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Incidence of Invasive Cancers Following Squamous Cell Skin Cancer

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The authors describe the incidence of new primary cancers among 4,639 cases of squamous cell skin cancer (SCC) diagnosed between 1974 and 1994 in the cancer registries of the Swiss cantons of Vaud and Neuchâtel (total person-years at risk = 23,152). Overall, 729 metachronous cancers were observed versus 527.6 expected, corresponding to a standardized incidence ratio (SIR) of 1.4 (95% confidence interval (CI) 1.3–1.5). After exclusion of skin cancers, however, 384 second primary neoplasms were observed versus 397.2 expected (SIR = 1.0). Excesses were observed for cancers of the lip (SIR = 3.1) and lung (SIR = 1.3), for basal cell (SIR = 4.3) and melanomatous skin cancers (SIR = 3.3), and non-Hodgkin's lymphomas (SIR = 1.7). Rates were elevated for cancers of the salivary glands (SIR = 4.3) and for Hodgkin's disease (SIR = 2.7), and, below age 65 years, for cancers of the lung (SIR = 1.6), breast (SIR = 1.5), and prostate (SIR = 1.8), for Hodgkin's disease (SIR = 15.8), as well as for all neoplasms except skin (SIR = 1.2; 95% CI 1.0–1.5). The cumulative risk of basal cell skin cancer reached 17% after 15 years. The authors believe that the excesses for basal cell carcinomas and melanomas of the skin following SCC, and possibly of lymphomas, were likely attributable to common phenotypic characteristics and exposure to UV radiation. The elevated rates of lung cancer are suggestive for a role of tobacco as a cause of squamous cell skin cancer. *Am J Epidemiol* 1997; 146:734–9.

carcinoma, squamous cell; lung neoplasms; neoplasms, second primary; registries; salivary gland neoplasms; skin; smoking; ultraviolet rays

Studies of multiple primary cancers have suggested that subjects diagnosed with squamous cell skin cancer (SCC) have increased incidence not only of other skin cancers, but also of a wide spectrum of other neoplasms, particularly of squamous cell cancers of the digestive and respiratory tract, of the salivary glands, as well as of non-Hodgkin's lymphomas and other lymphoid neoplasms (1–6). Thus, analysis of new primary cancers following squamous cell skin cancer have a public health and risk assessment interest, as well as potential implications for etiologic inference.

The Cancer Registries of the French-speaking cantons of Vaud and Neuchâtel, Switzerland, have been operating since 1972 in a particularly favorable environment for skin cancer registration, because traditionally the large majority of surgically resected cutaneous lesions in the two cantons are examined by a pathologist (7, 8). As a consequence, a large series of squamous cell skin neoplasms have been followed for a uniquely long period of time. Previously, we have reported an excess of non-Hodgkin's lymphomas, and of chronic lymphocytic leukemia, in this data set (6). Similar analyses extended to other neoplasms are now presented here.

MATERIALS AND METHODS

Data for the present report were abstracted from the Vaud and Neuchâtel Cancer Registries files, which include incident cases of malignant neoplasms in the cantons (9, 10), whose populations, according to the 1990 Census, were about 602,000 and 164,000 inhabitants, respectively. In these cantons, cancer registration systems have been implemented since 1972, and population-based incidence data have been available since 1974. The registries are tumor-based, and multiple primaries in the same person are entered separately. Most cases are registered repeatedly and from different institutions, thus improving completeness and accuracy of registration. Information from death

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Abbreviations: CI, confidence interval; ICD-O, *International Classification of Diseases for Oncology*; SCC, squamous cell skin cancer; SIR, standardized incidence ratio; UV radiation, ultraviolet radiation.

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certificates is routinely integrated in the data file; cases known only through death certificates amount to fewer than 5 percent of the average number of cases registered per year. Overall histologic confirmation and completeness exceed 90 percent (9, 10).

The information available from the registries comprises sociodemographic characteristics of the patient (i.e., age, sex), primary site and histologic type of the tumor according to the standard *International Classification of Diseases for Oncology* (ICD-O) (11), and date of diagnostic confirmation. Passive and active follow-up is recorded, 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 = 56, i.e., 50 basal cell and 1 melanoma skin cancers, 3 squamous cell carcinomas of the oropharynx, 1 small cell carcinoma of the lung, and 1 adenocarcinoma of the prostate), the present series comprises a total of 4,639 histologically confirmed squamous cell carcinomas of the skin (ICD-O topography: 173.0–173.9 and morphology codes: 8051–2, 8070–6, 8094, 8560) diagnosed between 1974 and 1994. The age range was 8–102 years (median age, 74 years).

