

Research Article

Nonmelanoma Skin Cancer and the Risk of Second Primary Cancers: a Systematic Review

Lee Wheless^{1,2}, Joshua Black³, and Anthony J. Alberg^{1,2}

Abstract

Background: Based on empirical evidence, a personal history of nonmelanoma skin cancer (NMSC) has been hypothesized to be a risk factor for other cancers. Others hypothesize that NMSC may be a marker of high cutaneous vitamin D synthesis and therefore inversely associated with risk of other malignancies. To reconcile these divergent views, we carried out a systematic review to determine the association between NMSC and subsequent risk of other cancers.

Methods: Bibliographic databases were searched through March 2009. Studies were included if sufficient information was presented to estimate the risk of developing other cancers following NMSC. Studies were reviewed and data were abstracted independently in duplicate with disagreements resolved by consensus.

Results: Of the 21 included studies, 15 reported the association between NMSC and risk of all other cancers combined. NMSC was significantly associated with increased risk of another malignancy among cohort studies based on cancer registries [summary random-effects relative risk (SRR), 1.12; 95% confidence interval (CI), 1.07-1.17; $n = 12$ studies] and those with individual-level data (SRR, 1.49; 95% CI, 1.12-1.98; $n = 3$). In stratified analyses of registry studies, this association held true for both squamous (SRR, 1.17; 95% CI, 1.12-1.23; $n = 7$) and basal cell carcinoma (SRR, 1.09; 95% CI, 1.01-1.17; $n = 7$), and both men (SRR, 1.14; 95% CI, 1.09-1.20; $n = 12$) and women (SRR, 1.10; 95% CI, 1.04-1.15; $n = 12$).

Conclusions: Strong, consistent evidence indicates that a personal history of NMSC is associated with increased risk of developing other malignancies.

Impact: For unknown reasons, NMSC may be a risk factor for other cancers. *Cancer Epidemiol Biomarkers Prev*; 19(7); 1686-95. ©2010 AACR.

Introduction

Nonmelanoma skin cancer (NMSC), comprised mainly of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is the most common malignancy in the United States, with more than 2 million new cases annually (1, 2). Disturbingly, NMSC incidence continues to increase (3). Although NMSC is frequently curable, its high prevalence and expense of treatment place NMSC as a major public health problem and among the costliest cancers in the United States (4). Accurate population-based data on the occurrence of NMSC have been difficult to obtain, as NMSC is not routinely included in most cancer registries and is often not rigorously followed up in prospective cohort studies. Some of the issues complicating population-based ascertainment of NMSC include

treatment based on clinical diagnosis without biopsy, and deferment of biopsy due to misclassification as premalignant or nonmalignant lesions.

The major cause of NMSC is exposure to solar UV radiation. Skin characteristics, such as ability to tan and pigmentation, largely determine host susceptibility to UV radiation in causing NMSC. Individuals with NMSC are at increased risk of developing subsequent NMSCs, as well as malignant melanoma, likely through the shared risk factor of UV radiation (1, 5).

Individuals with a personal history of NMSC may also be at an increased risk for second primary cancers other than just NMSC and melanoma (6-29). Despite accumulating evidence that seems to support this association, some have hypothesized that individuals with prior NMSC may in fact have a decreased risk of other cancers (28, 30-32). The hypothesis of an inverse association is based on the supposition that the extensive exposure to sunlight among those who develop NMSC serves as a proxy for elevated levels of vitamin D due to the cutaneous synthesis that occurs upon exposure to sunlight. In turn, vitamin D is hypothesized to have anticancer properties (33).

Clarifying this issue has important scientific, clinical, and public health implications. To help reconcile these divergent views of the relationship between a personal

Authors' Affiliations: ¹Division of Biostatistics and Epidemiology, Department of Medicine and ²Hollings Cancer Center, Medical University of South Carolina, Charleston, South Carolina; and ³Department of Medicine, Yale University, New Haven, Connecticut

Corresponding Author: Anthony J. Alberg, Hollings Cancer Center, Medical University of South Carolina, 86 Jonathan Lucas Street, PO Box 250955, Charleston, SC 29425. Phone: 843-792-3426; Fax: 843-792-9588. E-mail: alberg@musc.edu

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history of NMSC and risk of subsequent malignancies, we carried out a systematic review of the evidence on this topic.

