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# AN ANALYSIS OF A MELANOMA EPIDEMIC

Robert C. BURTON[1,4], Marylon S. COATES[2], Peter HERSEY[1], Graeme ROBERTS[1], M.P. CHETTY[1], Stan CHEN[1], Monica H. HAYES[1], Chris G. HOWE[1] and Bruce K. ARMSTRONG[3]

[1]*Newcastle Melanoma Unit, Wallsend District Hospital, Wallsend, NSW 2287;* [2]*New South Wales Cancer Registry, Sydney, Australia; and* [3]*International Agency for Research on Cancer, Lyon, France.*

**Between 1986 and 1988 the annual incidence of invasive melanoma in the Hunter area of New South Wales, Australia, almost doubled to 52.5 per 100,000 in men and 42.9 per 100,000 in women. These rates have been maintained and are similar to those reported for 1987 in Queensland, Australia, which are the highest in the world. Most of the increase in incidence was in melanomas less than 1.50 mm in thickness, and adults of both sexes and all ages were affected. Thicker melanomas also increased in incidence but only in adults 45 years and older, and mainly in men. An analysis of health insurance data on treatment of skin lesions and data from a histopathology laboratory suggested that diagnosis and treatment of skin lesions generally in the Hunter area had increased almost 2-fold over this period. Advancement of the time of diagnosis and a real increase in incidence were likely explanations for some of the observed trends. Increasing diagnosis of a non-metastasising form of thin melanoma, consequent upon increasing removal of pigmented skin lesions by medical practitioners, may also explain some of the observed increase in the incidence of the disease. This possibility has important implications for proposed population screening programs, and methods are needed to distinguish such lesions, if they exist, from potentially fatal melanoma.**


From the early 1960s to about 1982 the incidence rate of invasive malignant melanoma (melanoma) increased by an average of between 3% and 7% per year both in males and in females in 20 white populations covered by the volumes of Cancer Incidence in Five Continents (Armstrong, 1988). Mortality rates also increased in a number of white populations in this period (Elwood *et al.*, 1989; Scotto *et al.*, 1991; Thorn *et al.*, 1992). Similar increases in incidence and mortality have also been reported from Australia (Giles *et al.*, 1989).

Recently there have appeared a number of reports of large increases in the incidence of melanoma in 5 regions of New Zealand, 4 Australian States and in Scotland (Brown and Palmer, 1991; Jones *et al.*, 1992; MacLennan *et al.*, 1992; Cooke *et al.*, 1992; McCredie *et al.*, 1992; Mackie *et al.*, 1992). According to those reports, incidence rates increased by 68% to 116% in males over periods of 2 to 7 years, and by 33% to 109% in females over periods of 4 to 8 years. These recent increases seem unexpectedly large against the background of the preceding long-term trends.

We too have observed a recent, rapid increase in the incidence of melanoma in the Hunter area of New South Wales (NSW), Australia, and have taken the opportunity to collect data which might shed light on the reasons for this increase and why it is not consistent with preceding trends.

## MATERIAL AND METHODS

The Hunter area of New South Wales (NSW) is located on the east coast of Australia, approximately 100 km north of Sydney. Its population in 1986 was 469,001 persons, approximately 95% Caucasian, of whom 285,158 resided in the city and suburbs of Newcastle (Hunter Health Statistics, 1990). In response to evidence provided by the Newcastle Melanoma Unit (NMU) that the incidence of melanoma had risen sharply in the area in 1987, the NSW Cancer Registry assigned staff to record accurately the incidence of invasive melanoma in the Hunter area for the period 1981 to 1987 inclusive. The staff visited all pathological laboratories in the Hunter area that provide histopathological services, plus certain laboratories in Sydney known to receive specimens from the Hunter area. Data for the Hunter area have also been obtained from the NSW Cancer Registry for 1976, the last year of the 1970–76 epidemiological survey of melanoma in NSW (McCarthy *et al.*, 1980), and for 1988 to 1990. In addition, Australian Bureau of Statistics data on mortality from melanoma by year during the 1980s for NSW as a whole were obtained from the NSW Cancer Registry.

