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INVESTIGATIVE REPORT

Burn Injuries and Skin Cancer: A Population-based Cohort Study

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Development of malignant tumours in chronic burn wounds or scars is extremely rare, but a frequently reported complication. Most of these tumours are squamous cell carcinoma and, more occasionally, basal cell carcinoma and malignant melanoma are reported. The interval between the initial burn and the diagnosis of the tumour is usually long; 20–30 years or more. A large number of case reports and small series of selected patients have been published. Only one epidemiological study has been performed recently, but it could not confirm any increased risk. We conducted a historical cohort study to assess the risk of cancer in Swedish patients with burn injuries. Using the national Inpatient Registry we identified 37,095 patients who had been hospitalized for burn injuries. This cohort was linked with the Swedish Cancer Registry for a virtually complete follow-up with regard to cancer. The mean follow-up time was 16.4 years (range >0–39). The risk of developing any form of cancer was slightly increased: standardized incidence ratio (SIR) 1.11 (95% confidence interval (CI) 1.06–1.16) based on 2227 patients with cancer. However, squamous cell carcinoma: SIR 0.88 (95% CI 0.70–1.09) and malignant melanoma: SIR 0.88 (95% CI 0.68–1.12) did not occur more often than expected. Also, in a subgroup of 12,783 patients who were followed for 20–39 years, no increased risk of skin cancer could be detected. This study does not support any casual association between burn injuries and a later risk of skin cancer. ***Key words: skin; cancer; burns; epidemiology; cohort.***

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Burn scar carcinomas, are uncommon tumours that have been reported to arise from an antecedent burn. They are also called Marjolin's ulcers, after Jean-Nicolas Marjolin who first described the development of skin carcinoma in old burn scars in 1828 (1). The association between malignancies and burn scars, chronic ulcers, and wounds has subsequently been established ever since the turn of the 19th century. Voluminous reports on burn scar neoplasms have continued to appear, usually in the form of case reports. Recently an exhaustive review summarized 146 articles between 1923 and 2004, including 1078 cases (2). Of these, 412 case reports could be analysed in detail. Seventy-one percent of the tumours were squamous cell carcinoma (SCC), 12% were basal cell carcinoma (BCC), 6% were malignant melanoma (MM), 5% were sarcoma and 6% were other neoplasms. Furthermore, the mean latency interval between the burn and malignancy was 31 years (2).

While the factors governing malignant transformation, subsequent recurrence and metastatic spread are not completely understood, several hypotheses have been offered. These include a role of inflammation and irritation in precipitating a cancer, hereditary factors, tissue toxins and co-carcinogens released by the burn, poor vascularization and no lymphatic channels in scars resulting in impaired immunological defence (2–5).

Recently, the first population-based epidemiological study was published, comprising 16,903 Danish patients admitted to a hospital for burns and followed-up in the national cancer registry for up to 25 years (6). In contrast to what has been reported for a long time, no increased risk of any type of skin cancer was found. This finding is surprising in the light of the clinical descriptions of a tendency of malignant degeneration of burn scars (2). We aimed to estimate the risk for skin cancer in a population-based cohort of 37,095 Swedish patients hospitalized for burn injuries. The patients were followed-up for 39 years.

PATIENTS AND METHODS

This study was approved by the Ethics Committee at the Karolinska Institute, Stockholm, Sweden.

Study population

Since 1964, the Swedish National Board of Health and Welfare has compiled data on individual hospital discharges in the national Inpatient Registry. For each discharge, date of admission, date of discharge, main and up to 5 contributory discharge diagnoses (coded according to ICD 7: 1964–1968, ICD 8: 1968–1986 and ICD 9 thereafter), surgical procedures, department and hospital are recorded, together with the individual's national registration number. This registry was not nationwide until 1987. In 1969, the register covered 60% of the Swedish population, in 1978, 75% and by the end of 1983, 85%. The inpatient cohort is presented in Table I. Eligible for the cohort were all Swedish residents recorded in the Inpatient Registry with a discharge diagnosis of a thermal or chemical burn injury: ICD-7 and ICD-8 codes: 940–948 and ICD-9 codes: 940–949. By this method we could identify 37,095 patients during the years 1964–96.

