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Skin cancer and non-Hodgkin's lymphoma as second malignancies: markers of impaired immune function?

K. Hemminki[a,b,*], Y. Jiang[a], G. Steineck[c]

[a]*Department of Biosciences at Novum, Karolinska Institute, 141 57 Huddinge, Sweden*
[b]*Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany*
[c]*Department of Oncology-Pathology, Karolinska Hospital 171 76 Stockholm, Sweden*

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Abstract

Successes in cancer therapy have led to increasing numbers of cancer survivors, who are at risk of developing second primary cancers. Therapy- or disease-induced suppression of the immune function may predispose cancer patients to a second malignancy. An excess of squamous cell skin cancers (SCC) and non-Hodgkin's lymphomas has been found in immunosuppressed patients. We used the nationwide Swedish Family-Cancer Database on 10.2 million individuals to calculate the risk of second primary skin cancers and non-Hodgkin's lymphomas following a previous malignancy. A total of 4301 second skin cancers and 1672 non-Hodgkin's lymphomas were identified. Standardised incidence ratios (SIR)s and 95% Confidence Intervals (CIs) were calculated and compared. Among 14 different sites for male or female first primary malignancies, 11 of these sites were followed by an increased risk of skin cancer (SIRs for males for risk of skin cancer as a second primary cancer: 14.1 for SCC; 9.7 for melanoma; 6.1 for leukaemia as the first site; SIRs for females for risk of skin cancer: 14.6 for SCC; 6.8 for larynx; 6.2 for upper aerodigestive tract (UADT) as the first site). The risk of non-Hodgkin's lymphoma was increased after 10 of 14 different male neoplasms and 12 of 17 different female neoplasms. (SIRs for males for risk of non-Hodgkin's lymphoma as a second primary cancer: 6.4 for non-Hodgkin's lymphoma; 3.2 for leukaemias; 3.1 for multiple myeloma as the first site; SIRs for females for risk of non-Hodgkin's lymphoma as a second primary cancer: 12.5 for leukaemias; 7.0 for Hodgkin's disease; 3.6 for UADT as the first site). The high, and after certain sites, very high risks of second skin cancer and non-Hodgkin's lymphoma suggest that immune suppression may be a contributory mechanism.

Keywords: Second cancer; Immunological factors; Immunosuppression; Therapeutic effects

1. Introduction

Second primary tumours may arise because of inherited and/or acquired mutations or other cellular deficiencies and they develop soon or late after treatment of the first primary tumour. An aging population and the increasing success of modern cancer therapy in achieving long-term remissions in many patients have resulted in a rapid increase in second primary tumours [1]. An excess of diagnosed second cancers after an initial primary can result from (1) intensive medical surveillance after the first diagnosis, (2) inability to distinguish recurrences from independent second primary tumours, (3) immunological disturbances caused by tumour-growth or surgical procedures, (4) therapy-related exposure to X-rays or antineoplastic agents and (5) shared environmental or heritable factors between the first and the second cancer [2–7]. The risk for second cancer after almost all primary neoplasms of moderate or good survival is higher or much higher than that for the first primary [6,8]. Many studies on second cancers are descriptive, but some studies investigating long-term evaluation of specific treatments have provided valuable data on human sensitivity to carcinogens [1,4,5,9–12].

In the present study, we investigate the occurrence of squamous cell carcinoma (SCC) of the skin ('skin cancer') and non-Hodgkin's lymphoma as second primary malignancies after any primary neoplasm of moderate

* Corresponding author. Tel.: +46-8-608-9243; fax: +46-8-608-1501.
E-mail address: kari.hemminki@cnt.ki.se (K. Hemminki).

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or good survival. Skin cancer and non-Hodgkin's lymphoma appear in large excess in immunosuppressed individuals [13–15], and we use these tumours as a marker of defective immune function. We examine the hypothesis that tumour- or therapy-induced immune dysfunction is a contributing cause for the occurrence of a second neoplasm. In Sweden, skin cancer incidence has increased more than any other cancer, and worldwide the incidence of non-Hodgkin's lymphoma has increased for unknown reasons [16,17]. As the data source for this study, we used the Swedish Family-Cancer Database, linked to the Swedish Cancer Registry from 1958 to 1998 and containing information on 760 000 first and 67 000 second primary invasive neoplasms [18].

