Risk of Developing a Subsequent Nonmelanoma Skin Cancer in Patients With a History of Nonmelanoma Skin Cancer

A Critical Review of the Literature and Meta-analysis

Isabelle Marcil, MD; Robert S. Stern, MD

**Objective:** To assess the risk of developing a basal cell carcinoma (BCC), and/or squamous cell carcinoma (SCC), and/or Bowen disease (SCC in situ) after a nonmelanoma skin cancer (NMSC) of a specific type.

**Data Sources:** Four electronic databases were searched from January 1, 1966, to October 21, 1999.

**Study Selection:** We included all studies published in English, identified by standard search strategies, that provided original data quantifying the risk of an NMSC among persons with a previous NMSC.

**Data Extraction:** For each study and separate histological type of index skin tumor and subsequent skin tumor (SCC, BCC, NMSC, or Bowen disease), we determined the 3-year cumulative risk and the incidence rate of second tumors per 100 000 person-years. In cases where more than 1 study was assessing the risk of one specific tumor type after another, we undertook a formal meta-analysis. We compared the incidence of a subsequent SCC after an index SCC and of a subsequent BCC after an index BCC with the incidence of the first occurrence of such tumors in the comparable general population.

**Data Synthesis:** We identified and reviewed 17 studies that included data for 26 tumor combinations. Overall, the 3-year cumulative risk of a subsequent SCC after an index SCC is 18%, at least a 10-fold increase in incidence compared with the incidence of first tumors in a comparable general population. For BCCs, the 3-year cumulative risk is 44%, also at least a 10-fold increase in incidence compared with the rate in a comparable general population. The risk of developing a BCC in patients with a prior SCC is about equal to that risk among persons with a prior BCC, but the risk of developing an SCC in patients with a prior BCC is low (6%).

**Conclusions:** Although these studies vary in their study type, location, and biases, their results are consistent. The risk of developing a subsequent skin cancer of a specific type depends on the type of prior NMSC and number of prior skin tumors of that type. Based on these findings, follow-up strategies for patients with BCC and SCC are suggested.

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BASAL CELL carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin are the most common malignant neoplasms in the white population. In the United States, their incidence is estimated to be increasing by 2% to 3% yearly.1-4 In 1999, about 200 000 SCCs and 800 000 BCCs were diagnosed in the United States.5 These tumors account for more than 95% of all nonmelanoma skin cancers (NMSCs) and are associated with substantial morbidity, including loss of function and disfigurement. Fortunately, mortality from these cancers is low.5,6

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MATERIALS AND METHODS

SEARCH STRATEGIES

We first developed a list of all the keywords and combination of keywords we thought might identify all studies quantifying the risk of an NMSC among persons with a previous NMSC. We searched in MEDLINE, Healthstar, AIDSLine, and Cancerlit in October 1999 for all articles published after January 1, 1986, and indexed in MEDLINE as of October 21, 1999. The keywords used were the following: "basal cell carcinoma," "squamous cell carcinoma," "baso-squamous carcinoma," "Bowen disease/squamous cell carcinoma in situ," "skin/skin disease," "subsequent," "reoccurrence," "recurrent," "second primary (neo)," "multiple (neo)," and "another." Each search combined these keywords in multiple ways. References of the selected articles were scanned for potentially relevant articles. We also used the PubMed Clinical Queries using Research Methodology Filters to attempt to better define the risk and risk factors of a new NMSC after having had one? Only articles published in English were included. Articles derived from special populations (ie, transplant, xeroderma pigmentosum, Gorlin) were excluded. All study types were included except case reports. The initial relevance of all retrieved articles was evaluated by one of us (I.M.) on the basis of title and abstract. The selected articles were then read by both of us to assess if they provided original data that addressed the risk of an NMSC following an NMSC.

