SECOND PRIMARY CANCERS IN NON-HODGKIN LYMPHOMA: BI-DIRECTIONAL ANALYSES SUGGESTING ROLE FOR IMMUNE DYSFUNCTION

Subhayan Chattopadhyay[1,2], Amit Sud[1,3], Guoqiao Zheng [1,2], Hongyao Yu [1,2], Kristina Sundquist[4,5,6], Jan Sundquist[4,5,6] Asta Försti[1,4] , Richard Houlston[3,7], Akseli Hemminki, [7,8] and Kari Hemminki, [1,4]

[1] Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 580, D-69120, Heidelberg, Germany
[2] Faculty of Medicine, University of Heidelberg, Heidelberg, Germany
[3] Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK.
[4] Center for Primary Health Care Research, Lund University, 205 02 Malmö, Sweden
[5] Department of Family Medicine and Community Health, Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, USA
[6] Center for Community-based Healthcare Research and Education (CoHRE), Department of Functional Pathology, School of Medicine, Shimane University, Japan
[7] Division of Molecular Pathology, The Institute of Cancer Research, London, UK.
[8] Cancer Gene Therapy Group, Faculty of Medicine, University of Helsinki, Finland
[9] Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland

Correspondence: Kari Hemminki, Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 580, Heidelberg 69120, Germany.
Telephone: +496221421800
Fax: +496221421810
Email: K.Hemminki@dkfz.de

Words: 245 (abstract), 2998(text)

Key words: second cancers, immune suppression, bi-directional risk, therapeutic implication.

Running title: Second cancers and NHL

NOVELTY AND IMPACT

The nationwide study found non-Hodgkin lymphoma and 7 cancers, including squamous cell skin cancer and melanoma, were bi-directionally associated with each other. Bi-directional associations may help to resolve the role for therapeutic side effects because treatment for two cancers is rarely similar, particularly considering primary surgical treatment for skin cancers. The data suggest that an immune suppressed state is a key contributing mechanism for second primary cancers and immune therapy in patient management will have a clinical impact.

ABSTRACT

Second primary cancers (SPCs) account for an increasing proportion of all cancer diagnoses. It is unlikely that prior therapy is solely responsible for SPC risk. To investigate risk of SPC after diagnosis of non-Hodgkin lymphoma (NHL) and 10 of its subtypes we conducted a novel bi-directional analysis, SPCs after NHL and NHL as SPC. Using the Swedish Family-Cancer Database, we identified 19,833 individuals with primary NHL diagnosed between 1993 and 2015. We calculated relative risks (RRs) of SPCs in NHL survivors and, for bi-directional analysis, risk of NHL as SPC. The overall RRs were significantly bi-directionally increased for NHL and 7 cancers. After diagnosis of NHL risks were increased for upper aerodigestive tract (RR=1.96), colorectal (1.35), kidney (3.10), bladder (1.54) and squamous cell skin cancer (SCC) (4.12), melanoma (1.98) and Hodgkin lymphoma (9.38). The concordance between RRs for each bi-directional association between NHL and 31 different cancers was highly significant (r= 0.86, $P<0.0001$). Melanoma was bi-directionally associated with all 10 subtypes of NHL. The observed bi-directional associations between NHL and cancer suggest that therapy-related carcinogenic mechanisms cannot solely explain the findings. Considering that skin SCC and melanoma are usually treated by surgery and that these cancers and NHL are most responsive of any cancer to immune suppression, the consistent bi-directional results provide population-level evidence that immune suppressed state is a key underlying mechanism in the context of SPCs. Furthermore, the quantified risks for NHL subtypes have direct clinical application in the management of NHL patients.

INTRODUCTION

Non-Hodgkin lymphoma (NHL), the most common hematological malignancy, is a cancer of the lymphatic system caused by either B- or T-cell clonal expansion [1, 2]. Established risk factors for NHL include immunosuppression and other types of immunodeficiency or autoimmunity, in addition to chronic inflammation induced by viral or other microbial causes [2].

There are multiple subtypes of NHL, including, and not restricted, to benign forms of follicular lymphoma, small lymphocytic lymphoma and mantle cell lymphoma and aggressive forms of diffuse large B-cell lymphoma and Burkitt lymphoma[1]. Perhaps not surprisingly, the epidemiology of NHL has been hampered by the changes in NHL classification and studies have been confined to the major subtypes, diffuse large B-cell lymphoma and follicular lymphoma [3].

