Multiple primary cancers in the Vaud Cancer Registry, Switzerland, 1974–89

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Summary Data collected by the Cancer Registry of the Swiss Canton of Vaud (whose population in 1980 was about 530,000 inhabitants) were used to estimate the incidence of second metachronous primary cancers following any specific neoplasm. Among 34,615 cases of incident neoplasms registered between 1974 and 1989 and followed through integrated active follow-up to the end of 1989, for a total of 118,241 person-years at risk, there were 2,185 second primaries (1,280 males, 905 females). For both sexes, the standardized incidence ratios (SIR) were significantly elevated by about 20%. Overall significantly elevated ratios were registered for cancers of the oral cavity and pharynx (SIR = 1.6 for males, 2.0 for females), oesophagus in males (SIR = 1.5), lung in males (SIR = 1.4), skin melanoma (SIR = 1.7 for males, 1.5 for females), non-melanomatous skin cancers (SIR = 1.6 for males, 1.5 for females), female breast (SIR = 1.3), kidney (SIR = 1.5 for males, 1.9 for females), and thyroid in males (SIR = 2.4). When specific first cancer sites were considered, the SIR following a cancer of the oral cavity and pharynx was around 3 in both sexes, mainly on account of a substantial excess of second primaries of the oral cavity, oesophagus, larynx and lung. The overall SIR following laryngeal cancer was 3.0, and significant excesses were observed for oral cavity and pharynx, oesophagus and lung. After lung cancer, the overall SIR was 1.7 for males and 2.6 for females, and significantly elevated SIRs were observed for oral cavity, lung and oesophagus. Following non-melanomatous skin cancers, elevated SIRs were observed in both sexes for skin melanoma and non-melanomas. The incidence of any cancer after breast cancer was significantly elevated (SIR = 1.2), mainly on account of an elevated risk of subsequent breast cancer (SIR = 1.7). With reference to cervical cancer, there was a significant excess for any subsequent primary cancer (SIR = 1.6), and for lung cancer (SIR = 1.8). Significantly elevated SIRs were observed for kidney, following bladder cancer, and for bladder after kidney cancer. In both sexes, the incidence of cancers of any site was elevated following leukaemias (SIR = 1.7 for males, 2.5 for females), and a significant excess was registered for lung in males and non-melanomatous skin cancers in both sexes. Some of the associations observed can be related to common risk factor exposure, such as tobacco (and alcohol) for multiple primaries of the upper digestive and respiratory tract, or tobacco for the excess of lung cancer following bladder and probably cervical cancer. However, the overall excess risk of a second primary cancer is relatively limited, and at least in part attributable to increased surveillance.

There are several reports of multiple primary cancers, mostly based on clinical or autopsy series (Berg, 1967, 1970; Schottenfeld, 1969, 1971; Watanabe et al., 1984). These have suggested elevated rates due to common aetiological factors (e.g., for tobacco or diet-related cancers), or the consequences of treatment (e.g., high leukaemia risk following treatment of Hodgkin's disease, cervical, ovarian cancer, kidney or other neoplasms) (Boice et al., 1985a; Boivin et al., 1985; Kaldor et al., 1987, 1990a, 1990b).

There are, however, only a few published series including systematic overviews of multiple primary cancers from cancer registration schemes, including one from Denmark (1943–80; Storm et al., 1985), one from Connecticut (1935–82; Curtis et al., 1985; see also US Department of Health and Human Services, 1985), and one from Finland (1953–79; Teppo et al., 1985). Although several patterns of associations were similar in these studies, there were various quantitative differences: for instance, in Connecticut cancer patients had an overall 31% increased risk of developing a subsequent cancer, whereas no excess risk was observed in Denmark or Finland.

Differences in study methodology may explain at least part of these apparent discrepancies, but it is also possible that the impact of common genetic susceptibility and environmental factors, such as aetiological aspects and/or consequences of cancer treatment are different in various populations (Boice et al., 1985b). Thus, to provide further quantitative information on the issue, we present in this paper a summary overview of multiple primary cancers registered in the Swiss Vaud Cancer Registry from 1974 to 1989.

Materials and methods

The data considered for the present analysis were derived from the Vaud Cancer Registry dataset, which includes information concerning incident cases of malignant neoplasms occurring in the canton (about 530,000 inhabitants in 1980) (Levi, 1982, 1987).

Notification is based on a voluntary agreement between the recording medical institutions of the canton and the registry. All hospitals, pathological laboratories and most practitioners are asked to report all new or past cases of cancer. The main source of notification is the Cantonal University Pathological Department of Lausanne which performs the majority of histological examinations for the population covered by the Registry.

The main information available from the register comprises sociodemographic characteristics of the patient (i.e., age, sex), primary site and histological type of the tumour according to the standard International Classification of Diseases for Oncology (ICD-O), and time of diagnostic confirmation (histological or clinical diagnosis).

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. Information coming from death certificate is added to the morbidity file. Cases known only through the death certificate ('Death Certificate Only' cases (DCO)) contribute less than 5% of the average number of new cases registered per year.

