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ORIGINAL CONTRIBUTION

Caffeine intake and risk of basal cell and squamous cell carcinomas of the skin in an 11-year prospective study

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Abstract
Purpose Caffeine may repair skin damage induced by excessive exposure to ultraviolet light. The purpose of this study was to investigate the association between caffeine intake and incidence of basal cell (BCC) and squamous cell carcinoma (SCC). We also assessed the associations between coffee consumption and incidence of these skin cancers.
Methods Caffeine intake and consumption of coffee were estimated from food frequency questionnaires assessed in 1992, 1994, and 1996 among 1,325 randomly selected adult residents of a subtropical Australian community. All histologically confirmed tumours of BCC and SCC occurring between 1997 and 2007 were recorded. Associations with BCC and SCC were assessed using Poisson and negative binomial regression models and were adjusted for confounders including skin type and indicators of past sun exposure.
Results There was no association between total caffeine intake and incidence of BCC or SCC. Participants with prior skin cancers, however, had a 25 % lower risk of BCC if they were in the highest tertile of total caffeine intake (equivalent to daily consumption of four cups of regular coffee) compared with the lowest tertile (multivariable RR 0.75; 95 % CI 0.57–0.97, P trend = 0.025). There was no dose–response relationship with SCC. Consumption of neither caffeinated nor decaffeinated coffee was associated with BCC or SCC.
Conclusions Among people with prior skin cancers, a relatively high caffeine intake may help prevent subsequent BCC development. However, caffeine intake appears not to influence the risk of SCC.

Keywords Basal cell carcinoma · Squamous cell carcinoma · Non-melanoma skin cancer · Caffeine · Coffee · Prospective study

Introduction

Keratinocyte skin cancers, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC) are the most common cancers among white populations including Australia [1, 2]. The major environmental cause of these cancers is exposure to ultraviolet (UV) light [2]. Some evidence from experimental studies suggests that caffeine may help repair skin damage caused by UV light. A number of animal studies have consistently reported that caffeine intake or topical administration of caffeine on the skin inhibits UV-induced skin cancer and tumours [3–5]. Human exposure to caffeine is common because of the high prevalence of consumption of coffee, which is the most usual source of caffeine in many populations [6]. Epidemiological evidence of associations between caffeine intake and skin cancers in human is scarce, however.

One previous study of caffeine intake and keratinocyte skin cancer reported a significant inverse association between total caffeine intake and risk of BCC but not SCC

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[6]. A few other studies have examined coffee consumption, as a marker of caffeine intake, and the risk of BCC or SCC. A Norwegian longitudinal study [7] and an US cross-sectional study [8] reported negative associations between coffee consumption and incidence of BCC and (in the US study) SCC. In contrast, two case–control studies from Europe reported no association with BCC [9, 10]. This small amount of evidence suggests a protective role for caffeine and possibly coffee consumption, but there are various limitations to these previous studies. For example, although these cancers have dissimilar biology and epidemiology, one study did not consider separate analyses for BCC and SCC [8]. Others did not distinguish between caffeinated and decaffeinated coffee [9, 10], which means that it is not possible to ascertain whether the observed protective effect is due to caffeine or other components of coffee.

We have, therefore, used data from an 11-year prospective investigation of skin cancer in Australian adults to study whether caffeine intake is associated with the incidence of BCC and SCC. In order to assess whether associations were specific to caffeine from coffee, we also examined the associations between total coffee intake as well as consumption of caffeinated and decaffeinated coffee and the incidence of BCC and SCC.

Methods

Study population

This 11-year prospective study from 1997 to 2007 was conducted among adults residing in Nambour (26°S), Queensland, Australia, who were originally randomly selected from the electoral role in 1986 for a study of skin cancer. They had participated in a field trial between 1992 and 1996 to assess the effectiveness of daily application of a broad-spectrum sunscreen and daily beta-carotene supplementation. Detailed descriptions of the trial and its outcomes have been reported previously [11, 12]. Trial participants were eligible for the present study if they had completed at least one food frequency questionnaire (FFQ). Ethical approval was obtained from the ethics committee of the Queensland Institute of Medical Research, and all participants provided informed written consent.