Materials and Methods

Data sources and searches

With the assistance of a research librarian, we conducted searches of the Ovid/MEDLINE and PubMed databases using the following Medical Subject Heading terms: Skin neoplasms; Neoplasms, second primary; and Risk. This search identified 107 potentially relevant articles as of March 3, 2009. Searching the Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus and Computer Retrieval of Information on Scientific Projects (CRISP) databases did not identify any current studies. The electronic searches were supplemented with hand-searches based on references in relevant articles and the related articles identified in PubMed citations. Authors were not contacted in the case of missing data.

Study selection

Studies eligible for inclusion in this systematic review met the following criteria: (a) were prospective studies in which those with and without NMSC were followed up over time for the occurrence of other cancers; (b) provided an estimate of relative risk (RR) for the association of NMSC and second primary cancers, plus 95% confidence interval (CI) or SEM; and (c) were reported in English. When study populations were overlapping, we used only the most recent data, or the report presenting the greatest levels of stratification. Potential studies were sequentially screened in duplicate for relevance by title, abstract, and then full text. Discrepancies in judgments of relevance to the topic were discussed and resolved by consensus.

One report presented the combined data from 13 national cancer registries (28). Due to overlap with published reports from many of these countries and the resultant loss of ability to perform stratified analyses, this study was not included in the primary analysis. To assess the effect of this report on the body of evidence, results from this large study were included in ancillary analyses. Results from these ancillary analyses are presented in instances when they differed from those of the primary analyses.

Data extraction and quality assessment

From each included study, RRs for the association between NMSC and subsequent risk of all other malignancies combined were abstracted in duplicate. If more than one RR was presented, the most fully adjusted estimate was used. To obtain a study-specific estimate of the overall association between NMSC and risk of another malignancy in studies that did not present this information, we calculated it from published results by combining stratum-specific estimates (usually males and females). Rather than conduct formal quality scoring of the included

studies, we conducted stratified analyses by study design as described below, in accordance with the recommendation of the Meta-analysis of Observational Studies in Epidemiology group (34).

Data synthesis and analysis

The evidence identified by the search was generated from two types of prospective study designs: (a) cancer registry-based studies that entailed linking nationwide databases and (b) cohort studies in which individual-level information was collected from study participants who were followed over time for the occurrence of cancer. As the methods used to analyze these two designs have different underlying assumptions limiting the comparability of their respective risk estimates, all analyses were stratified by study design (registry-based studies versus cohort studies with individual-level data). To measure the association between NMSC and the risk of second primary cancers, we combined the study-specific results. Summary RRs (SRR) and 95% CIs were calculated using the Dersimonian and Laird random effects models (35). Analyses were stratified by sex and histologic type (BCC and SCC). SRRs were calculated for specific anatomic cancer sites in instances when the association between NMSC and that cancer site was reported in at least five studies. Consequently, stratified analyses were not conducted for cohort studies with individual-level data ($n = 3$), but rather were limited to registry-based studies only ($n = 12$). I^2 was used to assess the magnitude of heterogeneity among studies (36). Funnel plots ($1/SE$) were constructed to assess publication bias, augmented by trim-and-fill plots. The results of these analyses did not provide evidence of publication bias.

SEMs were estimated to weight each study in calculating the SRR measure. For those studies reporting a 95% CI only and not a SEM, we calculated the SEM using the equation: $SEM = [\ln(\text{upper limit}) - \ln(\text{lower limit})] / 3.92$. Where the published lower limit was zero, we estimated the SEM using the equation: $SEM = [\ln(\text{upper limit}) - \ln(RR)] / 1.96$. For registry-based studies that presented only results stratified by gender or NMSC histology, we combined strata to obtain measures for total NMSC by adding the stratum-specific observed and expected numbers of cases, then dividing the total number of observed cases by the total number of expected cases to calculate the standardized incidence ratio (SIR) for the total unstratified population. If the expected number of cases was not reported, we estimated it using the equation: $\text{expected} = \text{observed} / \text{SIR}$. 95% CIs were calculated assuming a Poisson distribution for the number of observed cancers following NMSC using exact limits (37).

To assess factors contributing to heterogeneity, a meta-regression was conducted for the overall association between NMSC and risk of subsequent cancer. Covariates that were considered in the regression models were histology, year of study, and latitude of study location.

