ORIGINAL CONTRIBUTIONS

Incidence of Invasive Cancers following Basal Cell Skin Cancer

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To obtain quantitative information on the risk of invasive cancers following a diagnosis of basal cell carcinoma (BCC) of the skin, patients with incident BCC cases listed in the cancer registries of the Swiss cantons of Vaud and Neuchâtel between 1974 and 1994 were actively followed up through December 31, 1994, for the occurrence of subsequent invasive neoplasms. Among 11,878 persons with incident BCC who were followed for a total of 76,510 person-years at risk, 1,543 metachronous cancers were observed versus 1,397.9 expected, corresponding to a standardized incidence ratio (SIR) of 1.1 (95% confidence interval (CI) 1.0–1.2). However, after exclusion of skin cancers (mostly squamous cell carcinoma and melanoma), 975 second primary cancers were observed versus 1,059 expected (SIR = 0.9, 95% CI 0.8–1.0). Significant excesses were registered for cancer of the lip (SIR = 2.2), for squamous cell skin cancer (SIR = 4.5) and melanoma of the skin (SIR = 2.5), and for non-Hodgkin's lymphoma (SIR = 1.9). The SIRs were also above unity, though not significantly, for cancers of the salivary glands (SIR = 2.8) and the small intestine (SIR = 2.1) and for soft-tissue sarcomas (SIR = 1.7). The SIR for lung cancer was 0.9. The SIRs for salivary gland and skin cancer were appreciably greater below age 70 years. For most sites, particularly for squamous cell cancer and melanoma of the skin, the SIRs remained elevated 5 or more years after BCC diagnosis. The cumulative incidence of squamous cell skin cancer was 13% at 19 years; this stresses the importance of carefully monitoring skin lesions among persons previously diagnosed with BCC. *Am J Epidemiol* 1998;147:722–6.

carcinoma, basal cell; neoplasms; skin neoplasms

Basal cell carcinoma (BCC) is the most common type of skin cancer (1–4). Because of the advanced age at which most cases occur, and because of its favorable prognosis, underregistration is frequent. The cancer registries of the French-speaking Swiss cantons of Vaud and Neuchâtel are among the few cancer registries that have paid specific attention to the issue of skin cancer; in these regions, cutaneous lesions that are surgically resected have traditionally been pathologically examined (1, 5).

We previously described an excess of non-Hodgkin's lymphoma following a diagnosis of BCC (1). However, an excess incidence of other neoplasms

after a diagnosis of BCC has also been reported, including cancers of the lip, salivary glands, larynx, lung, breast, and kidney, in addition to the well-known (but still inadequately quantified) excess of other types of skin cancer (6–9).

To obtain further quantitative information on this question, which has both pathogenic and public health implications, we computed the incidence of second primary cancers among almost 12,000 subjects registered by the Vaud and Neuchâtel cancer registries who were followed for a maximum of 20 years.

MATERIALS AND METHODS

Data for the present report were abstracted from the Vaud and Neuchâtel cancer registry files, which include all incident cases of malignant neoplasms diagnosed in these cantons (10, 11). According to the 1990 Swiss census (12), the populations of these areas number approximately 600,000 and 160,000, respectively. In these cantons, cancer registration systems have been in place since 1972, and population-based incidence data have been available since 1974. The registries are tumor-based, and multiple primary malignancies found in the same person are entered separately. Most cases are registered repeatedly and

from different institutions, which improves the completeness and accuracy of registration. The basic information available from the registries comprises sociodemographic characteristics of the patient (age, sex), the primary site and histologic type of the tumor according to the *International Classification of Diseases,* Ninth Revision (13), and the date of diagnostic confirmation (histologic or clinical diagnosis).

Both passive follow-up (through computer linkage with official mortality data files) and active follow-up (through verification of the vital status of apparently nondeceased cases using registries of current residence) are conducted, and each subsequent item of information concerning an already registered case is used to complete the record of that patient.

After exclusion of synchronous cancers ($n = 61$), the present series comprised a total of 11,878 histologically confirmed BCCs of the skin (13) diagnosed between 1974 and 1994. The age range was 15–100 years (median age, 68 years). These persons were followed up to the end of 1994 for the occurrence of a second primary neoplasm (excluding basal cell skin carcinomas), emigration, or death.

Calculation of expected numbers of cases was based on site-, sex-, age-, and calendar period-specific incidence rates, multiplied by the corresponding number of person-years at risk. The significance of the observed : expected ratios (standardized incidence ratios (SIRs)) and their corresponding 95 percent confidence intervals was based on the Poisson distribution (14). Cumulative incidence was computed using the standard life table approach (15).