Until the advent of multidrug chemotherapy to complement radiotherapy in the 1970s, including the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisone), and variations thereof, patient outcome of NHL was typically poor [1]. In the late 1990s the monoclonal antibody directed against tumor antigens was licensed to be used in combination with chemotherapy and radiotherapy [1, 2]. Subsequently, other monoclonal antibodies, some radioactive labeled, have been developed for treatment of specific NHL subtypes, including most recently immune checkpoint inhibitors [2, 4].

While the advances in the management of NHL over the past 40 years have undoubtedly led to a markedly improved survival, this has come at the cost of an increased number of second primary cancers (SPCs) and other treatment-related complications. A number of studies have estimated risks of SPCs after NHL but have confined their analyses to the most common NHL subtypes [5-10].

Here we report analysis of the Swedish Cancer Registry to assess risks of SPCs following the diagnosis of NHL, and also the risk of NHL after the diagnosis of another cancer. The rationale for the bi-directional analysis was to understand mechanisms for SPC susceptibility beyond therapeutic side effects and shared risk factors [11, 12]. Indeed, the novel bi-directional analysis of 19,833 NHL patients (including 10 NHL subtypes) is a powerful approach in search of evidence for reciprocal relationships between cancer risks which may suggest that SPCs may be a model of tumor biology.

PATIENTS AND METHODS

The Swedish Family-Cancer Database includes the whole Swedish population organized in families and linked to the national Cancer Registry with more than 2 million cancers registered since 1958 [13]. The registry is based on compulsory cancer notifications from clinicians and pathologists/cytologists [14]. All registered NHL cases were histologically verified. While the cancer registry does not publish statistics on histological verification of SPCs they are included with primary cancers for which histological verification has been around 98% from the 1970s [15]. An *ad hoc* study on the diagnostic accuracy of second neoplasms found 98% to be correctly classified. [16]. NHL subtypes were identified through reference to the 10th revision of International Classification of Diseases (ICD) in combination with SNOMED (ICD-O2) codes that were introduced in 1993. The Swedish Cancer Registry orders tumors by diagnostic date into first, second, third etc. primary cancers. This ordering was used either to select NHL as first primary cancer or as SPC after another primary cancer. We did not study patients diagnosed with NHL after NHL. NHL patients were followed from diagnosis until death, detection of a SPC, emigration or December 31, 2015, whichever came first. Person-years and SPCs were categorized according to age (5-year bands), sex, socioeconomic index (six groups), region (four groups), calendar year (1993-99, 2000-09, 2010-15), time since NHL diagnosis and age at NHL diagnosis. Category-specific incidence rates among NHL patients were multiplied by the corresponding person-years at risk to estimate the expected number of malignancies in respective strata. In stratified analyses over calendar periods case accrual was stopped at the termination of the period to allow uniform follow-up times.

Relative risks (RRs) were assessed by means of incidence rate ratios, regressed over a fixed-effects generalized Poisson model. RRs for SPCs were obtained by comparing incidence rates for each SPC in NHL patients with respective population background rates for the primary cancer. In the reverse analysis, RRs for specific NHLs were considered as SPCs following any primary cancer. Sex, age group, calendar-period, socio-economic status and residential area were treated as potential confounders and were adjusted for in the regression model. Confidence intervals (CIs) were calculated for 5% level of significance and p-values associated with RRs were obtained with two-tailed tests against Chi-square distribution with one degree of freedom [17]. In referring to differences between RRs we call risks only when they are significant (i.e., 95%CIs are non-overlapping). The concordance between RRs was assessed by Pearsonian correlation. All analyses are performed in SAS (v9.4) or R (v3.3.4).

The study was approved by the Ethical Committee of Lund University.

RESULTS

Of the 19,833 NHL patients, 1,731 developed a SPC with a median follow-up of 4 years. Out of the 940,811 other cancer patients, 2,571 developed second NHL with a median follow-up of 6 years (Table 1).

Risks for SPCs following a diagnosis of NHL and risk of NHL following the diagnosis of 31 non-NHL cancers are shown in Table 2. Overall, the risk of SPC was increased 1.53-fold. RRs were significantly increased for 12 cancers with the largest RRs being shown for Hodgkin lymphoma (RR: 9.38,), squamous cell skin (SCC, 4.12,) and kidney cancers (3.10). Statistically significant RRs of more than 2.00 were also documented for leukemia, anal and thyroid tumors. In the reverse analysis, for all non-NHL cancers the risk of being diagnosed subsequently with NHL was significantly increased 1.40-fold (Table 2). RRs were significantly increased for 14 cancers with the largest RRs being shown for Hodgkin lymphoma (7.29), followed by skin SCC (2.44) and testicular cancer (2.29). The concordance between RR for each non-NHL cancer following a diagnosis of NHL and RR for NHL following diagnosis of a non-NHL cancer was highly statistically significant (r=0.86, $P<0.0001$).