Mix software, version 1.7, was used for all primary analyses (38, 39), except that the meta-regression was

Table 1. Included studies on the risk of subsequent cancers in individuals with a personal history of NMSC compared with those with no prior history of NMSC

First author	Year	Location	Study type	Study years	No. of NMSC cases	No. of subsequent cancers	Mean follow up for cases (y)	Adjustments
Bower	2000	United Kingdom	Registry based (South and West)	1981-1995	13,961	789	8.45	Cancer site, age
Cantwell	2009	Ireland	Registry based (Northern Ireland)	1993-2002	20,843	1,377	Not reported	Age, 5-y period, sex
Chen	2008	Maryland	Cohort with individual-level data (CLUE II)	1989-2005	769	181	8.02	Age, sex, BMI, smoking, education
Crocetti	2001	Italy	Registry based	1976-1995	198,303	6,974	2.57	Cancer site, age, sex, registry, 5-y period
de Vries	2007	The Netherlands	Registry-based (Eindhoven)	1972-2002	12,078	253 (prostate)	5.0 SCC, 5.6 BCC	Age, 5-y period
Efird	2002	California	Cohort with individual-level data (Kaiser Permanente)	1974-1995	822	144	7.80	Education, BMI (alcohol, smoking, occupational exposure, marital status did not change model)
Friedman	2000	California	Cohort with individual-level data (Kaiser Permanente)	1974-1997	3,164	556	11.30	Matched on sex, zip code, skin color, age ± 2, date joined. Multivariate: age at diagnosis, parent history cancer, marital status, education, smoking, alcohol, occupational exposure, BMI, parity, age at menarche, and menopause
Frisch	1995	Denmark	Registry based	1978-1989	5,132	815	4.47	Cancer site, age, sex
Frisch	1996	Denmark	Registry based	1978-1991	37,674	3,663	5.07	Cancer site, age, sex, calendar period
Hemminki	2000	Sweden		1958-1996	17,673	3,624	Not reported	Age, sex, calendar period

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Table 1. Included studies on the risk of subsequent cancers in individuals with a personal history of NMSC compared with those with no prior history of NMSC (Cont'd)

First author	Year	Location	Study type	Study years	No. of NMSC cases	No. of subsequent cancers	Mean follow up for cases (y)	Adjustments
Hemminki	2001	Sweden	Registry based (Sweden)	1958-1996	17,280	192 (human papillomavirus-related cancers)	Not reported	Age, sex, calendar period
Hemminki	2003	Sweden	Registry based (Sweden)	1958-1998	Not reported	120 (non-Hodgkin)	Not reported	Age, sex, calendar period
Jaeger	1999	Denmark	Registry based	1978-1993	1,147	201	5.63	Sex, age, period, cancer site
Levi	1997	Switzerland	Registry based (Vaud, Neuchatel)	1974-1994	4,639	729	4.99	Cancer site, age, calendar period
Levi	1998	Switzerland	Registry based (Vaud, Neuchatel)	1974-1994	11,878	1,543	6.44	Cancer site, sex, age, calendar period
Levi	2008	Switzerland	Registry based (Vaud, Neuchatel)	1974-2005	28,031	1,517 (prostate, breast, colorectal)	Not reported	Cancer site, sex, age, calendar period
Lindelof	1991	Sweden	Registry based (Sweden)	1971-1983	1,973	236	6.5	Sex, cancer site
Maitra	2005	United Kingdom	Registry based (Thames)	1961-2000	25,731	3,359	Not reported	Cancer site, age, sex
Milan	2000	Finland	Registry based (Finland)	1953-1995	71,924	11,042	8.69	Cancer site, age, sex, period
Nugent	2005	Manitoba	Registry based (Manitoba)	1956-2000	36,789	5,935	9.36	Cancer site, age, sex
Soerjomataram	2008	The Netherlands	Registry based (Eindhoven)	1972-2002	23,408	463 (breast and colorectal)	5.65	Cancer site, age, sex, stage, duration of follow-up

Abbreviations: BMI, body mass index.

