

Nonmelanoma Skin Cancer and Risk for Subsequent Malignancy

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- Background** Individuals with a personal history of nonmelanoma skin cancer (NMSC) may have an increased risk of subsequent noncutaneous malignancies. To test this hypothesis, we carried out a community-based, prospective cohort study.
- Methods** In the CLUE (Give Us a Clue to Cancer and Heart Disease) II cohort, which was established in Washington County, MD, in 1989, the risk of new malignancies was compared among individuals with ($n = 769$) and without ($n = 18405$) a personal history of NMSC (total $n = 19174$) during a 16-year follow-up period. Pathologically confirmed NMSC (and other malignancies) were ascertained from the Washington County Cancer Registry. Cox regression analysis with time-dependent covariates was used to determine the hazard ratios (presented as multivariable-adjusted relative risks [RRs]) and 95% confidence intervals (CIs) of second primary malignancies associated with a previously confirmed NMSC diagnosis. All statistical tests were two-sided.
- Results** The crude incidence rate (per 10000 person-years) of subsequent cancers other than NMSC among participants with a positive personal history of NMSC was 293.5 and with a negative history was 77.8. Compared with persons with no personal history of NMSC, those with such a history had a statistically significantly increased risk of being diagnosed with a subsequent cancer other than NMSC (RR = 1.99, 95% CI = 1.70 to 2.33) after adjusting for age, sex, body mass index, smoking status, and educational level. The association was observed for both basal cell carcinoma (multivariable-adjusted RR = 2.03, 95% CI = 1.70 to 2.42) and squamous cell carcinoma (multivariable-adjusted RR = 1.97, 95% CI = 1.50 to 2.59) of the skin. NMSC was a statistically significantly stronger cancer risk factor in younger age groups than in older age groups (P for interaction = .022).
- Conclusions** This community-based, prospective cohort study provides evidence for an association between an NMSC diagnosis and an increased risk of subsequent cancer, even after adjusting for individual-level risk factors.

J Natl Cancer Inst 2008;100:1215–1222

With more than one million patients diagnosed each year in the United States, basal cell carcinoma and squamous cell carcinoma, in combination referred to as nonmelanoma skin cancer (NMSC), are by far the most common form of human malignancy (1). NMSC is usually not life threatening (2), but it is a major source of morbidity and causes more than 1000 deaths annually in the United States (1). Despite the low mortality, because so many patients are diagnosed with NMSC each year, the economic costs from NMSC are enormous (3).

The major environmental cause of NMSC is exposure to solar ultraviolet radiation (2). Individual risk for NMSC appears to be determined largely by cumulative exposure to solar radiation, in combination with individual susceptibility (2). Susceptibility appears to be determined largely by factors such as skin types with a propensity for sunburn (2,4). A personal history of NMSC is predictive of diagnoses of subsequent new primary NMSC or recurrent NMSC (5). A history of NMSC is also a risk factor for malignant melanoma (6–15), likely because of the shared risk factor of exposure to ultraviolet radiation (4).

The risk of other malignancies in persons who have had an NMSC diagnosis may not be limited to skin cancers. Results of

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See "Notes" following "References."

DOI: 10.1093/jnci/djn260

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CONTEXT AND CAVEATS

Prior knowledge

Prior studies have suggested that people with a personal history of nonmelanoma skin cancer (NMSC) have an increased risk of subsequent noncutaneous malignancies. However, the study designs made clear conclusions difficult.

Study design

Community-based prospective cohort study of the association of a personal history of NMSC with subsequent cancers, compared with no such history. Follow-up was 16 years.

Contribution

The crude incidence rate of subsequent cancers other than NMSC among participants with a positive personal history of NMSC was 293.5 per 10000 person-years and with a negative history was 77.8 per 10000 person-years. Persons with a personal history of NMSC had a statistically significantly higher adjusted risk of being diagnosed with a subsequent cancer other than NMSC than those without such a history. The association was observed for both basal and squamous cell carcinomas, and it was robust even after adjusting for potential confounding variables and accounting for sun exposure.

Implications

NMSC appears to be a clinically important and substantial risk marker for subsequent malignancies and may be a marker of a general high-cancer risk phenotype. Additional research on this association is thus warranted.

