Skin Cancer Arising in Scars: A Systematic Review

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BACKGROUND Despite numerous case reports, epidemiologic evidence regarding true rate of skin cancer in scars of any etiology is sparse.

METHODS Systematic literature review of all published epidemiologic studies on skin cancer in scar tissue from surgery, ulcers, or burns using citation databases and manual review.

RESULTS There were no epidemiologic data to quantify risk of skin cancer in surgical scars or chronic ulcers. Two eligible cohort studies were identified, from Denmark and Sweden, in which skin cancers in 16, 903 and 37,095 burn patients, respectively, were ascertained through cancer registry follow-up. Each reported standardized incidence ratios (SIRs) for skin cancer types on any site that were uniformly less than unity compared with the general population. Only the Danish cohort assessed skin cancers specifically on past burn injury sites and found a burn-site-specific SIR of 1.2 (95% confidence interval (CI) = 0.4–2.7) for squamous cell carcinoma (SCC), 0.7 (95% CI = 0.4–1.1) for basal cell carcinoma, and 0.3 (95% CI = 0.0–1.2) for melanoma.

CONCLUSIONS Available epidemiologic data suggest that burn patients are not at higher risk of skin cancers in general, although a modest excess of SCC in burn scars cannot be excluded, nor can excess risk with longer follow-up. Risk of skin cancer in scars other than burn scars has not been investigated epidemiologically.

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Skin cancers are the most common malignancies worldwide, with approximately 2 to 3 million cases of keratinocytic skin cancers and 132,000 cases of melanoma occurring annually.[1] Ultraviolet radiation (UVR) exposure from the sun is the most important environmental cause of skin cancer, but cutaneous malignancies have also been reported to result from scars caused by vaccinations, burns, and other injuries.[2,3] In nonwhite ethnic groups, in whom UVR exposure plays a minor role in skin carcinogenesis, scar tissue is thought to have greater influence.[4] Although proportions in the general population can vary according to country, the most frequently occurring types of skin cancers are basal cell carcinoma (BCC) (~70%), followed by squamous cell carcinoma (SCC) (~15%) and cutaneous melanomas (~10%).[5] Of malignancies arising in scars, SCCs are reportedly the most common[6] and are typically found in chronic ulcerating scar tissue from burns known as Marjolin's ulcers.[7] Burn scar carcinomas appear to constitute the majority of all recorded scar neoplasms, including several types of burn scar carcinomas, such as Kangri, Kang, and Kairo cancers, associated with various cultural practices related to self-warming and heating methods.[7–9] One of the earliest case series estimated that 2% of SCC and 0.03% of BCC arise from burn scars,[7] but there appear to have been no population-based estimates of the incidence of skin cancer arising in scars.

Between 1923 and 2004, some 1,078 cases of skin cancer occurring in scar tissue were detailed in case reports;[6] 412 of these, mostly from Europe, Australia, and the United States, were captured in a major review conducted by Kowal-Vern and Criswell in

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2005.[6] They noted that 71% of the reported cases were SCC, 12% BCC, and 6% cutaneous melanoma. Whereas SCC was reported equally in men and women, BCC was more common in men and melanoma in women. The majority of the case reports concerned skin cancer arising in burns sustained during childhood, with BCC having the shortest latency period to malignancy in patients who were significantly older when burned than patients with other skin cancers.

The etiology of cancers occurring in scars is not fully understood, although the prevailing hypotheses include prolonged proliferation due to chronic inflammation and irritation of tissue, ongoing exposure of tissues to toxins and co-carcinogens after the injury, and poor vascularization of the scar tissue resulting in impaired immunological defence.[6,10] It has also been suggested that genetic factors might play a role, including for example, mutations in the p53[11] and *Fas*[12] genes in patients with burn scar carcinoma.

In view of the paradox of a large volume of case reports but an apparent dearth of epidemiologic evidence associating skin cancer with scars, we sought to review the existing literature systematically to quantify the risk of the major types of skin cancers arising in scar tissue of any etiology.

Materials and Methods

Eligibility Criteria

We included observational studies of all designs in the systematic review provided that they permitted quantitative assessment of the association between skin cancer (including BCC, SCC, and cutaneous melanoma) and scar tissue of any kind.

Literature Search

Eligible studies to August 2010 were identified by searching Medline 1950 (U.S. National Library of Medicine, Bethesda, MD; using PubMed software as the search interface) and Embase 1966 (Elsevier Science, Amsterdam, Holland; using the Embase search interface) and hand-searching the reference lists of the retrieved articles.

