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Second primary malignancies in patients with non-melanoma skin cancer: Results from a cancer registry–based study in Emilia Romagna, north-east Italy

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ABSTRACT

Background: previous research on the risk of subsequent, primary non-cutaneous malignancies among patients with non-melanoma skin cancers (NMSCs) led to conflicting results. We aimed to investigate a possible link between NMSC and second primary malignancies by using the population-based data available in cancer registries.

Methods: this observational study retrospectively assessed the risk of occurrence of both synchronous and metachronous second primary tumours in a cohort of cancer patients whose first diagnosis was NMSC. The cohort came from the network of general cancer registries of the Emilia-Romagna Region, northeast Italy, in the period between 1978 and 2012, and was compared with the general population living in the same area. Two main indexes were used: i) Standardized Incidence Ratio (SIR), calculated as the ratio between the observed and the expected number of second cancers and ii) Excess Absolute Risk (EAR), expressing the absolute excess or deficit of second cancer incidence.

Results: in the period analysed (1978–2012, 72,503,157 person/years, PYs), 89,912 primary NMSC were found in 76,414 patients. Among them, 14,195 developed a second primary cancer in the subsequent 501,763 follow-up PYs. NMSC patients showed an overall SIR of 1.22 (CI 95% 1.20-1,24) and an EAR of 5.11 cases/1000 PYs (CI 95% 4.48–5.74).

Conclusions: the study results showed that NMSC patients had an increase in relative risk and, at least for some tumours, in absolute risk of developing a second cancer when compared with the general population. Genetic, environmental and personal risk factors may influence this finding.

1. Introduction

Cancer survivors have increased over the past few decades, due to the increase in early diagnosis and the improvement in treatment and supportive care [1–3]. One of the most serious late effects among cancer survivors is the development of additional malignancies, either recurrences or new primary cancers. They arise as a result of numerous factors, such as genetic predisposition, aging, lifestyle choices, environmental exposures, mutagenic effects of previous cancer treatments, and their interactions [4]. The reported incidence of new malignancies in cancer survivors varies considerably, but they are estimated to account for 16% of all cancers [5].

Non-melanoma skin cancers (NMSCs), which essentially include basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are by far the most common malignancies in white populations [6]. Although NMSCs are usually curable, they represent a major public health

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problem due to their high prevalence and expense of treatment [7]. Subjects with NMSCs are known to be at increased risk of developing subsequent NMSCs, as well as malignant melanoma, probably due to the shared phenotypic and environmental risk factor, mainly ultraviolet (UV) radiation [8–10]. Biased ascertainment of new skin primaries as a result of increased dermatological surveillance should be taken into account, too. Accumulating evidence seems to support the fact that a personal history of NMSC also exposes to an increased risk for second primary cancers other than just skin tumours [11], although an inverse association has been found as well [12].

A recent systematic review, which aimed to address this issue by assessing the available evidence on this topic, mostly based on national cancer registry data, revealed strong evidence that NMSC is associated with an approximately 10% increased risk of subsequent primary cancer other than NMSC [13].

The purpose of the present study was to investigate a possible link between NMSC and subsequent primary malignancies by using the population-based data available in cancer registries.

2. Materials and methods

2.1. Study setting

This observational study analysed a retrospective cohort of cancer patients whose first diagnosis was non-melanoma skin cancer (NMSC). The cohort came from the network of general cancer registries of the Emilia-Romagna Region in northeast Italy, (with about 3,500,000 residents in 2010) belonging to the Italian Cancer Registry Association (AIRTUM). All data were validated by the International Agency for Research on Cancer (IARC) [14] and covered an overall period from 1978 to 2012, but were different for each province (due to the longer casuistry of the Parma province, with its 426,000 inhabitants, from 1978 to 2012 with respect to the period 2006–2011 for the Piacenza province, with 290,000 inhabitants).

NMSC included in the study were SCC, BCC, appendage carcinomas and mixed tumours (carcino-sarcomas), according to the ICD-O 3classification [15] topography (codes from C44.0 to C44.9) and morphology (M-8000 – M-8575; M-8940; M-8980, with behaviour 5th code /3). A brief analysis considering separately patients with primary SCC (ICD-O 3 M-8050-8084) and those with primary BCC (ICD-O 3 M-8090-8110) was conducted as well. In accordance with the IARC and European Network of Cancer registries (ENCR) rules, for each patient, a tumour to be considered and included as a second primary cancer should not be an extension, a recurrence or a metastasis from a previous tumour [16,17]. SCC and BCC were considered “different” tumours (multiple) when present in a single patient. A check by IARCcrgTools [18] program was performed in order to avoid registration errors or biases for first and second primaries.

The study assessed the risk of occurrence of second primary tumours in NMSC patients, both synchronous (*i.e.* within 2 months from the diagnosis of primary NMSC) and methachronous (diagnosed 2 months or later after the first tumour) [19], compared with the risk of the general population living in the same area.

2.2. Analysis

Person-years at risk (PYs) were defined as the period from first NMSC to the second cancer incidence or last known vital status/death or last follow-up (2013 or 2014 depending on each registry). Patients without follow-up after the first primary NMSC, for example in the case of Death Certification Only or autopsy diagnosis, were excluded from this analysis.

Two main indexes were used to check the hypothesis of a higher cancer incidence risk of NMSC patients in respect to the general population: i) Standardized Incidence Ratio (SIR), calculated as the ratio between the observed and the expected number of second cancers (the latter on the basis of their incidence in the general reference population), and ii) Excess Absolute Risk (EAR), expressing the absolute excess or deficit of second cancer incidence (difference between the rate of the observed number of second cancers and the rate of expected ones).

