RESEARCH COMMUNICATION

# Are Cutaneous Melanomas of Specified Thickness Showing Deeper Levels of Invasion at Diagnosis?

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## Abstract

**Secular trends in Clark level were investigated by Breslow category for 8,432 invasive cutaneous melanomas diagnosed in South Australia in 1980-2000. More recently diagnosed lesions were found to have deeper levels. After adjusting for age at diagnosis, tumour site, histology, and thickness measured in half millimetres, the relative odds (95% confidence limits) of penetration to the reticular dermis or subcutaneous fat were 1.99 (1.59, 2.50) for the 1987-93 diagnostic period, and 2.82 (2.25, 3.54) for 1994-2000, when compared with 1980-86. After adjusting for melanoma thickness, the secular trends for deeper lesions applied to a broad cross-section of socio-demographic sub-groups, tumour sites, and histological types. While this similarity in trend would be consistent with a measurement effect, a real change cannot be ruled out and increased emphasis on earlier detection may be warranted. The prognostic implications of changes in inter-relationships between measures of thickness and level require periodic re-evaluation.**

**Key Word**: Cutaneous melanomas - Clark level of invesion - Breslow thickness - measurement effect

*Asian Pacific J Cancer Prev,* **4**, 307-311

## Introduction

Clark level of invasion and Breslow thickness were proposed as staging systems for cutaneous melanoma around 1970 (Clark et al, 1975; Breslow, 1979) and subsequently were incorporated into the TNM classification (Balch et al, 2001; Sobin and Wittekind, 2002). Clark level was categorised as 1 to 5 depending on depth of invasion of the lesion through levels of the dermis to the sub-cutaneous fat. By comparison, Breslow thickness was a measure by micrometer of the depth in millimetres (to 2 decimal places) of invasion of the dermis.

Both measures are highly predictive of survival (Herlyn et al, 2001). For example, in South Australia, 10-year survival from invasive melanoma has ranged from 96.9% for level 2 (level 1 is for in-situ disease) to 51.4% for level 5; and from 98.0% when the thickness did not exceed 0.75mm to 52.9% when it was 3.01mm or more (SACR, 1998). Breslow thickness is considered to be a more objective measure, with greater prognostic reproducibility (Herlyn et al, 2001; Mastranglo et al, 1985), and has been given greater weight than Clark level in recent versions of the TNM classification (Balch et al, 2001; Sobin and Wittekind, 2002; Sobin and Wittekind, 1997).

Secular variations in relationship between Breslow thickness and Clark level have been suggested in South Australia, with deeper levels of invasion applying within individual thickness categories for the more recent diagnostic periods (Luke et al, 2003). The percentage of lesions classified as level 4 or 5 (i.e., penetrating the reticular dermis or sub-cutaneous fat) increased between 1980-86 and 1994-2000 from 2.1% to 4.2% when the thickness was <=0.75mm; 19.0% to 44.0% when it was 0.76-1.50mm; 60.4% to 82.3% when it was 1.51-3.00mm; and 80.8% to 93.7% when it exceeded 3.00mm.

The clinical significance of this trend remains uncertain. We are unaware of methodological changes in measurement that would explain it, although the measurement of Clark level is relatively subjective and the possibility of such changes exists (Herlyn et al, 2001; Mastranglo et al, 1985). Alternatively the trend may be real, reflecting a change in the biology of the disease (Luke et al, 2003). If so, it may

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have prognostic importance and signify a need for earlier detection.

In this study, South Australian Cancer Registry data for 1980-2000 have been used to determine secular trends in Clark level by socio-demographic characteristic, site of lesion, and histological type, after adjusting for thickness. We hypothesised a priori that consistent trends might be more indicative of measurement changes, whereas variable trends might assist hypothesis development in relation to biological explanations.

## Materials and Methods

*Data Collection*

Invasive cutaneous melanomas were diagnosed in 9,519 South Australians in 1980-2000 and notified as a legal requirement to the State Cancer Registry. Data-collection processes have been detailed in annual registry reports (SACR, 1998; SACR, 2001). Data items collected during this period included the ICD-9 4-digit topographical site (WHO, 1977); SNOMED II histological code (College of American Pathologists, 1979); date of diagnosis; age at diagnosis; sex; and location of residence, recorded as Adelaide (the State capital) or a country area.

