Metachronous malignancies in men with previous prostate cancer in Umbria, Italy, 1994-2003

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ABSTRACT

Data about second primary tumors after prostate carcinoma are controversial. Some authors emphasize an increased incidence of some cancer sites, others an overall diminution. With the aim to provide further information to define the issue, we have analyzed the frequency of second metachronous primary malignancies in patients with diagnosed prostate cancer in the Umbria region of Italy. A total of 410 metachronous cancers among 4528 prostate cancer patients were abstracted from incident cases of the RTUP over the period 1994-2003. This cohort was compared with all cases (except prostate cancers) recorded in the RTUP archive. The expected number of cases was obtained from indirect standardization with regional incidence rates of several sites. The significance of the observed/expected ratios and the corresponding 95% confidence intervals were based on the Poisson distribution. A significant standardized incidence ratio was found for all sites but prostate, with 410/351 observed/expected cases. The significance disappears considering all sites except prostate and skin non-melanomas. Among several sites, significant standardized incidence ratios were found for skin non-melanomas, for bladder, for rectum, but not for colon cancers. Kidney, ureter and urethra showed a nonsignificant standardized incidence ratio. Nasopharynx showed a significant standardized incidence ratio, but the result was based on a very small number of cases. In our data, the increase in urinary bladder and rectal cancers, after prostate cancer diagnosis, seems to be real: it is plausible that the number of second cancers may be due to increased urologist surveillance, which, in our Region, does not seem to be reduced in elderly men.

Introduction

The last report of the Italian Association of Cancer Registries\(^1\) indicated that prostate cancer incidence in Italy currently accounts for 14.4% of total newly diagnosed cancers, second only to skin cancer (15.2%), whereas the mortality is second to lung cancer (14.5% vs 28.3%). In the age group over 65 years, prostate cancer incidence ranks first. Very similar patterns in incidence and mortality were reported by the Umbrian Population Cancer Registry (RTUP) for the Umbria region of Italy in the last few years\(^2\). In the period 1994-2003, the RTUP registered 4228 new cases and 1500 deaths from prostate cancer, with an increasing trend of crude rates in both incidence and mortality, due mainly to aging of the male population and to diffusion of opportunistic screening practices\(^2\).\(^4\).

Data about second primary tumors after prostate carcinoma are controversial, especially regarding the increased incidence of some sites deriving from irradiation of the prostate, particularly bladder cancer\(^5\)-\(^9\). Singh et al.\(^10\) reported a statically significant standardized incidence ratio (SIR) of 5.63 of a second cancer of the bladder in men affected by prostate cancer, not related to irradiation. In contrast, a reduction in overall risk of multiple tumors has been reported by several authors\(^11\)-\(^13\). Levi et al.\(^11\)
reported a statistically significant SIR of 0.7 for total sites and 0.6 for overall sites except for skin non-melanoma.

To provide further information to clarify the issue, we analyzed the frequency of second metachronous primary malignancies in patients with diagnosed prostate cancer, using the RTUP data covering the total regional population of Umbria starting from 1994. In our database, the number of metachronous cases occurring ≥5 years after prostate cancer is small and thus it could be difficult to assess a possible role of radiotherapy in determining an elevated risk of new primaries.

**Patients and methods**

The 4528 prostate cancer patients were collected from the Umbrian Population Cancer Registry as incident cases from January 1, 1994, to December 31, 2003. Over the same period, 410 non-synchronous second cancers in 410 patients were recorded among them. Table 1 reports the distribution of these multiple cancers by site. The cases were collected, coded, stored and analyzed in accord with the standard methods recommended for cancer registries\textsuperscript{14}, using the ICD 10\textsuperscript{15}. All bladder cancers were considered malignant if not reported as non-infiltrating. The person-years (14,995) were calculated starting from the date of prostate cancer diagnosis up to the date of death or follow-up at December 31, 2003.

This cohort of prostate cancer patients was compared with all cases (except prostate cancers) recorded in the RTUP archive over the period 1994-2003. The expected number of cases was obtained from indirect standardization with regional incidence rates of several sites relative to the overall period. The significance of the observed/expected ratios (SIR) and the corresponding 95% confidence intervals were based on the Poisson distribution\textsuperscript{16}.