2. Patients and methods

The Swedish Family-Cancer Database was initially created in the middle of the 1990s by linking an administrative family register on all Swedish families to the Swedish Cancer Registry [18,19]. For each child, there are data on both parents at the time of birth. Each person has been assigned a unique technical identification number (which is different from the national civic registration number). The Database includes practically everyone born in Sweden after 1931 with their biological parents, totalling over 10.2 million individuals. It has been updated at the beginning of 2001 to include cancers from the nationwide Swedish Cancer Registry from 1958 to 1998. The Database included 760 000 first primary invasive cancers and 67 200 multiple primaries; the incidence rates of cancer are practically identical in the Family-Cancer Database and in the Cancer Registry [18].

The completeness of cancer registration in the 1970s was estimated to be over 95%, and is now considered to be close to 100%. The percentage of cytologically- or histologically-verified cancer cases is close to 100% [16].

The Swedish Cancer Registry is based on a compulsory notification of cases [16]. The four-digit diagnostic code according to the seventh revision of the International Classification of Diseases (ICD-7) was used. We studied squamous cell carcinoma (SCC, ICD-7 code 201) of the skin and non-Hodgkin's lymphoma (ICD-7 codes 200 and 202) as second malignancies after selected first malignancies, which had to fulfill two criteria: median survival had to be at least 2 years [6], and the expected number of second skin cancers and non-Hodgkin's lymphomas had to be reasonably large (30 or more expected cases). Oesophageal, gastric, liver and pancreatic cancer did not fulfill the first criterion; the second criterion ruled out many rare cancers. As an exception, we included all lymphoheamatopoietic sites because of their relatedness to non-Hodgkin's lymphoma. The following ICD-7 codes were pooled: "upper aerodigestive tract (UADT)" cancer, codes 140–148 (lip, mouth, tongue, pharynx), except for code 142 (salivary glands), and 'leukaemia', codes 204–207 (leukaemias), 208 (polycythemia vera) and 209 (myelofibrosis). According to the ICD-7 classification, lymphomas are classified as lymphomas irrespective of the site at which they occur. All non-melanoma skin cancers are SCC in the Cancer Registry.

Tumour incidence rates were based on data in the Family-Cancer Database. All individuals, parents and offspring, were included in the analysis of second cancers. Even synchronous second cancers were included and the follow-up time was divided into three periods (<1 year, 1–10 years, >10 years), allowing an assessment of the effect of follow-up. Follow-up was started at the diagnosis of malignancy and it was terminated at the diagnosis of second malignancy, death, emigration, or the closing date of the study, 31 December 1998. Standardised incidence ratios (SIRs) were calculated as the ratio of observed (O) to expected (E) number of cases. The expected numbers were calculated from 5-year-age, sex-, tumour type-, region (three regions)-, period (10 intervals)- and socio-economic status (four groups)-specific standard incidence rates. Confidence intervals (95% CI) were calculated assuming a Poisson distribution of the observed number of cases.

3. Results

The study identified 31 881 male and 33 239 female second malignancies in the period from 1958 to 1998. After the index malignancies, 4301 SCC skin cancers and 1672 non-Hodgkin's lymphomas were recorded as second cancers. Following first malignancies in males at 14 different sites, skin cancer was increased in 11 sites (Table 1). The highest increase was observed after skin cancer, SIR 14.1, melanoma, 9.7, leukaemia 6.1, non-Hodgkin's lymphoma 5.9 and UADT 5.2. We included concordant skin cancers and non-Hodgkin's lymphomas only for references purposes, because we cannot exclude that they are recurrences. No increase was noted after colon, rectal or kidney cancers. The data by the length of follow-up showed typical patterns. For neoplasms at the UADT, larynx and skin (both squamous cell carcinoma and melanoma), there was a steadily decreasing trend with increasing follow-up time. For prostate cancer, Hodgkin's disease and myeloma the increases showed no clear trend. For bladder and nervous system cancer, the SIRs increased with longer follow-up periods.

