

Melanoma epidemic: a midsummer night's dream?

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Summary

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Conflicts of interest

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Background The reported incidence of melanoma has greatly increased and this has been attributed to ultraviolet exposure.

Objectives We considered the possibility that the increase was an artefact caused by diagnostic drift.

Methods We tested this by analysing the histological diagnosis, mortality and incidence of all lesions reported as melanomas in East Anglia between 1991 and 2004.

Results There were 3971 melanomas in all, and their annual incidence increased from 9.39 to 13.91 cases per 100 000 per year during the period studied. This increased incidence was almost entirely due to minimal, stage 1 disease. There was no change in the combined incidence of the other stages of the disease, and the overall mortality only increased from 2.16 to 2.54 cases per 100 000 per year.

Conclusions We therefore conclude that the large increase in reported incidence is likely to be due to diagnostic drift which classifies benign lesions as stage 1 melanoma. This conclusion could be confirmed by direct histological comparison of contemporary and past histological samples. The distribution of the lesions reported did not correspond to the sites of lesions caused by solar exposure. These findings should lead to a reconsideration of the treatment of 'early' lesions, a search for better diagnostic methods to distinguish them from truly malignant melanomas, re-evaluation of the role of ultraviolet radiation and recommendations for protection from it, as well as the need for a new direction in the search for the cause of melanoma.

There is a widespread belief that excessive ultraviolet (UV) exposure has led to an increased incidence of melanoma,^{1,2} and this has been passed on to the public in an alarmist way. In July 2007, for example, the BBC warned that 'Rates of the deadliest form of skin cancer are continuing to rise', reporting an 18% increase between 2003 and 2005.³ We have examined the alternative possibility that the reported increase in melanoma incidence is an artefact, caused by a diagnostic drift, which reclassified what were previously found to be benign melanocytic naevi^{4,5} as truly malignant melanomas.

To test this possibility, we examined the nature of the reported melanomas in detail. If the increased incidence was real, there would be an increase in all of the usual presentational forms of the lesions, from minimal to advanced, as well as the mortality from them; but if the explanation is diagnostic drift, the increased incidence would be entirely due to minimal lesions, and there would be little or no change in mortality or incidence of more advanced disease. To distinguish between these possibilities, we analysed the changes in

melanoma incidence, stage and mortality in the Eastern Region of the U.K. from 1991 to 2004.

Methods

We identified 3971 patients diagnosed with malignant melanoma (ICD10 site C43) between 1991 and 2004 from the Eastern Cancer Registration and Information Centre (ECRIC) database. All these patients were resident in East Anglia, which is taken to comprise the counties of Norfolk, Suffolk and Cambridgeshire (including Peterborough Unitary Authority). The population of this area increased from approximately 2.1 to 2.2 million people during this period.

The primary sources of registration data are reports from all pathology laboratories and hospital patient notes; these are viewed by registry staff, who are either based at all the major NHS hospitals in the region, or visit them at least monthly. The diagnosis of 96.2% of all registered melanomas was confirmed histologically. Both electronic and paper-based reports

are received by the registry, and a high level of completeness of registration was achieved (estimated to be 96.2% by the flow method⁶). Tumours were staged using the condensed TNM system⁷ throughout the study period. Survival of each individual patient was actively determined for this study by ECRIC, early in 2007, through the National Health Service Strategic Tracing Service, so it is expected that our data are substantially complete and reliable. Patients with stage 0 disease (melanoma in situ) were excluded from the analysis.

Melanoma incidence and mortality were calculated as European age-standardized rates.⁸ Relative survival was analysed by the method of Hakulinen and Tenkanen,⁹ using life tables developed by the U.K. Government Actuary's Department.¹⁰ Changes in rates were analysed by linear regression and fitted trend lines were plotted; rates at the beginning and end of the study periods were calculated from the best-fit trend lines.