2.3. Statistics

Analyses were performed by MP-SIR session of SEERStat Software [20]: SIR and EAR were expressed by sex, latency of the second tumour, attained age and period at the second diagnosis. Confidence Intervals (CIs) at 95% and 99.9% were calculated according to Poisson distribution. Statistical p was considered significant for values < 0.05 and < 0.001.

3. Results

3.1. Overall second cancer occurrence risk

In the period studied (1978–2012, 72,503,157 person/years), 89,912 primary NMSC were found in 76,414 patients. Among them, 14,195 developed a second primary cancer in the subsequent 501,763 follow-up PYs. Therefore, these patients showed an overall SIR of 1.22 (CI 95% 1.20–1.24) and an EAR of 5.11 cases/1000 PYs (CI 95% 4.48–5.74). Second cancers after at least a 2-months interval from the first were 13,525 (in 489,207 p/y), with a SIR of 1.19 (CI 95% 1.17–1.21) and an EAR of 4.42 cancers/1000 PY (CI 95% 4.48–5.74).

3.2. Second cancer occurrence by gender

In male subjects, relevant second methachronous cancer risk excesses were found in head and neck cancer (SIR = 1.36, higher after a 12 month latency), salivary glands (SIR = 3.77, higher in the first 5 years of latency), liver (SIR = 1.22), lung (SIR = 1.24), skin melanomas and other skin cancers (SIR = 2.38 and 1.30, respectively, constant in all ≥2 months follow-up period), soft tissues (SIR = 1.63), prostate (SIR = 1.17, constant from 2 to over 120 months of follow up), non-Hodgkin lymphomas (SIR = 1.45, constant in the first ten years after primary NMSC), leukemias (SIR = 1.22), all-site tumors (SIR = 1.20) and all sites excluding NMSC and melanomas (SIR = 1.17).

Absolute excess (EAR) of second synchronous and metachronous tumours was, respectively, 66.10 and 57.97/10,000 PYs. Higher risks were observed in other skin carcinomas (total EAR≅27; metachronous EAR≅17), lung (both EAR≅10), prostate (both EAR≅8), melanomas (both EAR≅5), non-Hodgkin lymphomas (both EAR≅3), head and neck (both EAR≅3) and liver (both EAR≅2). Only soft tissue metachronous tumours showed a significant reduction of EAR (≅0.6). Detailed SIRs by follow-up period and EARs for males are reported in Table 1.

In female subjects the excesses of overall risks of multiple (metachronous) tumours mainly concerned salivary glands (SIR = 3.62), oesophagus (SIR = 1.89), stomach (SIR = 1.18), colon (SIR = 1.16), pancreas (SIR = 1.23), lung (SIR = 1.23), cutaneous melanoma (SIR = 2.35, present in all follow-up periods and higher in the first year), soft tissues (SIR = 1.61), breast (SIR = 1.19, constant after the first year)), kidney (SIR = 1.27), urinary tract (renal pelvis and ureter SIR = 1.94), Hodgkin and non-Hodgkin lymphomas (SIR = 2.02 and 1.31 respectively), leukemias (SIR = 1.36), all-site tumours (SIR = 1.17) and all sites excluding NMSC and melanomas (SIR = 1.20).

In females, EAR x 10,000 PYs showed excesses in breast cancer (EAR≅5 both synchronous and metachronous), skin melanoma (EAR≅3), other skin carcinomas (overall EAR≅6, concentrated in the early follow up), colon (EAR≅2), lung and non-Hodgkin lymphomas (EAR≅2). Overall EAR, including both synchronous and metachronous cancers, was ≅33, whereas it was ≅28 for metachronous tumours only. Detailed data for SIR and EAR for several follow-up periods are shown in Table 2. A brief overview of SIRs in males and females by latency of

Table 1
SIR & EAR x 1000 male skin carcinoma patients by 2nd cancer site and follow-up period.

