Acta Dermatovener (Stockholm) 51: 151–156, 1971

ANALYSIS OF ETIOLOGICAL FACTORS OF SQUAMOUS CELL SKIN CANCER OF DIFFERENT LOCATIONS

4. *Concluding Remarks*

Gunnar Swanbeck and Lars Hillström

From the Department of Dermatology, Karolinska sjukhuset, Stockholm and the Department of Dermatology, University Hospital, Uppsala, Sweden

Abstract. Some aspects common to our three earlier papers on squamous cell skin cancer of different locations are further treated. The following subjects are discussed: 1) The frequency of squamous cell skin cancer for different body locations per year per one million people. 2) The differences in incidence rate in the northern and southern parts of Sweden for different locations of the cancers. 3) Interpretation of the age-specific incidence rate curves. 4) An estimate of the statistical lifetime risk of getting squamous cell skin cancer in Sweden. 5) The effect of certain skin diseases and dermatological therapy on the incidence rate of squamous cell skin cancer. 6) The frequency of metastases from squamous cell skin cancers of different locations. 7) Reliability of the presented data.

In the preceding three papers in this series we have presented epidemiological data on squamous cell skin cancer (s.c.s.c.) in Sweden (6, 17, 18). To some extent the findings have already been discussed in the separate papers. Some aspects common to the three earlier papers will here be further analysed.

Some new data on age-specific incidence of other tumours are presented in the present paper. The material and methods on which these have been based are analogous to those of the earlier papers.

The following topics will be discussed:

1. The frequency of squamous cell skin cancer on different body locations.
2. Differences in incidence-rate of squamous cell skin cancer in northern and southern Sweden.
3. Possible interpretation of age-specific incidence rate curves.
4. The statistical lifetime risk of incidence of squamous cell skin cancer.
5. The effect of skin diseases and dermatological therapy on the incidence rate of squamous cell skin cancer.
6. How often does squamous cell skin cancer metastasize?
7. Reliability of presented data and conclusions.

1. *The frequency of squamous cell skin cancer on different body locations*

To get comparable data on the frequency of s.c.s.c on different body regions we have calculated the number of cases per year per 1 million people for each body region. The material we have presented earlier covers approximately a 10 year period for the head material and approximately a 5 year period for the rest of the body. We have calculated with 8 million inhabitants in Sweden. The data are given in Table I. Except for the genitals the number of cases per year per 1 million people exceeds 1 only for body regions that often are exposed to sun radiation.

2. *Differences in incidence-rate of squamous cell skin cancer in the northern and southern part of Sweden*

The difference in incidence rate of skin cancer in geographical regions situated at different latitudes has been discussed by several investigators (2, 3, 7, 11, 12, 15, 20).

Sweden is a country that lies in a roughly north–south orientation with its limits at 55°20′

Table I. *Number of cases with squamous cell skin cancer at different body locations per year per 1 million people*

In Sweden 49.9% of the population are women and 50.1% men

Location	♂	♀	Total
Eye-lids	1.3	0.93	2.2
External ear	11	1.2	12
Face	16	14	30
Scalp and neck	2.4	1.4	3.8
Back	0.37	0.30	0.67
Chest	0.10	0.05	0.15
Abdomen	0.19	0.19	0.38
Hip and buttock	0.28	0.12	0.40
Genital region	7.1	16	23.1
Arm	0.33	0.30	0.63
Hand	2.4	0.82	3.2
Thigh	0.15	0.17	0.32
Leg	0.90	1.3	2.2
Foot	0.17	0.23	0.40
The whole body	43	38	81

and 69°4′ north and has a rather homogeneous white population. The vast extent of the country explains the differences in amount of sun radiation reaching the northern and southern parts of Sweden. From Fig. 1 it can be seen that the northern part of the country receives about 65 kcal per cm^2 per year in contrast to about 85 kcal per cm^2 per year for the most southerly part. In the figure, correction has been made for the effects of cloud formation. The average incidence of sunshine for the whole year is fairly uniform in the different parts of the country but the intensity varies somewhat. It should be noted however, that the midnight sun is concentrated to the summer period in the northern part of Sweden and that the amount of sun radiation thus reaching the inhabitants becomes less, as the sun also shines at night when people sleep.

