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Multiple primary cancer incidence in Italy

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Abstract

Data collected from eleven Italian population-based cancer registries (overall population 7 200 000 inhabitants) were used to compute the incidence of second independent cancers (MP) in a cohort of cancer patients aged 15 years or more. Overall, 240 111 patients have been followed for 544 438 person-years during which 8766 second primary cancers were diagnosed leading to an observed to expected ratio (SIR) of MP of 1.08 (95% Confidence Interval (CI): 1.05–1.12). Restricting the analysis to metachronous cancers, there were 6974 second primary cancers diagnosed among 198 303 patients during 508,648 person-years with an SIR of 0.93 (95% CI: 0.90–0.96). According to the time since first cancer diagnosis, the SIR was significantly higher than expected during the first 2 months, then the overall risk was slightly lower than 1 up to 10 years after diagnosis. No differences were observed according to gender. The SIR significantly differed among the age groups with consistent excess risks in subjects younger than 65 years in comparison with older ones. Overall, significantly elevated SIR for metachronous cancers were evidenced for oral cavity and pharynx, larynx, connective, skin non-melanoma, ovary and kidney cancers. For each cancer site, the site-specific risk of further MP has been evaluated. The identification of strong site-specific associations may be useful for clinicians when following-up patients.

Keywords: Multiple primary cancers; Population-based; Incidence; Epidemiology

1. Introduction

Multiple independent primary cancers (MP) arising in the same patient have been described since the last century [1], firstly in case reports, then in clinical series [2,3] and more recently, quantified as incidence rates in population-based series [4–8]. Since tumours are relatively rare, e.g. arising in Italy with an overall annual rate of 250–900 cases every 100 000 subjects [9], and MP may be diagnosed only in cancer patients, it is necessary to follow a huge cohort of cancer patients to identify some MP. Therefore, the first population-based systematic studies on MP incidence have been carried out by long standing cancer registries [10] and at the national level [5,6]. Among the published studies, some results are consistent, especially those referring to cancers sharing common aetiological exposures, but others are still controversial. Part of the inconsistencies may be related to the different criteria adopted for the definition of MP inclusion, or may be due to differences in terms of genetic susceptibility, availability of diagnostic devices, diagnostic aggressiveness, treatment procedures and environmental exposures to carcinogens among the studied populations.

In Italy, 13 population-based cancer registries are active [9], most of which starting during the 1980s, the oldest ones just before the end of the 1970s. A first explorative study carried out in Italy evidenced that a wide co-operative approach was necessary to gain sufficient power for a descriptive study on MP [11]. In this study, the case series of eleven Italian cancer registries has been pooled to produce an estimate of the average risk of developing a second independent cancer in a cohort of population-based cancer patients aged 15 years or older.

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2. Patients and methods

Eleven registries were involved in the study out of the 13 population-based cancer registries that were active in Italy at the time of the study. The following list indicates the name and in brackets the starting year of activity and the mean annual covered population of the participating registries: Cancer Registry of Ragusa (1981, 290 000 inhabitants), Cancer Registry of Romagna (1985, 480 000), Ligurian Cancer Registry (1986, 700 000), Lombardy Cancer Registry (1976, 800 000), Macerata Province Cancer Registry (1991, 280 000). Modena Cancer Registry (1984, 400 000), Parma Cancer Registry (1978, 390 000), Piedmont Cancer Registry (1985, 1 000 000), Tumor Registry of Ferrara Province (1991, 360 000), Tuscany Cancer Registry (1985, 1 100 000), and Venetian Cancer Registry (1987, 1 150 000).

All registries involved in the study met the quality standards for the definition of incident cases, completeness of case collection and accuracy of coding necessary to be accepted in the Italian Association of Cancer Registries (IACR) [9] and to be included in the Cancer Incidence in Five Continents publication [12]. The overall population covered by the participating registries was around 7 200 000 inhabitants corresponding to approximately 13% of the total Italian population.

The inclusion criteria in the cohort were cancer patients (International Classification of Disease, 9a revision codes 140-208) [13] diagnosed in the period of registry activity and resident at the time of diagnosis in the area covered by the registry.

