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Short Communication

Second primary cancers in patients with squamous cell carcinoma of the skin

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The occurrence of second primary cancers was explored in patients with squamous cell cancer of the skin (SCC). The excess incidence subsequent to SCC was mainly in cancers related to sunlight and smoking, and in lymphoproliferative malignancies, it was largest (10-fold) in salivary gland cancer.

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Malignant tumours of the skin are common cancers, typically affecting fair skinned racial groups (Armstrong and Kricker, 2001). The UV component of sunlight is regarded as the most important factor leading to squamous cell cancer (SCC). Other dominant risk factors are smoking and immunosuppression. A number of studies have found significantly increased risks of various second primary cancers in SCC patients (Frisch and Melbye, 1995; Levi et al, 1997; Wassberg et al, 1999; Askling et al, 1999; Hemminki and Dong, 2000; Hemminki et al, 2001; Efird et al, 2002). Some general patterns can be seen from these studies. There is an increased risk for the development of subsequent skin cancers, cancers of the lip, lungs, pharynx, larynx, the salivary glands and non-Hodgkin’s lymphoma.

We have examined the occurrence of primary cancer subsequent to the development of SCC.

RESULTS

There were 3359 cases of second primary cancers after SCC diagnosis, of which 2567 were in male patients and 792 were in female patients (Table 1). The SIR for the occurrence of any second primary cancer was 1.2 in both male and female subjects.

There was an increased risk for non melanoma skin cancer (BCC was not included). Risk for malignant melanoma was significantly increased in both male and female subjects (SIR male 3.0; female 2.9). Lip cancer risk was greatly elevated (SIR male 3.5; female 7.7). Relative risk of cancer of the pharynx was elevated, and statistically significantly so in female subjects. Risk of oesophagus cancer was increased in males, and colon cancer incidence was increased in both sexes. Salivary gland cancer risk was particularly elevated (SIR male 11.0; female 10.6).

The respiratory system in general was at an increased susceptibility to second primary cancers. Lung cancer occurrence was especially striking, not only due to the increased SIR values in both sexes (SIR male 1.3; female 1.2), but also because of the large absolute excess incidence. Lung cancer accounted for 24% of the total second primary cancer occurrence, and 28% of the excess burden of cancer in the cohort. The nasal cavity (and ear) was at a significantly increased risk in female subjects and laryngeal cancer displayed a significantly increased risk in male subjects.

There was an evident increase in occurrence of lymphoma and leukaemia. Hodgkin’s disease had a raised SIR value (1.4) in males only. However, non-Hodgkin’s lymphomas (comprising follicular,
**Table 1** Standardised incidence ratios (SIR) and 95% confidence intervals for second cancers subsequent to SCC.