Results

Figure 1 shows age-standardized incidence and mortality rates for malignant melanoma of the skin (ICD10 site C43) in East Anglia from 1991 to 2004. During this period the incidence rate increased continuously each year, and the overall increase of 4.52 cases per 100 000 population per year, from 9.39 to 13.91 cases per 100 000 population per year, was highly significant ($r^2 = 0.754$, $P < 0.001$). In contrast, mortality rates increased only by 0.38 cases per 100 000 population per year, from 2.16 to 2.54 cases per 100 000 population per year ($r^2 = 0.240$, $P = 0.043$), giving a ratio of changes in incidence to mortality of 11.9 : 1. There were a total of 2192 deaths due to melanoma in the study population.

The change in incidence rates was analysed separately for the various TNM stages (Fig. 2). The rate of stage 1 melano-

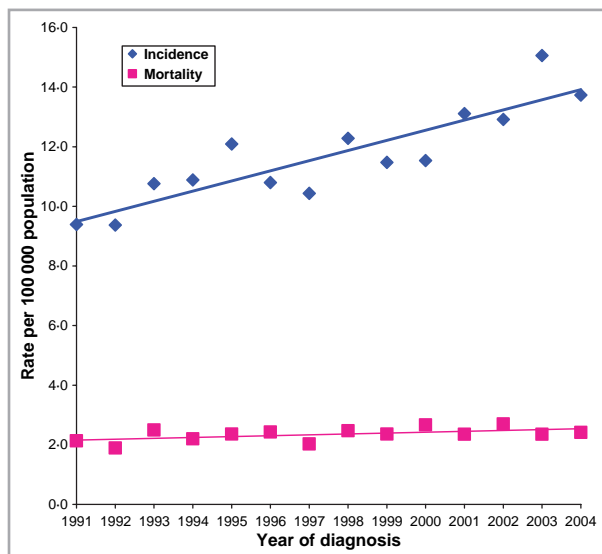


Fig 1. European age-standardized incidence and mortality rates for malignant melanoma in Norfolk, Suffolk and Cambridgeshire in 1991–2004.

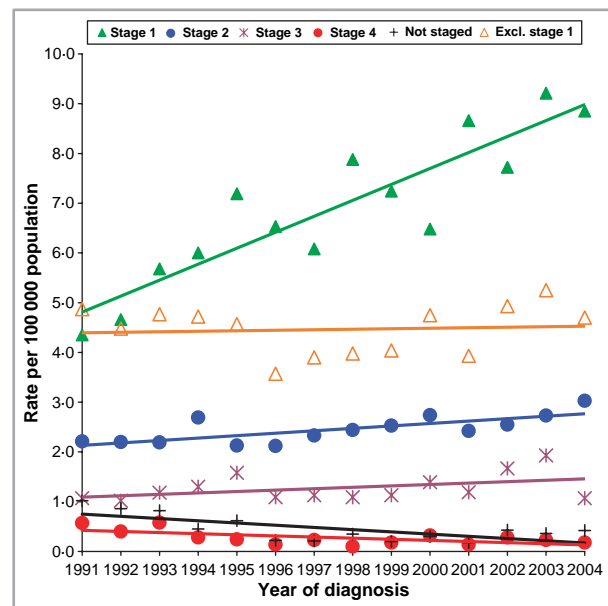


Fig 2. European age-standardized incidence rates of malignant melanoma by stage in Norfolk, Suffolk and Cambridgeshire in 1991–2004.

mas showed an increase of 4.17 cases per 100 000 population per year ($r^2 = 0.79$, $P < 0.001$), the rate nearly doubling from 4.81 to 8.98 cases per 100 000 per year between 1991 and 2004. By contrast, the combined rate of the other stages, excluding stage 1, did not change at all ($r^2 = 0.007$, $P = 0.771$).

Subgroup analysis of these patients showed only small changes. There was a significant increase in the incidence of stage 2, from 2.13 to 2.77 cases per 100 000 per year ($r^2 = 0.51$, $P = 0.002$); there was no significant change in stage 3 incidence ($r^2 = 0.12$, $P = 0.124$); and there was a decrease in stage 4 incidence from 0.42 to 0.13 cases per 100 000 per year ($r^2 = 0.40$, $P = 0.015$), although the value of this analysis was limited by the small numbers of more advanced tumours reported. Finally, there was a decrease in 'not staged' cases from 0.75 to 0.17 per 100 000 per year ($r^2 = 0.43$, $P = 0.006$), probably due to improvement in data collection.

