Cutaneous malignant melanoma in Scotland: incidence, survival, and mortality, 1979-94

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Abstract

Objective: To determine the changing incidence of and mortality from cutaneous malignant melanoma in Scotland from 1979 to 1994.

Design: Detailed registration of clinical and pathological features, surgical and other treatment, and follow up of all cases of cutaneous malignant melanoma diagnosed from 1979 to 1994 and registered with specialist database for Scotland.

Setting: Scotland.

Subjects: 6288 patients with invasive primary cutaneous malignant melanoma diagnosed between 1 January 1979 and 31 December 1994.

Results: The annual age standardised incidence of cutaneous malignant melanoma rose significantly from 3.5 to 7.8 per 100 000 per year in men and from 6.8 to 12.3 per 100 000 per year in women ($P < 0.001$ for both). World standardised rates increased from 2.7 to 6.0 per 100 000 per year in men and 4.6 to 8.50 per 100 000 in women. The incidence of melanoma continued to increase significantly in men of all ages during the study, but the rate stabilised in women after 1986. Mortality from cutaneous malignant melanoma was 1.3 per million per annum in men in 1979, rising to 2.3 per million per annum in 1994 ($P < 0.01$); it was 2.4 per million per annum in women in 1979, falling to 1.9 per million per annum in 1994 ($P = 0.09$). The underlying mortality trends showed a continuing rise for men but a downward trend for women that was not significant ($P = 0.09$). In men, melanoma free survival was 69% at 5 years and 61% at 10 years; in women the corresponding rates were 82% and 75%. Younger patients had higher survival rates, which were not entirely explained by thinner tumours. Over the 15 year period, survival rates improved by 12% overall, only partly owing to thinner tumours.

Conclusions: In Scotland the incidence of melanoma in women has stabilised, while mortality associated with melanoma in women shows a downward trend.

Introduction

The incidence of cutaneous malignant melanoma has continued to rise over the past 20 years in most parts of the world where data are available.¹ Mortality from melanoma also continues to rise in men and older

women, indicating that the rising incidence reflects a potentially lethal tumour.

In 1979 the Scottish Melanoma Group was established, with the aim of recording detailed information on the incidence, clinical and pathological features, treatment, and follow up of all primary cutaneous malignant melanomas diagnosed in Scotland. The unique aspect of this project is the detailed observation of the changing pattern of both clinical and pathological presentations and survival from melanoma in a comparatively stable northern European population.

We have reported the incidence and changing trends in the first 5 and 10 years of the group's activities.^{2,3} In this paper we report mortality from melanoma and the underlying trends in the population after 16 years of data collection and rigorous case ascertainment.

Patients and methods

The Scottish Melanoma Group records clinical and pathological details of all patients in whom malignant melanoma is diagnosed in Scotland (latitude 50-54° north; population 5.1 million in 1991 census). All pathologists reporting cases in NHS hospitals, trusts, academic departments, and private laboratories collaborate with each other and register cases with five local coordinators, who obtain detailed clinical and treatment information on the patients. Completeness of registration is cross checked annually with the pathologists in all Scottish pathology laboratories, and the records of the Scottish Melanoma Group are also cross checked with the cases recorded in the Scottish Cancer Registry. Follow up information is sought on all patients at 2, 5, 10, and 15 years after registration, and additional data on recurrent disease are entered in the database as patients present for further treatment.

Over the period of observation, 6288 patients with invasive melanomas (level 2 or deeper) and 372 patients with in situ melanomas (level 1) were registered. In this paper we analysed data on only the 6288 patients with invasive melanomas (level 2 or deeper).

Statistical methods

Incidence and mortality were age standardised both to the 1991 Scottish population and to the notional world population. In the figures data have been averaged for

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Fig 1 Incidence of invasive cutaneous malignant melanoma during 1979-94. Each point is average of two consecutive years, SE of each estimate being less than 0.4 in men and 0.5 in women

each of the eight consecutive two year periods from 1979 to 1994. Significance of the underlying trends was assessed according to the gradients of the linear regressions of incidence and mortality on time for 1979-84 (before the introduction of the education campaign) and 1985-1994 (after its introduction).

