Nodular Type and Older Age as the Most Significant Associations of Thick Melanoma in Victoria, Australia

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Objectives: To explore the clinical associations of thick melanoma and to compare the clinicopathological variables of nodular and superficial spreading types.

Design: Cross-sectional study of all invasive primary melanomas recorded by the Victorian Cancer Registry for 1998 and those reviewed by the Victorian Melanoma Service between October 1, 1994, and April 31, 1999.


Patients: This study included 1422 patients recorded by the Victorian Cancer Registry and 674 patients who had attended the Victorian Melanoma Service; unclassifiable tumor types were excluded, leaving 1144 and 645 patients, respectively, eligible for analysis.

Main Outcome Measures: Melanomas were categorized by thickness into thin (≤1 mm), intermediate (>1-3 mm), and thick (>3 mm) and compared according to patient age, sex, and tumor type and site. Superficial spreading and nodular types were also compared in this manner. Use of the Victorian Melanoma Service database enabled a more comprehensive analysis of historical and phenotypic characteristics.

Results: Thick melanoma was predominantly nodular, occurring in older men, mostly on the head and neck and associated with fewer nevi. Nodular melanoma was thicker and found mostly on the lower limbs or head and neck; it had a greater association with a history of solar keratoses than did superficial spreading melanoma.

Conclusion: Nodular type and older age are the most significant associations of thick melanoma.

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Australia has the highest incidence of melanoma in the world,1 and this incidence continues to increase. The lifetime risk of developing a melanoma for an Australian is estimated to be 1 in 30 before age 75 years.3 On a global scale, the rate of increase in the incidence of melanoma is greater than that of any other malignancy in white populations. The most accurate measure of prognosis with respect to primary cutaneous melanoma is Breslow thickness. Currently, tumors with a thickness less than 1 mm are generally cured with surgery, whereas 5-year survival for those thicker than 4 mm is approximately 50%.3

During the past few decades, large increases in the incidence of melanoma have been reported in various countries, including Australia.4 Most of this increase in incidence has been in thin lesions.1,3,6-9 The substantial decline in median tumor thickness during this period has been attributed to large-scale efforts to improve early detection. Despite these trends, the incidence of thick melanoma is stable or increasing in Australia,1,6 the United States,8 and parts of Europe.10-13

See also pages 603 and 678

These thick lesions are responsible for driving melanoma mortality rates, which have been steadily increasing for many decades in Australia but now seem to be stabilizing in men and declining in women.14 The key measure of success of secondary prevention programs will be a sustained decline in melanoma mortality rates for both sexes. The burden of thick lesions must be reduced if this is to be achieved. Several studies in Australia and elsewhere have shown that thick lesions are more often nodular15-18 and suggest that it is predominantly older men who have these advanced tumors.15-19 There is some evi-
PATIENTS AND METHODS

PATIENTS AND DATA COLLECTION

We based our study on 2 groups of patients with invasive primary melanoma—those derived from the VCR, a state-based cancer registry, and those from the VMS, a state-based multidisciplinary consultative treatment service established in 1994 to coordinate management of cutaneous melanoma. Victoria is the second most populous state in Australia, occupying the southeastern corner of the continent (latitude, 34°–39° south; population, 4.37 million at the 1996 census).

The computerized records of 674 patients attending the VMS at Alfred Hospital between October 12, 1994, and March 31, 1999, were examined. Twenty-nine patients with unclassifiable tumor type were excluded, leaving 645 (337 men and 308 women) eligible for the analysis. We estimate that 6% to 10% of the VCR patients were also included in the VMS dataset, but case matching was not possible because of confidentiality requirements.