Sensitivity analysis was performed on data shown in Table 2 by deleting in both of the reciprocal analyses the first year of follow-up after first diagnosis of cancer (Supplementary Table 1). No essential differences in RRs to Table 2 were noted even though case numbers were reduced. The overall risks for SPC increased to 1.62 from 1.53 and the overall risks of NHL as SPC remained at 1.40.

Data in Table 2 were adjusted for sex, age group, calendar-period, socio-economic status and residential area. In order to put the data in Table 2 in perspective of some key variables we conducted age- and period-stratified analyses in Supplementary Tables 2 to 5. Supplementary Table 2 shows RRs separately for SPC after NHL when NHL was diagnosed before age 66 or after 65 years. The overall and individual RRs were stable in the two age groups and no single RR showed a significant difference, with the exception of stomach cancer with a higher risk at the early onset group (95%CIs overlapped). RRs for kidney cancer, melanoma and skin SCC were almost equal between the two age groups. We tested a wide range of age cut-off points and, even though case numbers varied, RRs were stable overall and for kidney cancer, melanoma and skin SCC up to age group over 80 years (data not shown). In the reverse analysis (Supplementary Table 3), NHL as SPC, early onset risks were significantly higher for NHL after kidney cancer and overall; for melanoma and skin SCC there were no differences. Stratification by period was done for two almost equally long periods (11 and 12 years), the latter covering increasing use of novel therapies (Supplementary Table 4). Much fewer SPCs were diagnosed in the early period and the overall RR for it was significantly lower (1.31) than that for the latter period (1.56). More significant associations for individual SPCs were noted in the latter period (e.g., stomach, colorectal and lung cancers) but none were significantly different compared to the early period. In the reverse analysis, NHL as SPC, the overall RRs were higher in the latter period but the only individual site with a significant difference was colorectal cancer (Supplementary Table 5).

Table 3 shows the RRs of all non-NHL cancers following diagnosis of each of the 5 of the major NHL subtypes. Statistically significant RRs were shown after mantle cell lymphoma (1.78), marginal zone lymphoma (1.70), follicular lymphoma (1.69), lymphoplasmacytic lymphoma (1.64, Waldenstrom macroglobulinemia) and diffuse large B-cell lymphoma (1.33). Skin SCC and melanoma risks were increased after all 5 NHL subtypes; the RR for skin SCC was 6.20 after mantle cell lymphoma. Lung and kidney cancer risks were increased after four NHLs. Risks for upper aerodigestive tract and bladder cancers, Hodgkin lymphoma and leukemia were increased after 3 NHLs; the RR for Hodgkin lymphoma was 9.64 after follicular lymphoma. Rare anal cancer risk was increased to 6.34 after follicular lymphoma.

The results of the reverse analysis, risk of the 5 NHL subtypes as SPC, are shown in Table 4. Melanoma and skin SCC were first primaries for five and four subtypes, respectively; RRs were highest for marginal zone lymphoma (after melanoma 2.81), for follicular lymphoma (after skin SCC 2.56) and for mantle cell lymphoma (after melanoma and skin SCC both 2.46). Testicular cancer was associated with high risks of lymphoplasmacytic lymphoma (4.59) and mantle cell lymphoma (5.27). Diffuse large B-cell lymphoma risk was increased to 13.76 after Hodgkin lymphoma.

Risks for SPC after 5 rare NHL subtypes are shown in Supplementary Table 6. The overall risks were increased and statistically significant for all of them, most for small lymphocytic lymphoma (1.85), followed by and anaplastic T-cell lymphoma (1.62). Skin SCC was increased after three of these subtypes, most after small lymphocytic lymphoma (7.41). Kidney cancer was increased after two NHL subtypes, cutaneous T-cell lymphoma and anaplastic T-cell lymphoma both with RRs exceeding 6.00. Melanoma (4.77) and leukemia (7.82) were increased after Burkitt lymphoma

Reverse analyses for 5 rare NHL subtypes as SPC are shown in Supplementary Table 7. The overall RRs were increased for small lymphocytic lymphoma (2.28) and cutaneous T-cell lymphoma (1.59). Skin SCC and cancer of connective tissue were first primaries for three NHL subtypes whereas kidney cancer and melanoma were primaries for two subtypes. Small lymphocytic lymphoma was increased to an RR of 13.51 after testicular cancer. Melanoma, skin SCC and connective tissue cancer each associated with increased risks of cutaneous T-cell lymphoma with RRs of 5.93, 4.11 and 9.22, respectively.