Five and ten year survival rates were calculated using actuarial techniques, with all cases diagnosed between 1979 and 1993 contributing. Dates of death up to 31 December 1994 were available from both the Scottish Melanoma Group and the registrar general for Scotland.

Comparison of survival between age groups and over time was undertaken using Cox's proportional hazards model after adjusting for the major prognostic factors of tumour thickness: ulceration, sex, and histogenetic type.

Table 1 Incidence of invasive melanoma (level 2 or more) in Scotland, 1979-94

Year	Men			Women		
	No of cases	Age standardised rates per 100 000 (SE)	World standardised rate per 100 000	No of cases	Age standardised rates per 100 000 (SE)	World standardised rate per 100 000
1979	80	3.5 (0.4)	2.7	172	6.8 (0.5)	4.6
1980	82	3.7 (0.4)	2.8	179	7.1 (0.5)	4.8
1981	83	3.6 (0.4)	2.7	160	6.4 (0.5)	4.2
1982	86	3.7 (0.4)	2.8	185	7.2 (0.5)	4.9
1983	104	4.4 (0.4)	3.3	204	8.0 (0.6)	5.7
1984	113	4.8 (0.5)	3.7	217	8.4 (0.6)	5.9
1985	150	6.3 (0.5)	4.8	259	10.0 (0.6)	7.6
1986	134	5.6 (0.5)	4.3	286	11.0 (0.7)	7.5
1987	133	5.5 (0.5)	4.2	247	9.5 (0.6)	6.6
1988	175	7.2 (0.5)	5.5	287	11.0 (0.7)	8.1
1989	180	7.4 (0.6)	5.8	280	10.7 (0.6)	7.7
1990	189	7.7 (0.6)	5.9	309	11.8 (0.7)	8.4
1991	183	7.4 (0.5)	5.6	295	11.2 (0.7)	7.8
1992	202	8.2 (0.6)	6.2	304	11.5 (0.7)	7.8
1993	185	7.4 (0.5)	5.7	300	11.3 (0.7)	7.6
1994	196	7.8 (0.6)	6.0	329	12.3 (0.7)	8.5
Total	2275	5.9 (0.1)	4.5	4013	9.7 (0.2)	6.7

Results

Table 1 and figure 1 show that the annual incidence of melanoma rose in both sexes over the 16 years of data collection. In 1979 the age standardised rate in Scotland was 3.5 per 100 000 per year in men and 6.8 per 100 000 in women, rising to 7.8 and 12.3 per 100 000 in 1994. The world standardised incidence rose from 2.7 to 6.0 per 100 000 per year in men and from 4.6 to 8.5 per 100 000 per year in women over the same time. The male to female ratio in 1979 was 0.47 but had risen to 0.60 by 1994.

Figure 1 shows the incidence trends for both sexes at all ages and for those under 65 years. In men the steepest rise in incidence occurred between 1983 and 1990, after which the rate of increasing incidence slowed. In women the steepest increase occurred from 1980 to 1986, after which it did not increase in women under 65 years of age.

Only 18 of the 6288 cases (0.28%) arose in children under the age of 15, but thereafter the incidence increased steadily with age. The incidence in women is greater than in men in all age groups, except in those over 85 at diagnosis. The pattern of increase by histogenetic type was of a continuing highly significant rise in superficial spreading melanomas in both sexes. Increases in the incidence of lentigo maligna melanoma, nodular melanoma, and acral melanoma were less obvious but still significant in men, but the incidence of nodular or acral melanomas did not change significantly during 1979-94 in women.

