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Review

Cutaneous Markers of Photo-Damage and Risk of Basal Cell Carcinoma of the Skin: A Meta-Analysis

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Abstract

Epidemiologic research has shown that cutaneous markers of photo-damage are associated with risk of basal cell carcinoma (BCC). However, there has been no previous attempt to calculate pooled risk estimates. We conducted a systematic review and meta-analysis after extracting relevant studies published up to January 2013 from five electronic databases. Eligible studies were those that permitted quantitative assessment of the association between histologically confirmed BCC and actinic keratoses, solar elastosis, solar lentigines, or telangiectasia. Seven eligible studies were identified and summary odds ratios (ORs) were calculated using both random and quality effects models. Having more than ten actinic keratoses was most strongly associated with BCC, conferring up to a fivefold increase in risk (OR: 4.97; 95% CI: 3.26–7.58). Other factors, including solar elastosis, solar lentigines, and telangiectasia had weaker but positive associations with BCC with ORs around 1.5. Markers of chronic photo-damage are positively associated with BCC. The presence of actinic keratoses was the most strongly associated with BCC of the markers examined. This work highlights the relatively modest association between markers of chronic ultraviolet exposure and BCC. *Cancer Epidemiol Biomarkers Prev; 22(9); 1483–9. ©2013 AACR.*

Introduction

Basal cell carcinoma (BCC) is the most commonly diagnosed cancer in Caucasian populations. BCC is not routinely captured in registries, but it is nevertheless clear that the incidence rates of BCC vary significantly around the world, ranging from 2 in east Asia to 1,600/100,000 per year in Queensland, Australia (1–7). The incidence rates seem to be increasing in several populations (8–11). Although mortality from BCC is low, morbidity can be considerable. Arguably, the greatest burden, however, is on health system budgets. The total annual cost of managing keratinocyte cancers has been estimated to be about 500 million dollars in Australia (12), and as BCCs account for more than 70% of all keratinocyte cancers (13), they are likely to account for a large proportion of this total cost. The personal and health system costs of BCC emphasize the need for scientific inquiry into better understanding the causes of these common cancers.

Ultraviolet radiation (UVR) is the major etiologic agent in the pathogenesis of BCC (14–16). However, while comparisons of BCC incidence between fair-skinned populations living in regions with different ambient UVR highlight the importance of sun exposure, studies of personal sun exposure suggest lower levels of risk, with typically less than a doubling in risk with high self-reported levels of sun exposure (17). There is a plateau of BCC incidence with age and a reportedly stronger association with recreational than with occupational or total exposure (15), and it has been suggested that childhood might represent a critically important exposure window (14). In addition, while BCC occurs predominantly on the head and neck, approximately 25% arise on less sun-exposed body sites such as the trunk (18–21). This is in contrast with squamous cell carcinoma (SCC) where only 8% of lesions occur on the trunk (18) and the strongest risks seem to result from a lifetime of high sun exposure (22).

Although epidemiologic studies have tended to downplay the role of chronic cumulative sun exposure in the etiology of BCC, most studies have relied largely on self-report to capture lifetime sun exposure, which is far from ideal. Sun exposure is ubiquitous and its recall is prone to nondifferential misclassification, shown by poor repeatability (23). Differential reporting according to skin cancer history is of potential concern in case–control studies. In addition, report of exposure to the sun does not necessarily capture the relevant dose at a cellular level due to differences in skin type. There are several markers of

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chronic sun exposure, including actinic keratosis (24), elastosis, telangiectasia, and solar lentigines (25–28) and assessment of the association between these and BCC provides a more objective measure of the impact of cumulative UVR exposure. Although there are studies that have explored this issue, there has been no previous attempt to synthesize this literature. We therefore conducted a systematic review and meta-analysis to better understand the impact of chronic UVR-related skin changes on the risk of BCC.

Materials and Methods

Literature search

Eligible studies published from 1965 up to January 2013 were identified by computerized literature searching using the MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Web of Knowledge, Cochrane databases, and hand-searching of the reference lists of the retrieved articles.