Limitations

Persons with a personal history of NMSC may have been more likely than those without such history to receive regular medical care that would enhance the likelihood of cancer detection. The cohort studied was established in a single county and so may not be representative of the total population. Adjustments for skin type and sunburn history were imputed for a large proportion of missing data. Uncertainty in the imputation could introduce uncertainty into the results.

From the Editors

various studies (11–14,16–21) support the notion that individuals with a previous diagnosis of NMSC also have an increased risk of developing subsequent noncutaneous primary malignancies. For instance, in studies (11,16) that used data from Denmark's cancer registry, a personal history of squamous cell carcinoma of the skin was associated with a 15%–30% higher risk for primary noncutaneous malignancies than that of the general population. In other studies, a personal history of NMSC was associated with increased overall cancer mortality (2) and poorer prognosis for surviving other cancer diagnoses (23).

Most previous reports, however, have been based on cancer registry data without adjustment for potential confounding lifestyle factors (eg, cigarette smoking and socioeconomic status) (11,13,14,16,18,19,21), were studies that were restricted to those with a history of NMSC (17), were cross-sectional studies (20), or were studies of cancer mortality (2). We therefore investigated whether a previous NMSC diagnosis was associated with an increased incidence of subsequent malignancies in a community-based prospective cohort study with substantial duration of follow-up and with individual-level data on potential confounding variables.

Subjects and Methods

Study Population

The study was approved by the Institutional Review Boards of the Johns Hopkins University Bloomberg School of Public Health and the Medical University of South Carolina. This study was carried out in the CLUE (Give us a Clue to Cancer and Heart Disease) II cohort, which was established when baseline data were collected from May 1, 1989, through November 30, 1989, from volunteers, most of whom were residents of Washington County, MD. During the baseline data collection, the participants completed a questionnaire that included information on cigarette smoking, height, weight, years of school completed, and other demographic information. Consent was indicated by completion and return of the questionnaire; there was no signed informed consent. For this report, the follow up extended until December 31, 2005, for a total of 16 years.

The entire cohort consisted of 32894 participants. From the total cohort, the analytic cohort for the current study was composed of 19174 participants who were residents of Washington County, who were not missing data on key variables of interest, and who at study baseline in 1989 were aged 25 years or older and had no personal history of cancer (except NMSC). To construct the analytical cohort, we excluded from the original cohort those who were non-Washington county residents ($n = 7818$), were younger than 25 years of age at study baseline in 1989 ($n = 3805$), had a personal history of cancer other than NMSC at study baseline ($n = 1706$), or were missing data on key variables such as age or sex ($n = 38$). As described in the "Statistical Analysis" section below, the fact that a self-reported diagnosis of NMSC was a censoring event necessitated the exclusion of those who had self-reported a personal history of NMSC by study baseline in medical records or in the baseline questionnaire but for whom we had no pathologic confirmation or subsequent evidence of pathologically confirmed NMSC ($n = 350$). Because the study question was to examine NMSC as a risk factor for subsequent cancer other than NMSC, we further excluded two NMSC patients whose diagnosis was ascertained from their death certificate and one patient for whom the recorded date of diagnosis of NMSC and with a cancer other than NMSC was the exact same day.

The independent variable in this study was a confirmed NMSC diagnosis. Of the 769 individuals with a confirmed NMSC diagnosis, 513 (67%) had a diagnosis of basal cell carcinoma, 165 (21%) had a diagnosis of squamous cell carcinoma, 60 (8%) had a diagnosis of both basal cell carcinoma and squamous cell carcinoma, and 31 (4%) had an unknown subtype. The exposure-positive group was composed of those with a pathologically confirmed diagnosis of NMSC that occurred before the development of another malignancy. The Washington County Cancer Registry, in operation since the 1960s, was used to ascertain data on patients with confirmed NMSC that had occurred by baseline in 1989 and during the follow-up period.