Data were obtained from the Australian Federal Government Health Insurance Commission (HIC) for the financial years 1984–85 through 1990–91 for all patients in the Hunter area of NSW for whom Medicare benefits were paid to a medical practitioner either for a skin biopsy or for excision of one or more skin tumours, cysts, ulcers, or scars up to 3 cm in diameter. These items accounted for 95% or more of all patients in each year who had (a) skin lesion(s) excised for which benefits were claimed. In addition, data were obtained for items which covered all other means of destroying skin lesions. All residents of Australia are eligible to receive Medicare benefits for these services. Payment for treatment of skin lesions in Australia does not depend upon referral of the lesion for histopathological diagnosis, and there was no change in these payment arrangements during the period of the study.

The NMU was set up in 1980 and collects data on the majority of all new melanoma patients in the Hunter area. More detailed data than could be obtained from the Cancer Registry were provided by the NMU for the period 1981–90 during which 87% of all the new Hunter melanoma patients who were reported to the Cancer Registry were also registered with the NMU. These data included the thickness of all but 40 of the primary cutaneous melanomas removed from the 1621 patients registered with the NMU in this period. In addition, 2 pathologists experienced in the diagnosis of melanoma (GR and MPC) audited the histopathology of 159 (87%) of the 182 new patients registered at the NMU with possible Stage-I invasive melanoma in 1987. GR examined the histological slides of 120 of these 159 patients (75%), using the same criteria for the diagnosis of melanoma (McGovern *et al.*, 1973, 1986) that he had used in the 1970–76 survey of melanoma in NSW (McCarthy *et al.*, 1980; Roberts *et al.*, 1981). In the 1970–76 study he examined a random sample of 449 histological sections from the 5611 new melanoma patients identified in NSW; independent review of 100 of these sections by Dr. A. Breslow confirmed his histopathological findings (McCarthy *et al.*, 1980).

## RESULTS

### *Incidence of invasive melanoma*

The number of cases of invasive melanoma recorded each year by the NSW Cancer Registry and the NMU for the period 1981–1990 are shown in Figure 1. For both sets of data annual numbers were relatively steady until 1987, when there was a sharp rise. This rise continued in 1988 but stopped in 1989 and

[4]To whom correspondence and reprint requests should be sent.

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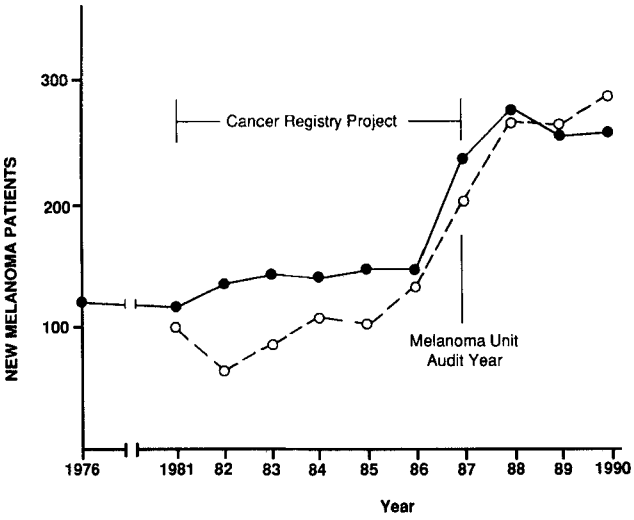


FIGURE 1 – Trends in registration of new cases of melanoma in the Hunter area as recorded by the Newcastle Melanoma Unit (○--○) and NSW Cancer Registry (●—●), 1976 to 1990.

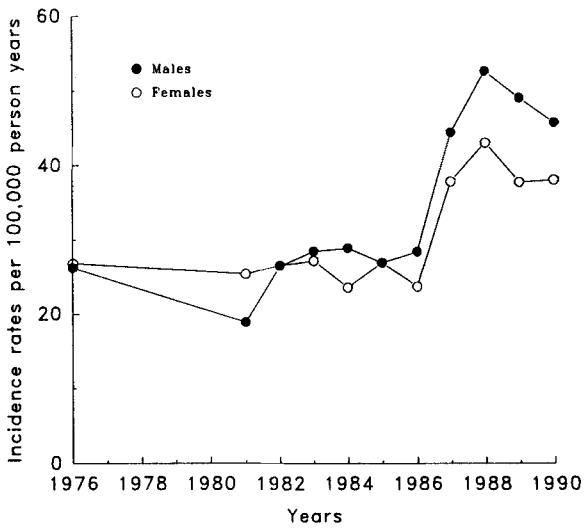


FIGURE 2 – Trends in age-standardized incidence of melanoma in the Hunter area, 1976 to 1990.