In the earlier papers we reported the incidence of s.c.s.c. in the northern and in the southern parts of Sweden. Our borderline between the two parts has been at about 60° north. The data are summarized in Table II. It is seen that for the sun-exposed parts of the body there is a statistically significant overrepresentation of s.c.s.c. in the southern part of Sweden.

As has been suggested by several authors, sun radiation is certainly the most important etiological factor but perhaps not the only atmospheric factor that might influence the incidence rate and localization of skin cancer.

3. *Age-specific incidence rate of squamous cell skin cancer*

Age-specific incidence rate curves have been analysed in order to check hypotheses about the etiology of several diseases (1, 4). These hypotheses are built on the assumption that it is one (or several) dependent or independent mutations which is the primary cause of the disease. For internal cancers a two-stage theory of carcinogenesis has earlier been proposed (1). In most such studies one assumes, for simplicity, that the environment giving rise to the mutations is constant. One also has to compensate for a certain latency period be-

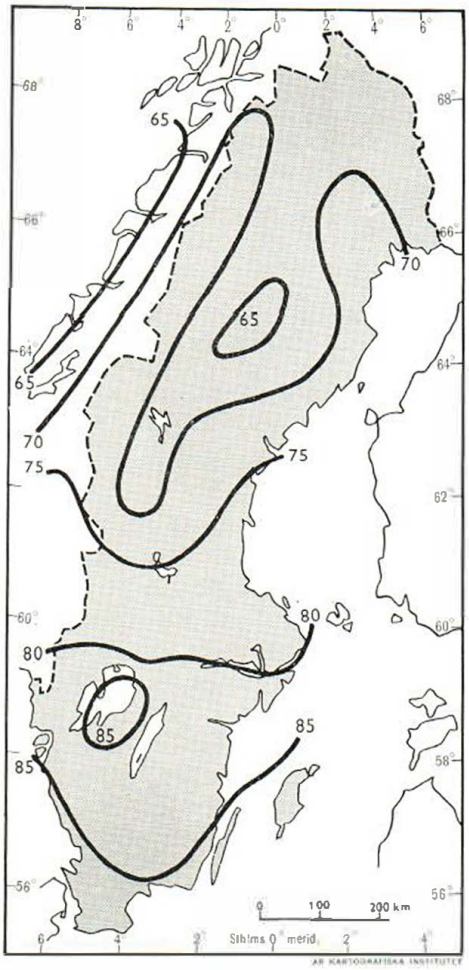

Fig. 1. Energy of incident sun radiation in different parts of Sweden in kcal per m^2 per year compensated for different meteorological factors (Reprinted from Ångström, Sveriges klimat. With the permission of the "Kartografiska Institutet" in Sweden.)

Table II. *Distribution of the cancers of different body regions with respect to northern and southern parts of Sweden*

In 1963 19.8 % of the population lived in the northern and 80.2 % in the southern part of Sweden

Location	Total number of patients	Percentage in northern part	Percentage in southern part	Quotient between incidence rate in southern and northern part	Statistically significant difference from distribution of the population
Head	3 819	14.6	85.4	1.44	Significant $p<0.001$
Hand	129	6.2	93.8	3.74	Significant $p<0.001$
Lower limb	143	12.6	87.4	1.71	Significant $p<0.05$
Trunk	100	16.0	84.0	1.30	Not significant
Genitals	1 416	20.0	80.0	0.99	Not significant
Arm	25	24.0	76.0	0.78	Not significant

tween the time when the disease is induced and when it is diagnosed. With regard to s.c.s.c. the most important factor in the environment is sun radiation, and it is reasonable to assume that the exposure of the face to sun radiation on the average has not changed during the time period studied.

