Keratinocyte Carcinoma and Risk for Another Type of Cancer: Assessment of a Dose-response Relationship

ASHLEY WILSON[1], JAMES SMALL[2], CATHERINE FLANAGAN[1], DAVID PERRY[3],
RICHARD MARCHELL[3], BRUCE THIERS[3] and ANTHONY J. ALBERG[1,2,4]

[1]Hollings Cancer Center, Medical University of South Carolina, Charleston, SC, U.S.A.;
[2]Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC, U.S.A.;
[3]Department of Dermatology and Dermatologic Surgery,
Medical University of South Carolina, Charleston, SC, U.S.A.;
[4]Department of Epidemiology and Biostatistics,
University of South Carolina Arnold School of Public Health, Columbia, SC, U.S.A.

Abstract. *Background/Aim: Keratinocyte carcinoma (KC) is a marker of increased risk of other cancer types. To assess if this association exhibits a dose-response relationship, a case-control study was carried out. Patients and Methods: This was a clinic-based study of cases with KC plus another type of cancer matched by age, race (all Caucasian), sex and histologic type to controls with KC only (n=48 matched pairs). Results: Compared with the KC only group, those with KC plus another cancer had a mean number of lesions that were 43%, 35%, and 41% greater for basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and total KC, respectively. The odds ratio (OR) of developing another type of cancer increased from 1.0 to 1.09 (95% confidence interval (CI)=0.23-5.13) to 2.12 (95%CI=0.50-9.08) according to whether the patient had zero, one, or ≥two BCC lesions; for SCC, the corresponding ORs were 1.0, 1.24 (95%CI=0.48-3.24), and 1.39 (95%CI=0.29-6.61). Conclusion: A dose-response relationship seems to exist between the number of skin lesions and the risk of another type of cancer, but the lack of statistical significance weakens this evidence.*

Keratinocyte carcinoma (KC), also referred to as non-melanoma skin cancer, is almost certainly the most commonly diagnosed cancer in the world, but the lack of systematically collected data makes this difficult to

Correspondence to: Anthony J. Alberg, Ph.D., MPH, Department of Epidemiology and Biostatistics, University of South Carolina Arnold School of Public Health, 915 Greene Street, Columbia, SC 29208, U.S.A. Tel: +1 8037776220, e-mail: alberg@mailbox.sc.edu

demonstrate definitively (1). An extensive body of evidence has clearly shown that a personal history of KC is indicative of increased risk of other cancer types (2-6). This increase in the risk of a subsequent cancer other than KC is consistent for the two major histological types of KC, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is observed in both males and females, and applies to a broad spectrum of other types of cancer (2-6). Thus, KC may be a marker for a cancer-prone phenotype.

Even though the association between personal history of KC and increased risk for other malignancies is well supported by evidence, important questions about this association remain unanswered. One key question that has yet to be thoroughly addressed is whether the risk of other cancers is increased as the number of KC lesions increases, meaning that there is a dose-response relationship present. The importance of assessing whether a dose-response association exists is two-fold: 1) within the framework of epidemiologic inferences, the presence of a dose-response relationship would further strengthen the evidence favoring an association between KC and risk of other cancers, and 2) it could have potential clinical implications related to risk stratification of patients. That is, if a history of many KC lesions confers a considerably higher risk for other cancers compared with a history of fewer KC lesions, perhaps enhanced cancer surveillance would be beneficial for patients with a history of many KC lesions but not for those with fewer KC lesions. Thus, the purpose of the present study was to address the following question: Does the risk of a subsequent cancer other than KC increase as the number of KC lesions increases?

Patients and Methods

This study was approved by the institutional review board of the Medical University of South Carolina (MUSC). This study was

a clinic-based matched case-control study that included recruitment of two groups of patients: A group of n=50 participants with a history of both KC and another cancer and another group with n=50 participants with a history of KC only. The two study groups were matched for sex, age, and KC histologic type. Possible combinations of KC histologic types were SCC only, BCC only, and both BCC and SCC. Missing data on the number of KC lesions necessitated exclusion of four participants. The final study population for this report included 48 matched pairs.

