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A prospective study of measured body size and height and risk of keratinocyte cancers and melanoma

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ABSTRACT

Background: The potential influence of measured body weight and height on keratinocyte skin cancer risk has scarcely been studied. Some evidence indicates melanoma risk increases as self-reported height increases, but an association with body mass index (BMI) is less certain.
Methods: We measured body weight and height of 1171 Australian men and women in a community-based skin cancer study in Queensland and prospectively examined the association of BMI, body surface area (BSA) and height and incidence of basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma while accounting for skin phenotype, sun exposure, clinical/cutaneous signs of chronic photodamage and other risk factors.
Results: During 16 years of follow-up, 334 and 188 participants newly developed BCC and SCC, respectively; 28 participants were diagnosed with primary melanoma. BMI and BSA were unrelated to skin cancer incidence. After full adjustment, height was significantly associated with SCC development in men (relative risk (RR) = 1.66; 95% confidence interval (CI) = 1.11–2.48, for ≥175 cm vs ≤171 cm, P_{trend} = 0.017), and BCC in women (P_{trend} = 0.043). Melanoma in men, was similarly positively associated with height (RR per 5 cm increment = 1.55; 95%CI 0.97–2.47, P = 0.067) though not significantly.
Conclusion: This study shows that after adjusting for sun exposure tall stature may be a risk factor for the most common types of skin cancer BCC, SCC, and melanoma, while body mass and surface area appear unrelated to risk.

1. Introduction

The keratinocyte skin cancers BCC and SCC are the most common human cancers diagnosed globally [1,2]. Melanoma is less common but continues to increase in incidence worldwide [3]. Excessive ultraviolet radiation (UVR) exposure is the major environmental cause of skin cancer risk [4,5] alongside skin phenotype [6]. Past evidence suggests that anthropometric measures and indices of obesity correlate strongly with risk of some adult cancers [7], but less strongly with melanoma [8–10] while very little is known about body size and keratinocyte cancers.

The four relevant investigations of BCC have given mixed results, some showing inverse associations with BMI [11–13], one a positive association with height [11], and one of our previous studies no association [14]. Only three reports to date appear to have examined cutaneous SCC exclusively, indicating an inverse association with BMI among women [12,13] or no association [15], but height has not been examined in relation to SCC. Only two studies adjusted for personal UVR exposure [11,12]; another two studies reporting findings on combined BCC and SCC cases [16,17] were not informative.

Regarding risk of melanoma, in one of the earliest relevant studies [18] the authors observed a positive association between BMI and BSA and melanoma among men, and a stronger association with height in both men and women. Recent meta-analyses, one of BMI and risk of different types of cancer [9] and another of BMI and melanoma risk [10] indicated weak to moderate positive associations (effect estimates 1.17–1.31) between increasing BMI and

Abbreviations: BCC, basal cell carcinoma; BMI, body mass index; BSA, body surface area; CI, confidence interval; RR, relative risk; SCC, squamous cell carcinoma.

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melanoma in men. A large pooled analysis of 8 case-control studies of melanoma in women showed no association with BMI or BSA [19], but women in the highest quartile of height had an elevated risk of melanoma compared to those with short stature. Similarly, in the UK Million Women Study [20], and the NIH-AARP Diet and Health Study [21], there was a significantly increased risk of melanoma with greater height (~32% and 14–18%, respectively, per 10 cm increment).

Findings from other prospective cohort studies, including women only, have corroborated the existence of a positive height-melanoma association [17,22–24]. All of these melanoma studies lacked adjustment for sun exposure, except one [19], and almost all studies to date have relied on self-reported weight and height.

Given these previously proposed links between obesity and height and the common types of skin cancer, with noticeable differences between sexes and mostly unadjusted for sun exposure, we aimed to examine the associations of selected adult anthropometric measures and incidence of BCC, SCC and melanoma simultaneously in a long-term community-based cohort study of skin cancer fully taking into account potential confounding by sun exposure and other established risk factors.

2. Methods

2.1. Study population and data collection

In this prospective study, 1621 residents of the Queensland township of Nambour, who were originally randomly selected from the population-based electoral roll [25] and who participated in the Nambour Skin Cancer Prevention Trial (1992–1996) [26,27] were followed up until 2007. Almost all study participants (99.7%) were of Caucasian descent. Trial participants were eligible for the present study if they had available data on anthropometric and physical activity measures as previously described [28]. Ethical approval was obtained from the ethics committee of the Queensland Institute of Medical Research (now QIMR Berghofer Medical Research Institute). We obtained written informed consent from all participants.

2.2. Assessment of body measures and skin cancer risk factors

At baseline in 1992, participants underwent a physical examination and completed a health and fitness questionnaire including information on outdoor behavior, pigment phenotype, previous skin cancer history, and other lifestyle and sociodemographic characteristics.

Weight and height were measured at the study clinic by trained staff using calibrated electronic weighing scales and a stationary stadiometer. Participants were measured in light clothing without shoes. Weight was recorded to the nearest 0.1 kg, and standing height to the nearest 0.1 cm. BMI was calculated as weight in kg divided by height in m^2 (kg/m^2) and categorized according to WHO criteria for overweight and obesity [29]. Body surface area was calculated according to the Mosteller formula [30,31]. Dermatologists carried out full skin examinations and recorded standard signs of cumulative photoaging, including elastosis of the neck, an objective clinical marker of chronic photodamage which was graded as mild to moderate (+) or severe (++) [32,33].

