burn patients. ~~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, respiratory tract and oesophagus. These results are similar to those found in a Danish study [22] 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. Interestingly, the results of no increase in skin melanoma risk after burn injury in this study support findings of other population-based studies.[22] [23]~~

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. 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. Interestingly, the results of no increase in skin melanoma risk after burn injury in this study support findings of other population-based studies.[12] [13]

An alternative explanation for this increased incidence in cancer post-burn may lie in the significant impact a burn injury has on the immune system, or the sustained oxidative and metabolic stress that are integral to the injury response. While burn injury predominantly affects the skin, it has been shown to cause significant depression of both humoral and cell-mediated immunity (CMI), [7] ~~[24] [25]~~ [28] [29] sustained elevated levels of oxidative stress ~~[26] [27]~~ [30] [31] and prolonged elevation of hyper-metabolic and

stress hormone levels. [28 29 32 33] These effects have been demonstrated to persist for up to 3 years post-injury and can lead to long-term systemic impacts on other organs of the body.[1 2 30 34 38] Severe burn injury has been demonstrated to induce endoplasmic reticulum (ER) stress, in particular, in the liver.[35 39] ER stress is a stress-response that initially facilitates cell survival but can switch to a pro-apoptotic signal with prolonged stress.[35 36 39 40] However, it has also been shown that the ER stress response can become maladaptive, facilitating adaptation to hypoxic environments and promoting tumour growth. [36 37 40 41] It is plausible that the array of host responses combined with the impact of the injury, therefore, creates an environment of increased susceptibility to cancer.

In addition to the observed increase in some of the selected site-specific cancers, the data support evidence for a gender dimorphism (a systematic difference between individuals of different sex in the same species) in the response to burn injury. After burn injury, gender has been shown to be an important factor with respect to poorer outcomes for mortality[38 41 42 45] and improved prognosis for multiple organ dysfunction syndrome,[42 46] and sepsis,[43 47] for females compared to males. Similar gender-based differences have also been reported in animal studies of burn injury.[44 48 48 52]

The impact of gender with respect to outcomes after burn injury is largely thought to stem from well-established differences in immune biology. There is a substantial volume of published literature to support a gender dimorphism in the immune response[49 52 53 56] and sepsis[43 47] following injury that have impacts on health and mortality.[39 40] The majority of these studies support a more efficient and effective innate and adaptive immune responses in females, leading to more rapid clearance of infectious organisms driven by tissue resident cell populations.[53 57] This 'advantageous' response reduces the risk of infection in females compared to males [53 54 57 58] but leads to elevated risk of autoimmune disease.[55 59] This dimorphism was thought to arise largely due to the impact of oestrogen on immune function.[56 57 60 61] However, recent papers have demonstrated these differences are not completely ablated by ovariectomy (in animal models) [53 57] and others have shown that oestrogen can be deleterious to the immune response.[58 62] This suggests a role of other mediators, most likely expressed on the X-chromosome, in the maintenance of the differential immune response. [59 60 63 64] The evidence for gender differences in the immune response, both to thermal and other trauma, and its impact on outcomes is substantial. Here, the evidence of increased cancer incidence in selected types of cancer after burn injury, with a greater effect in females, suggests the systemic immune response to burn injury may be a mediator of cancer susceptibility.

5. Conclusion

Using population-based linked data of all burn patients in both Western Australia and Scotland, consistent trends were found in excesses in cancer notifications for a range of selected site specific cancers with an elevated and more widespread increase in female burn patients. Overall, however, the increased cancer risk affected small proportions of the respective burn patient cohorts. More research is required to understand the underlying mechanism(s) that may link burn injury to an increased risk of some cancers and why this is elevated in females, which may in turn enable identification of possible sites for intervention.

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Table 1 **Characteristics of burn injury patients included in analyses with no record of cancer prior to separation date of index burn admission, 1983-2008, by country.**

Characteristics	Western Australia N (%)	Scotland N (%)
Total number burn admissions*	22,705	37,506
Gender: Male	15,481 (68.2)	23,896 (63.7)
Age at index admission (Years)		
<15	8,135 (35.8)	14,579 (38.9)
15-24	4,364 (19.2)	4,495 (12.0)
25-49	7,147 (31.5)	9,554 (25.5)
50-64	1,736 (7.7)	4,080 (10.9)
65+	1,323 (5.8)	4,798 (12.8)
Site of burn**		
Head and neck	6,784 (15.4)	7,592 (16.1)
Trunk	7,553 (17.2)	8,815 (21.0)
Hand, wrist, upper limb	15,801 (35.9)	6,984 (14.8)
Hip , lower limb	11,798 (26.8)	9,531 (3.4)
Eye	379 (0.9)	1,087 (2.3)
Respiratory tract	212 (0.5)	163 (0.3)
Other internal organs	124 (0.3)	165 (0.3)
Multiple regions	656 (1.5)	3,677 (7.8)
Unspecified region	694 (1.6)	858 (1.8)
Burn site depth**		
Erythema	8,929 (20.9)	4,815 (11.5)
Partial thickness	18,449 (41.9)	6,302 (15.0)
Full thickness	7,095 (16.1)	4,924 (11.7)
Unspecified	9,528 (21.7)	25,869 (61.7)
Calendar period of admission		
1983-1988	5,431 (23.9)	11,507 (30.7)
1989-1993	4,200 (18.5)	7,876 (21.0)
1994-1998	4,755 (20.9)	7,130 (19.0)
1999-2003	4,265 (18.9)	5,980 (15.9)
2004-2008	4,054 (17.9)	5,013 (13.4)
Any co-morbidity at index burn		
Yes	2,798 (12.3)	7,679 (20.5)

* No previous record of cancer

** Patients may have multiple burn sites per anatomical region per depth

Table 2 **Standardised incidence ratios and 95% confidence intervals and observed and expected numbers for all-cause cancer in persons hospitalised for burn injury in Western Australia and Scotland, during the periods 1983-2008 and 1983-1988.**

	Western Australia††			Scotland		
	Combined SIR 95%CI* O:E**	Male† SIR 95%CI O:E	Female† SIR 95%CI O:E	Combined SIR 95%CI O:E	Male† SIR 95%CI O:E	Female† SIR 95%CI O:E
Total cohort 1983-2008	0.97 (0.9 to 1.0) 759: 785.5	0.9 (0.8 to 1.0) 515: 569.5	1.1 (1.0 to 1.3) 244: 216.0	1.09 (1.05 to 1.10) 2260: 2075.9	0.96 (0.90 to 1.0) 1249: 1303.2	1.3 (1.2 to 1.4) 1011: 772.6
Sub-cohort 1983-1988	1.0 (0.9 to 1.1) 294:294.9	0.9 (0.8 to 1.0) 190:220.3	1.4 (1.1 to 1.7) 104: 74.6	0.9 (0.8 to 0.9) 838: 953.4	0.8 (0.7 to 0.9) 491: 614.3	1.0 (0.9 to 1.2) 347: 339.1

*SIR (95%CI): Standardised Incidence Ratio (95% confidence interval) adjusted for age and gender

** O: E: Observed: Expected

†SIR (95%CI): Standardised Incidence Ratio (95% confidence interval) adjusted for age

†† Western Australian comparison data Duke et al. Burns 2011; 38:340-47.

Table 3 **Standardised incidence ratios and 95% confidence intervals and observed and expected numbers for selected types of cancer in persons hospitalised for burns Western Australia and Scotland, 1983-2008.**