Second cancer site	SIR[1]							EAR[2]	
	≥2 months	≥0 months	0–1 months	2–11 months	12–59 months	60–119 months	≥120 months	≥2 months	≥0 months
Patients at interval beginning	41.637	42.609	42.609	41.637	37.743	21.116	9.542	41.637	42.609
Person-years (PYs)	265,162	272,156	6,994	32,973	115,343	72,707	44,140	265,162	272,156
C00-06;09-14; 30-32 Upper aerodig. tract	**1.36****	**1.33****	0.36	1.39	**1.39****	**1.42***	1.14	**2.82****	**2.65***
C07-08 Salivary glands	**3.77****	**3.68****	0.00	**6.55****	**4.96****	2.02	2.03	**1.09****	**1.07****
C15 Oesophagus	1.07	1.11	2.89	2.03	1.14	0.96	0.41	0.11	0.18
C16 Stomach	1.08	1.07	0.66	0.88	**1.23***	1.04	0.92	1.43	1.26
C18 Colon	1.08	1.07	0.93	**1.26***	1.09	1.01	1.04	1.84	1.76
C19-21 Rectosigmoid junction-rectum	0.97	0.96	0.47	**0.56***	1.02	1.04	1.03	0.00	−0.40
C22 Liver	**1.22***	**1.20***	0.57	1.21	**1.23***	1.22	1.20	**1.77****	**1.65***
C23-24 Gallbladder, bile ducts	0.97	0.98	1.22	0.77	0.86	1.31	0.81	−0.07	−0.07
C25 Pancreas	1.04	1.02	0.21	1.02	0.87	1.16	1.22	0.26	0.14
C33-34 Trachea, bronchus, lung	**1.24****	**1.24****	1.13	**1.25****	**1.20****	**1.33****	**1.18****	**9.96****	**9.81****
C40-41 Bone	0.70	0.68	0.00	1.45	0.00	0.63	1.98	−0.07	−0.07
C43 Skin melanoma	**2.38****	**2.50****	**7.62****	**2.16****	**2.26****	**2.41****	**2.72****	**4.86****	**5.29***
C44 Other skin	**1.30****	**1.47****	**8.70****	**1.75****	**1.33****	**1.18****	**1.17****	**17.16****	**26.56****
C45 Mesothelioma	1.00	0.98	0.00	1.25	0.51	1.58	1.07	0.00	−0.04
C46 Kaposi sarcoma	1.04	1.02	0.00	0.56	1.55	0.46	1.06	0.04	0.00
C47,49 Soft tissues	**1.63***	**1.63***	1.66	1.40	1.24	1.55	**2.74***	**0.60***	0.59
C50 Breast	1.13	1.10	0.00	0.70	1.34	1.15	0.87	0.08	0.04
C61 Prostate	**1.17****	**1.17****	1.03	**1.26***	**1.15****	**1.15***	**1.20***	**8.18****	**8.01****
C62 Testis	0.95	1.06	5.00	0.00	0.62	1.51	1.69	0.00	0.00
C64 Kidney	1.05	1.04	0.61	0.90	1.02	1.23	0.96	0.42	0.33
C65-66;68 Renal pelvis, other urinary	1.01	1.01	0.99	2.07	0.91	0.92	0.75	0.04	0.04
C67 Bladder	1.07	1.05	**0.42***	1.09	1.00	1.15	1.09	1.25	0.96
C70-72 Meninges, central nervous system	1.04	1.03	0.56	0.71	1.05	1.31	0.79	0.11	0.07
C73 Thyroid	1.04	1.01	0.00	0.91	1.07	1.04	1.05	0.04	0.04
C81 Hodgkin lymphoma	1.46	1.42	0.00	1.57	1.58	1.06	1.71	0.19	0.15
C82-85;96 Non-Hodgkin lymphomas	**1.45****	**1.48****	**2.51***	1.45	**1.49****	**1.52****	1.25	**3.32****	**3.49****
C88-90 Myeloma	1.01	0.99	0.37	1.02	1.04	1.17	0.70	0.04	−0.03
C91-95 Leukemias	**1.22***	**1.22***	1.01	1.17	**1.37***	0.92	1.38	1.32	1.29
C01-96 All sites excl. skin cancers/ melanomas	**1.17****	**1.17****	0.96	**1.19****	**1.17****	**1.20****	**1.13****	**41.18****	**39.94***
C01-96 All sites	**1.20****	**1.23****	**2.41****	**1.30****	**1.20****	**1.19****	**1.14****	**57.97****	**66.10****

(1) Standardized Incidence Ratio.
(2) Excess absolute risk (x10,000).
Significant values in bold.
* $p < 0.05$.
** $p < 0.001$.

second tumour is also shown in Fig. 1.

3.3. Second cancer occurrence by study period

Three different periods of the study (1978-; 1990-; 2000-) with progressively longer follow-up for each patient (average 2.5; 3.9; 6.1 years, respectively) were taken into account (Table 3). Males showed an increased risk of second methachronous (latency ≥2 months) salivary glands, lung, other skin and all-sites tumours over the entire observational period. Head and neck, skin melanomas, and non-Hodgkin lymphomas showed higher SIR only from the nineties onwards, whereas liver, soft tissues and prostate only over the last period (2000-). In females, the excesses of risk regarded mainly the salivary glands, melanomas and the breast, from the middle of the period studied, (from 1990 onwards), with the extension of patient follow-up.

3.4. Second cancer occurrence by the patients' age

Analysing the age of second tumour occurrence (Table 4), cutaneous melanomas, other skin tumours and non-Hodgkin lymphomas in males, skin melanomas and the breast in females, showed the highest risks at all ages, with a decreasing gradient as life progresses. All tumours showed the same excess of risk and the same gradient.

3.5. Second cancer occurrence by sex in patients with SCC and BCC

A brief overview of risks of subsequent cancers in patients with SCC and BCC, considered separately, is shown in Table 5. Overall, SCC tended to be associated with a higher risk of multiple cancers, compared to BCC. BCCs were associated with a higher risk, both in males and females, especially for skin melanomas.

4. Discussion

Previous studies examining a possible relationship between NMSCs and subsequent increased risk of primary non-cutaneous malignancies have yielded conflicting findings [21–30].

In order to further assess this issue, the present study took into consideration a large number of NMSC patients over a notable amount of time. The source of data from population cancer registries guaranteed against selection biases, which can affect studies based on different sources. Emilia Romagna cancer registries record all cases of histologically confirmed NMSC, excised from both inpatients and outpatients. The choice to include only second tumours was made to avoid the confounding effect of other cancers, and relative therapies, on the risk of multiple primaries. The assessment of both second synchronous and metachronous tumours, which occurred at different time intervals from the first NMSC diagnosis, was aimed at differentiating the potential effect of "screening" of the patient in relation to the first diagnosis, from the effective incidence of a second tumour.

Table 2
SIR & EAR x 1000 female skin carcinoma patients by 2nd cancer site and follow-up period.

