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Author

Youlden, Danny R, Khosrotehrani, Kiarash, Green, Adele C, Soyer, H Peter, Kimlin, Michael G, Youl, Philippa H, Aitken, Joanne F, Baade, Peter D

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

Authors: Danny R Youlden1, Kiarash Khosrotehrani2, Adele C Green3,4, H Peter Soyer5, Michael G Kimlin6, Philippa H Youl1, Joanne F Aitken1, Peter D Baade1

1 Cancer Council Queensland, Brisbane, Queensland, Australia.

2 The University of Queensland Centre for Clinical Research, Brisbane, Queensland, Australia.

3 QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia.

4 CRUK Manchester Institute, University of Manchester, Manchester, United Kingdom.

5 Dermatology Research Centre, The University of Queensland, School of Medicine, Translational Research Institute, Brisbane, Queensland, Australia

6 University of the Sunshine Coast, Sunshine Coast, Queensland, Australia.

Corresponding author: Mr Danny Youlden, Cancer Council Queensland, PO Box 201, Spring Hill, QLD 4004, Australia; E-mail: dannyyoulden@cancerqld.org.au; Telephone: +61-7-36345351.

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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 diagnosis of an invasive lesion, irrespective of whether an *in situ* melanoma was also present. We conclude that *in situ* melanomas do not alter the prognosis of an invasive melanoma.

Key words: melanoma, invasive, *in situ*, 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. They are thought to be precursors of invasive melanoma, although this is yet to be proven.[1] Studies have found that survival following 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 any prognostic implications, it is possible that they might modify the host immune system,[5] and hence carry the potential to impact the prognosis of a subsequent or preceding invasive tumour. We therefore examined whether survival for persons 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 one day following diagnosis were included. For each eligible person,

information on prior or subsequent *in situ* melanomas that were diagnosed within five years of the index case were 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 differences in survival by the length of time between diagnosis of the invasive and *in situ* melanomas.

Mortality status was followed up until 31 December 2012. For persons who had not died prior, 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] 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 two knot points, and including time-varying effects for body site, thickness group and ulceration.

A total of 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 two to five years prior to the invasive melanoma (Table 1). Persons with a subsequent *in situ* melanoma tended to have more favourable prognostic attributes for the invasive melanoma compared to 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, less nodular melanomas and fewer tumours thicker than 2mm.

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 two years subsequently, with an intermediate result (90%) for cases with an invasive melanoma only (Table 2 and Figure 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).

Conclusion

Several recent studies[7-9] have examined the effect of multiple melanomas on survival outcomes. These papers have reported conflicting results, mainly because they differ in their approach to defining multiple invasive melanomas, with some authors also including multiple *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 melanoma compared to those with multiple invasive melanomas.

A small increase in the unadjusted survival rates that was 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 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 utlised 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 if and when an *in situ* melanoma was also diagnosed, and thereby may alter the percentage apportioned to the remaining subtypes. Data on mitoses, another key prognostic indicator for melanoma, was 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 persons 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 survival, continued surveillance following diagnosis of an *in situ* melanoma should remain a priority.