Participation was limited to non-Hispanic Caucasians between 30-80 years old who were able to speak and understand English. This study was limited to non-Hispanic Caucasians because the risk of KC is predominant within this group (5). Individuals who were prisoners, institutionalized, pregnant, or cognitively impaired were not eligible to participate in the study.

During 2013-2014, participants were recruited from MUSC dermatology clinics. Prior to their clinic appointment, eligible patients were mailed an information packet. The study coordinator then contacted patients by telephone to assess their interest and eligibility. An appointment was scheduled during the clinic visit for those eligible and interested in participating, during which participants completed an informed consent form, HIPPA authorization, medical release forms, and an interviewer-administered questionnaire. Patients were compensated for participating in the study.

Data from participants were collected via an interviewer-administered questionnaire as well as a medical record review. The questionnaire consisted of questions regarding socio-demographic factors, health status, comorbidities, skin cancer risk factors, risk factors for other types of cancer, and other lifestyle factors. Information obtained from medical records consisted of body mass index, comorbidities other than cancer, KC history with regard to histologic type, location, number of lesions, and other cancer history with regard to location, cancer stage, and treatment. Self-reported history of other types of cancer was confirmed via medical record review including linkage to the South Carolina Central Cancer Registry.

Medical record data were prioritized over self-reported information for measuring KC history because although self-reported patient information is relatively accurate concerning skin cancer diagnoses, the accuracy decreases with respect to specific details such as the number of skin cancers and the histologic type (7, 8). In instances where the medical record data were missing or lacked information on the patient's skin cancer history, the patient's self-reported history was used.

In the data analyses, the dose-response association was assessed for BCC, SCC and for the total KC combined. The mean number of KC lesions were compared between groups using a paired t-test. Matched odds ratios and 95% confidence intervals were calculated using conditional logistic regression models to analyze the frequency of KC lesions between groups in relation to the risk of a type of cancer other than KC. p-Values for trend in these odds ratios were calculated via a Cochran-Mantel-Haenszel test by fitting a single variable within ordered categories in a conditional logistic regression model. Additional variables adjusted for were education, body mass index, and cigarette smoking because each is a cross-cutting risk factor for many types of cancer. Further adding to its potential confounding role, cigarette smoking is associated with risky sun exposure behaviors even in those with a personal history of skin cancer (9).

Table I. *Percentage distributions[a] of demographic characteristics of patients with history of history of keratinocyte carcinoma (KC) plus another cancer and keratinocyte carcinoma only.*

Characteristic	KC plus another cancer (n=48)	KC only (n=48)
Mean age	68 years	68 years
Gender		
Female	35%	35%
Male	65%	65%
Race/ethnicity		
Non-Hispanic white	100%	100%
Education		
Less than college graduate	31%	31%
College graduate or greater	69%	69%
Smoking history		
Never	33%	54%
Former	63%	40%
Current	4%	6%
Self-reported health status		
Poor or fair	15%	4%
Good	48%	38%
Very good or excellent	38%	58%
BMI (mean)	28 kg/m^2	27 kg/m^2
Reaction to an hour of sunlight[b]		
Tan	54%	46%
Sunburn	46%	54%
Mean hours of daily sunlight: teens		
0-2	17%	13%
3-4	33%	44%
5-6	29%	23%
≥7	21%	21%
Mean hours daily sunlight: last ten years		
0-2	42%	56%
3-4	40%	31%
5-6	15%	6%
≥7	4%	6%
Personal KC histologic type		
BCC only	50%	58%
SCC only	8%	15%
Both BCC and SCC	42%	27%

KC: Keratinocyte carcinoma; BCC: basal cell carcinoma; SCC: squamous cell carcinoma; BMI: body mass index. [a]Frequencies may not add to exactly 100% due to rounding; [b]If participant's survey response was "tan or darken with no sunburn" or "no change in skin color", they were categorized as "tan". If participant's survey response was "blistering sunburn", "sunburn without blisters", or "mild sunburn that becomes a tan", they were categorized as "burn".