RESULTS

Table 1 gives the distribution of the 11,878 cases of BCC by age group, the corresponding incidence rates for the entire calendar period, and the numbers of person-years at risk in separate strata of time since diagnosis, for a total of 76,510 person-years at risk.

Table 2 gives the observed and expected numbers of all neoplasms and of cancers at selected sites. Overall, 1,543 metachronous cancers were observed versus 1,397.9 expected, corresponding to an SIR of 1.1 (95 percent confidence interval (CI) 1.0–1.2). However, after exclusion of skin cancers (mostly squamous cell carcinoma and melanoma), 975 second primary cancers were observed versus 1,059.0 expected (SIR = 0.9, 95 percent CI 0.8–1.0). Significant excesses were registered for cancer of the lip (9 observed, 4.1 expected; SIR = 2.2), for squamous cell skin cancer (501 observed, 111.7 expected; SIR = 4.5) and melanoma of the skin (54 observed, 21.4 expected; SIR = 2.5), for other skin cancers (13 observed, 4.7 expected; SIR = 2.8), and for non-Hodgkin's lymphoma (43 observed, 22.5 expected; SIR = 1.9). The SIRs were also above unity, though not significantly, for cancer of the salivary glands (SIR = 2.8), the small intestine (SIR = 2.1), and the breast (SIR = 1.2) and for soft-tissue sarcoma (SIR = 1.7). The SIR was significantly below unity for cancer of the esophagus (11 observed, 24.4 expected; SIR = 0.5), stomach (26 observed, 56.2 expected; SIR = 0.5), and gallbladder (8 observed, 16.7 expected; SIR = 0.5). The SIR was 0.9 (95 percent CI 0.8–1.1) for cancer of the lung, 0.5

TABLE 1. Incidence of basal cell carcinoma of the skin, by age group and sex: Vaud and Neuchâtel, Switzerland, 1974–1994*

	Person-years at risk for subsequent cancers	No. of cases		Incidence rate (per 100,000)	
		Males	Females	Males	Females
Age group (years)					
<30		44	59	1.2	1.5
30–39		161	223	14.2	19.7
40–49		472	598	47.7	59.3
50–59		1,036	902	126.3	103.0
60–69		1,650	1,348	259.4	174.0
70–79		1,724	1,572	414.4	252.4
≥80		860	1,229	550.2	364.1
Total (all ages)		5,947	5,931	55.6†	43.0†
Time (years) since diagnosis					
<1	11,118				
1–4	32,272				
5–9	21,223				
≥10	11,897				
Total	76,510				

* Denominators in 1980: Vaud, 529,000; Neuchâtel, 158,000. Denominators in 1990: Vaud, 602,000; Neuchâtel, 164,000.
† Age-standardized to the world population.

TABLE 2.   Observed and expected numbers of second primary cancers at selected* sites after an initial diagnosis of basal cell carcinoma of the skin, with corresponding standardized incidence ratios: Vaud and Neuchâtel, Switzerland, 1974–1994

Site	ICD-9† code(s)	No. of cases		SIR†	95% confidence interval
		Observed	Expected		
Lip	140	9	4.1	2.2	1.0–4.2
Salivary glands	142	5	1.8	2.8	0.9–6.4
Mouth	141, 143, 144	7	10.2	0.7	0.3–1.4
Pharynx	145–148	18	17.9	1.0	0.6–1.6
Esophagus	150	11	24.4	0.5	0.2–0.8
Stomach	151	26	56.2	0.5	0.3–0.7
Small intestine	152	6	2.9	2.1	0.8–4.5
Colon	153	103	103.7	1.0	0.8–1.2
Rectum	154	47	62.1	0.8	0.6–1.0
Liver	155	20	18.6	1.1	0.7–1.7
Gallbladder	156	8	16.7	0.5	0.2–0.9
Pancreas	157	28	38.4	0.7	0.5–1.1
Larynx	161	7	13.2	0.5	0.2–1.1
Lung	162	128	139.1	0.9	0.8–1.1
Soft tissue	171	6	3.6	1.7	0.6–3.7
Skin, squamous cell carcinoma	173	501	111.7	4.5	4.1–4.9
Skin, melanoma	172	54	21.4	2.5	1.9–3.3
Skin, other‡	173	13	4.7	2.8	1.5–4.8
Breast (females)	174	126	108.5	1.2	1.0–1.4
Uterine cervix	180	7	11.0	0.6	0.3–1.3
Corpus uteri	182	23	23.4	1.0	0.6–1.5
Ovary	183	17	17.3	1.0	0.6–1.6
Prostate	185	155	142.2	1.1	0.9–1.3
Bladder	188	51	48.6	1.1	0.8–1.4
Kidney	189	18	23.7	0.8	0.4–1.2
Brain and nerves	191, 192	3	9.1	0.3	0.1–1.0
Thyroid	193	7	6.8	1.0	0.4–2.1
Hodgkin's disease	201	2	3.1	0.6	0.1–2.3
Other lymphoma	200, 202	43	22.5	1.9	1.4–2.6
Myeloma	203	10	13.4	0.8	0.4–1.4
Leukemia	204–207	19	28.1	0.7	0.4–1.1
Total (all sites)		1,543	1,397.9	1.1	1.0–1.2
Total (except skin)		975	1,059.0	0.9	0.8–1.0