Determination of cases and outcomes

The intensive surveillance system of incident skin cancers established during the trial continued during the entire post-trial follow-up period (1997–2007). Questionnaires were mailed twice yearly to participants from 1997 to 2002 and yearly from 2003 to 2007. Any reported skin cancers were confirmed through histological reports. In 2007, all remaining active participants underwent a full-body skin examination. Finally, independent pathology laboratories throughout Queensland provided histology reports for all skin cancers diagnosed among study participants throughout the follow-up period. These methods ensured virtually 100 % ascertainment of histologically confirmed skin cancers in the study population [13].

The two outcomes of analyses were (1) person-based incidence of BCC or SCC, calculated as the number of persons affected by a new BCC or SCC after completion of the trial from January 1, 1997, to December 31, 2007, divided by the person-years of follow-up accumulated between these dates and expressed per 100,000 person-years; and (2) incidence of BCC or SCC tumours during the same person-years of follow-up time as calculated for the person-based analysis. Tumours diagnosed in 1996 were not included in the analyses to exclude disease that already existed during the baseline nutritional assessment. The occurrence of BCC or SCC person-years of follow-up was counted until the date of withdrawal from the study, date of death, or December 31, 2007, whichever came first.

Assessment of coffee and caffeine intake

Habitual coffee and other foods and beverages known to have high caffeine content were assessed using a validated self-administered, semi-quantitative FFQ in 1992, 1994, and 1996. Prior to calculating average intake over the three survey periods, dietary records were excluded if participants did not indicate consumption frequencies for 10 % or more of the FFQ food/beverage items or if energy intakes were outside recommended limits: >16,800 kJ/day and <3,360 kJ/day for men and >14,700 kJ/day and <2,100 kJ for women [14].

The FFQ was originally developed for the US Nurses' Health Study and adapted for the Australian setting. For example, we used the metric system (e.g. mL) rather than imperial (e.g. ounce). We also changed the name of some food items as some foods are referred to differently between Australia and the United States (e.g. green beans instead of string beans, and pumpkin rather than squash). All participants were asked to estimate how often, on average, they had consumed the given amount of food/beverage over the 6 months (1 cup (250 mL) for coffee and tea, 375-mL can for soft drinks, and 30 g for chocolate). The nine response options were 'never' to '≥4 times/day'. The food and beverages considered in order to estimate caffeine intake in this study are as follows: caffeinated coffee, decaffeinated coffee, black tea, cola, low-calorie cola, other soft drinks, and other low-calorie soft drinks, chocolate, chocolate-coated biscuits, and chocolate-containing breakfast cereals.

Total caffeine intake was calculated using three steps: (1) Intake in grams per day of each food/beverage was multiplied by caffeine content of the food/beverage to obtain daily caffeine intake (in mg) per food; (2) daily caffeine intake from all of the caffeine-containing food/beverage items was summed; and (3) the mean daily caffeine intake per participant was calculated over the three survey periods. This approach aimed to achieve the best possible estimates of long-term average intake of caffeine [15].

The caffeine content of each food and beverage was estimated based on the NUTTAB 2006 database, which is the national Australian nutrient database developed for estimating nutrient intakes from foods, beverages, and dietary supplements [16]. For example, caffeine content of foods used for these calculations was as follows: caffeinated coffee = 77.5 mg/cup (250 mL), decaffeinated coffee = 2.5 mg/cup, tea = 47.5 mg/cup, cola soft drink = 33.8 mg/can (375 mL), and chocolate = 6 mg/serving (30 g).

The FFQ has been validated in a subsample of Nambour trial participants by comparing intake estimates derived from the FFQ against those from 12-day weighed food records [17, 18]. The results of the validation study indicated that the FFQ estimates for the food groups considered in the present analyses generally showed good agreement: Spearman correlation coefficients ≥0.80 for tea and coffee, and ≥0.60 for soft drink, cakes and biscuits, sweets, and breakfast cereals (all $P < 0.05$).

Other variables

Detailed information on demographic and phenotypic characteristics such as skin colour, propensity to burn, lifetime number of sunburns, occupational and leisure-time sun exposure, and smoking status was collected at the start of the trial using standard questionnaires. Sun exposure and sun protection behaviour and smoking status were updated annually until 2007. During physical examination in 1996, elastosis on the neck was assessed as a measure of long-term sun exposure.