Skin-phenotypic characteristics included history of skin cancer before 1992 (BCC and SCC, y/n), and other categorically grouped variables, namely tanning ability of skin, painful sunburns throughout life, freckling of the back, clinical elastosis of the neck, and sunscreen use. Other factors considered as confounders were education four categories: grade 12 or less, trade/apprenticeship, technical certificate/diploma, university (bachelor or higher); smoking status at baseline (never, former, current smoker); and total recreational activity (hrs/wk), a summed variable of walking, moderate and vigorous exercise done for sports, recreation or fitness during the past 2 weeks with reference category no reported activity [28].

2.3. Endpoints and ascertainment of cases

After the scheduled trial completion in 1996, participants completed biannual or annual questionnaires about all new skin cancers, including melanoma. Participants who withdrew from active trial participation or active follow-up agreed to continue with ongoing passive monitoring of skin cancers through their medical records [26].

Incident BCC and SCC were identified through detailed assessment procedures described previously [26,27,34] and all BCC and SCC were verified histologically. The outcome used in the analysis was incidence of persons affected by new BCC and SCC diagnosed after the baseline 1992 skin examination survey through to 31 December 2007, in the person-years of follow-up accumulated between these dates and expressed per 100,000 person years. BCC and SCC tumors and person-years of follow-up were counted for each participant from baseline until date of withdrawal from the study, or date of death, or 31 December 2007, whichever came first. This analysis included 334 persons with new BCC (160 men, 174 women) and 188 persons with new SCC (98 men, 90 women).

Information on incident melanomas was obtained through notifications by regional pathology laboratories in all participants and cross-checked by a search of the Queensland Cancer Registry (melanoma registration is compulsory) [35]. Study participants were followed from baseline (1992) until first melanoma diagnosis, death, or end of the follow-up period (31 December 2007). This analysis included 28 incident melanoma cases (11 men, 17 women).

2.4. Statistical Analysis

We used different regression analyses for calculating risk estimates for keratinocyte cancers (multiple events) and melanoma (single event). A sex-stratified analysis was performed due to expected differences in body size and behavior between men and women.

For keratinocyte cancers (person-based analysis), relative risks (RRs) with 95% confidence intervals (95% CI) of BCC and SCC incidence for each categorical or continuous body measure were estimated by generalised linear models, specifying Poisson distribution with a robust error variance [36] and person-years of follow-up as offset. Multivariable models were simultaneously adjusted for the following established risk factors and potential confounders that were significantly associated with BMI age at baseline, history of BCC or SCC (before 1992), clinical elastosis of the neck, freckling of the back, and smoking status (other potential confounders including recreational sun exposure, occupational sun exposure and sunburns were not associated with outcomes). Treatment allocation (betacarotene supplements and/or daily sunscreen) in the trial 1992–1996 was included as a study design variable. We did not adjust for natural skin or hair color, or tanning ability in the multivariable model because these innate characteristics were captured when clinical elastosis of the neck, a composite measure of sun sensitivity and cumulative sun exposure, was included in the model [32,33]. Trend tests were calculated using quartile-based scores, assigning a score of 1–4 to an individual according to the interquartile interval of the selected body measure.

For melanoma, Cox proportional hazards models with follow-up time as underlying time variable in the counting process were used to estimate age-adjusted RRs and 95% CIs of melanoma incidence for each body measure. Due to the small number of melanoma cases, we used continuous exposure variables and report RRs by 1 unit increment in BMI, 1 SD-unit increment in BSA (1 SD = 0.2 in both sexes) and 5 cm increment in height. Multivariable models were adjusted for the following melanoma risk factors age at baseline (years), treatment allocation, skin cancer history (combined BCC and SCC history), elastosis of the neck, and smoking status.

To examine the potential effect modification of associations by history of skin cancer, interaction terms for selected body measures with skin cancer history were tested. A *P* value for interaction was calculated, referring to the interaction term of the skin cancer history variable and BMI/BSA/height (categorical) over the entire cohort. The interaction terms were not statistically significant ($P > 0.05$). Further, we conducted sensitivity analysis by additionally adjusting for education or outdoor behavior, and weight or BMI in models with height as exposure variable (BCC, SCC), and presence of nevi in the melanoma models. All analyses were conducted using the SAS statistical software, version 9.1

Table 1
Characteristics of study participants by body mass index ($n = 1171$).