1990. Registration with the NMU has continued at this higher level, with 295 new patients in 1991 and 334 in 1992. Between 1986 and 1988 the number of cases of melanoma diagnosed in the Hunter area more than doubled.

Corresponding age-standardized incidence rates (the "world" population was used as the standard; Boyle and Parkin, 1991) are shown in Figure 2. In males the rate per 100,000 person years was 26.2 (95% confidence interval (CI) 20.0 to 32.4) in 1976 and 28.3 (CI 21.9 to 34.7) in 1986. The corresponding rates for females were 26.8 (CI 20.5 to 33.1) in 1976 and 23.6 (CI 17.8 to 29.4) in 1986 (Figure 2). The rates then increased to 52.5 (CI 43.9 to 61.1) in males and 42.9 (CI 34.9 to 50.9) in females in 1988.

Figure 3 shows the age-specific incidence trends. All those 20 years of age and older were affected by increases in incidence. The largest increases were in the oldest age group (65+), where there was almost a 2-fold increase in males (1986: 110.8, CI 66.2 to 155.4; 1988: 198.7, CI 141.1 to 256.3) and a more than 60% increase in females (1986: 70.0, CI 39.5 to 100.5; 1988: 114.3, CI 74.7 to 153.9). For comparison with these incidence trends, age-specific mortality rates for NSW as a whole during the 1980s are shown in Figure 4 (Hunter deaths were too few in number for useful analysis). These data show evidence of increasing mortality in males and females over the age of 65 years, with males being affected more than females. In contrast, trends in those aged less than 65 years were flat, with perhaps some evidence of falling mortality in those aged 20 to 44 years.

*Trends in skin-lesion excision and destruction*

The number of Hunter area patients having one or more skin lesions excised increased on average by 14% per year between July 1, 1984 and June 30, 1991 (Fig. 5). The population of the Hunter area was stable in the 1980s, being 472,785 persons in 1981 and 469,001 persons in 1986 (Hunter Health Statistics, 1986, 1990). In the same period the number of patients having skin lesions destroyed by means other than excision increased on average by 58% per year. The rate of excision of skin lesions showed a sharp rise above the existing trend between 1986/87 and 1987/88 and then returned to the previous trend. The rate of skin-lesion destructions showed a similar sharp rise which has continued through 1990–91.

*Pathology data*

In 1987, 182 Hunter area residents with a new histopathological diagnosis of possible invasive Stage-I melanoma (27 pathologists) were referred to the NMU. After review by GR and MPC the diagnosis was accepted in 174 patients. In 4 patients the diagnosis was changed to a naevus and in 4 others the melanoma was graded as non-invasive (*in situ*).

The pathology laboratory which performed the histopathology for most of the patients referred to the NMU cooperated in a review of the reports of its 1984 and 1988 skin histopathology data. This laboratory consistently received more than 50% of melanomas referred for diagnosis in the Hunter area between 1981 and 1990. The results of this review revealed a 2-fold increase, from 4696 to 9814, in the number of skin lesions referred for diagnosis between 1984 and 1988. The number of Hunter area patients having skin lesions treated by excision or destruction doubled (12,120 to 25,913) between 1984/85 and 1988/89 (Fig. 5). Therefore the ratio of skin lesions referred to that laboratory for diagnosis to total patients having skin lesions treated in the Hunter area remained constant over this time period. Between 1984 and 1988 the number of melanomas diagnosed by that laboratory also doubled (91 to 197), and the number of naevi tripled (1065 to 3208). This resulted in a fall in the ratio of melanomas to naevi diagnosed from 1 to 11 in 1984 to 1 to 16 in 1988.