The study outcome was the occurrence of a first confirmed primary cancer other than NMSC diagnosed from January 1, 1990, through December 31, 2005. Cancer diagnoses occurring in the CLUE II cohort were ascertained through linkage with the Washington County Cancer Registry, which since 1992 has been

supplemented by additional linkage to the Maryland Cancer Registry. However, of these two registries, only the Washington County Cancer Registry includes diagnoses of NMSC. The International Classification of Disease (ICD) 8th, 9th, and 10th versions were used to code cancer: ICD8 for cancers from 1989 to 1991, ICD9 for those from 1992 to 2000, and ICD10 for those from 2001 through 2005. A summary of the number of persons, person-years of follow-up, and number of incidents cancers other than NMSC diagnosed during the follow-up period among those with an without an NMSC diagnosis is provided in Table 1.

Statistical Analysis

The baseline characteristics of participants according to NMSC status (confirmed NMSC vs no NMSC) were compared by use of Student *t* test for continuous variables and Pearson χ^2 test for categorical variables. No statistical power calculations were performed because the main results of the study were highly statistically significant. We analyzed the total cohort without stratification by sex.

Cox regression analysis with time-dependent covariates was used to determine the hazard ratios (henceforth referred to as relative risks [RRs]) and 95% confidence intervals (CIs) of second primary malignancies associated with a previously confirmed NMSC diagnosis compared with no personal history of NMSC. For our study question, the independent variable was the presence or absence of a pathologically confirmed NMSC diagnosis among individuals with no previous cancer history; this variable was studied in relation to the risk of cancers other than NMSC. The follow-up period for all analyses was through December 31, 2005, with person-time of follow up counted until the first diagnosis of a subsequent cancer other than NMSC or until the end of follow-up. We checked the proportional hazards assumption by use of the Schoenfeld residuals, plotting them against time and using appropriate statistical tests (29).

NMSC status could change during the follow-up period; that is, a participant with no history of NMSC at baseline in 1989 could

be diagnosed with confirmed NMSC during the follow-up period. Among those with no previous personal history of cancers other than NMSC, a total of 219 individuals were classified as having confirmed NMSC on entry into the study and another 550 were added to the confirmed NMSC category during the follow-up period. Cox regression analysis with time-dependent covariates was used to determine relative risks and 95% confidence intervals of second primary malignancies associated with a previous NMSC diagnosis. For individuals with no personal history of cancer at baseline who went on to be diagnosed with NMSC as a first-time cancer diagnosis during follow up, the follow-up period before the NMSC diagnosis contributed person-time to the exposure-negative group and the follow-up period after the NMSC diagnosis contributed person-time to the exposure-positive category. The follow-up period of individuals with no previous history of NMSC or other cancer at baseline who went on to self-report an NMSC diagnosis for which we had no pathologic confirmation was censored at the date of the self-reported NMSC diagnosis. Individuals who were censored on the basis of a self-reported NMSC diagnosis re-entered the follow up to contribute person-time to the NMSC group if they received a subsequent confirmed NMSC diagnosis.

Estimates of the relative risk and 95% confidence interval of developing subsequent cancer other than NMSC in individuals with or without NMSC were derived first from a model that adjusted only for age (continuous) at study baseline and then from a model that also included additional adjustments for the following characteristics measured at baseline: sex, body mass index (continuous), cigarette smoking (never, former, or current), and years of schooling (<12 years, 12 years, or >12 years).

On a follow-up questionnaire that was administered in 2003, approximately 40% of the analytic cohort (n = 8093) provided information on their skin type and sunburn history. A complete case analysis assumes the data to be missing completely at

Table 1. Summary data for participants with and without a personal history of NMSC: CLUE (Give us a Clue to Cancer and Heart Disease) II Cohort, Washington County, MD (1989–2005)*

Characteristic	No. of individuals	Total person-years of follow-up	No. of incident cancer cases	Crude incidence rate†
Diagnosis				
No NMSC	18 405	277 102	2156	77.8
NMSC	769	6166	181	293.5
Age group				
25–44 y				
No NMSC	7978	127 097	345	27.1
NMSC	35	336	3	89.3
45–59 y				
No NMSC	5411	80 688	738	91.5
NMSC	161	1325	26	196.2
≥60 y				
No NMSC	5016	69 317	1073	154.8
NMSC	573	4505	152	337.4
Histologic type of NMSC				
BCC‡	573	4789	139	290.2
SCC‡	225	1653	55	332.7

* NMSC = nonmelanoma skin cancer; BCC = basal cell carcinoma; SCC = squamous cell carcinoma.