Second cancer site	SIR[1]							EAR[2]	
	≥2 months	≥0 months	0–1 months	2–11 months	12–59 months	60–119 months	≥120 months	≥2 months	≥0 months
Patients at interval beginning	33.102	33.774	33.774	33.102	30.368	17,700	8.483	33.102	33.774
Person-years (PYs)	224,045	229,608	5,563	26,406	93,942	62,490	41,207	224,045	229,608
C00-06;09-14; 30-32 Upper aerodig. tract	1.34	1.33	1.15	1.20	1.24	1.56	1.29	0.58	0.57
C07-08 Salivary glands	**3.62****	**3.54****	0.00	3.45	**5.16****	**4.03***	0.00	**0.63***	**0.61***
C15 Oesophagus	**1.89***	**1.93***	3.79	2.37	**2.35***	1.20	1.68	0.45	0.48
C16 Stomach	**1.18***	**1.17***	0.91	0.92	1.12	1.19	**1.44***	1.79	1.74
C18 Colon	**1.16***	**1.16***	1.01	0.90	**1.31****	1.05	1.18	**2.50***	**2.44***
C19-21 Rectosigmoid junction-rectum	1.09	1.07	0.00	**1.62***	0.97	0.99	1.21	0.54	0.39
C22 Liver	1.19	1.17	0.54	0.79	1.31	1.16	1.19	0.67	0.61
C23-24 Gallbladder, bile ducts	0.87	0.86	0.75	0.31	0.90	1.04	0.86	−0.36	−0.35
C25 Pancreas	**1.23***	**1.21***	0.62	**1.60***	**1.35***	1.14	0.93	1.52	1.39
C33-34 Trachea, bronchus, lung	**1.23***	**1.23***	1.09	**1.63***	1.16	0.99	**1.49***	**2.10***	**2.05***
C40-41 Bone	1.45	1.42	0.00	0.00	2.12	2.06	0.00	0.09	0.04
C43 Skin melanoma	**2.35****	**2.40****	**4.24***	**2.84****	**2.10****	**2.46****	**2.45****	**3.04****	**3.14****
C44 Other skin	1.02	**1.22****	**9.96****	**1.58****	0.97	0.95	0.94	0.71	**6.45****
C45 Mesothelioma	0.76	0.74	0.00	1.40	1.14	0.53	0.00	−0.09	−0,08
C46 Kaposi sarcoma	1.33	1.47	7.60	3.16	0.42	1.75	1.59	0.09	0.13
C47,49 Soft tissues	**1.61***	**1.65***	3.16	0.00	1.81	2.07	1.47	0.36	0.39
C50 Breast	**1.19****	**1.18****	0.80	1.19	**1.16***	**1.15***	**1.30***	**5.67***	**5.40***
C51-52 Vulva, vagina	1.06	1.12	3.89	1.08	0.81	1.07	1.53	0.09	0.17
C53 Cervix uteri	1.03	1.00	0.00	1.29	0.89	0.94	1.31	0.04	0.00
C54 Corpus uteri	0.83	0.85	1.65	1.11	**0.67***	1.09	0.62	−0.98	−0.87
C55 Uterus NOS	1.55	1.52	0.00	0.00	1.74	**3.01***	0.00	0.18	0.17
C56 Ovary	0.91	0.92	1.42	0.69	0.77	1.00	1.22	−0.36	−0.31
C64 Kidney	**1.27***	**1.25***	0.58	1.46	1.18	1.25	1.36	0.89	0.83
C65-66;68 Renal pelvis, other urinary	**1.94***	**1.98***	3.67	2.29	1.22	1.70	**3.45***	0.54	0.52
C67 Bladder	1.22	1.22	1.11	1.39	**1.38***	0.98	1.13	0.76	0.74
C70-72 Meninges, central nervous system	1.30	1.29	1.00	1.25	**1.75***	0.72	1.24	0.58	0.57
C73 Thyroid	1.23	1.22	0.63	**2.10***	1.09	1.22	1.04	0.67	0.65
C81 Hodgkin lymphoma	**2.02***	**1.97***	0.00	0.00	2.37	**3.66***	0.00	0.27	0.26
C82-85;96 Non-Hodgkin lymphomas	**1.31***	**1.33****	1.89	**1.66***	**1.47***	1.09	1.12	**1.61***	**1.61***
C88-90 Myeloma	1.17	1.18	1.38	0.72	1.33	0.84	1.58	0.49	0.52
C91-95 Leukemias	**1.36***	**1.38***	2.08	1.19	**1.86***	1.09	0.83	**1.34***	**1.35***
C01-96 All sites excl. skin cancers/ melanomas	**1.20****	**1.20****	1.06	**1.22****	**1.22****	**1.14****	**1.25****	**27.72****	**27.22****
C01-96 All sites	**1.17****	**1.20****	**2.62****	**1.29****	**1.18****	**1.10****	**1.19****	**27.99****	**33.27****

(1)Standardized Incidence Ratio.
(2) Excess absolute risk (x10,000).
Significant values in bold.
* $p < 0.05$.
** $p < 0.001$.

In this study, we considered the relative (SIR) excess of risk, calculated also in previous studies, but also the absolute (EAR) excess of risk. In relatively rare events, such as those addressed, a high relative risk does not always mean an effective excess of observed cases. Thus, we chose to investigate both SIR and EAR for a better definition of the real burden of this risk for health care.