Data on female second skin cancers are shown in Table 2 after 17 primary neoplasms. The overall SIR of skin cancer was increased after 11 primary neoplasms, eight of which agreed with the male findings; the only disagreements were for second skin cancer after nervous system cancer and myeloma, which were not increased

Table 1
SIR for skin cancer after first primary cancers in men[a]

First cancer sites	Follow-up interval (years)															
	<1				1–10				>10				All			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
UADT	24	**11.5**	**7.3**	**16.5**	113	**5.5**	**4.5**	**6.5**	50	**3.7**	**0.6**	**4.0**	187	**5.2**	**4.4**	**5.9**
Colon	7	0.8	0.3	1.5	68	1.1	0.9	1.4	29	1.2	0.8	1.6	104	1.1	0.9	1.3
Rectum	4	0.7	0.2	1.5	62	1.5	1.2	1.9	12	0.7	0.4	1.2	78	1.2	1.0	1.5
Larynx	4	**4.6**	**1.2**	**10.2**	33	**3.1**	**2.1**	**4.2**	15	**2.2**	**1.2**	**3.4**	52	**2.8**	**2.1**	**3.6**
Prostate	49	1.3	0.9	1.6	410	**1.3**	**1.2**	**1.4**	68	1.3	1.0	1.6	527	**1.3**	**1.2**	**1.4**
Kidney	4	1.2	0.3	2.7	16	0.8	0.5	1.3	11	1.1	0.5	1.7	31	0.9	0.6	1.3
Bladder	9	1.0	0.5	1.8	109	**1.3**	**1.1**	**1.6**	50	**1.5**	**1.1**	**1.9**	168	**1.4**	**1.2**	**1.6**
Melanoma	51	**29.5**	**22.0**	**38.2**	161	**9.3**	**7.9**	**10.8**	49	**6.3**	**4.6**	**8.2**	261	**9.7**	**8.6**	**11.0**
Skin, SCC	170	**22.0**	**18.8**	**25.4**	920	**14.6**	**13.7**	**15.6**	140	**8.4**	**7.0**	**9.8**	1230	**14.1**	**13.3**	**14.9**
Nervous system	1	0.6	0.0	2.3	10	1.3	0.6	2.3	15	**2.1**	**1.2**	**3.2**	26	**1.6**	**1.0**	**2.2**
Non-Hodgkin's lymphoma	12	**3.6**	**1.9**	**5.9**	130	**6.8**	**5.7**	**8.0**	18	**3.7**	**2.2**	**5.7**	**160**	**5.9**	**5.0**	**6.8**
Hodgkin's disease	0				9	**5.0**	**2.3**	**8.8**	8	**4.3**	**1.9**	**7.9**	17	**4.3**	**2.5**	**6.6**
Multiple myeloma	6	**3.3**	**1.2**	**6.4**	18	**2.0**	**1.2**	**3.1**	3	2.5	0.5	6.1	27	**2.3**	**1.5**	**3.2**
Leukaemia	6	1.9	0.7	3.7	127	**7.3**	**6.1**	**8.7**	19	**4.4**	2.7	**6.7**	152	**6.1**	**5.2**	**7.1**

O, observed; SIR, standardised incidence ratio; 95% CI, 95% Confidence Interval; UADT, upper aerodigestive tract. All expected numbers were calculated based on site, age, period, residence and socioeconomic level-specific incidence.
[a] Bolding indicates significance.

Table 2
SIR for skin cancer after first primary cancers in women[a]