Cancer Site	Western Australia			Scotland		
	Combined SIR 95%CI* O:E**	Male SIR 95%CI† O:E	Female SIR 95%CI† O:E	Combined SIR 95%CI* O:E	Male SIR 95%CI† O:E	Female SIR 95%CI† O:E
Buccal cavity C00 to C14	1.4 (1.03 to 1.9) 45: 32.6	1.4 (1.0 to 1.9) 38:28.1	1.5 (0.7 to 3.2) 7: 4.6	2.6 (2.2 to 3.1) 117: 45.0	2.4 (1.9 to 2.9) 83: 35.1	3.4 (2.5 to 4.8) 34:9.9
Oesophagus C15	1.4 (0.9 to 2.4) 15:10.50	1.5 (0.9 to 2.6) 13: 8.7	1.1 (0.3 to 4.5) 2: 1.8	1.6 (1.3 to 2.0) 82: 51.4	1.5 (1.1 to 1.9) 53:36.1	1.9 (1.3 to 2.7) 29:15.3
Stomach C16	0.6 (0.3 to 1.1) 10:17.0	0.5 (0.2 to 1.1) 7: 13.4	0.8 (0.3 to 2.6) 3: 3.6	1.2 (0.9 to 1.5) 73:63.2	1.1 (0.8 to 1.5) 1.2 5: 2.8	1.3 (0.9 to 1.9) 25:19.5
Colorectal C18 to C20	0.7 (0.6 to 0.9) 69: 96.3	0.7 (0.5 to 0.9) 45: 69.1	0.9 (0.6 to 1.3) 24: 27.2	1.2 (1.1 to 1.4) 268:221.8	1.0 (0.9 to 1.2) 142:140.5	1.4 (1.3 to 1.8) 125: 81.3
Liver C22	2.6 (1.6 to 4.0) 19: 7.4	2.2 (1.3 to 3.7) 14: 6.3	4.7 (2.0 to 11.4) 5: 1.1	1.7 (1.2 to 2.5) 31:18.0	1.5 (1.1 to 2.5) 22: 13.3	1.9 (1.0 to 3.7) 9: 4.7
Pancreas C25	0.7 (0.4 to 1.3) 11: 15.3	0.9 (0.5 to 1.7) 9: 10.4	0.4 (0.1 to 1.6) 2: 5.0	1.1 (0.8 to 1.5) 44:39.6	1.5 (1.03 to 2.0) 34: 23.4	0.6 (0.3 to 1.2) 10: 16.2
Larynx C32	5.7 (0.9 to 3.3) 10: 5.7	1.5 (0.7 to 3.0) 8: 5.4	6.0 (1.5 to 24.1) 2: 0.3	1.9 (1.4 to 2.5) 39: 21.1	1.5 (1.1 to 2.2) 28: 18.5	4.2(2.3 to 7.7) 11:2.6
Respiratory tract C33 to C34	1.4 (1.1 to 1.6) 101: 74.8	1.3 (1.1 to 1.7) 79:59.3	1.4 (0.9 to 2.2) 22:15.4	1.5 (1.4 to 1.7) 448:298.1	1.3 (1.2 to 1.5) 279:210.4	1.9 (1.7 to 2.2) 169:87.7
Skin –melanoma C44	0.7 (0.6 to 0.9) 72: 102.0	0.7 (0.6 to 1.0) 57: 77.9	0.6 (0.4 to 1.0) 15: 24.1	0.8 (0.6 to 1.1) 38:48.5	0.7 (0.4 to 1.1) 19:28.4	1.0 (0.4 to 1.1) 19:20.0
Breast C50	1.0 (0.8 to 1.3) 65: 62.4	1.3 (0.2 to 9.2) 1: 0.8	1.0 (0.8 to 1.3) 64:61.7	1.7 (1.5 to 1.9) 271:161.4	0.7 (0.1 to 4.8) 1:1.5	1.6 (1.5 to 1.9) 270: 160.0
Female genital tract (combined) C51 to C57			1.4 (1.0 to 2.0) 31:26.7			1.7 (1.4 to 2.0) 114: 67.2
Male genital tract (combined) C60 to C63		0.9 (0.8 to 1.1) 141: 150.7			1.1 (1.0 to 1.3) 210: 192.6	
Prostate C61		0.8 (0.6 to 0.9) 102: 135.9			1.1 (0.9 to 1.2) 177: 165.5	
Kidney, Bladder, UT C64 to C68	0.5 (0.3 to 0.7) 17: 37.9	0.4 (0.2 to 0.7) 12: 30.9	0.7 (0.3 to 1.7) 5: 7.0	1.2 (1.0 to 1.4) 135: 110.9	1.2 (1.0 to 1.4) 96: 82.8	1.4 (1.0 to 1.9) 39: 28.0
Brain C71	1.2 (0.7 to 1.9) 16: 13.9	1.0 (0.5 to 1.8) 10: 10.5	1.7 (0.8 to 3.9) 6: 3.5	1.5 (1.1 to 2.0) 39:27.0	1.4 (0.9 to 2.0) 26:19.2	1.7 (1.0 to 2.9) 13:7.8
Lymphomas to all	1.0 (0.7 to 1.4) 36: 35.5	0.8 (0.5 to 1.2) 20: 26.0	1.7 (1.03 to 2.7) 16:9.6	1.1 (0.9 to 1.4) 75:68.0	1.1 (0.8 to 1.4) 48:45.0	1.2 (0.8 to 1.7) 27:23.0
Myeloma/ plasma	1.3 (0.7 to 2.3) 11: 8.6	1.3 (0.7 to 2.6) 8:6.1	1.2 (0.4 to 3.7) 3: 2.49	1.1 (0.7 to 1.6) 22:21.0	1.0 (0.6 to 1.7) 13:13.2	1.2 (0.6 to 2.2) 9: 7.8
Leukaemia's to all	1.1 (0.8 to 1.7) 26: 22.9	1.1 (0.7 to 1.8) 19: 17.0	1.2 (0.6 to 2.5) 7: 6.0	1.3 (1.01 to 1.7) 63:48.6	1.0 (0.73 to 1.4) 34:33.1	1.8 (1.3 to 2.7) 29: 15.5

*SIR (95%CI): Standardised Incidence Ratio adjusted for age and gender (95% confidence interval)

** O: E: Observed: Expected

†SIR (95%CI): Standardised Incidence Ratio adjusted for age (95% confidence interval)

Table 4 **Standardised incidence ratios and 95% confidence intervals and observed and expected numbers for all-cause cancer incidence, for persons hospitalised for burns Western Australia and Scotland, by age group, 1983 to 1988.**

Age at first burn years	SIR (95%CI) (observed: expected)		
	combined gender*	Male†	Female†
<15			
WA	1.17 (0.82 to 1.68) (30:25)	1.19 (0.77 to 1.84) (20:16)	1.15 (0.62 to 2.14) (10:8.6)
Scotland	0.94 (0.69 to 1.28) (41:43.69)	0.72 (0.47 to 1.12) (20:27.77)	1.32 (0.86 to 2.02) (21:15.92)
15 to 49			
WA	0.87 (0.77 to 0.99) (273: 313)	0.87 (0.75 to 1.00) (197: 226)	0.86 (0.69 to 1.1) (76: 87)
Scotland	1.21 (1.12 to 1.31) (617: 509.16)	1.04 (0.94 to 1.16) (345: 331.68)	1.53 (1.36 to 1.73) (272: 177.48)
≥ 50			
WA	1.02 (0.93 to 1.12) (456: 446)	0.91 (0.82 to 1.02) (298: 326)	1.32 (1.13 to 1.54) (158: 120)
Scotland	1.05 (1.00 to 1.11) (1602: 1523)	0.94 (0.88 to 1.00) (884: 943.75)	1.23 (1.15 to 1.33) (718:579.25)

*SIR (95%CI): Standardised Incidence Ratio adjusted for age and gender (95% confidence interval)
†SIR (95%CI): Standardised Incidence Ratio adjusted for age (95% confidence interval)

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

Page numbers in this checklist – relate to page numbers of the final pdf version of uploaded manuscript file

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract *Population-based retrospective cohort record linkage study – in abstract* *Title: Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia. (Pages 1, 5)*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found *Abstract - Page 5*
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported *While burns predominantly affect the skin, burns are associated with significant systemic effects, depressed immune functioning and prolonged periods of systemic catabolism and hypermetabolism, that may increase a person's risk of cancer. (Page 6)*
Objectives	3	State specific objectives, including any prespecified hypotheses *Done: Firstly, confirm the increased risk of 'all-cause' cancer observed in the preliminary Western Australian study of female burn survivors using the Scottish data; and, secondly, examine site-specific cancer risk amongst survivors of burn injury (Page 6)*
Methods		
Study design	4	Present key elements of study design early in the paper *Clearly presented in Introduction and Methods sections (Pages 5- 8)*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection *Clearly presented in Methods section (Pages 6 - 8)*
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Population-based study of linked health administrative datasets: whole of population data are used. (Pages 6-8)* *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable *Burn exposure (Page 7) and cancer outcomes (Page 8) clearly defined.*

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 *Data sources clearly defined in Methods: Information Service Division (ISD) Scotland Western Australia Data Linkage System (Page 7) and reference population-based age and gender cancer incidence rates (Page 7-8)*
Bias	9	Describe any efforts to address potential sources of bias *Population-level linked administrative data minimises issues of selection and reporting bias, and loss to follow-up.*
Study size	10	Explain how the study size was arrived at *Whole of population study undertaken (Scotland and Western Australia) stated in Methods (Page 6-8).*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why *Groupings described / defined in Methods (Page 8)*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding *All analyses clearly presented in Methods for each cohort of burn patients hospitalised in both Scotland and Western Australia: 1) from 1983 to 2008; 2) sub-group 1983-1988; and 3) by grouped age at admission (<15; ≥15 and <50; ≥ 50 years) (Page 8)* *Whole of population examination of observed versus expected cancer cases using Standardised Incidence Ratios, adjusting for 5-year age group and gender, and calendar period from 1983-2008.*
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Whole of population based study using linked data (Page 6-8)* *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed *Numbers of patient records included in study clearly stated in Results (Pages 8-9)*
		(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 *Data presented in Table 1(Page 15)*
		(b) Indicate number of participants with missing data for each variable of interest *N/A*
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) *Average follow up time presented for each patient cohort in Results (Page9)*

Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time *Presented in Results (Page 9) and Table 2 (Page 16), Table 3 (Page 17) and Table 4 (Page 18)*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included *Standardised Incidence Ratio (SIR) and 95% Confidence Intervals clearly presented in text and Tables with appropriate labelling of variables standardised for (e.g. 5-year age groups, gender). Presented in Results (Page 9) and Table 2 (Page 16), Table 3 (Page 17) and Table 4 (Page 18)*
		(*b*) Report category boundaries when continuous variables were categorized Age boundaries clearly reported
		(*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 *All results of sub-group analyses presented. (Tables 2-4 – Pages 16-18)*
Discussion		
Key results	18	Summarise key results with reference to study objectives *Page 12*
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 *Strengths and limitations of the study have been presented in the Discussion 4.2 Methodological Issues (Pages 10-11).* *The burn patient cohorts under study are part of the respective reference populations, and as such, this may have a diluting effect in the standardised incidence ratios. The results presented are for the total burn patient cohorts including both severe and non-severe burns; the results are therefore, conservative.*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. *The results are conservative and results have been interpreted in light of current literature on the impacts of burn injury on the immune system and other systemic effects. (Pages 10 – 13)*
Generalisability	21	Discuss the generalisability (external validity) of the study results *Expected that the sex dimorphic effects on cancer post-burn are generalisable.* *The evidence of increased cancer incidence after burn injury, with a greater effect in females, suggests the systemic immune response to burn injury may be a mediator of cancer susceptibility. (Page 13)*
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 *Funding sources disclosed (Pages 3, 14)*

*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.

Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia

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Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia

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Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia

Abstract

Objective: To investigate risk of cancer and potential gender effects in persons hospitalised with burn injury.

Design: Population-based retrospective cohort study using record-linkage systems in Scotland and Western Australia

Subjects: Records of 37,890 and 23,450 persons admitted with a burn injury in Scotland and Western Australia, respectively, from 1983 to 2008. De-identified extraction of all linked hospital morbidity records, mortality and cancer records were provided by the Information Service Division Scotland and the Western Australian Data Linkage Service.

Main outcome measures: Total and gender specific numbers of observed and expected cases of total ('all sites') and site-specific cancers and standardised incidence ratios.

Results: From 1983-2008, for female burn survivors there was a greater number of observed versus expected notifications of total cancer with 1011 (standardised incidence ratio (SIR), 95% confidence interval (CI): 1.3, 1.2 to 1.4) and 244 (SIR, 95%CI: 1.12, 1.05 to 1.30), respectively, for Scotland and Western Australia. No statistically significant difference in total cancer risk was found for males. Significant excesses in observed cancers amongst burn survivors (combined gender) in Scotland and Western Australian were found for buccal cavity, liver, larynx and respiratory tract, and for cancers of the female genital tract.

Conclusions: Results from the Scotland data confirmed the increased risk of total ('all-sites') cancer previously observed amongst female burn survivors in Western Australia. The gender dimorphism observed in this study may be related to the role of gender in the immune response to burn injury. More research is required to understand the underlying mechanism(s) that may link burn injury with an increased risk of some cancers.