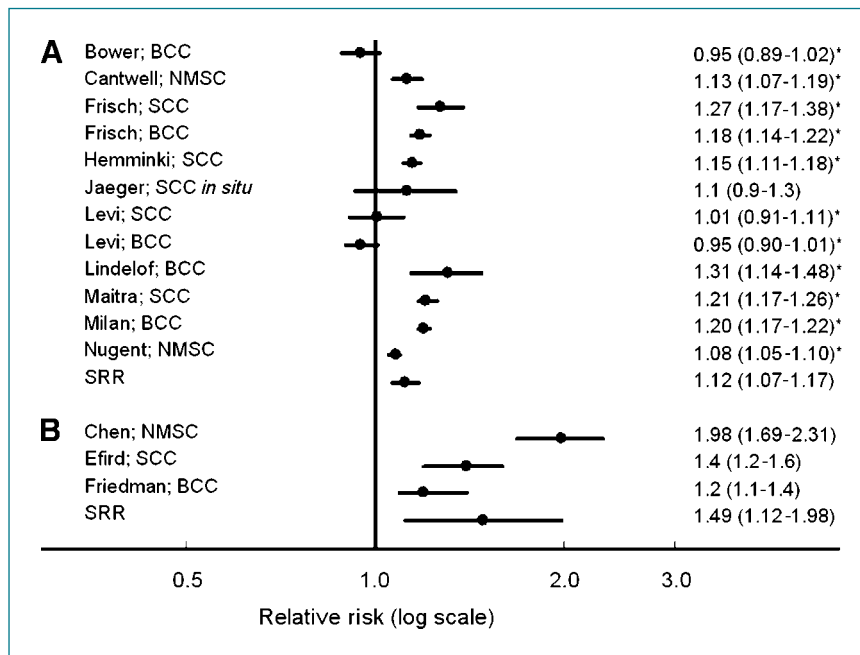


Figure 1. Risk of subsequent cancer following a diagnosis of NMSC, compared with those with no prior history of skin cancer among (A) registry-based studies and (B) cohort studies. *, calculated from data presented to include all gender and subtype strata, as well as melanoma.

conducted using SAS 9.1 (SAS Institute; ref. 40). Two-sided *P* values of <0.05 were considered statistically significant.

Results

The initial search yielded 107 studies. Of these, 81 did not measure the incidence of second cancers after NMSC, three studies were duplications, one study presented a point estimate outside of its CI, and one study did not present gender strata that were obtainable from earlier studies. The hand searches did not identify any additional studies. This left 21 articles that met the inclusion criteria (Table 1). Of these, 18 were registry-based studies, and three were cohort studies that collected individual-level data (9, 11, 12). These represented 13 populations from 10 countries in Europe (Denmark, United Kingdom, Finland, Ireland, Italy, the Netherlands, Sweden, Switzerland) and North America (Canada and United States). Six of the registry-based studies presented data on only specific cancer sites and not on the risk of cancer overall (10, 16, 17, 22, 30, 32).

Classification of NMSC status is a key study quality criterion. Not all studies registered BCC, but all of the studies except one reported using pathologic confirmation of registered NMSCs (24). Even for the study that did not specify using pathologic confirmation, a report from the registry used in the study indicated that in the final year of the study's data collection, >96% of registered cases of SCC had pathologic confirmation, and completeness was estimated to be 98% (41). Greater than 90% completeness was reported for the studies in Switzerland (20-22), whereas the remaining studies based on national cancer registries were assumed by the authors to have completeness near 100%. These studies

relied on mandated reporting and national health systems with universal coverage to provide high detection and confirmation rates. The two cohorts similarly had access to pathology reports for confirmation of lesions.

Among registry-based studies, compared with those with no NMSC diagnosis, those with a personal history of NMSC had a statistically significant 12% increased risk of developing subsequent malignancies other than NMSC (SRR, 1.12; 95% CI, 1.07-1.17; *n* = 12; *I*² = 92%), whereas among cohort studies with individual-level data, a much stronger association was observed (SRR, 1.49; 95% CI, 1.12-1.98; *n* = 3; *I*² = 92%; Fig. 1). As previously described, the following stratified analyses were conducted in the 12 registry-based studies only.

The association between NMSC and increased risk of subsequent cancer persisted in males (RR, 1.14; 95% CI, 1.09-1.20; *n* = 12; *I*² = 89%) and females (RR, 1.10; 95% CI, 1.04-1.15; *n* = 12; *I*² = 79%). The significantly increased risk was present following both BCC (RR, 1.09; 95% CI, 1.01-1.17; *n* = 7; *I*² = 95%) and SCC (RR, 1.17; 95% CI, 1.12-1.23; *n* = 7; *I*² = 78%; Table 2).

