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ORIGINAL PAPER

Second primary cancers in patients with nasopharyngeal carcinoma: a pooled analysis of 13 cancer registries

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Abstract
Objective To study the risk of second primary cancers in nasopharyngeal carcinoma (NPC) patients and the risk of NPC as second primary cancer.
Methods We used data from the cancer registries from Singapore and from 12 low-incidence areas, including a total of 8,947 first occurring NPC cases, and 167 second occurring cases. We calculated standardized incidence ratios (SIRs) by comparing the second cancer incidence in NPC patients to the first primary cancer incidence in non-cancer population. We also calculated SIRs of second NPC after other primaries.

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Results In Singapore, the risk of cancers of the lung (SIR = 0.42), stomach (SIR = 0.41), and colon (SIR = 0.23) was significantly decreased after NPC, whereas that of cancer of the tongue (SIR = 11.1) was significantly increased. In Australia, Canada, and Europe, the risk of non-Hodgkin's lymphoma (NHL) (SIR = 3.06), tongue cancer (SIR = 5.29), brain cancer (SIR = 3.89), myeloid leukemia (SIR = 3.85), and non-melanoma skin cancer (NMSC) (SIR = 3.47) was significantly increased after NPC. Incidences of second occurring NPCs following various primary cancers were not significantly altered compared to the incidence of first occurring NPCs.
Conclusions Immune suppression (NHL, NMSC), shared genetic factors (lung cancer, NHL, myeloid leukemia), and shared environmental risk factors (tongue and brain cancers) might explain the associations. Except for NHL, there was no evidence of association with other Epstein-Barr virus-related cancers.

Keywords Nasopharyngeal carcinoma · Second primary cancers · Cancer registry

Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy with unusually variable incidence rates across the world. While NPC is rare in most parts of the world (e.g., 8 cases/1,000,000/year in the United Kingdom), it is an endemic disease in South-East Asia and in North Africa, with incidence rates 10- to 40-fold higher than in non-endemic areas [1].

Although histological classification of NPC is still being discussed and boundaries between the categories are not always clear, NPC is usually classified as keratinizing squamous cell carcinoma and non-keratinizing carcinoma [2]. The proportion of keratinizing squamous cell carcinoma among all NPC is probably higher in low-incidence (73% in the USA [3]) compared with high-incidence areas (2% in China [4]). Although most epidemiological studies on NPC have been conducted in high-incidence areas, different histological type distributions might indicate that different risk factors are involved in different regions.

An aetiological link between NPC and infection with Epstein-Barr virus (EBV) is well established [5]. Certain human leukocyte antigen (HLA) genotypes, traditionally preserved food (particularly eating Chinese-style salted fish in early life), and occupational exposure to formaldehyde and wood dust are also recognized risk factors [6]. IARC Monographs [7] recently considered that there was sufficient evidence to causally link tobacco smoking and nasopharyngeal cancer, based on studies conducted in both low- and high-incidence areas.

Studying the occurrence of NPC before or after other neoplasms may help to formulate aetiological hypotheses, mainly when an association is symmetrical, i.e., a specific cancer is found more frequently after as well as before NPC. While second cancers after other forms of oral and pharyngeal cancer have been extensively studied, only five population-based studies have been conducted on the risk of second primary cancer in NPC patients; four in Asia [8–11] and one in the United States of America [12]. These studies included relatively low numbers of NPC cases and were thus not informative as to the risk of subsequent individual cancers.

We report here the results of a pooled analysis of data from 13 population-based cancer registries, including a registry from a high-incidence area (Singapore), on second primary cancers in NPC patients.

Materials and methods

In order to conduct a systematic analysis of second cancers, an international multicenter study was established involving large cancer registries that have been in operation for at least 20 years (range of first calendar year of coverage: 1943–1978). Details of data handling and standardization between the 13 participating registries have been described elsewhere

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[13, 14]. These registries cover the following areas: British Columbia, Manitoba and Saskatchewan (Canada), Denmark, Finland, Iceland, New South Wales (Australia), Norway, Scotland (United Kingdom), Singapore, Slovenia, Sweden, and Zaragoza (Spain).

