Second neoplasms after cancers of unknown primary

Even in populations with optimal structures for cancer diagnosis and certification, 3%–5% of neoplasms are classified as cancer of unknown primary (CUP) [1]. In the Vaud Cancer Registry, they account for 2%–3% of all neoplasms only [2].

CUPs tend to have poor prognosis and hence short survival, i.e. 1-year survival was 15% in the Vaud Cancer Registry [2]. Still, incidence of second primary cancers may be increased after CUP. Thus, in the Swedish Family Cancer Database, the standardized incidence ratio (SIR) of subsequent cancer following a CUP was 1.69, and several cancers had increased SIR, including skin and infection-related cancer [1].

We consider in the present report data on selected cancers following CUP using the Vaud Cancer Registry dataset [2]. This includes incident cases of malignant neoplasms in the Canton [3], whose population according to the 2000 Census was ~616 000 inhabitants. 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. The present series comprises a total of 2163 first CUP diagnosed from 1974 to 2007 and followed up to the end of 2007 for the occurrence of a second primary cancer of any site and morphological type [according to the standard International Classification of Diseases for Oncology, 9th Edition (ICD-O-9), except basal cell carcinoma of the skin], emigration or death, for a total of 1872.7 person-years. Calculation of expected numbers was based on site-, sex-, age- and calendar year-specific incidence rates, multiplied by the corresponding number of person-years at risk. The significance of the observed/expected ratios (SIRs) and the corresponding 95% confidence intervals (CIs) were based on the Poisson distribution.

Table 1. Observed (O) and expected (E) number of second primary cancers following 2163 first cancers of unknown primary site (Vaud, Switzerland, 1974–2007)

Site of second primary	O	E	SIR	95% CI
Oral cavity and pharynx	8	0.93	8.61	3.71–16.97
Skin, squamous cell carcinoma	8	3.73	2.14	0.92–4.22
Prostate	5	4.51	1.11	0.36–2.59
Other sites[a]	22	20.74	1.06	0.67–1.61
All sites	43	29.91	1.44	1.04–1.94

[a]Include: one cancer of esophagus, liver, biliary tract, lung, skin melanoma, male breast, endometrium, testis, bladder, thyroid and lymphoma; two cancers of kidney; three cancers of stomach, colorectum, female breast. SIR, standardized incidence ratio; CI, confidence interval.

Overall, 43 second cancers were reported after CUP versus 29.9 expected, corresponding to a SIR of 1.4 (95% CI 1.0–1.9) (Table 1). Significant excess risks were observed for cancer of the oral cavity and pharynx (eight observed, SIR 8.6, 95% CI 3.7–17.0). There were 8 squamous cell carcinomas (SCCs) of the skin (SIR 2.1, 95% CI 0.9–4.2), 5 cancers of the prostate (SIR 1.1, 95% CI 0.4–2.6) and 22 other neoplasms (SIR 1.1, 95% CI 0.7–1.6).

Thus, the present data confirm, and further quantify, the existence of excess cancer risk following CUP. Part of such excess risk may be due to recurrences and diagnosis of primary neoplasm, though the criteria for registration of second primary neoplasms in the Vaud Cancer Registry were strict [4]. There is also an increased medical surveillance after CUP diagnosis. This may account, partly or largely, for the slight apparent excess risk of prostate cancer restricted to the first year after CUP diagnosis (SIR 1.8, based on three cases) since prostate cancer is strongly influenced by prostate-specific antigen and other diagnostic procedures [5–7]. This cannot explain, however, the excess risk for other neoplasm: the SIR for all sites was 1.2 (95% CI 0.6–2.0, based on 13 cases) during the first year after CUP, 1.3 (95% CI 0.6–2.2, 13 cases) from 1 to 4 years and 2.0 (95% CI 1.2–3.2, 17 cases) ≥5 years after CUP diagnosis.

The excess risk for oral, pharyngeal and skin SCC are however apparently greater than for other neoplasms. Since some of these neoplasms are related to infectious agents (human papillomavirus) [8–11], this supports the concept that CUP-related (or treatment-induced) immunosuppression is a relevant underlying mechanism [12, 13] of the excess cancer risk after CUP. No cervical cancer was observed after CUP. This can be explained, however, by adequate surveillance for cervical cancer in this population [14].

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