If only one mutation is necessary to initiate a cancer in the skin the specific incidence rate would be constant for all ages except for a certain latency period. One can show that if two mutations are necessary, whether dependent or independent of each other, the specific incidence rate will not increase faster than linearly with age. If we assume any combination of mutations necessary to induce a cancer, the increase of the incidence rate curve with age will never be exponential if the mutability of the genes does not increase with age or a factor protecting against mutations decreases with age (5). The genetic material, deoxyribonucleic acid (DNA), does not change chemically in a significant manner during life, thus the mutability of the genes may be regarded as constant. However, in normal skin there are enzymes that can repair ultraviolet-induced mutations: DNA-repairing enzymes. In Xeroderma pigmentosum one of these enzymes is lacking and the patients develop skin cancer at a very early age (14). The DNA-repairing enzymes are thus of great importance for the protection of the skin against malignant transformation. One possible explanation for the exponential increase in the age-specific incidence rate of s.c.s.c. on the head, the hands and the lower limbs may be a decrease in the activity of the DNA-repairing enzymes with age. Today the activity of these enzymes can be measured, thus permitting testing of this hypothesis. Another possibility is that there has been a gradual increase in sun-bathing or sun exposure of the skin during recent decades.

The ultraviolet mutations occur mainly through a dimer formation of neighbouring pyrimidine residues in the DNA. The pyrimidine residues in such a dimer do not function in the replication of the DNA (16). The DNA-repairing enzymes remove such defective parts and restore the original sequence of nucleotides. This repairing mechanism can only protect against ultraviolet-induced mutations. In our earlier three papers on s.c.s.c. we have only plotted age-specific incidence rate curves

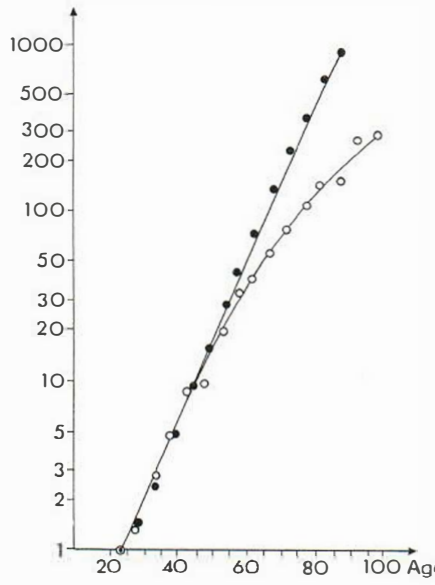

Fig. 2. Age-specific incidence rate curves for s.c.s.c. of the face (●) and of the genitals (○).

Table III. *Metastatic frequency of cancers of different body regions*

Location of primary tumour	Number of cases	Metastases only to regional lymph nodes	Metastases also to other organs
Lower limb	143	18 (12.6%)	8 (5.6%)
Trunk	100	14 (14.0%)	5 (5.0%)
Hand	129	3 (2.3%)	5 (3.9%)
Arm	25	2 (8.0%)	2 (8.0%)

for skin cancers localized on sun-exposed parts of the body, as the number of cases has been too small for other regions of the body. If a decrease of the activity of the DNA-repairing enzymes is the explanation for the exponential increase in the age-specific incidence rate, the increase with age of the incidence rate should be less rapid for tumours not induced by ultraviolet light. We have now completed our material of s.c.s.c. on the genitals and as is seen in Fig. 2 the age-specific incidence rate curve is not exponential. Similar curves are obtained for a number of other neoplasms (9).

4. *Lifetime risk of incidence of squamous cell skin cancer*

In Sweden there are just over 500 cases with s.c.s.c. per year in a population of about 8 million people (13) which gives a risk of about 0.5% of getting s.c.s.c. before 70 years of age. Certain professional groups, mainly out-door workers, have a considerably higher risk of getting s.c.s.c. We found for s.c.s.c. on the hands that about half the number of patients were farmers or workers on farms. This group constitutes about 10% of the economically active population and about 5% of the whole population. Their risk of getting s.c.s.c. before 70 years of age will thus be 5 to 10 times higher on sun exposed body regions than for the average Swedish inhabitant, which means 2–5%.

Intensive sun bathing at the Swedish latitudes may give a stronger accumulated exposure than the hands of a farmer will get and the risk will increase with the area exposed to sun radiation. The risk of getting s.c.s.c. with increasing age will probably not be negligible for people regularly exposing a large part of the body to sun radiation during the summer even at the latitudes of Sweden. To get an approximate estimate of the expectancy risk over 70 years of life the risk may be multiplied by 2 for each 7.5 years over 70.