Statistical analysis

Daily total caffeine intake (in mg) and caffeine intake by food source (coffee and other sources) were examined as continuous variables as well as categorical variables by classifying into ranked thirds. Consumption of caffeinated and decaffeinated coffee (measured in number of cups/day) was analysed as continuous variables as well as in the following categories: none, >0 to <1 cup/day, ≥1 cup to <2 cups/day, and ≥2 cups/day for caffeinated coffee, and none, >0 to <1 cup/day, and ≥1 cup/day for decaffeinated coffee (only 2 % of participants reported to consume ≥2 cups of decaffeinated coffee daily). The lowest intake group was the referent category for all analyses.

For person-based analyses, relative risks (RRs) with 95 % confidence intervals (95 % CIs) of having at least one post-trial BCC or SCC for increasing the levels of dietary intake were estimated by generalized linear models specifying Poisson distribution with a robust error variance and person-year of follow-up as the offset [19]. RR and 95 % CI for tumour-based analyses were estimated using generalized linear models with negative binomial distribution and person-years of follow-up as offset [20].

The first 'minimally adjusted' multivariable models were adjusting for age, sex, and randomized trial treatment allocation (daily sunscreen and/or beta-carotene supplementation). In order to control for potential confounding effects, we also assessed a number of variables for a 'fully adjusted' model: skin colour (fair, medium, olive/blown/black), tanning ability (always burn, burn then tan, only tan), hair colour (blonde, light brown, auburn, dark brown/black), eye colour (blue-grey, hazel-green, light brown/dark brown), number of painful sunburns (never, once, 2–5 times, >5 times), freckling of the back (none, mild, moderate, severe), elastosis of neck (a clinical measure of photo-ageing, graded as none, mild, moderate, severe), total number of solar keratosis (0, 1, 2–4, 5–10, 11–20, ≥21), habitual sunscreen use (never, <50 % of time, ≥50 % of time), pack-year of smoking (non-smoker, >0 to 7, >7 to 20), mean daily energy intake (kJ/day), dietary supplement use (yes/no), body mass index (kg/m^2), weekday and weekend hours spent outdoors (up to 1, 2–4, 5–8, 9–12 h), previous history of skin cancer before January 1, 1997 (yes/no), habitual sunscreen use after the trial (<50 % or ≥50 % of time), habitual sun protection behaviour after the trial (e.g. sunglasses and hat) (summary score ranged from 1 to 20), and habitual sun exposure behaviour after the trial (<50 % or ≥50 % of time). Among these, the factors that changed the risk estimates by ≥10 % were kept in the final multivariable models as they were considered as significant confounders [21]. We also evaluated the final models using the quasi-likelihood information criterion for person-based [22, 23] and the Akaike information criterion for tumour-based models [23]. The variables included in the final models were age, sex, treatment allocation, history of skin cancer, elastosis of the neck, freckling of the back, and tanning ability for BCC, and age, sex, treatment allocation, history of skin cancer, freckling of the back, tanning ability, and pack-years of smoking for SCC models.

To test for linear trends, categories of caffeine or coffee intake were modelled as ordinal variables (with category values taking the median of the range). People with a history of skin cancer have an increased risk of developing subsequent skin cancers [24, 25], and previous analyses

have shown that their skin cancer risk may be more prone to modification by dietary factors [26, 27]. Therefore, all analyses were repeated using stratification for previous history of skin cancers prior to 1997. Information on skin cancer history was based on skin cancers identified during skin examinations and histology reports from 1986 until the end of December 1996 [11, 12, 28–30].

All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, USA). All statistical tests were two-sided and were considered statistically significant when $P < 0.05$ or when the 95 % CIs did not include 1.0.

Results

Of the 1,339 trial participants who consented to be actively followed up post-trial, 1,330 had at least one valid FFQ. Two persons died shortly after the commencement of the study, and further three persons were excluded because they did not have data on tanning ability or freckling of the back, leaving 1,325 in the present study. No significant difference was found between the 1,325 study participants and those excluded in terms of age, sex, randomized treatment allocation, education, occupation, smoking status, or use of dietary supplements. Risk factors for skin cancer did not differ between the two groups, with the exception of number of painful sunburns and tanning ability: Retained participants were more likely to have skin that tended to tan and to have greater number of painful sunburns compared with those who were excluded from the analyses. Study participants had a mean age of 49.3 years (SD 12.9) at baseline, 56 % were female, majority of participants ($n = 1{,}022$, 77 %) completed all three FFQs, $n = 235$ (18 %) provided two FFQs, and only $n = 68$ (5 %) of participants had only one FFQ. The median caffeine intake was 194 mg/day (minimum 0, maximum 510 mg/day). The median intake of caffeine for each ranked thirds of intake group was as follows: low = 106 mg/day, middle = 195 mg/day, and high = 294 mg/day, which is approximately equivalent to daily consumption of 1.5 cups, 2.5 cups, and 4 cups of regular coffee, respectively.

