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BRIEF REPORT

Diagnosis of an additional *in situ* melanoma does not influence survival for patients with a single invasive melanoma: A registry-based follow-up study

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ABSTRACT

Using a large (N= 25 493) population-based cohort from Queensland, Australia, we compared melanoma survival among cases with a single invasive melanoma only against those who also had a diagnosis of a single *in situ* melanoma. After adjustment for sex, age, body site, clinicopathological subtype, thickness and ulceration, it was found that there was no difference (P = 0.99) in 10-year melanoma-specific mortality following a diagnosis of an invasive lesion, whether or not an *in situ* melanoma was also present. We conclude that *in situ* melanomas do not alter the prognosis of an invasive melanoma.

Key words: *in situ*, invasive, melanoma, survival.

INTRODUCTION

It has long been recognised that people diagnosed with melanoma face an increased risk of being diagnosed with a subsequent *in situ* or invasive melanoma.[1,2] In addition to increased awareness and medical surveillance, one possible explanation is that these people may possess certain characteristics that predispose them to develop this disease.[3,4]

In situ melanoma is the earliest stage of the disease and occurs when a malignant melanocytic proliferation is confined to the epidermis. This is thought to be a precursor of invasive melanoma, although it is yet to be proven.[1] Studies have found that survival following the diagnosis of an *in situ* melanoma is equivalent to that of the general population,[1,3] which is to be expected given the lack of potential for an *in situ* melanoma to metastasise.

While these findings seem to suggest that *in situ* melanomas do not have prognostic implications, it is possible that they might modify the host immune system,[5] and hence carry a potential to impact on the prognosis of a subsequent or preceding invasive tumour. We therefore examined whether survival for patients with a single primary invasive melanoma varied by the presence or timing of an additional *in situ* melanoma.

METHODS AND RESULTS

The study cohort consisted of all patients diagnosed with a single primary invasive cutaneous melanoma (ICD-O site code C44 and clinicopathological subtype M872–M879, excluding autopsy or death certificate only) in Queensland, Australia, between 1995 and 2007 and recorded in the Queensland Cancer Registry. People aged 15–89 years at diagnosis and who survived for at least 1 day following diagnosis were included. For each eligible person, information on prior or subsequent *in situ* melanomas that were diagnosed within 5 years of the index case was also extracted.

The study cohort was stratified into the six categories shown in the column headings of Table 1, depending on whether and when an *in situ* melanoma was diagnosed in relation to the invasive melanoma. These categories were arbitrarily selected in order to detect any possible

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Conflict of interest: none

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Table 1 Cohort characteristics of single primary invasive melanoma cases by presence and timing of *in situ* melanoma, Queensland, 1995–2007*

	Single primary invasive melanoma only	Preceding *in situ* melanoma (2–5 years before)	Preceding *in situ* melanoma (60 days–2 years before)	Synchronous *in situ* melanoma (within ± 60 days)	Subsequent *in situ* melanoma (60 days–2 years after)	Subsequent *in situ* melanoma (2–5 years after)
Eligible cases (number)	24 197	176	148	322	291	359
Median follow-up (years)	9.0	7.1	7.7	8.8	8.1	7.9
Median age at diagnosis (years)	56	70	64	65	62	63
Melanoma specific mortality status as at 31 Dec 2012						
Alive or censored	91	88	91	89	92	96
Melanoma-related death	9	12	9	11	8	4
			χ^2 = 12.58; d.f. = 5; P = 0.01			
Sex						
Males	56	57	63	63	61	64
Females	44	43	37	37	40	37
			χ^2 = 20.93; d.f. = 5; P < 0.01			
Body site of invasive melanoma						
Head and neck	15	21	16	19	15	13
Trunk	34	31	39	35	39	36
Upper limbs and shoulders	24	21	21	23	24	30
Lower limbs	22	20	18	18	21	18
Not specified	5	8	7	4	2	3
			χ^2 = 38.12; d.f. = 20; P = 0.01			
Clinicopathological subtype of invasive melanoma						
Nodular melanoma	8	9	8	10	6	7
Melanoma in junctional naevus	2	2	1	3	2	4
Lentigo maligna melanoma	5	9	10	8	8	7
Superficial spreading melanoma	54	47	53	50	55	56
Other specified melanoma	4	2	5	4	6	6
Not otherwise specified	27	31	23	26	24	21
			χ^2 = 48.56; d.f. = 25; P < 0.01			
Thickness of invasive melanoma						
< 1 mm	68	67	71	70	66	72
1 mm to < 2 mm	13	7	12	11	20	16
≥ 2 mm	12	15	10	14	11	8
Not recorded	7	11	7	6	3	4
			χ^2 = 45.82; d.f. = 15; P < 0.01			
Ulceration of invasive melanoma						
No	55	49	53	54	62	59
Yes	9	9	7	10	8	9
Not recorded	36	42	40	37	30	32
			χ^2 =12.58; d.f. = 10; P = 0.25			