Article Focus

- Burn injury not only affects the skin but also has other systemic effects
- Inflammatory and immune response to burns may mediate cancer risk
- Gender differences in cancer risk after burn injury may be related to the immune response

Key messages

- Burn injury can have impacts on longer term health
- Increased risk of some cancers post-burn injury is greater in females than males

Strengths and Limitations

- Population-level linked administrative data minimises issues of selection and reporting bias, and loss to follow-up
- Consistency of results using population-level data from two patient populations provides greater support for link between burn injury and some cancers
- Unable to examine impact of burn severity on cancer risk due to lack of available data

Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia

1. Introduction

The burden of burn injury is a significant issue, not only in terms of the acute care perspective but also the chronic health effects resulting from both the injury event and the subsequent treatments. While burns predominantly affect the skin, burns are associated with significant systemic effects [1-3], depressed immune functioning[4-8] and prolonged periods of systemic catabolism and hypermetabolism.[9] Prompted by a clinical scenario of a diagnosis of hepatocellular carcinoma in a young male burn patient,[10] and the potential for malignancy after burn, an initial study of burn injury and total (all-sites) cancer risk was undertaken.[11]

Results of our initial study demonstrated a gender effect with female burn survivors having an increased risk of all types of cancer.[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).

This previous study of burn injury and cancer risk used population-based data linked by the Western Australian Data Linkage System (WADLS). [14] Western Australia has a population of approximately 2.2 million, and as such, did not support detailed gender and site-specific cancer incidence assessments with adequate statistical power. While the WADLS has linked datasets of Western Australians since the 1970s, other Australian States have only recently established record linkage systems and were not able to support this study. To extend the population-base and enable further detailed examination of the observed gender effect and site specific cancer incidence, approval was sought to access the Scottish population-based record linkage system, the Information Service Division (ISD) Scotland,[15] that has routinely linked health data since the 1980s.

This paper reports a retrospective longitudinal study to explore cancer risk after burn injury using linked hospital morbidity, cancer and death data of persons hospitalised for burn injury in both Western Australia and Scotland. The study aimed to, firstly, confirm the increased risk of total ('all-sites') cancer observed in the preliminary Western Australian study of female burn survivors using the Scottish data; and, secondly, examine site-specific cancer risk amongst survivors of burn injury.

2. Methods

Study data were obtained from the Western Australian Data Linkage Service (WADLS) [14] and the Information and Services Division (ISD Scotland) of the National Health Service National Services Scotland[15] with approval from Curtin University, the Western Australia Department of Health Human Research Ethics Committees and the NHS National Services Scotland Privacy Advisory Committee. The WADLS and ISD Scotland are validated record linkage systems that routinely link administrative health data from core datasets for the entire population of Western Australia and Scotland, respectively.

An index burn injury was defined as the first hospital admission with a burn injury using primary and additional diagnosis International Classification of Diseases (ICD) codes 940-949 (ICD9) and T20-T31 (ICD10). A de-identified extraction of all linked hospital morbidity records (Hospital Morbidity Data System (HMDS), mortality (Death Register, Western Australia) and cancer records (Western Australia Cancer Registry (WACR)) for all persons admitted to hospital with an index burn injury in Western Australia, for the period 1 January 1983 to 31 December 2008, was performed by WADLS [16]. A corresponding de-identified extraction of all linked hospital morbidity records (Scottish Morbidity Records (SMR) 01), cancer registrations (SMR06) and death records (General Register Office for Scotland (GROS)) using the same burn cohort definition was undertaken by ISD Scotland. Hospital admissions data items included age at admission, gender, admission date, separation (or discharge) date, principal and additional diagnoses and external cause of injury.

The Western Australia Cancer Registry (WACR) was established in 1981 and is a population-based cancer registry based on mandatory notification of cancers from pathologists, haematologists and radiation oncologist, and cancer information from death records.[17] Malignant cancers are coded according to a modified Australian version of the International Classification of Diseases, Tenth Revision (ICD10-AM) and International Classification of Diseases for Oncology (ICD-O-3).

The Scotland Cancer Registry (SMR06) has recorded all incident cancers in Scotland from 1958, and since 1997 registration has been centralised at ISD Scotland.[18] The registry is responsible for the collection of information on all new cases of primary malignant neoplasms, carcinoma in situ (including grade III intra-epithelial neoplasia), neoplasms of uncertain behaviour and (since 1 January 2000) benign brain and spinal cord tumours arising in residents of Scotland. Data quality is monitored using routine indicators, computer validation and ad hoc studies of data accuracy and completeness of ascertainment.[19] [20] The Scottish cancer notifications are coded using the International Classification of Diseases (ICD version 10) and the International Classification of Diseases for Oncology (ICD-O).

Methods for analysis have been previously published. [11] An incident cancer was defined as a cancer diagnosis notification (C00-C96, excluding C44) after hospital admission for index burn injury. Analysis was restricted to malignant neoplasm notifications (C00-C96, excluding C44) for which total (all-sites) and site-specific cancer incident rates were provided by WACR and ISD Scotland for respective populations. Records were excluded from the analysis if the date of cancer diagnosis was prior to date of discharge for index burn hospitalisation. When a record was identified as having more than one malignant neoplasm notification, each neoplasm was counted as an individual record, however, if multiple tumours of the skin (C43) with identical morphological characteristics (that is, the first three digits ICD-O-3 morphology code) were identified, they were recorded only once. Gender and age-specific cancer (total C00-C96, excluding C44) incident rates for the Western Australian and Scottish populations were pooled for the calendar periods 1983-1988, 1989-1993, 1994-1998, 1999-2003 and 2004-2008 to allow for changes in population cancer incidence during the study period.

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 the 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]

Separate SIR analyses for total (all-sites) and site-specific cancers were conducted using country specific data for respective burn patient cohorts (all burn depth) for cohorts hospitalised from 1983-2008; total (all-sites) SIRs repeated for sub-cohorts of burn admissions from 1983-1987, with optimum follow-up time. To further explore the gender impact of burn injury on cancer risk, total (all-sites) cancer SIR analyses were repeated on age-restricted sub-cohorts classified to reflect reproductive age at admission for burn injury: <15 years; 15-49 years; and, ≥50 years. All statistical analyses were performed using Stata statistical software V 11 (StataCorp LP, College Station, Tex).

3. Results

As previously reported, in Western Australia from 1983 to 2008, there were 23,450 hospital index admissions for burn-related injury.[16] After exclusion of records with a history of cancer prior to separation date or death during hospital admission for burn, a total of 22,705 patient records were included in the analysis.[11] There were 673 patients with a first cancer notification after date of separation for burn injury hospitalisation, and with inclusion of multiple malignancies, 759 cancer notifications were included in the standardised incident ratio analyses as independent observations.

In Scotland from 1983-2008, there were a total of 37,890 persons hospitalised for an index burn-related injury. After exclusion of those with a history of cancer prior to separation date or death during hospital admission for burn, a total of 37,506 patients were included in the analysis. There were 2,005 patients with a first cancer notification after date of separation for burn injury hospitalisation, and with inclusion of multiple malignancies, 2,260 cancer notifications were included in the standardised incident ratio analyses as independent observations. Characteristics of the Western Australia and Scotland cohorts are presented in Table 1.

The Western Australia cohort (1983-2008; combined gender) was followed for a total of 283,306 person-years, with mean follow-up time of 12.3 years (range: >0 – 25.9 years). Mean follow-up time for those with a cancer notification was 9.4 years (range: >0 – 25.4) and for those with no cancer notification, 12.4 years (range: >0 – 25.9). The Scotland cohort (1983-2008; combined gender) was followed for a total of 474,489 person-years, with mean follow-up time of 12.6 years (range: 0 -26.0 years). Mean follow-up time for those with a cancer notification was 9.4 years (range: >0-25.8) and for those with no cancer notification, 12.7 years (range: >0-26.0).

For the Scottish cohort of burn injury patients (combined gender) there was marginal but significant difference (SIR, 95%CI: 1.09, 1.05-1.10) in the overall risk of cancer for persons with a burn injury hospitalisation for the period 1983 to 2008, compared with the general population of Scotland. While a significant increase of 30% in cancer risk was estimated for females there was no difference in cancer risk for males, when compared with the general population of Scotland (refer to Table 2). For the sub-cohort of burn injury patients 1983-1988, the total observed number of cases of cancer (n=838) was statistically significantly lower than expected (n=953.4) with SIR (95%CI) of 0.88 (0.82 to 0.94), with males having a statistically significantly lower number of cases observed than expected. Refer to Table 2 for gender specific SIRs for total (all-sites) cancer for Scotland and Western Australian burn patients, hospitalised during 1983-1988 and 1983-2008.[11]

Female genital cancers were grouped due to the small numbers of observed cancers in sub-groups in the Western Australian data and unstable SIR results. Statistically significant increases in observed genital (combined) cancers for female burn patients in both Western Australia and Scotland were

found. The increased breast cancer incidence was statistically significant amongst female burn survivors in Scotland. Statistically significant increases in cancer incidence for combined gender for both Western Australia and Scottish data were observed for cancers of the buccal cavity, liver and respiratory tract. Refer to Table 3 for gender and site-specific cancer SIRs. For each of these cancers, female burn survivors in both Western Australia and Scotland had higher incidence than males when compared with respective general population data. For the majority of site-specific cancers selected, female burn survivors in both Western Australia and Scotland had higher numbers of observed cancers than expected, with SIRs of similar magnitude. However, SIR results for Scottish data reached statistical significance, reflecting the larger population-base and respective higher number of cancer notifications.

Table 4 presents an SIR analyses of total (all-sites) cancer risk repeated on age-restricted sub-cohorts, classified to reflect reproductive age (<15 years; 15-49 years; and, ≥50 years) at admission for burn injury. For males in both WA and Scotland, no statistically significant differences were found across the three age groups. For female burn survivors in Scotland, the observed numbers of cancers total (all-sites) exceeded that expected for each of the three age groups, with statistically significant results observed for the age groups 15-49, and 50 years and older. In the Western Australia data, excess cancers were observed for those younger than 15 years and for those 50 years and older, with statistically significance reached for the older age group; for females 15-49 years at burn injury, no difference in observed and expected total (all-sites) cancer was found.

