Non-melanoma skin cancer

Distribution and natural course are still open questions

Non-melanoma cancer of the skin and its precursor states are among the most common forms of cancer in Britain with an incidence second only to lung cancer in men and breast cancer in women. Yet despite their high incidence these cancers are among the least adequately studied from a population perspective. This paper examines what is known about their distribution and natural course to identify clinical lessons and some priorities for further research.

We may start by asking why there should be such a contrast between the frequent occurrence of cancers of this type and the relatively low level of interest they arouse.[1] Firstly, these cancers are seen correctly as less serious than many other forms. The aggressiveness of malignant melanoma has tended to divert attention from the other forms of skin cancer. Yet though malignant melanoma may be twice as important in terms of mortality (993 deaths in England and Wales in 1984 compared with 439 deaths from other forms of skin cancer), the registered cases of non-melanoma skin cancer exceed registered cases of malignant melanoma by a factor of 10 (22 254 cases registered in 1984 in England and Wales compared with 2231 cases of malignant melanoma).[2,3] Moreover, the numbers quoted for non-melanoma skin cancer are likely to be underestimates: one study found that registrations underestimated its incidence by between 14% and 28% even in an area with a highly efficient cancer registry.[4]

A second possible reason for the relative lack of interest in these lesions in Britain compared with countries such as Australia and the United States[5-7] is that the British climate includes fewer hours of sunshine than many other countries. But this generally negative view of the British climate may distract from the exposure to the sun of certain sections of the population through their occupation, choice of leisure activity, or travel. Furthermore, people of Celtic origin may be at considerably greater risk than other fair skinned people—a finding with obvious implications for the incidence of non-melanoma skin cancer on the western side of the British Isles.[8-11]

Finally, this relative neglect may stem from these lesions being seen as an inevitable concomitant of aging. In fact, the view that the skin changes seen in the elderly are a necessary result of aging is largely mistaken. Comparison of the exposed skin of the face with the unexposed skin of the buttock suggests that environmental factors are more important than the passage of time in producing many of the changes generally associated with aging.[12]

Perhaps the key question is the extent to which the prevalence of non-melanoma skin cancer in the British Isles differs from that in countries where its public health importance is acknowledged. Our examination of published reports suggests that in reality non-melanoma skin cancer may be just as large a public health problem in Britain as it is recognised to be in Australia and the United States.

Descriptive epidemiology

The epidemiological objective of describing the extent of a disease in a particular locality may be approached in various ways. Some impression can be gained by counting the number of patients who have been treated by the health facilities over time. But in the case of a chronic non-fatal disease, rates derived in this way are likely to reflect the extent to which people seek medical advice and not the true population distribution of the condition. For this reason a community based (as opposed to a health facility based) study on a properly drawn sample is the only reliable means of establishing incidence and prevalence. More formal diagnostic criteria are required for such studies than are conventional in clinical practice.[13] Several investigators have examined the accuracy of clinical diagnosis in this condition when compared with that of histological diagnosis and have found substantial disparities.[14-17]

The most extensive attempts to examine the distribution of non-melanoma skin cancer have been undertaken in Australia. Some have been based on hospital populations (table) and therefore have an uncertain relation to the prevalence in the population,[18,21] but four studies have been reported in non-hospital populations. Two of these are of limited value either because an atypical population was used[19] or because the method of case ascertainment was of doubtful validity.[20,27] The larger of the two remaining[22,28] sought to examine all those over 40 years living in the town of Maryborough[22]; 2113 volunteers were examined and suspicious lesions were biopsied. A high prevalence of solar keratoses (56·9%) and of non-melanoma skin cancer (2·32%) was found. Some 65% of the eligible population attended, but these were volunteers and the direction and size of any resulting bias is unknown.

Similar problems arise from a study in which 30 976 people were asked during a large commercial market research survey whether they had been treated for skin cancer during the previous year.[5] These diagnoses were validated by contacting the clinicians concerned. The incidence of non-melanoma skin cancer of 823/100 000 a year would make this by far the most common cancer in Australia. Not only did the study ultimately rely on medical recognition of cases but also there are problems with the validity of such self reported diagnoses. In this study only 31% of self reported skin cancers were validated, and the extent to which people who actually had non-melanoma skin cancer but answered the question negatively is unknown.