Figure 1 shows plots of the RRs over follow-up time since the diagnoses of NHL and non-NHL cancer. Following diagnosis of NHL, risks of SPCs were persistent and somewhat increasing for all non-NHL cancers, skin SCC and melanoma. For NHL following the diagnosis of a non-NHL cancers, risks were moderately decreasing.

DISCUSSION

Novel findings of the present study were the demonstration of an increase in overall SPC risk after each of the 10 different subtypes of NHL and, conversely, an increase of six of these NHL subtypes as SPC. Skin SCC risk was most systematically increased and was found in excess after 8 NHL subtypes, followed by melanoma after 7 NHL subtypes and kidney cancer after 6 NHL subtypes. In the reverse analysis on NHL as SPC, melanoma and skin SCC were the most common primary cancers, both of which were followed by an excess risk of 7 NHL subtypes as SPC. The correlation of the bidirectional associations was highly significant $P<0.0001$. Sensitivity analyses on data for which the first year of follow-up were excluded did not change results; this would be expected on cancer cases with practically complete histological confirmation. Nor showed age- and period-stratified data unexpected findings on individual cancers, including melanoma and skin SCC.

A major strength of this study is that we have avoided ascertainment bias in patient selection because our cohort analysis was based on the Swedish population, for which there is near complete case registration with long-term follow-up. We do acknowledge, however, that as a limitation of our study we did not have the opportunity to incorporate information on treatment.

Therapy-related side effects are generally considered to be the cause of many SPCs. Since chemotherapy and radiotherapy regimes are generally used to treat NHL the finding of an increased risk of cancers such as those of the lung and colorectum reported herein and documented by others [5-10], has a plausible etiology. Such a mechanism is not however likely to be solely responsible for any SPC risk as evidenced by the bi-directional associations we observed. Indeed, given the diversity of cancer treatment across tumor types the prominent inter-relationships shown between NHL and kidney, skin, bladder and melanoma invite alternative hypotheses.

Aside from some form of shared environmental/lifestyle factors common to cancers, the association of NHL with skin SCC and melanoma for which surgery is the primary mode of treatment raises the possibility of immune dysfunction playing a role. In keeping with such a postulate is the fact that immunosuppressed organ transplantion patients have an increased risk of not only skin SCC and NHL (20-fold) but also kidney cancer (15-fold), melanoma, leukemia and anogenital cancers (5-fold) and other cancers [18]. High risks were reported also on lip, oral and pharyngeal cancers, which in the present study were included as minor components under ‘upper aerodigestive tract’ cancers [19, 20]. The bi-directional spectrum of cancer risk seen in the present analysis is reminiscent such observations. Even though observational results may be persuasive in suggesting a contribution for immune dysfunction, experimental evidence is required to establish it as a mechanistic underpinning.

As only a small proportion of NHL patients will have been therapeutically immune suppressed because of bone marrow transplantation, for immune dysfuntion to play any role requires an alternative explanation. Increasingly it is being recognized that tumors can influence immune function, specifically T-cell function, which again mirrors the impact of any iatrogenic immune suppression [21]. NF-kappaB signaling is a master regulator of cancer-associated chronic inflammation which contributes to immunosuppression through induction of proinflammatory mediators and activation of immune suppressor cells [22-24]. Myeloid-derived suppressor cells are the main type of tumor-associated macrophages that produce chemokines, cytokines, growth factors and proteases which are involved in extracellular matrix remodeling [25].

Although there were similarities in the bi-directional risks between NHL subtypes and cancers, there were also differences. The highest overall RRs for SPC after NHL were associated with small lymphocytic, mantle cell and marginal zone lymphoma with the smallest effect being shown in respect of Burkitt lymphoma; these risks were approximately correlated with known survival for these subtypes, and hence good survival increases the life-time chance for a SPC. Myeloma risk was high only after lymphoplasmacytic lymphoma (Waldenstrom) which could be predicted from the known familial association between the two diseases [26]; consistently, lymphoplasmacytic lymphoma was also increased as SPC after myeloma. Other types of unique findings included anal cancer with a high risk after follicular lymphoma, high risk of leukemia after mantle cell and Burkitt lymphoma and high risk of kidney cancer after cutaneous and anaplastic T-cell lymphoma. In the reverse analysis high risks were noted for diffuse large B-cell lymphoma after Hodgkin lymphoma and cervical cancer, the latter even influencing the risk of mantle cell lymphoma. Finally, testis cancer was associated with a high risk of small lymphocytic lymphoma, mantle cell lymphoma and lymphoplasmacytic lymphoma.