† Data are expressed as the crude incidence rate of all cancers other than NMSC per 10 000 person-years.

‡ Each group included 60 patients with diagnoses of both BCC and SCC.

random, which is extremely unlikely in practice; however, ignoring the missing data entirely can create severe biases (24). Therefore, we used multiple imputations to account for the missing data in skin type and sunburn history (25–27). This approach assumes that the data are missing at random; that is, that the pattern of missing data depends only on observed data, a much less stringent assumption than missing completely at random. Instead of ignoring missing data, inference is made by averaging across it by use of distributions for the values of the missing data that are based on the observed data. The missing data were completed by sampling from this distribution, and 10 complete data sets were constructed. The reported results were based on the parameter estimates and standard errors derived from the individual completed data sets, accounting for the variability of the estimates within a data set and between all data sets. The actual imputation

was carried out by use of the tree-based approach described by Dai et al (8).

Because an increased risk of melanoma among persons who have a previous NMSC diagnosis is well established and is thought to be attributed predominantly to the common risk factor of sun exposure, we also evaluated the association between NMSC and all noncutaneous malignancies (ie, with malignant melanoma excluded) as the outcome. This approach allowed us to determine the extent to which malignant melanoma was contributing to the results and to infer the extent to which sun exposure could be influencing the overall cancer risks. We also assessed the association between NMSC and risk of developing selected site-specific cancers that were diagnosed in more than 10 patients in the NMSC group. Furthermore, analyses were performed to assess whether the overall association observed with NMSC held true for both squamous cell carcinoma and basal cell carcinoma. We included all 60 patients who were diagnosed with both basal cell carcinoma and squamous cell carcinoma in both the basal cell carcinoma and squamous cell carcinoma analyses. To more carefully account for the possible confounding or modifying effects of age, we also conducted an age-stratified analysis. To quantify the interaction, we centered the age variable by subtracting 50 from each subject's observed age (cohort mean age = 49.7 years; median age = 49 years) and added an interaction term for this centered age variable with the NMSC status in the model. The resulting parameter estimate obtained for NMSC status quantified the magnitude of the association with second primary malignancies for people 50 years of age.

Data were analyzed by use of SAS release 8.2 (SAS Institute, Cary, NC) and R version 2.6.0 (the R Project for Statistical Computing, <http://www.r-project.org/>). All statistical tests were two-sided.

Results

The crude incidence rate (per 10 000 person-years) among participants with a positive personal history of NMSC was 293.5 and among those with a negative history was 77.8 (Table 1). The baseline characteristics of the study participants according to NMSC status are shown in Table 2. Compared with those with no history of NMSC, participants with a personal history of NMSC were more likely to be older, male, and former cigarette smokers and to have fewer years of schooling. As anticipated, among participants in the subgroup who responded to the 2003 follow-up questionnaire, the NMSC group also was more likely than the NMSC-free group to have a skin type that was more likely to burn or blister than to tan when exposed to the sun and more likely to have had more than 10 blistering sunburns.

After adjusting for age, the risk of developing subsequent cancer other than NMSC was statistically significantly associated with a personal history of confirmed NMSC (RR = 2.04, 95% CI = 1.75 to 2.39) (Table 3). Additional adjustments for sex, body mass index, cigarette smoking, and years of education barely altered this association (RR = 1.99, 95% CI = 1.70 to 2.33) (Table 3). The association remained robust after further adjusting for sunburn history and skin type (RR = 1.98, 95% CI = 1.69 to 2.31) (Table 3).