When we examined the association between NMSC and risk of specific types of cancer, 13 of 15 associations were in the direction of increased risk (Wilcoxon signed-rank *P* = 0.003; Table 3). However, not all of these associations were statistically significant and the magnitude of the associations varied considerably across cancer sites (Fig. 2). Cervical and pancreatic cancers were the only malignancies with a SRR of <1.0. For breast, prostate, colorectal, bladder, and esophageal cancers, the SRRs were weak (<1.08) and not statistically significant. The strongest associations were observed for cancers of the salivary glands (SRR, 4.57; 95% CI, 2.92-7.15), melanoma (SRR, 2.74; 95% CI, 2.49-3.02), lip (SRR, 2.38; 95% CI,

Table 2. Summary relative risk (SRR) for cancers other than NMSC among those with prior NMSC, compared with those with no prior NMSC

NMSC	SRR (95% CI)*	I ²
Individual-level cohort studies (n = 3)	1.49 (1.12-1.98)	92%
Registry-based studies (n = 12)	1.12 (1.07-1.17)	93%
Males (n = 12)	1.14 (1.09-1.20)	89%
Females (n = 12)	1.10 (1.04-1.15)	79%
BCC (n = 7)	1.09 (1.01-1.17)	95%
Males (n = 7)	1.09 (1.00-1.18) [†]	93%
Females (n = 7)	1.09 (1.02-1.16)	82%
SCC (n = 7)	1.17 (1.12-1.23)	78%
Males (n = 7)	1.20 (1.15-1.26)	61%
Females (n = 7)	1.09 (1.00-1.19)	75%

*95% confidence interval.

[†]CI excludes 1.00.

2.03-2.79), mouth and pharynx (SRR, 1.69; 95% CI, 1.31-2.18), and for non-Hodgkin lymphoma (SRR, 1.58; 95% CI, 1.37-1.81).

The increase in total cancer risk remained upon inclusion of the study by Tuohimaa et al. (28) and excluding

the studies with overlapping data, although this result was no longer statistically significant (SRR, 1.10; 95% CI, 0.96-1.26; *n* = 6). The only two instances in which inclusion of the study of Tuohimaa et al. (28) yielded a different conclusion were with thyroid cancer following NMSC, and esophageal cancer after specifically SCC, both of which became statistically significant upon inclusion (thyroid: SRR, 1.41; 95% CI, 1.20-1.66 versus SRR, 1.28; 95% CI, 0.95-1.71; esophagus: SRR, 1.26; 95% CI, 1.02-1.56, versus SRR, 1.06; 95% CI, 0.85-1.32).

In the results described above, considerable heterogeneity was present. In the meta-regression to investigate potential sources of heterogeneity among the registry-based studies, differences in latitude accounted for 55% of the variation, whereas histology (10%) and year of publication (2%) were much weaker individual contributors. The association between NMSC and risk of other cancers was stronger the further from the equator (*P* < 0.01).

Discussion

Differing views have been expressed about whether a personal history of NMSC is associated with increased (6-29) or decreased (28, 30-32) risk of subsequent non-cutaneous malignancy. Some have suggested that NMSC may be inversely associated with subsequent cancer risk based on the hypothesis that the sunlight exposure that causes NMSC also increases cutaneous synthesis of vitamin D, which in turn may protect against cancer. To help resolve this issue, we carried out a systematic review to

Table 3. Summary relative risk (SRR) of site-specific cancers following NMSC, BCC, and SCC among registry-based studies