First cancer sites	Follow-up interval (years)															
	<1				1–10				>10				All			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
UADT	2	4.1	0.4	11.7	31	**7.9**	**5.4**	**10.9**	7	**3.4**	**1.4**	**6.4**	40	**6.2**	**4.4**	**8.2**
Colon	4	1.0	0.3	2.1	43	1.3	1.0	1.8	21	1.2	0.8	1.8	68	1.3	1.0	1.6
Rectum	1	0.5	0.0	2.1	21	1.4	0.9	2.1	8	1.0	0.4	1.8	30	1.2	0.8	1.7
Larynx	0				5	**8.8**	**2.8**	**18.2**	2	4.9	0.5	14.0	7	**6.8**	**2.7**	**12.8**
Breast	11	1.2	0.6	2.0	165	**1.5**	**1.2**	**1.7**	128	**1.7**	**1.4**	**2.0**	304	**1.5**	**1.4**	**1.7**
Cervix	0				14	1.5	0.8	2.3	32	1.3	0.9	1.8	46	1.3	1.0	1.7
Endometrium	2	1.0	0.1	2.8	46	**1.8**	**1.3**	**2.4**	47	**1.6**	**1.2**	**2.1**	95	**1.7**	**1.4**	**2.1**
Ovary	3	1.8	0.3	4.5	21	**1.8**	**1.1**	**2.7**	19	1.5	0.9	2.3	43	**1.7**	**1.2**	**2.2**
Kidney	1	0.9	0.0	3.4	7	0.9	0.4	1.7	7	1.4	0.6	2.6	15	1.1	0.6	1.7
Bladder	4	3.3	0.9	7.4	17	1.5	0.9	2.4	9	1.5	0.7	2.4	30	**1.6**	**1.1**	**2.3**
Melanoma	7	**7.0**	**2.8**	**13.1**	43	**3.3**	**2.4**	**4.3**	27	**2.8**	**1.8**	**3.9**	77	**3.2**	**2.5**	**4.0**
Skin, SCC	62	**27.0**	**20.7**	**34.2**	288	**15.3**	**13.6**	**17.1**	53	**8.3**	**6.2**	**10.6**	403	**14.6**	**13.2**	**16.1**
Nervous system	0				7	1.0	0.4	1.9	9	1.1	0.5	2.0	16	1.0	0.6	1.6
Non-Hodgkin's lymphoma	2	1.5	0.1	4.3	32	**3.9**	**2.7**	**5.4**	12	**4.3**	**2.2**	**7.0**	46	**3.7**	**2.7**	**4.9**
Hodgkin's disease	1	9.1	0.0	35.8	3	3.8	0.7	9.3	5	**6.0**	**1.9**	**12.5**	9	**5.2**	**2.4**	**9.2**
Multiple myeloma	1	1.5	0.0	5.8	7	1.9	0.7	3.5	0				8	1.6	0.7	3.0
Leukaemia	2	1.8	0.2	5.1	34	**4.7**	**3.3**	**6.4**	8	**3.9**	**1.7**	**7.1**	44	**4.2**	**3.1**	**5.6**

O, observed; SIR, standardised incidence ratio; 95% CI, 95% Confidence Interval; UADT, upper aerodigestive tract. All expected numbers were calculated based on site, age, period, residence and socioeconomic level-specific incidence.
[a] Bolding indicates significance.

among women. Among the sex-specific cancers, breast, endometrial and ovarian cancers were followed by an increased risk and identical time course of skin cancer. The highest overall SIRs were after skin (14.6), laryngeal (6.8) and UADT (6.2) cancers and after Hodgkin's disease (5.2). The decreasing pattern of risk was noted after neoplasms at the UADT, larynx and skin (both squamous cell carcinoma and melanoma), in agreement with the male trends.

SIRs for second non-Hodgkin's lymphoma are given for men in Table 3. The overall risk for non-Hodgkin's lymphoma was increased after 10 of 14 primary neoplasms, and there was an agreement with Table 1 for all but three sites: larynx and bladder cancer, were not followed by an increased risk of non-Hodgkin's lymphoma whereas kidney cancer was associated with an increased risk. The overall SIRs were highest for non-Hodgkin's

Table 3
SIR for non-Hodgkin's lymphoma after first primary cancers in men[a]