The main finding of the present study was that NMSC patients were shown to have a higher risk (average +22%) of developing a second primary malignant cancer in comparison with the general population, both in males (+23%) and females (+20%). It is worthy of note that an increased occurrence of subsequent primary malignant cancers in NMSC patients, compared with those who had no such history, was found also excluding skin cancers. SIR values were quite similar when considering the second tumours as a whole and excluding the second skin tumours. This suggests that this relative excess of risk was independent from belonging to the same anatomical district. For some tumours, such as skin cancers and melanoma, female breast, male upper aerodigestive tract, lung, prostate, liver, and non-Hodgkin lymphomas, this higher relative risk also resulted in a relevant, effective increase in cancer occurrence when compared to those expected. Some risk differences were found according to gender (Tables 1 and 2), period of observation (Table 3) and the patients' age (Table 4). Considering SCC and BCC separately, we found some differences too (Table 5). This is not surprising as these two tumours, although both belonging to keratinocytes, are very different from many points of view, such as etiology, pathogenesis, behaviour, growth, and metastatic capability [31,32]. In particular, differences in molecular and genetic factors involved in SCC and BCC carcinogenesis may account for their different associations with subsequent primary tumours. Although a tendency to a higher risk of subsequent cancers was found for SCC compared to BCC, the latter was highly significantly associated with the risk of subsequent skin melanoma. Aberrant activation of Hedgehog (HH) signalling, which is a key regulator of tissue development, is involved in several cancer types, mainly, at skin level, BCC [33]. Recent studies showed that HH signalling is dysregulated also in cutaneous melanoma [34,35], suggesting a shared pathway between BCC and melanoma which could, at least in part, explain our finding.

Overall, the recognized increase in incidence of multiple tumours in recent years can be explained by several factors, like the increase in survival, growing diagnostic sensitivity, particularly for indolent neoplasms, and increased clinical and instrumental surveillance of patients treated for cancer. In our population, the highest SIR observed in the first month after the diagnosis of NMSC (Fig. 1) may be partly due to the medical consultation related to skin cancer. This may have favoured the finding of further concomitant cancers. However, specific genetic, environmental and personal risk factors concur to this trend as well

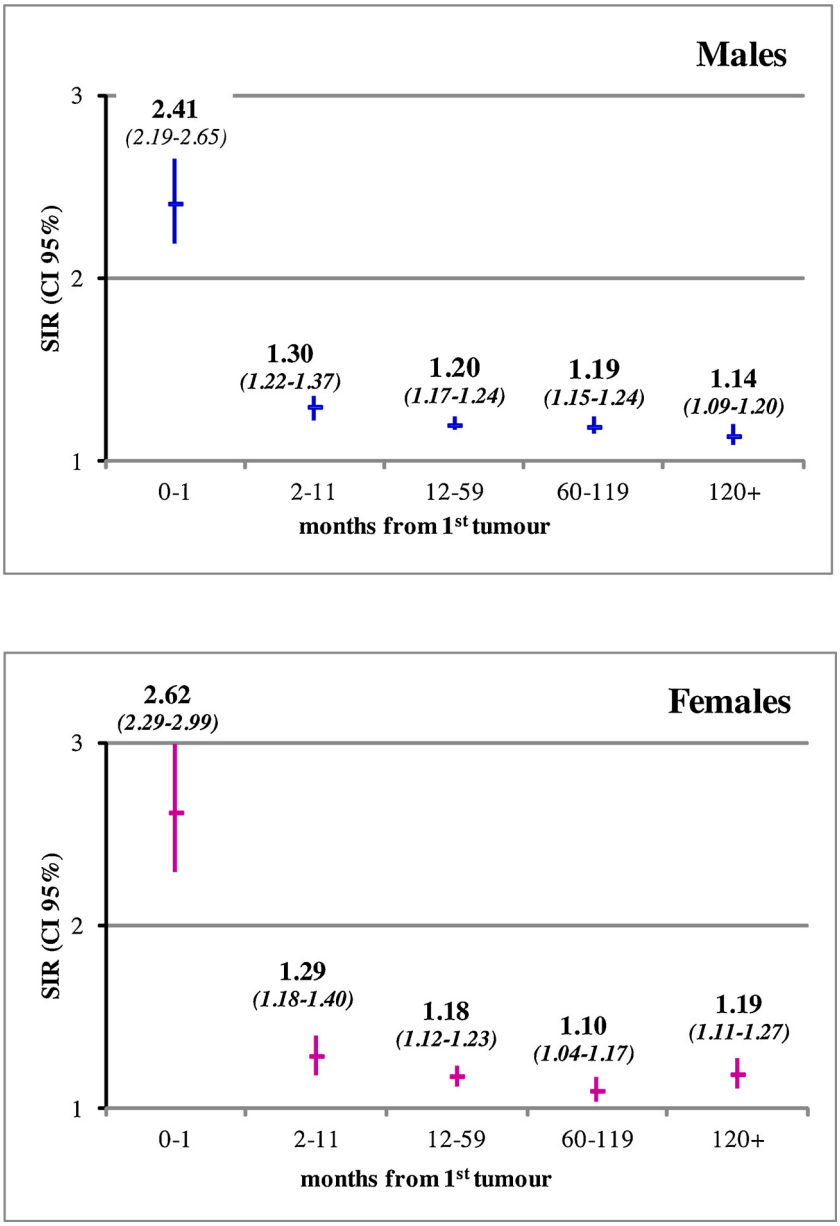

Fig. 1. SIR of second cancers in males and females (ICD-10 C00-C96, all sites).

[36,37]. In keeping with this, the risk of subsequent cancer remained higher in patients with NMSC, compared to the general population, even years after the diagnosis of the first tumour (Fig. 1). We give the results of our focus on the most relevant associations between NMSCs and second primary tumours below, and try to identify possible explanations for these associations.