A number of descriptive studies have also been undertaken in the United States, mostly based on medically recognised cases.[29-37] Two of these, which were organised by the National Cancer Institute,[31,32] showed that the incidence of non-melanoma skin cancer in the Minneapolis and San Francisco areas had increased by 3% a year between 1971 and 1977.[37]

Truly community based studies are as uncommon in the United States as in Australia. In one such study of 978 people the prevalence of non-melanoma skin cancer at all ages was found to be 4·4%; all age prevalence of solar keratoses was 16·3%.[23] As part of the first national health and nutrition examination survey, which was undertaken between 1971 and 1974, 20 749 randomly selected subjects were examined by dermatologists.[24] The results showed the expected rising

Distribution of non-melanoma skin cancer in various studies

Reference	Country	No of subjects or cases	Nature	Age of study group (years)	Incidence*	Prevalence*	Methodological issues
Carmichael and Silverstone[18]	Australia (Queensland)	1000 in each of four towns	Random sample of hospital case records	All ages	50/10^5/year (age 25) 1500-4000/10^5/year (age 75)		No definition of tumours studied Based on hospital cases alone
Carmichael[19]	Australia (Queensland)	2024 (82% response)	All members of Farmers Association	30-50		Overall 14·4 (includes all skin cancers and solar keratoses)	Postal questionnaire method with self diagnosis. Atypical study population
Silverstone *et al*[20]	Australia (Queensland)	494 (82% response)	Longstanding residents (>20 years) in two locations	>20		Solar keratoses (53·9 men, 39·0 women), non-melanoma skin cancer (11·3 men, 9·5 women)	Examination by medical students. No verification by biopsy
Goodman *et al*[21]	Australia (Victoria)	2000	Hospital inpatients	>40		Skin cancer 37·7, non-melanoma skin cancer 3	Atypical study population. Verification by biopsy in suspected non-melanoma skin cancer
Marks *et al*[22]	Australia (Victoria)	2113 (65% response)	Population of one town	>40		Skin cancer 56·9, non-melanoma skin cancer 2·3	Clinical diagnosis with biopsy of suspected non-melanoma skin cancer. Patients attended screening centre
Giles *et al*[5]	Australia	30 976	Quota sample	>14	823/10^5/year		Quota sample. Poor validity of self reporting of treatment for skin cancer
Zagula-Mally *et al*[23]	United States (Tennessee)	978 Caucasians	Cluster sampling of households	>21		Skin cancer 16·3, non-melanoma skin cancer 4·4	Examination by trained nurses. No biopsies
Johnson *et al*[24]	United States	20 749 (74% reponse)	Probability sample of United States population	1-74		All skin cancer 3·6 (age groups 65-74)	Clinical examinations by dermatologists. Survey of all skin pathology
Whitaker *et al*[25]	United Kingdom (North West region)	781 Cases of squamous cell carcinoma	All cases reported to cancer registry 1967-9	All ages	Men 9·5/10^5/year, women 5·6/10^5/year		Confined to squamous cell carcinoma. Cancer registry cases alone
Rea *et al*[26]	United Kingdom (London)	2180 (90% response)	Stratified random sample with private census	15-74		1 case of non-melanoma skin cancer. No cases of solar keratoses	Questionnaire involving self reporting of skin problems. Subsample visited by team of doctors
O'Beirn *et al*[9]	Ireland	1338 (81% response)	Systematic sample of voters	>21		All ages. Skin cancer 10·6, non-melanoma skin cancer 1·9	Not specified who undertook examinations

*Unless otherwise stated values are percentages.

prevalence of non-melanoma skin cancer with age, with a prevalence of 44/1000 in the age group 65-74 years (number examined=3466). The rate of solar keratoses in the same age group was surprisingly low at 96·3/1000. The possibility arises that the examination, which required information on a wide range of conditions, was perhaps biased towards the more serious diseases under study.

In Britain even less epidemiological information is available. Whitaker *et al* used three years' data from the North West Cancer Registry and found a crude incidence among men of 9·5/100 000 a year,[25] a similar figure to that obtained in Sweden.[38] Only one community based prevalence study has been undertaken. This examined a wide range of skin conditions in a random population sample in London.[26 39] A postal questionnaire was used as a screening device, and a subsample of both positive and negative respondents were visited. Only one case of non-melanoma skin cancer was identified among the original sample of 2180 adults between 15 and 74 years old. No solar keratoses were identified.

A study from Ireland by O'Beirn *et al* is the only community based prevalence study concerned exclusively with skin cancer that has been performed in north west Europe.[9] A 1·5% systematic sample of the electoral register for Galway was taken; 1338 interviews were conducted (81% response rate). The all age prevalence of solar keratoses was 10·6%. In men over 70 the prevalence of non-melanoma skin cancer was 14%, 12/85).