First cancer sites	Follow-up interval (years)															
	<1				1–10				>10				All			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
UADT	8	**5.6**	**2.4**	**10.2**	18	1.3	0.8	2.0	7	1.0	0.4	1.8	33	**1.5**	**1.0**	**2.0**
Colon	15	**2.9**	**1.6**	**4.6**	31	1.0	0.6	1.3	11	0.9	0.5	1.5	57	1.1	0.9	1.5
Rectum	8	2.4	1.0	4.3	20	0.9	0.5	1.3	11	1.4	0.7	2.4	39	1.1	0.8	1.5
Larynx	1	1.6	0.0	6.2	9	1.3	0.6	2.2	4	1.1	0.3	2.4	14	1.2	0.7	2.0
Prostate	58	**2.8**	**2.1**	**3.5**	181	1.2	1.0	1.3	20	1.0	0.6	1.4	259	**1.3**	**1.1**	**1.5**
Kidney	7	**3.1**	**1.2**	**5.8**	19	1.4	0.8	2.1	8	1.3	0.6	2.3	34	**1.5**	**1.1**	**2.1**
Bladder	6	1.2	0.4	2.3	51	1.1	0.8	1.4	25	1.5	1.0	2.1	82	1.2	1.0	1.5
Melanoma	4	2.4	0.6	5.4	35	**2.0**	**1.4**	**2.7**	11	1.3	0.7	2.2	50	**1.8**	**1.3**	**2.3**
Skin, SCC	11	**3.4**	**1.7**	**5.7**	59	**2.1**	**1.6**	**2.6**	13	1.7	0.9	2.8	83	**2.1**	**1.7**	**2.6**
Nervous system	6	**4.2**	**1.5**	**8.3**	11	1.6	0.8	2.7	10	1.8	0.9	3.1	27	**2.0**	**1.3**	**2.8**
Non-Hodgkin's lymphoma	7	**3.0**	**1.2**	**5.6**	39	**3.0**	**2.2**	**4.0**	10	**3.1**	**1.5**	**5.2**	56	**3.0**	**2.3**	**3.9**
Hodgkin's disease	4	**15.9**	**4.2**	**35.4**	18	**9.6**	**5.7**	**14.5**	14	**8.1**	**4.4**	**12.9**	36	**6.4**	**2.3**	**12.5**
Multiple myeloma	2	1.8	0.2	5.1	19	**3.5**	**2.1**	**5.2**	1	1.7	0.0	6.7	22	**3.1**	**1.9**	**4.1**
Leukaemia	4	2.0	0.5	4.5	37	**3.4**	**2.4**	**4.5**	8	**3.4**	**1.4**	**6.1**	49	**3.2**	**2.4**	**4.1**

O, observed; SIR, standardised incidence ratio; 95% CI, 95% Confidence Interval; UADT, upper aerodigestive tract. All expected numbers were calculated based on site, age, period, residence and socioeconomic level-specific incidence.
[a] Bolding indicates significance.

lymphoma after Hodgkin's disease (6.4) and other lymphohaematopoietic neoplasms (SIRs 3.0 or more). The SIRs showed decreasing trend after UADT and skin cancer, melanoma and Hodgkin's disease. A significant increase of non-Hodgkin's lymphoma was observed only during the shortest follow-up period after colon, prostate, kidney and nervous system cancers.

SIRs for second non-Hodgkin's lymphoma are given for women in Table 4. The risk for non-Hodgkin's lymphoma was increased after 12 of 17 primary neoplasms, and there was an agreement with Table 2 for all but seven sites: laryngeal, endometrial and bladder cancers were not followed by an increased risk of non-Hodgkin's lymphoma, whereas those with primaries of the colon, cervix, kidney and nervous system were at increased risk. Among the 13 common male and female sites, all but colon cancer and multiple myeloma agreed, and even for the latter the female SIR was of borderline significance. The overall SIRs were highest for non-Hodgkin's lymphoma after leukaemia (12.5), Hodgkin's disease (7.0) and UADT cancer (3.6). The SIRs showed a decreasing trend after kidney and nervous system cancers, and Hodgkin's disease. After leukaemia, the trend increased with longer follow-up, only the longest follow-up time showed an increased risk for patients with primaries of the cervix, ovary and bladder.

4. Discussion

There is good evidence that immunosuppressed kidney transplantation patients experience a high excess risk of SCC skin cancer and non-Hodgkin's lymphoma, in addition to many other neoplasms [13–15]. The incidence of non-Hodgkin's lymphoma is also increased in subjects with human immunodeficiency virus-associated immunosuppression, but SCC skin cancer is a rarer manifestation in that disease [15,20]. After transplantation, tumours may appear within a short period after the onset of therapy, depending on the severity of immunosuppression [15]. Clustering of skin cancers and non-Hodgkin's lymphomas as multiple primaries occurs in a number of populations [21–28]. The suggested causes have included immunological disturbances, perhaps allowing an escape of Epstein–Barr virus [26,28,29] and exposure to solar irradiation. Presentation of skin cancer in patients with non-Hodgkin's lymphoma has been suggested to be a poor prognostic marker [30].