NMSC patients, both squamous and basal cell type, had higher relative risk of incidence of salivary gland tumours, as documented by other studies [23,38], although the absolute risk estimated in this study is low. From a biological point of view, the basis of this association could be due to risk factors in common between the two tumours, namely tobacco smoking, UV exposure, and immunodeficiency, all of which potentially mutate p53 alleles [39].

Women with previous NMSC showed a moderate, but significantly higher risk of developing gastric cancer in respect to the general population, as shown by other studies [28,38]. In this association, tobacco smoking may represent a shared risk factor [40], together with the inflammatory response to *helicobacter pylori* infection that plays a role in other skin diseases [41], like other common pathways linked to interleukin 10 [42,43]. Both NMSC and gastric cancer recognize the aberrant HH signalling activation [44].

The Danish cancer registry found a higher SIR of respiratory tract cancers among NMSC patients similar to that shown in the present study [26] as well as in others [11,13,28,37,38]. Tobacco is obviously a common risk factor [45]. Among the biological bases of this association, the alterations of p53 and p16 probably represent a shared pathway [46]. Furthermore, a shared mutation of CSMD1 was found in 36% of lung tumours, 29% of skin SCC and in 17% of BCC [47].

The association between NMCC and cutaneous melanoma had been widely reported [11,13,25,26,28,38]. The genotoxic effect of UV radiation is the greatest common risk factor, although SCC onset has been notoriously associated with chronic exposition to UV, while an intermittent UV exposure is mainly linked to skin melanoma and BCC occurrence [48]. This latter point may further support the stronger association observed in our study between BCC and subsequent melanoma, together with the aforesaid common dysregulation of HH signalling. Apart from the mutagenic effect of UV exposure, mainly on CDKN2A [49], defective DNA repair, chronic inflammation and

Table 3
SIR by sex, periods and 2nd cancer site *(latency ≥ 2 months)*.

Second cancer site	SIR[1] males			SIR[1] females		
	1978–1989	1990–1999	2000–2012	1978–1989	1990–1999	2000–2012
Patients at interval beginning	2.065	13.934	37.341	1.332	10.451	33.102
Person-years (PYs)	5.248	54.222	205.693	3.333	41.719	224.045
C00-06;09-14; 30-32 Upper aerodig. tract	1.64	**1.63****	**1.27****	2.33	**2.46***	1.12
C07-08 Salivary glands	**19.03***	**3.98***	**3.43****	0.00	**4.15***	**3.54****
C15 Oesophagus	0.00	1.16	1.07	0.00	0.48	2.23
C16 Stomach	0.91	**1.38****	0.99	0.81	1.06	**1.23***
C18 Colon	0.65	1.13	1.07	1.93	1.16	**1.15***
C19-21 Rectosigmoid junction-rectum	1.02	1.08	0.94	0.53	1.24	1.07
C22 Liver	0.73	1.22	**1.23****	0.00	1.47	1.14
C23-24 Gallbladder, bile ducts	2.00	1.27	0.88	1.15	0.95	0.84
C25 Pancreas	1.43	0.89	1.06	2.05	1.09	1.24
C33-34 Trachea, bronchus, lung	**1.65***	**1.40****	**1.19****	1.13	0.77	**1.31****
C40-41 Bone	0.00	0.86	0.67	0.00	3.07	1.09
C43 Skin melanoma	0.00	**2.95****	**2.31****	0.00	**2.23***	**2.40****
C44 Other skin	**2.24****	**1.23****	**1.31****	**2.66***	0.93	1.03
C45 Mesothelioma	0.00	1.18	0.98	0.00	1.07	0.71
C46 Kaposi sarcoma	0.00	0.96	1.08	0.00	0.89	1.45
C47,49 Soft tissues	0.00	2.18	**1.55***	6.41	0.91	1.68
C50 Breast	0.00	1.76	1.00	1.40	**1.22***	**1.18****
C51-52 Vulva, vagina	–	–	–	0.00	1.28	1.02
C53 Cervix uteri	–	–	–	0.00	0.63	1.20
C54 Corpus uteri	–	–	–	0.00	0.82	0.84
C55 Uterus NOS	–	–	–	0.00	0.68	1.86
C56 Ovary	–	–	–	1.47	0.82	0.92
C61 Prostate	1.40	1.10	**1.18****	–	–	–
C62 Testis	0.00	0.00	1.18	–	–	–
C64 Kidney	1.30	0.88	1.09	0.00	1.20	1.29
C65-66;68 Renal pelvis, other urinary	**6.61***	1.08	0.93	0.00	2.22	1.91
C67 Bladder	1.07	1.15	1.05	0.92	1.48	1.16
C70-72 Meninges, central nervous system	3.27	1.03	1.00	0.00	1.63	1.25
C73 Thyroid	0.00	0.81	1.07	0.00	1.42	1.22
C81 Hodgkin lymphoma	0.00	0.00	1.78	7.40	0.85	2.16
C82-85;96 Non-Hodgkin lymphomas	0.45	**1.63****	**1.42****	2.82	**1.85****	1.17
C88-90 Myeloma	1.82	1.16	0.95	0.00	1.65	1.08
C91-95 Leukemias	1.88	**1.38***	1.16	2.75	1.46	1.32
C01-96 All sites excl. skin cancers/melanomas	**1.27***	**1.27****	**1.15****	1.13	**1.21****	**1.20****
C01-96 All sites	**1.37****	**1.26****	**1.18****	1.27	**1.17****	**1.17****

(1)Standardized Incidence Ratio.
Significant values in bold.
* $p < 0.05$.
** $p < 0.001$.

immunosuppression also play a shared role both in melanoma and NMSC incidence.