Figure 2 shows the increase by body site and by tumour thickness divided into three arbitrary categories: thin (0-1.49 mm), intermediate (1.5-3.49 mm), and thick (3.5 mm and over). In men the greatest increase was on the trunk and in women on the leg. Since 1986, however, the incidence of lesions on the leg has levelled off in women, and this trend has continued to date. Trends in tumour thickness showed a significant increase in melanomas under 1.5 mm thick during 1979-84 in both sexes ($P < 0.001$ for both), but this levelled off in women towards the end of the study. There was also an increase in the number of intermediate thickness ($P < 0.001$) and thick ($P < 0.05$) primary tumours in men but no significant increase in either of these categories in women.

Figures 3 and 4 show mortality and actuarial survival for both sexes during the study. In men the trend was significantly upwards at all ages, but this trend was less obvious in those aged under 65 years. In women aged under 65 years the trend was downwards but not significant ($P = 0.09$). The actuarial survival curves for both sexes show the divergence in survival between the sexes during the first five years after diagnosis and treatment, this difference being maintained in the next five years. They also clearly show the steady and continuing death rate from melanoma during follow up over 5-10 years, confirming that survival to 5 years is not a guarantee of cure.

Table 2 shows 5 and 10 year melanoma free survival in men and women by age group and tumour thickness. Women consistently showed better survival at all ages and in all categories of thickness of the primary tumour. Younger patients of both sexes also had better survival rates. Although younger patients tend to have thinner primary tumours, this only partly explains their better

Table 2 Five and 10 year survival by age group and tumour thickness

	5 year survival (%)		10 year survival (%)	
	Men	Women	Men	Women
Age group (years)				
<35	75	92	73	86
35-44	80	90	73	85
45-54	68	84	61	77
65-74	61	76	47	65
≥75	69	66	49	51
Tumour thickness (mm)				
<1.5	91	96	88	92
1.5-3.49	66	81	55	69
≥3.5	42	54	30	43

survival: there still remains a significant and substantial survival benefit associated with younger age after adjustment for other recognised prognostic factors.

Table 3 shows survival, both overall and in four cohorts covering 1979-81, 1982-4, 1985-7, and 1988-90, with a multifactorial analysis of factors independently influencing survival. Overall 69% of men survived 5 years free of melanoma compared with 82% of women; 10 year survival was 61% and 75% respectively. The four cohorts showed no improvement in survival at 5 years in those diagnosed before 1985. They did, however, show a 10% improvement in male survival and 6% improvement in female survival for those whose melanoma had been diagnosed between 1985 and 1987, with a further improvement for those with a diagnosis between 1988 and 1990. A greater proportion of thinner tumours were diagnosed between 1985 and 1987, which explains the first improvement, but the further improvement between 1985 and 1987 cannot be explained by this factor.

There were no significant differences in survival by body site or histogenetic type once tumour thickness was controlled for in the Cox model.

Discussion

This study has shown interesting trends in incidence of and survival from malignant melanoma over a 15 year period in the Scottish population.

Table 3 Survival by year of diagnosis, with Cox's multifactorial analysis of factors independently influencing survival

	Year of diagnosis				
	1979-90	1979-81	1982-4	1985-7	1988-90
Men					
% surviving 5 years	69	60	59	69	76
% surviving 10 years	61				
Women					
% surviving 5 years	82	75	79	83	89
% surviving 10 years	75				
Cox's proportional hazards model†					
Unadjusted	1.33***	1.20*	1	0.71***	
Adjusted for:					
Breslow thickness	1.10	1.00	1	0.79**	
Breslow thickness, sex, and age	1.14	1.03	1	0.75***	
Breslow thickness, sex, age, ulceration, histology, and site	1.15	1.05	1	0.76**	

*P<0.05, **P<0.01, ***P<0.001.

†Baseline group are patients in whom malignant melanoma was diagnosed between 1985 and 1987.