*Trends in melanoma thickness*

The thicknesses of melanomas registered with the NMU were compared for two 2-year periods on either side of the sharp rise in incidence, 1984–85 and 1988–89. Those under 20 years of age were omitted from this analysis, since only 20 of the 754 new patients registered in those 4 years were in this age range. The greatest increase in registration rates was in melanomas less than 1.50 mm in thickness (Table I). These thin melanomas accounted for 135 of the 222 new patients registered in 1984–1985 (60.8%) and for 386 of the 522 new patients registered in 1988–1989 (73.9%). The increase in thin melanomas was more than 3-fold in all adult male age groups (Table II), and was 2- to 8-fold for adult females, depending on the age group, with the greatest relative increase occurring in older women. Registration rates of intermediate thickness (1.50 to 3.00 mm) and thick (>3.00 mm) melanomas also increased (Table I), but relatively much less and mainly in those over 65 years of age (Table II). There was no increase in registration rates of thicker melanomas in the youngest age group in either sex. Preliminary analysis of the 1990–91 NMU thickness data (data not shown) has shown that the 1988–89

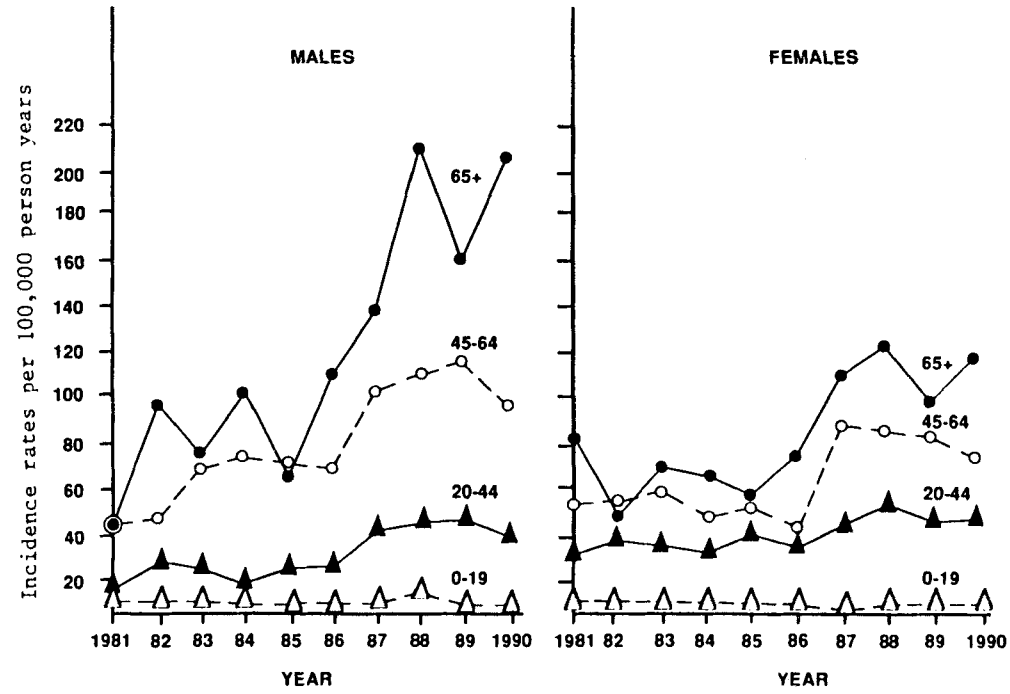


FIGURE 3 – Trends in age-specific incidence rates of melanoma in the Hunter area, 1981 to 1990.