Table 2. Baseline characteristics according to a personal history of NMSC by the end of follow-up: CLUE (Give us a Clue to Cancer and Heart Disease) II Cohort, Washington County, MD (1989–2005)*

Characteristic	NMSC (n = 769)	No NMSC (n = 18 405)	P value†
Age group, %			
25–34 y	0.8	19.7	
35–44 y	3.8	23.7	
45–54 y	12.0	20.4	
55–64 y	22.4	18.5	
65–74 y	33.7	13.4	
≥75 y	27.4	4.4	<.001
Mean age, y (SD)‡	66.8 (11.7)	49.0 (14.6)	<.001
Mean BMI, kg/m ² (SD)	26.2 (4.3)	26.4 (4.9)	.19
Sex, %			
Female	46.0	57.8	
Male	54.0	42.2	<.001
Cigarette smoking, %			
Never	48.6	52.0	
Former	38.4	28.5	
Current	13.0	19.5	<.001
Education, %			
<12 y	29.3	19.1	
12 y	41.1	45.4	
>12 y	29.6	34.7	<.001
Skin type, %§			
Blistering sunburn	14.6	10.7	
Sunburn without blisters	38.3	28.7	
Mild sunburn turns tan	33.8	44.7	
Tan without sunburn	10.4	13.3	
No change in skin color	2.9	2.5	<.001
No. lifetime sunburns, %§			
None	20.9	26.7	
1–2	34.7	34.8	
3–4	19.9	21.0	
5–9	10.0	10.1	
10–19	8.7	4.6	
≥20	5.8	2.9	<.001

* NMSC = nonmelanoma skin cancer; BMI = body mass index.

† P value compared with those with no history of NMSC (no NMSC) using t-test for continuous variables and χ^2 tests for categorical variables. All statistical tests were two-sided.

‡ Age in NMSC group is age at diagnosis of NMSC.

§ These characteristics were measured in 2003, not in 1989. The number of participants for the skin type and sunburn variables analyzed was 8093.

In age-stratified analyses adjusted for sex, smoking, education, and body mass index and with age included as a continuous variable to control for potential residual confounding within age strata, NMSC was associated with a statistically significantly increased risk in all age groups, but the relative risks were strongest in the younger age groups. Specifically, the strongest association was observed in those aged 25–44 years (RR = 2.61, 95% CI = 0.83 to 8.18), with the relative risks gradually decreasing in those aged 45–59 years (RR = 2.21, 95% CI = 1.49 to 3.29) and those aged 60 years or older (RR = 1.89, 95% CI = 1.59 to 2.25). When age was considered as a continuous variable, the interaction between age and NMSC status was statistically significant (P for interaction = .022; Table 3). The interaction also was evident when we checked the proportional hazards assumption by use of the Schoenfeld residuals. In plots of these residuals against time and in statistical tests (9), no departures were evident for the study variables except for a slight departure from this assumption for age and for NMSC status. Including the interaction term in the model alleviated the deviation from proportionality, reinforcing the potential relevance of this interaction. The fitted values from the interaction model were compatible with the observed age-stratified analyses (eg, the modeled RRs were 3.22, 2.72, and 2.30 at age 40, 50, and 60 years, respectively). In separate analyses that were limited to those with confirmed diagnoses of either basal cell carcinoma or squamous cell carcinoma, the increased risk of subsequent cancers other than NMSC was observed in both groups (for basal cell carcinoma, multivariable-adjusted RR = 2.03, 95% CI = 1.70 to 2.42; for squamous cell carcinoma, multivariable-adjusted RR = 1.97, 95% CI = 1.50 to 2.59) (Table 3).

A comparison of the distributions of malignancies by anatomic site revealed no marked differences between participants with a previous personal history of NMSC and those without such a history (Table 4). The most frequently diagnosed cancers in this cohort that we examined were those that occur most commonly in the general population—namely, lung, colorectal, breast, and prostate cancer. The study had limited statistical power to assess the association between NMSC and risk of specific malignancies, but we per-

Table 3. Risk of developing cancers other than NMSC among those with compared to those without a personal history of NMSC: CLUE (Give us a Clue to Cancer and Heart Disease) II Cohort, Washington County, MD (1989–2005)*

NMSC status	Age-adjusted RR (95% CI)	Multivariable-adjusted RR (95% CI)†
No NMSC	1.00 (referent)	1.00 (referent)
NMSC	2.04 (1.75 to 2.39)	1.99 (1.70 to 2.33)
NMSC plus adjustments for skin type and sunburn history	1.96 (1.68 to 2.31)	1.98 (1.69 to 2.31)
Age group		
25–44 y	2.92 (0.93 to 9.12)	2.61 (0.83 to 8.18)
45–59 y	2.25 (1.52 to 3.34)	2.21 (1.49 to 3.29)
≥60 y	2.03 (1.71 to 2.42)	1.89 (1.59 to 2.25)
P for interaction‡	0.019	0.022
Histologic type§		
Basal cell carcinoma	2.07 (1.74 to 2.47)	2.03 (1.70 to 2.42)
Squamous cell carcinoma	2.08 (1.59 to 2.73)	1.97 (1.50 to 2.59)

* RR = relative risk; CI = confidence interval; NMSC = nonmelanoma skin cancer.