Characteristics	Women, quartiles of BMI ($n = 665$)					Men, quartiles of BMI ($n = 506$)				
	Q1	Q2	Q3	Q4	*p*-value	Q1	Q2	Q3	Q4	*p*-value
Number	169	162	166	168		125	126	130	125	
Range	17.6–22.6	22.7–24.8	24.9–28.1	28.2–48.5		17.2–24.0	24.1–26.2	26.3–28.7	28.8–43.2	
Median	21.3	23.7	26.3	31.0		22.3	25.2	27.5	30.6	
		Mean (SD)					*Mean (SD)*			
Age (years) in 1992	44.3 ± 12.5	49.3 ± 11.5	52.2 ± 11.5	51.6 ± 11.7	<0.001	49.7 (14.2)	49.4 ± 14.0	51.1 ± 12.8	51.8 ± 13.0	0.460
		Percent					*Percent*			
History of skin cancer[a]	21.3	22.8	27.7	31.0	0.159	29.6	31.0	27.0	32.8	0.773
Education										
High school only	63.3	63.6	62.7	68.5	0.876	33.6	39.7	45.4	42.4	0.150
Trade/other	5.3	5.6	5.4	6.0		33.6	33.3	35.4	38.4	
Certificate/diploma	25.4	26.5	28.9	20.8		22.4	14.3	13.1	14.4	
University	5.9	4.3	3.0	4.8		10.4	12.7	6.2	4.8	
Smoking status										
Non-smoker	56.8	74.7	68.1	64.9	0.012	45.6	57.9	36.2	31.2	<0.001
Ex-smoker	27.8	19.1	25.3	23.8		29.6	30.2	49.2	52.0	
Smoker	15.4	6.2	6.6	11.3		24.8	11.9	14.6	16.8	
Recreational activity (hrs/wk)										
None	28.4	29.0	37.3	38.7	0.274	38.4	34.9	40.0	46.4	0.136
F ≤ 1, M ≤ 1.5	26.0	27.2	19.3	19.6		23.2	22.2	23.8	13.6	
F ≤ 3, M ≤ 4	24.3	25.3	19.3	21.4		19.2	16.7	23.1	21.6	
F > 3, M > 4	21.3	18.5	24.1	20.2		19.2	26.2	13.1	18.4	
Tanning ability of skin										
Always burn	24.9	19.8	28.3	25.0	0.067	21.8	11.9	13.1	20.0	0.111
Burn then tan	69.2	65.4	63.3	61.3		67.7	80.2	79.2	67.2	
Only tan	5.9	14.8	8.4	13.7		10.5	7.9	7.7	12.8	
Painful sunburns throughout life (1992)										
Never	8.9	13.0	9.0	12.5	0.273	14.5	13.5	10.0	12.0	0.284
Once	19.5	22.2	17.5	22.0		11.3	18.3	10.0	15.2	
2–5 times	40.2	45.7	45.2	44.6		37.9	43.7	50.0	39.2	
More than 5 times	31.4	19.1	28.3	20.8		36.3	24.6	30.0	33.6	
Freckling of the back (1992)[b]										
Nil	32.1	32.9	32.5	34.8	0.432	27.3	28.7	36.5	25.2	0.237
Mild	41.8	32.9	41.1	34.1		32.2	35.2	31.0	34.5	
Moderate	15.2	25.3	18.4	23.2		21.5	14.8	15.9	26.9	
Severe	10.9	8.9	8.0	7.9		19.0	21.3	16.7	13.4	
Clinical elastosis of the neck (1992)[b]										
Nil	34.9	24.7	18.1	21.4	0.018	14.4	15.9	14.6	13.8	0.988
Mild	43.2	47.5	50.0	51.8		44.8	47.6	48.5	49.6	
Severe	21.9	27.8	31.9	26.8		40.8	36.5	36.9	36.6	
Sunscreen use 1992										
Non-user	13.6	16.7	26.5	28.6	<0.001	34.7	34.1	26.2	35.2	0.123
Irregular user	33.7	44.4	39.2	40.5		41.1	35.7	51.5	46.4	
Regular user	52.7	38.9	34.3	31.0		24.2	30.2	22.3	18.4	

[a] history of BCC and/or SCC.
[b] Column percentages may not sum to 100% due to missing values (freckling of the back: women $n = 15$, men $n = 18$; elastosis: men $n = 2$).

(SAS Institute, Cary, NC), and statistical tests were 2-sided with *P*-values <0.05 considered statistically significant.

3. Results

For the present study, participants with missing data on BMI ($n = 168$) and physical activity ($n = 282$) were excluded as previously described [28], leaving a study cohort of 1171 men and women. Participants who were excluded from the analysis tended to be slightly younger than their included counterparts, excluded women were more likely to have a lower education, and excluded men were more likely to have a lower grading of clinical elastosis and less likely to have skin cancer prior to 1992 than those included. Study participants aged 25–75 years at baseline (1992) were followed for an average period of 14.4 (±3.8) years, yielding a total of 16,887 person-years.

Table 1 provides the characteristics of the study participants by BMI quartile and sex. Participants in higher BMI categories tended to be older than those in the lowest BMI category, but this was statistically significant in women only. Both women and men in the lowest BMI category had the highest proportion of smokers compared to those with higher BMI. Women in the higher BMI categories had higher grading of clinical elastosis, and were less likely to be regular sunscreen users than those in the lower BMI groups. Other characteristics including recreational activity and sunburns did not significantly vary by BMI status (Table 1), BSA or height (data not shown).

In age-adjusted and multivariable-adjusted models, higher BMI or BSA were not associated with risk of BCC (Table 2) or SCC (Table 3) in either sex. In contrast, height was positively associated with BCC in women ($P_{trend} = 0.043$), but none of the risk estimates based on quartiles approached statistical significance (Table 2). When height was fitted as a continuous term, the RR (95% CI) was 1.09 (1.00–1.20; $P = 0.052$) per 5 cm increment of height. There was a significant positive association between height and SCC ($P_{trend} = 0.017$) among men (Table 3). In the fully adjusted model, we observed a 66% increased risk of SCC in the third quartile (175–180 cm) compared with the lowest (reference, <171 cm). Men grouped in the highest quartile (>180 cm) also had an elevated risk (53%), but the risk estimate was not significant. The RR (95% CI) was 1.11 (0.98–1.26; $P = 0.110$) for continuous height (per 5 cm increase).