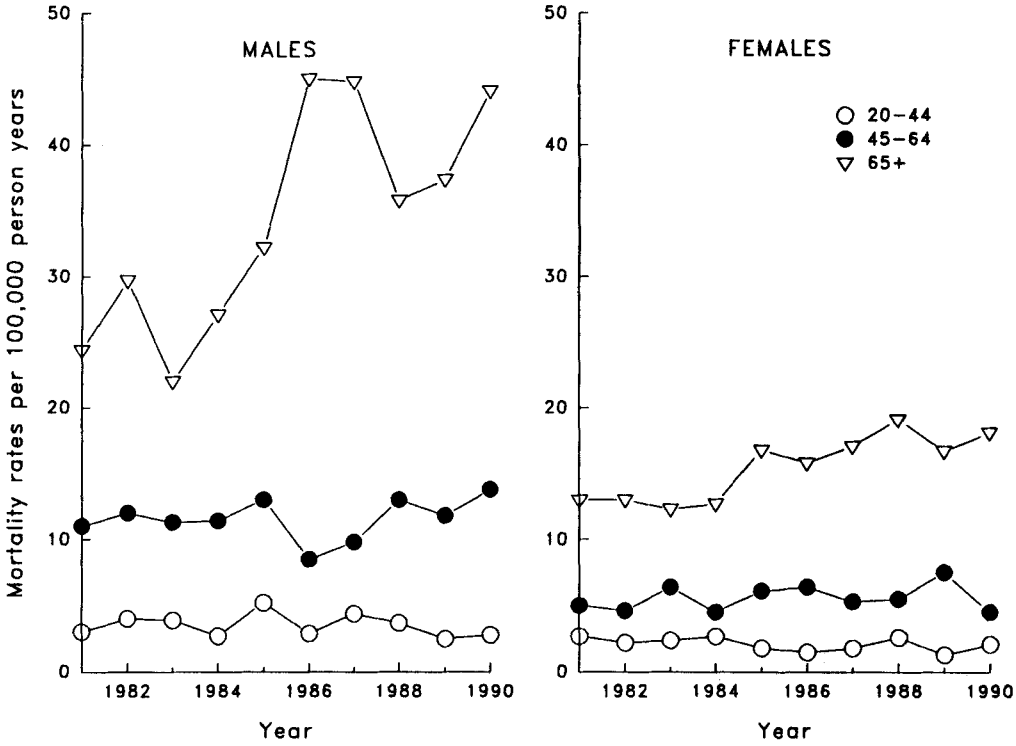


FIGURE 4 – Trends in age-specific melanoma mortality rates in NSW, 1981 to 1990.

pattern has persisted, with 74.7% of new melanomas being less than 1.50 mm in thickness.

## DISCUSSION

We have observed sharp increases in the incidence of melanoma in the Hunter area of NSW between 1986 and 1988. All adult age groups were affected in both sexes, with those aged 65 years or older showing the greatest increases. Most of the increase was accounted for by melanomas less than 1.50 mm thick, although intermediate thickness and thick melanomas also increased in older age groups. Similar trends, including a sharp rise in incidence in the mid-1980s preceded and followed by a relative plateau, have recently been reported for

some other Australian populations (Jones *et al.*, 1992; McCredie *et al.*, 1992).

There are several possible explanations for these incidence increases: improved ascertainment of all lesions diagnosed; a change in the application of histopathological criteria for distinguishing between invasive and non-invasive melanomas or between melanomas and benign melanocytic lesions; an increase in the fraction of excised skin lesions being referred by medical practitioners for histopathological examination; advancement of the time of diagnosis because of increased public and professional concern about the disease; increasing detection of a form of melanoma which, if not detected, would either not progress or would regress spontaneously; and a real increase in the incidence of melanoma.

Increased ascertainment of diagnosed melanoma is an unlikely cause for the increase. Incidence data for 1981–1987 were collected in a standard manner from all applicable histopathology laboratories by Cancer Registry staff. The same staff abstracted data for all years at the same time. Since 1988 was not subject to the same incidence ascertainment efforts, a fall rather than a rise in new patients might have been expected in that year if ascertainment was a problem.

Appreciable changes in histopathological diagnosis are also unlikely. Expert audit of the 1987 NMU new patients confirmed the diagnosis of invasive melanoma in 151 of the 159 slides examined (95%). The diagnostic criteria used in this audit were the same as those which had been used in the 1970–76 NSW epidemiological survey. In a substantial study of trends in histopathological diagnosis of melanocytic lesions, Van der Esch *et al.* (1991) found minimal change in diagnostic practices on review of histopathological slides of melanomas and naevi in a number of countries over the period 1950 to 1980. Among the investigators reporting recent increases in the incidence of melanoma, MacKie *et al.* (1992) systematically checked and found no evidence that histopathological criteria had changed over the period of the increase.

If there had been a change in medical practice between 1984 and 1988, with medical practitioners referring for histopathological diagnosis skin lesions they would formerly have destroyed or excised and discarded, then the ratio of the numbers of skin lesions diagnosed histopathologically by the main pathology laboratory to the total number of patients having skin lesions treated in the Hunter area should have risen. No such change was evident.