These cases of incident squamous cell skin carcinomas were followed to the end of 1994 for the occurrence of a second (other than SCC) primary cancer, emigration, or death. As a rule of cancer registration in Switzerland, SCCs (either synchronous or metachronous) are registered only at the first recognized tumor of the same morphologic type.

Calculation of expected numbers was based on site-, age-, and calendar period-specific incidence rates from the cancer registries, multiplied by the observed corresponding number of person-years at risk. The significance of the observed/expected ratios (standardized incidence ratios (SIR)), and the corresponding 95 percent confidence intervals, were based on the Poisson distribution (12). Cumulative rates were computed using the life table approach (13).

RESULTS

Table 1 gives the distribution of 4,639 cases of squamous cell skin cancer according to age, the corresponding incidence rates for the whole calendar period, and the person-years at risk in separate strata of time since diagnosis, for a total of 23,152 person-years at risk.

Table 2 gives the observed and expected numbers of all neoplasms, and of selected subsequent cancer sites. Overall, 729 metachronous cancers were observed versus 527.6 expected (SIR = 1.4, 95 percent confidence interval (CI) 1.3–1.5). After exclusion of all other skin cancers, however, 384 second primary neoplasms were observed versus 397.2 expected (SIR = 1.0, 95 percent CI 0.9–1.1). Excesses were observed for cancer of the lip (SIR = 3.1) and lung (SIR = 1.3), for basal cell skin cancer (SIR = 4.3), skin melanoma (SIR = 3.3), and non-Hodgkin's lymphomas (SIR = 1.7). Nonsignificant elevated rates were also observed for cancers of the salivary gland (SIR = 4.3) and Hodgkin's disease (SIR = 2.7).

Sites of second primaries showing significant excesses or meaningful patterns are further considered in table 3 in separate strata for sex, age at squamous cell skin cancer diagnosis, and time since diagnosis. The excess rates of lung and other skin cancers and lymphatic neoplasms were similar for males and females, but tended to be systematically higher below age 65 years. Thus, standardized incidence ratios for lung cancer were 1.6 below age 65 years and 1.1 at age ≥65 years, while those for breast cancer were 1.5 and 0.8, for prostate cancer 1.8 and 1.1, and for basal cell skin cancer 7.5 and 3.6, respectively. Below age 65 years, significantly elevated standardized incidence ratios were also observed for Hodgkin's disease (SIR = 15.8) as well as for all neoplasms (SIR = 2.2, 95 percent CI 1.9–2.6). After excluding other skin neoplasms, the standardized incidence ratio for all neoplasms was 1.2 (95 percent CI 1.0–1.5) below age 65

TABLE 1. Age distribution of 4,639 cases of squamous cell carcinoma of the skin and corresponding incidence rates, and person-years at risk by time since diagnosis, Vaud and Neuchâtel, Switzerland, 1974–1994*

	No. of cases		Incidence rate per 100,000	
	Males	Females	Males	Females
Age group (years)				
<30	9	5	0.3	0.2
30–39	32	27	2.8	2.4
40–49	107	97	10.7	9.5
50–59	235	185	29.0	21.3
60–69	585	375	92.6	49.1
70–79	901	646	221.2	106.0
≥80	660	775	424.2	226.6
Total, all ages	2,529	2,110	21.6†	12.2†

Time since diagnosis (years)	Person-years at risk
<1	4,209
1–4	11,064
5–9	5,814
10–14	2,065
Total	23,152

* Denominators in 1980—Vaud, 529,000; Neuchâtel, 158,000. In 1990—Vaud, 602,000; Neuchâtel, 164,000.
† Incidence rate age standardized on the world population.

TABLE 2. Observed and expected cases, and standardized incidence ratios (SIR) of selected* subsequent cancer sites after an initial diagnosis of squamous cell carcinoma of the skin, and corresponding overall standardized incidence ratios (SIR) and 95% confidence intervals (CI), Vaud and Neuchâtel, Switzerland, 1974–1994

Site	ICD-9†	No. of cases		SIR	95% CI
		Observed	Expected		
Lip	140	5	1.6	3.1	1.0–7.3
Salivary gland	142	3	0.7	4.3	0.9–12.6
Mouth or pharynx	141, 143–8	8	9.1	0.9	0.4–1.8
Esophagus	150	5	9.4	0.5	0.2–1.2
Stomach	151	18	23.0	0.8	0.5–1.2
Colon	153	29	41.0	0.7	0.5–1.0
Rectum	154	19	23.7	0.8	0.5–1.3
Gallbladder	156	6	6.4	1.0	0.4–2.1
Pancreas	157	13	14.8	0.9	0.5–1.5
Lung	162	62	48.8	1.3	1.0–1.6
Skin, melanoma	172	23	7.0	3.3	2.1–4.9
Skin, basal cell	173	317	73.9	4.3	3.8–4.8
Breast (females)	174	32	32.7	1.0	0.7–1.4
Uterus, corpus	182	6	6.5	0.9	0.3–2.0
Prostate	185	74	64.8	1.1	0.9–1.4
Bladder	188	16	19.7	0.8	0.5–1.3
Kidney	189	11	8.2	1.4	0.7–2.4
Hodgkin's disease	201	3	1.1	2.7	0.6–8.0
Other lymphomas	200, 202	20	12.1	1.7	1.0–2.6
Myeloma	203	6	4.9	1.2	0.4–2.7
Leukemias	204–7	6	11.1	0.5	0.2–1.2
Total, all sites		729	527.6	1.4	1.3–1.5
Total, minus skin‡		384	397.2	1.0	0.9–1.1