Site of second primary cancer	NMSC SRR (95% CI)*	NMSC: males SRR (95% CI)*	NMSC: females SRR (95% CI)*	BCC SRR (95% CI)*	SCC SRR (95% CI)*
Lung	1.23 (1.13-1.33)	1.27 (1.16-1.39)	1.19 (1.06-1.33)	1.13 (1.01-1.27)	1.34 (1.22-1.47)
Breast	1.04 (0.96-1.14)	— [†]	1.04 (0.96-1.14)	1.08 (0.99-1.19)	0.97 (0.88-1.08)
Colorectal	1.05 (0.97-1.13)	1.05 (0.95-1.16)	1.03 (0.94-1.13)	1.02 (0.93-1.13)	1.03 (0.93-1.15)
Melanoma	2.74 (2.49-3.02)	2.73 (2.52-2.96)	2.61 (2.24-3.05)	2.75 (2.39-3.16)	2.84 (2.45-3.29)
Pancreas	0.94 (0.82-1.07)	1.07 (0.97-1.18)	0.91 (0.78-1.06)	— [‡]	— [‡]
Leukemia	1.26 (1.04-1.52)	1.45 (1.17-1.79)	1.24 (0.99-1.55)	1.12 (0.93-1.35)	1.45 (0.93-2.11)
Cervix	0.93 (0.62-1.41)	— [†]	0.93 (0.62-1.41)	0.84 (0.50-1.41)	— [‡]
Non-Hodgkin lymphoma	1.58 (1.37-1.81)	1.56 (1.33-1.84)	1.58 (1.37-1.82)	1.39 (1.22-1.58)	2.00 (1.80-2.22)
Myeloma	1.18 (1.06-1.32)	— [‡]	— [‡]	— [‡]	— [‡]
Salivary gland	4.57 (2.92-7.15)	5.22 (3.32-8.22)	3.65 (1.91-6.95)	— [‡]	7.15 (4.09-12.52)
Thyroid	1.28 (0.95-1.71)	1.72 (0.55-5.33)	1.23 (0.99-1.53)	1.24 (0.92-1.67)	— [‡]
Prostate	1.04 (0.98-1.12)	1.04 (0.98-1.12)	— [†]	1.07 (0.97-1.17)	1.00 (0.94-1.07)
Lip	2.38 (2.03-2.79)	2.09 (1.88-2.31)	4.45 (2.76-7.19)	— [‡]	3.79 (3.15-4.57)
Mouth and pharynx	1.69 (1.31-2.18)	1.94 (1.50-2.49)	1.87 (1.26-2.78)	1.32 (1.13-1.55)	2.05 (1.33-3.19)
Esophagus	1.06 (0.85-1.32)	1.15 (0.92-1.45)	1.11 (0.90-1.36)	0.90 (0.67-1.21)	1.21 (0.83-1.74)

*95% confidence interval.

[†]Not applicable.[‡]RR estimate presented in fewer than 5 studies.

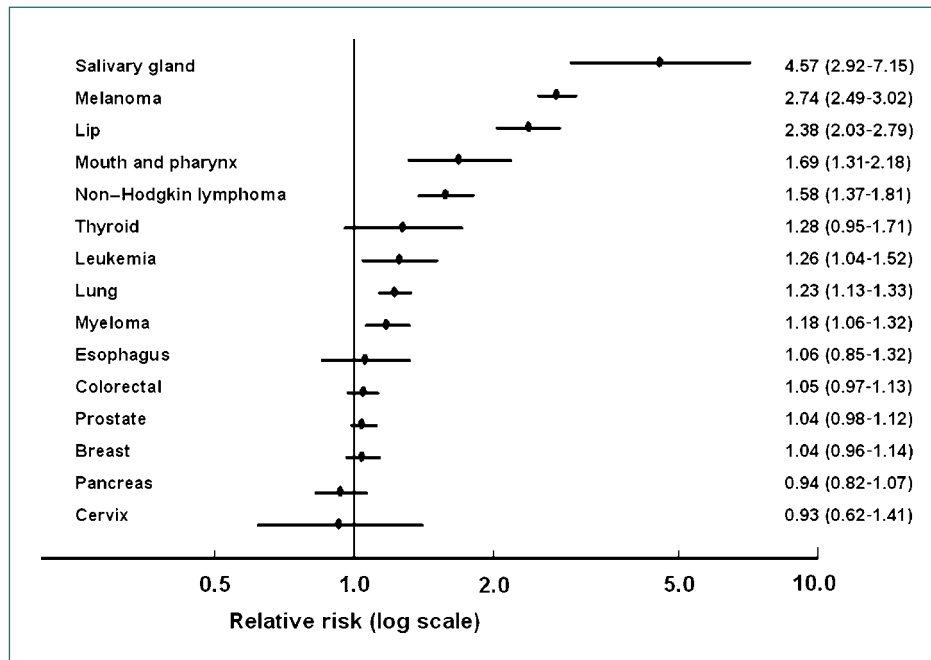


Figure 2. Summary relative risk (and 95% CI) of developing specific cancers following NMSC, compared with those with no prior NMSC.

objectively summarize the available evidence on this topic. The synthesis was based on a substantial body of evidence: 21 reports, mostly based on national cancer registry data, from a total of 13 different populations in 10 different countries. We did not find evidence of a significant protective association overall or for any individual cancer site in any of our analyses.