Advancement of the time of diagnosis of melanoma due to increasing concern about the disease is a possibility. Indeed, sudden increases in diagnosis of melanoma in Australia have been attributed to the nationwide screening of a current-affairs television program on melanoma in October 1987 and January 1988 (McCarthy and Shaw, 1990; Theobald *et al.*, 1991). In the Hunter area the NMU registered 185 new patients in the year July 1 1986 to June 30 1987 and 343 new patients in the following year, during which these screenings took place. Over this same period the number of Hunter patients having one or more skin lesions excised increased by 60% (Fig. 5), and over a 4-year period, which includes these 2 years, the main pathology laboratory recorded a 3-fold increase in referrals of lesions diagnosed as naevi with a fall in the ratio of melanomas to naevi diagnosed. A rapid increase in the excision rates of skin lesions over the period described above was also recorded for NSW (McCarthy and Shaw, 1990) and for Australia as a whole (data not shown). Therefore, there is substantial evidence of a rapid increase in excision of "suspicious" pigmented skin lesions which would be expected to lead to advancement of the time of diagnosis of the disease in many patients.

However, if the increase was simply due to advancement of the time of diagnosis, a concurrent or subsequent fall in the incidence of thicker melanomas would have been expected, as would a later fall in total incidence. No such falls have yet been observed. Indeed, following the rise there has been a plateau in total incidence extending to 1990 (Fig. 2) and to 1992 for NMU registrations. Moreover, if the real, underlying incidence of melanoma in the Hunter area is accurately represented by the plateau which extended from 1976 to 1986 (Fig. 1, NSW Cancer Registry data), which averaged 137 patients per annum, then the 1655 patients registered at the NMU between 1986 and 1992 would contain 833 patients in excess of those expected to occur, or all the new melanoma patients that would have been expected to be diagnosed between 1993 and 1998. Advancement of the time of diagnosis, therefore, is not an attractive explanation for all of the increase in incidence.

The picture of a sharp increase in incidence in mainly thin melanomas followed by a new, higher, steady incidence rate is

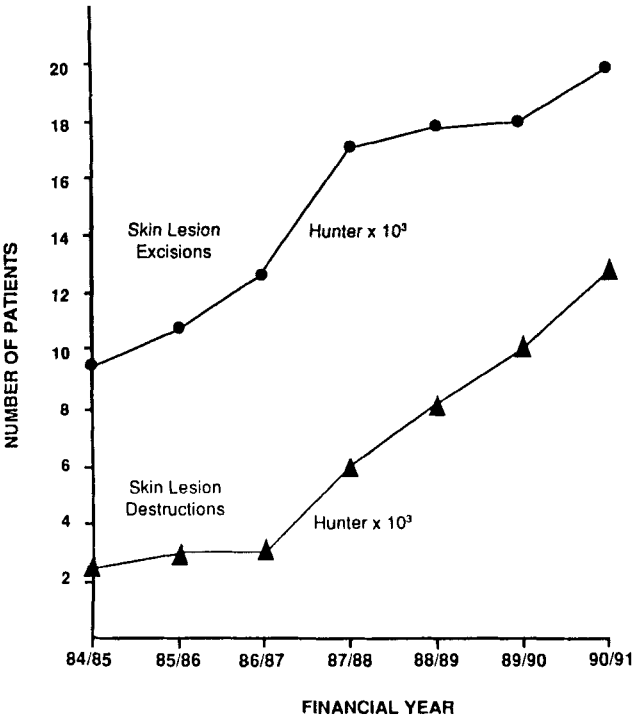


FIGURE 5 – Trends in excision and destruction of skin lesions for patients in the Hunter area, 1984/85 to 1990/91.

TABLE I – ANNUAL AVERAGE RATES OF REGISTRATION OF MELANOMA, BY SEX AND THICKNESS, WITH THE NEWCASTLE MELANOMA UNIT 1984–1985 AND 1988–1989

