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Physician skin checks before the diagnosis of melanoma correlate with tumor characteristics

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Short Title: Physician skin checks and melanoma

Dear Editor,

Tumor thickness is the most important prognostic factor in invasive melanoma (Balch et al, 2001; Balch et al, 2009), and early detection has the potential to reduce both mortality and morbidity by diagnosing thinner melanomas. Full body skin examinations by physicians can facilitate early detection.

Previous research has shown that patients with thin melanomas were more likely to report having clinician skin checks prior to their diagnosis (Geller et al, 1992; Geller et al, 2009a; Aitken et al, 2010; Urech et al, 2016) . Notably, however, those studies relied on self-reports of skin checks after melanoma diagnosis, resulting in the potential for systematic recall bias as well as random misclassification. We sought to examine the relationship between physician skin checks and characteristics of melanoma cases diagnosed prospectively in a large population-based cohort.

We included all incident melanoma diagnoses (invasive or *in situ*) arising in the QSkin Study cohort from recruitment in 2011 until 31 December 2014. The cohort includes men and women aged 40 through 69 years at recruitment who were sampled randomly from the Queensland population (n=43,794) (Olsen et al, 2012). Data on melanoma diagnoses were obtained from the Queensland Cancer Registry (melanoma notifications are mandatory). We obtained information about health service use during follow-up through linkage with Medicare, Australia's universal health insurance scheme covering all age groups. The baseline survey asked "During the past 3 years how many times has all or nearly all of your skin been deliberately checked by a Doctor?"

We used Cox proportional hazards models to compare the incidence of melanoma among participants grouped according to history of physician skin checks (categorized as 0, 1, 2+). We examined several outcomes: invasive (all, ≤1mm, >1mm); *in situ*; and all cutaneous melanomas (invasive + *in situ*). To examine characteristics of incident melanomas according to history of skin checks, we compared categorical variables using Pearson χ^2 and/or Fisher exact test, and continuous variables using analysis of variance. Full details of the cohort recruitment and statistical analyses are presented in Supplementary material (available online). The Human Research Ethics Committee at the QIMR Berghofer Medical Research Institute approved the study, and all participants gave written informed consent to take part.

Of the entire cohort, 72% of participants reported having one or more skin checks in the 3 years prior to baseline. Over a median follow-up of 3.4 years (mean 3.5 years), 819 study participants developed melanoma. We excluded 164 (20%) participants who had a melanoma prior to baseline leaving 655 incident cases for analysis (invasive melanoma 251 cases; *in situ* melanoma 404). The age-standardized (US 2000) invasive melanoma incidence rate was 153 per 100,000 person-years. Of participants diagnosed with incident melanoma, 87% had reported having one or more physician skin checks in the 3 years prior to baseline (25% reported having one, 62% more than one). After adjustment for potentially confounding factors, relative to those with no history of physician skin checks in the three years prior to baseline, those who had such checks had a higher incidence of *in situ* and thin (≤1mm) but not thick (>1mm) invasive melanomas (Table 1).

Melanoma cases who reported having physician skin checks were more likely than other cases to have a high perceived likelihood of developing melanoma ($p<0.001$) and to have private health insurance ($p=0.01$) (Table 1). They were also more likely to have a higher number of visits to General Practitioners (GP) and dermatologists, higher number of skin biopsies and higher number of excisions for keratinocyte skin cancers (KC) during follow-up (up to 30 days prior to melanoma diagnosis) than other cases, although these were not statistically significant (Supplementary Table 1). There was no difference between cases who did and did not report skin checks in terms of their highest attained educational level, ethnicity, or phenotypic characteristics including skin color, eye color, hair color, skin phototype, freckling tendency, and moliness at age 21 (all $p>0.10$). We have previously described factors predicting skin examination practices in the full cohort (Olsen et al, 2015).

The mean thickness of invasive melanomas amongst cases who reported having any skin checks was significantly lower than among those cases who had reported having none (0.78mm vs 1.39 mm; $p=0.005$) (Table 2). Compared with cases who had reported no skin checks prior to baseline, those who reported one or more skin checks were more likely to have lentigo maligna (LM) subtype (Table 2). Mean thickness did not differ significantly according to number of skin biopsies, GP visits or excisions for KC during follow-up. We also examined the characteristics of melanoma cases and their first incident tumor amongst people who had reported one vs. two or more skin checks in the three years prior to baseline. We found no differences between these two groups for any characteristics, except number of dermatologist visits during follow-up, which increased with higher numbers of skin checks ($p<0.001$) (Supplementary Tables 2 and 3).

In our cohort, cases who had undergone any prior physician skin checks had thinner melanomas on average. Other markers of health service use were not significantly associated with melanoma thickness. Our findings accord with previous research based on retrospective reporting of skin checks (Geller et al, 1992; Urech et al, 2016).

Strengths of our study include the population-based sampling frame, prospective design leading to an absence of recall bias, and complete ascertainment of melanoma diagnoses (including *in situ)* during follow-up. We were also able to examine health service use during follow-up, as an adjunct to the self-reported information collected at baseline. Limitations include low response rate and reliance on self-report of prior physician skin checks.