A total of 323 participants with 740 histologically confirmed new BCC tumours were diagnosed during 13,925 person-years of follow-up. Among participants with no history of skin cancer prior to 1997, the BCC person-based incidence rates were 1,313 per 100,000 person-years (tumour-based incidence rate 2,116 per 100,000 person-years), whereas the person-based incidence rates of those with prior cancers were 4,549 per 100,000 (tumour-based incidence rate 12,399 per 100,000). During the same follow-up period, a total of 170 participants with 368 histologically confirmed new SCC tumours were diagnosed. The corresponding person-based (tumour-based) SCC incidence rates among participants with no history of skin cancer were 657 per 100,000 (907 per 100,000). Participants with prior skin cancers had much higher rates, with person-based SCC incidence rates of 3,071 per 100,000 person-years (6,488 per 100,000).

Participants affected by BCC or SCC were more likely to be male, to be older, to report outdoor work, to have fair skin colour, to always sunburn on acute sun exposure, to have severe elastosis of the neck and freckling on the back on clinical assessment, and to report having had skin cancer before this study (Table 1). Additionally, participants affected by SCC were also more likely to have smoked. The proportion of painful sunburns and supplement use was not different between participants who were or were not affected by BCC or SCC.

From the person-based analyses, after adjustment for potential confounding factors, total daily caffeine intake measured as continuous variable (per 100 mg) was not associated with the number of persons affected by BCC or SCC (Table 2). When the analyses were undertaken using tertiles of total caffeine intake, persons in the highest tertile of caffeine intake had a lower risk of BCC compared with persons in the lowest tertile; however, this was not statistically significant (fully adjusted RR 0.87; 95 % CI 0.69, 1.08; P trend = 0.20). The risk of SCC did not differ across the levels of caffeine intake (Table 2).

When the person-based analyses were stratified according to whether participants had a history of skin cancer before the study, total caffeine intake was associated with a reduced risk of BCC only among participants who had history of skin cancer (Table 3). After adjustment for all confounding factors, participants in the highest tertile of total caffeine intake had a significantly low risk of BCC compared with the lowest tertile (RR 0.75; 95 % CI 0.57, 0.97; P trend = 0.025). Persons in the highest tertile of caffeine intake from regular (caffeinated) coffee (responsible for 54 % of total caffeine intake) or caffeine from other sources (42 % from tea, 3 % from soft drinks, and 1 % from food and decaffeinated coffee) also showed a lower risk among those who had a history of skin cancer; however, this was not statistically significant. In contrast, no dose–response trends were observed in associations between total caffeine intake and the risk of SCC, both in the strata of participants with and those without a past history of skin cancer. Caffeine intake from different sources was also examined; however, caffeine from neither coffee nor other food sources was associated with SCC regardless of the history of cancer.

Results from the tumour-based analyses were similar to those of the person-based analyses (results not shown). Among those who had a history of skin cancer, the

Table 1 Baseline characteristics by skin cancer status of participants ($N = 1{,}325$)