† Adjusted for age (continuous), sex, body mass index (continuous), cigarette smoking status (never, former, or current), and years of education in 1989 (<12, 12, or >12 years). RRs and 95% CI were estimated from Cox regression analysis with time-dependent covariates.

‡ The P value for age-by-NMSC interaction was based on age as a continuous variable in the Cox regression analysis with time-dependent covariates. All statistical tests were two-sided.

§ Includes 60 patients with diagnoses of both basal cell carcinoma and squamous cell carcinoma.

formed analyses for cancer sites that had more than 10 patients in the NMSC group—ie, melanoma and cancers of the lung, colon and rectum, breast, and prostate (Table 4). Compared with the multivariable-adjusted association between NMSC and overall risk of cancer (RR = 1.99), the site-specific analyses yielded associations that were much stronger for melanoma (RR = 7.94); roughly comparable for

Table 4. Distributions of diagnoses of cancer at selected sites and the corresponding risks among participants with and without a personal history of NMSC: CLUE (Give us a Clue to Cancer and Heart Disease) II Cohort, Washington County, MD (1989–2005)*

Cancer site	Males, No. (%)		Females, No. (%)		Total, No. (%)		Multivariable-adjusted RR (95% CI)‡
	No NMSC	NMSC	No NMSC	NMSC	No NMSC	NMSC	
Lung	150 (15.6)	15 (13.6)	106 (8.9)	11 (15.5)	256 (11.9)	26 (14.4)	1.92 (1.26 to 2.92)
Colorectal	99 (10.2)	11 (10.0)	132 (11.1)	10 (14.1)	231 (10.7)	21 (11.6)	1.78 (1.12 to 2.82)
Breast	0 (0)	0 (0)	345 (29.0)	16 (22.5)	345 (16.0)	16 (8.8)	1.64 (0.98 to 2.73)
Prostate	356 (36.8)	35 (31.8)	n/a	n/a	356 (16.5)	35 (19.3)	1.27 (0.88 to 1.82)
Melanoma	34 (3.5)	11 (10.0)	36 (3.0)	2 (2.8)	70 (3.2)	13 (7.2)	7.94 (4.11 to 15.35)
Pancreas	23 (2.4)	2 (1.8)	30 (2.5)	4 (5.6)	53 (2.5)	6 (3.3)	NC§
Bladder	59 (6.1)	9 (8.2)	23 (1.9)	1 (1.4)	82 (3.8)	10 (5.5)	NC§
Other	246 (25.4)	27 (25.5)	517 (43.5)	27 (38.0)	763 (35.4)	54 (30.4)	2.02 (1.52 to 2.69)
Total excluding melanoma†	933 (96.5)	99 (90.0)	1153 (97.0)	69 (97.2)	2086 (96.8)	168 (92.8)	1.87 (1.59 to 2.21)

* NMSC = nonmelanoma skin cancer; RR = relative risk; CI = confidence interval; n/a = not applicable; NC = not calculated.

† The results are shown for “Total excluding melanoma” to characterize the overall association between NMSC and risk of non-skin cancers.

‡ Analyses were based on a model that was adjusted for age (continuous), sex, body mass index (continuous), cigarette smoking status (never, former, or current), and years of education in 1989 (<12, 12, or >12 years). Analyses for breast and prostate cancer were limited to females and males, respectively.

§ Relative risk was calculated only in instances when more than 10 patients with cancer at this site were in the NMSC group.

lung (RR = 1.92), colorectal (RR = 1.78), and breast (RR = 1.64) cancers; and somewhat weaker for prostate cancer (RR = 1.27) (Table 4). The association between confirmed NMSC and second primary malignancies was only slightly weaker after excluding malignant melanoma from the outcome (multivariable-adjusted RR = 1.87, 95% CI = 1.59 to 2.21) (Table 4).