* Only one case each was observed for cancers of the nasal cavity, bones, testis, thyroid; no case of cervical cancer was registered; 2 cases were observed for small intestine cancer (SIR = 1.8), 2 for liver (SIR = 0.3), 4 for larynx (SIR = 0.9), 2 for soft tissue (SIR = 1.8), 3 for ovaries (SIR = 0.6), and 3 for brain and nerves (SIR = 1.1).

† ICD-9, *International Classification of Diseases*, 9th Revision.

‡ Basal cell carcinoma, malignant melanomas, and 5 other primary skin cancers (2 dermatofibrosarcomas, 2 sebaceous carcinomas, and 1 leiomyosarcoma) were excluded.

years, but 0.9 at ages ≥65 years. After age 65 years, significantly elevated standardized incidence ratios were observed for non-Hodgkin's lymphomas (SIR = 1.9). With reference to time since squamous cell skin cancer diagnosis, the SIR for basal cell skin cancer was 8.5 <1 year after diagnosis, but remained elevated after 1–4 and ≥5 years since diagnosis (SIR = 3.4), indicating that the excess rates cannot be attributed only to increased surveillance in the few years after skin cancer diagnosis. For skin melanoma, the standardized incidence ratios tended to increase with increasing time since SCC (SIR = 1.3 for <1 year, 2.7 for 1–4 years, and 5.0 after ≥5 years since diagnosis). No consistent pattern of trend with time since SCC was observed for any of the other neoplasms.

Cumulative incidence of basal cell skin cancer following a diagnosis of squamous cell cancer was also estimated. A steady rise was evident up to 15 years after squamous cell skin cancer, with cumulative rates of 6 percent at 5 years, 11 percent at 10 years, and 17 percent at 15 years.

DISCUSSION

The present study is based on a long-term follow-up of a large population-based series of squamous cell skin cancers from a particularly well surveilled population. The study is also, to our knowledge, based on the largest to date number of person-years at risk following SCC. It confirms that rates of a few defined groups of neoplasms, including not only other skin cancers, but also cancers of the salivary gland neoplasm and lung, and Hodgkin's and non-Hodgkin's lymphomas, are increased among subjects diagnosed with SCCs, and that the excess rates persist for ≥10 years after skin cancer diagnosis.

The excesses for basal cell carcinoma and melanoma of the skin following SCC were likely attributable to shared risk factors, i.e., common phenotypic characteristics and exposure to sunshine and other sources of UV radiation (8, 14–18). It is of interest that the standardized incidence ratios remained elevated several years after diagnosis, particularly for

TABLE 3. Observed cases and standardized incidence ratios (SIR), with corresponding 95% confidence intervals (CI), of selected subsequent cancer sites after an initial diagnosis of skin squamous cell carcinoma in strata of selected covariates, Vaud and Neuchâtel, Switzerland, 1974–1994