These studies are summarised in the table, which shows the inadequacies of the existing epidemiological evidence in terms of the selection of people for study and in terms of adequate validation of findings. The only population of the British Isles to have been examined adequately showed a prevalence of the same order as that suggested by Australian and American studies.[9] The key implication of the studies reviewed is that the epidemiological pattern of non-melanoma skin cancer in Britain is an open question.

Natural course

Two questions concern the relation between non-melanoma skin cancers and previous solar keratoses and the probability of metastasis.

Treatment is often recommended for solar keratoses, though their natural history is poorly documented. During the Maryborough study, however, a longitudinal element was added to the cross sectional investigation.[40] People were invited to attend for screening again one year after the initial screen, and half (1040/2113) did so. Solar keratoses were marked on the same chart and any remissions or new keratoses were noted. One quarter (485/1873) of the solar keratoses had remitted, and 44% (458/1040) of subjects had developed at least one new lesion—though identifying these lesions accurately from such charts may have been difficult. A five year follow up of this study has reported that the risk of any one solar keratosis undergoing malignant transformation is less than 0·1% a year.[41] The authors suggest that treatment of solar keratoses may be useless in view of their tendency to remit spontaneously and their low potential for malignant change. Indeed solar keratoses may not be premalignant at all.[42]

Many dermatologists might believe, however, that the accurate mapping of lesions as small as solar keratoses is fraught with such difficulties as to call into question the accuracy of these estimates of rate of remission and malignant transformation. Just because, for example, a squamous cell carcinoma develops in the vicinity of a pre-existing solar keratosis it does not necessarily follow that it developed from that lesion or that the prophylactic removal of the keratosis would have prevented the development of the tumour. Dysplastic changes are known to be present in the apparently normal but chronically sun damaged skin around solar keratoses.[43]

The management of squamous cell cancers of the skin has been strongly influenced by the work of Lund.[44] He reported

that metastasis occurred in only 0·1% (4/3700) of a series of squamous cell cancers of the skin, though the follow up period was not clear in the report. This work has led to a widespread belief that a squamous cell carcinoma developing in a site exposed to sun is very unlikely to metastasise.[16] Several other studies, however, have suggested higher rates of metastasis.[16 45-48] The two most recent have reported proportions of 2·6% (6/228)[16] and 3·3% (5/153)[48]—though again the length of follow up was unclear.

The probability of metastasis from basal cell carcinoma is also contentious.[49] Beerman suggested a figure of between 0·1% and 0·54%[50] whereas an Australian survey reported the much lower proportion of 0·0028% (14/estimated 500 000),[51] though neither study specified the duration and success of follow up. In short, the question of the natural course of solar keratoses and non-melanoma cancer of the skin is in important respects still an open one.

Conclusions

Most non-melanoma skin cancers in white populations are due to ultraviolet radiation, and a change in habits with regard to exposure to sun could greatly reduce their incidence.[52-54] Public awareness campaigns have been launched in Australia, South Africa, the United States, and Britain.[55 56] The emphasis of much of the publicity has been on the relation between exposure to sun and malignant melanoma—for the understandable reasons that melanoma is the most aggressive form of skin cancer, that it tends to affect a younger age group, and because its incidence has shown a steady increase.[12] It is important to note, however, that the exact nature of the relation between malignant melanoma and exposure to sun is still a matter of some debate[1] and that the probability of developing malignant melanoma is small when compared with the probability of developing non-melanoma skin cancer. The release of chlorofluorocarbons and nitrogen oxides into the upper atmosphere may be severely depleting the ozone layer, which protects us from most of the ultraviolet B component in solar radiation.[57] It has been estimated that for every 1% decline in the ozone layer there will be a 2-3% increase in the incidence of non-melanoma skin cancer.[58] Adequate baseline measures of the distribution of these lesions are essential if we are to be able to measure any such changes in incidence.

Studies of the natural course of non-melanoma skin cancer show the largest uncertainty to be with solar keratoses—that is, their potential for malignant transformation and their tendency to remit spontaneously. Reliable data are of substantial clinical importance as the time and effort devoted to treating solar keratoses may well be unnecessary.