4. Discussion

4.1 Methodological Issues

When population-level administrative data are used, data linkage minimises issues of selection and reporting bias, as well as loss to follow-up. Data quality of the Western Australia and Scottish Cancer Registers[17 19 20] and hospital morbidity datasets[24 25] are assessed continually for both accuracy and quality. Data of all index burn hospitalisations in Western Australia and Scotland from 1983 to 2008 were analysed with follow-up time from discharge date, allowing for exclusion of prevalent cancers to support temporality of burn exposure and incident cancer. Cancer diagnoses from cancer registries in Western Australia and Scotland were independent of the record of burn injury in the respective hospital morbidity datasets. Minor burns treated in emergency departments were not included in the study. The burn patient cohorts under study are part of the respective reference populations, and as such, this may have a small diluting effect in the standardised incidence ratios. Using parallel datasets from Western Australia and Scotland, of populations 2.2 million and 5.5

million, respectively, allowed examination of the consistency of results and trends across the populations.

The Western Australia hospital morbidity data records the principal diagnosis and up to 20 additional diagnosis fields, whereas, the Scottish morbidity data includes the principal diagnosis and 5 additional diagnosis fields. Consequent to the reduced number of additional diagnosis fields in the Scottish data, there was an absence of recorded supplementary total body surface area burned (TBSA%) data (ICD9 946; ICD10 T31) and greater use of ICD codes for burns to multiple regions of the body (ICD9 946; ICD10 T29) rather individual anatomic burn sites, reflected in Table 1 This limited both SIR analyses restricted to more severe burns of TBSA 20% or greater and incident rate ratio analysis to examine the effects of severity of burn injury (burn depth and TBSA%). Previous SIR analyses of total (all-sites) cancer risk in Western Australia showed similar trends in results for all burn patients (severe and non-severe).[11]

Although this study had a follow-up period of up to 26 years from the date of separation for admission for burn injury, the follow up period for many patients may not have provided sufficient observation time to enable identification of all potential malignancies, given the long latency period for many cancers. 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.

4.2 Findings

Analysis of ISD Scotland data confirmed the results of our previous study: a statistically significant increase in total (all-sites) cancer risk for female burn survivors with males experiencing no difference. The site specific analyses clearly showed statistically significant increases in the number of observed cancers for combined gender in both the Western Australia and Scottish data for the buccal cavity, larynx, liver, respiratory tract and oesophagus. 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. Sub group analyses, defined crudely by reproductive age, did not elucidate any clear patterns of the influence of oestrogen on cancer incidence, with female burn survivors in Scotland showing increased risk across all age groups. For female burn survivors in WA, an increased risk for total (all-sites) cancer was found for those younger than 15 years (pre-pubescent) and 50 years and older (post-menopausal). The lack of gender difference for the sub-cohort of burn patients in Scotland 1983-88 for total (all-sites) cancer risk is difficult to explain. Possible reasons may include that females: sustained less severe (<20% TBSA) burns during

this period; had less comorbidities; and / or had better lifestyle factors than females hospitalised for burns during the remainder of the study period.

The site-specific analyses showed that whilst statistically significant increases in female genital cancers were found, there was also a general trend amongst female burn patients for excesses across a number of site-specific cancers examined, although these excesses did not always reach statistical significance, possibly due to small numbers. 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, respiratory tract and oesophagus. 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. Interestingly, the results of no increase in skin melanoma risk after burn injury in this study support findings of other population-based studies.[12 13]

An alternative explanation for this increased incidence in cancer post-burn may lie in the significant impact a burn injury has on the immune system, or the sustained oxidative and metabolic stress that are integral to the injury response. While burn injury predominantly affects the skin, it has been shown to cause significant depression of both humoral and cell-mediated immunity (CMI), [7 26 27] sustained elevated levels of oxidative stress [28 29] and prolonged elevation of hyper-metabolic and stress hormone levels. [30 31] These effects have been demonstrated to persist for up to 3 years post-injury and can lead to long-term systemic impacts on other organs of the body.[1 2 32-36] Severe burn injury has been demonstrated to induce endoplasmic reticulum (ER) stress, in particular, in the liver.[37] ER stress is a stress-response that initially facilitates cell survival but can switch to a pro-apoptotic signal with prolonged stress.[37 38] However, it has also been shown that the ER stress response can become maladaptive, facilitating adaptation to hypoxic environments and promoting tumour growth. [38 39] It is plausible that the array of host responses combined with the impact of the injury, therefore, creates an environment of increased susceptibility to cancer.

In addition to the observed increase in some of the selected site-specific cancers, the data support evidence for a gender dimorphism (a systematic difference between individuals of different sex in the same species) in the response to burn injury. After burn injury, gender has been shown to be an important factor with respect to poorer outcomes for mortality[40-43] and improved prognosis for multiple organ dysfunction syndrome,[44] and sepsis,[45] for females compared to males. Similar gender-based differences have also been reported in animal studies of burn injury.[46-50]

The impact of gender with respect to outcomes after burn injury is largely thought to stem from well-established differences in immune biology. There is a substantial volume of published literature to support a gender dimorphism in the immune response[51-54] and sepsis[45] following injury that have impacts on health and mortality.[41 42] The majority of these studies support a more efficient and effective innate and adaptive immune responses in females, leading to more rapid clearance of infectious organisms driven by tissue resident cell populations.[55] This 'advantageous' response reduces the risk of infection in females compared to males [55 56] but leads to elevated risk of autoimmune disease.[57] This dimorphism was thought to arise largely due to the impact of oestrogen on immune function.[58 59] However, recent papers have demonstrated these differences are not completely ablated by ovariectomy (in animal models) [55] and others have shown that oestrogen can be deleterious to the immune response.[60] This suggests a role of other mediators, most likely expressed on the X-chromosome, in the maintenance of the differential immune response. [61 62] The evidence for gender differences in the immune response, both to thermal and other trauma, and its impact on outcomes is substantial. Here, the evidence of increased cancer incidence in selected types of cancer after burn injury, with a greater effect in females, suggests the systemic immune response to burn injury may be a mediator of cancer susceptibility.

5. Conclusion

Using population-based linked data of all burn patients in both Western Australia and Scotland, consistent trends were found in excesses in cancer notifications for a range of selected site specific cancers with an elevated and more widespread increase in female burn patients. Overall, however, the increased cancer risk affected small proportions of the respective burn patient cohorts. More research is required to understand the underlying mechanism(s) that may link burn injury to an increased risk of some cancers and why this is elevated in females, which may in turn enable identification of possible sites for intervention.

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Table 1 **Characteristics of burn injury patients included in analyses with no record of cancer prior to separation date of index burn admission, 1983-2008, by country.**

Characteristics	Western Australia N (%)	Scotland N (%)
Total number burn admissions*	22,705	37,506
Gender: Male	15,481 (68.2)	23,896 (63.7)
Age at index admission (Years)		
<15	8,135 (35.8)	14,579 (38.9)
15-24	4,364 (19.2)	4,495 (12.0)
25-49	7,147 (31.5)	9,554 (25.5)
50-64	1,736 (7.7)	4,080 (10.9)
65+	1,323 (5.8)	4,798 (12.8)
Site of burn**		
Head and neck	6,784 (15.4)	7,592 (16.1)
Trunk	7,553 (17.2)	8,815 (21.0)
Hand, wrist, upper limb	15,801 (35.9)	6,984 (14.8)
Hip , lower limb	11,798 (26.8)	9,531 (3.4)
Eye	379 (0.9)	1,087 (2.3)
Respiratory tract	212 (0.5)	163 (0.3)
Other internal organs	124 (0.3)	165 (0.3)
Multiple regions	656 (1.5)	3,677 (7.8)
Unspecified region	694 (1.6)	858 (1.8)
Burn site depth**		
Erythema	8,929 (20.9)	4,815 (11.5)
Partial thickness	18,449 (41.9)	6,302 (15.0)
Full thickness	7,095 (16.1)	4,924 (11.7)
Unspecified	9,528 (21.7)	25,869 (61.7)
Calendar period of admission		
1983-1988	5,431 (23.9)	11,507 (30.7)
1989-1993	4,200 (18.5)	7,876 (21.0)
1994-1998	4,755 (20.9)	7,130 (19.0)
1999-2003	4,265 (18.9)	5,980 (15.9)
2004-2008	4,054 (17.9)	5,013 (13.4)
Any co-morbidity at index burn		
Yes	2,798 (12.3)	7,679 (20.5)

***** No previous record of cancer

** Patients may have multiple burn sites per anatomical region per depth

Table 2 **Standardised incidence ratios and 95% confidence intervals and observed and expected numbers for total (all-sites) cancer in persons hospitalised for burn injury in Western Australia and Scotland, during the periods 1983-2008 and 1983-1988.**

	Western Australia††			Scotland		
	Combined SIR 95%CI* O:E**	Male† SIR 95%CI O:E	Female† SIR 95%CI O:E	Combined SIR 95%CI O:E	Male† SIR 95%CI O:E	Female† SIR 95%CI O:E
Total cohort 1983-2008	0.97 (0.9 to 1.0) 759: 785.5	0.9 (0.8 to 1.0) 515: 569.5	1.1 (1.0 to 1.3) 244: 216.0	1.09 (1.05 to 1.10) 2260: 2075.9	0.96 (0.90 to 1.0) 1249: 1303.2	1.3 (1.2 to 1.4) 1011: 772.6
Sub-cohort 1983-1988	1.0 (0.9 to 1.1) 294:294.9	0.9 (0.8 to 1.0) 190:220.3	1.4 (1.1 to 1.7) 104: 74.6	0.9 (0.8 to 0.9) 838: 953.4	0.8 (0.7 to 0.9) 491: 614.3	1.0 (0.9 to 1.2) 347: 339.1

*SIR (95%CI): Standardised Incidence Ratio (95% confidence interval) adjusted for age and gender
** O: E: Observed: Expected
†SIR (95%CI): Standardised Incidence Ratio (95% confidence interval) adjusted for age
†† Western Australian comparison data Duke et al. Burns 2011; 38:340-47.

