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SUPPLEMENTARY MATERIAL

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More People Die from Thin Melanomas (⩽1 mm) than from Thick Melanomas (>4 mm) in Queensland, Australia

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TO THE EDITOR

Melanoma incidence has been rising steadily in fair-skinned populations around the world, with most of the increase due to greater numbers of thin lesions being diagnosed (Welch *et al.*, 2005; Coory *et al.*, 2006; Gimotty *et al.*, 2007). Melanoma mortality has also been rising, albeit less rapidly compared with incidence (Welch *et al.*, 2005; MacKie *et al.*, 2007). Survival from melanoma is strongly correlated with tumor thickness; patients with thin lesions (⩽1 mm) have a 20-year survival approaching 96%, whereas thicker lesions confer substantially higher risks of premature mortality (Balch *et al.*, 2009; Green *et al.*, 2012). On the basis of these prognostic associations, there is a widespread perception that the majority of deaths from melanoma result from thick lesions. However, data describing population distributions of lethal melanomas by thickness have been seldom reported (Criscione and Weinstock, 2010) and may have been biased by missing thickness data (Shaikh *et al.*, 2013). Such analyses are important for understanding where the burden of melanoma mortality lies and would serve to inform melanoma control strategies. We therefore performed an analysis of melanoma incidence and mortality in Queensland, Australia, the

Abbreviation: QCR, Queensland Cancer Registry

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Table 1. Incidence and mortality of melanoma in the Queensland population 1990–2009, by thickness

Characteristic	1990–1994		1995–1999		2000–2004		2005–2009	
	n (%)[1]	ASR (95% CI)	*n* (%)	ASR (95% CI)	*n* (%)	ASR (95% CI)	*n* (%)	ASR (95% CI)
Incidence								
⩽1 mm	4,796 (64.2)	34.5 (33.5–35.5)	6,797 (67.4)	42.7 (41.7–43.8)	8,272 (69.3)	45.9 (44.9–46.9)	9,376 (68.0)	44.9 (44.0–45.9)
1.01–2.00 mm	1,005 (13.5)	7.4 (7.0–7.9)	1,250 (12.4)	8.0 (7.6–8.5)	1,521 (12.7)	8.5 (8.0–8.9)	1,882 (13.6)	9.1 (8.7–9.5)
2.01–4.00 mm	559 (7.5)	4.3 (3.9–4.7)	735 (7.3)	4.9 (4.5–5.2)	943 (7.9)	5.3 (5.0–5.7)	1,106 (8.0)	5.4 (5.0–5.7)
>4 mm	286 (3.8)	2.2 (2.0–2.5)	414 (4.1)	2.8 (2.5–3.1)	478 (4.0)	2.7 (2.5–3.0)	642 (4.7)	3.1 (2.9–3.4)
Metastasis only	351 (4.7)	2.6 (2.3–2.9)	385 (3.8)	2.5 (2.3–2.8)	366 (3.1)	2.0 (1.8–2.3)	391 (2.8)	1.9 (1.7–2.1)
Unknown	475 (6.8)	3.5 (3.2–3.9)	511 (5.1)	3.3 (3.0–3.6)	364 (3.0)	2.1 (1.9–2.3)	393 (2.8)	1.9 (1.7–2.1)
Total	7,472		10,092		11,944		13,790	
Mortality								
⩽1 mm	112 (14.0)	0.94 (0.60–1.28)	169 (17.3)	1.06 (0.72–1.40)	219 (19.3)	1.20 (0.85–1.55)	296 (22.7)	1.41 (1.05–1.77)
1.01–2.00 mm	126 (15.8)	0.92 (0.58–1.27)	153 (15.7)	0.97 (0.64–1.30)	194 (17.1)	1.06 (0.73–1.39)	272 (20.8)	1.30 (0.95–1.64)
2.01–4.00 mm	138 (17.3)	1.04 (0.68–1.40)	167 (17.1)	1.09 (0.74–1.44)	212 (18.7)	1.17 (0.82–1.52)	267 (20.4)	1.28 (0.94–1.63)
>4 mm	90 (11.3)	0.69 (0.40–0.99)	129 (13.2)	0.85 (0.54–1.16)	165 (14.5)	0.93 (0.62–1.24)	186 (14.2)	0.89 (0.61–1.18)
Metastasis only	207 (25.9)	1.52 (1.09–1.96)	251 (25.7)	1.62 (1.19–2.05)	243 (21.4)	1.34 (0.97–1.70)	207 (15.9)	0.98 (0.68–1.27)
Unknown	126 (15.8)	0.95 (0.60–1.29)	107 (11.0)	0.71 (0.43–0.99)	104 (9.2)	0.58 (0.34–0.82)	78 (6.0)	0.37 (0.19–0.56)
Total	799		976		1,137		1,306	

Abbreviations: ASR, age-standardized rates (United States population year 2000); CI, confidence interval.
Data source: Queensland Cancer Registry, 1982–2011 extract.
Invasive melanoma, all ages combined.
Generated on 15 July 2014.
[1]Totals may not sum up to 100.0% because of rounding.

jurisdiction with the world's highest rates of this malignancy.