In analyses combining men and women, BMI was not associated with BCC (RR, 95% CI Q2 (0.90, 0.71–1.14), Q3 (0.84, 0.66–1.07), Q4 (0.93, 0.74–1.18) or SCC (RR, 95% CI: Q2 (0.81, 0.58–1.13), Q3 (0.81, 0.56–1.15), Q4 (0.97, 0.69–1.35) as reflected in the sex-stratified analyses. Height was positively associated with BCC (RR, 95% CI: Q2 1.03, (0.80–1.31), Q3 (1.29, 1.02–1.64), Q4 (1.28, 1.01–1.62), $P_{trend} = 0.015$), but not associated with SCC (RR, 95% CI: Q2 (0.94, 0.67–1.31), Q3 (1.18, 0.85–1.63), Q4 (1.11, 0.78–1.58).

Table 4 shows the age- and fully adjusted RRs for melanoma for each anthropometric measure by sex. Average time to melanoma incidence among 28 participants was 9.7 (±4.8) years, yielding a total of 271.6 person-years. Due to the limited number of cases (women $n = 17$, men $n = 11$) we fitted all anthropometric measures as continuous variables. Specifically among men, the risk estimate for height suggested an increased risk in melanoma (~50% increase in risk per 5 cm increment), though the dose-response trend was not statistically significant. BMI and BSA were unrelated to melanoma risk in both men and women and overall. The risk estimates for women and men combined were as follows BMI (RR, 95% CI: 1.00, 0.91–1.09 per 1 unit increment), BSA (RR, 95% CI: 1.24, 0.82–1.89 per 1 SD- unit increment), and height (RR, 95% CI: 1.28, 0.97–1.71 per 5 cm increment).

In additional analyses (data not shown), we further adjusted for education to account for residual confounding, but risk estimates were not substantially altered. Additional adjustments for weight or BMI did not materially change the associations between height

Table 2
Relative risks (RRs) and 95% CI of BCC (1992–2007) according to body size measure, stratified by sex.

Body measure	Women with BCC/Total	Age-adjusted RR (95% CI) ($n = 665$)	Multivariable[a] RR (95% CI) ($n = 650$)	Men with BCC/Total	Age-adjusted RR (95% CI) ($n = 506$)	Multivariable[a] RR (95% CI) ($n = 486$)
BMI quartile[b]						
Q1	41/169	Reference	Reference	42/125	Reference	Reference
Q2	43/162	0.93 (0.64,1.34)	0.96 (0.67,1.37)	38/126	0.93 (0.66,1.29)	0.84 (0.60,1.17)
Q3	46/166	0.92 (0.65,1.32)	0.90 (0.64,1.27)	38/130	0.82 (0.58,1.15)	0.79 (0.56,1.11)
Q4	44/168	0.96 (0.67,1.37)	0.95 (0.68,1.33)	42/125	0.97 (0.70,1.34)	0.91 (0.65,1.27)
p trend		0.851	0.708		0.680	0.513
BMI categorical						
<25	84/335	Reference	Reference	63/177	Reference	Reference
25–30	60/213	1.03 (0.78,1.36)	1.01 (0.77,1.32)	67/246	0.76 (0.58,1.00)	0.75 (0.58,0.98)
>30	30/117	0.96 (0.68,1.35)	0.89 (0.64,1.23)	30/83	1.04 (0.74,1.44)	1.06 (0.76,1.48)
p trend		0.888	0.543		0.699	0.673
BSA quartile[c]						
Q1	40/166	Reference	Reference	52/126	Reference	Reference
Q2	48/166	1.17 (0.82,1.67)	1.13 (0.80,1.60)	32/127	0.68 (0.48,0.96)	0.65 (0.47,0.90)
Q3	38/167	0.89 (0.61,1.30)	0.95 (0.66,1.36)	37/127	0.79 (0.57,1.09)	0.83 (0.60,1.14)
Q4	48/166	1.25 (0.88,1.77)	1.10 (0.78,1.55)	39/126	0.90 (0.65,1.24)	0.94 (0.68,1.31)
p trend		0.488	0.852		0.610	0.843
Height quartile[d]						
Q1	41/165	Reference	Reference	46/124	Reference	Reference
Q2	39/165	1.04 (0.71,1.51)	1.02 (0.72,1.45)	35/129	0.86 (0.61,1.21)	1.04 (0.73,1.48)
Q3	45/169	1.28 (0.89,1.85)	1.31 (0.92,1.89)	43/127	1.10 (0.80,1.53)	1.26 (0.92,1.72)
Q4	49/166	1.50 (1.05,2.15)	1.35 (0.96,1.90)	36/126	1.08 (0.78,1.51)	1.21 (0.86,1.70)
p trend		0.017	0.043		0.391	0.142

[a] Model adjusted for age (years), treatment allocation, BCC history, elastosis of the neck, freckling of the back, and smoking status.
[b] Cutpoints BMI (kg/m^2): women 22.7, 24.9, 28.2; men 24.1, 26.3, 28.8.
[c] Cutpoints BSA (m^2, SD unit): women 1.63, 1.72, 1.83; men 1.87, 1.98, 2.08.
[d] Cutpoints height (cm) : women 158.0, 161.8, 166.5; men 170.9, 174.8, 179.9.