Results

Due to the matched study design, the proportion of males and females was identical in the group with KC plus another type of cancer compared with the group with KC only (Table I). All but two matched pairs were within ±3 years of age with a mean age of 68 years in both study groups. In both groups, most patients had a personal history of BCC either alone or in combination with SCC; 92% in the group with

Table II. *Mean number of keratinocyte carcinoma lesions in patients with keratinocyte carcinoma plus another cancer compared with patients with keratinocyte carcinoma only.*

	Keratinocyte carcinoma plus another cancer (n=48)	Keratinocyte carcinoma only (n=48)	Percentage difference[a]	*p*-Value[b]
Basal cell carcinoma	3.50	2.44	+43%	0.22
Squamous cell carcinoma	1.27	0.94	+35%	0.36
Total keratinocyte carcinoma	4.77	3.38	+41%	0.19

[a]Calculated as $\left[\dfrac{\text{mean lesions KC plus another cancer} - \text{mean lesions KC only}}{\text{mean lesions KC only}}\right] \times 100$

[b]Paired *t*-test.

Table III. *Odds ratios (and 95% confidence intervals) for the association between number of keratinocyte carcinoma lesions and risk of another type of cancer.*

	KC plus another cancer (n=48)	KC only (n=48)	Matched OR (95%CI)	Adjusted matched OR (95%CI)[a]
BCC				
0	8.3%	14.6%	1.0 (referent)	1.0 (referent)
1	41.7%	52.1%	1.29 (0.35-4.75)	1.09 (0.23-5.13)
≥2	50.0%	33.3%	2.62 (0.67-10.26)	2.12 (0.50-9.08)
p_{trend}			0.10	0.18
SCC				
0	50.0%	58.3%	1.0 (referent)	1.0 (referent)
1	27.1%	25.0%	1.20 (0.52-2.79)	1.24 (0.48-3.24)
≥2	20.8%	14.6%	2.13 (0.52-8.79)	1.39 (0.29-6.61)
p_{trend}			0.31	0.60
Total KC				
1	51.1%	27.7%	1.0 (referent)	1.0 (referent)
2	10.6%	25.5%	3.33 (0.99-11.19)	3.03 (0.86-10.64)
≥3	38.3%	46.8%	2.74 (0.84-8.80)	2.15 (0.62-7.47)
p_{trend}			0.07	0.18

[a]Adjusted for education, BMI, and smoking. KC: Keratinocyte carcinoma; BCC: basal cell carcinoma; SCC: squamous cell carcinoma; OR: odds ratio; CI: confidence interval.

KC plus another cancer compared with 85% in those with KC only (Table I).

Compared with the group with KC only, the mean number of KC lesions was increased in those with KC plus another cancer by 43% for BCC (*p*=0.22), 35% for SCC (*p*=0.36), and 41% for total KC (*p*=0.19) (Table II). None of these differences were statistically significant.

In the odds ratio analysis, a pattern of association consistent with a dose-response trend was observed for BCC and SCC, although none of the trends were statistically significant (Table III). For BCC, the odds ratio of developing another type of cancer was increased from 1.0 (referent) to 1.29 (95%CI=0.35-4.75) to 2.62 (95%CI=0.67-10.26) according to whether the patient had zero, one, or ≥two BCC lesions (*p*-for-trend=0.10). For SCC, the odds ratio of developing another type of cancer increased from 1.0 (referent), to 1.20 (95%CI=0.52-2.79), to 2.13 (95%CI=0.52-8.79) according to whether the patient had zero, one, or ≥two SCC lesions (*p*-for-trend=0.31). For total KC there was not a monotonic trend with odds ratios of 1.0 (referent), 3.33 (95%CI=0.99-16.84), and 2.74 (95%CI=0.84-8.80) for the categories of 1, 2, and ≥3 lesions, respectively (*p*-for-trend=0.07). Upon further adjustment for body mass index (BMI), education, and smoking, the pattern of the odds ratios continued to be consistent with a dose-response trend for BCC and SCC, although the associations were slightly weakened (Table III).