For computer searches, we used the following MeSH terms or text words (using both the United Kingdom and the United States spellings and plurals where applicable): "Carcinoma, Basal Cell"[Mesh], "Basal Cell Carcinomas", "Basal Cell Epithelioma", "BCC" "Nonmelanoma skin cancer", "Non-melanoma skin cancer", "Non melanoma skin cancer", "NMSC", "Keratosis, Actinic"[Mesh], "solar keratosis", "Elastosis", "lentigines", "lentigo", "Telangiectasis"[Mesh], and "Telangiectasia".

Study selection

We included observational studies of case–control and cohort designs in the meta-analysis provided that they permitted quantitative assessment of the association between histologically confirmed BCC and actinic keratoses, solar elastosis, solar lentigines, and telangiectasia. Studies published in languages other than English were not eligible (29, 30). A single reviewer (M. Khalesi) read the abstracts of all identified studies and excluded those that were clearly not relevant. He subsequently read the full texts of the remaining articles to determine whether they met the study inclusion criteria. Where multiple reports from one study were found, the most recent or most complete publication was used. We did not exclude any studies from the analysis because of study quality, as quality was adjusted for in our quantitative model.

Data extraction

After initial review of the abstracts identified by the primary computerized literature search, we identified 70 potentially eligible studies and hand-searched the reference lists of these. After review, we excluded 63 studies because no photo-damage marker was reported ($n = 37$), they were not independent of other included studies ($n = 18$), were not in English ($n = 2$; refs. 29, 30), they reported combined data for BCC, SCC, or actinic keratoses together ($n = 5$; refs. 31–35), or the study was conducted in a high-risk group ($n = 1$; refs. 36). We retrieved seven articles for further assessment, all of which met the eligibility criteria: one cohort study and six case–control studies. Of the eligible case–control studies, one was population-based and five were clinic/hospital-based (Table 1).

Reported data for any relevant variable for which analysis was conducted were extracted. We also extracted a wide range of variables that may influence study validity or contribute to heterogeneity. These included country, year of publication, study design, sample size, case definitions, method of case ascertainment, whether the analysis was adjusted for age, sex, time spent outdoors or skin color/type, and results [relative risk (RR), odds ratio (OR), and 95% confidence interval (CI)].

Quality assessment

We used a quality scoring checklist (Supplementary Table) which included 16 questions for case–control studies and 13 questions for cohort studies based on a published template for assessing observational studies (37). We specifically tailored it to our meta-analysis to rate the methodologic quality of individual studies by including such items as method of assessment (observed or self-reported) and whether the variable was adjusted for time spent outdoors or skin color/type. A single scorer (M. Khalesi) did the scoring. The quality score was calculated

Table 1. Characteristics of the seven studies included in the meta-analysis of cutaneous markers of photo-damage and risk of basal cell carcinoma of the skin

First author	Year of publication	Study location	Source of cases/cohort	Source of controls	Sample size	Actinic keratosis	Solar elastosis	Solar lentigines	Telangiectasia	Quality score
Cohort					Cases/cohort					
Green A (45)	1996	Australia	Population	—	250/2095	√	√	√	√	0.84
Population-based case–control					Cases/controls					
Kricker S (46)	1991	Australia	Population	Population	226/1021	√	√	√	√	0.81
Clinic/hospital-based case–control					Cases/controls					
Dessinioti C (47)	2011	Greece	Clinic/hospital	Clinic/hospital	199/200	√		√		0.75
Gon A (50)	2011	Brazil	Clinic/hospital	Clinic/hospital	127/280	√	√	√	√	0.69
Walther U (48)	2004	Germany	Clinic/hospital	Clinic/hospital	213/411	√	√	√		0.56
Corona R (51)	2001	Italy	Clinic/hospital	Clinic/hospital	166/158	√	√	√		0.69
Naldi L (49)	2000	Italy	Clinic/hospital	Clinic/hospital	528/512	√		√		0.81

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as the total score divided by the number of items (16 for case–control studies and 13 for the cohort study). Normalized scores ranged from 0 (worst) to 1 (best). A summary of the quality score for each paper is shown in Table 1.