The topographical code C11 in the 10th version of the International Classification of Diseases [15], as well as the other corresponding three-digit codes of various classifications utilized over time, were used to select nasopharyngeal cancer cases. We selected the malignant NPC cases using the morphological codes recorded by the registries, based on the WHO Classification of Tumors [2]. In the various classifications used, extra-nodal non-Hodgkin's lymphomas (NHL) were classified under lymphoma categories.

The International Association of Cancer Registries (IACR)/International Agency for Research on Cancer (IARC) rules on second cancers [16] were adopted as a common set to define second cancers. This was possible as all participating cancer registries had used the IACR/IARC rules, or a set of more detailed rules. According to these rules, in situ cancers are not considered as second primary cancers. Also, second tumors that occurred in the nasopharynx after a first primary nasopharyngeal cancer were not analyzed because rules were not compatible between registries or over time.

To assess the possible excess of second cancers after NPC, we calculated standardized incidence ratios (SIRs) to compare the observed number of cases of individual second cancers to the expected number derived from the age-, sex-, calendar period- and registry-specific incidence rates of first primary cancers. Details of statistical analysis have been described elsewhere [13, 14]. In all analyses, SIRs were stratified by geographical area (Singapore *versus* Australia, Canada, and Europe together), as the important difference in incidence rates is likely to reflect different aetiological factors. NPC has a peculiar age distribution peaking around 40–45 years old in high-incidence areas [17]. We stratified the results by age at diagnosis using the categories <40, 40–49, 50–59, and 60 years old or more. Results were also stratified by sex, follow-up duration since NPC diagnosis (<1 year, 1–4 years, 5–9 years, and 10 years or more), and by calendar period at NPC diagnosis (<1974, 1974–81, 1982–87, 1988 or later).

We subsequently calculated the SIR for NPC as a second primary after each of the other cancers, using the same indirect standardization approach by comparing the observed cases of NPC as a second cancer to the expected cases derived from the age-, sex-, calendar period- and registry-specific rates of first NPC.

Results

Among a total of over four million cases of first primary cancer, we identified 8,947 cases of NPC, and 291 of them subsequently developed a cancer at another site. In addition, there were 167 cases of NPC that occurred after a first cancer at a different site. Table 1 reports the main characteristics of NPC patients at diagnosis. Among the first NPC cases, 6,609 (74%)

Table 1 Distribution of nasopharyngeal carcinoma (NPC) patients as first and second cancer by geographical area and by sex, age, and calendar period at diagnosis

Characteristics	Singapore		Australia, Canada, Europe		Overall	
	No. of first NPC (%)	No. of second NPC* (%)	No. of first NPC (%)	No. of second NPC* (%)	No. of first NPC (%)	No. of second NPC* (%)
Total	5,182	38	3,765	129	8,947	167
Sex						
Women	1,525 (29.4)	20 (52.6)	1,196 (31.8)	51 (39.5)	2,721 (30.4)	71 (42.5)
Men	3,657 (70.6)	18 (47.4)	2,569 (68.2)	78 (60.5)	6,226 (69.6)	96 (57.5)
Age at diagnosis						
<40	1,532 (29.6)	3 (7.9)	554 (14.7)	2 (1.55)	2,086 (23.3)	5 (3.0)
40–49	1,564 (30.2)	2 (5.3)	578 (15.4)	5 (3.88)	2,142 (23.9)	7 (4.2)
50–59	1,224 (23.6)	13 (34.2)	904 (24.0)	23 (17.8)	2,128 (23.8)	36 (21.6)
60+	862 (16.6)	20 (52.6)	1,729 (45.9)	99 (76.7)	2,591 (29.0)	119 (71.3)
Mean (standard deviation)	47 (13)	61 (14)	56 (16)	68 (11)	51 (15)	66 (12)
Calendar period at diagnosis						
<1974	890 (17.2)	0(0)	1,254 (33.3)	25 (19.4)	2,144 (24.0)	25 (15.0)
1974–1981	1,500 (28.9)	8 (21.1)	825 (21.9)	19 (14.7)	2,325 (26.0)	27 (16.2)
1982–1987	1,364 (26.3)	13 (34.2)	582 (15.5)	25 (19.4)	1,946 (21.7)	38 (22.8)
1988+	1,428 (27.6)	17 (44.7)	1,104 (29.3)	60 (46.5)	2,532 (28.3)	77 (46.1)