Discussion

A case-control study was carried out to determine if the association between KC and risk of malignancies other than KC was consistent with a dose-response trend, *i.e.*, if the risk

of types of cancer other than KC increases with an increase in frequency of KC lesions. The results of the present study consistently showed that the mean number of KC lesions was higher in those with KC plus another cancer compared with those with a personal history of KC only. Similarly, for BCC and SCC, monotonic trends in the odds ratios were observed showing increased risk of cancers other than KC with increased number of KC lesions. This pattern of associations provides evidence to support the presence of a dose-response trend, but this evidence is weakened by the fact that none of these associations were statistically significant.

All prior evidence on this topic has focused solely on BCC. To date, the major study of this topic was a case-control retrospective review using the Truven MarketScan insurance claims database comprised of approximately 124,000 patients with BCC (10). Compared with those with no personal history of BCC, the age- and sex-adjusted ORs for the risk of other malignancies were 1.61 (95%CI=1.58-1.65) for one BCC, 3.12 (95%CI=2.98-3.26) for ≥6 BCCs, and 4.15 (95%CI=3.79-4.53) for ≥12 BCCs (the latter two categories were apparently not mutually exclusive) (10). Three additional studies added limited information because assessing for the presence of a dose-response trend was not the central line of inquiry. Of these three studies, two observed a trend of non-significant increased risk of malignancies with more BCCs (11, 12), whereas one study observed a statistically significant reduced risk for other cancers with a history of multiple BCCs compared to one (13). Overall, the prior evidence supports the presence of a dose-response association with greater number of BCCs associated with increased risk of other malignancies.

Against this backdrop, the results of the present study provide complementary evidence to further support the presence of a dose-response trend with BCCs and raise the notion that a dose-response trend may also be true for SCC. Strengths of the present investigation lie in studying both SCC and BCC in the context of a case-control study that was well designed to assess this question, with matching by age, sex, and histologic type of KC and with further adjustments for some major cancer risk factors. A limitation of the present study was the small sample size. Thus, despite observing a pattern of association consistent with a dose-response trend, the resulting lack of statistical precision led to results that were not statistically significant. The results of the present study were compatible with the presence of a dose-response trend for BCC that supports prior evidence, and the results further hint that a dose-response trend may also exist for SCC. Additional studies on this topic will help to further refine understanding of this association. This is an important line of inquiry, as it holds promise for leading to a better understanding of the link between KC and the risk of other malignancies. Further, this question has implications for clarifying the potential for translating this information into the clinical setting, emphasizing not only the importance of continued skin cancer surveillance (14), but also the potential use of multiple BCC and/or SCC lesions for purposes of risk stratification to carry out surveillance for non-cutaneous malignancies.

Conflicts of Interest

Authors' Contributions

Ashley Wilson: drafted manuscript; manuscript revisions; James Small: data cleaning and data analyses; manuscript review and revisions; Catherine Flanagan: study implementation, including patient recruitment, data collection, data management; manuscript review and revisions; David Perry: assisted with medical record review; manuscript review and revisions; Richard Marchell: assisted with patient recruitment and clinical implementation; manuscript review and revisions. Bruce Thiers: securing funding, oversight of study design and study implementation; manuscript review and revisions; Anthony J. Alberg: securing funding, oversight of study design, study implementation, data analysis and interpretation; drafting and revising the manuscript.

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