For computer searches, we used the following medical subject headings, terms, or text words (using both U.K. and U.S. spellings): "scar," "burn scar," "surgical scar," "burn scar carcinoma," "skin cancer," "malignancies" "incidence," "neoplasms," "basal cell carcinoma," "squamous cell carcinoma" and/or "Marjolin's ulcer." The same terms and phrases were used to cross-check Google Scholar for additional literature that the PubMed search may not have captured. Only studies of adult populations (≥ 18) were included. The search was limited to studies published in English. We read the abstracts of all identified studies to exclude those that were clearly not relevant. The full texts of the remaining articles were read to determine whether they met the study inclusion criteria. No attempt was made to identify unpublished literature.

Results

Although some 457 case studies were identified, only two population-based cohort studies emerged.[13,14] Both were cohort studies that considered only skin cancer in people with scarring as a result of burn injuries. No epidemiologic studies of skin cancer arising in other types of scars were found (Table 1).

The first analytical study examined the occurrence of skin cancer in a cohort study of 16,903 patients admitted to hospital in Denmark with thermal or chemical burn injuries between 1978 and 1993.[13] Two-thirds of the burn cohort were male, and 42% were younger than 20 when they sustained their injury. Thermal burns accounted for 80% of burns, the remaining being chemical burns, and the extremities were the most commonly affected sites. Mean follow-up time was 15.6 years (Table 1).

This cohort was followed up until 2002 for the occurrence of skin cancer using the Danish Cancer Registry and 94 BCCs, 18 SCCs, and 21 melanomas

TABLE 1. Burn Injuries and Skin Cancer: Comparison of Results from Two Cohorts

	Mellenkjaer et al., 2006[13]	*Lindelof et al., 2008*[14]
Study location	Denmark	Sweden
Cohort size	16,903	37,095
Ascertainment period, follow up	1978–1993, to 2002	1964–1996, to 2003
Person-years	263,578	607,531
Follow-up time, years, mean (range)	15.6 (0–25)	16.4 (0–39)
Age at burn	42% <20	Mean age 29.3
Male, %	71	67
#Skin cancers observed, *n*		
SCC	18	86
BCC	94	NA
Melanoma	21	68
SIR (95% CI)*		
SCC	0.9 (0.6–1.5)	0.88 (0.7–1.09)
BCC	0.7 (0.6–0.9)	NA
Melanoma	0.7 (0.4–1.1)	0.88 (0.68–1.12)
Burn-site-specific, SIR (95% CI)		
SCC	1.2 (0.4–2.7)	NA
BCC	0.7 (0.4–1.1)	NA
Melanoma	0.3 (0.0–1.2)	NA

*Not adjusted for covariates.
SCC, squamous cell carcinoma; BCC, basal cell carcinoma; NA, not applicable; SIR, standardized incidence ratio; CI, confidence interval.

were recorded in people with burn injuries. There was no difference in the rates of skin cancer (in general, on any site) compared with the general Danish population. Standardized incidence ratios (SIRs) were 0.9 (95% CI = 0.6–1.5) for SCC, 0.7 (95% CI = 0.6–0.9) for BCC, and 0.7 (95% CI = 0.4–1.1) for melanoma. Risks of different types of skin malignancy did not differ according to sex or age at injury. When analyses of skin cancers were restricted to the anatomic site of the previous burn injury, there was again no significant increase or decrease in skin cancer occurrence, the SIR was unchanged for BCC at 0.7 (95% CI = 0.4–1.1) but increased to 1.2 (95% CI = 0.4–2.7) for SCC and decreased for melanoma (0.3, 95% CI = 0.0–1.2). Further analysis according to severity of burn showed no significant difference in risk of any skin cancer type.

A more recently published cohort study conducted in Sweden identified 37,095 people with a hospital discharge diagnosis of thermal or chemical burn injury between 1964 and 1996 and followed them until 2003 (mean follow-up 16.4 years).[14] The mean age of patients discharged after burn injury was 29; 71% were male. Subsequent SCCs and melanomas were identified through linkage with the Swedish Cancer Registry (BCCs were not registered in the database at the time of study). There were 86 SCCs and 68 melanomas in those with burn injuries. SIRs for both types of skin cancer occurring in burn patients compared with the general Swedish population were less than 1.0, although nonsignificantly (SIR = 0.88, 95% CI = 0.70–1.09 for SCC; SIR = 0.88, 95% CI = 0.68–1.12 for melanoma). Subgroup analyses examining the risks within different age groups and for different follow-up times did not show any appreciable change in the risk estimates. No site-specific estimates of skin cancer incidence were made according to site of burn injury.

Discussion

The malignant potential of scar tissue has been extensively described on a case-by-case basis but has not been well researched at the population level.