Fig 2 Incidence of melanoma by sex, anatomical site, and tumour thickness, 1979-94

Comparison of melanoma incidence in England and Wales

The incidence of invasive melanoma in men of all ages and in older women has increased in Scotland as it has in other countries. Reported incidence in England and Wales for 1990 (the most recent data available) show an age adjusted rate of 6.1 per 100 000 in men and 8.5 per 100 000 in women,⁴ compared with 7.4 and 10.7 per 100 000 in Scottish patients in the same year. The higher rate recorded in Scotland may be due to more complete registration in a specialist registry compared with a general cancer registry or it may indicate a true difference in incidence, possibly because the Scottish population is fair skinned and therefore more susceptible to melanoma. The fact that a recent audit of completeness of melanoma registration in selected centres in England showed considerable underregistration makes the former explanation likely.⁵ The observed rising incidence in Scotland is not due to changing

Fig 3 Mortality from melanoma during 1979-94 for all ages and for those aged under 65 years. Maximum SE for any point on both graphs is 0.2

pathological diagnostic criteria as the pathologists of the Scottish Melanoma Group have maintained consistent diagnostic criteria since the establishment of the group, with regular twice yearly meetings to discuss difficult cases.

Our data show a stabilisation of the incidence of melanoma after 1986 in women aged under 65. Although we would expect an additional temporary increase in 1985 and 1986 in association with the introduction of the education campaign, this should then have been followed by a return to the trend apparent before the introduction of the campaign. This is not the case and implies that some degree of levelling off has occurred. Follow up is necessary to confirm this trend, which is encouraging in terms of meeting the health of the nation target of halting the year on year rise in the incidence of skin cancer by 2005. It is particularly important that this trend is seen in melanoma, the form of skin cancer responsible for most deaths related to skin cancer.

Fig 4 Actuarial disease free survival from melanoma by sex in cases diagnosed during 1979-94

Current incidence trends in Australia may imply that a proportion of thin melanomas have a non-metastasising phenotype and are non-progressive lesions.^{6 7} This is highly likely to be true in the case of thin level 1 lesions, but our study does not include such lesions. It may apply to a proportion of level 2 primary melanomas in the so called radial or horizontal growth phase, when few cells invade the dermis. However, the hypothesis that such lesions would never have become lesions capable of metastatic spread if left in situ cannot be proved as the entire lesion must be examined pathologically to establish the diagnosis and growth phase. The fact that patients who have such melanomas excised while the lesions are still in the radial or horizontal growth phase have later developed metastatic diseases clearly indicates that simple microscopic examination with conventional stains is not enough to positively exclude metastatic potential and justifies the removal of early invasive primary melanomas.⁸

Improvement in melanoma free survival

The improvement in 5 year survival in cases diagnosed between 1985 and 1987, which can be explained by a greater proportion of thinner tumours, could at least in part be the result of the active public education campaign aimed at encouraging earlier diagnosis that was running in Scotland at this time.⁹ However, the continuing improvement in survival later, during 1988-90, seems to be due to factors other than tumour thickness. Changes in treatment are unlikely to explain this improvement because during the study the only change has been a steady trend to narrow the excision margins for primary melanomas. Women continue to have better survival rates at 5 and 10 years, and these are not fully explained by tumour thickness and age.

The problem of lead and length time bias affects all studies aimed at improving survival in patients with cancer by bringing forward the time of diagnosis. In melanoma, tumour thickness is taken as a surrogate for lead time bias, and the Cox's proportional hazards model used in table 3 takes this into account and indicates that a high proportion of the improvement in survival prospects for patients whose melanoma was diagnosed between 1985 and 1987 is due to lead time bias. Discussions on lead time bias do not allow for the fact that a clone of cells with full metastatic potential might develop in an untreated initially in situ primary melanoma; some of these cells could move from the primary site before the primary tumour is eventually excised. Long term follow up of patients who have had thin primary melanomas excised is essential to establish whether they are truly cured or whether disseminated tumour cells are present even at an early stage that will eventually develop into metastatic deposits and cause the patient's death. This will establish whether melanoma is a systemic disease from the outset or whether it is a localised disease at some time and therefore can be cured by local treatments.