The VMS data collection process is as follows. Historical aspects, recorded by an oncology nurse by means of a standardized questionnaire, include previous NMSC, previous SKs, number of blistering sunburns (0, 1–5, or >5), skin phototype (I, II, III, or IV–VI), eye color (blue, green, light brown, or brown), and hair color (blond, red, light brown, brown, or black). All patients are examined by a dermatology registrar and a dermatologist (J.W.K.). Total numbers of melanocytic nevi are grouped (<20, 20–50, >50–100, >100–200, >200) and dysplastic nevi are counted exactly, whereas freckles and solar lentigines are recorded as few, moderate, or many. Histopathologic findings for all cases are reviewed by a single expert dermatopathologist (J.P.D.).

A total of 1422 cases of invasive cutaneous melanoma recorded by the VCR for 1998 were also examined. We excluded 278 patients for which no tumor type was recorded on the pathology report, leaving 1144 (581 men and 563 women) eligible for the analysis. Details held by the VCR were limited to date of birth, date of diagnosis, sex, site, tumor type, thickness, and level.

The VCR, a population-based registry established in 1982, was made possible because of amendments to the Victorian Cancer Act (1958) that made notification of all cancers mandatory for all hospitals and pathology laboratories. Pathology reporting is in the form of full-text copies of the pathologists’ reports. Currently, approximately 250 hospitals and 50 pathology laboratories report cancer to the registry. Incoming notifications are matched against the register to determine whether the case has been reported by another source. Demographic details and International Classification of Diseases, Ninth Revision,20 and International Classification of Diseases–Oncology21 codes for tumor site and histologic features, respectively, are entered into the system and then examined for internal consistency and completeness. Further notifications or inconsistent data are resolved by follow-up with notifying agencies or by reference to the VCR’s consultant pathologist.

For the purpose of the analyses, tumor thickness was categorized into 3 groups—thin (≤1 mm), intermediate (>1–3 mm), and thick (>3 mm). These categories were chosen to make best use of the available data considering that melanoma thickness has been shown to represent a steady continuum of risk with no natural break points.

Tumor type was classified as SSM, NM, or lentigo maligna melanoma according to the classification systems of Clark et al22 and McGovern et al.23 Nodular melanoma is characterized by dermal invasion wherever there is intraepidermal growth, that is, vertical growth without evidence of an associated radial growth phase. If the intraepidermal component extends beyond the width of 3 rete ridges beyond the invasive component in any section, the melanoma is classified as having a radial growth phase. Superficial spreading melanoma is the archetypal radial growth phase melanoma and is characterized by a pagetoid distribution of malignant melanocytes. Lentigo maligna melanoma is characterized by the proliferation of atypical melanocytes along the dermoeipidermal junction and downward appendages in association with atrophy and solar elastosis. A final group, designated “other,” referred to a variety of less common types of melanoma, including acral lentiginous, desmoplastic, spitzoid, and spindle cell melanoma, which were grouped because of low numbers. Within the VCR data set, this also included balloon cell and nevoid melanoma. Categories for age were 30 years and younger, 31 to 50 years, 51 to 70 years, and older than 70 years. Tumor site was recorded as anterior trunk, back, head and neck, and upper or lower limb.

STATISTICAL METHODS

The association of thickness category with age group, sex, and tumor type and site was tested using the χ² statistic. Mean tumor thicknesses for age group, sex, and tumor type and site were calculated, and differences between groups were tested using t tests and analysis of variance. Logistic regression was used to examine the risk of having a thick melanoma (>3 mm) compared with having a thin melanoma (≤1 mm) by the variables age group, sex, and tumor type and site. Similar analyses were performed for tumor type (NM vs SSM) with the variables age group, sex, thickness category, and site. Statistical analyses were performed using a software program (SPSS, release 9.0.1; SPSS Inc, Chicago, Ill).

dence16–30 suggesting that the head and neck is a relatively more common site for thick melanoma.