After the exclusion of cases diagnosed by death certificate only which ranged in different registries from 0.9 to 3.9% and autopsy only (exceptionally performed in Italy), this series included a total of 240 111 patients aged 15 years or older. The case series had a mean age at first cancer diagnosis of 65.6 years (range between registries 64.1–67.3 years) and a mean male/female ratio of 54.2% (range between registries 52.7–56.8%).

All the registries reported to be using the IARC/IACR rules to define MP [12]. These rules define MP as two or more tumours arising in different sites—defined by the first three digits of the International Classification of Disease for Oncology [14,15] or at the same site when histology is different according to Berg [16]. Only one tumour can be counted in paired organs or for systemic diseases unless the histology differs. Basal and squamous cell cancers of the skin were considered as MP.

Eighty-one percent of the first primary and 84.3% of second primary cancers were confirmed with a pathology diagnosis.

Each patient was followed from the incidence date up to death, diagnosis of a second primary cancer, or the end date which varied among the registries from 31 December 1989 to 31 December 1995 according to the up-date of follow-up. The status of life of each patient was actively checked at the municipality of residence and, in case of migration within Italy, at the new (or further) one. Those subjects who migrated to foreign countries (e.g. in 1997, 0.09% of the Italian resident population) were lost-to-follow-up. The Registries do not collect further clinical information on previous resident subjects after their migration.

The expected number of MP was calculated by multiplying the age-, gender-, 5-year period-, site- and registry-specific incidence rates by the same categories of person-years. The observed second primary cancers were compared with those expected by standardised morbidity rates, through the observed/expected ratio (standardised incidence ratio = SIR). Ninety-five percent confidence intervals (95% CIs) of SIR were computed assuming a Poisson distribution for observed cases. The measure of observed and of expected MP was a mean of the different registries contribution weighted by the person-years of each registry.

The relative risks for second primary cancers were evaluated as overall risks and as risk specific by gender, time since first cancer diagnosis (first 2 months, from 2 to 11 months, from 1 to 4 years, from 5 to 9 years and 10 or more years), site of second cancer, and as the association between the first and second cancer sites.

Synchronous cancers were defined as those diagnosed within the first 2 months after the first cancer and results are shown both excluding and including these tumours.

3. Results

Overall 240 111 patients have been followed for 544 438 person-years (2.3 years of mean follow-up) during which 8766 second primary cancers were diagnosed. Restricting the analysis to metachronous events (excluding both observed cases and person-years during the first 2 months), there were 6974 second primary cancers diagnosed in 198 303 patients during a follow-up period of 508 648 person-years (2.6 years of mean follow-up).

In Table 1, the number of second primary cancers and the SIR are shown, according to the site of the second cancer and the time of diagnosis since first cancer onset. The overall SIR was 1.08 (95% CI: 1.05–1.12), corresponding to an approximately 10% statistically significant increase in the risk of cancer of all sites among cancer patients in comparison with the general population. The overall result was mainly due to synchronous cancers, in fact, during the first 2 months the incidence of second independent cancers was 3.2 times greater than that expected in the general population. (95% CI: 2.92–3.53) Excluding the patients observed for less than

Table 1
Standardised incidence ratios (SIR) between observed and expected cases of second primary cancer according to the site of second cancer and the time since first cancer diagnosis: age at diagnosis of first cancer 15 years or older[a]