A formal estimate of risk based on a meta-analysis was performed when there was more than one study addressing the risk of a specific type of NMSC to another. Multiple estimates were available for each tumor type to the same tumor type (SCC to SCC and BCC to BCC), and for SCC after BCC. For each tumor type to the same tumor type (SCC to SCC and BCC to BCC), we calculated pooled estimates of incidence using the Meta-Analyzer software. Unless the incidence rate for the general population analyzed was specified in the study, we estimated that incidence using the incidence rate for that specific tumor type, matched for country and adjusted for age and sex. We identified 4 studies that quantified the risk of an NMSC of any type after an NMSC. We summarized those results, but did not undertake formal meta-analyses. For other combinations (SCC to BCC, NMSC to SCC, NMSC to BCC, SCC to NMSC, Bowen disease to Bowen disease, and Bowen disease to SCC), fewer sources of data were available and we discussed the findings of these studies in relation to our primary analyses.

The different searches performed yielded 3000 references, including duplications among the results of the different searches. On the basis of title and keywords, references were evaluated for relevance. Of those, 195 articles were identified. On initial reading of the abstracts of these 195 studies, 60 articles were identified as potentially having data for the critical review and meta-analysis. Based on reading these 60 articles and agreement by both of us, 17 studies were selected as providing data relevant to the study topic.17-33 The remaining 43 articles were excluded more frequently because they provided data only on the incidence of the first tumor or recurrent tumors, but not on the risk of a subsequent tumor. The 17 selected studies were 6 prospective cohort studies,17-20,21,25,26 1 retrospective cohort study, and 10 retrospective record-linkage studies.20,23,24,27-33

Table 1 provides a summary of the characteristics of the patient populations in these 17 studies,17-33 including study type, number of patients enrolled, average duration of follow-up, and number of tumors that met the criteria for inclusion. The studies varied considerably in characteristics of the patient populations and methods used to assess risk; the study type distribution is shown in Table 1. We can make only limited comparisons, as the studies quantified the risk of an NMSC following an NMSC.

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Number of Patients</th>
<th>Average Duration of Follow-Up</th>
<th>Number of Tumors</th>
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<tr>
<td>Cohort</td>
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</tr>
<tr>
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<td>2000</td>
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<tr>
<td>Cohort</td>
<td>4000</td>
<td>20 years</td>
<td>2500</td>
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</table>

The risk factors for the development of a first SCC or BCC and their respective incidence have been quantified in numerous populations. In the United States, the largest study, completed in 1978, estimates an age-adjusted incidence for SCC of 65 per 100000 person-years for males and 24 per 100000 person-years for females.7 For BCC, the age-adjusted incidences are of 247 and 150 per 100000 person-years for males and females, respectively.7 Risk factors for a first NMSC include cumulative and childhood sun exposure, geographic location, older age, male sex, fair skin (skin that tans poorly and burns easily after exposure to the sun), freckling, Celtic ancestry, red or blond hair, and blue eyes.8-14 In addition, certain genodermatoses increase the risk of both tumor types (xeroderma pigmentosum) and others of either SCC (epidermodyplasia verruciformis) or BCC (nevoid BCC syndrome). Environmental exposures and some medical conditions and therapies also increase the risk of an NMSC, particularly an SCC. These include ionizing radiation, chronic ulceration and inflammation, scarring dermatosis, immunosuppressed states, human papillomavirus infection, and chemical carcinogens such as coal-tar products, psoralens, and UV-A, arsenic, and cigarette smoking.15

The risk and risk factors associated with the development of subsequent NMSC in persons who have developed a first NMSC are less well defined. Establishing this risk would help in the design of rational follow-up strategies. Most published studies of risk of a second NMSC consider BCC and SCC together. Yet the risk and risk factors of a subsequent tumor may differ for SCC and BCC. The difference in the clinical significance of these tumors makes separate quantification of the risk of a subsequent tumor seem appropriate. The benefit of early detection of a BCC, presumably at a smaller size, is to reduce scarring with a concomitant better cosmetic outcome, and potentially to reduce the cost of therapy. For an SCC, the additional, but small possibility, of avoiding mortality makes early detection of even greater benefit. Unfortunately, the rate of growth of either type of NMSC after it could be first clinically detected is not known.