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Table I. *Descriptive characteristics of the cohort of patients hospitalized for burn injuries*

Variables		*n*	%
Total		37 095	100
Sex			
	Males	26 397	71.2
	Females	10 698	28.8
Age (years) at hospital admission			
	0–9	10 619	28.6
	10–19	4 474	12.1
	20–29	5 597	15.1
	30–39	4 386	11.8
	40–49	3 721	10.0
	50–59	3 191	8.6
	60–69	2 036	5.5
	70–79	1 863	5.0
	≥80	1 208	3.3
Years of follow-up			
	>0–19	24 312	66
	≥20	12 783	34
Calendar year			
	1964–69	1 832	4.9
	1970–79	10 077	27.2
	1980–89	14 902	40.2
	1990–96	10 284	27.7

Swedish Cancer Registry and Cause-of-death Registry

Information from the Swedish Cancer Registry from 1964 through 2003 was correlated with the cohort of the 37,095 patients hospitalized for burn injuries, in order to identify those with cancer.

Nationwide information on the incidence of cancer in Sweden is available for all the years since 1958, when compulsory registration began (7). The cancer registry collects information on diagnosed cancers from clinicians and pathologists. If a person has more than one cancer, each one is registered separately. The completeness of registration is close to 100% for all cancers. At the time of the study BCC was not registered. Thus, the registered non-melanoma skin cancers are mainly SCC (92.1% SCC, 6.7% SCC/BCC type mixed, and 1.2% other primary malignant tumours of the skin) (8).

The Cause-of-death Registry includes information on all deceased persons listed in the parish registers, whether they died in Sweden or abroad. The underlying cause of death is generally determined from data on medical death certificates, which were designed in accordance with the internationally established norm.

The individually unique 10-digit national registration number ascribed to every Swedish citizen since January 1, 1947, ensures accurate identification and follow-up of each patient.

Analysis and statistics

Expected numbers of cancers were calculated by multiplying the age, gender and calendar-year-specific risk time by the corresponding cancer incidence rates of the general Swedish population. The standardized incidence ratio (SIR); the ratio of the observed to the expected number of incident cancers, was used to estimate the relative risk of tumours for different categories. We only counted first cancers after the discharge, and disregarded multiple cancers and cancers detected incidentally at autopsy, both in the cohort and in the expected rates. Confidence intervals (CI) of SIR were calculated assuming that the observed number of events followed a Poisson distribution (9). Follow-up started after the date of discharge and continued until the date of immigration or death, if applicable, or 31 December 2003, whichever occurred first.

RESULTS

Table I presents descriptive characteristics of the inpatient cohort. Mean age at discharge was 29.3 years (range 0–106). The cohort was followed for a total of 607,531 person-years and the mean follow-up time was 16.4 years (range >0–39 years). A subgroup of 12,783 patients was followed for a total of 80,897 person-years, with a follow-up time of 20 years or more.

Table II provides summary information on the cancer analysis. The overall number of observed cancer cases was slightly elevated: SIR 1.11 (95% CI 1.06–1.16). The risk of lung cancer was also increased with a SIR of 1.39 (95% CI 1.21–1.59) based on 216 lung cancer cases.

The risk for SCC and MM was not elevated: SIR 0.88 (95% CI 0.70–1.09) and 0.88 (95% confidence interval (CI) 0.68–1.12), respectively. Different follow-up periods and different age group at burn injury were analysed separately for the skin cancers (Table I), but, again, no increased or decreased risks could be detected.

DISCUSSION

Malignant degeneration of chronic burn ulcers or scars has been described extensively in the literature, (2) but this phenomenon has never been quantified in an epidemiological study until recently in Denmark (6). In contrast to what could be expected on the base of the large number of case reports, the Danish study of 16,903 patients who had been admitted to a hospital with a thermal or a chemical burn showed no increased risk of skin cancer when followed-up in the national cancer registry. Instead, a slightly statistical significant reduced risk was observed for all types of skin cancer: SIR 0.7 (95% CI 0.6–0.9). This reduced risk was mainly the result of a reduced risk of BCC and MM. The observed number of SCC was closed to expected. There was no consistent increase in risk for skin cancer in subgroups of patients with the most severe burns or with the longest periods of follow-up. The mean follow-up period was 15.6 years (range >0–25 years) (6).