* Only one case each was observed for cancers of the bone (1.1 expected) and testis (2.3 expected); two cases were observed for cancers of the nasal cavity (2.4 expected) and the eye (2.4 expected).

† ICD-9, International Classification of Diseases, Ninth Revision; SIR, standardized incidence ratio.

‡ Four cases of sebaceous adenocarcinoma, three cases of malignant carcinoid carcinoma, two cases of lymphoepithelial carcinoma, one case of apocrine adenocarcinoma, one case of Paget's disease, one small cell carcinoma, and one "not otherwise specified" carcinoma were included.

(95 percent CI 0.2–1.1) for the larynx, and 0.6 (95 percent CI 0.3–1.3) for the uterine cervix.

Sites of second primary malignancies showing significant excesses or meaningful patterns are considered further in table 3 by sex, age at BCC diagnosis, and time since diagnosis. The elevated rates of skin neoplasms and non-Hodgkin's lymphoma were similar in males and females. The SIRs for cancers of the lip, salivary glands, and skin were appreciably greater below age 70 years. For most sites, particularly for squamous cell cancer and melanoma of the skin, no consistent pattern of trend was observed with time since BCC diagnosis, and the SIRs remained significantly above unity 5 or more years after BCC diagnosis. This indicates that the excess rates cannot be simply explained in terms of increased surveillance

around and after BCC diagnosis.

Figure 1 shows the cumulative incidence of squamous cell skin cancer following a diagnosis of BCC. A steady increase was evident up to 19 years after BCC diagnosis, reaching a cumulative incidence of 13 percent.

DISCUSSION

The present study, based on more than 11,800 subjects diagnosed with BCC and more than 76,000 person-years at risk, and on a population in which skin lesions have long been pathologically examined, confirms that rates of various types of skin cancer, as well as cancer of the lip and non-Hodgkin's lymphoma, are significantly increased after a diagnosis of BCC.

TABLE 3. Observed numbers of second primary cancers at selected sites after an initial diagnosis of basal cell carcinoma of the skin, with corresponding standardized incidence ratios, by sex, age, and time since diagnosis: Vaud and Neuchâtel, Switzerland, 1974-1994

Site	Sex				Age (years)				Time since diagnosis (years)					
	Males		Females		<70		≥70		<1		1-4		≥5	
	Obs*	SIR* (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)
Lip	6	1.8 (0.7-3.9)	3	3.9 (0.8-11.3)	6	3.1 (1.1-6.8)	3	1.4 (0.3-4.1)	†	—	5	3.0 (1.0-7.0)	4	2.1 (0.6-5.5)
Salivary glands	5	4.8 (1.5-11.2)	—	—	3	3.8 (0.8-11.1)	2	1.0 (0.1-7.6)	1	4.1 (0.1-23.0)	2	2.7 (0.3-9.9)	2	2.4 (0.3-8.6)
Skin, squamous cell carcinoma	308	4.4 (3.9-4.9)	193	4.7 (4.0-6.4)	266	6.9 (6.1-7.8)	235	3.2 (2.8-4.0)	80	5.6 (4.4-6.9)	182	4.2 (3.6-4.8)	239	4.5 (3.9-5.1)
Skin, melanoma	32	3.0 (2.1-4.3)	22	2.0 (1.3-3.1)	39	3.2 (2.3-4.4)	15	1.8 (0.9-2.6)	8	2.0 (0.7-4.3)	26	2.9 (1.9-4.3)	22	2.3 (1.4-3.5)
Non-Hodgkin's lymphoma	23	1.8 (1.1-2.7)	20	2.2 (1.3-3.4)	19	1.8 (1.1-2.8)	24	2.0 (1.3-3.0)	7	2.4 (0.9-4.9)	18	2.0 (1.2-3.2)	18	1.8 (1.0-2.8)
Total (all sites)	932	1.1 (1.0-1.2)	611	1.1 (1.0-1.2)	805	1.2 (1.1-1.3)	738	1.2 (1.1-1.3)	217	1.2 (1.0-1.3)	637	1.1 (1.0-1.2)	689	1.1 (1.0-1.2)
Total (except skin)	588	0.9 (0.8-1.0)	389	1.0 (0.9-1.1)	491	1.0 (0.9-1.1)	484	0.9 (0.8-1.0)	128	0.9 (0.7-1.1)	425	1.0 (0.9-1.1)	422	0.9 (0.8-1.0)