*All values shown are column percentages unless otherwise specified.

differences in survival by the length of time between the diagnosis of the invasive and *in situ* melanomas.

Mortality status was followed up until 31 December 2012. For patients who remained alive, survival was censored either at that date or 10 years from the time of diagnosis of the invasive melanoma, whichever occurred first. Unadjusted cause-specific 10-year survival was calculated using the Kaplan–Meier method, with delayed entry where the *in situ* melanoma was diagnosed after the invasive melanoma. Corresponding adjusted hazard ratios and 95% confidence intervals were obtained from multivariate flexible parametric survival models[6] and

adjusted for sex as well as body site, clinicopathological subtype, thickness and ulceration of the invasive melanoma. The model providing the best fit was on the normal scale with 2 knot points, and included time-varying effects for body site, thickness group and ulceration.

In total, 25 493 individuals were included in the study cohort. Median age at diagnosis of the invasive melanoma varied from 56 years for those without an *in situ* melanoma to 70 years where the *in situ* melanoma was diagnosed between 2–5 years prior to the invasive melanoma (Table 1). Patients with a subsequent *in situ* melanoma tended to have more favourable prognostic attributes for the invasive melanoma than those without an *in situ* melanoma or who had either a prior or synchronous *in situ* melanoma; for example, the former group contained a lower proportion of invasive lesions on the head and neck, fewer nodular melanomas and fewer invasive tumours thicker than 2 mm.

Unadjusted cause-specific 10-year survival ranged from 88% for those with a preceding *in situ* melanoma diagnosed two or more years prior to the invasive melanoma, to 94% if an *in situ* melanoma was diagnosed at least 2 years subsequently, with an intermediate result (90%) for cases with an invasive melanoma only (Table 2 and Fig. 1). However, no significant differences in 10-year cause-specific mortality were detected by the presence or timing of an *in situ* melanoma after multivariate adjustment ($P = 0.99$ for the overall effect).

Table 2 Ten-year unadjusted cause-specific survival estimates and adjusted hazard ratios for single primary invasive melanoma cases by presence and timing of *in situ* melanoma, Queensland, 1995–2007[†]

Melanoma group[‡]	*n*	Unadjusted 10-year survival estimates (95% CI)	Adjusted hazard ratio[‡] (95% CI)	*P*
Invasive only	24 197	90.0 (89.6–90.4)	1.00	
Preceding *in situ* (2–5 years)	176	87.4 (81.3–91.7)	1.17 (0.67–2.03)	0.58
Preceding *in situ* (< 2 years)	148	90.5 (84.0–94.4)	1.03 (0.53–2.00)	0.94
Synchronous *in situ*	322	88.6 (84.4–91.7)	1.05 (0.67–1.64)	0.83
Subsequent *in situ* (< 2 years)	291	90.2 (85.2–93.5)	0.93 (0.53–1.63)	0.80
Subsequent *in situ* (2–5 years)	359	94.0 (89.7–96.6)	0.97 (0.46–2.04)	0.94
		Overall effect: $\chi^2 = 0.42$; d.f. = 5; $P = 0.99$		

[†]Patients who remained alive were followed up to 31 December 2012.

[‡]Hazard ratios were adjusted for sex and for the following variables relating to the invasive melanoma: age at diagnosis, body site, clinicopathological subtype, thickness and ulceration.