| Site                        | Male | Female |
|-----------------------------|------|--------|
|                             | Observed | Expected | SIR | Observed | Expected | SIR |
| Lip                         | 10    | 2.9    | 3.5 (1.9–6.4) | 3     | 0.4    | 7.7 (2.5–24.0) |
| Salivary gland              | 36    | 3.3    | 11.0 (8.0–15.3) | 9     | 0.9    | 10.6 (5.5–20.3) |
| Oropharynx                  | 3     | 1.2    | 2.6 (0.8–8.0) | 2     | 0.2    | 11.3 (2.8–45.4) |
| Hypopharynx                 | 3     | 1.4    | 2.2 (0.7–6.8) | 4     | 0.7    | 5.7 (2.1–15.3) |
| Oesophagus                  | 73    | 58.0   | 1.3 (1.0–1.6) | 14    | 15.8   | 0.9 (0.5–1.5) |
| Stomach                     | 137   | 139.0  | 1.0 (0.8–1.2) | 35    | 33.1   | 1.1 (0.8–1.5) |
| Colon                       | 187   | 159.3  | 1.2 (1.0–1.4) | 83    | 70.9   | 1.2 (1.0–1.5) |
| Liver                       | 22    | 15.1   | 1.5 (1.0–2.2) | 3     | 3.4    | 0.9 (0.3–2.7) |
| Pancreas                    | 69    | 69.0   | 1.0 (0.8–1.3) | 30    | 26.2   | 1.1 (0.8–1.6) |
| Nasal cavity and ear        | 4     | 1.9    | 2.1 (0.8–5.6) | 4     | 0.6    | 6.8 (2.5–18.1) |
| Larynx                      | 46    | 27.6   | 1.7 (1.2–2.2) | 3     | 1.9    | 1.5 (0.5–4.8) |
| Bronchus and lung           | 710   | 558.6  | 1.3 (1.2–1.4) | 95    | 80.2   | 1.2 (1.0–1.4) |
| Skin malignant melanoma     | 48    | 15.8   | 3.0 (2.3–4.0) | 24    | 8.3    | 2.9 (1.9–4.3) |
| Other skin neoplasms (excl. BCC) | 83 | 80.7 | 1.0 (0.8–1.3) | 24    | 16.1   | 1.5 (1.0–2.2) |
| Breast                      | 3     | 4.4    | 0.7 (0.2–2.1) | 140   | 146.7  | 1.0 (0.8–1.1) |
| Prostate                    | 389   | 385.6  | 1.0 (0.9–1.1) | 25    | 22.5   | 1.1 (0.8–1.6) |
| Bladder                     | 154   | 167.4  | 0.9 (0.8–1.1) | 1     | 1.5    | 0.7 (0.1–4.8) |
| Hodgkin’s disease           | 6     | 4.3    | 1.4 (0.6–3.1) | 5     | 1.1    | 4.7 (2.0–11.3) |
| Follicular NHL              | 6     | 2.2    | 2.7 (1.2–6.0) | 6     | 3.6    | 1.7 (0.7–3.7) |
| Diffuse NHL                 | 18    | 10.2   | 1.8 (1.1–2.8) | 6     | 3.6    | 1.7 (0.7–3.7) |
| Peripheral/cutaneous T-cell lymphoma | 10 | 2.3    | 4.4 (2.3–8.1) | 1     | 0.5    | 2.0 (0.3–13.9) |
| Other NHL                   | 77    | 33.7   | 2.3 (1.8–2.9) | 21    | 12.4   | 1.7 (1.1–2.6) |
| Lymphoid leukaemia          | 41    | 24.8   | 1.7 (1.2–2.3) | 12    | 6.8    | 1.8 (1.0–3.1) |
| Myeloid leukaemia           | 31    | 24.3   | 1.3 (0.9–1.9) | 10    | 7.1    | 1.4 (0.8–2.6) |
| Total Number of all cancers incl. those not shown above | 2567  | 2118.4 | 1.2 (1.2–1.3) | 792   | 648.0  | 1.2 (1.1–1.3) |

**DISCUSSION**

This study confirms that there is a significantly increased relative risk of second primary cancers in individuals with SCC. The UV component of sunlight is widely believed to be the main risk factor for skin and lip cancer and this may explain the subsequent excess of malignant melanomas and SCCs of the lip.

It has been observed previously that the southern US (with higher exposure to UV radiation) has a significantly higher incidence of salivary gland cancer than the northern states (Spitz et al., 1988). In addition, it has been observed that there is an increased risk for melanoma and lip cancers subsequent to salivary gland cancer (Spitz et al., 1990). There is strong previous evidence for the association of skin cancers with non-Hodgkin’s lymphoma and leukaemias, implying a causative role of UV light (Adami et al., 1995). Non-Hodgkin’s lymphoma and SCC have been specifically associated, with the suggestion that UV radiation may have a suppressive effect on the immune system (Hall et al., 1995).

The great majority of the excess cancer occurrence in SCC is associated with smoking. This includes cancer of the lung, lip, salivary gland, oesophagus, larynx and pharynx, and leukaemia. This is consistent with the carcinogenic effects of smoking.

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