The SEIFA index also was calculated to indicate socio-economic status (ABS, 1998). This was derived from census data for residential postcodes on income, educational levels and proportions of residents in skilled occupations. Index scores were derived by principal component analysis and categorised into four ordinal categories.

Meanwhile, Breslow thickness was recorded in millimetres (to 2 decimal places) and categorised as <=0.75mm, 0.76-1.50mm, 1.51-3.00mm, and >=3.01mm (Breslow, 1979). Clark level of invasion was coded according to depth of penetration as: 1 for in-situ lesions (not applicable for this study); 2 for the papillary dermis; 3 for the papillary dermis with compression of the reticular dermis; 4 for the reticular dermis; and 5 for the sub-cutaneous fat (Clark et al, 1975). Thickness and level were notified for 90% and 93% of the study group, respectively.

*Statistical Analysis*

A de-identified registry file was extracted and analysed under legal authority of Section 42a of the Public and Environmental Health Act, using STATA 7.0 software (STATA Corporation, 2001). Associations of Breslow thickness and Clark level with diagnostic period (1980-86, 1987-93, and 1994-2000) were tested, using the Spearman rank correlation. Associations of Clark level with diagnostic period were similarly tested within individual Breslow categories.

The relative odds of deep lesions (Clark level 4 or 5) also were analysed using multivariable logistic regression (STATA Corporation, 2001; Armitage and Berry, 1987). Diagnostic period, tumour and socio-demographic variables were entered, with backwards elimination of variables where this did not reduce the fit of the model (p>0.050 for change in chi-square goodness-of-fit) or condition the regression coefficients for diagnostic period. Thickness was entered in half millimetre categories in this analysis to minimise the likelihood of residual confounding. Assumptions underlying the model, such as a lack of colinearity, were tested and found to be met. Acceptable levels of model calibration (Hosmer-Lemeshow chi square (df =8); p=0.243) and discrimination (area under ROC curve=0.922) were found (STATA Corporation, 2001).

In addition, separate multivariable logistic models were developed for individual socio-demographic sub-groups, tumour sites, and histological types to determine the relative odds of deep lesions (Clark level 4 or 5) for successive calendar years, after adjusting for thickness. The relative odds (95% confidence limits) obtained from these models were compared to assess the similarity of secular trends across sub-groups.

## Results

Thickness reduced between the 1980-86 and 1994-2000 diagnostic periods (p<0.001), with the proportion of lesions measuring 0.75mm or less increasing from 42.6% to 57.8%, and the proportion measuring 3.01mm or more reducing from 14.1% to 8.2% (Table 1). While a change in level was not observed for all thickness categories combined (p=0.270), secular trends for deeper levels applied within individual thickness categories (p<=0.012) (Table 2).

Multivariable analysis showed a progressive increase in the relative odds of deep lesions (Clark level 4 or 5) with increase in thickness up to 2.51-3.00mm, but without a consistent progression thereafter (Table 3). Higher relative odds of deep lesions were evident for older than younger age groups and for nodular and desmoplastic than other histological types. Compared with lesions on other sites, those on the trunk and upper limbs had lower relative odds. After adjusting for age, site, histological type and thickness, the relative odds (95% confidence limits) of deep lesions were higher at 1.99 (1.59, 2.50) for 1987-93 and 2.82 (2.25, 3.54) for 1994-2000, when compared with the 1980-86 reference period.

After adjusting for thickness, the relative odds of a deep lesion (Clark level 4 or 5) increased annually in all age groups, all socio-economic strata, males and females, and in both Adelaide and country areas (Table 4). All sub-groups had relative odds with overlapping 95% confidence intervals that encompassed the relative odds for all patients combined of 1.08 (1.07, 1.10). Similarly, after adjusting for thickness, the relative odds of a deep lesion increased annually for each tumour site and most histological types (Table 5). Only acral lentiginous and desmoplastic lesions did not show an increase, but the numbers of these cancers were small (n=58 and 63 respectively) and the 95% confidence intervals of their relative odds were broad. Indeed, all sites and histological types had relative odds with overlapping 95% confidence intervals that encompassed the relative odds for all patients combined.