Falling mortality from melanoma in Scottish women

Mortality from melanoma in Scotland currently shows a continuing significant upward trend in men but a downward trend in women under 65 which is not yet

significant ($P=0.09$). Data available from the Information and Statistics Division of the Scottish Home and Health Department on mortality from melanoma in women for 1970-8 shows a steady upward trend which reverses in the early 1980s and continues to fall to date. We have undertaken an age birth cohort analysis of the death rates in women, but there is no evidence of any cohort effect which might explain this decrease in younger women (data available on request). Balzi et al have recently published a report on mortality from melanoma in Europe for 1970-90, and they independently comment on the decrease in female mortality in Scotland since 1985.¹⁰ A recent reported from England and Wales shows mortality levelling off in women aged 35-54 and a reduction in mortality in women aged 15-34.¹¹ Mortality from melanoma in 1993 in England and Wales was 2.8 per 100 000 in men and 3.0 per 100 000 in women compared with our figures of 2.2 and 2.1 per 100 000 respectively.¹¹ Recent reports from both the United States^{13 14} and Australia¹⁵ also suggest a levelling off in mortality from melanoma in these countries. The Australian experience indicates that changes in mortality from melanoma occurred in women five years before they were seen in men,¹⁵ and it will be of interest to see if this pattern is repeated in Scotland over the next five years.

In summary, the incidence of malignant melanoma in Scotland seems now to have stabilised in women, and mortality from melanoma in younger women shows a downward trend. Further observation will establish whether this trend will also be seen in men.

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Conflict of interest: None.

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Key messages

- Data from Scotland based on 6288 patients with primary invasive cutaneous malignant melanoma show a rise overall in the incidence of melanoma over 15 years but a stabilisation in the incidence of melanoma in women under 65 since 1986
- Mortality associated with melanoma is now falling in women of all ages, especially in women under 65
- Survival prospects remain strongly related to tumour thickness at the time of diagnosis: disease free survival at 5 years for patients with melanoma thinner than 1.5 mm was 96% in women and 91% in men, while for those with tumours thicker than 3.5 mm survival was 54% and 42% respectively

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A memorable doctor

"We never met"

I never met him, not in person. But I did meet him through his receptionist, his scrambled notes, his scruffy premises, and most of all through his patients.

He was an inner city general practitioner and I was his locum for the day. This was my first experience of a singlehanded practice, having trained and worked in highly thought of group practices. My spirit had been squashed by the transitory life of a locum. The simple problems that patients brought I dealt with adequately enough, but, without investment, the complex problems required time and follow up that I could not offer.

The practice premises were on the ground floor of a dilapidated terrace house. Inside it was cold and damp, the cylinder gas heaters hadn't had time to warm the air. I was presented with Lloyd George case files near to bursting. All of this seemed unfamiliar to someone who had trained in a flagship practice in purpose built premises. Irritation took hold as I fumbled through copious correspondence in a patient's notes. Each letter had been carefully folded individually, so that I had painstakingly to open up and then refold each letter in turn. The

handwriting was hard to decipher and there was no computer to cross check medicines on. I was forced to grapple with how this man thought and slowly I crept further into his head.

His name cropped up in every consultation and the patients' fondness for the man shone out. I learnt not only of a doctor but also of a man with a wife and children, a gracious manner, and a passion for football. Sitting at his desk, taking tea from his teacup, wearing this man's shoes for a day I started to get to know him. Late in the afternoon I saw a man who had coronary artery disease and he helped fill me in with his past medical history. "I'd had chest pains for some months, Dr A treated it as indigestion, up until my heart attack, that is. My heart stopped twice you know, they had to shock me." I braced myself to defend a colleague over an apparent medical mishap. I then realised that there was no hint of anger or malice in the man's voice, but rather affection for his doctor, human and imperfect.

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