However, these studies of thick melanoma are limited in their examination of phenotypic associations. Therefore, the first objective of our study was to examine a broad range of phenotypic factors associated with thick melanoma to identify potential risk groups. Our study aimed to confirm the results of previous studies in this area and to examine additional risk factors, such as the association between melanoma thickness and dysplastic nevus and total nevus numbers along with numbers of solar keratoses (SKs) and history of sunburns or nonmelanoma skin cancer (NMSC). We hoped to identify goals for screening strategies and public education programs aimed at early detection.

Our second objective was to examine the tumor type most associated with thick melanoma, namely, nodular melanoma (NM), and to compare this with the most common tumor type, superficial spreading melanoma (SSM), to identify any associations with the phenotypic factors.
Our study was based on 2 databases. The Victorian Melanoma Service (VMS) database incorporates detailed phenotypic data and is supported by a review of all histopathologic findings by a single expert dermatopathologist (J.P.D.). The VMS is a subset of cases held by the population-based Victorian Cancer Registry (VCR). Our study examines both of these Victorian sets of data.

### RESULTS

#### CHARACTERISTICS OF THICK MELANOMA

##### Victorian Cancer Registry

The sex ratios (masculinity) for thin, intermediate, and thick melanomas were 0.93:1, 1.15:1, and 1.72:1, respectively. Thick melanomas were predominantly NM and were found on older persons, particularly on the head and neck (Table 1).

The significant variables in the univariate analyses were entered into a multivariate analysis, with thick vs thin lesions as the outcome variable. Superficial spreading melanoma and upper limb were the reference groups for type and site, respectively. After adjusting for other variables, NM (odds ratio [OR], 67.05; 95% confidence interval [CI], 32.56-138.07) and the rarer variants of melanoma (OR, 7.21; 95% CI, 2.74-18.98) were more likely to be thick. Older persons (OR, 1.06; 95% CI, 1.04-1.08) were more likely to have thick lesions than were younger persons. Men (OR, 1.63; 95% CI, 0.91-2.89) were somewhat more likely than women to have thick lesions, but this did not reach statistical significance. When other factors were accounted for, there were no significant differences in tumor site between thick and thin lesions.

##### Victorian Melanoma Service

In the univariate analyses of the VMS data, similar results as those from the VCR were seen with respect to thick melanomas. Of 645 patients analyzed, 194 men (30%) and 207 women (32%) had thin melanomas, 93 men (14%) and 78 women (12%) had intermediate-thickness melanomas, and 50 men (8%) and 23 women (4%) had thick melanomas. Thick lesions were more likely to occur in men (2.17:1), to be of nodular type (67%), to be found in older people (67% were >50 years), and to occur on the head and neck (where 22% were >3 mm and 13% were ≤1 mm) or anterior trunk (where 15% were >3 mm and 7% were ≤1 mm). When all factors were considered in the multivariate analysis, patient sex, age, and tumor type and site remained significant. As shown with the VCR data, the OR for NM (OR, 125.41; 95% CI, 43.82-358.92) was large and that for age (OR, 1.05; 95% CI, 1.02-1.08) was small. The association with male sex was significant (OR, 5.81; 95% CI, 2.18-15.43). Melanomas on the anterior trunk (OR, 13.79; 95% CI, 2.01-94.82) and lower limb (OR, 8.62; 95% CI, 1.58-46.89) were more likely to be thick than those on other sites, although the confidence intervals were wide.

The historical details and phenotypic characteristics recorded for each VMS case were also examined according to the thickness categories. Total nevus number was the only variable to show a significant association with tumor thickness, with thicker lesions being associated with lower nevus counts (Table 2). Variables that did not show an association with thick melanoma included history of NMSC, history of SKs, history of blistering sunburns, number of dysplastic nevi, number of freckles, number of lentigines, skin prototype, hair color, and eye color.