Notification of cancer to the Queensland Cancer Registry (QCR) has been legally mandated since 1982, and reporting of melanoma has been near complete since 1990. We obtained a de-identified data set of all melanoma diagnoses in Queensland from 1990 to 2009, including notifications of all people whose underlying cause of death (ICD-O-3) was cutaneous melanoma. (If a person was diagnosed with melanoma before that date, but subsequently died, their diagnostic details are recorded in the QCR.) The study was approved by the QCR prior to data linkage and release. For each person who died from melanoma, we obtained information on their sex, age group, and month and year of death. We also obtained linked information on any prior melanoma diagnoses, including year of notification, thickness, histology, and anatomic site. Using these data, we calculated age-standardized incidence and mortality rates for each year for all melanomas and by thickness of the first primary (⩽1, 1.01–2, 2.01–4, and >4 mm). For the primary mortality analysis, we included all melanoma decedents and assumed that the first primary was lethal. This assumption, although reasonable, is contestable; hence, we repeated the mortality analyses after excluding those patients who had more than one primary melanoma.We used SAS (version 9.2; SAS Institute, Cary, NC) for all analyses.

From 1990 to 2009, 4,218 Queensland residents died from cutaneous melanoma (67% males; 33% females; Table 1). Overall, 22% of patients with lethal melanomas first presented with metastatic disease, 68% presented with a single primary lesion, and 10% had multiple primary melanomas. Thin melanomas (⩽1 mm) accounted for 19% of melanoma deaths overall (68% of all melanomas) but increased from 14% in 1990–1994 to 23% in 2005–2009. Thus, in the most recent period (2005–2009), more melanoma deaths in Queensland were attributable to thin tumors (⩽1 mm, 23% of deaths; 68% of all melanomas) than thick tumors (>4 mm, 14% of deaths; 3% of all melanomas) or metastatic presentations (16% of deaths; 3% of all melanomas). The patterns of mortality by thickness category were essentially unchanged when we restricted the analyses to those with only one primary melanoma notification (data not shown). As expected, the intervals from diagnosis to death were significantly shorter for thicker tumors than for thinner tumors (Table 2).

Because thickness information was missing for nearly 10% of melanomas, we repeated the analyses after imputing melanoma thicknesses for those patients with missing data. We imputed thicknesses on the basis of distributions of patients with lethal melanomas of known thickness using age, sex, histological type, anatomic site, time period, and time from diagnosis to death as potential predictors. Including imputed thickness data made negligible difference to the patterns reported above (Supplementary Table S1 online).

These data, from a population with a very high incidence of melanoma and a long history of melanoma education,

Table 2. Characteristics of melanoma decedents in the Queensland population 1990–2009

Characteristic	1990–1994 (*n* = 799)	1995–1999 (*n* = 976)	2000–2004 (*n* = 1,137)	2005–2009 (*n* = 1,306)	Total (*n* = 4,218)
Age at death (years)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
<30	39 (4.9)	50 (5.1)	55 (4.8)	49 (3.8)	193 (4.6)
30–39	70 (8.8)	81 (8.3)	70 (6.2)	86 (6.6)	307 (7.3)
40–49	124 (15.5)	118 (12.1)	146 (12.8)	146 (11.2)	534 (12.7)
50–59	122 (15.3)	172 (17.6)	191 (16.8)	217 (16.6)	702 (16.6)
60–69	191 (23.9)	195 (20.0)	232 (20.4)	244 (18.7)	862 (20.4)
70–79	181 (22.7)	223 (22.9)	265 (23.3)	325 (24.9)	994 (23.6)
80+	72 (9.0)	137 (14.0)	178 (15.7)	239 (18.3)	626 (14.8)
Sex					
Male	539 (67.5)	633 (64.9)	789 (69.4)	888 (68.0)	2,849 (67.5)
Female	260 (32.5)	343 (35.1)	348 (30.6)	418 (32.0)	1,369 (32.5)
Number of primary melanomas					
1	546 (68.3)	647 (66.3)	764 (67.2)	922 (70.6)	2,879 (68.3)
2	36 (4.5)	61 (6.3)	100 (8.8)	123 (9.4)	320 (7.6)
3	7 (0.9)	12 (1.2)	25 (2.2)	32 (2.5)	76 (1.8)
4+	3 (0.4)	5 (0.5)	5 (0.4)	22 (1.7)	35 (0.8)
Metastasis only	207 (25.9)	251 (25.7)	243 (21.4)	207 (15.9)	908 (21.5)
Body site of first primary melanoma					
Head/neck	134 (16.8)	146 (15.0)	200 (17.6)	267 (20.4)	747 (17.7)
Trunk	210 (26.3)	267 (27.4)	347 (30.5)	370 (28.3)	1,194 (28.3)
Upper limbs	110 (13.8)	145 (14.9)	162 (14.3)	216 (16.5)	633 (15.0)
Lower limbs	124 (15.5)	155 (15.9)	171 (15.0)	229 (17.5)	679 (16.1)
Not specified	14 (1.8)	12 (1.2)	14 (1.2)	17 (1.3)	57 (1.4)
Metastasis only	207 (25.9)	251 (25.7)	243 (21.4)	207 (15.8)	908 (21.5)
Median (25%, 75%) duration between first melanoma diagnosis and death by thickness of first primary					
⩽1mm	5 (3–6)	6 (3–9)	7 (3–11)	7 (4–13)	6 (3–10)
1.01–2.00 mm	4 (2–6)	4 (3–7)	4 (2–8)	5 (2–8)	4 (2–7)
2.01–4.00 mm	2 (1–5)	3 (2–5)	3 (2–5.5)	3 (2–6)	3 (2–5)
>4 mm	2 (1–3)	2 (1–4)	4 (2–6)	2 (1–3)	2 (1–4)
Unknown	2 (1–4)	2 (1–5)	3 (1–9)	4.5 (1–15)	3 (1–7)
Metastasis only	1 (0–2)	1 (0–1)	1 (0–2)	1 (0–2)	1 (0–2)