| Thickness | Years | Males | | | Females | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Number | Rate | C.I. | Number | Rate | C.I. | Number | Rate | C.I. |
| Less than 1.50 mm | 1984–1985 | 58 | 18.2 | 13.5–22.9 | 77 | 23.6 | 18.3–28.9 | 135 | 20.9 | 17.4–24.4 |
| | 1988–1989 | 202 | 63.3 | 54.6–72.0 | 184 | 56.4 | 48.2–64.6 | 386 | 59.8 | 53.8–65.8 |
| 1.50 to 3.00 nm | 1984–1985 | 26 | 8.1 | 5.0–11.2 | 21 | 6.4 | 3.6–9.2 | 47 | 7.3 | 5.2–9.4 |
| | 1988–1989 | 46 | 14.4 | 10.2–18.6 | 31 | 9.5 | 6.2–12.8 | 77 | 11.9 | 9.2–14.6 |
| 3.00+ mm | 1984–1985 | 28 | 8.8 | 5.6–12.0 | 12 | 3.7 | 1.6–5.8 | 40 | 6.2 | 4.3–8.1 |
| | 1988–1989 | 36 | 11.3 | 7.6–15.0 | 13 | 4.0 | 1.8–6.2 | 49 | 7.6 | 5.5–9.7 |

TABLE II – ANNUAL AVERAGE RATES OF REGISTRATION OF MELANOMA, BY AGE AND SEX AND THICKNESS, WITH THE NEWCASTLE MELANOMA UNIT 1984–1985 AND 1988–1989

| Thickness | Years | Age | | | | | |
|---|---|---|---|---|---|---|---|
| | | Males | | | Females | | |
| | | 20–44 | 45–64 | 65+ | 20–44 | 45–64 | 65+ |
| Less than 1.50 mm | | | | | | | |
| Number of cases | 1984–85 | 22 | 22 | 14 | 41 | 32 | 4 |
| Crude rate | | 12.1 | 23.9 | 30.9 | 23.9 | 34.7 | 6.4 |
| C.I. | | 7.0–17.2 | 13.9–33.9 | 14.7–47.1 | 16.6–31.2 | 22.7–46.7 | 0.1–12.7 |
| Number of cases | 1988–89 | 73 | 85 | 44 | 80 | 71 | 33 |
| Crude rate | | 40.2 | 92.3 | 97.2 | 46.6 | 77.0 | 53.1 |
| C.I. | | 31.0–49.4 | 72.7–111.9 | 68.5–125.9 | 36.4–56.8 | 59.1–94.9 | 35.0–71.2 |
| 1.50 to 3.00 mm | | | | | | | |
| Number of cases | 1984–85 | 6 | 16 | 4 | 6 | 9 | 6 |
| Crude rate | | 3.3 | 17.4 | 8.8 | 3.5 | 9.8 | 9.7 |
| C.I. | | 0.7–5.9 | 8.9–25.9 | 0.1–17.5 | 0.7–6.3 | 3.4–16.2 | 2.0–17.4 |
| Number of cases | 1988–89 | 5 | 21 | 20 | 4 | 10 | 17 |
| Crude rate | | 2.8 | 22.8 | 44.2 | 2.4 | 10.9 | 27.4 |
| C.I. | | 0.4–5.2 | 13.1–32.5 | 24.8–63.6 | 0.1–4.7 | 4.2–17.6 | 14.4–40.4 |
| 3.00+ mm | | | | | | | |
| Number of cases | 1984–85 | 5 | 11 | 12 | 3 | 0 | 9 |
| Crude rate | | 2.8 | 12.0 | 26.5 | 1.8 | 0 | 14.5 |
| C.I. | | 0.4–5.2 | 4.9–19.1 | 11.5–41.5 | 0.0–3.8 | 0 | 5.0–24.0 |
| Number of cases | 1988–89 | 4 | 8 | 24 | 1 | 1 | 11 |
| Crude Rate | | 2.2 | 8.7 | 53.0 | 0.6 | 1.1 | 17.7 |
| C.I. | | 0.0–4.4 | 2.7–14.7 | 31.8–74.2 | 0.0–1.7 | 0.0–3.2 | 7.2–28.2 |

compatible with increasing detection of a class of lesion which, although invasive melanoma histopathologically, behaves clinically in a non-life-threatening manner. Such lesions may have always been present but relatively undetected, and therefore susceptible to increased detection with increasing professional and public attention to the disease. There are a number of reasons for considering this possibility.