In fact, the data synthesis showed that compared with those with no prior NMSC, among registry-based studies, those with a personal history of NMSC had a significant 12% increased risk of subsequent cancers other than NMSC. The association between NMSC and other cancers not only persisted but was consistent with a much stronger 49% increased risk in cohort studies with individual-level data ($n = 3$) that adjusted for potential confounders such as smoking status (Fig. 1; refs. 9, 11, 12). The registry-based studies were unable to control for individual-level confounders other than age and sex, which limits the strength of the inferences; however, the large study populations tended to offer more precise risk estimates, as well as risk estimates for rarer cancers not observed in the cohort studies with smaller sample sizes but more detailed data collection. There did not seem to be meaningful differences between the two types of study designs with respect to confirmation of NMSC, as all studies had access to pathology reports. Each study also linked to national or regional cancer registries for data on confirmed second primary cancers. The completeness of the ascertainment of NMSC may be relevant to the differing results by study design, but the information to assess this issue in greater detail is not readily available. The fact that cohort studies with the ability

to adjust for individual-level risk factors have thus far observed stronger associations suggests that the registry-based studies may be biased toward the null, but additional cohort studies are needed to definitively determine if this is the case.

Despite consistent evidence of a positive association, two registry-based studies found a nonsignificant inverse association (7, 20). Both of these studies examined second cancers after BCC. The RR following SCC in these countries was greater than one, as was consistently seen in every instance in which both estimates were presented. There were no obvious differences in study design or methods that would explain the lack of perfect consistency in the direction of the associations, so they may have been due to chance.

The systematic review approach is of particular value for summing up the data across the subgroups in which strata from single studies may be lacking in statistical precision. A contribution of this systematic review is clarifying that the increased cancer risk is equally relevant for both sexes and major histologic types of NMSC, and seems to be relevant to numerous anatomic cancer sites, as the association between a personal history of NMSC and risk of other malignancies was in the direction of increased risk for 13 of 15 cancer sites with sufficient data (Fig. 2). This systematic review also highlights the difference in the risk estimates based on two major study designs.

For many reasons, the association between NMSC and risk of other cancers is likely to represent a true etiologic association. First, we limited the evidence synthesis to studies reporting follow-up after NMSC, unequivocally establishing that the NMSC diagnosis preceded the

occurrence of other malignancies. Second, the large number of studies was remarkably consistent: almost all studies showed a significantly increased risk for all other cancers. Third, the association between NMSC and other cancers not only persisted but actually increased in strength among studies adjusting for potential confounders such as smoking status (9, 11, 12). This raises the possibility that lack of control for confounding may be generating a bias toward the null in the registry-based studies. There are also several plausible biological mechanisms that could explain the association between NMSC and risk of other cancers, including immunosuppression, chronic inflammation, and variation in DNA repair efficiency, all of which act systemically and play a role in cutaneous and internal carcinogenesis.

NMSC also has several unique features that make it particularly well suited for study as a risk factor for other cancers. Most NMSCs are nonfatal, allowing for follow-up sufficiently long to detect second primary cancers. The majority of NMSCs will also be cured by surgical excision, eliminating the need for systemic chemotherapy, radiation, and their concomitant side effects. When studying the risk of second cancers, primary cancers that are more lethal run the risk of introducing a survival bias whereby individuals with aggressive cancers do not live long enough to develop second primary cancers, whereas the treatments themselves may also be carcinogenic. If there were a common risk factor for both cutaneous and internal malignancies, one would expect to see increased risk of NMSC after other cancers as well. For reasons just mentioned, this association would be very difficult to isolate, although several unadjusted studies have indeed observed an increased risk of NMSC after other cancers, especially following cancers of hematopoietic origin (6, 10, 17, 42-44).