The association between breast carcinoma and NMSC had emerged from previous studies [11,23,26,28,38]. Possible common biological pathways are CDKN2A and p53 genetic and epigenetic mutations [48,50].

An increased risk of prostate cancer after NMSC had already been observed in other studies. In this association as well tobacco smoke plays a relevant role. Heavy smokers are at high risk for prostate cancer and they frequently develop a high grade carcinoma [51]. UV exposure could also be a common risk factor. Indeed, the immunosuppression induced by UV radiation had already been associated with prostate cancer onset as well [52]. Finally, aberrant HH signalling activation had been referred to basal cell and prostate carcinoma incidence [53,54].

NMSC patients also have a higher risk of onset of non-Hodgkin lymphoma, as seen in several other population studies [13,26,38]. Immunosuppression, both iatrogenic and induced by UV exposure, or infections (HIV), may represent the main shared risk factor [55].

Several studies have shown the relationships between NMSC and leukemia incidence [13,26–28,38]. Apart from immunosuppression [56], also the exposure to toxic agents like benzene, present in tobacco smoke as well, could be the *trait d'union* between the onset of NMSC and of acute myeloid leukemia (most frequent in adults). Other studies have found that in smokers the risk of acute myeloid leukemia increases up to 40% [57] and that of NMSC to 52% [58]. Some gene polymorphisms had been linked to both NMSC and leukemia incidence risk; in particular some polymorphisms of IRF4, belonging to Interferon Regulatory Factor (IRF), could intervene both in the development and the progression of skin and haematological tumours, playing an essential role in their pathogenesis [59].

Therefore, in view of what is currently conceivable, both multiple environmental agents and intrinsic risk factors, such as genetic and epigenetic changes favouring cellular transformation in different tissues, may be responsible for the risk of multiple tumours in NMSC patients.

While commenting on the results of the study, it is necessary to underline that some factors potentially predisposing to an increased chance of second tumour diagnosis for many types of cancer have less relevance for skin tumours, especially NMSCs. NMSC patients are subjected neither to aggressive therapies nor to in-depth screening. For these reasons, the association between NMSC and the risk of developing other cancers is likely to represent a true etiologic association. On the other hand, the indolence of NMSCs and the prolonged survival of NMSC patients allow them to be followed up for a long time. Thus, NMSCs can be a model for studying the development of multiple tumours, specifically the pathomechanisms underlying this phenomenon.

The present study showed an increase not only in the relative risk but, at least for some tumours, also in the absolute risk among NMSC

Table 4
SIR by sex, age and 2nd cancer site *(latency ≥ 2 months)*.

Second cancer site	SIR[1] males				SIR[1] females			
	0–44	45–49	60–74	75+	0–44	45–49	60–74	75+
Patients at interval beginning	1.949	7.855	21.481	24.704	2.485	6.685	13.492	21.137
Person-years (PYs)	8.714	35.784	105.12	115.545	10.945	32.149	68.698	112.253
C00-06;09-14; 30-32 Upper aerodig. tract	0.00	**1.63***	**1.35***	**1.33***	4.28	1.92	0.92	1.42
C07-08 Salivary glands	19.15	4.11	**4.58****	**3.28****	0.00	2.91	2.77	**4.09****
C15 Oesophagus	0.00	0.84	1.04	1.11	0.00	0.00	1.25	**2.18***
C16 Stomach	0.00	1.41	**1.21***	1.02	0.00	1.02	**1.44***	1.13
C18 Colon	3.41	1.13	1.11	1.06	0.00	0.89	**1.23***	**1.16***
C19-21 Rectosigmoid junction-rectum	0.00	1.24	1.00	0.94	0.00	1.43	0.83	1.17
C22 Liver	0.00	1.47	**1.32***	1.15	0.00	0.67	0.98	1.26
C23-24 Gallbladder, bile ducts	0.00	0.00	0.90	1.02	0.00	0.00	1.00	0.86
C25 Pancreas	0.00	0.33	0.97	1.10	0.00	1.17	0.96	**1.30***
C33-34 Trachea, bronchus, lung	1.67	**1.72****	**1.28****	**1.19****	0.00	0.64	**1.28****	**1.26****
C40-41 Bone	0.00	0.00	0.48	0.94	0.00	0.00	1.02	1.84
C43 Skin melanoma	**6.19****	**3.29****	**2.67****	**1.98****	**3.58****	**3.93****	**2.10****	**2.03****
C44 Other skin	1.87	**1.72****	**1.28****	**1.29****	0.87	0.79	**0.78***	**1.11***
C45 Mesothelioma	0.00	0.91	0.93	1.06	0.00	2.96	0.00	1.03
C46 Kaposi sarcoma	0.00	1.37	1.24	0.96	0.00	0.00	3.58	0.99
C47,49 Soft tissues	0.00	0.82	1.49	**1.79***	0.00	2.08	1.40	1.68
C50 Breast	0.00	0.00	1.02	1.27	1.43	**1.27***	**1.23***	**1.13***
C51-52 Vulva, vagina	–	–	–	–	0.00	0.00	1.76	0.92
C53 Cervix uteri	–	–	–	–	0.79	0.67	1.25	1.02
C54 Corpus uteri	–	–	–	–	0.00	0.58	0.79	0.92
C55 Uterus NOS	–	–	–	–	0.00	0.00	0.00	1.82
C56 Ovary	–	–	–	–	1.30	1.14	0.78	0.94
C61 Prostate	0.00	**1.68****	**1.25****	**1.09***	–	–	–	–
C62 Testis	1.13	0.70	0.44	1.43	–	–	–	–
C64 Kidney	1.64	**1.71***	0.99	1.03	2.49	1.25	**1.47***	1.17
C65-66;68 Renal pelvis, other urinary	0.00	3.27	1.20	0.82	0.00	4.15	1.06	**2.16***
C67 Bladder	3.65	1.36	1.12	1.03	0.00	1.84	1.40	1.14
C70-72 Meninges, central nervous system	2.30	1.21	1.17	0.90	0.00	1.53	1.47	1.22
C73 Thyroid	2.16	1.53	1.01	0.75	1.21	1.06	1.31	1.27
C81 Hodgkin lymphoma	0.00	2.37	0.67	2.14	0.00	4.16	1.63	2.04
C82-85;96 Non-Hodgkin lymphomas	**4.03***	**2.07***	**1.49****	**1.35****	0.00	1.69	1.17	**1.36***
C88-90 Myeloma	0.00	1.13	1.05	0.99	0.00	1.23	1.07	1.21
C91-95 Leukemias	2.29	1.17	1.25	**1.20***	0.00	1.70	**1.68***	1.26
C01-96 All sites excl. skin cancers/melanomas	**2.23****	**1.52****	**1.23****	**1.12****	1.25	**1.23****	**1.21****	**1.20****
C01-96 All sites	**2.19****	**1.56****	**1.24****	**1.16****	1.17	**1.18****	**1.14****	**1.18****