	BCC			SCC		
	Present $n = 323$ n (%)	Absent $n = 1{,}002$ n (%)	P value[a]	Present $n = 196$ n (%)	Absent $n = 1{,}129$ n (%)	P value[a]
Sex						
Male	159 (49)	422 (42)	0.025	102 (52)	479 (42)	0.012
Female	164 (51)	580 (58)		94 (48)	650 (58)	
Age (y) [mean (SD)]	54 (12)	48 (13)	<0.001	59 (11)	48 (13)	<0.001
Occupation						
Mainly outdoors	60 (19)	174 (18)	0.032	52 (27)	182 (17)	<0.001
Both	129 (41)	323 (33)		76 (40)	376 (34)	
Mainly indoors	129 (41)	470 (49)		63 (33)	536 (49)	
Pack-years smoked						
Lifelong non-smoker	182 (56)	558 (56)	0.86	94 (48)	646 (57)	0.014
>0–7 pack-years	53 (16)	169 (17)		32 (16)	190 (17)	
7–19 pack-years	33 (10)	117 (12)		24 (12)	126 (11)	
≥20 pack-years	55 (17)	158 (16)		46 (23)	167 (15)	
Skin colour						
Fair	195 (60)	539 (54)	0.035	128 (65)	606 (54)	0.004
Medium	114 (35)	385 (38)		62 (32)	437 (39)	
Olive/black/brown	14 (4)	78 (8)		6 (3)	86 (8)	
Skin type						
Always burn, never tan	79 (24)	194 (19)	0.042	70 (36)	203 (18)	<0.001
Burn/tan	220 (68)	697 (70)		112 (57)	805 (71)	
Only tan	24 (7)	111 (11)		14 (7)	121 (11)	
Painful sunburns						
Never	35 (11)	109 (11)	0.13	26 (13)	118 (10)	0.07
Once	45 (14)	179 (18)		41 (21)	183 (16)	
2–5 burns	135 (42)	439 (44)		69 (35)	505 (45)	
≥5 burns	108 (33)	274 (27)		60 (31)	322 (29)	
Elastosis of the neck						
None	20 (6)	201 (20)	<0.001	4 (2)	217 (19)	<0.001
Mild/moderate	167 (52)	574 (57)		85 (43)	656 (58)	
Severe	136 (42)	227 (23)		107 (55)	256 (23)	
Freckling of the back						
None	48 (15)	224 (22)	<0.001	24 (12)	248 (22)	<0.001
Mild	127 (39)	438 (44)		78 (40)	487 (43)	
Moderate	95 (29)	237 (24)		57 (29)	275 (24)	
Severe	53 (16)	103 (10)		37 (19)	119 (11)	
History of skin cancer						
Yes	197 (61)	230 (23)	<0.001	133 (68)	294 (26)	<0.001
No	126 (39)	772 (77)		63 (32)	835 (74)	
Supplement use						
Yes	182 (56)	540 (54)	0.44	104 (53)	618 (55)	0.66
No	141 (44)	462 (46)		92 (47)	511 (45)	

BCC basal cell carcinoma, *SCC* squamous cell carcinoma

[a] P value from chi-square (categorical) or ANOVA (continuous variable)

Table 2 Relative risk of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) in 1997 to 2007 by total caffeine intake[a], person-based analysis ($N = 1,325$)

	BCC RR (95 % CI)		SCC RR (95 % CI)	
	Minimally adjusted model[b]	Fully adjusted model[c]	Minimally adjusted model[b]	Fully adjusted model[d]
Total caffeine intake (per 100 mg)	0.97 (0.88, 1.07)	0.96 (0.87, 1.05)	1.02 (0.90, 1.16)	0.99 (0.87, 1.12)
Total caffeine intake[e] (tertile)				
Low ($n = 440$)	1.00	1.00	1.00	1.00
Middle ($n = 442$)	1.01 (0.82, 1.25)	1.01 (0.82, 1.24)	1.09 (0.81, 1.46)	1.13 (0.84, 1.52)
High ($n = 443$)	0.89 (0.70, 1.13)	0.87 (0.69, 1.08)	1.09 (0.80, 1.48)	1.05 (0.77, 1.42)
P trend	0.32	0.20	0.60	0.79

[a] Mean of 1992, 1994, and 1996 intakes

[b] Adjusted for age, sex, and treatment allocation

[c] Adjusted for age, sex, treatment allocation, history of skin cancer, tanning ability, elastosis of neck, and freckling of the back

[d] Adjusted for age, sex, treatment allocation, history of skin cancer, tanning ability, freckling of the back, and pack-year smoked

[e] Median total daily caffeine intake(minimum, maximum): low = 106 mg (0, 152); middle = 195 mg (153, 228); high = 294 mg (229, 510)

incidence of BCC tumours was significantly lower in the highest tertile of total caffeine intake compared with the lowest tertile of intake (fully adjusted RR 0.66, 95 % CI 0.45, 0.97; *P* trend = 0.035). There were no other significant associations with BCC or SCC tumour incidence.