Statistical analysis

The primary outcome was the odds of BCC in those with the marker of interest compared with those without the marker. We preferentially used adjusted ORs reported by the authors, only using crude estimates if no adjusted estimates were reported. One cohort study reported RRs rather than ORs—we converted these to ORs using the OR2RR online software (http://epigear.com/index_files/or2rr.html). Most studies presented data as the marker of interest present versus absent. For those that presented data in more categories, we combined the ORs, weighting for the size of the category, to enable a meta-analysis of the odds of present versus absent.

Heterogeneity was determined to be present when the value of τ^2 was more than zero and/or the Q-statistic was significant at $P < 0.1$ (38). Although the standard approach for handling heterogeneity between studies is to use the random effects model (39), the present study uses bias adjustment via the quality effects model (40, 41). When a meta-analysis is conducted in studies with large heterogeneity, the CIs are substantially wider in random effects models than in quality effects models (41, 42). We have reported the random effects results for comparative purposes. Because of the small number of studies, we did not conduct analyses stratified according to potential sources of heterogeneity including study design, sources of cases/cohort and controls, study location, and adjustment for potential confounders. We conducted leave-one-out sensitivity analyses in which we omitted each study in turn to determine whether the results could have been influenced significantly by any particular study.

All analyses were conducted using MetaXL version 1.3 (www.epigear.com). Publication bias was examined visually by funnel plots using MetaXL as well as with the aid of the Begg rank correlation method and the Egger regression method using Stata statistical software (43, 44). We considered the funnel plot to be asymmetric if the intercept on Egger's regression deviated from zero with a $P < 0.1$.

Results

Actinic keratosis

All seven studies presented data on the association between actinic keratoses and BCC (Table 2). Compared with people with no actinic keratoses, those with actinic keratoses were at a markedly higher risk of BCC (quality effects model OR: 3.28; 95% CI: 2.71–3.96; Fig. 1A). We also assessed the effect of having a greater number of actinic keratoses by meta-analyzing the three studies that presented OR for different categories of actinic keratoses count (45–47). There was evidence of a dose-response, with the OR increasing from 2.22 (95% CI: 1.71–2.89) in those with fewer than 10 actinic keratoses to 4.97 (95% CI: 3.26–7.58) in people with at least 10 actinic keratoses. There was no heterogeneity in risk estimates across studies and the pooled ORs were approximately similar when we used a random effects model (Table 2).

Solar elastosis

Five studies presented data on the association between solar elastosis and BCC (Table 2). Having solar elastosis was associated with an increased risk of BCC (quality effects model OR: 1.58; 95% CI: 1.04–2.40; Fig. 1B). In one study, the presence of solar elastosis was associated with reduced risk of BCC (OR: 0.1; 95% CI: 0.05–0.42; ref. 48). There was significant heterogeneity across studies but no individual study seemed to account for this. Even taking out the study with the paradoxical result did not remove the heterogeneity. The pooled OR using the random effects model was considerably lower and no longer

Table 2. Meta-analysis results using the quality effects and random effects models: risk of basal cell carcinoma associated with cutaneous markers of photo-damage

	Studies	Quality effects model OR (95% CI)	Random effects model OR (95% CI)	I^2 (%)	$P_{heterogeneity}$
Actinic keratosis					
Present vs. absent	7	3.28 (2.71–3.96)	3.19 (2.57–3.95)	33.0	0.17
Less than 10	3	2.22 (1.71–2.89)	2.26 (1.71–2.99)	20.0	0.28
More than 10	3	4.97 (3.26–7.58)	4.96 (2.83–8.69)	67.0	0.05
Solar elastosis					
Present vs. absent	5	1.58 (1.04–2.40)	1.13 (0.52–2.45)	90.0	0.00
Solar lentigines					
Present vs. absent	7	1.44 (1.10–1.89)	1.71 (1.17–2.48)	85.0	0.00
Telangiectasia					
Present vs. absent	3	1.59 (1.31–1.93)	1.59 (1.31–1.93)	00.0	0.90