Site of second cancer	<2 months	2–11 months	1–4 years	5–9 years	>10 and + years	All		All metachronous	
	SIR	SIR	SIR	SIR	SIR	O	SIR	O	SIR
Oral-pharynx	4.2C	1.3A	1.4C	2.5C	0.6	273	1.7C	226	1.5C
Oesophagus	4.2C	1.2	1.0	1.9B	1.2	112	1.4C	88	1.2
Stomach	1.8C	0.7C	0.8C	0.9	0.9	651	0.9C	551	0.8C
Colon	3.8C	0.8A	1.0	1.1	1.3	763	1.2C	593	1.0
Rectum	3.4C	1.0	1.0	0.8A	1.0	383	1.1A	300	0.9
Liver	1.7A	0.6B	0.7	0.7	0.4	164	0.8C	139	0.7C
Bladder	2.3B	0.7A	0.7B	0.9	1.0	93	0.8	76	0.7B
Pancreas	1.3	0.7A	0.8A	0.7	1.5	179	0.8B	160	0.8B
Larynx	3.6C	0.9	1.4B	1.1	2.8[b]	206	1.3C	164	1.2A
Lung	2.1C	0.7C	1.1A	1.2B	1.5A	1221	1.1C	1050	1.0
Bone	1.3	1.5	0.9	1.5	0.2[b]	12	1.2	11	1.2
Connective tissue	3.6B	2.1A	1.3	1.3	7.1B	49	1.8C	42	1.6B
Skin, melanoma	2.7B	1.2	1.3A	1.1	1.7[b]	96	1.3B	83	1.2
Skin, non-melanoma	4.0C	1.2B	1.2C	0.9	1.8	1099	1.4C	877	1.2C
Female breast	2.2C	0.7C	0.7C	0.6C	0.6	495	0.8C	415	0.7C
Cervix uteri	3.4C	1.7A	0.8	0.8	0.8[b]	66	1.2	54	1.0
Corpus uteri	8.9C	0.9	1.1	0.8	1.0	190	1.4C	123	1.3
Ovary	10.4C	1.7B	1.2	1.2	1.1	183	1.8C	123	1.3C
Prostate	4.2C	0.9	0.7C	1.0	0.6	536	1.1	377	0.8C
Testis	4.1	1.7[b]	1.5	3.4[b]	0.8[b]	7	1.1	5	0.8
Urinary bladder	4.2C	0.8A	0.9A	0.8	0.7	609	1.1B	437	0.9C
Kidney	7.8C	1.7C	1.3C	1.3	1.4	395	1.8C	281	1.4C
CNS	0.9	0.4B	0.5C	0.9	1.6	51	0.6C	46	0.6C
Thyroid	8.3C	1.3	1.1	1.1	1.0[b]	67	1.6C	45	1.1
Non-Hodgkin's lymphoma	3.7C	1.0	0.8	0.6A	0.5	213	1.0	163	0.8A
Hodgkin's lymphoma	1.9	0.7	1.5	1.0	0.4[b]	27	1.2	24	1.2
Multiple myeloma	2.2B	0.9	0.8	0.5A	0.9	89	0.9	74	0.8A
Leukaemia	3.6C	0.7A	0.9	0.9	1.1	163	1.0	123	0.8A
All sites	3.20C	0.88C	0.94C	0.95	1.07	8766	1.08C	6974	0.93C
95% CI	2.92–3.53	0.82–0.94	0.90–0.98	0.88–1.04	0.83–1.32	1.05–1.12		0.90-0.96	
Person-years	35 790	131 084	287 643	78 065	11 856	544 438		508 648	

CI, Confidence Interval; CNS, central nervous system; O, observed.
[a] A = $P<0.05$; B = $P<0.01$; C = $P<0.001$.
[b] When no cases were observed, instead of the SIR, the expected number of cases is reported.

2 months, the ratio between the observed and expected MP was 0.93 (95% CI: 0.90–0.96).

According to the time since first cancer diagnosis, after an increase during the first 2 months, the overall risk was slightly lower than 1 up to 10 years after diagnosis (SIR = 0.88, 95% CI: 0.82–0.94 from the second to the eleventh month, SIR = 0.94, 95% CI: 0.90–0.98 from the second to the fourth year, SIR = 0.95, 95% CI: 0.88–1.04 from the fifth to the ninth year and SIR = 1.07, 95% CI: 0.83–1.32 afterwards).

According to gender, latency and age at first cancer diagnosis (15–64 years and 65 years and older) (data not shown), there was an excess of cases diagnosed synchronously in both age groups and both genders. For metachronous cancers, the SIR pattern differed among age groups with consistently excess risks in younger subjects and the SIR constantly lower than 1 for older ones. No differences were observed according to gender. According to the period of first cancer diagnosis, the SIR was slightly constant being 0.9 for 1978–1982, and 1.1 for the other three following periods, 1983–1987, 1988–1992 and 1993–1995.