In order to examine whether the associations with total caffeine intake remained significant after other food or nutrient intakes were taken into account, we repeated the analyses by adjusting caffeine intake for total energy intake by using the residual method as described by Willet [14]. We also adjusted for all other food groups previously found to be associated with BCC or SCC [26, 31]. In addition, the confounding effect of fruit and vegetable intake (serves/day) was examined as a marker for the quality of the diet. The results of these repeated analyses were essentially the same as those for the fully adjusted models presented above for both BCC and SCC.

Caffeinated and decaffeinated coffee intake was not associated with the risk of BCC and SCC (Table 4). We also stratified these analyses by history of cancer; however, results were similar to those presented for caffeine intake (detailed results not shown).

Discussion

In this 11-year prospective study, caffeine intake was inversely associated with the incidence of BCC among participants with a history of skin cancer. This association was not evident among those without prior skin cancer. There was no coherent dose–response relationship between caffeine intake and SCC, regardless of skin cancer history.

While the mechanism of any effect of caffeine on BCC formation is unproven, a protective effect is plausible. Previous experimental studies have reported that caffeine has the ability to induce apoptosis in UV-damaged keratinocytes, thereby protecting from UV-induced carcinogenesis in animals [3–5]. Additionally, the photo-protective effect of caffeine has also been seen in cultured human keratinocytes [32].

Our findings are similar to a recent prospective study among US adults, which showed a negative association between total caffeine intake and the risk of BCC [6]. This study also reported no association with SCC and no association between decaffeinated coffee consumption and BCC and SCC [6]. When coffee consumption, rather than caffeine intake, was considered, prospective studies in the Unites States [6] and Norway [7] also found an inverse association with BCC. Although the same direction of association was observed in our study compared to these earlier studies, our results showed no significant association between coffee intake and skin cancer risk. A possible reason for this may be the relatively low amount of coffee usually consumed by the participants in our study compared to other studies: 12 % of the Norwegian study population consumed ≥7 cups of coffee/day [7], 12 % of the US study participants consumed ≥3 cups of coffee daily [6], and 9 % of the participants of the current study consumed ≥3 cups of coffee daily. Therefore, our participants' level of coffee consumption may have been too low to observe any significant associations, because caffeine intake from coffee would be lower than that in the earlier studies [6, 7]. It may also be possible that the non-significant association observed with coffee intake may be due to the relatively small sample size of our study, especially once the analyses were stratified by history of skin cancer. However, because a significant association was observed between total caffeine intake and BCC in the present analyses and our previous analyses that used similar or smaller sample sizes have shown several significant

Table 3 Relative risk of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) in 1997–2007 by tertile of mean caffeine intake, stratified by history of skin cancer prior to the study[a], person-based analysis ($N = 1{,}325$)