show that an increasing proportion of melanoma deaths occurred among patients who were diagnosed originally with thin tumors. Indeed, more people died from thin melanomas (⩽1 mm) than died from thick melanomas (>4 mm) in the most recent reporting period, raising questions about the optimum strategy for stemming melanoma mortality.

Two complementary approaches have been pursued for melanoma control, namely primary prevention and early detection. Whereas primary prevention strategies aim to reduce sun exposure and thereby reduce overall melanoma incidence, early detection strategies seek to educate patients and doctors to identify suspicious lesions, with the aim of reducing morbidity and mortality. Widespread early detection is thought to underlie the shift toward higher incidences of thin melanoma reported in Australia (Coory *et al.*, 2006; Baade *et al.*, 2012), the United States, (Geller *et al.*, 2013), and to some extent Europe (de Vries *et al.*, 2004). However, there are concerns that the emphasis on skin examinations has contributed to the rapidly rising incidence of thin melanomas through the phenomenon of overdiagnosis (Burton and Armstrong, 1994; Welch *et al.*, 2005).

The findings here underscore the dilemma posed by early detection strategies when applied to the population, which attempt to strike a balance between the potential lethality of thin melanomas on the one hand (as demonstrated by these data) and the burden of overdiagnosis on the other. These data demonstrate that thin melanomas comprise a substantial fraction of the overall burden of lethal melanomas in the high incidence population of Queensland.

The earlier US study also reported that a high proportion of fatal melanomas were attributable to thin melanomas (27%) (Criscione and Weinstock, 2010). Moreover, the proportion of deaths attributable to thin melanomas in Queensland is rising. Such a distribution, although entirely concordant with the respective trends in incidence and case fatality of thin and thick melanomas, is arguably not widely appreciated. Interestingly, and in contrast to the Queensland experience, was the observation in the SEER data that the proportion of deaths attributable to thick melanomas increased over the observation period (Criscione and Weinstock, 2010).

Although early detection strategies should continue, clinicians must be mindful that thin melanomas contribute substantially to overall melanoma mortality, notwithstanding their overall favorable prognosis. Identifying the clinical and molecular features of thin melanomas that confer poor prognosis should be the focus of continued research. From a public health perspective, it can be argued that primary prevention activities aimed at reducing the occurrence of melanoma in the entire population should be accorded a very high priority.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

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Peripheral Neuro-Immune Pathology in Recessive Dystrophic Epidermolysis Bullosa

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TO THE EDITOR

Chronic pain and itch are substantial quality-of-life obstacles for patients with the genetic skin disorder recessive dystrophic epidermolysis bullosa (RDEB). RDEB is caused by loss-of-function mutations in the anchoring fibril protein type VII collagen. Extreme skin fragility leads to chronic wounds and inflammation that are accompanied by significant pain and itch. Itchy skin has been consistently rated as the highest burden in RDEB patients (van Scheppingen *et al.*, 2008; Danial *et al.*, 2014), and another study found that 93% of dystrophic EB patients experienced itch symptoms (Snauwaert *et al.*, 2014). Compounding the burden of itching in RDEB, scratching can be associated with new lesions and secondary infection, exacerbating the disease's symptoms and undermining treatment.

The second-highest burden in RDEB is pain (van Scheppingen *et al.*, 2008;

Abbreviations: ECM, extracellular matrix; ENF, epidermal nerve fiber; JEB, junctional epidermolysis bullosa; MC, mast cell; PGP9.5, protein gene product 9.5; PNS, peripheral nervous system; RDEB, recessive dystrophic epidermolysis bullosa; SNP, subepidermal neural plexus

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