Knowledge of skin cancer risk factors in Queensland is very high and we have previously shown that people with high-risk phenotypes are more likely to undergo physician skin checks (Olsen et al, 2015). This aligns with other research suggesting that people who present for skin checks are more aware of their importance, and of the criteria to detect a lesion suspicious of melanoma (Geller et al, 2009b). Clinical skin examination appears to be increasing in the Queensland community as a result of greater awareness associated with the skin cancer prevention campaigns that began in the early 1980s (Marks, 1990).Our results may not generalize to other populations where awareness of risk factors and of the importance of seeking early medical attention for suspicious lesions is lower. Some may contend that our findings reflect over-diagnosis of indolent lesions (i.e. thinner lesions, and of the LM subtype) (Welch and Black, 2010), given the higher prevalence of screening behaviors amongst melanoma cases compared with non-cases (Olsen et al, 2015) and our finding that participants who reported skin checks had a higher

incidence of *in situ* and thin (≤1mm) but not thick (>1mm) invasive melanomas. Long-term follow-up of cases for progression and survival outcomes would be informative in this regard.

In summary, our findings suggest that physician skin checks are widespread among melanoma cases and are associated with the detection of melanoma at its earliest stages.

CONFLICT OF INTEREST

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Table 1. History of doctor skin checks and risk of invasive melanoma among 38,854 men and women in the QSkin study cohort.

Number of skin checks by a doctor in the past 3 years	Participants with melanoma			Multivariate model[2]
	No	Yes		
	n (%)[1]	n (%)[1]	P value	HR (95%CI)
All invasive melanoma				
0	11,510 (28.6)	38 (14.9)		Reference
1	12,167 (30.2)	62 (24.3)		1.40 (0.93-2.11)
2 or more	16,585 (41.2)	155 (60.8)	<0.001	2.01 (1.39-2.89)
Invasive melanoma ≤1 mm				
0	11,510 (28.6)	27 (13.3)		Reference
1	12,167 (30.2)	50 (24.6)		1.59 (0.99-2.55)
2 or more	16,585 (41.2)	126 (62.1)	<0.001	2.36 (1.54-3.60)
Invasive melanoma >1 mm				
0	11,510 (28.6)	11 (22.9)		Reference
1	12,167 (30.2)	12 (25.0)		0.96 (0.41-2.23)
2 or more	16,585 (41.2)	25 (52.1)	0.31	0.98 (0.46-2.11)
***In situ* melanoma**				
0	11,465 (28.8)	49 (11.6)		Reference
1	12,063 (30.3)	110 (25.9)		2.00 (1.42-2.81)
2 or more	16,339 (41.0)	265 (62.5)	<0.001	2.94 (2.14-4.03)
All melanoma (invasive + *in situ*)				
0	11,465 (28.8)	83 (12.8)		Reference
1	12,063 (30.3)	166 (25.4)		1.76 (1.35-2.31)
2 or more	16,339 (41.0)	401 (61.7)	<0.001	2.55 (2.00-3.26)

[1] Numbers may not sum to total due to missing data; six cases had an *in situ* melanoma diagnosed before an invasive melanoma.
[2] Adjusted for age, sex, tanning ability, hair color, moles at age 21, and family history of melanoma.

Table 2. Characteristics of first incident melanomas, stratified by self-reported history of having a skin check by a Doctor in the 3 years prior to baseline.

Variables	**No skin check** (n=83) **N (%)**[1]	**Skin check** (n=567) **N (%)**[1]	**Chi-Square** ***P*** **value**
Melanoma type			
In situ	45 (54.2)	356 (62.8)	
Invasive	38 (45.8)	211 (37.2)	0.13
Invasive melanomas			
Age-standardized rate[2]	81.9/100,000 PY	182.3/100,000 PY	
Thickness			
Mean (SD)	1.39 (1.66)	0.78 (0.89)	0.005[3]
Median (IQR)	0.71 (0.40-1.20)	0.50 (0.30-0.82)	0.057[4]
≤0.5 mm	15 (39.5)	112 (54.6)	
0.51-1.00 mm	12 (31.6)	58 (28.3)	
1.01-1.99 mm	5 (13.2)	18 (8.8)	
2.00+ mm	6 (15.8)	17 (8.3)	0.25
Melanoma type			
Superficial spreading	21 (55.3)	130 (61.6)	
Lentigo malignant	0	15 (7.1)	
Nodular	5 (13.2)	7 (3.3)	
Other	12 (31.6)	59 (28.0)	0.023
All melanomas			
Age-standardized rate[2]	185.9/100,000 PY	485.9/100,000 PY	
Body site			
Head/neck	16 (19.3)	114 (20.1)	
Trunk	29 (34.9)	202 (35.6)	
Upper limbs	22 (26.5)	142 (25.0)	
Lower limbs	14 (16.9)	96 (16.9)	
Overlapping/NOS	2 (2.4)	13 (2.3)	0.99
Melanoma type			
Superficial spreading	33 (39.8)	241 (42.5)	
Lentigo maligna/malignant	12 (14.5)	132 (23.3)	
Nodular	5 (6.0)	7 (1.2)	
Other	33 (39.8)	187 (33.0)	0.006

[1] Numbers may not sum to total due to missing data; data is missing on skin checks by a doctor for 5 melanoma cases (2 invasive); thickness is missing for 6 invasive melanomas

SD standard deviation; IQR inter-quartile range

[2] Standardised to US 2000
[3] P-value for significant difference in mean values (Ryan-Einot-Gabriel-Welsch multiple range test)
[4] P-value for significant difference in the median values (Wilcoxon rank sum test)