Table 3 **Standardised incidence ratios and 95% confidence intervals and observed and expected numbers for selected types of cancer in persons hospitalised for burns Western Australia and Scotland, 1983-2008.**

Cancer Site ICD-10‡	Western Australia			Scotland		
	Combined SIR 95%CI* O:E**	Male SIR 95%CI† O:E	Female SIR 95%CI† O:E	Combined SIR 95%CI* O:E	Male SIR 95%CI† O:E	Female SIR 95%CI† O:E
Buccal cavity C00 to C14	1.4 (1.03 to 1.9) 45: 32.6	1.4 (1.0 to 1.9) 38:28.1	1.5 (0.7 to 3.2) 7: 4.6	2.6 (2.2 to 3.1) 117: 45.0	2.4 (1.9 to 2.9) 83: 35.1	3.4 (2.5 to 4.8) 34:9.9
Oesophagus C15	1.4 (0.9 to 2.4) 15:10.50	1.5 (0.9 to 2.6) 13: 8.7	1.1 (0.3 to 4.5) 2: 1.8	1.6 (1.3 to 2.0) 82: 51.4	1.5 (1.1 to 1.9) 53:36.1	1.9 (1.3 to 2.7) 29:15.3
Stomach C16	0.6 (0.3 to 1.1) 10:17.0	0.5 (0.2 to 1.1) 7: 13.4	0.8 (0.3 to 2.6) 3: 3.6	1.2 (0.9 to 1.5) 73:63.2	1.1 (0.8 to 1.5) 1.2 5: 2.8	1.3 (0.9 to 1.9) 25:19.5
Colorectal C18 to C20	0.7 (0.6 to 0.9) 69: 96.3	0.7 (0.5 to 0.9) 45: 69.1	0.9 (0.6 to 1.3) 24: 27.2	1.2 (1.1 to 1.4) 268:221.8	1.0 (0.9 to 1.2) 142:140.5	1.4 (1.3 to 1.8) 125: 81.3
Liver C22	2.6 (1.6 to 4.0) 19: 7.4	2.2 (1.3 to 3.7) 14: 6.3	4.7 (2.0 to 11.4) 5: 1.1	1.7 (1.2 to 2.5) 31:18.0	1.5 (1.1 to 2.5) 22: 13.3	1.9 (1.0 to 3.7) 9: 4.7
Pancreas C25	0.7 (0.4 to 1.3) 11: 15.3	0.9 (0.5 to 1.7) 9: 10.4	0.4 (0.1 to 1.6) 2: 5.0	1.1 (0.8 to 1.5) 44:39.6	1.5 (1.03 to 2.0) 34: 23.4	0.6 (0.3 to 1.2) 10: 16.2
Larynx C32	5.7 (0.9 to 3.3) 10: 5.7	1.5 (0.7 to 3.0) 8: 5.4	6.0 (1.5 to 24.1) 2: 0.3	1.9 (1.4 to 2.5) 39: 21.1	1.5 (1.1 to 2.2) 28: 18.5	4.2(2.3 to 7.7) 11:2.6
Respiratory tract C33 to C34	1.4 (1.1 to 1.6) 101: 74.8	1.3 (1.1 to 1.7) 79:59.3	1.4 (0.9 to 2.2) 22:15.4	1.5 (1.4 to 1.7) 448:298.1	1.3 (1.2 to 1.5) 279:210.4	1.9 (1.7 to 2.2) 169:87.7
Skin – malignant melanoma C43	0.7 (0.6 to 0.9) 72: 102.0	0.7 (0.6 to 1.0) 57: 77.9	0.6 (0.4 to 1.0) 15: 24.1	0.8 (0.6 to 1.1) 38:48.5	0.7 (0.4 to 1.1) 19:28.4	1.0 (0.4 to 1.1) 19:20.0
Breast C50	1.0 (0.8 to 1.3) 65: 62.4	1.3 (0.2 to 9.2) 1: 0.8	1.0 (0.8 to 1.3) 64:61.7	1.7 (1.5 to 1.9) 271:161.4	0.7 (0.1 to 4.8) 1:1.5	1.6 (1.5 to 1.9) 270: 160.0
Female genital tract (combined) C51 to C57			1.4 (1.0 to 2.0) 31:26.7			1.7 (1.4 to 2.0) 114: 67.2
Male genital tract (combined) C60 to C63		0.9 (0.8 to 1.1) 141: 150.7			1.1 (1.0 to 1.3) 210: 192.6	
Prostate C61		0.8 (0.6 to 0.9) 102: 135.9			1.1 (0.9 to 1.2) 177: 165.5	
Kidney, Bladder, UT C64 to C68	0.5 (0.3 to 0.7) 17: 37.9	0.4 (0.2 to 0.7) 12: 30.9	0.7 (0.3 to 1.7) 5: 7.0	1.2 (1.0 to 1.4) 135: 110.9	1.2 (1.0 to 1.4) 96: 82.8	1.4 (1.0 to 1.9) 39: 28.0
Brain C71	1.2 (0.7 to 1.9) 16: 13.9	1.0 (0.5 to 1.8) 10: 10.5	1.7 (0.8 to 3.9) 6: 3.5	1.5 (1.1 to 2.0) 39:27.0	1.4 (0.9 to 2.0) 26:19.2	1.7 (1.0 to 2.9) 13:7.8
Lymphomas to all	1.0 (0.7 to 1.4) 36: 35.5	0.8 (0.5 to 1.2) 20: 26.0	1.7 (1.03 to 2.7) 16:9.6	1.1 (0.9 to 1.4) 75:68.0	1.1 (0.8 to 1.4) 48:45.0	1.2 (0.8 to 1.7) 27:23.0
Myeloma/ plasma	1.3 (0.7 to 2.3) 11: 8.6	1.3 (0.7 to 2.6) 8:6.1	1.2 (0.4 to 3.7) 3: 2.49	1.1 (0.7 to 1.6) 22:21.0	1.0 (0.6 to 1.7) 13:13.2	1.2 (0.6 to 2.2) 9: 7.8
Leukaemia's to all	1.1 (0.8 to 1.7) 26: 22.9	1.1 (0.7 to 1.8) 19: 17.0	1.2 (0.6 to 2.5) 7: 6.0	1.3 (1.01 to 1.7) 63:48.6	1.0 (0.73 to 1.4) 34:33.1	1.8 (1.3 to 2.7) 29: 15.5

*SIR (95%CI): Standardised Incidence Ratio adjusted for age and gender (95% confidence interval)

** O: E: Observed: Expected

†SIR (95%CI): Standardised Incidence Ratio adjusted for age (95% confidence interval)

‡ ICD-10: International Classification of Disease s (ICD) version 10

Table 4 **Standardised incidence ratios and 95% confidence intervals and observed and expected numbers for total (all-sites) cancer incidence, for persons hospitalised for burns Western Australia and Scotland, by age group, 1983 to 1988.**

Age at first burn years	SIR (95%CI) (observed: expected)		
	combined gender*	Male†	Female†
<15			
WA	1.17 (0.82 to 1.68) (30:25)	1.19 (0.77 to 1.84) (20:16)	1.15 (0.62 to 2.14) (10:8.6)
Scotland	0.94 (0.69 to 1.28) (41:43.69)	0.72 (0.47 to 1.12) (20:27.77)	1.32 (0.86 to 2.02) (21:15.92)
15 to 49			
WA	0.87 (0.77 to 0.99) (273: 313)	0.87 (0.75 to 1.00) (197: 226)	0.86 (0.69 to 1.1) (76: 87)
Scotland	1.21 (1.12 to 1.31) (617: 509.16)	1.04 (0.94 to 1.16) (345: 331.68)	1.53 (1.36 to 1.73) (272: 177.48)
≥ 50			
WA	1.02 (0.93 to 1.12) (456: 446)	0.91 (0.82 to 1.02) (298: 326)	1.32 (1.13 to 1.54) (158: 120)
Scotland	1.05 (1.00 to 1.11) (1602: 1523)	0.94 (0.88 to 1.00) (884: 943.75)	1.23 (1.15 to 1.33) (718:579.25)

*SIR (95%CI): Standardised Incidence Ratio adjusted for age and gender (95% confidence interval)
†SIR (95%CI): Standardised Incidence Ratio adjusted for age (95% confidence interval)

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Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia

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James Boyd: Planning, conduct and reporting

Jacqui Bauer: Conduct and reporting

Mark Fear: Reporting

Suzanne Rea: Reporting

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Article Focus

- Burn injury not only affects the skin but also has other systemic effects
- Inflammatory and immune response to burns may mediate cancer risk
- Gender differences in cancer risk after burn injury may be related to the immune response

Key messages

- Burn injury can have impacts on longer term health
- Increased risk of some cancers post-burn injury is greater in females than males

Strengths and Limitations

- Population-level linked administrative data minimises issues of selection and reporting bias, and loss to follow-up
- Consistency of results using population-level data from two patient populations provides greater support for link between burn injury and some cancers
- Unable to examine impact of burn severity on cancer risk due to lack of available data

Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia

Abstract

Objective: To investigate risk of cancer and potential gender effects in persons hospitalised with burn injury.

Design: Population-based retrospective cohort study using record-linkage systems in Scotland and Western Australia

Subjects: Records of 37,890 and 23,450 persons admitted with a burn injury in Scotland and Western Australia, respectively, from 1983 to 2008. De-identified extraction of all linked hospital morbidity records, mortality and cancer records were provided by the Information Service Division Scotland and the Western Australian Data Linkage Service.

Main outcome measures: Total and gender specific numbers of observed and expected cases of total ('all sites') and site-specific cancers and standardised incidence ratios.

Results: From 1983-2008, for female burn survivors there was a greater number of observed versus expected notifications of total cancer with 1011 (standardised incidence ratio (SIR), 95% confidence interval (CI): 1.3, 1.2 to 1.4) and 244 (SIR, 95%CI: 1.12, 1.05 to 1.30), respectively, for Scotland and Western Australia. No statistically significant difference in total cancer risk was found for males. Significant excesses in observed cancers amongst burn survivors (combined gender) in Scotland and Western Australian were found for buccal cavity, liver, larynx and respiratory tract, and for cancers of the female genital tract.

Conclusions: Results from the Scotland data confirmed the increased risk of total ('all-sites') cancer previously observed amongst female burn survivors in Western Australia. The gender dimorphism observed in this study may be related to the role of gender in the immune response to burn injury. More research is required to understand the underlying mechanism(s) that may link burn injury with an increased risk of some cancers.

Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia

1. Introduction

The burden of burn injury is a significant issue, not only in terms of the acute care perspective but also the chronic health effects resulting from both the injury event and the subsequent treatments. While burns predominantly affect the skin, burns are associated with significant systemic effects [1-3], depressed immune functioning[4-8] and prolonged periods of systemic catabolism and hypermetabolism.[9] Prompted by a clinical scenario of a diagnosis of hepatocellular carcinoma in a young male burn patient,[10] and the potential for malignancy after burn, an initial study of burn injury and total (all-sites) cancer risk was undertaken.[11]

Results of our initial study demonstrated a gender effect with female burn survivors having an increased risk of all types of cancer.[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).