* Excluding those following a nasopharyngeal cancer

Table 2 Standardized incidence ratios of selected second primary cancers following nasopharyngeal carcinoma (NPC) by geographical areas

Cancer sites (ICD 9th revision)	Geographical areas						p for heterogeneity
	Singapore			Australia, Canada, Europe			
	Obs	SIR	95% CI	Obs	SIR	95% CI	
All Malignant (140–208, excl. 147)	76	**0.76**	0.60–0.95	215	**1.46**	1.27–1.67	<0.01
Upper aerodigestive tract (140–149, excl. 147)	9	**3.79**	1.74–7.21	13	**3.33**	1.77–5.70	0.76
Tongue (141)	6	**11.1**	4.08–24.2	3	**5.29**	1.09–15.5	0.28
Salivary gland (142)	0 (exp. = 0.27)			1	**3.07**	0.08–17.1	0.37
Mouth (143–145)	2	**3.07**	0.37–11.1	2	**2.50**	0.30–9.02	0.84
Stomach (151)	5	**0.41**	0.13–0.95	12	**1.41**	0.73–2.46	0.01
Colon (153)	2	**0.23**	0.03–0.83	8	**0.75**	0.32–1.47	0.11
Rectum (154)	5	**0.77**	0.25–1.79	7	**0.93**	0.37–1.91	0.75
Pancreas (157)	1	**0.51**	0.01–2.85	7	**1.50**	0.60–3.09	0.29
Nose and nasal cavity (160)	2	**5.04**	0.61–18.2	2	**6.41**	0.78–23.2	0.80
Larynx (161)	2	**0.94**	0.11–3.39	3	**1.78**	0.37–5.20	0.48
Lung (162)	10	**0.42**	0.20–0.78	27	**1.35**	0.89–1.96	<0.01
Soft tissue sarcoma (171)	0 (exp. = 0.54)			2	**2.75**	0.33–9.94	0.22
Cutaneous melanoma (172)	0 (exp. = 0.21)			5	**1.26**	0.41–2.94	0.61
Non-melanoma skin cancer (173)	4	**1.11**	0.30–2.85	28	**3.47**	2.31–5.02	0.03
Female breast (174)	2	**0.36**	0.04–1.31	10	**0.99**	0.47–1.82	0.18
Cervix uteri (180)	6	**2.06**	0.76–4.48	2	**1.40**	0.17–5.07	0.64
Ovary (183)	3	**2.16**	0.44–6.30	3	**1.43**	0.29–4.17	0.61
Prostate (185)	5	**2.57**	0.83–5.99	20	**0.89**	0.55–1.38	0.03
Bladder (188, 189.3, 189.4)	2	**0.83**	0.10–3.01	8	**1.02**	0.44–2.00	0.80
Kidney (189) (excl. 189.3, 189.4)	0 (exp. = 1.41)			7	**1.59**	0.64–3.27	0.13
Brain, nervous system (191, 192)	1	**1.81**	0.05–10.1	8	**3.89**	1.68–7.66	0.46
Non-Hodgkin's lymphoma (200, 202)	5	**2.43**	0.79–5.66	12	**3.06**	1.58–5.35	0.66
Hodgkin's disease (201)	0 (exp. = 0.20)			0 (exp. = 0.60)			–
Multiple myeloma (203)	0 (exp. = 0.48)			5	**2.43**	0.79–5.66	0.28
Myeloid leukemia (205)	2	**2.01**	0.24–7.25	4	**3.85**	1.05–9.86	0.44

provided at least one year of follow-up, with a mean of 4.7 years of follow-up (median = 2.3 years). During the follow-up period, 5,702 (63.7%) of the patients died. In total, NPC patients were followed for 42,332 person-years. Singapore, as expected, was the registry with the largest contribution, with 57.9% of the first and 22.8% of the second NPC cases. Sweden, Denmark, Finland, Norway, British Columbia, and New South Wales each provided between 3 and 10% of the cases, while each of the remaining registries provided less than 2% of the cases.