#### Table 1. Association of Melanoma Thickness Categories With Patient Sex and Age and Tumor Type and Site in 1144 Patients Recorded by the Victorian Cancer Registry in 1998

<table>
<thead>
<tr>
<th>Thickness, mm</th>
<th>Sex</th>
<th>Type</th>
<th>Age, y</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>≤30</td>
<td></td>
</tr>
<tr>
<td>≤1 (n = 808)</td>
<td>389 (48)</td>
<td>419 (52)</td>
<td>53 (7)</td>
<td>54 (7)</td>
</tr>
<tr>
<td>&gt;1-3 (n = 211)</td>
<td>113 (54)</td>
<td>98 (46)</td>
<td>5 (2)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>&gt;3 (n = 125)</td>
<td>79 (63)</td>
<td>46 (37)</td>
<td>4 (3)</td>
<td>7 (6)</td>
</tr>
</tbody>
</table>

**P Value**

- <.005
- 0.88
- 3.19
- 0.88
- 2.43
- 0.88
- 1.27
- 1.66
- 1.08
- 0.86
- 0.88
- 0.89
- 1.18
- 1.10
- 1.59
- 1.04
- 1.32

*Data are given as number (percentage) of patients. SSM indicates superficial spreading melanoma; NM, nodular melanoma; and LMM, lentigo maligna melanoma. Data given by site do not reach totals because some occurred on other sites not listed here.

†χ² Test for difference in proportions.
COMPARISONS BETWEEN NM AND SSM

Victorian Cancer Registry

The sex (masculinity) ratios for SSM and NM were 0.92:1 and 1.19:1, respectively. Nodular melanoma showed a slight male preponderance that did not reach statistical significance \( (P = .08) \). Most NMs were thicker than 3 mm and occurred in older persons. Nodular melanoma showed a predilection for lower limb and head and neck sites (Table 3).

A multivariate analysis was performed with NM vs SSM type as the outcome variable. Thin lesions and upper limb were the reference groups for thickness and site, respectively. After adjusting for other variables, lesions thicker than 3 mm were highly likely to be NM (OR, 57.78; 95% CI, 30.47-109.54). Lesions of intermediate thickness were also more likely to be NM (OR, 16.15; 95% CI, 9.39-27.78) than SSM. With respect to tumor site, lesions on the lower limb (OR, 2.44; 95% CI, 1.32-4.51) or head and neck (OR, 2.42; 95% CI, 1.23-4.77) were more likely to be NM. Age was no longer significantly associated with NM after adjusting for other variables.

Victorian Melanoma Service

Of the 581 patients analyzed, the distribution by type and sex was as follows: 241 men (41%) and 216 women (37%) had SSM and 68 men (12%) and 56 women (10%) had NM. Sex (masculinity) ratios for SSM and NM were 1.12:1 and 1.19:1, respectively. The univariate analyses of the VMS data demonstrated that NM was more likely than SSM to be thicker than 3 mm (OR, 57.78; 95% CI, 30.47-109.54). Lesions of intermediate thickness were more likely to be NM (OR, 16.15; 95% CI, 9.39-27.78) than SSM. With respect to tumor site, lesions of intermediate thickness were also more likely to be NM (OR, 16.15; 95% CI, 9.39-27.78) than SSM. The VMS data indicate that thick melanoma is predominantly nodular (56%) and mainly affects older persons (87% were >50 years). Men are affected more than women (2:1), and the head and neck is the most common site (35%). When all factors are considered together, nodular type and older age are the only significant predictors of thickness. Furthermore, nodular type proved to be the single most important determinant of thick melanoma. The VMS findings were similar to those of the VCR, although male sex remained a significant variable in multivariate analysis. The VMS analysis produced a novel finding in the association between thick melanoma and lower numbers of melanocytic nevi.

The key difference between NM and SSM was thickness, and this was apparent for both sets of data. Nodular melanoma showed a predilection for the head and neck and the lower limb in the statewide data alone, whereas the VMS data demonstrated that older age was a differentiating feature. In addition, NM showed an association with SKs, although there was no difference with respect to history of NMSC.

