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.

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Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; SIR, standardized incidence ratio.

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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*

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Person-years at risk for subsequent cancers</th>
<th>No. of cases</th>
<th>Incidence rate (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td></td>
<td>44 (Male)</td>
<td>1.2</td>
</tr>
<tr>
<td>30–39</td>
<td></td>
<td>223 (Female)</td>
<td>1.5</td>
</tr>
<tr>
<td>40–49</td>
<td></td>
<td>508 (Male)</td>
<td>14.2</td>
</tr>
<tr>
<td>50–69</td>
<td></td>
<td>1,036 (Male)</td>
<td>47.7</td>
</tr>
<tr>
<td>60–69</td>
<td></td>
<td>902 (Male)</td>
<td>126.3</td>
</tr>
<tr>
<td>70–79</td>
<td></td>
<td>1,348 (Male)</td>
<td>269.4</td>
</tr>
<tr>
<td>≥80</td>
<td></td>
<td>1,572 (Male)</td>
<td>414.4</td>
</tr>
<tr>
<td>Total (all ages)</td>
<td></td>
<td>5,947 (Male)</td>
<td>55.6†</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (years) since diagnosis</th>
<th>Person-years at risk</th>
<th>No. of cases</th>
<th>Incidence rate (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>11,118</td>
<td>11,118 (Male)</td>
<td>32,272</td>
</tr>
<tr>
<td>1–4</td>
<td>32,272</td>
<td>32,272 (Male)</td>
<td>21,223</td>
</tr>
<tr>
<td>≥10</td>
<td>11,897</td>
<td>11,897 (Male)</td>
<td>76,510</td>
</tr>
</tbody>
</table>

* Denominators in 1980: Vaud, 529,000; Neuchâtel, 156,000. 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

<table>
<thead>
<tr>
<th>Site</th>
<th>ICD-9† code(s)</th>
<th>No. of cases</th>
<th>SIR†</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Observed</td>
<td>Expected</td>
<td></td>
</tr>
<tr>
<td>Lip</td>
<td>140</td>
<td>9</td>
<td>4.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>142</td>
<td>5</td>
<td>1.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Mouth</td>
<td>141, 143, 144</td>
<td>7</td>
<td>10.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Pharynx</td>
<td>145-148</td>
<td>18</td>
<td>17.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Esophagus</td>
<td>150</td>
<td>11</td>
<td>24.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Stomach</td>
<td>151</td>
<td>26</td>
<td>56.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Small intestine</td>
<td>152</td>
<td>6</td>
<td>2.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Colon</td>
<td>153</td>
<td>103</td>
<td>103.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Rectum</td>
<td>154</td>
<td>47</td>
<td>62.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Liver</td>
<td>155</td>
<td>20</td>
<td>18.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>156</td>
<td>8</td>
<td>16.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Pancreas</td>
<td>157</td>
<td>28</td>
<td>36.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Larynx</td>
<td>161</td>
<td>7</td>
<td>13.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Lung</td>
<td>162</td>
<td>128</td>
<td>139.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>171</td>
<td>6</td>
<td>3.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Skin, squamous cell carcinoma</td>
<td>173</td>
<td>501</td>
<td>511.7</td>
<td>4.5</td>
</tr>
<tr>
<td>Skin, melanoma</td>
<td>172</td>
<td>54</td>
<td>21.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Skin, other†</td>
<td>173</td>
<td>13</td>
<td>4.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Breast (females)</td>
<td>174</td>
<td>126</td>
<td>108.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>180</td>
<td>7</td>
<td>11.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Corpus uteri</td>
<td>182</td>
<td>23</td>
<td>23.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Ovary</td>
<td>183</td>
<td>17</td>
<td>17.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Prostate</td>
<td>185</td>
<td>155</td>
<td>142.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Bladder</td>
<td>198</td>
<td>51</td>
<td>48.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Kidney</td>
<td>189</td>
<td>18</td>
<td>23.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Brain and nerves</td>
<td>191, 192</td>
<td>3</td>
<td>9.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Thyroid</td>
<td>193</td>
<td>7</td>
<td>6.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>201</td>
<td>2</td>
<td>3.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Other lymphoma</td>
<td>200, 202</td>
<td>43</td>
<td>22.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Myeloma</td>
<td>203</td>
<td>10</td>
<td>13.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Leukemia</td>
<td>204-207</td>
<td>19</td>
<td>26.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Total (all sites)</td>
<td></td>
<td>1,543</td>
<td>1,397.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Total (except skin)</td>
<td></td>
<td>975</td>
<td>1,056.0</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* Only one case each was observed for cancers of the bone (1.1 expected) and tests (2.3 expected); two cases were observed for cancers of the nasal cavity (2.4 expected) and four for 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.
The excess incidence of squamous cell and melanomatous 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 neo-
plasms, 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
enhanced 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 con-
vincing 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 lymph-
oma 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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