

# Leg Ulcers and Squamous Cell Carcinoma

## An Epidemiological Study and a Review of the Literature

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**There has been concern about the possible risk of malignification of venous leg ulcers. To investigate the incidence of squamous cell carcinoma in venous ulcers, data on 1,170 patients with venous leg ulcers and 511 patients with other types of non-traumatic ulcers were matched with corresponding data from the Swedish Cancer Registry to determine the incidence of squamous cell carcinoma in these patients. Mean follow-up time was 8.3 years. Seven cases of squamous cell cancer were observed, while the expected number was 10.56 (relative risk = 0.66; 95% confidence interval = 0.27 to 1.36). However, four of the observed cancers were located on the lower leg in venous ulcers, the expected number being 0.68 (relative risk = 5.89; 95% confidence interval = 1.60 to 15.08). This indicates that a certain alertness is necessary when treating this common disease. The literature on cancer in venous ulcers, where 152 cases of squamous cell carcinoma in venous ulcers are reported, is reviewed.**

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Ever since Marjolin's account of malignification of chronic ulcers in 1828 (1), the precarcinogenicity of venous leg ulcers has been suspected. There are numerous case reports of ulcers degenerating into squamous cell carcinomas (SCC) (2-20), and other studies of ulcer degeneration (3, 21, 22). Basal cell cancer (BCC) and other rarer forms of malignancy have also been associated with venous ulcers (4-6, 14, 16, 23-35).

Because venous ulcers are so common, some writers have postulated that the cancer occasionally found in venous ulcers is unconnected with the ulcer and that the statistical probability of getting cancer on the lower leg is the same whether the patient has a venous ulcer or not (3). Others maintain that there is indeed an increased risk of cancer in chronic leg ulcers and that a certain alertness is necessary, especially with ulcers that heal very slowly or not at all (4, 8).

Since the difficulties involved in following a large number of patients for many years may have biased the results of earlier studies, and given the excellent opportunity of an almost perfect follow-up with regard to cancer that the Swedish Cancer Registry provides (36), we decided to investigate the incidence of SCC in patients who have attended the Dermatology Clinic at the Karolinska Hospital in Stockholm for venous leg ulcers and to review the literature on cancer in venous leg ulcers. To form an idea of the possible carcinogenicity of various other types of ulcers, we included these as a pilot study.

## PATIENTS AND METHODS

### Patients

1,681 patients with non-traumatic ulcers of 6 types diagnosed according to the Herman system (37) were seen at the Department of Dermatology, Karolinska Hospital, Stockholm between 1969 and 1987. Records for 1974 and 1975 were unfortunately not available. The diagnosis, year of first diagnosis and each patient's unique identification number (used in all population statistics in Sweden) were extracted from the records. From these data the sex and age of each patient at the first visit to the clinic, and the follow-up period, were determined. The venous ulcer group consisted of 359 males with a mean age of 64.5 years and 811 females (mean age 70.8). The mean follow-up period for these 1,170 patients was 8.6 years. Three hundred and forty-nine patients had arterial ulcer, 58 necrobiosis lipoidica, 36 pyoderma gangrenosum and the remaining 68 an unspecified ulcer of the leg.

### The Swedish Cancer Registry

The Swedish Cancer Registry, Stockholm, has collected information on cancer incidence in Sweden since 1958, when compulsory registration of cancers began. Reported cancer diagnoses are classified according to the International Classification of Diseases, 7th Revision (ICD 7). Reports of diagnosed cancers come from clinicians and pathologists. Thus most cases are reported by two sources (38). Data on each patient were matched using his or her unique identification number. The Swedish Cancer Registry records 95-97% of cases of all types of cancer (36). Basal cell carcinomas are not registered. The last year on-line at the Swedish Cancer Registry at time of the study was 1988.

### Statistics

The expected number of malignancies was estimated on the basis of observation time and incidence data from the Swedish Cancer Registry. These calculations were made by the CANEST computer program (39). This program calculates for each individual the probability of developing cancer for each year during the study and sums up the individual probabilities. Thus it is possible to calculate with good accuracy the probable incidence of every malignancy registered with regard to sex and age. The ratio between observed and expected numbers of a certain malignancy, the relative risk (RR), was calculated. Confidence intervals (CI) were calculated assuming the RR to have a Poisson distribution (41). This method is described in detail elsewhere (39).

The proportion of lower-limb SCC was calculated from the incidence on lower limb and the incidence on total body surface in the years 1977 to 1987 (40). This proportion was 12.8% for the age group 70-74 in females.

A case control study based on hospital records was carried out on the patients with SCC on the lower limb.

## RESULTS

An SCC was registered in 7 patients during the follow-up period. All were females in the venous ulcer group. The expected number for the whole group of 1,681 patients was 10.56 (RR = 0.66; CI = 0.27-1.36).