This previous study of burn injury and cancer risk used population-based data linked by the Western Australian Data Linkage System (WADLS). [14] Western Australia has a population of approximately 2.2 million, and as such, did not support detailed gender and site-specific cancer incidence assessments with adequate statistical power. While the WADLS has linked datasets of Western Australians since the 1970s, other Australian States have only recently established record linkage systems and were not able to support this study. To extend the population-base and enable further detailed examination of the observed gender effect and site specific cancer incidence, approval was sought to access the Scottish population-based record linkage system, the Information Service Division (ISD) Scotland,[15] that has routinely linked health data since the 1980s.

This paper reports a retrospective longitudinal study to explore cancer risk after burn injury using linked hospital morbidity, cancer and death data of persons hospitalised for burn injury in both Western Australia and Scotland. The study aimed to, firstly, confirm the increased risk of total ('all-sites') cancer observed in the preliminary Western Australian study of female burn survivors using the Scottish data; and, secondly, examine site-specific cancer risk amongst survivors of burn injury.

2. Methods

Study data were obtained from the Western Australian Data Linkage Service (WADLS) [14] and the Information and Services Division (ISD Scotland) of the National Health Service National Services Scotland[15] with approval from Curtin University, the Western Australia Department of Health Human Research Ethics Committees and the NHS National Services Scotland Privacy Advisory Committee. The WADLS and ISD Scotland are validated record linkage systems that routinely link administrative health data from core datasets for the entire population of Western Australia and Scotland, respectively.

An index burn injury was defined as the first hospital admission with a burn injury using primary and additional diagnosis International Classification of Diseases (ICD) codes 940-949 (ICD9) and T20-T31 (ICD10). A de-identified extraction of all linked hospital morbidity records (Hospital Morbidity Data System (HMDS), mortality (Death Register, Western Australia) and cancer records (Western Australia Cancer Registry (WACR)) for all persons admitted to hospital with an index burn injury in Western Australia, for the period 1 January 1983 to 31 December 2008, was performed by WADLS [16]. A corresponding de-identified extraction of all linked hospital morbidity records (Scottish Morbidity Records (SMR) 01), cancer registrations (SMR06) and death records (General Register Office for Scotland (GROS)) using the same burn cohort definition was undertaken by ISD Scotland. Hospital admissions data items included age at admission, gender, admission date, separation (or discharge) date, principal and additional diagnoses and external cause of injury.

The Western Australia Cancer Registry (WACR) was established in 1981 and is a population-based cancer registry based on mandatory notification of cancers from pathologists, haematologists and radiation oncologist, and cancer information from death records.[17] Malignant cancers are coded according to a modified Australian version of the International Classification of Diseases, Tenth Revision (ICD10-AM) and International Classification of Diseases for Oncology (ICD-O-3).

The Scotland Cancer Registry (SMR06) has recorded all incident cancers in Scotland from 1958, and since 1997 registration has been centralised at ISD Scotland.[18] The registry is responsible for the collection of information on all new cases of primary malignant neoplasms, carcinoma in situ (including grade III intra-epithelial neoplasia), neoplasms of uncertain behaviour and (since 1 January 2000) benign brain and spinal cord tumours arising in residents of Scotland. Data quality is monitored using routine indicators, computer validation and ad hoc studies of data accuracy and completeness of ascertainment.[19] [20] The Scottish cancer notifications are coded using the International Classification of Diseases (ICD version 10) and the International Classification of Diseases for Oncology (ICD-O).

Methods for analysis have been previously published. [11] An incident cancer was defined as a cancer diagnosis notification (C00-C96, excluding C44) after hospital admission for index burn injury. Analysis was restricted to malignant neoplasm notifications (C00-C96, excluding C44) for which total (all-sites) and site-specific cancer incident rates were provided by WACR and ISD Scotland for respective populations. Records were excluded from the analysis if the date of cancer diagnosis was prior to date of discharge for index burn hospitalisation. When a record was identified as having more than one malignant neoplasm notification, each neoplasm was counted as an individual record, however, if multiple tumours of the skin (C43) with identical morphological characteristics (that is, the first three digits ICD-O-3 morphology code) were identified, they were recorded only once. Gender and age-specific cancer (total C00-C96, excluding C44) incident rates for the Western Australian and Scottish populations were pooled for the calendar periods 1983-1988, 1989-1993, 1994-1998, 1999-2003 and 2004-2008 to allow for changes in population cancer incidence during the study period.

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 the 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]

Separate SIR analyses for total (all-sites) and site-specific cancers were conducted using country specific data for respective burn patient cohorts (all burn depth) for cohorts hospitalised from 1983-2008; total (all-sites) SIRs repeated for sub-cohorts of burn admissions from 1983-1987, with optimum follow-up time. To further explore the gender impact of burn injury on cancer risk, total (all-sites) cancer SIR analyses were repeated on age-restricted sub-cohorts classified to reflect reproductive age at admission for burn injury: <15 years; 15-49 years; and, ≥50 years. All statistical analyses were performed using Stata statistical software V 11 (StataCorp LP, College Station, Tex).

3. Results

As previously reported, in Western Australia from 1983 to 2008, there were 23,450 hospital index admissions for burn-related injury.[16] After exclusion of records with a history of cancer prior to separation date or death during hospital admission for burn, a total of 22,705 patient records were included in the analysis.[11] There were 673 patients with a first cancer notification after date of separation for burn injury hospitalisation, and with inclusion of multiple malignancies, 759 cancer notifications were included in the standardised incident ratio analyses as independent observations.

In Scotland from 1983-2008, there were a total of 37,890 persons hospitalised for an index burn-related injury. After exclusion of those with a history of cancer prior to separation date or death during hospital admission for burn, a total of 37,506 patients were included in the analysis. There were 2,005 patients with a first cancer notification after date of separation for burn injury hospitalisation, and with inclusion of multiple malignancies, 2,260 cancer notifications were included in the standardised incident ratio analyses as independent observations. Characteristics of the Western Australia and Scotland cohorts are presented in Table 1.

The Western Australia cohort (1983-2008; combined gender) was followed for a total of 283,306 person-years, with mean follow-up time of 12.3 years (range: >0 – 25.9 years). Mean follow-up time for those with a cancer notification was 9.4 years (range: >0 – 25.4) and for those with no cancer notification, 12.4 years (range: >0 – 25.9). The Scotland cohort (1983-2008; combined gender) was followed for a total of 474,489 person-years, with mean follow-up time of 12.6 years (range: 0 -26.0 years). Mean follow-up time for those with a cancer notification was 9.4 years (range: >0-25.8) and for those with no cancer notification, 12.7 years (range: >0-26.0).

For the Scottish cohort of burn injury patients (combined gender) there was marginal but significant difference (SIR, 95%CI: 1.09, 1.05-1.10) in the overall risk of cancer for persons with a burn injury hospitalisation for the period 1983 to 2008, compared with the general population of Scotland. While a significant increase of 30% in cancer risk was estimated for females there was no difference in cancer risk for males, when compared with the general population of Scotland (refer to Table 2). For the sub-cohort of burn injury patients 1983-1988, the total observed number of cases of cancer (n=838) was statistically significantly lower than expected (n=953.4) with SIR (95%CI) of 0.88 (0.82 to 0.94), with males having a statistically significantly lower number of cases observed than expected. Refer to Table 2 for gender specific SIRs for total (all-sites) cancer for Scotland and Western Australian burn patients, hospitalised during 1983-1988 and 1983-2008.[11]

Female genital cancers were grouped due to the small numbers of observed cancers in sub-groups in the Western Australian data and unstable SIR results. Statistically significant increases in observed genital (combined) cancers for female burn patients in both Western Australia and Scotland were

found. The increased breast cancer incidence was statistically significant amongst female burn survivors in Scotland. Statistically significant increases in cancer incidence for combined gender for both Western Australia and Scottish data were observed for cancers of the buccal cavity, liver and respiratory tract. Refer to Table 3 for gender and site-specific cancer SIRs. For each of these cancers, female burn survivors in both Western Australia and Scotland had higher incidence than males when compared with respective general population data. For the majority of site-specific cancers selected, female burn survivors in both Western Australia and Scotland had higher numbers of observed cancers than expected, with SIRs of similar magnitude. However, SIR results for Scottish data reached statistical significance, reflecting the larger population-base and respective higher number of cancer notifications.

Table 4 presents an SIR analyses of total (all-sites) cancer risk repeated on age-restricted sub-cohorts, classified to reflect reproductive age (<15 years; 15-49 years; and, ≥50 years) at admission for burn injury. For males in both WA and Scotland, no statistically significant differences were found across the three age groups. For female burn survivors in Scotland, the observed numbers of cancers total (all-sites) exceeded that expected for each of the three age groups, with statistically significant results observed for the age groups 15-49, and 50 years and older. In the Western Australia data, excess cancers were observed for those younger than 15 years and for those 50 years and older, with statistically significance reached for the older age group; for females 15-49 years at burn injury, no difference in observed and expected total (all-sites) cancer was found.

4. Discussion

4.1 Methodological Issues

When population-level administrative data are used, data linkage minimises issues of selection and reporting bias, as well as loss to follow-up. Data quality of the Western Australia and Scottish Cancer Registers[17 19 20] and hospital morbidity datasets[24 25] are assessed continually for both accuracy and quality. Data of all index burn hospitalisations in Western Australia and Scotland from 1983 to 2008 were analysed with follow-up time from discharge date, allowing for exclusion of prevalent cancers to support temporality of burn exposure and incident cancer. Cancer diagnoses from cancer registries in Western Australia and Scotland were independent of the record of burn injury in the respective hospital morbidity datasets. Minor burns treated in emergency departments were not included in the study. The burn patient cohorts under study are part of the respective reference populations, and as such, this may have a small diluting effect in the standardised incidence ratios. Using parallel datasets from Western Australia and Scotland, of populations 2.2 million and 5.5

million, respectively, allowed examination of the consistency of results and trends across the populations.