The diagnosis of skin cancer and non-Hodgkin's lymphoma has been histologically- and cytologically-verified in close to 100% of cases in the Swedish Cancer Registry, suggesting that a decreased specificity in diagnostic misclassification should not be an issue in the present study. In an *ad hoc* study on 209 multiple primary tumours reported to the Cancer Registry, the re-evaluation found 98% of second malignancies to be correctly classified [31]. However, there is no certainty that concordant skin cancers and non-Hodgkin's lymphomas were independent malignancies and they were included only for reference purposes. In the present study, sensitivity may be an issue, as illustrated by the large number of second skin cancers diagnosed after first skin cancer and melanoma. Surveillance bias, increasing sensitivity in one group, may depend on palpation of lymph nodes in search of metastasis after the first malignancy; presentation of enlarged masses may

Table 4
SIR for non-Hodgkin's lymphoma after first primary cancers in women[a]

First cancer sites	Follow-up interval (years)															
	<1				1–10				>10				All			
	O	SIR	95% CI		O	SI	95% CI		O	SIR	95% CI		O	SIR	95%CI	
UADT	0				14	**4.2**	**2.3**	**6.7**	5	3.1	1.0	6.5	19	**3.6**	**2.2**	**5.4**
Colon	6	1.7	0.6	3.4	39	**1.6**	**1.1**	**2.1**	16	1.3	0.8	2.1	61	**1.5**	**1.2**	**1.9**
Rectum	2	1.3	0.1	3.6	11	0.9	0.4	1.5	5	0.9	0.3	1.8	18	0.9	0.5	1.4
Larynx	0				0				1	2.7	0.0	10.7	1	1.0	0.0	4.0
Breast	21	**2.3**	**1.4**	**3.4**	109	1.0	0.8	1.2	111	**1.7**	**1.4**	**2.1**	241	**1.3**	**1.2**	**1.5**
Cervix	1	1.1	0.0	4.2	19	1.5	0.9	2.3	48	**1.9**	**1.4**	**2.4**	68	**1.7**	**1.3**	**2.2**
Endometrium	4	1.8	0.5	4.1	36	1.3	0.9	1.8	25	1.0	0.7	1.5	65	1.2	0.9	1.5
Ovary	2	1.1	0.1	3.1	18	1.3	0.8	2.0	20	**1.8**	**1.1**	**2.6**	40	**1.5**	**1.1**	**2.0**
Kidney	7	**6.2**	**2.5**	**11.7**	15	**2.0**	**1.1**	**3.1**	4	1.0	0.3	2.2	26	**2.0**	**1.3**	**2.9**
Bladder	0				8	0.9	0.4	1.6	10	**2.3**	**1.1**	**3.9**	18	1.2	0.7	1.9
Melanoma	2	2.0	0.2	5.8	26	**2.0**	**1.3**	**2.9**	13	1.5	0.8	2.4	41	**1.8**	**1.3**	**2.4**
Skin, SCC	3	2.3	0.4	5.6	26	**2.2**	**1.4**	**3.1**	8	1.9	0.8	3.5	37	**2.1**	**1.5**	**2.9**
Nervous system	7	**6.4**	**2.5**	**12.0**	15	**1.8**	**1.0**	**2.9**	12	1.7	0.9	2.7	34	**2.1**	**1.4**	**2.8**
Non-Hodgkin's lymphoma	1	0.8	0.0	3.0	28	**3.7**	**2.5**	**5.2**	7	**3.1**	**1.2**	**5.8**	36	**3.2**	**2.3**	**4.4**
Hodgkin's disease	2	**17.3**	**1.6**	**49.7**	8	**8.4**	**3.6**	**15.2**	4	**4.3**	**1.1**	**9.6**	14	**7.0**	**3.8**	**11.1**
Multiple myeloma	4	**6.6**	**1.7**	**14.7**	4	1.2	0.3	2.7	1	2.4	0.0	9.5	9	2.1	1.0	3.7
Leukaemia	9	**8.5**	**3.8**	**14.9**	64	**11.1**	**8.5**	**13.9**	30	**21.8**	**14.7**	**30.3**	103	**12.5**	**10.2**	**15.1**

O, observed; SIR, standardised incidence ratio; 95% CI, 95% Confidence Interval; UADT, upper aerodigestive tract. All expected numbers were calculated based on site, age, period, residence and socioeconomic level-specific incidence.