**Table 1. Percentage Distribution of Breslow Thickness and Clark level of Invasive Cutaneous Melanoma by Diagnostic Period; South Australia, 1980-2000***

| | Diagnostic period | | | |
|---|---|---|---|---|
| | 1980-86 | 1987-93 | 1994-2000 | P value** |
| Thickness (mm): | (n=1,493) | (n=3,085) | (n=3,971) | |
| ≤ 0.75 (n=4,622) | 42.6 | 54.7 | 57.8 | |
| 0.76-1.50 (n=2,008) | 25.3 | 22.9 | 23.3 | p<0.001 |
| 1.51-3.00 (n=1,088) | 18.0 | 12.7 | 10.7 | |
| 3.01+ (n=831) | 14.1 | 9.6 | 8.2 | |
| Total (n=8,549) | 100 | 100 | 100 | |
| Level: | (n=1,753) | (n=3,093) | (n=3,983) | |
| 2 (n=4,144) | 45.9 | 46.1 | 48.0 | |
| 3 (n=2,188) | 25.6 | 26.5 | 23.1 | p=0.270 |
| 4 (n=2,151) | 23.6 | 23.5 | 25.4 | |
| 5 (n=346) | 4.9 | 3.9 | 3.5 | |
| Total (n=8,829) | 100 | 100 | 100 | |

* Data source: South Australian Cancer Registry.
** P values derived from Spearman rank correlation.

**Table 2. Percentage Distribution of Clark level of Invasive Cutaneous Melanoma by Diagnostic Period, Stratifying by Breslow thickness; South Australia, 1980-2000***

| | | Diagnostic period | | | |
|---|---|---|---|---|---|
| Thickness (mm) | Level | 1980-86 | 1987-93 | 1994-2000 | P value** |
| ≤ 0.75 | | (n=629) | (n=1,682) | (n=2,286) | |
| | 2 (n=3,650) | 84.9 | 78.4 | 78.6 | |
| | 3 (n=796) | 13.0 | 19.0 | 17.2 | p=0.012 |
| | 4 (n=148) | 2.1 | 2.6 | 4.0 | |
| | 5 (n=3) | 0.0 | 0.0 | 0.1 | |
| | Total (n=4,597) | 100 | 100 | 100 | |
| 0.76-1.50 | | (n=373) | (n=701) | (n=914) | |
| | 2 (n=267) | 30.6 | 10.8 | 8.4 | |
| | 3 (n=1,012) | 50.4 | 55.5 | 47.6 | p<0.001 |
| | 4 (n=705) | 19.0 | 33.7 | 43.5 | |
| | 5 (n=4) | 0.0 | 0.0 | 0.4 | |
| | Total (n=1,988) | 100 | 100 | 100 | |
| 1.51-3.00 | | (n=255) | (n=379) | (n=418) | |
| | 2 (n=17) | 3.9 | 0.3 | 1.4 | |
| | 3 (n=241) | 35.7 | 21.6 | 16.3 | p<0.001 |
| | 4 (n=737) | 57.3 | 71.8 | 76.3 | |
| | 5 (n=57) | 3.1 | 6.3 | 6.0 | |
| | Total (n=1,052) | 100 | 100 | 100 | |
| 3.01+ | | (n=198) | (n=282) | (n=315) | |
| | 2 (n=10) | 3.5 | 0.0 | 1.0 | |
| | 3 (n=74) | 15.7 | 9.2 | 5.4 | p=0.005 |
| | 4 (n=472) | 55.1 | 59.2 | 62.2 | |
| | 5 (n=239) | 25.8 | 31.6 | 31.4 | |
| | Total (n=795) | 100 | 100 | 100 | |

* Data source: South Australian Cancer Registry.
** P values derived from Spearman rank correlation.
. NB: Analyses include 8,432 cases with complete data on thickness and level.