Thus it was the change in the rate of stage 1 melanoma [pT1 or pT2 (i.e. Clark level II or III, < 1.5 mm thickness); N0 (no regional lymph node metastases); M0 (no distant metastases)] that effectively accounted for the overall change in melanoma incidence.

The prognosis for stage 1 melanoma was shown to be excellent compared with more advanced disease (Fig. 3). This comparison was based on a cohort analysis for cases diagnosed between 1996 and 2000, these years being chosen to represent the average prognosis over the full study period. The annual survival findings (Fig. 3) show that all grades of tumour were diagnosed at first presentation. Survival with stage 1 melanoma was effectively 100% and remained at that level throughout the period 1989–2001 (Fig. 4). Furthermore,

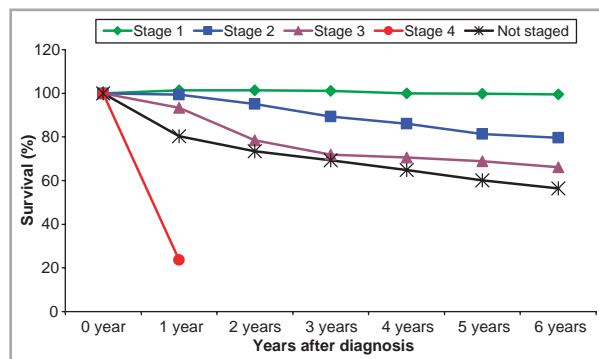


Fig 3. Relative survival with malignant melanoma diagnosed 1996–2000 in Norfolk, Suffolk and Cambridgeshire according to TNM stage.

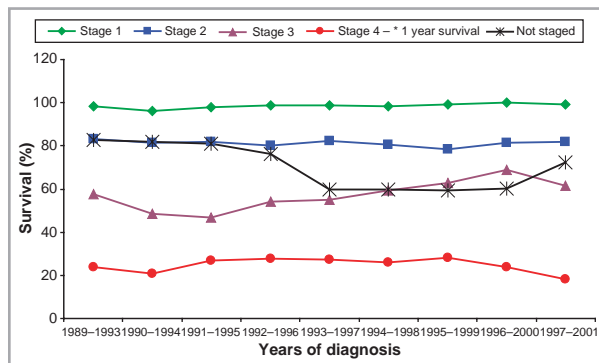


Fig 4. Five-year relative survival with malignant melanoma diagnosed 1989–93 to 1997–2001 in Norfolk, Suffolk and Cambridgeshire according to TNM stage.

the 5-year survival rate for each of the other stages was little different over the whole period of analysis (Fig. 4), which makes it unlikely there had been a significant improvement in therapeutic response. The distribution of the lesions is shown in Figure 5 and is not predominantly that of solar exposure.

Stage 1 lesions, which comprise the bulk of the increase in incidence, were found mostly in relatively less exposed skin sites.

Discussion

The present findings are that between 1991 and 2004 in Norfolk, Suffolk and Cambridgeshire, an area with a population of 2.1 million, there was a marked and continuous increase in the reported incidence of melanoma. This increase was due to changes in the incidence of stage 1 disease, the combined incidence of more advanced stages being unchanged, and despite this appreciable increase, there was only a slight increase in disease mortality, the ratio of the increase in incidence and mortality being 11.9 : 1.