	With skin cancer prior to study ($n = 427$)				No skin cancer prior to study ($n = 898$)			
	Tertile of intake				Tertile of intake			
	Low	Middle	High	*P* trend	Low	Middle	High	*P* trend
BCC (RR, 95 % CI)								
Total caffeine intake[a,b]	$n = 138$	$n = 144$	$n = 145$		$n = 302$	$n = 298$	$n = 298$	
Minimally adjusted model[c]	1.00	0.97 (0.77, 1.21)	0.75 (0.58, 0.97)	0.027	1.00	1.11 (0.75, 1.63)	1.12 (0.75, 1.67)	0.60
Fully adjusted model[d]	1.00	0.95 (0.76, 1.19)	0.75 (0.57, 0.97)	0.025	1.00	1.08 (0.74, 1.59)	1.06 (0.70, 1.59)	0.79
Persons (*n*)[e]	72	71	54		38	45	43	
Person-years of follow-up (year)	1,413	1,464	1,454		3,227	3,208	3,160	
Caffeine from regular coffee[a,f]	$n = 139$	$n = 147$	$n = 141$		302	297	299	
Minimally adjusted model[c]	1.00	0.93 (0.74, 1.18)	0.83 (0.64, 1.08)	0.16	1.00	0.97 (0.65, 1.44)	1.10 (0.75, 1.62)	0.60
Fully adjusted model[d]	1.00	0.94 (0.75, 1.18)	0.83 (0.64, 1.08)	0.15	1.00	0.99 (0.67, 1.47)	1.05 (0.70, 1.57)	0.81
Persons (*n*)[e]	72	68	57		43	39	44	
Person-years of follow-up (year)	1,444	1,552	1,514		3,205	3,190	3,199	
Caffeine from other sources[a,g]	123	152	152		317	291	290	
Minimally adjusted model[c]	1.00	0.86 (0.67, 1.11)	0.90 (0.70, 1.15)	0.42	1.00	1.30 (0.87, 1.95)	1.19 (0.79, 1.79)	0.38
Fully adjusted model[d]	1.00	0.85 (0.67, 1.10)	0.88 (0.69, 1.13)	0.34	1.00	1.27 (0.85, 1.89)	1.17 (0.78, 1.76)	0.42
Persons (*n*)[e]	61	67	69		36	46	44	
Person-years of follow-up (year)	1,264	1,551	1,514		3,361	3,159	3,074	
SCC (RR, 95 % CI)								
Total caffeine intake[a,b]	$n = 138$	$n = 144$	$n = 145$		$n = 302$	$n = 298$	$n = 298$	
Minimally adjusted model[c]	1.00	1.41 (1.02, 1.96)	1.28 (0.91, 1.81)	0.17	1.00	0.73 (0.42, 1.26)	0.78 (0.44, 1.39)	0.42
Fully adjusted model[h]	1.00	1.40 (1.01, 1.95)	1.21 (0.85, 1.73)	0.31	1.00	0.70 (0.41, 1.20)	0.77 (0.42, 1.40)	0.33
Persons (*n*)[e]	38	51	44		24	20	19	
Person-years of follow-up (year)	1,413	1,464	1,454		3,227	3,208	3,160	
Caffeine from regular coffee[a,f]	$n = 139$	$n = 147$	$n = 141$		302	297	299	
Minimally adjusted model[c]	1.00	1.06 (0.77, 1.46)	1.06 (0.76, 1.48)	0.75	1.00	0.97 (0.56, 1.67)	0.71 (0.38, 1.33)	0.27
Fully adjusted model[h]	1.00	1.07 (0.78, 1.47)	1.01 (0.72, 1.41)	0.99	1.00	1.10 (0.64, 1.91)	0.74 (0.38, 1.43)	0.27
Persons (*n*)[e]	47	47	39		26	22	15	
Person-years of follow-up (year)	1,444	1,552	1,514		3,205	3,190	3,199	
Caffeine from other sources[a,g]	$n = 123$	$n = 152$	$n = 152$		$n = 317$	$n = 265$	$n = 268$	
Minimally adjusted model[c]	1.00	0.84 (0.58, 1.21)	1.07 (0.77, 1.48)	0.61	1.00	1.62 (0.89, 2.97)	1.25 (0.66, 2.35)	0.51
Fully adjusted model[h]	1.00	0.82 (0.57, 1.18)	1.05 (0.76, 1.45)	0.68	1.00	1.52 (0.81, 2.85)	1.16 (0.62, 2.18)	0.69

Table 3 continued

	With skin cancer prior to study ($n = 427$)				No skin cancer prior to study ($n = 898$)			
	Tertile of intake				Tertile of intake			
	Low	Middle	High	*P* trend	Low	Middle	High	*P* trend
Persons (n)[e]	36	42	55		15	26	22	
Person-years of follow-up (year)	1,264	1,551	1,514		3,361	3,159	3,074	

[a] Mean of 1992, 1994, and 1996 caffeine intake

[b] Median total daily caffeine intake (minimum, maximum): low = 106 mg (0, 152); middle = 195 mg (153, 228); high = 294 mg (229, 510)

[c] Adjusted for age, sex, and treatment allocation

[d] Adjusted for age, sex, treatment allocation, tanning ability, elastosis of neck, and freckling of the back

[e] Number of persons with lesions

[f] Median daily caffeine intake from regular coffee (minimum, maximum): low = 2 mg (0, 32); middle = 78 mg (33, 150); high = 194 mg (155, 310)

[g] Median daily caffeine intake from other sources (minimum, maximum): low = 13 mg (0, 48); middle = 90 mg (49, 120); high = 158 mg (121, 243)

[h] Adjusted for age, sex, treatment allocation, tanning ability, freckling of the back, and pack-year smoked

associations between nutritional factors and skin cancer incidence [26, 27, 33], our sample size may not necessarily have been too small to detect associations (if any).