Discussion

In this 16-year follow-up of a community-based cohort of 19174 participants, a history of confirmed NMSC was associated with a statistically significantly increased risk (RR = 1.98, 95% CI = 1.69 to 2.31) of developing a subsequent cancer other than NMSC, compared with no history of NMSC, after adjusting for age, sex, body mass index, cigarette smoking, education, skin type, and sunburn history. This association persisted even after excluding malignant melanoma from the secondary cancer outcomes, indicating that the overall risk for subsequent cancers was not simply attributable to increased risk for a cancer outcome that is strongly linked to sun exposure. The association between NMSC and subsequent malignancies was observed among those in the basal cell carcinoma group and the squamous cell carcinoma group.

We observed a statistically significant interaction, whereby the association between NMSC and risk of subsequent malignancy was stronger among those who were diagnosed with NSMC at younger ages. Evidence that this association is stronger among those in younger age groups than those in older age groups has previously been observed for the risk of cancer other than NMSC subsequent to diagnoses of NMSC (21), as well as for squamous cell carcinoma (9,16,18) and basal cell carcinoma (11,14). Our study is, to our knowledge, the first to document a statistically significant interaction and to document this interaction across such a broad age continuum. This pattern of associations, with earlier age of NMSC diagnosis being linked more strongly to the risk of developing subsequent malignancies, is consistent with the pattern that one would expect for a marker of inherited predisposition to cancer.

Our results provide only limited evidence to assess the extent to which a personal history of NMSC differentially affects risk of specific malignancies. Nevertheless, the results revealed some heterogeneity in the association between NMSC and subsequent cancer risk for cancers for which we were able to measure the association. As expected, the risk of melanoma was substantially elevated among those with a personal history of NMSC. The risks of lung, colorectal, and breast cancers were in keeping with the association observed for overall malignancies, although the association for breast cancer was not statistically significant. A weak and not statistically significant association was found for prostate cancer. This pattern of associations indicates that the overall cancer risk associated with an NMSC diagnosis may apply to many, but not necessarily all, malignancies.

Our study distinguished those with a self-reported history of NMSC from those with a confirmed NMSC and those with no history of NMSC. This approach reduced misclassification of NMSC, thereby strengthening the inferences for the association between confirmed NMSC and subsequent cancer risk. The strength of the associations observed and the internal consistency of the study findings collectively indicate that a personal history of

NMSC is associated with a statistically significant and clinically important increased risk of subsequent malignancy. When considered in combination with previous evidence (11,13,14,16,18–22) reported on this topic, the current study, with its advantageous cohort design, strengthens the evidence that this association is valid and substantial. The noteworthy feature of the current study, compared with previous studies on this topic, includes having all of the following features in the same study: 1) being a community-based prospective study with 16 years of follow-up, 2) studying a cohort that was not restricted to individuals with a personal history of NMSC, 3) adjusting for individual-level factors that could potentially confound the association, and 4) establishing a temporal relationship between NMSC and the incidence (as opposed to mortality) of other cancers. Some previous population studies have been restricted to one sex [eg, (15,20)] and were limited to narrow age ranges that only included older adults [eg, (15,20)]. Our study includes both males and females and includes a broad age range.

Compared with the usual complications of studying a single cancer type in relation to risk for subsequent malignancy, the study of NMSC is more straightforward. First, the fact that NMSC is rarely fatal avoids the biases that might be introduced by differential survival from the initial cancer diagnosis. Second, unlike most other malignancies that are treated commonly with chemotherapy and radiation, most NMSCs are surgically excised or locally treated. These circumstances eliminate the challenge of disentangling the potential long-term cancer-causing effects of cancer treatment from host factors that may be associated with cancer risk.