* Obs, observed number of cases; SIR, standardized incidence ratio; CI, confidence interval.
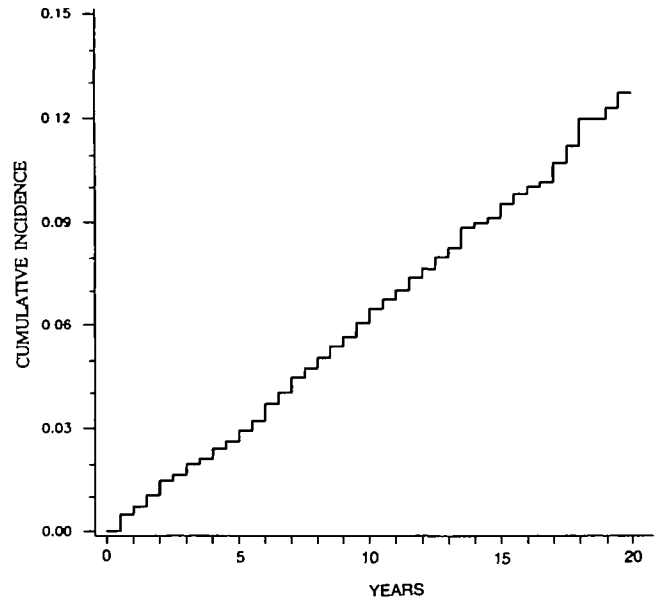† No cases observed.

FIGURE 1. Cumulative incidence (proportion) of squamous cell skin carcinoma (n = 501) after initial diagnosis of basal cell skin carcinoma (n = 11,878), by time interval, in the cantons of Vaud and Neuchâtel, Switzerland, 1974-1994. (Data were obtained from the Vaud and Neuchâtel cancer registries.)

The excess incidence of squamous cell and melano-matous skin cancers is probably due to a shared predisposition—phenotypic characteristics and inherited cancer susceptibility syndromes, such as nevoid BCC syndrome—and risk factors, i.e., excess exposure to sunshine and other sources of ultraviolet radiation (16-18). This may explain, at least in part, the excess incidence of non-Hodgkin's lymphoma as well, assuming that ultraviolet radiation causes immunosuppression (1, 19). More difficult to interpret are the appreciable excesses of salivary gland and skin cancers in patients younger than 70 years. This may reflect a predisposition to these neoplasms or a major role of extensive exposure to selected risk factors at a younger age (9).

The excess rate of salivary gland cancer is probably real, since it has also been observed in other data sets (20, 21), although the causes of salivary gland cancer—apart from ionizing radiation—remain largely undefined. The association has generally been attributed to the common embryologic origin of the salivary glands and skin (both are derived from the ectodermal layer of the fetus) (22).

A relation between tobacco use and squamous cell skin cancer has been reported (21, 23). It is therefore interesting to note the absence of an association, in this data set, between BCC and subsequent lung cancer. The lower rates of cancer of the esophagus, stomach, larynx, uterine cervix, and mouth are also of interest. They may reflect different social class correlates or

other general lifestyle factors related to these neoplasms, since in this population skin and breast cancer tend to have favorable social class correlates, while esophageal, larynx, gastric, and cervical cancer have unfavorable ones (24). The SIR for breast cancer was also moderately elevated in a Danish data set (19).

The absence of excess risk for all neoplasms except skin cancer is also of interest, since a moderately elevated SIR (1.15) was reported from a Danish study (8). This may reflect different correlates of BCC risk in various populations. In any case, there is no convincing evidence of a generalized excess of nonskin cancer following BCC.

In conclusion, this study, which was based on a large data set and had a uniquely long period of follow-up, confirms that subjects diagnosed with BCC do not have a generalized excess risk of nonskin neoplasms, with the exception of non-Hodgkin's lymphoma and cancers of the lip and salivary glands. Given the small numbers of cases observed and the relatively moderate excess risks, this finding cannot be said to have prevention or screening implications, but it may be of some interest in the diagnostic process for these neoplasms. The excess rate of other skin cancers, however, is large enough to suggest a need for careful surveillance of skin lesions in BCC patients.

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