**Table 3. Relative Odds (95% Confidence Limits) of Penetration of Invasive Cutaneous Melanoma to the Reticular Dermis or Sub-cutaneous Fat by Diagnostic Period; South Australia, 1980-2000***

| Predictors | - Multivariable logistic regression - Relative Odds |
|---|---|
| Age at diagnostic (yrs.): | |
| Under 30 (n=545) | 1.00 |
| 30-39 (n=918) | 1.49 (1.02, 2.19) |
| 40-49 (n=1,166) | 1.40 (0.97, 2.04) |
| 50-59 (n=1,121) | 1.65 (1.14, 2.37) |
| 60-69 (n=1,267) | 1.93 (1.35, 2.75) |
| 70-79 (n=1,153) | 2.31 (1.61, 3.31) |
| 80+ (n=559) | 3.61 (2.39, 5.44) |
| Site: | |
| Other (n=3,338) | 1.00 |
| Trunk (n=1,945) | 0.62 (0.51, 0.75) |
| Upper limb (n=1,446) | 0.77 (0.63, 0.95) |
| Histological type: | |
| Other (n=5,819) | 1.00 |
| Nodular (n=847) | 1.41 (1.12, 1.76) |
| Desmoplastic (n=63) | 12.94 (3.41, 49.07) |
| Thickness (mm): | |
| ≤0.50 (n=2,396) | 1.00 |
| 0.51-1.00 (n=2,144) | 12.24 (8.33, 17.98) |
| 1.01-1.50 (n=703) | 73.59 (49.51, 109.37) |
| 1.51-2.00 (n=396) | 199.21 (129.00, 307.64) |
| 2.01-2.50 (n=258) | 227.98 (141.51, 367.30) |
| 2.51-3.00 (n=190) | 408.12 (234.75, 709.52) |
| 3.01-3.50 (n=131) | 307.20 (170.30, 554.14) |
| 3.51-4.00 (n=114) | 428.15 (220.39, 831.78) |
| 4.01-4.50 (n=125) | 1,374.00 (574.45, 3,286.38) |
| 4.51-5.00 (n=89) | 560.71 (250.36, 1,255.78) |
| 5.01-5.50 (n=35) | 350.20 (129.07, 950.20) |
| 5.51-6.00 (n=55) | 407.94 (165.48, 1,005.63) |
| 6.01+ (n=93) | 937.32 (370.55, 2,371.01) |
| Diagnostic period: | |
| 1980-86 (n=1,208) | 1.00 |
| 1987-93 (n=2,553) | 1.99 (1.59, 2.50) |
| 1994-2000 (n=2,968) | 2.82 (2.25, 3.54) |

*Data source: South Australian Cancer Registry.
NB: Analysis includes 6,729 cases with complete data on these predictors.

## Discussion

When stratifying invasive melanomas by Breslow thickness, results showed secular trends towards deeper Clark levels of invasion. An increased likelihood of penetration into the reticular dermis or sub-cutaneous fat was also evident after adjusting for age at diagnosis, site of lesion, histological type and thickness. Secular trends, adjusted for thickness, were not found to vary across sub-groups of patients classified by age, sex, residential location, socio-economic status, site of lesion or histological type.

**Table 4. Annual Relative Odds (95% Confidence Limits) of Penetration of Invasive Cutaneous Melanoma to the Reticular Dermis or Sub-cutaneous Fat in Sub-groups of Patients Classified by Age at Diagnosis and Socio-demographic characteristics; South Australia, 1980-2000***

| Sub-group | Annual relative odds |
|---|---|
| Age at diagnostic (yrs.): | |
| Under 30 (n=686) | 1.11 (1.05, 1.18) |
| 30-39 (n=1,137) | 1.05 (1.02, 1.09) |
| 40-49 (n=1,441) | 1.07 (1.04, 1.11) |
| 50-59 (n=1,419) | 1.10 (1.06, 1.13) |
| 60-69 (n=1,598) | 1.07 (1.04, 1.10) |
| 70-79 (n=1,450) | 1.06 (1.03, 1.10) |
| 80+ (n=701) | 1.05 (1.00, 1.10) |
| Sex: | |
| Males (n=4,186) | 1.09 (1.07, 1.11) |
| Females (n=4,246) | 1.08 (1.06, 1.10) |
| Place of residence: | |
| Adelaide (n=6,328) | 1.08 (1.06, 1.09) |
| Country area (n=2,104) | 1.10 (1.07, 1.13) |
| Socio-economic status: | |
| Low (n=2,260) | 1.08 (1.06, 1.11) |
| Mid-low (n=1,869) | 1.08 (1.05, 1.11) |
| Mid-high (n=1,721) | 1.08 (1.05, 1.12) |
| High (n=2,582) | 1.08 (1.05, 1.11) |

*Results of 15 multivariable logistic regression analyses (1 per sub-group), with adjustment for thickness (see text).
Data source: South Australian Cancer Registry.
NB: Analyses include 8,432 cases with complete data on thickness and level.