The registry is a tumour based and multiple primaries occurring in the same person are included separately whenever morphologically different (according to the pathological report) or occurring at different anatomical sites (defined as the third-digit level of the ICD-O topographical code). However, multiple non-melanomatous skin tumours are classified by

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the site of the first recognised tumour of the same morphological type.

After exclusion of 1,416 (4%) cases diagnosed at autopsy or by death certificate alone (811 and 605 among males and females, respectively), the present series comprises a total of 34,615 cases of first diagnosed cancer primaries (18,001 and 16,614 among males and females, respectively) registered from 1974 to 1989 in the population of the Swiss canton of Vaud.

Among these cases of incident neoplasms, followed-up to the end of 1989 for a total of 118,241 person-years at risk, there were 2,185 (1,280 males, 905 females) metachronous (i.e. diagnosed at least two months after the first primary) second primaries. Tumours occurring synchronously, accounting for about 25% of all the pairs of primaries, were excluded from the present analysis. Histological confirmation was performed in 93% of the first as well as second primaries considered.

Calculation of expected numbers was based on sex-, age-, and calendar year-specific incidence rates multiplied by the observed number of person-years at risk. The end of the follow-up was determined by a second primary, death, emigration or the end of the study period at 31 December 1989. The significance of the observed/expected ratios (standardised incidence ratio, SIR) was based on the exact Poisson distribution applied to the observed numbers (Breslow & Day, 1987).

Results

Table I gives the total number of second primary cancers following any first primary site, and the corresponding SIR for each selected cancer site and sex. Over the 14-year period considered a total of 2,185 second primaries were registered in the Vaud Cancer Registry (1,280 males, 905 females). For both sexes, these figures were significantly elevated by about 20% (SIR 1.2 in both sexes). When specific cancer sites were considered, significantly elevated rates were registered for cancers of the oral cavity and pharynx in both sexes (SIR = 1.6 for males, 2.0 for females), oesophagus and lung in males (SIR = 1.5 and 1.4, respectively), skin melanoma

Table II Subsequent primary malignant tumours at selected sites, and corresponding standardised incidence ratios (SIR), following selected cancers for males and females in Vaud, Switzerland, 1974–1989

| Site of second primary tumour | Males | Females |
|-----------------------------|-------|---------|
| Oral cavity and pharynx     | 59    | 1.6b   |
| Oesophagus                  | 37    | 1.5b   |
| Stomach                     | 37    | 0.8    |
| Colorectum                  | 120   | 1.1    |
| Liver                       | 16    | 0.9    |
| Gall bladder                | 8     | 1.1    |
| Pancreas                    | 18    | 0.7    |
| Larynx                      | 15    | 1.0    |
| Lung                        | 215   | 1.4c   |
| Bone                        | 6     | 2.2c   |
| Connective and soft tissue  | 6     | 2.2c   |
| Skin melanoma               | 24    | 1.7b   |
| Skin non-melanoma           | 363   | 1.6c   |
| Breast                      | 3     | 1.3    |
| Cervix uteri                | 9     | 0.5    |
| Corpus uteri                | 31    | 0.9    |
| Ovary                       | 19    | 0.8    |
| Prostate                    | 161   | 1.0    |
| Testis                      | 6     | 2.2    |
| Bladder                     | 54    | 1.2    |
| Kidney                      | 27    | 1.5*   |
| Brain and nerves            | 4     | 0.6    |
| Thyroid                     | 6     | 2.4a   |
| Lymphomas                   | 32    | 1.2    |
| Hodgkin's disease           | 2     | 1.0    |
| Multiple myelomas           | 7     | 0.7    |
| Leukaemias                  | 23    | 1.2    |
| All sites                    | 1280  | 1.2c   |
| skin non-melanoma           | 197   | 1.2c   |

* P < 0.05; ** P < 0.01; *** P < 0.001.
Table II - continued

| Site of second primary tumour | Males Observed | Males SIR | Females Observed | Females SIR |
|-------------------------------|----------------|-----------|------------------|-------------|
| Any site*                     | 32.1           | 1.1       | 5.06             | 0.99        |
| Lung                          | 9.1            | 1.6       | 0                |             |
| Prostate                      | 10.1           | 1.8       |                  |             |
| Kidney                        | 4.5           | 5.8a      | 2.196b          |             |
| Site of first cancer: Kidney  |                |           |                  |             |
| Any site*                     | 16.1           | 1.2       | 6.12             |             |
| Skin non-melanoma             | 4.1            | 1.1       | 4.28             |             |
| Prostate                      | 4.1            | 1.7       |                  |             |
| Bladder                       | 5.72a         | 3         | 30.06b          |             |
| Site of first cancer: Lymphomas|             |           |                  |             |
| Any site*                     | 29.1           | 1.3       | 12.1             |             |
| Lung                          | 12.28b        | 1         | 2.1              |             |
| Skin non-melanoma             | 11.18a        | 12        | 3.62             |             |
| Site of first cancer: Leukaemias|          |           |                  |             |
| Any site*                     | 18.1           | 1.7b      | 12.25b          |             |
| Lung                          | 6.30b         | 0         |                  |             |
| Skin non-melanoma             | 9.30b         | 4.29b     |                  |             |

*Non-melanoma skin cancer excluded. #: P < 0.05; #: P < 0.01; cP < 0.001.