To attempt to better define the risk and risk factors of a new NMSC after a first NMSC, we performed a meta-analysis of the published literature that separately quantified the risk of an SCC following an SCC and that of a BCC following a BCC.

The results of these studies allow a comparison of the relative risks of developing a first SCC or BCC, and of a subsequent SCC or BCC, after having had one of the same tumor type. In the case of the risk of an SCC following an SCC, the data were sufficient to perform a meta-analysis. For SCC following BCC, and BCC following SCC, there was insufficient data to perform a meta-analysis. The data indicate that the risk of developing a subsequent SCC is approximately the same as the risk of developing a first SCC, provided that the patient has already had one or more SCC. For BCC, the risk of developing a subsequent BCC is lower than the risk of developing a first BCC, provided that the patient has already had one or more BCC. However, the risk of developing a subsequent SCC is significantly higher than the risk of developing a first SCC, provided that the patient has already had one or more BCC.
ration of follow-up, location, histological type of index tumor and subsequent tumor (SCC to SCC, BCC to BCC, NMSC to NMSC, Bowen disease to Bowen disease, or the risk of one type of NMSC following another type), cumulative risk at 3 years, and incidence rate. The cumulative 3-year risk is defined as the proportion of patients developing a subsequent tumor within 3 years, based on life-table analysis. The incidence rate is the number of patients with a second tumor divided by the number of person-years of follow-up at risk. From these 17 studies, 26 analyses of the risk of a subsequent skin tumor among persons with a prior NMSC were evaluable (ie, SCC to SCC, BCC to BCC, BCC to SCC, NMSC to NMSC, SCC to SCC, NMSC to SCC, NMSC to BCC, SCC to NMSC, Bowen disease to Bowen disease, and Bowen disease to SCC).

### SCC TO SCC

We identified 5 studies that assessed the risk of developing a subsequent SCC after a first one (Table 2). The cumulative 3-year risk of a new SCC is less than 25% in all 5 studies, ranging from 9% to 23% (mean risk, 18%). The lowest cumulative 3-year risk is from the incidence study by Chuang et al,28 Rochester, Minn. This study uses the first occurrence of SCC as the index SCC and excludes Bowen disease (SCC in situ) and recurrences. The highest cumulative risk of 23% at 3 years is from 2 studies: an incidence study by Chuang et al27 in Hawaii using the same criteria as in the other study, and a study by Frankel et al19 from 2 Mohs practices in the United States. Thirteen percent of the patients included in the study by Frankel et al19 had had more than one previous SCC and Bowen disease included as index tumors. In all 5 studies, the index SCC was not always the first NMSC. Only the study by Frankel et al19 discussed the risk factors associated with an increased risk of a subsequent SCC. No relation of age and sex to risk was noted. The higher the number of SCCs prior to the index SCC, the greater the risk of another SCC. Within 5 years, persons with 2 or more previous SCCs had 2.5 times the risk of developing another SCC compared with patients with only 1 prior SCC.

### Table 1. Characteristics of the 17 Studies Identified*

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Study Type</th>
<th>No. of Patients Enrolled</th>
<th>Mean Follow-up, y</th>
<th>Location</th>
<th>Index Tumor to Next</th>
<th>3-Year Risk, %†</th>
<th>Incidence Rate per 100 000 Person-years‡</th>
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<td>1973</td>
<td>6.5</td>
<td></td>
<td>Sweden</td>
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</table>

*SCC indicates squamous cell carcinoma; BCC, basal cell carcinoma; NMSC, nonmelanoma skin cancer; and Bowen disease, SCC in situ.
†Proportion of patients developing a subsequent skin cancer (ie, SCC, BCC, NMSC, or Bowen disease) within 3 years, based on a life-table analysis.
‡Calculated as the number of patients with a subsequent skin cancer divided by the number of person-years of follow-up at risk.
The retrospective, population-based study from Rochester, Minn, by Chute et al assessed the risk of developing a Bowen disease (SCC in situ) after Bowen disease. The cumulative risk was 12.7% after an average 4.3 years of follow-up, a crude incidence rate of 2951 per 100 000 person-years. The retrospective study through the Cancer Registry of Denmark by Jaeger et al, assessed the risk of developing an SCC after having had Bowen disease. The crude incidence rate of SCC was 1284 per 100 000 person-years, with a cumulative risk at 3 years of 4%. These 2 studies suggest that the risk of Bowen disease or SCC after Bowen disease is lower than the risk of an SCC after an SCC.24,30