Four of the carcinomas were located on the lower leg, all in

Table I. Observed and expected cases of squamous cell carcinoma (SCC) in 359 males and 811 females with venous leg ulcers

Site of SCC	Males			Females		
	Obs / Exp	RR	95% CI	Obs / Exp	RR	95% CI
All sites	0 / 2.70	0	0.00–1.37	7 / 5.53	1.27	0.51–2.61
Lower limb	0 / 0.19	0	0.00–19.42	4 / 0.49	8.21	2.24–21.02

a venous ulcer. Two were on the face and one in the sacral area.

The expected number of SCC on the leg was 0.68 for the venous ulcer group, making the RR 5.89 and the 95% CI 1.60–15.08. When analyzing the group of females with venous leg ulcers the expected number was 0.49 (RR = 8.21; CI 2.24–21.02). The results for the venous ulcer group are summarized in Table I.

## CASE REPORTS

### Case 1

A 70-year-old female with a 40-year history of leg ulcers arising after a deep venous thrombosis was admitted to the Dermatology Department at the Karolinska Hospital, Stockholm, in January 1987. There were ulcers on the lateral and medial malleolar areas bilaterally of which the ulcer in the medial left malleolar region had deteriorated greatly in the preceding year; its dimensions were 18 × 10 cm. A biopsy performed in the periphery of this ulcer showed an SCC.

### Case 2

A 77-year-old female who had had relapsing and remitting leg ulcers for nearly 40 years was admitted to the Department of Plastic Surgery at the Sabbatsberg Hospital, Stockholm, in January 1978. An earlier venography had shown the absence of valves in the veins of the legs. Ulcers were present on all four malleoli. A history of quick deterioration of the ulcer on the lateral left malleolus with necrosis of the fibular bone, and a vegetative character of the ulcer that was 13 × 7 cm, led to biopsies that showed a highly differentiated SCC.

### Case 3

A 75-year-old female with a 6-year history of leg ulcers on both legs was treated for her ulcers at the Department of Dermatology, St Görans Hospital, Stockholm. A recent deterioration of the ulcer on the lateral side of right malleolus, with the dimensions 10 × 5 cm, and the presence of an exophytic tumour in the ulcer led to suspicion of malignancy. A biopsy showed a not very highly differentiated SCC.

### Case 4

A 69-year-old female with a long history of varicosities and hypostatic eczema, especially on the right leg, was admitted to the Dermatology Department at the Karolinska Hospital, Stockholm, for treatment of a spreading hypostatic eczema and a leg ulcer on the lateral right leg that had started 2 years earlier. It had shown signs of good healing until 6 months earlier when it became much worse, measuring 8 × 5 cm. The clinical appearance, with a part of the ulcer edge raised, led to a biopsy that showed an SCC.

## DISCUSSION

In the available literature concerning cancer in venous leg ulcers, regrettably omitting Russian and Chinese reports, a total of 157 SCC, 13 BCC, 10 sarcomas and 2 tumours of other types arising in venous ulcers have been reported (Table II). Care was taken not to include the same case more than once when referring to cases indirectly (2, 4, 5, 7).

When making the diagnosis of cancer-complicating venous ulcer, a minimal duration of the venous ulcer is required, to exclude primary cancer as the cause of the ulcer. Tenopyr & Silverman set this period to 3 years (3). The authors of the articles reviewed here usually have 2–3 years as the minimal time before the diagnosis of cancer in venous leg ulcers.

Table II. A summary of the literature on cancer in venous leg ulcers

SCC = squamous cell carcinoma; BCC = basal cell carcinoma; MM = malignant melanoma.

Year	Source	Type of cancer	Own cases	Reported cases
1925	Knox (2)	SCC	2	59
1932	Tenopyr & Silverman (3)	SCC	4	–
1934	Rubinfeld (4)	SCC	–	3
		BCC	1	–
1939	Glasser (30)	sarcoma	1	–
1952	Black (5)	SCC	4	–
		sarcoma	2	3
1963	Cruikshank et al. (6)	SCC	23	–
		sarcoma	1	–
1965	Gromoll & Herrmann (7)	SCC	11	27
1965	Pennel & Hightower (8)	SCC	3	–
1966	Beccaria & Troncone (9)	SCC	2	–
1967	Albertazzi & Leigheb (10)	SCC	1	–
1968	Halliday (11)	SCC	1	–
1971	Ebner & Seidl (12)	SCC	2	–
1971	Dawson & McIntosh (31)	sarcoma	1	–
1974	Nguyen (13)	SCC	2	–
		BCC	1	–
1975	Liddell (14)	SCC	1	–
		BCC	1	–
1976	Languasco et al. (23)	BCC	1	–
1977	Barrière et al. (15)	SCC	6	–
1978	Burns & Calnan (24)	BCC	1	–
1981	Nunnery & Lipper (32)	leiomyo-sarcoma	1	–
1982	Lanehart et al. (25)	BCC	1	1
1983	Ackroyd & Young (16)	SCC	1	–
		BCC	2	–
1987	Guero & Glicenstein (34)	MM	1	–
1988	Blin (17)	SCC	1	–
1988	Kofler et al. (33)	hemangio-sarcoma	1	–
1989	Ryan (27)	BCC	1	–
1989	Riess (19)	SCC	1	–
1989	Castrati et al. (18)	SCC	2	–
1989	Berth-Jones et al. (35)	fibrous histiocytoma	3	–
1990	Blank & Schnyder (20)	SCC	1	–
		BCC	1	–
1991	Gosain et al. (29)	BCC	1	–
1991	Phillips et al. (28)	BCC	2	–