Table 2 gives the observed number of metachronous second cancers and the SIR according to the site of first cancer and to gender (data are shown for all the second sites with significantly increased SIR in at least one gender). Patients affected by cancer of the oral cavity and pharynx had increased SIR in both genders for cancers of the oral cavity and pharynx (sites other than the primary) and the oesophagus, for the lung and non-melanoma skin cancers in males and for cervix uteri cancers and non-Hodgkin's lymphoma among females. Males oesophagus cancer patients showed a significantly increased risk of cancers of the oral cavity and pharynx. Thyroid cancers among males were significantly high in stomach cancer patients.

Among colon and rectum cancers, 32 females developed a further cancer of the ovary. A total of 8 patients

Table 2
Second metachronous cancers observed (O) at selected sites and corresponding standardised incidence ratios (SIR) and 95% Confidence Intervals (95% CI) according to site of first cancer and gender: age at diagnosis of first cancer 15 years or older

Site of second	Males			Females		
Primary cancer	O	SIR	95% CI	O	SIR	95% C.I.
Site of first cancer: Oral cavity and pharynx						
Oral cavity and pharynx	30	5.5	3.7–7.9	5	14.3	4.6–33.3
Oesophagus	19	7.4	4.5–11.6	3	16.7	3.4–48.7
Lung	88	2.6	2.1–3.2	5	3.1	1.0–7.3
Skin, non-melanoma	29	1.9	1.3–2.7	5	1.7	0.6–4.0
Cervix uteri				4	6.5	1.8–16.5
Non-Hodgkin's lymphomas	3	0.8	0.2–2.2	5	5.2	1.6–12.0
Site of first cancer: Oesophagus						
Oral cavity and pharynx	4	5.9	1.6–15.1	0	0.0[a]	
Site of first cancer: Stomach						
Thyroid	4	4.8	1.3–12.2	1	0.8	0.0–5.9
Site of first cancer: Colon						
Ovary				23	2.8	1.8–4.2
Site of first cancer: Rectum						
Ovary				9	2.4	1.1–4.1
Site of first cancer: Pancreas						
Female breast				8	2.6	1.4–6.4
Site of first cancer: Larynx						
Oral cavity and pharynx	18	2.1	1.5–3.7	2	15.4	0.8–71.3
Oesophagus	17	4.2	2.5–6.8	0	0.1[a]	
Lung	146	2.5	2.1–2.9	4	6.2	1.7–15.8
Site of first cancer: Lung						
Oral cavity and pharynx	37	3.1	2.2–4.3	0	0.4[a]	
Larynx	28	2.1	1.4–3.0	1	2.2	0.0–16.5
Site of first cancer: Bone						
Connective tissue	2	100	12.2–361.3	0	0.0[a]	
Site of first cancer: Connective tissue						
Oral cavity and pharynx	0	0.7[a]		2	15.4	1.9–55.6
Site of first cancer: Melanoma						
Skin, non-melanoma	6	1.6	0.6–3.4	9	2.4	1.1–4.5
Prostate	10	2.7	1.3–5.0			
Site of first cancer: Skin, non-melanoma						
Oral cavity and pharynx	34	1.8	1.2–2.5	10	2.7	1.3–5.0
Larynx	31	1.6	1.1–2.2	0	0.8[a]	
Lung	184	1.3	1.1–1.5	13	0.8	0.4–1.4
Melanoma	13	2.5	1.3–4.3	11	2.8	1.4–5.0
Non-Hodgkin's lymphoma	14	0.8	0.4–1.3	24	2.2	1.4–3.2
Site of first cancer Female breast						
Ovary				44	2.4	1.7–3.2
Site of first cancer: Cervix uteri						
Lung				15	3.9	2.2–6.5
Urinary bladder				10	4.7	2.3–8.7
Site of first cancer: Corpus uteri						
Lung				18	2.0	1.2–3.1
Female breast				63	1.4	1.1–1.8
Site of first cancer: Ovary						
Colon				14	2.4	1.3–3.9
Site of first cancer: Prostate						
Melanoma	10	2.6	1.3–4.9			
Site of first cancer: Urinary bladder						
Lung	152	1.2	1.0–1.4	12	2.8	1.4–4.8
Larynx	34	1.8	1.2–2.5	0	0.3[a]	
Connective tissue	3	1.5	0.3–4.3	4	12.9	3.5–33.0
Cervix uteri				5	3.5	1.1–8.2
Prostate	88	1.3	1.1–1.6			
Kidney	72	3.5	2.8–4.4	13	7.3	3.9–12.4