There are two possible explanations for these findings. The first is that the reported change was due to a progressive increase in the incidence of genuine, potentially fatal malignant melanoma. But if this were the case, the presentation and course should have followed the well-established nature of the disease and its outcome, which was not found for either presentation or outcome. If, therefore, the increase in incidence is genuine, it has further to be concluded (i) that, fortuitously, nearly all of this increase was due to lesions of stage 1 disease, instead of the usual mixed presentation of melanoma types and (ii) that this coincided almost precisely with an increased therapeutic response to surgical treatment, so that the lesions were cured by simple excision. A similar coincidence was given as the explanation of increased incidence but not mortality over a 5-year period in Yorkshire.¹

The level of coincidence necessary to make the reported melanoma mountain credible is too extraordinary to countenance. It would be remarkable enough if an epidemic of a fatal disease were precisely matched in time and degree by an improved therapeutic response (in this case, to the same simple local excision), so that the net outcome was little or no change in mortality. It would be even more remarkable for an

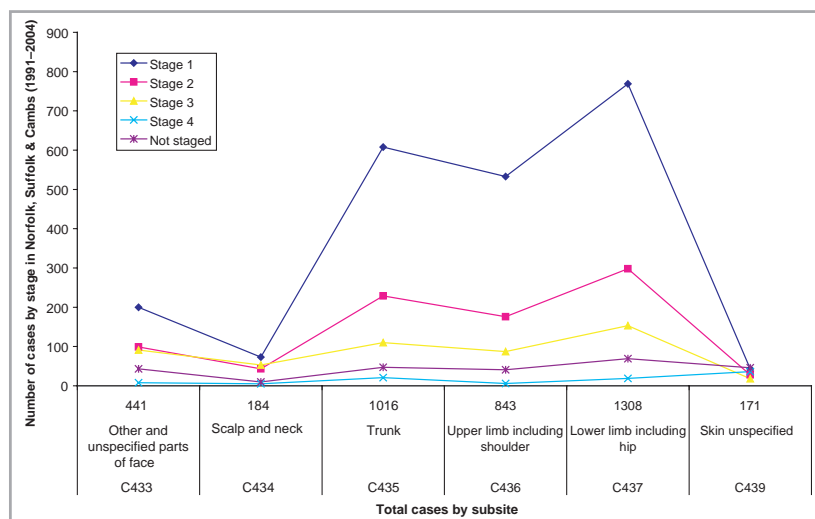


Fig 5. Malignant melanomas by subsite—distribution by stage.

epidemic of a cancer known for its variability, to present only with the most minimal form of the disease, without any of the more serious forms, which regularly occur at the first presentation of the disease, as our findings of outcome in the first years of presentation have confirmed. Furthermore, our findings also show that these more severe forms of the disease have an unchanged risk of fatal outcome regardless of early diagnosis and treatment, their mortality changing little over the period of study. Thus, we deduce that encouragement of patients to present early for treatment does not explain our findings. We must therefore conclude that the present findings make it extremely unlikely that the reported large increase in the incidence of melanoma is real.

If, as it now appears from our findings, the reported large increase in incidence is not due to true malignant melanoma, we are therefore left with the possibility that the increase, which we have found to be almost entirely due to stage 1 disease, has come about because of a change in histopathological diagnosis. Lesions previously diagnosed as simple, or dysplastic naevi, were considered benign, because they were observed not to progress if left (as they were in the past, when pigmented lesion removal was less enthusiastically pursued than now), are now being diagnosed as stage 1 melanoma.^{4,5} It is not surprising, therefore, that the incidence of 'melanoma' has increased, but not its mortality. A variant of our suggestion of diagnostic shift is that stage 1 melanoma may include a discrete benign disease.¹¹

How could this diagnostic drift have come about? The ultimate diagnosis of melanoma is histological appearance, and this is not a problem with advanced lesions. But histological appearance is too subjective for definition of early lesions, especially as many of the features used to define malignancy are commonly seen in benign disorders, e.g. after partial (shave-removal) of a benign naevus and in benign childhood 'melanomas'. But if lack of histopathological precision allowed the diagnostic drift that explains the present over diagnosis of melanoma, what powered that movement?

Dermatologists, pathologists and other medical practitioners have become more cautious in the last two decades, as the consequences of a wrong diagnosis have become more pervasive. One mistake can be ruinous; fear of humiliation and disgrace has increased, and compensation has outbid apology. Defensive medicine is regrettable but understandable, and it is not surprising that there is a pressure to err on the side of caution, in borderline cases, when making the distinction between benign and malignant changes. Consequently, when a patient presents with a slightly atypical pigmented lesion, a biopsy is now often taken, 'just to be sure'. Every time this is done, the melanoma point on the grey, subjective scale of diagnosis is moved imperceptibly, and this, in turn, weights subsequent decisions. Therefore the numbers of 'melanomas' are reported to increase, and are likely to continue to do so, while mortality and presentation of potentially harmful disease remains constant.