The first of two milestones in this context is the paper by Knox (2), who in a thorough review found 59 cases of SCC in venous ulcers in the literature, adding 2 of her own, with equal numbers of males and females. She expressed amazement at the rarity of cancer in chronic venous ulcers and hesitated to consider the ulcer as a cause of the cancer.

The second milestone is the study by Tenopyr & Silverman (3), who maintained that skin cancer was no more common in venous leg ulcers than on other parts of the legs. They found 4 cases of SCC in 1,000 patients with venous leg ulcers, suggesting the incidence to be 0.4%. They considered this to approximate the incidence in the normal population. This figure is very close to the observed proportion in the present study, where 4 cancers appeared in 1,170 patients with venous leg ulcers, but the incidence in the normal population is much lower. Our results seem to challenge the statement of Tenopyr & Silverman.

In the present study, 4 SCC in venous ulcers were found in the cohort. This is a low number, nevertheless giving a statistically significant increase of SCC of the leg in females with venous ulcers. Whether the ulcers with the shortest duration were true venous ulcers or ulcerating carcinomas is hard to say in retrospect. From the case histories, however, and the sudden deterioration of the ulcers 6 months to 1 year before diagnosis of cancer we judge them as primary venous ulcers developing a secondary malignancy.

Diagnosis is best achieved by histologic examination of one or more biopsies, the main difference between authors being the degree of suspicion they advocate. Some recommend a biopsy of all ulcers more than 3–4 months old (8, 16, 28), others on clinical suspicion only (14). All emphasize the importance of taking many biopsies. A comment made by Nunnery & Lipper (32), to the effect that sarcomas may arise in the centre of the ulcer rather than in the margin as SCC often do, seems to justify a central biopsy when malignancy of an ulcer is suspected.

Ackroyd & Young (16) and Phillips et al. (28) both emphasize the similar appearance of ulcerative BCC and venous leg ulcers.

After reviewing the literature on cancer in venous leg ulcers, and finding so many cases, we cannot consider this condition a rarity. Furthermore we cannot but reflect on the validity of case reports as an indication of the incidence of the disease. We maintain that only a fraction of cases of SCC in venous ulcers are reported. To support this statement we refer to the study by Swanbeck & Hillström (21), who tried to map the skin cancer incidence in different regions of the skin and in different parts of Sweden with data from the Swedish Cancer Registry's first 8 years. Of 143 SCC on the leg, 39 arose in an unspecified leg ulcer of more than 4 years' duration. A considerable number of these can be assumed to be venous in origin, but none has to our knowledge been reported in the international literature as an SCC in a venous ulcer. This probably also shows a certain acceptance of SCC as a complication of venous leg ulcers, as it is not reported.

As regards other types of tumours, such as sarcomas, this review shows that these are extremely rare. The same applies to malignant melanomas (Table II).

The proportional increase of SCC on the legs in females compared to males in the Swedish population, 12% vs 7% in the age group 65–69, is interesting (40). The reason might be a different pattern of actinic radiation due to different clothing habits. A possible connection between sunlight and high incidence of SCC on the outside of the leg of females is mentioned in the study by Swanbeck & Hillström (21). Actinic radiation on the legs and chronic venous ulcers, as two co-carcinogens, explain perhaps the overrepresentation of females with cancer in their leg ulcer in this study. Knox (2) found equal numbers of males and females in her material from the first decades of the century, when sunlight exposure of the legs of females was probably much less due to long skirts.

The results of the study indicate that SCC is a complication of venous leg ulcers. This should prompt a degree of suspicion and alertness when treating venous leg ulcers. To biopsy all leg ulcers of more than, for example, 3 months' duration would probably not lead to increased diagnosis of cancer because of the enormous variation of the latency period, approximated in one article to a mean of 25.5 years (7). However, when clinical suspicion arises, three to four biopsies from the suspected changes are essential.

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