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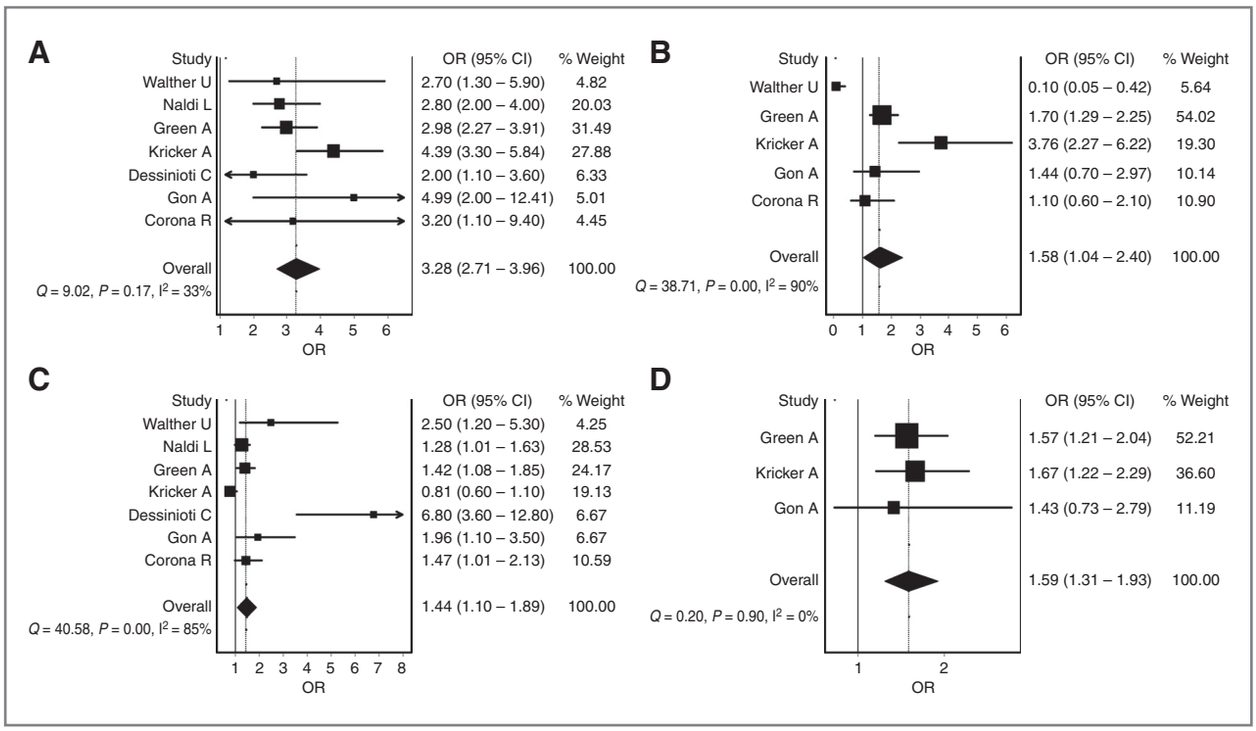

Figure 1. A–D, forest plots of the association between actinic keratosis (A), solar elastosis (B), solar lentigines (C), telangiectasia (D), and BCC using quality effects models. Each line represents an individual study result with the width of the horizontal line indicating 95% CI, the position of the box representing the OR, and the size of the box being proportional to the weight of the study.

significant (random effects model OR: 1.13; 95% CI: 0.52–2.45).

Solar lentigines

Seven studies presented data on solar lentigines and BCC risk (Table 2). The presence of solar lentigines was associated with an approximately 1.5-fold increased risk of BCC using the quality effects model (OR: 1.44; 95% CI: 1.10–1.89; Fig. 1C), and a 1.7-fold increased risk using the random effects model (OR: 1.71; 95% CI: 1.17–2.48; Table 2). There was evidence of significant heterogeneity but no individual study seemed to account for this.

Telangiectasia

Three studies presented data on the association between telangiectasia and BCC (Table 2). Compared with people with no telangiectasia, those with telangiectasia were at a higher risk of BCC (quality effects model OR: 1.59; 95% CI: 1.31–1.93; Fig. 1D). The pooled ORs using quality effects and random effects models were the same, with no heterogeneity in risk estimates across studies.