(1)Standardized Incidence Ratio.
Significant values in bold.
* $p < 0.05$.
** $p < 0.001$.

patients of developing a second cancer. However, a general screening and a specifically planned follow up for NMSC patients remain difficult to justify, considering their enormous number, especially in Western countries.

The present study has some limitations. Being registry-based, it lacks information about hypothesised risk factors, including UV or other environmental exposures, lifestyle choices, socioeconomic status, treatments. NMSCs either not histologically diagnosed or misdiagnosed, for example as pre-malignant lesions, are missed. Our study included a predominantly white population and cannot be applied to other ethnic groups.

5. Conclusions

In conclusion, based on our study findings, NMSC could be considered a kind of “sentinel event” indicating a population with a long-lasting, increased risk regarding several multiple primaries, thus confirming previous findings. Although there are no requirements supporting an active screening for these patients, NMSC highlights the presence of shared, environmental risks to be removed and active biological pathways which should be further investigated.

Authorship contribution

Alessandro Borghi: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, and final approval of the version to be published.

Monica Corazza: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, and final approval of the version to be published.

Giorgio Chiaranda: acquisition of data, revising the article critically for important intellectual content, and final approval of the version to be published

Maria Michiara: acquisition of data, revising the article critically for important intellectual content, and final approval of the version to be published

Lucia Mangone: acquisition of data, revising the article critically for important intellectual content, and final approval of the version to be published

Bianca Caruso: acquisition of data, revising the article critically for important intellectual content, and final approval of the version to be published

Fabio Falcini: acquisition of data, revising the article critically for important intellectual content, and final approval of the version to be published

Iva Maestri: acquisition of data, revising the article critically for

Table 5
SIR by sex, morphological subtypes of 1st cancer and 2nd cancer site *(latency ≥ 2 months)*.

Second cancer site	SIR[1] males		SIR[1] females	
	Squamous cell carcinomas	Basal cell carcinomas	Squamous cell carcinomas	Basal cell carcinomas
Patients at interval beginning	8,802	32,247	5,309	27,157
Person-years (PYs)	48,342	213,980	27,791	193,092
C00-06;09-14; 30-32 Upper aerodig. tract	**1.78****	**1.24***	**2.17***	1.22
C07-08 Salivary glands	**9.41****	**2.30***	**7.49****	**2.29***
C16 Stomach	**1.24***	1.02	**3.07***	**1.18***
C18 Colon	1.08	1.08	1.11	**1.16***
C22 Liver	1.31	**1.16***	0.86	**1.27***
C25 Pancreas	1.13	1.00	**1.46***	1.15
C33-34 Trachea, bronchus, lung	**1.47****	**1.15****	1.02	**1.26***
C43 Skin melanoma	**2.12****	**2.47****	1.41	**2.48****
C44 Other skin	**2.46****	0.98	**2.55****	**0.72****
C47;49 Soft tissues	1.92	**1.58***	1.03	**1.74***
C50 Breast	0.78	1.23	1.16	**1.18****
C54 Corpus uteri	–	–	1.29	**0.77***
C61 Prostate	0.93	**1.23****	–	–
C65-66;68 Urinary tract	1.25	0.93	**3.57***	1.57
C81 Hodgkin lymphoma	1.64	1.44	**5.66***	1.55
C82-85;96 Non-Hodgkin lymphomas	**1.53***	**1.42****	**1.78***	**1.23***
C91-95 Leukemias	**1.59***	1.12	**2.28****	1.16
C01-96 All sites excl. skin cancers/melanomas	**1.24****	**1.15****	**1.27****	**1.18****
C01-96 All sites	**1.48****	**1.12****	**1.53****	**1.10****

(1) Standardized Incidence Ratio.
Significant values in bold.
* $p < 0.05$.
** $p < 0.001$.

important intellectual content, and final approval of the version to be published

Stefano Ferretti: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, and final approval of the version to be published.

Declaration of Competing Interest

None.

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