An important difference between our present study and earlier studies is that we examined the association between caffeine intake and BCC or SCC according to the participants' history of skin cancer. The findings from these analyses suggest that the protective effect of caffeine intake on the development of BCC may be different according to the individual's susceptibility of skin cancer. This is an important finding as earlier studies did not assess the previous history of skin cancer in the association between caffeine intake and non-melanoma skin cancer. Individuals who have had skin cancer may be more sensitive to the effect of caffeine, which promotes apoptosis in damaged keratinocytes, than those who have never had skin cancer. As BCC is one of the most common types of cancer in many countries, and individuals who develop non-melanoma skin cancer are more likely to develop new skin cancers [2], our findings suggest that caffeine intake may play a role in the prevention of this common cancer.

A report from the World Cancer Research Fund and American Institute for Cancer Research [34] stated that arsenic contamination of drinking water is a probable cause of skin cancers. Thus, if coffee is made using contaminated water, there may be an increased skin cancer risk through coffee consumption. However, there is no known contamination of drinking water by arsenic in Australia [35], and no arsenic-related lesions have been seen in our study population [33].

Our findings need to be interpreted with the following strengths and limitations in mind. We were not able to assess the brewing strength of coffee that may reduce the strength of the association by under- or overestimation of caffeine intake. As mentioned previously, our sample size is relatively small compared with the previous studies [6, 7]. Additionally, the Nambour study participants did not consume a large number of cups of coffee on average, and especially, decaffeinated coffee consumption was low.

A major strength of this study is its prospective nature, the long follow-up period, and our ability to fully assess potential confounding given the extensive and rigorous data collections in this study population. Our study is based on the analyses of histologically confirmed BCC and SCC identified through a comprehensive surveillance system; thus, it is unlikely that study participants were misclassified through missed cases or misdiagnosis. This study used repeated measures of dietary intake that may reflect the consumption of coffee and caffeine intake over time rather than estimating intake from a single point in time.

In conclusion, our results suggest that caffeine may reduce the risk of BCC among people with prior skin cancers, in particular in persons with relatively high

Table 4 Relative risk of BCC and SCC in 1997–2007 by mean intake of caffeinated or decaffeinated coffee (in number of cups[a]), person-based analysis ($N = 1{,}325$)

	BCC RR (95 % CI)		SCC RR (95 % CI)	
	Minimally adjusted model[b]	Fully adjusted model[c]	Minimally adjusted model[b]	Fully adjusted model[d]
Caffeinated coffee intake[e]				
None ($n = 150$)	1.00	1.00	1.00	1.00
>0 to <1/day ($n = 476$)	1.19 (0.87, 1.63)	1.05 (0.77, 1.41)	1.61 (1.02, 2.54)	1.49 (0.91, 2.36)
≥1 to <2/day ($n = 259$)	0.94 (0.66, 1.36)	0.88 (0.63, 1.24)	1.29 (0.77, 2.16)	1.25 (0.75, 2.07)
≥2/day ($n = 440$)	1.08 (0.78, 1.51)	0.92 (0.67, 1.28)	1.33 (0.82, 2.18)	1.17 (0.71, 1.91)
P trend	0.60	0.34	0.61	0.31
Decaffeinated coffee intake[e]				
None ($n = 822$)	1.00	1.00	1.00	1.00
>0 to <1/day ($n = 425$)	1.06 (0.86, 1.29)	1.00 (0.82, 1.21)	1.06 (0.81, 1.38)	1.00 (0.77, 1.30)
≥1/day ($n = 78$)	1.06 (0.72, 1.57)	1.05 (0.73, 1.52)	1.14 (0.68, 1.92)	1.15 (0.69, 1.92)
P trend	0.81	0.78	0.65	0.60

[a] 1 cup = 250 mL

[b] Adjusted for age, sex, and treatment allocation

[c] Adjusted for age, sex, treatment allocation, history of skin cancer, tanning ability, elastosis of neck, and freckling of the back

[d] Adjusted for age, sex, treatment allocation, history of skin cancer, tanning ability, freckling of the back, and pack-year smoked

[e] Mean of 1992, 1994, and 1996 intakes

caffeine intake, equating to caffeine from daily consumption of four cups of regular coffee on average or equivalent. Our results also suggest that caffeine intake does not influence the development of SCC. Replication in other population groups is needed to confirm the potential protective effect of caffeine on BCC formation, and the level of exposure needed to achieve such protection.

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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