This study has several limitations. If individuals with a personal history of NMSC were more likely than those without such history to receive regular, high-quality medical care that enhanced the likelihood of cancer detection, this difference would represent a potential source of bias that could contribute to the observed associations. The pattern of associations that we observed, if attributable to surveillance bias and not to a true increase in cancer risk, could result if the group with confirmed NMSC had greater access to health care and were evaluated for cancer more frequently than those with no personal history of NMSC. In one study that accounted for this issue (20), the likelihood of having a health care provider differed only slightly between individuals with an NMSC diagnosis (96%) and those with no such diagnosis (95%), but this analysis provides only a crude measure of potential surveillance. The current study was based on a cohort that was established in a single county. Many previous studies have had wider geographic variability, such as the multicenter studies (9,15,20) in the United States and studies [eg, (11,13,14,16,18,21)] that were based on nationwide registries in Scandinavia. An additional limitation is that 11% of the study cohort was lost to follow-up. If the association between NMSC and risk of subsequent malignancy differed between those who were lost to follow-up and those who remained under observation, then this difference would introduce a bias in the reported results. Another potential limitation is that the CLUE II cohort was composed of community volunteers. For the current study, it is difficult to envision that a cohort of volunteers would differ systematically from nonvolunteers with respect to both personal history of a present or future NMSC diagnosis and future risk of other malignancies in a

way that would introduce an important selection bias. Another limitation is that in our adjustments for skin type and sunburn history, we imputed a large proportion of missing data, so the uncertainty in the imputation could have offset the potential influence of these skin cancer risk factors on the association between NMSC and the risk of subsequent malignancies.

If NMSC is truly a marker of a high-cancer risk phenotype regardless of sun exposure history, then investigating the mechanisms underlying the relationship between NMSC and subsequent primary cancers may provide valuable clues to the understanding of intrinsic cancer risk factors. Two potential pathways that may relate NMSC risk to overall cancer risk are DNA repair and inflammatory and/or immune response pathways. Ultraviolet radiation can cause skin cancer by inducing mutations in the cellular DNA of skin cells (30,31). Defective nucleotide excision repair has been strongly linked to NMSC risk (2), and an intrinsic deficient nucleotide excision repair capability may also put cells in all tissues at risk for various environmental carcinogens. Evidence in favor of this hypothesis as a potential explanation would be strengthened if suboptimal nucleotide excision repair could be linked to both NMSC and overall cancer risk. In a previous study (3) that was based in the CLUE II cohort, patients with confirmed NMSC who had genotypes associated with less proficient nucleotide excision repair capability were more susceptible to a subsequent cancer other than NMSC than those with genotypes associated with more proficient nucleotide excision repair capability.

Alternatively, ultraviolet radiation may cause NMSC by inducing immune suppression in the skin, which presumably compromises normal immune surveillance against nascent tumor cells (4). A systemic suboptimal inflammatory and/or immune response has also been hypothesized to be linked to carcinogenesis in general (5), making it plausible to speculate that impaired immunity results in an increased risk for multiple cancers, including NMSC.

In summary, this community-based prospective cohort study with 16 years of follow up provides evidence that NMSC may be a clinically significant and substantial risk marker for subsequent malignancies. This association was robust even after adjusting for potential confounding variables and accounting for sun exposure, the major environmental risk factor for NMSC. By generating evidence from a prospective study of cancer incidence and adjusting for some important potential confounding variables, these results address critical data gaps and bolster the evidence that an NMSC diagnosis may be a marker of a general high cancer-risk phenotype.

The evidence that people with a prior confirmed diagnosis of NMSC have a higher risk of developing subsequent malignancies is now strong enough to justify hypothesis-driven mechanistic research into the association. The apparent absence of any single environmental agent that could explain the multiple cancer risks indicates that intrinsic risk factors may be responsible for this phenomenon. These factors are likely to be genetic and may represent deficiencies of genes in biochemical and physiological pathways responsible for protecting against cellular transformation in all tissues, such as DNA repair or immune responses. Further work is needed to identify the intrinsic factors that can increase general cancer risk across many different tissues because they may provide key insights into the central mechanisms of carcinogenesis in humans.

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Notes

This research was made possible by funding from the National Cancer Institute (NCI) (CA105069). J.C. received support from NCI's Cancer Prevention Fellowship Program. The authors had full responsibility for the design of the study, the collection of the data, the analysis and interpretation of the data, the decision to submit the manuscript for publication, and the writing of the manuscript.

Manuscript received November 27, 2007; revised June 4, 2008; accepted June 30, 2008.