Table 3
Relative risks (RRs) and 95% CI of SCC (1992–2007) according to body size measure, stratified by sex.

Body measure	Women with SCC/Total	Age-adjusted RR (95% CI) (n = 665)	Multivariable[a] RR (95% CI) (n = 650)	Men with SCC/Total	Age-adjusted RR (95% CI) (n = 506)	Multivariable[a] RR (95% CI) (n = 486)
BMI quartile[b]						
Q1	23/169	Reference	Reference	22/125	Reference	Reference
Q2	19/162	0.67 (0.39,1.14)	0.58 (0.35,0.99)	25/126	1.17 (0.74,1.87)	1.04 (0.66,1.65)
Q3	25/166	0.76 (0.46,1.26)	0.64 (0.37,1.05)	23/130	0.94 (0.57,1.54)	0.98 (0.59,1.62)
Q4	23/168	0.78 (0.47,1.30)	0.78 (0.47,1.27)	28/125	1.23 (0.77,1.95)	1.23 (0.77,1.95)
p trend		0.492	0.484		0.592	0.456
BMI categorical						
<25	42/335	Reference	Reference	37/177	Reference	Reference
25–30	31/213	0.96 (0.63,1.45)	0.90 (0.59,1.36)	44/246	0.84 (0.60,1.23)	0.92 (0.64,1.32)
>30	17/117	0.96 (0.58,1.61)	1.03 (0.61, 1.73)	17/83	1.03 (0.62,1.71)	1.06 (0.66,1.72)
p trend		0.855	0.956		0.881	0.944
BSA quartile[c]						
Q1	23/166	Reference	Reference	30/126	Reference	Reference
Q2	25/166	1.07 (0.66,1.76)	0.87 (0.52,1.46)	21/127	0.86 (0.54,1.37)	0.80 (0.50,1.29)
Q3	20/167	0.79 (0.46,1.37)	0.79 (0.48,1.32)	26/127	1.05 (0.69,1.60)	1.10 (0.74,1.64)
Q4	22/166	1.05 (0.62,1.78)	0.84 (0.50,1.42)	21/126	0.97 (0.60,1.55)	1.09 (0.68,1.76)
p trend		0.835	0.472		0.916	0.501
Height quartile[d]						
Q1	29/165	Reference	Reference	27/124	Reference	Reference
Q2	22/165	0.91 (0.55,1.48)	0.86 (0.53,1.39)	20/129	0.92 (0.57,1.50)	1.05 (0.66,1.67)
Q3	20/169	0.95 (0.57,1.61)	0.86 (0.51,1.47)	30/127	1.48 (0.96,2.28)	1.66 (1.11,2.48)
Q4	19/166	1.04 (0.61,1.79)	0.80 (0.47,1.37)	21/126	1.33 (0.83,2.15)	1.53 (0.93,2.51)
p trend		0.889	0.432		0.072	0.017

[a] Model adjusted for age (years), treatment allocation, SCC history, elastosis of the neck, freckling of the back, and smoking status.
[b] Cutpoints BMI (kg/m^2): women 22.7, 24.9, 28.2; men 24.1, 26.3, 28.8.
[c] Cutpoints BSA (m^2, SD unit) : women 1.63, 1.72, 1.83; men 1.87, 1.98, 2.08.
[d] Cutpoints height (cm) : women 158.0, 161.8, 166.5; men 170.9, 174.8, 179.9.

Table 4
Relative risks (RRs) and 95% CI of cutaneous malignant melanoma (1992–2007) for continuous body measures, stratified by sex, in 506 men and 665 women.

Body measure	Cases	Age-adjusted RR (95% CI)	Multivariable[a] RR (95% CI)
BMI (kg/m^2)			
Men	11	0.90 (0.75,1.08) p = 0.240	0.90 (0.74–1.08) p = 0.260)
Women	17	1.03 (0.94–1.13) p = 0.509	1.03 (0.94–1.13) p = 0.528
BSA (m^2), SD units[c]			
Men	11	1.08 (0.54–2.16) p = 0.828	1.06 (0.53–2.12) p = 0.862
Women	17	1.33 (0.80-2.21) p = 0.273	1.32 (0.79–2.21) p = 0.293
Height (cm)[b]			
Men	11	1.53 (0.98–2.39) p = 0.065	1.55 (0.97–2.47) p = 0.067
Women	17	1.12 (0.76–1.65) p = 0.556	1.12 (0.76–1.64) p = 0.567

[a] RR adjusted for age (years), treatment allocation, skin cancer history, elastosis of the neck, and smoking status.
[b] Height in 5 cm increments.
[c] SD unit = 0.2 (in both sexes).

and skin cancers, nor did adjustment for presence of nevi (melanoma only) change observed associations. Further adjustments for outdoor behavior variables did not alter the observed associations.

4. Discussion

In this longitudinal study of Australian adults, neither adult BMI nor BSA was significantly associated with incidence of cutaneous BCC, SCC or melanoma. In men, however, we observed an elevated risk of SCC and a suggestive positive association with melanoma with increasing height. Among women, there was a trend of increased BCC risk with increasing height. These associations were independent of sun exposure and other risk factors. Our study is novel in its prospective and simultaneous investigation of measured body size and height in relation to risk of BCC, SCC, and melanoma in both sexes in the same general population sample, fully assessing their associations with sun exposure and adjusting for the confounding effect of clinical elastosis, an objective marker of chronic photodamage, in all final models.