Because our literature search found that only two analytic studies have reported quantitative data on this topic, pooling these studies as an assessment of overall risk for skin cancer in scars was of little value. Neither cohort study found any greater occurrence of skin cancer in general in those with burn injuries than in the general population; both found skin cancer occurrence rates overall to be lower than expected, although only the overall lower prevalence of BCC in the Danish burn cohort was significant. Only the Danish study reported the estimate of skin cancer incidence most appropriate to evaluating the question of scar tissue etiology, namely the estimates of skin cancer incidence in relation to anatomic site of past burn injury. There was no difference between incidence estimates for BCC in general and on burn sites, and there was a large deficit of melanoma on burn sites, consistent with a lack of increase in burn tissue. There was a reversal of the overall deficit of SCC in burns patients in general, to a small (20%) excess of incident SCC observed versus the rates expected on the corresponding sites in the Danish population at large.[13] Because the reversal in the direction of association was seen only for SCC, congruent with the bulk of case reports, and because scars are sites of chronic inflammation long known as an underlying factor in the development of malignant tumors,[15] it is unlikely that the observed SCC excess in burn scars in the Danish cohort, albeit modest, was due to chance, and a truly greater risk of SCC arising in burn scars cannot be excluded based on this evidence. The failure of the difference in SCC in burn scars to achieve significance was likely to reflect, to some degree, the young age of the cohort (almost half <20) at the time the burn was sustained. Also, although the duration of the Danish study was 25 years,[13] it is possible that this period was insufficient to cover the full latent period between exposure (time of burn injury) and disease (skin cancer development) in patients with burn scars, because clinical studies have reported mean latent periods ranging from 23 to 48 years.[16–19]

The two population-based studies identified in this systematic review were well-defined cohorts accrued through national hospital inpatient registration. Because cancer registration is mandatory and almost 100% for all cancers in Denmark and Sweden, including keratinocytic skin cancers, it is likely that case ascertainment was close to complete, particularly for skin cancers occurring at the site of a previous burn injury. It may be relevant to interpreting results that both studies were conducted in Scandinavian populations living at high latitudes where ambient UVR is low. It is unknown whether the incidence of skin cancer in burn scars might be greater in other populations where ambient UVR and skin cancer incidence are high. Furthermore, these results relate only to burn scars, and thus the potential carcinogenicity of scars of other etiology remains unquantified.

Although the malignant potential of burn scars is widely recognized,[17] the possible mechanisms are unclear. It has been suggested that, rather than increasing the rate at which skin cancer is initiated, burn scar tissue may increase tumor progression in cells in which cancer is already initiated,[13] although in temperate climates, this would apply only to adults. Clinical and epidemiologic evidence linking inflammation and skin cancer derives from studies of Marjolin's ulcer and other nonhealing wounds, including those associated with lupus erythematosus and osteomyelitis,[20] in which malignant transformation occurs in association with the prolonged cell proliferation of chronic inflammation. Multiple SCCs arising in areas of scarring from discoid lupus erythematosus have been reported[21] and SCC can arise in the sinus tracts of patients with chronic osteomyelitis[22] and in the acral skin of patients with epidermolysis bullosa.[23] Cytokines and growth factors play a major role in epidermal wound healing, of which interleukin (IL)-1-α, transforming growth factor beta (TGF-β)1, -β2, and -β3 are the most important to initiate keratinocyte proliferation and tissue repair.[24] Apart from normal wound healing, IL-6 and TGF-β1, -β2, and -β3 are also associated in vitro with tumorigenesis[25,26] and it is hypothesized that this is due to an imbalance of cytokines and growth factors.[24] TGF-β1 and -β2 are observed in

adult wound-healing processes with scarring,[24] and TGF-β3 is also associated with scar-free embryonic wound healing.[27] The main difference between adult and embryonic wound healing is the lack of scarring in the embryo, probably because of a lack of inflammation.[28] Investigations have been inconclusive regarding the possible role of cytokines in tumor progression related to wound healing, in contrast to tumor initiation.

To address some of the limitations of previously conducted studies and to investigate the malignant potential of scars of all etiologies at the population level, further epidemiologic studies are required. For example, a population-based prospective cohort study following patients with any scar—surgical, burn, or otherwise—over an extended period of time would be an ideal method of obtaining definitive, population-level estimates of the incidence of skin cancers arising in scar tissue. This type of study would be conducted most easily in countries with compulsory reporting of keratinocytic skin cancers (e.g., Sweden) but should also be conducted in populations with high sun exposure and skin cancer rates, such as Australia.

In conclusion, this review has identified a major gap in scientific knowledge regarding the incidence of scar neoplasms, despite a plenitude of case reports. Although burn patients are not at higher risk of skin cancers in general, a modest excess of SCC at sites of past burn injuries cannot be excluded nor can excess risk in longer study follow-up periods. Risk of skin cancer arising in scars other than burn scars has not been investigated epidemiologically. To answer these continuing questions and quantify the risk, well-designed epidemiologic studies in defined populations followed over sufficiently long time periods are required.

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