The SIRs for second primary cancers following NPC by geographical area are presented in Table 2. The overall risk of developing a new primary cancer was significantly decreased in Singapore (SIR = 0.76, 95% CI 0.60–0.95) and increased in other countries (SIR = 1.46, 95% CI 1.27–1.67). Results for individual cancer sites are shown only when at least four cases occurred overall, except for cancers with an established or suspected association with EBV (non-Hodgkin's lymphoma (NHL), Hodgkin's disease, gastric cancer, soft tissue sarcoma, salivary gland cancer, nasal cavity cancer, and lung cancer) [18–20]. Statistical significant differences in SIRs between Singapore and the other countries were observed for all second cancers together, and cancers of the lung, stomach, prostate, and skin (non-melanoma, NMSC). In Singapore, the risk of second cancers of the lung, stomach, and colon (based on two cases) was significantly decreased, whereas that of cancer of the tongue was significantly increased. In Australia, Canada, and Europe, several individual cancers had a significantly increased risk: NHL, tongue cancer, brain cancer, myeloid leukemia, and NMSC.

There was no statistically significant difference between men and women in the risk of cancer following NPC (data not shown), though the overall decreased risk in Singapore was found in men (n = 49, SIR = 0.67 95% CI 0.50–0.89) but not in women (n = 27, SIR = 1.00 95% CI 0.66–1.46).

Table 3 shows the SIRs stratified by time since NPC diagnosis for second cancers that had a significantly altered risk in at least one geographical area. The risk of second cancer overall was significantly decreased in Singapore only in the first five years following the diagnosis, while the risk was significantly increased in

Table 3 Standardized incidence ratios of selected second primary cancers following nasopharyngeal carcinoma (NPC) by follow-up duration

Cancer sites (ICD 9th revision)	Geographical areas	Follow-up duration (years)											
		<1			1–4			5–9			10+		
		Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% Cl
All Malignant (140–208, excl. 147)	Singapore	8	**0.50**	0.22–0.99	20	**0.57**	0.35–0.88	25	**1.05**	0.68–1.54	23	**0.91**	0.58–1.37
	Australia, Canada, Europe	29	**1.23**	0.82–1.76	78	**1.62**	1.28–2.02	45	**1.37**	1.00–1.83	63	**1.47**	1.13–1.89
Upper aerodigestive tract (140–149, excl. 147)	Singapore	1	**2.62**	0.07–14.6	2	**2.34**	0.28–8.44	1	**1.82**	0.05–10.1	5	**8.53**	2.77–19.9
	Australia, Canada, Europe	3	**4.49**	0.93–13.1	0 (exp. = 1.36)			5	**5.76**	1.87–13.5	5	**4.95**	1.61–11.5
Tongue (141)	Singapore	0 (exp. = 0.09)			1	**5.11**	0.13–28.5	1	**8.10**	0.20–45.1	4	**31.2**	8.51–80.0
	Australia, Canada, Europe	1	**10.6**	0.27–59.3	0 (exp. = 0.20)			1	**7.89**	0.20–43.9	1	**6.65**	0.17–37.1
Stomach (151)	Singapore	0 (exp. = 2.05)			3	**0.69**	0.14–2.02	1	**0.35**	0.01–1.95	1	**0.33**	0.01–1.84
	Australia, Canada, Europe	2	**1.16**	0.14–4.21	4	**1.35**	0.37–3.45	3	**1.68**	0.35–4.90	3	**1.48**	0.30–4.31
Colon (153)	Singapore	0 (exp. = 1.26)			0 (exp. = 2.94)			1	**0.48**	0.01–2.69	1	**0.40**	0.01–2.25
	Australia, Canada, Europe	1	**0.60**	0.01–3.33	3	**0.88**	0.18–2.57	3	**1.25**	0.26–3.66	1	**0.31**	0.01–1.72
Lung (162)	Singapore	0 (exp. = 3.69)			3	**0.38**	0.08–1.10	7	**1.24**	0.50–2.56	0 (exp. = 6.30)		
	Australia, Canada, Europe	0 (exp. = 3.30)			16	**2.36**	1.35–3.83	4	**0.89**	0.24–2.27	7	**1.28**	0.51–2.64
Non-melanoma skin cancer (173)	Singapore	1	**1.92**	0.05–10.7	1	**0.80**	0.02–4.48	0 (exp. = 0.86)			2	**2.07**	0.25–7.48
	Australia, Canada. Europe	2	**1.60**	0.19–5.77	4	**1.58**	0.43–4.04	7	**3.93**	1.58–8.10	15	**5.99**	3.35–9.88
Brain, nervous system (191, 192)	Singapore	0 (exp. = 0.10)			0 (exp. = 0.21)			1	**7.94**	0.20–44.2	0 (exp. = 0.12)		
	Australia, Canada, Europe	0 (exp. = 0.33)			4	**5.49**	1.50–14.1	2	**4.46**	0.54–16.1	2	**3.65**	0.44–13.2
Non-Hodgkin's lymphoma (200, 202)	Singapore	1	**3.14**	0.08–17.5	1	**1.37**	0.03–7.65	2	**4.01**	0.49–14.5	1	**1.94**	0.05–10.8
	Australia, Canada, Europe	3	**5.09**	1.05–14.9	4	**3.12**	0.85–8.00	2	**2.31**	0.28–8.33	3	**2.54**	0.52–7.41
Myeloid leukemia (205)	Singapore	0 (exp. = 0.17)			1	**2.73**	0.07–15.2	0 (exp. = 0.23)			1	**4.25**	0.11–23.7
	Australia, Canada, Europe	1	**5.77**	0.14–32.2	**2**	**5.74**	0.70–20.8	1	**4.36**	0.11–24.3	0 (exp. = 0.29)		