We observed a positive height-BCC association in women, which is corroborated by a report from the large US radiologic technologists cohort Study [11], where height was also shown to be positively associated with BCC in women (Q5 vs Q1 HR = 1.64, CI 1.40–1.93, $p_{trend} < 0.0001$) and men (HR = 1.34, CI 0.94–1.89, $p_{trend} = 0.05$) accounting for UV susceptibility factors and UV exposure. We have not identified any height-SCC study with which to compare our results.

Our null findings for BMI and risk of BCC and SCC correspond with results from two previous studies [14,15], but are not in agreement with other reports showing an inverse association for BCC [11–13,16] and for SCC [12,13].

In our cohort, there was a suggestive positive linear risk pattern (p = 0.07) between height and melanoma among men. The lack of statistical significance may be due to the limited power in our study (male cases n = 11) since a positive association has also been reported by Thune and co-workers [18] in their large Norwegian cohort (HR = 1.60, CI 1.39–1.84, Q5 vs Q1) and Wiren et al. [17] in their pooled study (HR 1.12, CI 1.08–1.19, per 10 cm increment). Other previous prospective studies [20–24] and one pooled analysis of case-control studies [19], among women, showed moderate to strong positive height-melanoma associations in

age- or multivariate adjusted models. Risk estimates ranged from 1.14–1.51 per 10 cm increment in height.

Studies examining the relation between BMI and/or BSA and melanoma risk have yielded mixed results, but have pointed to a positive association [9,10,18,37], not observed in this study.

Despite many consistent height-cancer links [38–40], including skin cancers, the mechanism remains unclear. Adult height is determined by genetic make-up and modifiable early life and childhood factors, such as nutrition, illness and socioeconomic status, which may collectively influence the development of both height, and cancer risk [39–42]. One hypothesis is that height is directly correlated with the size of organs and thus numbers of target cells, including stem cells, hence providing a greater opportunity for mutations and malignant transformations [43,44]. However, BSA (or BMI) was not related to skin cancer in this study nor in an earlier report on BCC of this cohort [14] or in other studies [19,24]. Therefore it seems unlikely that larger skin surface area has driven the association with height.

Another possibility is the influence of hormone levels, particularly insulin-growth-factors (IGFs) in cancer development [20,39,45]. The limited evidence on adult insulin factors and melanoma risk, however, is unclear, either showing no association between IGF level and melanoma [46] or suggesting that insulin resistance as a possible risk factor [47]. Further, recent findings on anthropometric features, including sitting-to-standing height ratio suggest that the effect of height components is not absolute but relative to total height, and melanoma development may be specifically related to childhood or pubertal IGF levels [24].

The most important limitation of this study was the limited power to detect relevant differences in multivariate melanoma analyses. Strengths of our study include the prospective design with measured anthropometric indicators and the separate examination of corresponding risks of BCC, SCC and melanoma in both sexes and adjustment for important confounding factors. The fact that outdoor behavior variables were not associated with anthropometric measures, and that our multivariable models were adjusted for clinical elastosis, as well as the similarity between the age- and multivariable adjusted analyses argue against extensive confounding by sun-related factors in this study. These factors do not explain the observed sex differential for BCC, SCC or melanoma.

Inclusion of sunscreen treatment allocation in all multivariate models as both a design variable and measure of sunscreen usage [48], meant that we overcame the common problem of confounding by indication, i.e. frequent users of sunscreens are also those frequently exposing themselves to the sun [49]. Finally these results point to biological mechanisms relevant to the aetiology of skin cancer [17,50].

In summary, this prospective study in Australian middle-aged adults provides new evidence for the role of height in SCC occurrence in men, and supports its role in BCC occurrence in women. Our data also suggest a positive association between height and melanoma risk in men seen in other studies, but do not support previous findings of any associations of BMI or BSA with skin cancer. This knowledge may be useful to clinicians in skin cancer risk prediction. Height is a potential addition to the list of risk factors useful in prioritizing patients at increased risk of disease, for preventive advice and surveillance.

Conflict of interest

The authors state no conflict of interest.

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Authorship Contributions

PHL conceived the analysis plan and design, carried out the statistical analysis, interpreted the data and drafted the manuscript. MCH provided technical assistance to statistical analysis and participated in the acquisition and interpretation of data. GMW made substantial contributions to the conception and design of the study and guided the statistical analysis. ACG conceived of the study, participated in its coordination and acquisition of data and helped to draft the manuscript. All authors read and approved the final manuscript.