The Western Australia hospital morbidity data records the principal diagnosis and up to 20 additional diagnosis fields, whereas, the Scottish morbidity data includes the principal diagnosis and 5 additional diagnosis fields. Consequent to the reduced number of additional diagnosis fields in the Scottish data, there was an absence of recorded supplementary total body surface area burned (TBSA%) data (ICD9 946; ICD10 T31) and greater use of ICD codes for burns to multiple regions of the body (ICD9 946; ICD10 T29) rather individual anatomic burn sites, reflected in Table 1 This limited both SIR analyses restricted to more severe burns of TBSA 20% or greater and incident rate ratio analysis to examine the effects of severity of burn injury (burn depth and TBSA%). Previous SIR analyses of total (all-sites) cancer risk in Western Australia showed similar trends in results for all burn patients (severe and non-severe).[11]

Although this study had a follow-up period of up to 26 years from the date of separation for admission for burn injury, the follow up period for many patients may not have provided sufficient observation time to enable identification of all potential malignancies, given the long latency period for many cancers. 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.

4.2 Findings

Analysis of ISD Scotland data confirmed the results of our previous study: a statistically significant increase in total (all-sites) cancer risk for female burn survivors with males experiencing no difference. The site specific analyses clearly showed statistically significant increases in the number of observed cancers for combined gender in both the Western Australia and Scottish data for the buccal cavity, larynx, liver, respiratory tract and oesophagus. 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. Sub group analyses, defined crudely by reproductive age, did not elucidate any clear patterns of the influence of oestrogen on cancer incidence, with female burn survivors in Scotland showing increased risk across all age groups. For female burn survivors in WA, an increased risk for total (all-sites) cancer was found for those younger than 15 years (pre-pubescent) and 50 years and older (post-menopausal). The lack of gender difference for the sub-cohort of burn patients in Scotland 1983-88 for total (all-sites) cancer risk is difficult to explain. Possible reasons may include that females: sustained less severe (<20% TBSA) burns during

this period; had less comorbidities; and / or had better lifestyle factors than females hospitalised for burns during the remainder of the study period.

The site-specific analyses showed that whilst statistically significant increases in female genital cancers were found, there was also a general trend amongst female burn patients for excesses across a number of site-specific cancers examined, although these excesses did not always reach statistical significance, possibly due to small numbers. 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, respiratory tract and oesophagus. 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. Interestingly, the results of no increase in skin melanoma risk after burn injury in this study support findings of other population-based studies.[12 13]

An alternative explanation for this increased incidence in cancer post-burn may lie in the significant impact a burn injury has on the immune system, or the sustained oxidative and metabolic stress that are integral to the injury response. While burn injury predominantly affects the skin, it has been shown to cause significant depression of both humoral and cell-mediated immunity (CMI), [7 26 27] sustained elevated levels of oxidative stress [28 29] and prolonged elevation of hyper-metabolic and stress hormone levels. [30 31] These effects have been demonstrated to persist for up to 3 years post-injury and can lead to long-term systemic impacts on other organs of the body.[1 2 32-36] Severe burn injury has been demonstrated to induce endoplasmic reticulum (ER) stress, in particular, in the liver.[37] ER stress is a stress-response that initially facilitates cell survival but can switch to a pro-apoptotic signal with prolonged stress.[37 38] However, it has also been shown that the ER stress response can become maladaptive, facilitating adaptation to hypoxic environments and promoting tumour growth. [38 39] It is plausible that the array of host responses combined with the impact of the injury, therefore, creates an environment of increased susceptibility to cancer.

In addition to the observed increase in some of the selected site-specific cancers, the data support evidence for a gender dimorphism (a systematic difference between individuals of different sex in the same species) in the response to burn injury. After burn injury, gender has been shown to be an important factor with respect to poorer outcomes for mortality[40-43] and improved prognosis for multiple organ dysfunction syndrome,[44] and sepsis,[45] for females compared to males. Similar gender-based differences have also been reported in animal studies of burn injury.[46-50]

The impact of gender with respect to outcomes after burn injury is largely thought to stem from well-established differences in immune biology. There is a substantial volume of published literature to support a gender dimorphism in the immune response[51-54] and sepsis[45] following injury that have impacts on health and mortality.[41 42] The majority of these studies support a more efficient and effective innate and adaptive immune responses in females, leading to more rapid clearance of infectious organisms driven by tissue resident cell populations.[55] This 'advantageous' response reduces the risk of infection in females compared to males [55 56] but leads to elevated risk of autoimmune disease.[57] This dimorphism was thought to arise largely due to the impact of oestrogen on immune function.[58 59] However, recent papers have demonstrated these differences are not completely ablated by ovariectomy (in animal models) [55] and others have shown that oestrogen can be deleterious to the immune response.[60] This suggests a role of other mediators, most likely expressed on the X-chromosome, in the maintenance of the differential immune response. [61 62] The evidence for gender differences in the immune response, both to thermal and other trauma, and its impact on outcomes is substantial. Here, the evidence of increased cancer incidence in selected types of cancer after burn injury, with a greater effect in females, suggests the systemic immune response to burn injury may be a mediator of cancer susceptibility.

5. Conclusion

Using population-based linked data of all burn patients in both Western Australia and Scotland, consistent trends were found in excesses in cancer notifications for a range of selected site specific cancers with an elevated and more widespread increase in female burn patients. Overall, however, the increased cancer risk affected small proportions of the respective burn patient cohorts. More research is required to understand the underlying mechanism(s) that may link burn injury to an increased risk of some cancers and why this is elevated in females, which may in turn enable identification of possible sites for intervention.

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Table 1 Characteristics of burn injury patients included in analyses with no record of cancer prior to separation date of index burn admission, 1983-2008, by country.

Characteristics	Western Australia N (%)	Scotland N (%)
Total number burn admissions*	22,705	37,506
Gender: Male	15,481 (68.2)	23,896 (63.7)
Age at index admission (Years)		
<15	8,135 (35.8)	14,579 (38.9)
15-24	4,364 (19.2)	4,495 (12.0)
25-49	7,147 (31.5)	9,554 (25.5)
50-64	1,736 (7.7)	4,080 (10.9)
65+	1,323 (5.8)	4,798 (12.8)
Site of burn**		
Head and neck	6,784 (15.4)	7,592 (16.1)
Trunk	7,553 (17.2)	8,815 (21.0)
Hand, wrist, upper limb	15,801 (35.9)	6,984 (14.8)
Hip , lower limb	11,798 (26.8)	9,531 (3.4)
Eye	379 (0.9)	1,087 (2.3)
Respiratory tract	212 (0.5)	163 (0.3)
Other internal organs	124 (0.3)	165 (0.3)
Multiple regions	656 (1.5)	3,677 (7.8)
Unspecified region	694 (1.6)	858 (1.8)
Burn site depth**		
Erythema	8,929 (20.9)	4,815 (11.5)
Partial thickness	18,449 (41.9)	6,302 (15.0)
Full thickness	7,095 (16.1)	4,924 (11.7)
Unspecified	9,528 (21.7)	25,869 (61.7)
Calendar period of admission		
1983-1988	5,431 (23.9)	11,507 (30.7)
1989-1993	4,200 (18.5)	7,876 (21.0)
1994-1998	4,755 (20.9)	7,130 (19.0)
1999-2003	4,265 (18.9)	5,980 (15.9)
2004-2008	4,054 (17.9)	5,013 (13.4)
Any co-morbidity at index burn		
Yes	2,798 (12.3)	7,679 (20.5)

***** No previous record of cancer

** Patients may have multiple burn sites per anatomical region per depth

Table 2 **Standardised incidence ratios and 95% confidence intervals and observed and expected numbers for total (all-sites) cancer in persons hospitalised for burn injury in Western Australia and Scotland, during the periods 1983-2008 and 1983-1988.**

	Western Australia††			Scotland		
	Combined SIR 95%CI* O:E**	Male† SIR 95%CI O:E	Female† SIR 95%CI O:E	Combined SIR 95%CI O:E	Male† SIR 95%CI O:E	Female† SIR 95%CI O:E
Total cohort 1983-2008	0.97 (0.9 to 1.0) 759: 785.5	0.9 (0.8 to 1.0) 515: 569.5	1.1 (1.0 to 1.3) 244: 216.0	1.09 (1.05 to 1.10) 2260: 2075.9	0.96 (0.90 to 1.0) 1249: 1303.2	1.3 (1.2 to 1.4) 1011: 772.6
Sub-cohort 1983-1988	1.0 (0.9 to 1.1) 294:294.9	0.9 (0.8 to 1.0) 190:220.3	1.4 (1.1 to 1.7) 104: 74.6	0.9 (0.8 to 0.9) 838: 953.4	0.8 (0.7 to 0.9) 491: 614.3	1.0 (0.9 to 1.2) 347: 339.1

*SIR (95%CI): Standardised Incidence Ratio (95% confidence interval) adjusted for age and gender

** O: E: Observed: Expected

†SIR (95%CI): Standardised Incidence Ratio (95% confidence interval) adjusted for age

†† Western Australian comparison data Duke et al. Burns 2011; 38:340-47.

Table 3 **Standardised incidence ratios and 95% confidence intervals and observed and expected numbers for selected types of cancer in persons hospitalised for burns Western Australia and Scotland, 1983-2008.**