References

1. Mocellin S, Nitti D. Cutaneous melanoma in situ: translational evidence from a large population-based study. *Oncologist*. 2011; **16:** 896-903.
2. Youlden DR, Youl PH, Soyer HP, *et al.* Distribution of subsequent primary invasive melanomas following a first primary invasive or in situ melanoma Queensland, Australia, 1982-2010. *JAMA Dermatol*. 2014; **150:** 526-34.
3. Higgins HW, 2nd, Lee KC, Galan A, *et al.* Melanoma in situ: Part I. Epidemiology, screening, and clinical features. *J Am Acad Dermatol*. 2015; **73:** 181-90.
4. Sturm RA, Fox C, McClenahan P, *et al.* Phenotypic characterization of nevus and tumor patterns in MITF E318K mutation carrier melanoma patients. *J Invest Dermatol*. 2014; **134:** 141-9.
5. Darrasse-Jeze G, Bergot AS, Durgeau A, *et al.* Tumor emergence is sensed by self-specific CD44hi memory Tregs that create a dominant tolerogenic environment for tumors in mice. *J Clin Invest*. 2009; **119:** 2648-62.
6. Royston P, Lambert PC, *Flexible Parametric Survival Analysis Using Stata: Beyond the Cox Model*. 2011, College Station, Texas: Stata Press.
7. Doubrovsky A, Menzies SW. Enhanced survival in patients with multiple primary melanoma. *Arch Dermatol*. 2003; **139:** 1013-8.
8. Kricker A, Armstrong BK, Goumas C, *et al.* Survival for patients with single and multiple primary melanomas: the genes, environment, and melanoma study. *JAMA Dermatol*. 2013; **149:** 921-7.
9. Rowe CJ, Law MH, Palmer JM, *et al.* Survival outcomes in patients with multiple primary melanomas. *J Eur Acad Dermatol Venereol*. 2015.
10. Lachiewicz AM, Berwick M, Wiggins CL, *et al.* Survival differences between patients with scalp or neck melanoma and those with melanoma of other sites in the Surveillance, Epidemiology, and End Results (SEER) program. *Arch Dermatol*. 2008; **144:** 515-21.

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 years-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 years-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
	Col %	Col %	Col %	Col %	Col %	Col %
Mortality status as at 31 Dec 2012						
Alive	90.9	88.1	91.2	89.4	92.4	96.1
Deceased	9.1	11.9	8.8	10.6	7.6	3.9
	Chi-squared = 12.58; d.f. = 5; p = 0.01					
Sex						
Males	55.8	57.4	62.8	63.4	60.5	63.5
Females	44.2	42.6	37.2	36.6	39.5	36.5
	Chi-squared = 20.93; d.f. = 5; p < 0.01					
Body site of invasive melanoma						
Head and neck	15.4	21.0	15.5	18.9	15.1	13.4
Trunk	34.3	30.7	39.2	35.4	38.8	36.2
Upper limbs and shoulders	23.7	20.5	21.0	23.3	23.7	29.8
Lower limbs	21.9	19.9	17.6	18.3	20.6	17.8
Not specified	4.8	8.0	6.8	4.0	1.7	2.8
	Chi-squared = 38.12; d.f. = 20; p = 0.01					
Clinicopathological subtype of invasive melanoma						
Nodular melanoma	8.3	9.1	8.1	10.3	5.8	6.7
Melanoma in junctional naevus	2.0	2.3	0.7	2.8	2.4	3.9
Lentigo maligna melanoma	5.1	8.5	9.5	7.8	7.6	6.7
Superficial spreading melanoma	53.6	47.2	53.4	50.0	55.0	55.7
Other specified melanoma	4.0	2.3	5.4	3.7	5.5	5.9
Not otherwise specified	27.0	30.7	23.0	25.5	23.7	21.2
	Chi-squared = 48.56; d.f. = 25; p < 0.01					
Thickness of invasive melanoma						
< 1mm	68.3	67.1	71.0	69.6	66.0	72.1
1mm to < 2mm	12.8	7.4	12.2	10.9	20.3	15.9
>= 2mm	11.6	14.8	9.5	13.7	10.7	8.4
Not recorded	7.3	10.8	7.4	5.9	3.1	3.6
	Chi-squared = 45.82; d.f. = 15; p < 0.01					
Ulceration of invasive melanoma						
No	55.1	48.9	53.4	53.7	61.5	59.3
Yes	8.8	9.1	6.8	9.6	8.3	8.6
Not recorded	36.1	42.1	39.9	36.7	30.2	32.0
	Chi-squared = 12.58; d.f. = 10; p = 0.25					

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[a]

Melanoma group[b]	n	Unadjusted 10-year survival estimates (95% CI)	Adjusted hazard ratio[b] (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-square = 0.42; Degrees of freedom = 5; p = 0.99				

Notes: a. Persons who remained alive were followed up to 31 Dec 2012.
b. 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.

Figure legend

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. Persons who remained alive were followed up to 31 Dec 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.