BCC TO BCC

We identified 7 studies17,20-22,25,26,29 that assessed the risk of developing a subsequent BCC after the first one (Table 3). The 3-year cumulative risk varies between the studies, ranging from 33% to 70% (mean risk, 44%). The highest rates of 60% and 70% are from the 2 studies by Epstein26 and Tangrea et al,25 respectively, which included a large proportion of patients with at least 2 prior BCCs. In Epstein’s study, 40% of the patients enrolled had 2 or more previous BCCs, as did all the patients in the study by Tangrea et al (62.6% had had ≥ 3 prior BCCs). Recurrences were excluded in all 7 studies. There were conflicting results concerning risk factors associated with a higher risk of a subsequent BCC. Epstein26 and Robinson21 both found no relation between risk and age and sex. Tangrea et al25 noted higher risk for older age, male sex, more actinic skin damage, and more previous NMSCs in the prior 5 years before study enrollment. Epstein26 also noted a relation of risk and the number of prior BCCs: 5% risk at 1 year after the first BCC, 21% after 2 BCCs, 39% after 3 to 7 BCCs, and 100% after 8 or more BCCs.

BCC TO SCC

Four studies, record linkage–based, assessed the risk of developing an SCC after having had a BCC (Table 4). The cumulative 3-year risk is ranging from 1% to 19%, with a mean of 6%, but a median of only 2%. Only the retrospective Arizona Cancer Registry–based study by Schreiber et al20 estimated a cumulative risk exceeding 5% at 3 years.
We identified 4 studies\textsuperscript{17,18,20,23} that assessed the risk of developing an NMSC of any type after the first NMSC (Table 5). The 3-year cumulative risk ranged from 35\% to 60\% (mean risk, 47\%). In an Australian study by Czarnecki et al,\textsuperscript{18} an increased risk of developing a subsequent NMSC was not associated with age or sex, but there was a strong association between risk and the number of previous NMSCs. For patients with fewer than 3 previous NMSCs, the 3-year cumulative risk was 38\%. For patients with 3 to 9 previous NMSCs, the risk was 93\%. Within 2 years, all patients with more than 9 prior NMSCs developed a new NMSC. All 4 studies excluded recurrences as subsequent NMSCs.

Our critical review and meta-analysis of the literature clearly demonstrate that the risk of an SCC after an SCC is more likely to be far lower (18\% at 3 years) than the risk of a BCC after a BCC (44\% at 3 years). Also, the risk of an SCC after a BCC (6\% at 3 years) seems to be substantially lower than the risk of an SCC in the following 3 years after an SCC. Patients diagnosed with a BCC are about 8 times more likely to develop another BCC than a first SCC. In contrast, the mean 3-year cumulative risk of developing a BCC for patients with a history of an SCC is remarkably similar to the risk of those with a history of BCC (43\% vs 44\%). This last estimate is based on a single retrospective cancer registry–based study and may be less stable than estimates based on analysis of multiple studies.\textsuperscript{20} Because BCC is the predominant type of NMSC (>85\% of all NMSCs), it is not surprising that the available analyses of the risk of a second NMSC after an NMSC of either type provide results similar to those observed for BCC.\textsuperscript{17-20,23}

Few studies systematically assessed risk factors for the development of a subsequent NMSC. The number of previous skin tumors seems to be the only consistent and strongly associated risk factor for an increased risk for the development of subsequent skin cancers. The 3-year cumulative risk is about doubled in patients with 3 or more prior NMSCs.\textsuperscript{17-19,23,20} Although increasing age and male sex are strong predictors of SCC and BCC risk in the general population, they do not seem to be strong risk factors for NMSC after an NMSC. Only 2 studies noted older age and male sex as modest risk factors.\textsuperscript{17,23} Perhaps, with enough accumulated carcinogenic exposure and passage of time for a first NMSC to occur, all the requirements for being at equally high risk for a subsequent NMSC are met, irrespective of a patient’s age and sex.