The data synthesis we report in this systematic review is subject to the limitations of the published studies. One possible explanation that has yet to be adequately addressed is surveillance bias, whereby individuals with a prior NMSC may be followed more closely than others and, as a result, may have a greater likelihood of having subsequent cancers detected. If this were true, the association between NMSC and risk of other cancers would be expected to dissipate with long-term follow-up. Although there were no data specifically on the frequency of surveillance, studies that have examined the length of follow-up have found that the risk of a subsequent primary cancer remains elevated as many as 15 years after NMSC (14, 15, 22, 25), suggesting that surveillance bias may not explain the association between NMSC and subsequent cancers. On the other hand, other studies have observed the risk diminish over time, leaving this an open question (18-20, 30, 32). The only study we are aware of to directly account for this issue had information about having a health care provider, which did not differ according to NMSC status (27), but this was only a crude measure of potential surveillance.

Not all studies that have reported on information relevant to this topic were included in the formal quanti-

tative synthesis of the evidence. These included cross-sectional studies (27), cohort studies comprised entirely of those with a personal history of NMSC (19), and studies with mortality as their end point (46). Results from the Women's Health Initiative, a cross-sectional study of >93,000 women ages 50 to 79 years, showed a significant association between self-reported NMSC and other self-reported cancers (odds ratio, 2.25; 95% CI, 2.11-2.39; ref. 27). In the American Cancer Society Cancer Prevention Study II ($n = 1,184,569$), compared with those with no prior NMSC, there was an increased risk of cancer mortality in individuals with previous NMSC (men: RR, 1.30; 95% CI, 1.23-1.36; women: RR, 1.26; 95% CI, 1.17-1.35; ref. 45), even after adjustment for age, race, education, smoking, obesity, exercise, alcohol, vegetable and fat intake, diabetes, aspirin use, menopausal status, oral contraceptive use, parity, and estrogen replacement therapy. Not all excluded studies found a significant association, though. One study, which was excluded due to the point estimate being outside its reported CI, found no overall association with cancers following NMSC, but a significantly increased risk after SCC (46). Another study was excluded because it collected cases from a single hospital and controls from the general population in Sweden, with known differences in BCC incidence between the two populations; this study found no increased risk following BCC (47). Other studies in Sweden consistently reported an increased risk following SCC (15-17), but there has not been another study of BCC in Sweden. It is thus reassuring that the results of the higher quality studies that were not included in the quantitative synthesis generally corroborate an association between NMSC and other cancers.

In contrast to our results, a previous meta-analysis on this topic concluded that solar UV exposure, as indicated by a personal history of NMSC, was associated with an overall decreased risk of cancer that was attributed to vitamin D (31). The previous result was obtained using most of the studies included in this systematic review, none of which showed a significantly decreased risk of second cancers. In addition to applying a less rigorous systematic review protocol, the author of this earlier meta-analysis attempted to control for cigarette smoking by using the RR for lung cancer as an internal reference value for each study against which all other cancer risks were compared. That is, RRs for total and site-specific cancers were divided by the stratum-specific RR for lung cancer. These differences in systematic review protocol clearly make a major difference in the results and interpretation of the data. That the three cohort studies with individual-level data that adjusted for smoking actually resulted in stronger associations than registry-based studies suggests it is important to rely on the observed data than attempt artificial corrections.

The results of the quantitative synthesis of the data were quite consistent, but substantial heterogeneity was present. We conducted a meta-regression to investigate contributing factors. Among registry-based studies, a

great deal of variation was explained by differences in latitude. The majority of studies included was based on national cancer registries and thus was unable to control for confounders such as cigarette smoking. As mentioned, the few studies with individual-level data on potential confounders actually observed a substantially stronger association (1.49 versus 1.12). Additional cohort studies with the ability to adjust for individual-level risk factors are needed to determine if this stronger association persists (48, 49).

In summary, this systematic review revealed strong evidence that NMSC is associated with ~10% increased risk of subsequent primary cancer in registry-based studies and that this association may be substantially larger (50% increased risk) based on cohort studies with more detailed individual-level data. This association applies to both NMSC subtypes, and both men and women. The increased risk associated with NMSC seems to apply to a broad spectrum of malignancies.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Lee Wheless, Joshua Black and Anthony J. Alberg

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