(*continued on next page*)

Table 2 (*continued*)

Site of second	Males			Females		
Primary cancer	O	SIR	95% CI	O	SIR	95% C.I.
Site of first cancer: Kidney						
Colon	13	1.1	0.6–1.8	13	2.6	1.4–4.5
Urinary bladder	47	3.0	2.2–4.0	11	7.5	3.7–13.4
Site of first cancer: Thyroid						
Colon	5	4.8	1.5–11.1	4	1.3	0.4–3.3
Pancreas	0	0.4[a]		5	5.2	1.7–12.0
Site of first cancer: Non-Hodgkin's lymphoma						
Skin, non-melanoma	29	2.6	1.8–3.8	17	2.6	1.5–4.1
Kidney	10	2.8	1.3–5.1	2	1.3	0.2–4.9
Hodgkin's lymphoma	4	12.5	3.4–32.0	1	4.8	0.1–26.5
Site of first cancer: Hodgkin's lymphoma						
Leukaemia	1	2.9	0.1–15.9	3	15.8	3.3–46.1
Site of first cancer: Leukaemia						
Skin, non-melanoma	19	2.5	1.5–3.9	10	2.4	1.2–4.5

[a] When no cases were observed, instead of the SIR the expected number of cases is reported.

with pancreas cancer developed female breast cancer (SIR = 2.6).

For patients affected by larynx cancer, 146 males and 4 females experienced lung cancer and significantly increased risks were also present for the oral cavity and pharynx and for the oesophagus in males. Male lung cancer patients had significantly increased risks for the oral cavity and pharynx and laryngeal cancer. Two male patients with bone tumours developed a subsequent cancer of the connective tissue (SIR = 100). A high-risk for cancers of the oral cavity and pharynx was seen for female connective tissue cancer patients.

In melanoma patients, there was a high risk for skin non-melanoma and for prostate cancer. A total of 824 males and 409 females experienced a second cancer diagnosis after skin non-melanoma. Significant excess ratios were evidenced for cancers of oral cavity and pharynx, larynx and lung in males and oral cavity and pharynx non-Hodgkin's lymphoma in females; there was an almost threefold SIR for melanoma in both genders.

With reference to female breast cancer, 44 women had a subsequent diagnosis of ovarian cancer, and the risk for cancer of the corpus uteri was also elevated, SIR = 1.3 (95% CI: 1.0–1.7). Significant excess ratios were observed after cervix uteri cancer for lung (SIR = 3.9) and urinary bladder cancers (SIR = 4.7) and almost significantly for rectal cancer SIR = 2.4 (95% CI: 1.0–4.6). 63 out of the 218 second cancers that arose among the patients with corpus uteri primary cancer were of the breast (SIR = 1.4), and patients with this primary cancer also had an excess risk for lung cancer. Women suffering from ovarian cancer experienced an excess of colon cancer and an increased risk for rectal cancer SIR = 2.5 (95% CI: 1.0–5.2).

There was an increased SIR for melanoma among prostate cancer patients. A total of 689 males and 100 females with urinary bladder cancer had a second cancer diagnosis; there were substantial excess risks for cancers in the larynx and prostate among males, lung and kidney in both genders and connective tissue and cervix uteri among females. Kidney cancers were followed by more urinary bladder cancers than expected; moreover, one fifth of the 67 second tumours among females were colon cancers (SIR = 2.6). A total of 17 males and 41 females had a further cancer diagnosis following thyroid cancer. Significant excess risks were observed for colon cancer among males and pancreatic cancer among females.

With respect to second primary cancers following lymphatic tumours, there were excesses for Hodgkin's lymphoma, kidney (significant in males only) and skin non-melanoma among non-Hodgkin's lymphoma patients and increased SIR for leukaemia, significant in females only, among those with Hodgkin's lymphoma. Among patients affected by leukaemia, an increased SIR was present in both genders for skin non-melanoma.