Our study is similar to the Danish study with regard to an inpatient historical cohort of burn injury patients and

Table II. *Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) of cancer amongst 37,095 patients hospitalized for burn injuries*

Type of cancer	Observed no.	SIR	95% CI
All types	2 227	1.11	1.06–1.16
Squamous cell carcinoma			
Total	86	0.88	0.70–1.09
Males	66	0.86	0.67–1.09
Females	20	0.96	0.59–1.48
Malignant melanoma			
Total	68	0.88	0.68–1.12
Males	44	0.77	0.56–1.03
Females	24	1.20	0.77–1.79

the linking of this cohort to a national cancer registry by means of a unique national registration number. However, our study is more than two times as large and the follow-up period is longer, up to 39 years. Nevertheless, also in our study no increased or decreased risk of skin cancer could be detected. The slightly decreased risk for all types of skin cancer, taken together in the Danish study, was explained by a reduced risk of BCC and MM. This might have been caused by a reduced exposure to the sun of the patients after the burn injury. In our study BCC was not included, which supports this explanation.

Now appears a controversy; on one side there is a large number of case reports (2) reporting an association between burn injuries and skin cancer, and on the other side there are two large population-based epidemiological studies, showing no such association. What answer should we give to the patients when they ask: am I more susceptible to skin cancer because of my burn injury? We believe that the Danish (6) and our own epidemiological study have well-defined inpatient cohorts and the number of observed and expected cancers is very reliable owing to the accurate population statistics used in Scandinavia. However, the populations of Denmark and Sweden share a number of factors that are important in skin cancer carcinogenesis; i.e. climate, sun exposure, sun habits, hereditary factors, etc. and it would therefore be relevant to determine if our result could be confirmed in other parts of the world. Also, is the power of the studies sufficient to detect an increased risk? Probably, because almost all burn patients in hospital care for a long period of time in two countries were included. Furthermore, is the follow-up period long enough? The mean latency interval between burn and skin cancer has been reported to be 31 years (2) when summarizing the case reports. Our subcohort of 12,783 patients followed for 20–39 years should be able to detect any increased risk, or at least a tendency.

How can we explain the large number of case reports with an association of burn injuries and skin cancer if such an association does not exist? One can propose a number of possible explanations. Skin cancer is common and SCC is a disorder of the elderly, and it is not surprising that some patients develop skin cancer in a scar or ulcer by chance (publication bias). Burn injuries are also common and affect a certain area of the skin and the larger the area, the greater is the probability for a skin cancer, arising at a normal rate, to appear in that area by chance. However, it is well-known that SCC is a complication of chronic venous leg ulcers, although the absolute risk is very small (10). Seen in all locations, SCC was reported to be most frequent on the lower extremities: 41% of 395 cases of burn patients from the 146 case reports (2), the same area as leg ulcers. Also, one can speculate that different treatment methods for chronic wounds, such as ointments and dressings, especially in the past, could have introduced potential carcinogens. Different co-carcinogens apart from sun-exposure might operate in certain geographical areas, for example arsenic-containing ground-water may be of importance in some cases.

It should also be pointed out that only a minority of patients in the cohort might be considered a relevant risk group. This conclusion is based on the fact that modern Western burn care does not leave scars and most of the burns are superficial and heal spontaneously. This was not the case in the past, when deep wounds were left to heal spontaneously, causing scarring and chronic ulceration. Many of the case reports on burn scar neoplasm had chronic ulcerations and, in line with the increased risk of SCC in venous leg ulcers (10), this might also cause an increased risk in chronic burn ulceration. However, the risk estimates of skin cancer in this study with narrow confidence intervals indicate that such a subgroup at risk, if it exists, is very small.

In line with the Danish study (6), this epidemiological study does not support any casual association between burn injuries and a later risk of skin cancer.

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