The significance of nodular type and older age has been demonstrated in several studies\(^ {15,18,24} \) examining thick melanoma. Hersey et al\(^ {16} \) found that 62% of melanomas thicker than 3 mm were nodular and that 75% were in patients older than 50 years. A Swedish study\(^ {15} \) demonstrated that nodular type is the most significant determinant of thick melanoma.

There is some evidence for a site predilection for thick melanomas. Several studies\(^ {16,18} \) concur that the head and neck is a more common site for thick lesions, and our data support this finding. Both data sets showed a pre-
dilection of thick lesions for the head and neck, but this did not remain significant in the multivariate analyses. Hanrahan et al\textsuperscript{14} made the same observation that tumor site was not related to thickness when tumor type was taken into account. Nodular melanoma, however, was associated with head and neck location in the multivariate analysis of the VCR data.

Similarly, there does not seem to be a consensus regarding sex. Although thick melanoma seems to occur more often in men, this has not been observed in every study. Hersey et al\textsuperscript{15} showed that more than two thirds of melanomas thicker than 3 mm occurred in men, and this trend has been supported elsewhere to lesser degrees.\textsuperscript{13,14} On the other hand, the New York Melanoma Cooperative Group found no difference in thickness between women and men in a study of more than 700 cases.\textsuperscript{17}

Multiple factors seem to contribute to the development of thick melanoma, including factors intrinsic to NM and those intrinsic to the elderly. There is now evidence\textsuperscript{23} to suggest that NM grows more rapidly, possessing greater biological “aggressivity” than other tumor types. It is established that NM has a poorer prognosis than SSM, but in a large study of prognostic factors,\textsuperscript{24} this was attributed to thickness alone. A few groups\textsuperscript{25,26} have shown a poorer prognosis for nodular growth pattern independent of tumor thickness.

Our data suggest that thick melanoma and NM occur more often on sites that are easily visible. There is evidence that thick lesions are no more likely than thin lesions to be found on sites that are difficult to observe.\textsuperscript{15} This is in conflict with the conclusion of Hanrahan et al\textsuperscript{24} that a predilection for “hard-to-see” sites is one of the key explanations why older persons develop thick melanomas. This particular study\textsuperscript{24} has also shown that persons 50 years and older are only marginally less likely (0.86:1) to recognize the changes of melanoma than are younger persons, which suggests that most possess the skills required to detect these tumors. Although the elderly have more benign pigmented lesions such as seborrheic keratoses, they tend to have fewer melanocytic nevi\textsuperscript{27} to obscure the detection of melanoma.

We showed an association between thick melanoma and fewer nevi, and this may be related to a greater average age of patients with thick lesions. Perhaps it is also related to the observation that NMs, which comprise most of the thick lesions, are less nevus associated than SSMs. Evidence suggests that this applies to clinical counts of total nevi\textsuperscript{20,31} and the histologic association of a preexisting nevus.\textsuperscript{31,32} It is also possible that persons with large numbers of nevi are more aware of their risk of melanoma and detect their melanomas earlier or receive closer medical surveillance.

Ambivalence on behalf of the elderly regarding their health and poorer medical care may also contribute to the problem of advanced melanoma. In some studies,\textsuperscript{20,27,33} age has been found to be an independent poor prognostic indicator, although this is only weak and considered by other researchers\textsuperscript{28} to be largely related to tumor thickness.

Allowing for the interplay between these factors, it follows that NMs are more difficult to diagnose at an early stage. Although the “ABCD” system of melanoma diagnosis has promoted the early diagnosis of flat lesions with radial growth, NMs often fail to fulfill these diagnostic criteria.\textsuperscript{35} Nodular melanomas are clinically distinct from melanomas with radial growth in that they are usually of smaller diameter, more symmetrical in shape, more uniform in color, and frequently amelanotic. At the same time, the diagnostic features of early NM are yet to be clearly defined. Hanrahan et al\textsuperscript{24} found that changes in sensation and bleeding were reported more often by patients with NM vs SSM, whereas a change in color was reported significantly less frequently.