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1 Urbach F. Cancer of the skin. In: Bourke GJ, ed. *The epidemiology of cancer*. London: Croom Helm, 1983:102-15.
2 Office of Population Censuses and Surveys. *1984 Mortality statistics: cause*. London: HMSO, 1985. (Series DH2 No 11.)
3 Office of Population Censuses and Surveys. *1984 Cancer statistics: registrations*. London: HMSO, 1988. (Series MB1 No 16.)
4 Beadle PC, Bullock D, Bedford G, *et al*. Accuracy of skin cancer incidence data in the United Kingdom. *Clin Exp Dermatol* 1983;7:255–60.
5 Giles GG, Marks R, Foley P. Incidence of non-melanocytic skin cancer treated in Australia. *Br Med J* 1988;**296**:13-7.
6 Marks R. Skin cancer—Australia's bicentennial celebration. *Med J Aust* 1985;**143**:433–4.
7 Marks R. Non-melanoma skin cancer and solar keratoses in Australia—a review. *Eur J Epidemiol* 1985;**1**:319-22.
8 Lane Brown MM, Sharpe CAB, Macmillan DS, McGovern VJ. Genetic predisposition to melanoma and other skin cancers in Australians. *Med J Aust* 1971;i:852-3.
9 O'Beirn SF, Judge P, Urbach F, MacCon CF, Martin F. Skin cancer in County Galway, Ireland. *Proceedings of the National Cancer Conference, Philadelphia* 1970;**6**:489–500.
10 Urbach F. Geographic distribution of skin cancer. *J Surg Oncol* 1971;**3**:219-34.
11 Marks R. Premalignant disease of the epidermis. *J R Coll Physicians Lond* 1986;**20**:116-21.
12 Mackie RM, Elwood JM, Hawk JLM. Links between exposure to ultraviolet radiation and skin cancer. *J R Coll Physicians Lond* 1987;**21**:91-6.
13 Jones DL, Jones HS. Conditions that mimic skin cancer. *Journal of Dermatologic Surgery* 1976;2:209-14.
14 Lightstone AC, Kopf AW, Garfinkel L. Diagnostic accuracy—a new approach to its evaluation. *Arch Dermatol* 1965;**91**:497-502.
15 Presser SE, Taylor JR. Clinical diagnostic accuracy of basal cell carcinoma. *J Am Acad Dermatol* 1987;**16**:988-90.
16 Nixon RL, Dorevitch AP, Marks R. Squamous cell carcinoma of the skin: accuracy of clinical diagnosis and outcome of follow-up in Australia. *Med J Aust* 1986;**144**:235-9.
17 Ponsford MW, Goodman G, Marks R. The prevalence and accuracy of diagnosis of non-melanotic skin cancer in Victoria. *Australasian Journal of Dermatology* 1983;**24**:79-82.
18 Carmichael GG, Silverstone H. The epidemiology of skin cancer in Queensland: the incidence. *Br J Cancer* 1961;**15**:409-24.
19 Carmichael GG. A survey of skin cancers and solar keratoses in country areas in Queensland. *Med J Aust* 1962;i:395-400.
20 Silverstone H, Campbell CB, Hosking CS, Lang LP, Richardson RG. Regional studies in skin cancer. First report: north western Queensland. *Med J Aust* 1963;i:312-5.
21 Goodman GJ, Marks R, Selwood TS, Ponsford MW, Pakes W. Non-melanotic skin cancer and solar keratoses in Victoria—clinical studies II. *Australasian Journal of Dermatology* 1984;**25**:103-6.
22 Marks R, Ponsford MW, Selwood TS, Goodman G, Mason G. Non-melanotic skin cancer and solar keratoses in Victoria. *Med J Aust* 1983;ii:619-22.
23 Zagula-Mally ZW, Rosenberg EW, Kashgarian M. Frequency of skin cancer and solar keratoses in a rural southern county as determined by population sampling. *Cancer* 1974;**34**:345-9.
24 Johnson M-LT, Roberts J. *Skin conditions and related need for medical care among persons 1-74 years, United States 1971-74*. Washington: United States Government Printing Office, 1978. (Vital and health statistics series 11 No 212.)
25 Whitaker CJ, Lee WR, Downes JE. Squamous cell skin cancer in the North-West of England, 1967-69, and its relation to occupation. *Br J Ind Med* 1979;**36**:43-51.
26 Rea JN, Newhouse ML, Halil T. Skin disease in Lambeth. *British Journal of Preventive and Social Medicine* 1976;**30**:107-14.
27 Silverstone H, Gordon D. Regional studies in skin cancer. Second report: wet tropical and subtropical coasts of Queensland. *Med J Aust* 1966;ii:733-40.
28 Quirk CJ. Skin disease in the Busselton Population survey. *Med J Aust* 1979;i:569-70.