Publication Bias

There was no evidence of publication bias using the Egger weighted regression method and the Begg rank correlation method for the analyses of all markers of interest with the exception of solar lentigines which showed significant publication bias with both methods (Table 3).

Discussion

This is the first study to systematically evaluate available epidemiologic evidence about the magnitude of the relationship between cutaneous markers of photo-damage and risk of BCC using estimates of OR derived through meta-analysis. The presence of actinic keratosis was most strongly associated with BCC, with more than 10 actinic keratoses conferring up to a 5-fold increase in risk. Other photo-damage markers including solar elastosis, solar lentigines, and telangiectasia had weaker but positive and similar associations with BCC, with ORs around 1.5.

This analysis is based on observational studies which were predominantly case–control in design. Although the markers of interest used in this study were not prone to recall bias, in most studies it was unclear if observers were blinded to skin cancer status before examination, potentially resulting in biased assessments (47–51). The most likely result of this would have been to overestimate the association between chronic skin damage and BCC. Only one cohort study (45) has included measures of actinic skin damage, so we were unable to estimate the potential for observer bias. The studies included in this analysis ranged in size from 127 cases to 528 cases and varied in quality. We took account of both size and quality in this

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Table 3. Results of publication bias tests using the Egger weighted regression method and the Begg rank correlation method

	P_{bias}	
	Begg method	**Egger method**
Actinic keratosis		
Present versus absent	0.764	0.696
Less than 10	0.296	0.020
More than 10	0.52	0.841
Solar elastosis		
Present versus absent	0.221	0.344
Solar lentigines		
Present versus absent	0.035	0.029
Telangiectasia		
Present versus absent	1.000	0.605

analysis to derive the best estimates of association between actinic skin damage and BCC.

Our results show that markers of chronic sun exposure do increase the risk of BCC, suggesting that cumulative exposure is etiologically relevant. However, with the exception of actinic keratoses, the associations were modest and the strength of association was similar to that found for self-reported cumulative sun exposure. This is in contrast with SCC where the presence of actinic keratoses increases risk by 30 to 40 times and telangiectasia and solar elastosis confer 3- and 6-fold increases in risk, respectively (46, 52). These relatively lower associations with BCC might suggest that different patterns of sun exposure such as intense exposure are important. It is also possible that the patterns of sun exposure that give rise to BCCs on different anatomic sites are different, and that chronic UVR is more important for lesions arising on sun-exposed sites, with intermittent exposure underpinning the development of BCCs on the trunk (53).

To our knowledge, this is the first study to systematically evaluate available epidemiologic evidence about the magnitude of the relationship between photo-damage markers of the skin and risk of BCC using estimates of OR derived through meta-analysis. We used a very comprehensive search strategy and, although the number of studies was too small to enable stratified analyses, we took account of variable study quality of studies. It is interesting to note that, despite the enormous burden of BCC, there are few studies that have used objective measures of sun exposure in risk assessment, and only one of these was prospective. In addition, while the proportion of BCCs arising on the trunk in the included studies ranged from 7% to 37% for the four studies (47–49, 51) that reported site distribution, there was no attempt to stratify by site or restrict the analyses to lesions arising on exposed sites, and this may have led to an underestimation of the role of chronic UVR in the etiology of BCC arising on sites that are routinely sun exposed.

This meta-analysis has highlighted the relatively modest role of chronic UVR in the etiology of BCC, suggesting that other factors must also be contributing to the marked differences observed at an ecological level. A better understanding of the patterns of sun exposure that are most important for BCC development, and the ways these interact with other factors such as genetic susceptibility, will enable the development of more strategic and informed strategies to reduce the impact of BCC on individuals and health systems.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M. Khalesi, R.E. Neale
Development of methodology: M. Khalesi, S.A.R. Doi, J. Clark
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Khalesi, J. Clark
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Khalesi, S.A.R. Doi, M.G. Kimlin
Writing, review, and/or revision of the manuscript: M. Khalesi, D.C. Whiteman, S.A.R. Doi, M.G. Kimlin, R.E. Neale
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Khalesi
Study supervision: D.C. Whiteman, M.G. Kimlin, R.E. Neale

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