CONCLUSION

Several recent studies[7–9] have examined the effect of multiple melanomas on survival outcomes. These articles have reported conflicting results, partly because they differ in their approach to defining multiple melanomas, with some authors also including *in situ* tumours. Our large population-based study demonstrates that an additional *in situ* melanoma does not have any prognostic influence on survival for an invasive melanoma, irrespective of whether the *in situ* melanoma was diagnosed prior, synchronously or subsequent to the invasive lesion. This is important because the unnecessary inclusion of *in situ* melanomas could act to dilute any potential differences in survival between patients with a single invasive melanoma compared to those with multiple invasive melanomas.

A small increase in the unadjusted survival rates, observed for invasive melanoma cases with a subsequent *in situ* melanoma compared to those with a prior *in situ* melanoma, appears to be linked to age at diagnosis. The disparity in the age distribution may also help to explain the higher proportion of some of the other more

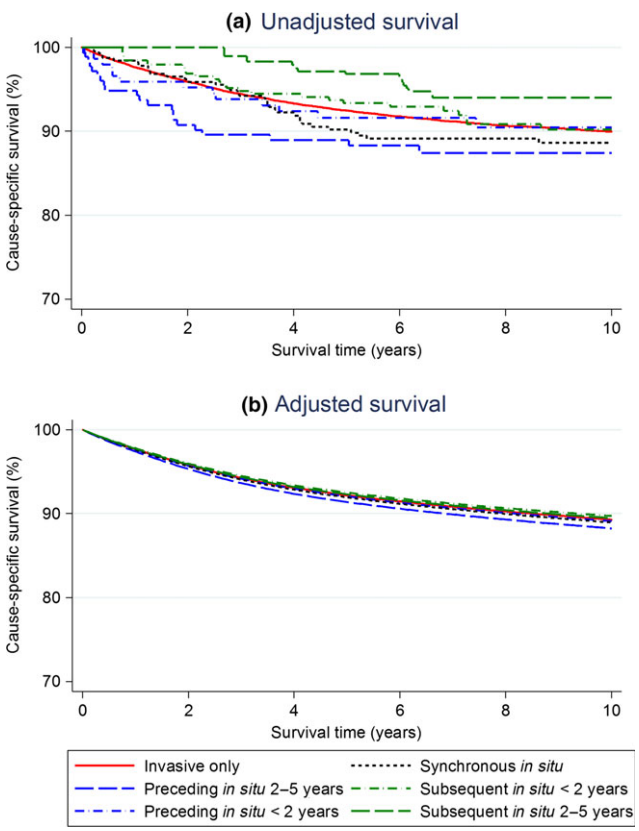

Figure 1 (a) Unadjusted and (b) adjusted cause-specific survival for single primary invasive melanoma cases by presence and timing of *in situ* melanoma, Queensland, 1995–2007. Patients who remained alive were followed up to 31 December 2012. The survival curves in Figure 1b were adjusted for sex and the following variables relating to the invasive melanoma: age at diagnosis, body site, clinicopathological subtype, thickness and ulceration.

favourable prognostic characteristics that were observed for individuals who had a subsequent *in situ* melanoma. For example, melanomas on the head and neck are associated with lower survival and are more common at an older age.[10]

An advantage of the current study is that it utilised a large, population-based cohort consisting of high quality data (> 98% histological verification). Data on key prognostic indicators were missing for some cases, particularly ulceration of the invasive melanoma (36% not stated); however, this distribution did not vary significantly across the various study cohorts. The proportion of invasive melanomas with clinicopathological subtype classified as 'not otherwise specified' differed from 21% to 31% depending on whether and when an *in situ* melanoma was also diagnosed, and this may alter the percentage apportioned to the remaining subtypes. Data on mitoses, another key prognostic indicator for melanoma, were not available from the Queensland Cancer Registry.

In summary, our study found that *in situ* melanoma has no additional impact on survival beyond that of an invasive melanoma, and so would support the premise that future studies of survival for multiple melanoma need only include invasive lesions. However, previous research has shown that individuals with an *in situ* melanoma have a significantly elevated risk of being subsequently diagnosed with an invasive melanoma.[2] Therefore, while the *in situ* melanoma itself does not impact on survival, continued surveillance following diagnosis of an *in situ* melanoma should remain a priority.

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