First, there is clinical and pathological evidence for a form of melanoma with little capacity to advance. Paul *et al.* (1989) calculated the speed of growth of melanoma based on the correlation between age at diagnosis and tumour thickness in 903 patients diagnosed in Germany between 1975 and 1988. They estimated the time to progress from <0.76 mm to 1.50 mm in thickness was 3 to 4 years, and from 0.76 to 1.50 mm to 1.51 to 3.00 mm about 3 years. A similar calculation based on the data of Shaw and McCarthy (1992) on 1022 NSW patients with thin melanomas, nearly 80% of whom were diagnosed after June 1, 1989, provides an estimate of the time to progress from <0.76 mm to 0.76 to 1.50 mm of 12.8 years. This would suggest either that the current rate of growth of thin melanomas in NSW is 3 to 4 times less than it was in Germany in the recent past, or that thin melanomas now diagnosed in NSW consist of 2 populations, one that is progressive and one that is not.

The latter possibility is consistent with the proposition, made on clinical and pathological grounds, that the invasive radial growth phase of melanoma is common, incapable of metastasis and indolent (Clark *et al.*, 1975, 1989; Guerry *et al.*, 1993). It is possible that some thin invasive melanomas, if left, would never acquire metastatic potential, and remain as a sub-population of non-life-threatening lesions or even regress. It is notable that partial histological regression has been reported in half or more of all thin melanomas examined in some studies, but it appears to be much less common in thick lesions (Blessing and McLaren, 1992; Brogelli *et al.*, 1992).

Finally, large increases in the incidence of melanoma were recorded in all adult age groups in the Hunter area in the 1980s, while mortality rates in NSW were stable over the same period, except in those aged 65 or more years. While it could be argued that 1990 may be too early for a mortality change to have manifested, this difference between incidence and mortality trends is exactly what would be expected from increasing diagnosis of a relatively benign disease.

Could there have been a real increase in the incidence of melanoma in the Hunter area during the late 1980s? Yes. An analysis of trends in mortality for melanoma in Australia to 1978 suggested that birth-cohort-based increases were occurring, but with cessation of the increase in those born around 1930 (Holman *et al.*, 1980). On this basis it was predicted that increases in mortality would continue in Australia into the early part of the 21st century, although affecting progressively older people. This pattern has persisted with the addition of data up to 1989 (Holman *et al.*, 1987; and unpublished data), and would predict continuing real increases in the incidence of melanoma in the latter half of the 1980s in those over 50 years of age. This prediction is consistent both with the observation that increases in incidence of melanomas more than 1.50 mm thick in the Hunter area were essentially confined to the $65^+$ age group, and also with the NSW mortality data. It is not consistent with the sharp, large increase in thin lesions affecting all adult age groups. While the possibility of new carcinogenic exposure affecting all adults and producing mainly thin melanomas cannot be rejected totally, the evidence that any such factor exists for melanoma is weak (Nelemans *et al.*, 1992). Thus trends due to advancement of the time of diagnosis and diagnosis of a previously unrecognized non-metastasising form of melanoma have probably been superimposed on a background of a preceding real increase in the incidence of melanoma in the Hunter area.

If, as we think, a substantial proportion of the observed increase in melanoma incidence in the Hunter area has been due to increased diagnosis of a non-metastasizing form of the disease, then a recent recommendation for the introduction of population screening for melanoma (NIH Consensus Conference, 1992) should be considered cautiously. While undoubtedly leading to some benefit, it is possible that the main result of such a program would be increased diagnosis and treatment of a non-fatal form of the disease. If screening is carried out, it may be best, therefore, to direct it to high-risk groups such as older males where thicker melanomas are most prevalent (Hersey *et al.*, 1991), and where a real increase in incidence is continuing. In addition, screening should be rigorously evaluated, both for its effectiveness in preventing death from cancer and its cost (not only in economic terms) before it is recommended as public policy.

We do however support the research directions proposed by the NIH Consensus Conference (1992) for melanoma, which

include "determining the cellular characteristics associated with malignancy, invasion and metastasis". We are currently planning to reprocess and re-examine random samples of thin melanomas which were excised from patients in the Hunter area before and after the sudden rise in incidence to compare the histological types of melanoma, extent of radial and vertical growth phases, presence of histological regression and other markers associated with the prognosis of the disease. In addition, an immunohistological study of the type reported by Elder *et al.* (1989) will be performed on the same specimens using monoclonal antibodies which can detect cell-surface markers in paraffin block specimens. Similar studies are planned for other parts of Australia where there have been sharp increases in the incidence of melanoma.

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