[a] Bolding indicates significance.

lead to a diagnosis of non-Hodgkin's lymphoma. At the same time, the doctor surveys parts of the patient's skin, which may lead to an early diagnosis of skin cancer and melanoma; the doctor would most readily diagnose changes at sun-exposed skin, common sites for skin cancer [32]. If, in the present study, increased sensitivity implies a lead time bias due to early reporting in the group with a first malignancy, the bias reasonably should be largest in the beginning of the follow-up. However, in the present study almost all SIRs were above unity throughout the follow-up period, and no SIR was anywhere close to being significantly decreased.

The first neoplasms in patients selected for the study were associated with a moderate to good survival and were common enough to result in a reasonable number of second malignancies. The study covered a period of 41 years. During this period, cancer therapy has changed remarkably, particularly since the large-scale introduction of chemotherapy in the 1960s. As second malignancies only occur in surviving patients, the options for curative therapies have been limited. Surgery has been the principal curative treatment in all non-haematopoietic solid tumours; in the present patient series we can assume that the majority of cases with solid tumours have had major surgery, with the exception of patients with prostate cancer. Men with prostate cancer have survived for many years without treatment or with androgen depletion only. More recently, in particular, radiotherapy has been used as an auxiliary therapy for cancers of the rectum, larynx, breast, cervix, ovary and nervous system. For breast, ovarian and bladder tumours, chemotherapy has been added to treatment regimens. For lymphohaematopoietic tumours, chemotherapy has been the treatment of choice for leukaemias, and in combination with radiotherapy, has been used to treat non-Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma.

Large tumour masses and ensuing surgical procedures are likely to cause immunological disturbances which may allow the escape of malignant cells from immune surveillance, with resulting skin cancer or non-Hodgkin's lymphoma [14,15]. Such tumours would be expected to arise relatively shortly after therapy and they should be commonest in patients whose primary malignancy has been treated with therapies causing bone marrow toxicity. Bone marrow toxicity is the dose-limiting effect for chemotherapy for lymphohaematopoietic malignancies, and according to the present hypothesis, both skin cancer and non-Hodgkin's lymphoma were in large excess after all these neoplasms, with the exception of myeloma among women. Furthermore, the largest excess was noted during the first or the second follow-up time, consistent with the induction-latency time seen during immunosuppressive therapies. Similar patterns of high SIRs at short follow-up periods were noted for skin cancer after skin cancer and melanoma, and UADT and larynx cancers among men and women. Non-Hodgkin's lymphoma was also increased after these neoplasms, with the exception of laryngeal cancer. Moreover, this pattern was noted for non-Hodgkin's lymphoma even after colon, prostate and kidney cancers.

Radiotherapy and many chemotherapy agents cause DNA damage, which may be related to the risk of subsequent cancer. A trend of an increasing relative risk with follow-up time would be evidence for a causal relationship between chemotherapy or radiotherapy for the primary cancer and the risk of a second cancer in the present study. However, because age of onset of the primary tumour may modify the risk, the time since first diagnosis may be a complex relationship, deviating from a linear function [11]. There was a clearly increasing relative risk with follow-up time for non-Hodgkin's lymphoma after leukaemia, but it was limited to women; there was an increase also among men but with no relationship to the follow-up time. Large increases were also observed after Hodgkin's disease, but they were probably not limited to the effects of treatment. Female cervical, ovarian and bladder cancers increased the risk of non-Hodgkin's lymphoma only at the longest follow-up times, which could be a sign of a treatment effect; similarly, breast cancer caused an increase in second non-Hodgkin's lymphomas in the latest follow-up period, possibly due to treatment. Radiotherapy causes a moderate increase in the risk of SCC skin cancer, while the effects of chemotherapy remain uncertain [11,33,34]. Although the time course of increased relative risk for skin cancer after some first cancers could suggest a therapy-induced effect, these were not consistent among males and females and thus fail to provide convincing evidence on therapy-related skin cancers.

The high risks of second skin cancer and non-Hodgkin's lymphoma suggest that immune suppression may be a contributing mechanism explaining a part of the excess risks for second primary neoplasms. This mechanism could operate also in other second cancers, but the subject is outside the scope of the present investigation. Undoubtedly, the current findings may be partly influenced by surveillance bias, i.e. the higher diagnostic intensity in patients with a primary cancer than in other subjects. The present evidence, together with earlier data, should encourage molecular epidemiological studies to quantify therapy-induced immunological aberrations in cancer and to delineate their role in the development of subsequent neoplasms.

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