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References

[1] M. Fransen, A. Karahalios, N. Sharma, D.R. English, G.G. Giles, R.D. Sinclair, Non-melanoma skin cancer in Australia, Med. J. Aust. 197 (2012) 565–568.
[2] A. Lomas, J. Leonardi-Bee, F. Bath-Hextall, A systematic review of worldwide incidence of nonmelanoma skin cancer, Br. J. Dermatol. 166 (2012) 1069–1080.
[3] F. Erdmann, J. Lortet-Tieulent, J. Schuz, H. Zeeb, R. Greinert, E.W. Breitbart, et al., International trends in the incidence of malignant melanoma 1953–2008—are recent generations at higher or lower risk? Int. J. Cancer 132 (2013) 385–400.
[4] T.L. Diepgen, V. Mahler, The epidemiology of skin cancer, Br. J. Dermatol. 146 (Suppl. 61) (2002) 1–6.
[5] C.D. Holman, B.K. Armstrong, P.J. Heenan, A theory of the etiology and pathogenesis of human cutaneous malignant melanoma, J. Nat. Cancer Inst. 71 (1983) 651–656.
[6] V. Madan, J.T. Lear, R.M. Szeimies, Non-melanoma skin cancer, Lancet 375 (2010) 673–685.
[7] WCRF-AICR, Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective, World Cancer Research Fund/American Institute for Cancer Research, 2007.
[8] K. Bhaskaran, I. Douglas, H. Forbes, I. dos-Santos-Silva, D.A. Leon, L. Smeeth, Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults, Lancet 384 (2014) 755–765.
[9] A.G. Renehan, M. Tyson, M. Egger, R.F. Heller, M. Zwahlen, Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies, Lancet 371 (2008) 569–578.
[10] T.N. Sergentanis, A.G. Antoniadis, H.J. Gogas, C.N. Antonopoulos, H.O. Adami, A. Ekbom, et al., Obesity and risk of malignant melanoma: a meta-analysis of cohort and case-control studies, Eur. J. Cancer 49 (2013) 642–657.
[11] M.R. Gerstenblith, P. Rajaraman, E. Khaykin, M.M. Doody, B.H. Alexander, M.S. Linet, et al., Basal cell carcinoma and anthropometric factors in the U.S. radiologic technologists cohort study, Int. J. Cancer 131 (2012) E149–E155.
[12] S. Pothiawala, A.A. Qureshi, Y. Li, J. Han, Obesity and the incidence of skin cancer in US Caucasians, Cancer Causes Control. 23 (2012) 717–726.
[13] C. Praestegaard, S.K. Kjaer, J. Christensen, A. Tjonneland, J. Halkjaer, A. Jensen, Obesity and risks for malignant melanoma and non-melanoma skin cancer: results from a large danish prospective cohort study, J. Invest. Dermatol. 135 (2015) 901–904.
[14] C.M. Olsen, M.C. Hughes, N. Pandeya, A.C. Green, Anthropometric measures in relation to basal cell carcinoma: a longitudinal study, BMC Cancer 6 (2006) 82.
[15] G. Nagel, T. Bjorge, T. Stocks, J. Manjer, G. Hallmans, M. Edlinger, et al., Metabolic risk factors and skin cancer in the metabolic syndrome and cancer project (Me-Can), Br. J. Dermatol. 167 (2012) 59–67.
[16] J.Y. Tang, M.T. Henderson, T. Hernandez-Boussard, J. Kubo, M. Desai, S.T. Sims, et al., Lower skin cancer risk in women with higher body mass index: the women's health initiative observational study, Cancer Epidemiol. Biomarkers Prev. 22 (2013) 2412–2415.
[17] S. Wiren, C. Haggstrom, H. Ulmer, J. Manjer, T. Bjorge, G. Nagel, et al., Pooled cohort study on height and risk of cancer and cancer death, Cancer Causes Control. 25 (2014) 151–159.
[18] I. Thune, A. Olsen, G. Albrektsen, S. Tretli, Cutaneous malignant melanoma: association with height, weight and body-surface area. a prospective study in Norway, Int. J. Cancer 55 (1993) 555–561.
[19] C.M. Olsen, A.C. Green, M.S. Zens, T.A. Stukel, V. Bataille, M. Berwick, et al., Anthropometric factors and risk of melanoma in women: a pooled analysis, Int. J. Cancer 122 (2008) 1100–1108.
[20] J. Green, B.J. Cairns, D. Casabonne, F.L. Wright, G. Reeves, V. Beral, Height and cancer incidence in the million women study: prospective cohort, and meta-analysis of prospective studies of height and total cancer risk, Lancet Oncol. 12 (2011) 785–794.
[21] G.C. Kabat, M.Y. Kim, A.R. Hollenbeck, T.E. Rohan, Attained height, sex, and risk of cancer at different anatomic sites in the NIH-AARP diet and health study, Cancer Causes Control CCC 25 (2014) 1697–1706.