other countries after the first year of follow-up. In Australia, Canada, and Europe, the risk of NMSC was significantly increased after a latency of five years. The risk of brain cancer was significantly increased one to five years after NPC diagnosis, and remained elevated thereafter although non-significantly. The risk of NHL was increased all over the follow-up periods, although the SIR was significant in the first year only. The risk of cancer of the upper aerodigestive tract was significantly increased after a latency of five years in Australia, Canada, and Europe, and of 10 years in Singapore.

SIRs stratified for calendar period and age at NPC diagnosis are shown in Table 4 for all second primaries together. In Singapore, the decreased risk of second primaries was attenuated from the 1980s compared to cases diagnosed earlier. In other countries, SIRs remained relatively stable. Concerning the results by age at NPC diagnosis in Singapore, a SIR of 2.60 was found for all second cancers together after a first NPC diagnosed before 40 years of age, whereas a decreased risk was found after NPC diagnosed at older ages. The same pattern of high risk after early-diagnosed NPC

Table 4 Standardized incidence ratios of all second primary cancers following nasopharyngeal carcinoma (NPC) by age and calendar period at NPC diagnosis

Characteristics at NPC diagnosis	Geographical areas					
	Singapore			Australia, Canada, Europe		
	Obs	SIR	95% CI	Obs	SIR	95% CI
Calendar period						
<1974	18	**0.56**	0.33–0.89	66	**1.24**	0.96–1.58
1974–81	24	**0.69**	0.44–1.02	65	**1.78**	1.37–2.26
1982–87	27	**1.15**	0.76–1.67	36	**1.27**	0.89–1.75
1988+	7	**0.74**	0.30–1.52	48	**1.64**	1.21–2.17
Age						
<40	24	**2.60**	1.66–3.87	20	**2.92**	1.79–4.51
40–49	18	**0.82**	0.48–1.29	27	**1.52**	1.00–2.21
50–59	20	**0.57**	0.35–0.88	70	**1.76**	1.37–2.23
60+	14	**0.42**	0.23–0.70	98	**1.18**	0.96–1.44

was found in other countries (SIR = 2.92), although, unlike in Singapore, a moderately increased risk remained after NPC diagnosed later in life. Table 5 shows detailed results for selected second primaries by age at NPC diagnosis (<40 years old, 40+ years old). In general, SIRs were higher for patients diagnosed before 40 years old than later in age.