Cancer Site ICD-10‡	Western Australia			Scotland		
	Combined SIR 95%CI* O:E**	Male SIR 95%CI† O:E	Female SIR 95%CI† O:E	Combined SIR 95%CI* O:E	Male SIR 95%CI† O:E	Female SIR 95%CI† O:E
Buccal cavity C00 to C14	1.4 (1.03 to 1.9) 45: 32.6	1.4 (1.0 to 1.9) 38:28.1	1.5 (0.7 to 3.2) 7: 4.6	2.6 (2.2 to 3.1) 117: 45.0	2.4 (1.9 to 2.9) 83: 35.1	3.4 (2.5 to 4.8) 34:9.9
Oesophagus C15	1.4 (0.9 to 2.4) 15:10.50	1.5 (0.9 to 2.6) 13: 8.7	1.1 (0.3 to 4.5) 2: 1.8	1.6 (1.3 to 2.0) 82: 51.4	1.5 (1.1 to 1.9) 53:36.1	1.9 (1.3 to 2.7) 29:15.3
Stomach C16	0.6 (0.3 to 1.1) 10:17.0	0.5 (0.2 to 1.1) 7: 13.4	0.8 (0.3 to 2.6) 3: 3.6	1.2 (0.9 to 1.5) 73:63.2	1.1 (0.8 to 1.5) 1.2 5: 2.8	1.3 (0.9 to 1.9) 25:19.5
Colorectal C18 to C20	0.7 (0.6 to 0.9) 69: 96.3	0.7 (0.5 to 0.9) 45: 69.1	0.9 (0.6 to 1.3) 24: 27.2	1.2 (1.1 to 1.4) 268:221.8	1.0 (0.9 to 1.2) 142:140.5	1.4 (1.3 to 1.8) 125: 81.3
Liver C22	2.6 (1.6 to 4.0) 19: 7.4	2.2 (1.3 to 3.7) 14: 6.3	4.7 (2.0 to 11.4) 5: 1.1	1.7 (1.2 to 2.5) 31:18.0	1.5 (1.1 to 2.5) 22: 13.3	1.9 (1.0 to 3.7) 9: 4.7
Pancreas C25	0.7 (0.4 to 1.3) 11: 15.3	0.9 (0.5 to 1.7) 9: 10.4	0.4 (0.1 to 1.6) 2: 5.0	1.1 (0.8 to 1.5) 44:39.6	1.5 (1.03 to 2.0) 34: 23.4	0.6 (0.3 to 1.2) 10: 16.2
Larynx C32	5.7 (0.9 to 3.3) 10: 5.7	1.5 (0.7 to 3.0) 8: 5.4	6.0 (1.5 to 24.1) 2: 0.3	1.9 (1.4 to 2.5) 39: 21.1	1.5 (1.1 to 2.2) 28: 18.5	4.2(2.3 to 7.7) 11:2.6
Respiratory tract C33 to C34	1.4 (1.1 to 1.6) 101: 74.8	1.3 (1.1 to 1.7) 79:59.3	1.4 (0.9 to 2.2) 22:15.4	1.5 (1.4 to 1.7) 448:298.1	1.3 (1.2 to 1.5) 279:210.4	1.9 (1.7 to 2.2) 169:87.7
Skin – malignant melanoma C43	0.7 (0.6 to 0.9) 72: 102.0	0.7 (0.6 to 1.0) 57: 77.9	0.6 (0.4 to 1.0) 15: 24.1	0.8 (0.6 to 1.1) 38:48.5	0.7 (0.4 to 1.1) 19:28.4	1.0 (0.4 to 1.1) 19:20.0
Breast C50	1.0 (0.8 to 1.3) 65: 62.4	1.3 (0.2 to 9.2) 1: 0.8	1.0 (0.8 to 1.3) 64:61.7	1.7 (1.5 to 1.9) 271:161.4	0.7 (0.1 to 4.8) 1:1.5	1.6 (1.5 to 1.9) 270: 160.0
Female genital tract (combined) C51 to C57			1.4 (1.0 to 2.0) 31:26.7			1.7 (1.4 to 2.0) 114: 67.2
Male genital tract (combined) C60 to C63		0.9 (0.8 to 1.1) 141: 150.7			1.1 (1.0 to 1.3) 210: 192.6	
Prostate C61		0.8 (0.6 to 0.9) 102: 135.9			1.1 (0.9 to 1.2) 177: 165.5	
Kidney, Bladder, UT C64 to C68	0.5 (0.3 to 0.7) 17: 37.9	0.4 (0.2 to 0.7) 12: 30.9	0.7 (0.3 to 1.7) 5: 7.0	1.2 (1.0 to 1.4) 135: 110.9	1.2 (1.0 to 1.4) 96: 82.8	1.4 (1.0 to 1.9) 39: 28.0
Brain C71	1.2 (0.7 to 1.9) 16: 13.9	1.0 (0.5 to 1.8) 10: 10.5	1.7 (0.8 to 3.9) 6: 3.5	1.5 (1.1 to 2.0) 39:27.0	1.4 (0.9 to 2.0) 26:19.2	1.7 (1.0 to 2.9) 13:7.8
Lymphomas to all	1.0 (0.7 to 1.4) 36: 35.5	0.8 (0.5 to 1.2) 20: 26.0	1.7 (1.03 to 2.7) 16:9.6	1.1 (0.9 to 1.4) 75:68.0	1.1 (0.8 to 1.4) 48:45.0	1.2 (0.8 to 1.7) 27:23.0
Myeloma/ plasma	1.3 (0.7 to 2.3) 11: 8.6	1.3 (0.7 to 2.6) 8:6.1	1.2 (0.4 to 3.7) 3: 2.49	1.1 (0.7 to 1.6) 22:21.0	1.0 (0.6 to 1.7) 13:13.2	1.2 (0.6 to 2.2) 9: 7.8
Leukaemia's to all	1.1 (0.8 to 1.7) 26: 22.9	1.1 (0.7 to 1.8) 19: 17.0	1.2 (0.6 to 2.5) 7: 6.0	1.3 (1.01 to 1.7) 63:48.6	1.0 (0.73 to 1.4) 34:33.1	1.8 (1.3 to 2.7) 29: 15.5

*SIR (95%CI): Standardised Incidence Ratio adjusted for age and gender (95% confidence interval)
** O: E: Observed: Expected
†SIR (95%CI): Standardised Incidence Ratio adjusted for age (95% confidence interval)
‡ ICD-10: International Classification of Disease s (ICD) version 10

Table 4 **Standardised incidence ratios and 95% confidence intervals and observed and expected numbers for total (all-sites) cancer incidence, for persons hospitalised for burns Western Australia and Scotland, by age group, 1983 to 1988.**

Age at first burn years	SIR (95%CI) (observed: expected)		
	combined gender*	Male†	Female†
<15			
WA	1.17 (0.82 to 1.68) (30:25)	1.19 (0.77 to 1.84) (20:16)	1.15 (0.62 to 2.14) (10:8.6)
Scotland	0.94 (0.69 to 1.28) (41:43.69)	0.72 (0.47 to 1.12) (20:27.77)	1.32 (0.86 to 2.02) (21:15.92)
15 to 49			
WA	0.87 (0.77 to 0.99) (273: 313)	0.87 (0.75 to 1.00) (197: 226)	0.86 (0.69 to 1.1) (76: 87)
Scotland	1.21 (1.12 to 1.31) (617: 509.16)	1.04 (0.94 to 1.16) (345: 331.68)	1.53 (1.36 to 1.73) (272: 177.48)
≥ 50			
WA	1.02 (0.93 to 1.12) (456: 446)	0.91 (0.82 to 1.02) (298: 326)	1.32 (1.13 to 1.54) (158: 120)
Scotland	1.05 (1.00 to 1.11) (1602: 1523)	0.94 (0.88 to 1.00) (884: 943.75)	1.23 (1.15 to 1.33) (718:579.25)

*SIR (95%CI): Standardised Incidence Ratio adjusted for age and gender (95% confidence interval)
†SIR (95%CI): Standardised Incidence Ratio adjusted for age (95% confidence interval)

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

Page numbers in this checklist – relate to page numbers of the final pdf version of uploaded manuscript file

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract *Population-based retrospective cohort record linkage study – in abstract* *Title: Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia. (Pages 1, 5)*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found *Abstract - Page 5*
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported *While burns predominantly affect the skin, burns are associated with significant systemic effects, depressed immune functioning and prolonged periods of systemic catabolism and hypermetabolism, that may increase a person's risk of cancer. (Page 6)*
Objectives	3	State specific objectives, including any prespecified hypotheses *Done: Firstly, confirm the increased risk of 'all-cause' cancer observed in the preliminary Western Australian study of female burn survivors using the Scottish data; and, secondly, examine site-specific cancer risk amongst survivors of burn injury (Page 6)*
Methods		
Study design	4	Present key elements of study design early in the paper *Clearly presented in Introduction and Methods sections (Pages 5- 8)*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection *Clearly presented in Methods section (Pages 6 - 8)*
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Population-based study of linked health administrative datasets: whole of population data are used. (Pages 6-8)* *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable *Burn exposure (Page 7) and cancer outcomes (Page 8) clearly defined.*

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 *Data sources clearly defined in Methods: Information Service Division (ISD) Scotland Western Australia Data Linkage System (Page 7) and reference population-based age and gender cancer incidence rates (Page 7-8)*
Bias	9	Describe any efforts to address potential sources of bias *Population-level linked administrative data minimises issues of selection and reporting bias, and loss to follow-up.*
Study size	10	Explain how the study size was arrived at *Whole of population study undertaken (Scotland and Western Australia) stated in Methods (Page 6-8).*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why *Groupings described / defined in Methods (Page 8)*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding *All analyses clearly presented in Methods for each cohort of burn patients hospitalised in both Scotland and Western Australia: 1) from 1983 to 2008; 2) sub-group 1983-1988; and 3) by grouped age at admission (<15; ≥15 and <50; ≥ 50 years) (Page 8)* *Whole of population examination of observed versus expected cancer cases using Standardised Incidence Ratios, adjusting for 5-year age group and gender, and calendar period from 1983-2008.*
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Whole of population based study using linked data (Page 6-8)* *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed *Numbers of patient records included in study clearly stated in Results (Pages 8-9)*
		(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 *Data presented in Table 1(Page 15)*
		(b) Indicate number of participants with missing data for each variable of interest *N/A*
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) *Average follow up time presented for each patient cohort in Results (Page9)*

Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time *Presented in Results (Page 9) and Table 2 (Page 16), Table 3 (Page 17) and Table 4 (Page 18)*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included *Standardised Incidence Ratio (SIR) and 95% Confidence Intervals clearly presented in text and Tables with appropriate labelling of variables standardised for (e.g. 5-year age groups, gender). Presented in Results (Page 9) and Table 2 (Page 16), Table 3 (Page 17) and Table 4 (Page 18)*
		(*b*) Report category boundaries when continuous variables were categorized Age boundaries clearly reported
		(*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 *All results of sub-group analyses presented. (Tables 2-4 – Pages 16-18)*
Discussion		
Key results	18	Summarise key results with reference to study objectives *Page 12*
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 *Strengths and limitations of the study have been presented in the Discussion 4.2 Methodological Issues (Pages 10-11).* *The burn patient cohorts under study are part of the respective reference populations, and as such, this may have a diluting effect in the standardised incidence ratios. The results presented are for the total burn patient cohorts including both severe and non-severe burns; the results are therefore, conservative.*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. *The results are conservative and results have been interpreted in light of current literature on the impacts of burn injury on the immune system and other systemic effects. (Pages 10 – 13)*
Generalisability	21	Discuss the generalisability (external validity) of the study results *Expected that the sex dimorphic effects on cancer post-burn are generalisable.* *The evidence of increased cancer incidence after burn injury, with a greater effect in females, suggests the systemic immune response to burn injury may be a mediator of cancer susceptibility. (Page 13)*
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 *Funding sources disclosed (Pages 3, 14)*

*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.