We used incidence data for the nearest geographical location and adjusted for age and sex to calculate the incidence of a specific tumor type in the general population. We then compared this incidence to the incidence of a subsequent tumor of the same histological type, to provide a rough estimate of the incidence rate ratio of

\begin{table}
\centering
\caption{Cumulative 3-Year Risk and Incidence Rate per 100 000 Person-years of a Squamous Cell Carcinoma Developing After an Index Basal Cell Carcinoma (BCC)}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Source, y & No. of Patients Enrolled & Mean Follow-up, y & 3-Year Risk, %* & Incidence Rate per 100 000 Person-years & More Than 1 Previous BCC, %\textsuperscript{†} &  \\
\hline
Schreiber et al,\textsuperscript{21} 1990 & 4670 & 2.8 & 19 & 6333 & NS &  \\
Frisch et al,\textsuperscript{21,31} 1994 & 37674 & 5.1 & 1 & 333 & 0 &  \\
Levi et al,\textsuperscript{26} 1998 & 11878 & 6.4 & 2 & 667 & NS &  \\
Lindelof et al,\textsuperscript{23,33} 1991 & 1973 & 6.5 & 1 & 333 & NS &  \\
\hline
\end{tabular}

*Proportion of patients developing a subsequent skin cancer (ie, squamous cell carcinoma, BCC, nonmelanoma skin cancer, or Bowen disease [squamous cell carcinoma in situ]) within 3 years, based on a life-table analysis.
†Calculated as the number of patients with a subsequent skin cancer divided by the number of person-years of follow-up at risk.
§The percentage of patients with more than 1 prior BCC included in this study. NS indicates not studied or not stated.
\end{table}

\begin{table}
\centering
\caption{Cumulative 3-Year Risk and Incidence Rate per 100 000 Person-years of a Nonmelanoma Skin Cancer (NMSC) Developing After an Index NMSC*}
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Source & No. of Patients Enrolled & Mean Follow-up, y & 3-Year Risk, % & Incidence Rate per 100 000 Person-years & More Than 1 Previous NMSC, %§ & Bowen Disease¶ & Recurrences†  \\
\hline
Karagas et al,\textsuperscript{17} 1992 & 1805 & 4.1 & 35 & 11667 & 53 & NS & Excluded  \\
Czarnecki et al,\textsuperscript{20} 1994 & 481 & 2.7 & 60 & 20000 & 33# & Excluded &  \\
Schreiber et al,\textsuperscript{23,24} 1990 & 6310 & 2.8 & 50 & 16667 & NS & NS & Excluded  \\
Bergstresser et al,\textsuperscript{26} 1975 & 558 & 1.5 & 44 & 14667 & NS & NS & Included††  \\
\hline
\end{tabular}

*NS indicates not studied or not stated.
†Proportion of patients developing a subsequent skin cancer (ie, squamous cell carcinoma, basal cell carcinoma, NMSC, or Bowen disease [squamous cell carcinoma in situ]) within 3 years, based on a life-table analysis.
‡Calculated as the number of patients with a subsequent skin cancer divided by the number of person-years of follow-up at risk.
§The percentage of patients with more than 1 prior NMSC of any type included in this study.
¶Bowen disease (squamous cell carcinoma in situ) included or excluded as subsequent tumor.
††Recurrences of the index NMSC included or excluded as subsequent tumor.
#Thirty-three percent of the patients had had 3 or more previous NMSCs.
**New NMSCs occurring within 3 months of the index NMSC are also excluded.
††New NMSCs and recurrences occurring within 2 months of the index NMSC are excluded.
\end{table}
a subsequent NMSC compared with the incidence in the general population. The incidence rate ratio for an SCC after an SCC compared with the incidence of SCC in the general population was 17 to 39. Population incidence data were ascertained in the same way as second tumors for 2 prospective incidence studies from areas with very different UV exposure levels, Hawaii and Rochester, Minn.27,28 These studies are the least likely to be subjected to detection and reporting biases. These 2 studies which consider any first SCC as the index SCC, estimate an incidence of SCC after an SCC about 20-fold higher than for a person of the same age and sex in the general population, a finding consistent with our calculations. Potential biases, including greater ascertainment bias in those with a prior tumor and underreporting in the general population, might lead to overestimates of the true increase in incidence for persons with a prior tumor compared with the general population. Even considering these biases, it seems likely that the incidence rate ratio of developing another SCC within 3 years after a first SCC compared with a person without a history of an SCC is at least 10.