**Results**

Table 1 reports the number of observed and expected cancer cases recorded by the RTUP among the 4528 prostate cancer patients and Umbrian general population, respectively. A significant SIR was found for all sites but the prostate (SIR = 1.17; CI = 1.06-1.29), with 410 observed and 351 expected cases. That significance disappeared when we considered all sites but the prostate and skin non-melanomas (SIR = 1.09; CI = 0.97-1.22), with 331 observed and 286 expected cases.

Among several sites, significant SIRs were found for skin non-melanomas (SIR = 1.53), bladder cancer (SIR = 1.59), and rectal cancer (SIR = 1.59), but not for colon cancer. Values of SIR lower than 1, but not significant, were found for lung (42 cases observed and 55 expected), stomach, liver, larynx and some less frequent cancers. Among the most frequent sites, SIR values greater than 1, but not significant, were shown for the colon (42 observed and 35 expected), pancreas, leukemia, myeloma, and brain cancer. Kidney, ureter and urethra, with 13 observed cases and 12 expected, showed a non-significant SIR equal to 1.08. Nasopharyngeal malignancies showed a significant SIR equal to 9.76 (CI = 1.84-28.89), but this result is based on only 3 cases.

**Discussion**

Several authors have associated the increase of second primary malignancies in prostate cancer patients with radiotherapy\textsuperscript{1,2,5,7-9,17-20}, estimating that the absolute risk is 1 to 290 for all prostate carcinoma patients treated with radiotherapy and 1 to 70 for long-term survivors\textsuperscript{3}. However, the latency period between radiation exposure and a radiation-induced malignancy, which has clearly occurred only within irradiated fields, is esti-
mated to be more than 5 years and ranges up to 15 years. Thus, second cancers that arise shortly after radiotherapy cannot be regarded as radiation related.\textsuperscript{7,8,19}

Some authors have not confirmed this association.\textsuperscript{6,21} Levi et al.\textsuperscript{11} affirmed that data referred to the Swiss Cantons of Vaud and Neuchâtel, over the period 1974-1994, support that the incidence rate for all neoplasms is reduced significantly in men diagnosed with prostate carcinoma. The authors explained this decrease as partly due to under-registration from misclassification between primary neoplasms and metastases, and, more likely, because of a reduced medical surveillance in elderly men with prostate carcinoma.\textsuperscript{11}

Our results indicate a non-significant increase in overall malignancies, when skin non-melanomas were disregarded, and, among those, a significant increase in the observed/expected ratio for urinary bladder and rectal sites, together with nasal cavity cancer. The significant increase in bladder cancer in prostate cancer patients may be due to a supposed association between the two sites,\textsuperscript{6,10} to a common pathway of carcinogenesis related to urinary stasis, to chronic inflammatory insults, or to genetic mutations\textsuperscript{10} beyond those induced by irradiation. In the RTUP database over the period 1994-2003, the number of multiple prostate-bladder cancers was more than 250, with about 60 synchronous cases. This association in Umbria is the strongest found among multiple primary tumors in males.\textsuperscript{22}

Barocas et al.\textsuperscript{23} emphasized a significant increase in kidney cancer in the same patients with prostate cancer and the converse. In our data, the SIR is very close to 1. Concerning the increased risk of rectal cancer derived from prostate irradiation, Kendal et al.\textsuperscript{21}, comparing prostate cancer survivors divided into three groups (radiotherapy, surgery and conservative treatment), concluded that it is only apparent from crude data analysis and it could be attributed to age and other unmeasured confounders associated with prostate cancer treatment and rectal cancer risk. In fact, the frequency of second rectal tumors increased from surgery to conservative treatment groups. Brenner\textsuperscript{24} affirmed that there are many plausible reasons (smoking habits, higher rate of prior heart attack and higher frequency of hormone therapy) why the conservative treatment group might be expected to have high secondary rectal cancer rates.

In our data, considering only metachronous cases, the increase in urinary bladder and rectal cancers after prostate cancer diagnosis seems to be real. Only 6 cases of bladder and as many of rectal cancer were diagnosed after 5 years from the prostate cancer. It is thus plausible that the number of second cancers may also be due to increased urologic surveillance, which in our Region does not seem to be reduced in elderly men.

Our study period was too short to separately analyze cases (on the total only 68, and among these 20 were skin carcinomas) diagnosed 5 years after the diagnosis of prostate cancer to verify in our data the possible effect of radiotherapy. In the future, with the availability of more prostate cancer cases and longer follow-up, it would also be interesting to retrieve radiotherapy history for all patients and proceed with a specific analysis to evaluate the excess of cancer risk by site following radiation treatment.

References