Site	Sex				Age (years)				Time since diagnosis (years)					
	Males		Females		<65		≥65		<1		1–4		≥5	
	Observed cases	SIR (95% CI)	Observed cases	SIR (95% CI)	Observed cases	SIR (95% CI)	Observed cases	SIR (95% CI)	Observed cases	SIR (95% CI)	Observed cases	SIR (95% CI)	Observed cases	SIR (95% CI)
Lip	5	3.7 (1.2–8.6)	–*	–	1	4.2 (0.1–23.4)	4	2.9 (0.8–7.4)	1	3.6 (0.1–19.9)	3	4.0 (0.8–11.8)	1	1.7 (0.0–9.6)
Lung	53	1.2 (0.9–1.6)	9	1.7 (0.8–3.3)	20	1.6 (1.0–2.5)	42	1.1 (0.8–1.5)	10	1.1 (0.5–2.1)	26	1.1 (0.7–1.6)	26	1.6 (1.0–2.3)
Skin melanoma	13	3.5 (1.9–6.0)	10	3.0 (1.5–5.6)	6	3.6 (1.3–7.2)	17	3.2 (1.9–5.1)	2	1.3 (0.2–5.7)	9	2.7 (1.2–5.1)	12	5.0 (2.6–8.8)
Skin basal cell	206	4.4 (3.9–5.1)	111	4.0 (3.3–4.9)	95	7.5 (6.1–9.2)	222	3.6 (3.2–4.1)	110	8.5 (7.0–10.2)	117	3.4 (2.8–4.0)	90	3.4 (2.8–4.2)
Breast (females)			32	1.0 (0.7–1.4)	10	1.5 (0.7–2.7)	22	0.8 (0.5–1.2)	5	0.9 (0.3–2.0)	18	1.2 (0.7–1.8)	9	0.8 (0.4–1.5)
Prostate	74	1.1 (0.9–1.4)			10	1.8 (0.9–3.3)	64	1.1 (0.9–1.4)	14	1.3 (0.7–2.2)	38	1.3 (0.9–1.8)	22	0.9 (0.6–1.4)
Hodgkin's disease	2	3.6 (0.4–13.1)	1	1.8 (0.0–10.2)	3	15.8 (3.3–46.1)	–	–	–	–	2	3.8 (0.4–13.9)	1	2.7 (0.0–14.7)
Other lymphomas	12	1.5 (0.8–2.6)	8	2.0 (0.9–3.9)	1	0.5 (0.0–2.8)	19	1.9 (1.1–3.0)	6	2.8 (1.0–6.2)	6	1.1 (0.4–2.5)	8	1.9 (0.8–3.7)
Total, all sites	498	1.4 (1.3–1.6)	231	1.3 (1.1–1.5)	178	2.2 (1.9–2.6)	551	1.2 (1.1–1.3)	186	2.0 (1.7–2.3)	323	1.3 (1.2–1.5)	220	1.2 (1.0–1.3)
Total, minus skin†	275	1.0 (0.9–1.2)	109	0.8 (0.7–1.0)	77	1.2 (1.0–1.5)	307	0.9 (0.8–1.0)	72	1.1 (0.9–1.4)	196	1.2 (1.0–1.3)	116	0.9 (0.8–1.1)

* –, indicates no observed cases.
† Basal cell carcinomas, malignant melanomas, and 5 other primary skin cancers (2 dermatofibrosarcomas, 2 sebaceous carcinomas, and 1 leiomyosarcoma) were excluded.

melanoma, suggesting either an action on one of the earliest stages of the process of carcinogenesis (19), or the persistence of risk determinants and risk factor exposures. Exposure to UV radiation may also explain, at least in part, the elevated rates of non-Hodgkin's lymphomas, assuming that UV radiation causes immunosuppression, although the issue is still open to discussion (5, 6, 20)

The elevated risk of cancer of the salivary glands after squamous cell skin cancer has been observed in other data sets, and is therefore probably real (4, 21–23). The causes of cancer of salivary glands, apart from a role of radiation (24) which has been associated with squamous cell skin cancer, too, are largely undefined. Thus, this association has been attributed to the common embryologic origin of salivary glands and skin from the ectodermal layer of the fetus, but the issue is still open to debate (25).

More interesting and important is the association between squamous cell cancer and lung cancer. This has been observed in other series (4), and is consistent with the evidence from case-control and cohort studies indicating that smoking is a risk factor for SCC. Thus, the relative risk of squamous cell skin cancer was 2.3 in a case-control study in the Montreal region (26), 2.6 in a case-control study carried out in Uruguay (27), and 1.5 in the Nurses' Health Study cohort (16). Further, in a cohort of subjects with prior skin cancers (1), an excess of subsequent squamous cell, but not basal cell skin cancers, was observed among current smokers. Although the data are insufficient to draw causal inferences, there is therefore suggestive evidence to include SCC among tobacco-related neoplasms. Other possible common risk factors, such as a fat-rich diet (28), may also contribute to explain the association observed.

The observation that the standardized incidence ratios for several neoplasms, including breast and prostate, were higher in subjects diagnosed with SCC under age 65 years may reflect genetic susceptibility, as well as a more extensive exposure to selected risk factors at younger age. A similar observation was made in a record linkage study from Denmark (4).

In conclusion, therefore, this study confirms that subjects diagnosed with SCC, while not having a substantial and significant excess risk of all subsequent neoplasms, show a few specific excesses for selected cancer sites, particularly for cancers diagnosed below age 65 years. This may shed interesting light on common etiologic and pathogenic factors. Further, for subsequent (basal cell and malignant melanoma) skin cancer the excess is so large and persistent to indicate that preventive intervention and long-term monitoring of skin lesions are required among subjects with SCC, and particularly among those diagnosed at a younger age.

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