The incidence of NPC after any other primary cancer was not different from the incidence of first NPC (Table 6). The risk of NPC was not significantly

Table 5 Standardized incidence ratios of selected second primary cancers following nasopharyngeal carcinoma (NPC) by age at NPC diagnosis

Cancer sites (ICD 9th revision)	Geographical areas	Age at NPC diagnosis (years)					
		<40			40+		
		Obs	SIR	95% CI	Obs	SIR	95% CI
All Malignant (140–208, excl. 147)	Singapore	24	**2.60**	1.66–3.87	52	**0.57**	0.43–0.75
	Australia, Canada, Europe	20	**2.92**	1.79–4.51	195	**1.39**	1.20–1.60
Upper aerodigestive tract (140–149, excl. 147)	Singapore	3	**13.5**	2.79–39.5	6	**2.79**	1.02–6.07
	Australia, Canada, Europe	0 (exp. = 0.22)			13	**3.53**	1.88–6.04
Tongue (141)	Singapore	2	**30.6**	3.71–111	4	**8.44**	2.30–21.6
	Australia, Canada, Europe	0 (exp. = 0.04)			3	**5.67**	1.17–16.6
Stomach (151)	Singapore	1	**1.36**	0.03–7.57	4	**0.35**	0.09–0.89
	Australia, Canada, Europe	1	**5.04**	0.13–28.1	11	**1.32**	0.66–2.37
Colon (153)	Singapore	0 (exp. = 0.72)			2	**0.25**	0.03–0.90
	Australia, Canada, Europe	0 (exp. = 0.32			8	**0.77**	0.33–1.52
Lung (162)	Singapore	1	**0.96**	0.02–5.33	9	**0.40**	0.18–0.76
	Australia, Canada, Europe	4	**6.68**	1.82–17.1	23	**1.18**	0.75–1.77
Non-melanoma skin cancer (173)	Singapore	0 (exp. = 0.33)			4	**1.23**	0.33–3.14
	Australia, Canada, Europe	7	**14.1**	5.67–29.1	21	**2.77**	1.72–4.24
Brain, nervous system (191, 192)	Singapore	0 (exp. = 0.13)			1	**2.35**	0.06–13.1
	Australia, Canada, Europe	2	**8.82**	1.07–31.9	6	**3.28**	1.20–7.13
Non-Hodgkin's lymphoma (200, 202)	Singapore	3	**9.90**	2.04–28.9	2	**1.14**	0.14–4.11
	Australia, Canada, Europe	1	**3.61**	0.09–20.1	11	**3.02**	1.51–5.40
Myeloid leukemia (205)	Singapore	2	**9.76**	1.18–35.3	0 (exp. = 0.79)		
	Australia, Canada, Europe	1	**11.6**	0.29–64.7	3	**3.15**	0.65–9.21

Table 6 Standardized incidence ratios of nasopharyngeal cancer (NPC) following selected first primary cancers by geographical areas