5. *The effect of skin diseases and dermatological therapy on the incidence rate of squamous cell skin cancer*

The presence of a skin cancer in a lesion of another skin disease or in a burn scar may be a coincidence without any etiological or pathogenetic relationship. The larger the area of the assumed cancer-predisposing lesion, the greater will be the risk of such a random coincidence. It is thus more probable that a skin cancer in a small lesion or in a lesion of a dermatose affecting a small part of the body surface has been predisposed by that particular dermatose or its treatment. If a dermatose affects the whole body surface and does not predispose to cancer it will be represented in a cancer material with the same frequency as in a non-cancer material. If a dermatose affects 50% of the body surface and the cancers are randomly distributed on the body surface the frequency in per cent of that dermatose in a cancer material will be half that of that particular dermatose in a non-cancer population. In an investigation of this type one must, however, be aware that a dermatose affecting a part of the body other than the one on which the cancer is located may be easily neglected in the medical records on which we have based our data. Taking such factors into account we will try to evaluate our data with respect to cancer-predisposing properties of different dermatoses and skin abnormalities.

With regard to psoriasis we found 1 case in 25 cancer cases on the arms (hands excluded), 3 psoriatic patients in 100 s.c.s.c on the trunk and 5 psoriatic cases in 143 s.c.s.c. on the lower limbs. In all, this makes 3.4% psoriasis in that material. If we assume that we in Sweden have 2% psoriasis in the whole population, there is no statistically significant overrepresentation of psoriasis in our material. If we take into account that psoriasis as a rule affects only a minor part of the body surface, we are liable to believe that psoriasis and/or its treatment may increase the risk of malignant growth somewhat but so little that it may be neglected when compared with sun exposure.

The frequency of eczema in our cancer material is about the same as for psoriasis, and eczema is at least as common as psoriasis in a non-cancer

population. We have therefore no reason to suspect that eczema significantly predisposes to s.c.s.c. Earlier, tar and tar ointments were very commonly used in eczema treatment. Althouh tar is a carcinogen, on experimental animals, it evidently does not increase the risk for s.c.s.c. significantly when used in dermatological therapy.

With regard to acrodermatitis chronica atrophicans Herxheimer, burn injury, and mechanical trauma, we have no frequency data for a normal population with which to compare. We feel, however, that they probably predispose to s.c.s.c. but that their effect is small compared with that of sun radiation.

Whether ulcerations on the legs predispose to s.c.s.c. is impossihle to say on the basis of our data. However, one should keep in mind that an ulceration on the leg not infrequently contains a s.c.s.c.

In our study we have found few arsenic-treated patients. We are of the opinion that the risk of getting s.c.s.c. after treatment with aresenic is not so high. That arsenic intake increases the risk of getting skin cancer has, however, been shown (19). The question about the risk of interna! malignancies after arsenic treatment is outside the scope of the present series of papers.

6. *How often does squamous cell carcinoma of the skin metastasize?*

The number of cases with metastases has been investigated only for four localizations of the primary tumour: the lower limb, the trunk, the arm, and the hand. We have also tried to get information on how far the metastases have been spread. The follow-up time is not the same for all cases. In some cases metastases were found when the cancer was diagnosed; in other cases they were discovered some years later, according to the medical records. The data are given in Table III.

The percentage of metastases is somewhat higher in our material than has been published by some other investigators (8, 10). Lund (10) has pointed out the sun-induced cancers have a lower metastatic frequency than s.c.s.c. of other etiology. This seems to be the case in our material also. One explanation for this fact may be that cancers on sun-exposed parts of the body are easily noticed and the patients will thus attend a physician earlier.

7. *Reliability of presented data and conclusions*

In clinical practice we often express and are obliged to express opinions about expectancy risks, cancer-predisposing factors, predilection sites of cancer, metastatic frequency, etc. based on general impressions and clinical experience on a selected material. In the present series of papers we have presented data and conclusions both in qualitative and quantitative terms from a population of about 8 million people collected during a period exceeding 5 years. We are aware of the possibility that there may be systematic errors in our study and that some estimates are crude although care has been taken to minimize the errors.