4. Discussion

This descriptive study provides quantitative information on the risk of developing second primary cancers in an Italian population-based cohort of approximately 240 000 cancer patients.

When only second metachronous cancers were considered, the cohort experienced a reduced risk of approximately 10% of developing further cancers in comparison with the general population.

This overall result is in agreement with the Danish study (SIR = 0.91, 95% CI: 0.89–0.93) [5] and the English and Walsh study (SIR = 0.77, 95% CI: 0.75–0.79) [17]. A previous study in Finland did not evidence any difference between cancer patients and the general population (SIR = 0.99, 95% CI: 0.95–1.03) [6], whereas increased risks were shown in a more recent Finnish study (SIR = 1.12, 95% CI: 1.10–1.13) [18], in Japan (SIR = 1.08, 95% CI: 1.03–1.13) [8], in Switzerland (SIR = 1.21, 95% CI: 1.13–1.29) [7] and in Connecticut (SIR = 1.31, 95% CI: 1.28–1.34) [4]. Part of the inconsistencies among the results are presumably due to different criteria in second cancer inclusion and definition. In addition, the synchronous time definition varied widely among cohorts, ranging from 2 months [4,5,7] to 3 months [8] up to 1 year [6,17,18].

In this cohort, synchronous cancers were excluded, according to previously published studies, to avoid bias in comparing the intensively investigated population of patients attending diagnosis and treatment for a first cancer, with the general one. However, the overall decreased SIR for metachronous cancers may well be due to the effect of this exclusion over a relatively short mean follow-up period (2.6 years). In fact, the changes of risk for all MP over time since diagnosis of the first primary observed in this study was similar to the theoretical trend of the incidence rate after a screening test, with a strong increase at time zero (synchronous period), when prevalent cases are identified through anticipation of cancer diagnosis, followed by a decrease due to the lack of diagnosis of cancers already identified and afterwards a steep or smooth slope of further increase until the usual incidence levels are reached again [19]. For MP the true incidence rate is not known and subsequent periodical checks for the first primary may affect the incidence rates of other cancers occurring in the investigated organs, through both over-diagnosis and diagnostic anticipation. In fact, our results confirmed the tendency of over-anticipated diagnosis during the first 2 months that has already been evidenced in Connecticut, Switzerland and in Denmark, where 20–30% of the whole MP series was diagnosed during the first 2 months after the first cancer diagnosis [4,5,7].

When all cancers, both synchronous and metachronous, were included not only was there a very high SIR during the first two months, but also the result for the whole follow-up period showed an approximately 10% increased risk.

Data on observed second cancers may be reduced due to migration of patients. In fact, information on further tumours incident in subjects previously resident in a registry area who then migrated outside are not collected. In Italy, the migration rate from the municipality of residence is rather low, being on average in 1996 2.1%, with a small number migrating to foreign countries (0.09%). Migration is slightly higher in the Northern regions (2.4%) than in the Centre (1.9%) and in the South (2.0%). Interestingly, nine out of the 11 Registries involved in the study covered an area including several municipalities (median number of municipalities = 31; range 5–235), therefore, part of the migration rate was towards other municipalities included in the same registry area. In fact, data from the province of Varese showed that in 1996, 62.5% of the migration was within the same registry area and therefore did not result in a loss of information. Moreover, migration involves young subjects, among whom cancer is rather infrequent, e.g. 92.3% of those who migrated out of the province of Varese were younger than 60 years of age. In conclusion, some second cancers may be lost due to migration, although it probably did not significantly affect the overall results.

Some of the evidenced associations between the cancer sites may be due to the effect of the same risk factor on the same tissue, classified as a different organ according to the adopted rules.

Exposure to tobacco smoking and alcohol could explain the elevated bi-directional risks evidenced between several cancers of upper aero-digestive system that shared the same squamous cell tissue [20], with consistent reciprocal associations between oral cavity, oesophagus, larynx, and lung as previously evidenced [4–7,21]. Moreover, as evidenced in a Norwegian cancer cohort, and also in this study, cervical cancer risk was significantly increased in women with smoking-related first cancers such as oral cavity and urinary bladder cancers [21]. Moreover, cervical cancer risk was increased (although not significantly) in those affected by laryngeal but not lung cancer. Conversely, women with cervix uteri cancer also had a higher risk of lung [4–6] and urinary bladder cancer.