Cancer sites (ICD 9th revision)	Number of first cancer Cases	Geographical areas						*p for heterogeneity*
		Singapore			Australia, Canada, Europe			
		Obs	SIR	95% CI	Obs	SIR	95% CI	
All Malignant (140–208, excl. 147)	4,181,341	38	**0.81**	0.57–1.11	129	**1.10**	0.91–1.30	*0.09*
Upper aerodigestive tract (140–149, excl. 147)	105,526	3	**1.96**	0.40–5.72	5	**0.90**	0.29–2.11	*0.28*
Tongue (141)	15,985	0 (exp. = 0.43)			1	**2.12**	0.05–11.8	*0.46*
Salivary gland (142)	11,108	1	**3.34**	0.08–18.6	0 (exp. = 0.55)			*0.18*
Mouth (143–145)	22,378	0 (exp. = 0.42)			3	**4.05**	0.83–11.8	*0.19*
Stomach (151)	245,625	2	**0.45**	0.05–1.63	4	**1.04**	0.28–2.67	*0.32*
Colon (153)	298,766	3	**0.63**	0.13–1.85	5	**0.61**	0.20–1.41	*0.96*
Rectum (154)	196,200	4	**1.20**	0.33–3.06	10	**1.59**	0.76–2.92	*0.63*
Pancreas (157)	105,771	0 (exp. = 0.30)			1	**1.99**	0.05–11.1	*0.44*
Nose and nasal cavity (160)	9,450	0 (exp. = 0.37)			2	**5.94**	0.72–21.5	*0.14*
Larynx (161)	40,190	0 (exp. = 1.46)			3	**1.33**	0.27–3.88	*0.80*
Lung (162)	450,602	3	**0.65**	0.13–1.90	6	**1.18**	0.43–2.56	*0.40*
Soft tissue sarcoma (171)	26,285	0 (exp. = 0.58)			1	**1.03**	0.03–5.73	*0.44*
Cutaneous melanoma (172)	140,100	0 (exp. = 0.15)			5	**0.88**	0.28–2.04	*0.59*
Non-melanoma skin cancer (173)	276,034	1	**0.26**	0.01–1.45	12	**0.99**	0.51–1.72	*0.17*
Female breast (174)	525,527	5	**1.07**	0.35–2.50	11	**0.80**	0.40–1.43	*0.59*
Cervix uteri (180)	115,455	3	**0.97**	0.20–2.83	8	**2.05**	0.88–4.04	*0.26*
Ovary (183)	107,038	1	**0.83**	0.02–4.65	1	**0.56**	0.01–3.11	*0.63*
Prostate (185)	357,253	1	**1.11**	0.03–6.19	10	**0.61**	0.29–1.12	*0.72*
Bladder (188,189.3,189.4)	179,238	2	**1.12**	0.14–4.04	11	**1.35**	0.68–2.42	*0.80*
Kidney (189)(excl. 189.3,189.4)	102,868	1	**1.27**	0.03–7.08	2	**0.63**	0.08–2.26	*0.56*
Brain, nervous system (191, 192)	72,516	0 (exp. = 0.34)			0 (exp. = 0.97)			–
Non-Hodgkin's lymphoma (200, 202)	109,451	2	**1.88**	0.23–6.81	5	**1.80**	0.59–4.21	*0.96*
Hodgkin's disease (201)	31,154	0 (exp. = 0.19)			2	**2.31**	0.28–8.35	*0.51*
Multiple myeloma (203)	50,051	0 (exp. = 0.21)			1	**0.95**	0.02–5.31	*0.56*
Myeloid leukemia (205)	33,892	0 (exp. = 0.27)			0 (exp. = 0.36)			–

increased or decreased after any of the cancers considered previously as second primaries. However, the risk of NPC was significantly increased after lymphoid leukemia in Australia, Canada, and Europe (SIR = 5.36, 95% CI 2.15–11.0); out of the 7 cases of second NPC that occurred after lymphoid leukemia, 6 occurred after 4–16 months of follow-up. Only two cases of lymphoid leukemia had occurred after NPC (SIR = 1.21, 95% CI 0.15–4.36).

Discussion

Our analysis of almost 9,000 cases of first NPC, including 291 cases who developed a subsequent cancer, showed a 46% increased risk of all second cancers combined in Australia, Canada, and Europe, and a 24% decreased risk in Singapore. The increase in Australia, Canada, and Europe was mainly due to an increased risk of cancers of the tongue, skin (non-melanoma), brain and nervous system, as well as NHL and myeloid leukemia, whereas the decrease in Singapore was attributed to decreased risk of cancers of the lung, stomach, and colon. The analysis of risk of NPC after another cancer was hampered by small numbers, but in general, similar associations were not suggested.

Due to small numbers and multiple comparisons that might lead to chance associations, our results should be considered as exploratory. Also, misclassification of recurrences (e.g., in oral cavity) as second primary cancer may have overestimated the SIR. This pooled data of well-established cancer registries are, however, the largest data set used for the study of second primaries in NPC patients. The general decreased risk of second primaries after NPC in Singapore is intriguing. This may be associated with the rather strict definition of second primary cancers taken by the Singapore Cancer Registry, requiring histological confirmation. The decreased risk of lung and stomach cancers was not detected in NPC patients from Singapore diagnosed after 1982, i.e., more recent cases for whom histological verification of second cancer was more likely to be systematic. However, when non-histologically confirmed second cancer cases where excluded from the 215 observed cases in Australia, Canada, and Europe ($n = 18$), the SIR was

still significantly elevated (SIR = 1.34, 95% CI 1.16–1.54), which might imply that difference in registration methods does not fully explain difference in SIRs between Singapore and other registries.