In our comparison of NM and SSM, the one consistent difference was tumor thickness. The site predilection for the head and neck and the lower limb demonstrated in the VCR data for NM was not borne out in the VMS data. Conversely, the association of NM with older age was seen only in the VMS data. We were unable to show any major difference with respect to historical and phenotypic variables, except for the association between a history of SKs and NM. Although age and sex may be partly responsible as confounding variables, this association with the subtype NM (albeit weak) has not been reported previously, to our knowledge.

Solar keratoses can be considered a marker of cumulative sun exposure, and case-control studies\textsuperscript{36,37} have shown that they are a significant risk factor for melanoma. The association between numbers of SKs and melanoma was no different between histologic subtypes in one recent Australian study,\textsuperscript{37} although NM has been linked to a greater degree of solar elastosis than SSM.\textsuperscript{38} The relationship between melanoma and sun exposure is complex and difficult to study. Although the incidence of NMSC (particularly squamous cell carcinoma) corresponds well with cumulative sun exposure, epidemiologic evidence\textsuperscript{39} indicates that melanoma risk corresponds more with intermittent sun exposure and severe sunburns. A Canadian study\textsuperscript{40} of 719 invasive melanomas (only 7% of which were lentigo maligna melanoma) suggests that the density of melanoma on (continuously) sun-exposed sites is higher than that on sun-protected (ie, intermittently exposed) sites in persons older than 50 years, but the converse is true for those younger than 50 years. These associations of NM with SKs and older age (VMS data) provide clues that cumulative UV exposure may be more important in the causation of NM than of SSM.

There has been some debate about the histogenesis of NM. It has been argued that all melanomas have a common original growth pattern and that the various clinical subtypes represent differences in the timing of onset of vertical growth as well as site-related differences.\textsuperscript{38,41,42} We, along with others,\textsuperscript{35} have identified early NMs (<1-mm thick and Clark level 2). If there is a common initial phase shared by NM and radial growth phase melanomas (SSM, lentigo maligna melanoma, and acral lentigious melanoma) then it would seem to occur so early in their evolution as to be unlikely to be clinically identifiable. Arguments about the histogenesis of NM do not alter the need to improve the early detection of this clinical subtype.

There were limitations to our study. First, although a single expert dermatopathologist reviewed all of the histopathologic findings for the VMS, those recorded by the VCR were derived from a variety of pathology services from around the state rather than a common pathologist. Al-
though a proportion of these pathologists are likely to have expertise in the histopathologic diagnosis of melanoma, we acknowledge that some general pathologists may not classify tumor type in the same rigorous manner as a specialist melanoma dermatopathologist, leading to the potential for bias. The fact that our results for tumor type in the thick category (VMS and VCR) are not dissimilar to those from another large Australian series[16] that examined thick melanoma supports their validity. Second, the VCR data are population based, whereas the VMS data may be subject to referral bias. Finally, the VMS is a tertiary referral service that deals with thicker lesions and those requiring more advanced surgery, and this was reflected in the mean thicknesses for each tumor type. For these reasons we chose to include analyses from both sources.

How then do we improve the secondary prevention of thick melanoma? Older persons clearly represent the high-risk group, in particular, but not exclusively, men. Further work is required to establish the best methods of early detection. The early features of NM need to be investigated, and this is the subject of current research at the VMS. The features of this subtype need to be promoted to the population older than 50 years and to general practitioners. Increased suspicion and a lower threshold for biopsy would also seem appropriate for head and neck lesions that are new or changing. If it becomes apparent that these melanomas truly evade early diagnosis, we may not see much more of an improvement in mortality rates for melanoma. Until this is clarified, this issue remains the most important challenge in the secondary prevention of deaths from melanoma.

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