29 Lynch FW, Seidman H, Hammond EC. Incidence of cutaneous cancer in Minnesota. *Cancer* 1970;**25**:83-91.
30 Schreiber MM, Shapiro SI, Berry CZ, Dahlen RF, Friedman RP. The incidence of skin cancer in Southern Arizona (Tucson). *Arch Dermatol* 1971;**104**:124-7.
31 Scotto J, Kopf AW, Urbach F. Non-melanoma skin cancer among caucasians in four areas of the United States. *Cancer* 1974;**34**:1333-8.
32 Scotto J, Fears TR, Fraumeni JF Jr. *Incidence of non-melanoma skin cancer in the United States*. Bethesda, Maryland: United States Department of Health and Human Services, 1983. (National Institutes of Health publication No 83-2433.)
33 Mason EE, Nance M, Radcliffe CE, Scotto J, Berg JW. Skin cancer in Iowa. *Journal of Iowa Medical Society* 1974;**64**:469-72.
34 Allison SD, Wong KL. Skin cancer: some ethnic differences. *Arch Dermatol* 1957;**76**:737-9.
35 Macdonald EJ. The epidemiology of skin cancer. *J Invest Dermatol* 1959;**32**:379-82.
36 Haenszel W. Variations in skin cancer incidence within the United States. In: Urbach F, ed. *The biology of cutaneous cancer*. Washington, DC: United States Gorvernment Printing Office, 1963:225-43. (National Cancer Institute Monograph No 10.)
37 Fears TR, Scotto J. Changes in skin cancer morbidity between 1971-72 and 1977-78. *JNCI* 1982;**69**:365-70.
38 Swanbeck G, Hillstrom L. Analysis of etiological factors of squamous cell skin cancer of different locations. 4. Concluding remarks. *Acta Derm Venereol (Stockh)* 1971;**51**:151-6.
39 Holland WW, Waller J. Population studies in the London borough of Lambeth. *Community Med* 1971;**126**:153-6.
40 Marks R, Foley P, Goodman G, Hage BH, Selwood TS. Spontaneous remission of solar keratoses: the case for conservative management. *Br J Dermatol* 1986;**115**:649-55.
41 Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma. *Lancet* 1988;i:795-7.
42 Carmichael GG. The epidemiology of skin cancer in Queensland: the significance of pre-malignant conditions. *Br J Cancer* 1961;**15**:425-8.
43 Pearse AD, Marks R. Actinic keratoses and the epidermis on which they arise. *Br J Dermatol* 1977;**96**:45-50.
44 Lund HZ. How often does squamous cell carcinoma of the skin metastasise? *Arch Dermatol* 1965;**92**:635-7.
45 Epstein E, Epstein NN, Bragg K, Linden G. Metastases from squamous cell carcinomas of the skin. *Arch Dermatol* 1968;**97**:245-9.
46 Immerman SC, Scanlon EF, Christ M, Knox KL. Recurrent squamous cell carcinoma of the skin. *Cancer* 1983;**51**:1537-40.
47 Katz AD, Urbach F, Lilienfeld AM. The frequency and risk of metastases in squamous-cell carcinoma of the skin. *Cancer* 1957;**10**:1162-6.
48 Moller R, Reymann F, Hou-Jensen K. Metastases in dermatological patients with squamous cell carcinoma. *Arch Dermatol* 1979;**115**:703-5.
49 Domarus HV, Stevens PJ. Metastatic basal cell carcinoma. *J Am Acad Dermatol* 1984;**10**:1043-60.
50 Beerman H. Some aspects of cutaneous malignancy. *Arch Dermatol* 1969;**99**:617-26.
51 Paver K, Poyzer K, Burry N, Deakin M. The incidence of basal carcinoma and their metastases in Australia and New Zealand. *Australasian Journal of Dermatology* 1973;**14**:53.
52 Fitzpatrick TB, Sober AJ. Sunlight and skin cancer. *N Engl J Med* 1985;**313**:818-9.
53 Urbach F. Ultraviolet radiation and skin cancer in man. *Prev Med* 1980;**9**:227-30.
54 Fears TR, Scotto J, Schneiderman MA. Mathematical models of age and ultraviolet effects on the incidence of skin cancer among whites in the United States. *Am J Epidemiol* 1977;**105**:420-7.
55 Doherty VR, Mackie RM. Reasons for poor prognosis in British patients with cutaneous malignant melanoma. *Br Med J* 1986;**292**:987-9.
56 Rigel DS, Friedman RJ, Kopf AW, *et al*. Importance of complete cutaneous examination for the detection of malignant melanoma. *J Am Acad Dermatol* 1986;**14**:857-60.
57 Jones RR. Ozone depletion and cancer risk. *Lancet* 1987;ii:443-6.
58 Beadle PC, Leach JF. Holidays, ozone and skin cancer. *Arch Dermatol Res* 1982;**274**:47-56.