With respect to selected second primaries following urinary tract (bladder and kidney) and prostate cancer, significantly elevated SIRs were observed for kidney following bladder cancer (SIR = 5.8 in males and 19.6 in females, based on 4 and 2 cases, respectively), and for bladder following kidney (SIR = 7.2 in males and 30.0 in females, based on 5 and 3 cases, respectively). A total of 91 second primary neoplasms were registered among first occurring prostate neoplasms. No significant excess risk was observed, although SIR were above unity for stomach (SIR = 1.3), bladder (SIR = 1.5), lymphomas (SIR = 1.5) and leukaemias (SIR = 1.9).

Finally, second primaries were considered following leukaemias and lymphomas. In both sexes, the incidence of cancers of any site was significantly elevated following leukaemia (SIR = 1.77 in males, 2.5 in females), with a significant excess for lung in males and of non-melanomatous skin cancers in both sexes. Likewise, following lymphomas, there was an excess of lung cancers in males (SIR = 2.8), and of melanomatous skin in both sexes.

Discussion

The present work has mainly a descriptive value, and provides further quantification on a population-based dataset of the subsequent risk of various (second metachronous) primary cancers following any specific neoplasm. Its main value lies in the fact that only a few similar series have been published (Curtis et al., 1985; Storm et al., 1985; Teppo et al., 1985), and hence the contribution of this study, at least in its quantitative terms of risk assessment, can be relevant. A further interest of the present dataset derives from the strict criteria adopted for the definition of second primaries, and the practically total histological confirmation and revision (Levi et al., 1982, 1987). An important limitation of the study, however, is due to the relatively limited size of the present study population and of the length of the follow-up, and hence of the total number of multiple primary cancers examined, at least in comparison with similar studies from Connecticut (Curtis et al., 1985), Denmark (Storm et al., 1985), or Finland (Teppo et al., 1985).

Another potential limitation of this study design is related to problems of registration of second cancers. Although these problems are reduced by an active follow-up of all registered cases (Levi et al., 1989b), registration may be incomplete for some site, such as non-melanoma skin cancers. Therefore, non-melanoma skin cancer was excluded from the total number of second primaries following each separate first primary (Table II). Still, even for skin cancer registration this is a privileged and particularly well surveilled population (Levi et al., 1988a). Some caution in the interpretation is also important, since over 1,000 comparisons were made, and hence some significant results are bound to occur by change alone.

Some of the associations emerged can be related to common risk factor exposure. For instance, the generally elevated risk of multiple primaries of the upper digestive and respiratory tract should be related to tobacco and alcohol consumption (Tuyns et al., 1977; Franceschi et al., 1990), and viewed against the baseline high rates of these neoplasms in French-speaking Switzerland (Levi et al., 1989a). Tobacco consumption may also explain the excess of these neoplasms following lung cancer, and the elevated incidence of lung cancer following bladder and (probably) cervical cancer (US Department of Health and Human Services, 1982; IARC, 1986), although it is not obvious to explain, on this basis alone, the elevated leukaemia risk (Kabat et al., 1988; Kinlen & Rogot, 1988).

In some instances tumours with different aetiologies may simply appear significantly associated because they share similar social class characteristics. Along this line, the excess of cancer of the colorectum and prostate subsequent to a diagnosis of skin melanoma, may be interpreted, at least in part, in terms of the more elevated prevalence of these three neoplasms in the highest social classes in Switzerland (Levi et al., 1988a).
Other associations are well known, although quantification, again, may be of some interest. For instance, the risk of metastatic second primary breast cancer was elevated by 70% on a population (public health) level, but the real excess risk for epidemiological and etiological inference is probably double, since most women have only one breast at risk following surgery for breast cancer (Peto, 1987). The excess breast cancer incidence following primary ovarian cancer may be due to genetic susceptibility (Parazzini et al., 1992), besides common aetiological correlates (Franceschi, 1989). The association between multiple colorectal cancers, kidney and bladder cancer and melanoma and non-melanomatous skin cancers may be due to the action of common risk factor exposure, but also to the increased surveillance following a cancer diagnosis, which may be of particular relevance for skin neoplasms and explain the association of non-melanomatous skin cancer with other neoplasms (e.g., leukaemias).

In general, and in conclusion, the overall excess risk of a second primary cancer is relatively limited (about 20% in both sexes), and at least in part attributable to increased surveillance. Thus, the true excess risk, due to risk factor exposure or the consequences of treatment of the first neoplasm is even lower and, on a population level, of limited public health importance for most cancer sites. Noteworthy exceptions are represented by tumours of the upper aero-digestive tract where more than 5-to-10 fold increased cancer risks are common and clearly would justify special preventive and therapeutic efforts.

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