The similarity in trends across sub-groups appears to be consistent with a change in measurement methodology. Clark level has long been recognized to be less objectively measured than Breslow thickness, with a lower reproducibility (Herlyn et al, 2001; Mastranglo et al, 1985), and so the potential exists for its application to have changed over time.

Even so, the possibility of a non-measurement dependent real change over time in Clark level, for a given Breslow thickness, cannot be ruled out. If the secular trends between Clark level and Breslow thickness that we have observed are not due to alterations in measurement technique or tissue preservation, it remains possible that the actual skin thickness might be reducing. In this event, lesions of equivalent Breslow thickness could be penetrating to deeper Clark levels, with implications for early detection.

Conjecturally, reduced skin thickness could perhaps be related to improved protection from ultra-violet light from the use of broad-spectrum sunscreens, hats and more restricted sun exposure over progressive time periods. We recognise, however, that the effects of ultra-violet irradiation exposure are complex and may vary by skin type and intensity and length of exposure (Gilchrest, 1996).

**Table 5. Annual Relative Odds (95% Confidence Limits) of Penetration of Invasive Cutaneous Melanoma to the Reticular Dermis or Sub-cutaneous Fat in Sub-groups of Patients Classified by Site of Lesion and Histological Type; South Australia, 1980-2000***

| Sub-group | Annual relative odds |
|---|---|
| Site: | |
| Face (n=1,266) | 1.12 (1.07, 1.16) |
| Rest of head/neck (n=520) | 1.09 (1.04, 1.15) |
| Trunk (n=2,470) | 1.06 (1.04, 1.09) |
| Upper limb (n=1,841) | 1.09 (1.06, 1.12) |
| Lower limb (n=2,294) | 1.08 (1.05, 1.10) |
| Other / unknown (n=41) | 1.07 (0.89, 1.28) |
| Histological type: | |
| Superficial spreading (n=5,099) | 1.07 (1.05, 1.09) |
| Lentigo maligna (n=673) | 1.12 (1.06, 1.18) |
| Nodular (n=848) | 1.09 (1.06, 1.13) |
| Acral lentiginous (n=58) | 0.82 (0.62, 1.09) |
| Desmoplastic (n=63) | 1.01 (0.83, 1.24) |
| Other / unknown (n=1,691) | 1.09 (1.05, 1.12) |

*Results of 12 multivariable logistic regression analyses (1 per sub-group), with adjustment for thickness (see text).
Data source: South Australian Cancer Registry.
NB: Analyses include 8,432 cases with complete data on thickness and level.

Irrespective of whether these trends are due to methodological changes or real effects, it is evident that relationships between measures of thickness and level have varied over time in South Australia. Potentially, this could affect prognostic assessments.

Clinical management strategies also could be influenced, since both Breslow thickness and Clark level are used when deciding individual patient care. We have observed that a small sub-group of melanomas of Breslow thickness of one millimetre or less metastasise. Clark level may assist in the prediction of this group with a poorer prognosis.

The present results warrant verification with registry data from other populations and continued re-assessment with subsequent data from this registry. In present editions of the TNM classification system, the role of Clark level has been reduced to differentiating between T1a and T1b lesions (i.e., those with a thickness of 1.00mm or less) (Balch et al, 2001; Sobin and Wittekind, 2002). Nonetheless, as these lesions now account for approximately two thirds of invasive melanomas in South Australia, it is evident that Clark level still has a prognostic role for a majority of patients. Ten-year disease-specific survival (+/- standard error) from T1 melanomas diagnosed in South Australia in 1980-2000 ranged from 98.1 (+/-0.3)% for Clark level 2 and 95.2(+/-0.8)% for Clark level 3 to 91.0 (+/-2.2)% for Clark levels 4 and 5 combined (Luke et al, 2003).

Multivariable analysis of case survival in South Australia indicates that thickness and level are independent prognostic indicators (Luke et al, 2003). Since the inter-relationships between these measures may vary over time, periodic re-evaluation is warranted of their respective prognostic implications.

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