The data we have presented have been based on medical records from the whole country. The reliability of the data is therefore dependent on the skill of the Swedish physicians and the care with which they have made the medical records. All diagnoses are verified histopathologically. We therefore believe that there is not a single case in our material who has not had s.c.s.c. but of course there must be several cases with s.c.s.c. who never attended a physician and have not been registered. It is also probable that there are cases in our material who may have had a skin disease not been mentioned in the medical records although this is not likely to be common. Our estimates are therefore minimum estimates especially with regard to predisposing factors other than sun radiation. With regard to the effect of sun radiation it should be kept in mind that Sweden is situated rather far north between the latitudes 55°20′ and 69°4′ north. The effect of sun radiation on white people at more southerly latitudes is probably more pronounced.

ACKNOWLEDGEMENT

This work has been supported by the Swedish Cancer Society.

REFERENCES

1. Armitage, P. & Doll, R.: A two-stage theory of carcinogenesis in relation to the age distribution of human cancer. Brit J Cancer *11*: 161, 1957.
2. Auerbach, H.: Geographic variation in incidence of skin cancer in the united states. Public Health Rep *76*: 345, 1961.
3. Belisario, J.: Epidemiology of the Commoner Skin Cancers, Solar Keratoses and Keratoacanthomas. The

Importance of Skin Pigment and Sunshine. Essays on Tropical Dermatology, p. 91. Excerpta Medica Foundation, Amsterdam, 1969.

4. Burch, P. R. J. & Rowell, N. R.: The sex- and age-distributions of chronic discoid lupus erythematosus in four countries. Possible actiological and pathogenetic significance. Acta Dermatovener (Stockholm) *48:* 33, 1968.
5. Eklund, G.: Personal communication, 1970.
6. Hillström, L. & Swanbeck, G.: Analysis of etiological factors of squamous cell skin cancer of different locations. 2. The trunk and the head. Acta Dermatovener (Stockholm) *50:* 129, 1970.
7. Jakae, D.: Die Bedeutung von Lichttrauma für die Entstehung Lokalisation und Frequenz des Hautkrebses. Hautarzt *19:* 157, 1968.
8. Katz, A. D., Urback, F. & Lilienfeld, A. M.: The frequency and risk of metastases in squamous-cell carcinoma of the skin. Cancer *10:* 1162, 1957.
9. Lilienfeld, A. M., Pedersen, E. & Dowd, J. E.: Cancer Epidemiology: Methods of Study, p. 48. John Hopkins Press, Baltimore, 1967.
10. Lund, H. Z.: How often does squamous cell carcinoma of the skin metastasize? Arch Derm (Chicago) *92:* 635, 1965.
11. MacDonald, E. J.: The epidemiology of skin cancer. J Invest Derm *32:* 379, 1959.
12. Miki, Y.: Incidence of skin cancer in Japan. Aust J Derm *9:* 178, 1967.
13. Ringertz, N., Ericsson, J., Sjöström, A. & Swensson, D.: Cancer Incidence in Sweden 1963. (National Board of Health. The Cancer Registry.) 1967.
14. Setlow, R. B., Reagan, J. D., German, J. & Carrier, W. L.: Evidence that xeroderma pigmentosum cells do not perform the first step in the repair of ultraviolet damage to their DNA. Proc Nat Acad Sci USA *64:* 1035, 1969.
15. Silverstone, H. & Gordon, D.: Regional studies in skin cancer. Second report: Wet tropical and subtropical coasts of Queensland. Med J Aust *2:* 733, 1966.
16. Smith, K. C.: Physical and chemical changes induced in nucleic acids by ultraviolet light. Radiat Res *6:* 54, 1966.
17. Swanbeck, G. & Hillström, L.: Analysis of etiological factors of squamous cell skin cancer of different locations. I. The lower limbs. Acta Dermatovener (Stockholm) *49:* 427, 1969.
18. — Analysis of etiological factors of squamous cell skin cancer of different locations. 3. The arm and the hand. Acta Dermatovener (Stockholm) *50:* 350, 1970.
19. Tseng, W. P., Chu, H. M., How, S. W., Fong, J. M., Lin, C. S. & Shu Yeh: Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J Nat Cancer Inst *40:* 453, 1968.
20. Urback, F.: Geographic Pathology of Skin Cancer. *In* The Biological Effects of Ultraviolet Radiation (ed. F. Urbach), p. 635. Pergamon Press, 1969.

Received June 30, 1970

Gunnar Swanbeck, M.D.
Department of Dermatology
Karolinska sjukhuset
S-104 01 Stockholm 60
Sweden