[22] G.C. Kabat, M.L. Anderson, M. Heo, H.D. Hosgood 3rd, V. Kamensky, J.W. Bea, et al., Adult stature and risk of cancer at different anatomic sites in a cohort of postmenopausal women, Cancer Epidemiol. Biomarkers Prev. 22 (2013) 1353–1363.
[23] G.C. Kabat, M. Heo, V. Kamensky, A.B. Miller, T.E. Rohan, Adult height in relation to risk of cancer in a cohort of Canadian women, Int. J. Cancer 132 (2013) 1125–1132.
[24] M. Kvaskoff, A. Bijon, S. Mesrine, A. Vilier, F. Clavel-Chapelon, M.C. Boutron-Ruault, Anthropometric features and cutaneous melanoma risk: a prospective cohort study in French women, Cancer Epidemiol. 38 (2014) 357–363.
[25] A. Green, G. Beardmore, V. Hart, D. Leslie, R. Marks, D. Staines, Skin cancer in a Queensland population, J. Am. Acad. Dermatol. 19 (1988) 1045–1052.
[26] A. Green, D. Battistutta, V. Hart, D. Leslie, G. Marks, G. Williams, et al., The nambour skin cancer and actinic eye disease prevention trial: design and baseline characteristics of participants, Control Clin. Trials 15 (1994) 512–522.
[27] A. Green, G. Williams, R. Neale, V. Hart, D. Leslie, P. Parsons, et al., Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial, Lancet 354 (1999) 723–729.
[28] P.H. Lahmann, A. Russell, A.C. Green, Prospective study of physical activity and risk of squamous cell carcinoma of the skin, BMC Cancer 11 (2011) 516.
[29] WHO, Obesity preventing and managing the global epidemic: report of a WHO consultation, WHO Technical Report Series (894), World Health Organization, Geneva, 2000.
[30] R.D. Mosteller, Simplified calculation of body-surface area, N. Engl. J. Med. 317 (1987) 1098.
[31] J. Verbraecken, P. Van de Heyning, W. De Backer, L. Van Gaal, Body surface area in normal-weight, overweight, and obese adults. A comparison study, Metabolism 55 (2006) 515–524.
[32] A.C. Green, M.C. Hughes, P. McBride, A. Fourtanier, Factors associated with premature skin aging (photoaging) before the age of 55: a population-based study, Dermatology 222 (2011) 74–80.
[33] N.M. Richmond-Sinclair, N. Pandeya, G.M. Williams, R.E. Neale, J.C. van der Pols, A.C. Green, Clinical signs of photodamage are associated with basal cell carcinoma multiplicity and site: a 16-year longitudinal study, Int. J. Cancer 127 (2010) 2622–2629.
[34] P.C. Valery, R. Neale, G. Williams, N. Pandeya, G. Siller, A. Green, The effect of skin examination surveys on the incidence of basal cell carcinoma in a Queensland community sample: a 10-year longitudinal study, J. Invest. Dermatol. Symp. Proc. 9 (2004) 148–151.
[35] A.C. Green, G.M. Williams, V. Logan, G.M. Strutton, Reduced melanoma after regular sunscreen use: randomized trial follow-up, J. Clin. Oncol. 29 (2011) 257–263.
[36] G. Zou, A modified poisson regression approach to prospective studies with binary data, Am. J. Epidemiol. 159 (2004) 702–706.
[37] L.K. Dennis, J.B. Lowe, C.F. Lynch, M.C. Alavanja, Cutaneous melanoma and obesity in the Agricultural health study, Ann. Epidemiol. 18 (2008) 214–221.
[38] D. Albanes, D.Y. Jones, A. Schatzkin, M.S. Micozzi, P.R. Taylor, Adult stature and risk of cancer, Cancer Res. 48 (1988) 1658–1662.
[39] D. Gunnell, M. Okasha, G.D. Smith, S.E. Oliver, J. Sandhu, J.M. Holly, Height, leg length, and cancer risk: a systematic review, Epidemiol. Rev. 23 (2001) 313–342.
[40] A.G. Renehan, Height and cancer: consistent links, but mechanisms unclear, Lancet Oncol. 12 (2011) 716–717.
[41] G.D. Batty, M.J. Shipley, D. Gunnell, R. Huxley, M. Kivimaki, M. Woodward, et al., Height, wealth, and health: an overview with new data from three longitudinal studies, Econ. Hum. Biol. 7 (2009) 137–152.
[42] A.R. Wood, T. Esko, J. Yang, S. Vedantam, T.H. Pers, S. Gustafsson, et al., Defining the role of common variation in the genomic and biological architecture of adult human height, Nat. Genet. 46 (2014) 1173–1186.
[43] D. Albanes, M. Winick, Are cell number and cell proliferation risk factors for cancer? J. Natl. Cancer Inst. 80 (1988) 772–774.
[44] D. Trichopoulos, L. Lipworth, Is cancer causation simpler than we thought, but more intractable? Epidemiology 6 (1995) 347–349.
[45] P.E. Clayton, I. Banerjee, P.G. Murray, A.G. Renehan, Growth hormone, the insulin-like growth factor axis, insulin and cancer risk, Nat. Rev. Endocrinol. 7 (2011) 11–24.
[46] S.L. Park, V.W. Setiawan, P.A. Kanetsky, Z.F. Zhang, L.R. Wilkens, L.N. Kolonel, et al., Serum insulin-like growth factor-I and insulin-like growth factor binding protein-3 levels with risk of malignant melanoma, Cancer Causes Control. 22 (2011) 1267–1275.
[47] A.G. Antoniadis, E.T. Petridou, C.N. Antonopoulos, N. Dessypris, P. Panagopoulou, J.P. Chamberland, et al., Insulin resistance in relation to melanoma risk, Melanoma Res. 21 (2011) 541–546.
[48] R. Neale, G. Williams, A. Green, Application patterns among participants randomized to daily sunscreen use in a skin cancer prevention trial, Arch. Dermatol. 138 (2002) 1319–1325.
[49] A.C. Green, G.M. Williams, Point sunscreen use is a safe and effective approach to skin cancer prevention, Cancer Epidemiol. Biomarkers Prev. 16 (2007) 1921–1922.
[50] S. Ribero, D. Glass, A. Aviv, T.D. Spector, V. Bataille, Height and bone mineral density are associated with naevus count supporting the importance of growth in melanoma susceptibility, PLoS One 10 (2015) e0116863.