In the 3 years following a BCC, we calculated a similar increase in incidence with incidence rate ratios of 15 to 38 for a subsequent BCC compared with the incidence of a first BCC in a comparable population. Although surveillance and detection biases in these studies and potential underestimates in population incidence also probably lead to overestimating the true increase in incidence, it also seems likely that in the 3 years after a BCC, the incidence rate ratio of a new BCC compared with a first BCC among persons of the same age and sex in the corresponding general population, is at least 10.

Only 2 studies quantified differences in the risk of a subsequent SCC in the first 3 years and subsequent years after the occurrence of an SCC. These studies provide contradicting results, one estimating a higher risk after the third year, and the other a decreased risk of a subsequent SCC after the third year.17,18 The 3 studies that provide data to assess risk of a new BCC within the initial 3 years of an index BCC and that risk after those 3 years, estimate the risk of a new BCC more than 3 years after an index BCC to be about half that risk during the first 3 years.17,21,22

Since SCC and BCC differ in incidence and clinical consequences, benefits from early detection will also differ. We believe optimal follow-up policies for patients with skin cancers should consider whether the prior tumor was an SCC or BCC and the number of prior tumors. Early detection of a smaller BCC may reduce scarring and disfigurement. Since more than 80% of BCCs are on the face and neck, sites more easily monitored by the patient or family, we believe that patient education and reevaluation seems particularly justified. Since the risk of developing a new subsequent BCC (mean risk, 44% at 3 years), for most patients, a once a year complete skin examination seems at least sufficient for detecting BCCs not yet noticed by the patient, particularly for those on covered parts of the body. Since the incidence of subsequent BCC does increase rapidly with the number of previous BCCs, patients with a history of multiple BCCs might merit longer or more frequent follow-ups. Because the risk of a subsequent BCC drops 3 years after an index tumor, the need for continued surveillance of patients with a BCC who have remained tumor free after 3 years is probably limited. Since the 3-year risk of developing an SCC after a BCC is low (about 6% at 3 years), following a patient with a history of BCC for detection of an SCC is probably not justified.

Because of greater clinical importance of an SCC and these patients’ high risk of both subsequent SCC and BCC, annual follow-up for at least 3 years as well as education and self-examination seems particularly justified. Since the risk of subsequent SCC does increase with number of previous SCCs, patients with multiple previous SCCs might merit more frequent examination. More data on the risk of SCC longer than 3 years after a prior SCC would help define the most appropriate length of follow-up after an SCC.

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**Editor’s Comment**

Patients with BCCs or SCCs commonly ask what their chances are for developing another one. Marcil and Stern provide useful data to help answer this question. The risk of developing a second SCC within 3 years of having one is about 18% and the risk of developing a second BCC within 3 years of having a BCC (or SCC) is about 44%. The risk of developing an SCC in patients with a prior BCC is low (6% within 3 years). Please see Trisha Greenhalgh’s “How to Read a Paper: Papers That Summarise Other Papers (Systematic Reviews and Meta-analyses)” in the British Medical Journal (1997;31:672-675 [Also available at: http://www.bmj.com/cgi/content/full/315/7109/672. Accessibility verified: October 17, 2000]) for a brief overview of meta-analysis.

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