Although our study leads us to conclude that the increased incidence of melanomas reported is spurious and due to the

artefact of a diagnostic shift, a process which older dermatologists saw develop,⁴ direct confirmation of this process would now be desirable. It could easily be achieved by blind comparison of lesions diagnosed in the past and more recently. It has been suggested that there have been no changes in the diagnostic criteria of melanoma. However, the study¹² on which this opinion was made was not done blind, sections were compared openly without testing the reliability of the comparisons, and no comparisons were made after 1980, which excludes the great increase in reported melanomas that has since occurred. Importantly, this study found a 30–40% increase in the critical group of lesions diagnosed as benign despite some 'dubious' features, which would be clear evidence that there has indeed been a diagnostic shift. This potentially important finding was treated inappropriately and was lost by statistical inclusion in a larger, unrelated group; but perhaps that was as well, as the unacceptably poor methodology of the study makes even this finding uncertain.

The observed site distribution of reported melanomas, both of stage 1 lesions, the predominant cause of the increase, as well as potentially fatal lesions, was mostly on the back, trunk and limbs, and not on the face and neck, which are the main sites of tumours known to be induced by UV. To overcome the poor correlation between the site distribution of melanoma and UV exposure, a 'correction'^{13,14} has been sometimes attempted for surface area, melanocyte or naevus lesion density. However, this is unjustifiable,¹⁵ because it is unknown whether the melanoma precursor cell is an epidermal or follicular melanocyte, or naevus cell. Nor is the pathological relationship of these cells known; we are equally uncertain of their cutaneous distribution. The evidence on melanocyte distribution is usually based on a 1960s study,¹⁶ which was not intended to establish the essential relationship to age, sex, race or environmental changes of both follicular and epidermal melanocytes. Likewise, whereas the crude distribution of clinical naevi is known, the quantitative evidence of the histological distribution of naevus cells, and their precursors, is completely unknown. As this information is necessary before attempting to find whether crude tumour distributions can be made more intelligible, we conclude that, in its absence, present attempts at corrections for surface area or putative precursor cell distribution are unacceptable and irrelevant. By contrast the origin of basal and squamous cell tumours does allow a surface area correction, and when this is done their solar predominance is even more apparent, and that of melanoma is less by comparison. We did not study lesions such as 'lentigo maligna', which often appear on sun-exposed skin of the elderly, which, despite their name, are benign and not malignant melanomas. However, regardless of the effect of UV on melanoma development, the present findings exclude an important role of UV in the increase in lesions reported as malignant over the period studied.

After decades of health professionals advising sun avoidance to protect against cancer, recent epidemiological studies suggest that sun exposure may reduce the incidence of breast, lung, lymphoma, prostate, pancreas and colon cancers^{17–20}

and even the outcome of malignant melanoma itself.²¹ While many findings from such static descriptive epidemiology have proved to be transient, and notwithstanding that the methodology involved is much the same as has been used to associate solar radiation with melanoma, achieving a balance between cutaneous and systemic effects, including those of mood, immune modulation and vitamin D synthesis, needs much more certainty about the benefits and risks of solar radiation.^{20,22,23} Until the necessary research is done, and the true story is established, including proof or refutation of our evidence that the reported increase in 'melanoma' is due to reclassification of benign lesions, encouragement of public anxiety about a melanoma epidemic and excessive avoidance of solar exposure for its prevention is unjustifiable.

There are important additional consequences of the diagnostic drift that our findings have indicated. It may have resulted in unnecessary excisions, health care and insurance costs, let alone the problems and anxieties given to patients and their families. Our findings are also important mechanistically: studies to identify melanoma genes may have been flawed by including benign disease. These findings inevitably challenge the validity of epidemiology studies linking increasing melanoma incidence with UV radiation, and suggest the need for a search for other ways in which the disease may be caused.

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