Common hormonal and dietary factors may explain the associations evidenced between colon and ovary (bi-directional), rectum and ovary, female breast and ovary, corpus uteri and female breast. The relationship among these organs agrees with the statistically significant bi-directional associations previously evidenced between breast and corpus uteri [4–6], breast and colon [4,6], breast and ovary [4,6], colon and corpus uteri [4–6], ovary and colon [4,5] and corpus uteri and ovary [5]. Hormonal factors may have played a role also in the bi-directional association between prostate and melanoma.

No information was available on the treatments given for the first cancers; however, radiotherapy or chemotherapy may have caused some associations, e.g. the increased risk of leukaemia after Hodgkin's lymphoma or after ovary cancer [22]. In addition, the evidenced increased risk for urinary bladder cancer after cervix uteri cancer may be related to radiation treatment, as previously evidenced in Ref. [23]. Moreover, the association between bone and connective tissue cancers, also evidenced in Connecticut [4] may be treatment-related.

An increased site-specific medical surveillance may explain at least part of the bi-directional increased risk between skin melanoma and non-melanoma cancers, while detection bias may explain some of the excess diagnosis of prostate cancer after urinary bladder neoplasias.

As evidenced in a Scandinavian cohort [24] and also in this study, there was an association between skin non-melanoma and non-Hodgkin's lymphoma, which may be related to the immunedeficiency induced by ultraviolet light.

In addition, several unexplained associations were identified, such as between the sites of the pancreas and female breast, connective tissue and oral cavity and pharynx, urinary bladder and connective tissue, and in agreement with previous observations, the thyroid and pancreas [4]. However, it is probable that due to the high number of comparisons performed these findings may be due to chance alone.

We evidenced several SIR significantly lower than 1 when site-specific risks were evaluated. These results are difficult to interpret. It is unlikely that cancer patients are biologically protected against other cancers, unless the protection is related to the treatment for the first cancer. This effect could account for the deficit of corpus uteri cancers among cervical cancer patients (SIR = 0.2) and vice versa (SIR = 0.3), probably due to the surgical removal of the organ. In other circumstances, a bias due to less intensive medical scrutiny may explain such results, as for the metachronous cancer deficit observed for patients older that 65 years. Moreover, reduced SIR may also be due to a reduced cancer notification when metastases are suspected, this may partially explain the low risk for lung cancers in stomach cancer patients (SIR = 0.6) or the low risk for liver cancer after colon (SIR = 0.5) and rectum (SIR = 0.2) cancers.

In conclusion, this study showed a slight modification of the risk of developing MP in Italian cancer patients in comparison with the general population. There was an overall approximately 10% decrease if only metachronous cancers are considered and approximately 10% increase when synchronous ones were included. These overall values do not point to a major public health problem and being strongly related to the method used do not have any evident clinical value. However, the identification of strong site-specific associations, that are still relevant according to the exclusion of synchronous cancers, may be useful for clinicians to quantify the risks of developing a MP after a specific primary cancer when following-up patients with cancer.

Appendix

Italian Multiple Primary Cancer working group: E. Buiatti (AS Firenze), L. Gafà, R. Tumino (Cancer Registry of Ragusa), F. Falcini (Cancer Registry of Romagna), M. Vercelli, M.A. Orengo, E. Marani (Ligurian Cancer Registry), P. Crosignani (Lombardy Cancer Registry), F. Pannelli, S. Vitarelli (Macerata Province Cancer Registry), M. Federico, L. Mangone (Modena Cancer Registry), V. De Lisi, L. Serventi (Parma Cancer Registry), R. Zanetti, S. Patriarca, S. Rosso (Piedmont Cancer Registry), S. Ferretti, S. Zago (Tumor Registry of Ferrara Province), E. Crocetti, P. Falini (Tuscany Cancer Registry), L. Simonato, S. Guzzinati (Venetian Cancer Registry).

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