The occurrence of a second primary cancer may be altered because of shared risk or protective factors (either environmental or genetic) and carcinogenic mechanisms, or effects of therapy administered for the first cancer. In the case of shared risk factors, the increased risk is likely to be constant over time since the diagnosis of the NPC, whereas a treatment effect may vary over time because of a latent period or cessation of therapy. Although treatment information was not available, this pattern in SIRs over time since first diagnosis may suggest a treatment effect. If shared risk factors are the reason for the increased risk, the relationship between the two cancers should be present in both directions and be of similar magnitude [21]. In our study, we could not find any significant reciprocal associations. However, the statistical power for such a finding was weak because of the small number of second NPCs, and the 95% CIs of the SIRs related to NPC as a second primary cancer after a given first primary cancer always included the point estimate of the SIR of that cancer after NPC.

Immune suppression hypothesis

A common mechanism of immune suppression has been put forward to explain the association between NHL and NMSC [13, 22]. Since cellular immunity is suppressed in patients with NPC and the suppressed condition still remains after remission [23], immune suppression might explain the increased incidence of NHL and NMSC after NPC. Although an increased NPC incidence was reported in HIV-infected persons in Africa based on three cases [24], a large study conducted in the US [25] did not show this association. Failing immunity is then not likely to play an important role in NPC development.

Shared genetic factor hypothesis

The increased risk of several second primary cancers after NPC was mainly found in early-onset diagnosed cases (lung cancer, NHL, myeloid leukemia). Common genetic susceptibility might be involved in these associations. Polymorphisms in two DNA repair genes, XRCC1 and HOGG1, have been reported to increase the risk of both lung cancer and NPC [26, 27]. Myeloid leukemia has also been linked to mutations in XRCC1 [28], whereas absent/minimal HOGG1 expression occurs in the majority of follicular lymphomas [29]. Defects in those and other DNA repair genes may then partly explain the association between early-onset NPC and lung cancer, myeloid leukemia, and NHL. However, the spectrum of cancers in carriers of DNA repair gene lesions is wide and genetic studies are needed to confirm whether NPC is linked to those.

Shared environmental risk factor hypothesis

Cancers of the tongue and brain may share environmental risk factors with NPC. Eating salted food, particularly Chinese-style salted fish, has been established as a risk factor for NPC. This diet habit has also been suggested as risk factor for cancers of the brain [30–32]. The increased risk of tongue cancer, as well as the non-significant increased risk of cancer of the nose and nasal cavity, might be explained by tobacco use. The increased risk of tongue cancer after NPC diagnosis may, however, be also explained by a treatment effect: NPC has mainly been treated with radiotherapy until recent adjunction of chemotherapy [33], and 5 out of the 9 cases of second tongue cancer occurred 10 or more years after NPC diagnosis (in Singapore: SIR = 31.2, 95% CI 8.51–80.0; in other countries: SIR = 6.65, 95% CI 0.17–37.1). Moreover, results from Teo et al. [8] also suggested that cases of tongue cancer occurring after NPC are likely to be radiation-induced malignancies.

Colon cancer risk and NPC risk were mutually decreased after each other, although non-significantly in the sequence colon cancer—NPC. Colon cancer has been associated with a high socioeconomic status in several countries [34–36], whereas NPC has been associated with low socioeconomic status among population with high or intermediated incidence [37, 38]. This opposition might then explain the negative association observed, although the environmental factors involved remain to be found.

Since EBV is an established cause of NPC, we expected an association with other EBV-related cancers. This was found only for NHL. Absence of an association with other EBV-related cancers may be explained by a lack of statistical power. For example, less than one case of Hodgkin's disease was expected after a NPC diagnosis, and no case occurred. Moreover, only specific histological types of carcinomas have been linked to infection with EBV [39] and SIRs were not histological type-specific. Our results are consistent, however, with Wang et al.'s study in Taiwan (2000), in which no EBV infection was found in second

tumors that occurred after NPC. Carcinogenicity of EBV might then use different mechanisms depending on the tissue infected, or different tissues might be susceptible to different EBV strains.

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