Immune suppression would be a timely explanation to the findings concerning cancers that are known to be increased in immunosuppressed patients, in view of the current successes in immune therapy. Immune-checkpoint inhibitors, which can promote cytotoxic activity of T cells, are effective in some individuals with NHL and are gaining wider clinical acceptance [4, 27, 28]. However, can we exclude other alternative explanations, such as shared familial risk, microbial agents or other environmental factors playing a role? Given that many cancer susceptibility genes have pleotropic effects it is plausible that a small part of the excess risk is enshrined in inherited genetic factors, either through high penetrance alleles or co-inheritance of multiple common risk variants. Neither would infection appear as a plausible candidate mechanism because of the multiple cancers involved. However, reactivation of endogenous viruses may be important, as for example Epstein-Barr virus activation is an essential mechanism in post-transplantation carcinogenesis [18]. Environmental risk factors, such as smoking, may interact with immunological factors in upper aerodigestive tract, kidney and lung cancers. Ultraviolet irradiation, a joint risk factor for skin SCC and

melanoma, has been suggested to be both a risk and protective factors for NHL but large prospective studies show no association [29, 30].

Generalizability of the results is likely to encompass the cancers with bi-directional significance (NHL, upper aerodigestive tract, kidney, bladder, melanoma, skin SCC and Hodgkin) which account for 28% of cancers in Sweden [15]; skin SCC is the most common of these, accounting for 10% of cancers in Sweden. Adding also colorectal cancer with modest bi-directional risks would increase the total to 39% of all cancers. The main limitation of our study in terms of understanding etiology is our reliance on purely cancer registry information. Another point of concern may be that we included all SPCs even though we know that upon diagnosis of first cancer a large number of SPCs are synchronously diagnosed. However the level of histological verification of all relevant cancers for this study is high and there is no reason to believe that diagnostic accuracy would have been compromised. Moreover, the data show that the risk for many SPC remains elevated after 15 years. Surveillance for these cancers with elevated risks should be considered for integration into ongoing cancer survivorship programs.

In conclusion, we have provided a comprehensive analysis of cancer risks associated with NHL. Additionally through analysis of NHL as SPC we propose that immune suppression is a key mechanisms responsible for the development of SPCs. Our findings further substantiate the significant cancer risks associated with survivorship from NHL and are informative in defining the long-term management of patients successfully treated for NHL in terms of surveillance for SPCs. When immune therapy will become widely used it will be possible to test the present hypothesis; if correct, the suggested immune-responsive SPCs should be suppressed.

ACKNOWLEDGEMENT

A.S. is the recipient of Guest Scientist Fellowship of DKFZ. Supported by the Harald Huppert Foundation, Deutsche Krebshilfe, Jane and Aatos Erkko Foundation, Sigrid Juselius Foundation, Finnish Cancer Organizations, University of Helsinki and Helsinki University Central Hospital

AUTHOR CONTRIBUTIONS

Design: KH, AS, SC
Acquisition of data: JS, KS
Statistical analysis and interpretation: SC, GZ, HY, KH, AH.
Manuscript writing: KH, RSH, SC, AS, AH, AF.
Approval of the final text: All authors

CONFLICTS OF INTEREST

A.H. is shareholder in Targovax ASA. A.H. is employee and shareholder in TILT Biotherapeutics Ltd.

Other authors declared no conflict of interest.

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FIGURE LEGEND

Figure 1 shows trend of RRs and 95%CIs over follow-up time since the diagnoses of NHL (blue) or non-NHL cancer (golden). For SPC in the kidney (a) the curve is U-shaped but for second NHL after kidney cancer the trend was decreasing, reaching 1.00 at 11-15 years. For skin SCC (b) the risk increased markedly after the first year and remained stable in further follow-up. RR for second skin SCC was monotonously decreasing. Second melanoma (c) risk reached a maximum at 6-10 years of follow-up while that for second NHL slowly decreased. The overall trends (d) were steadily increasing for all non-NHL cancer and were fairly stable for second NHL.

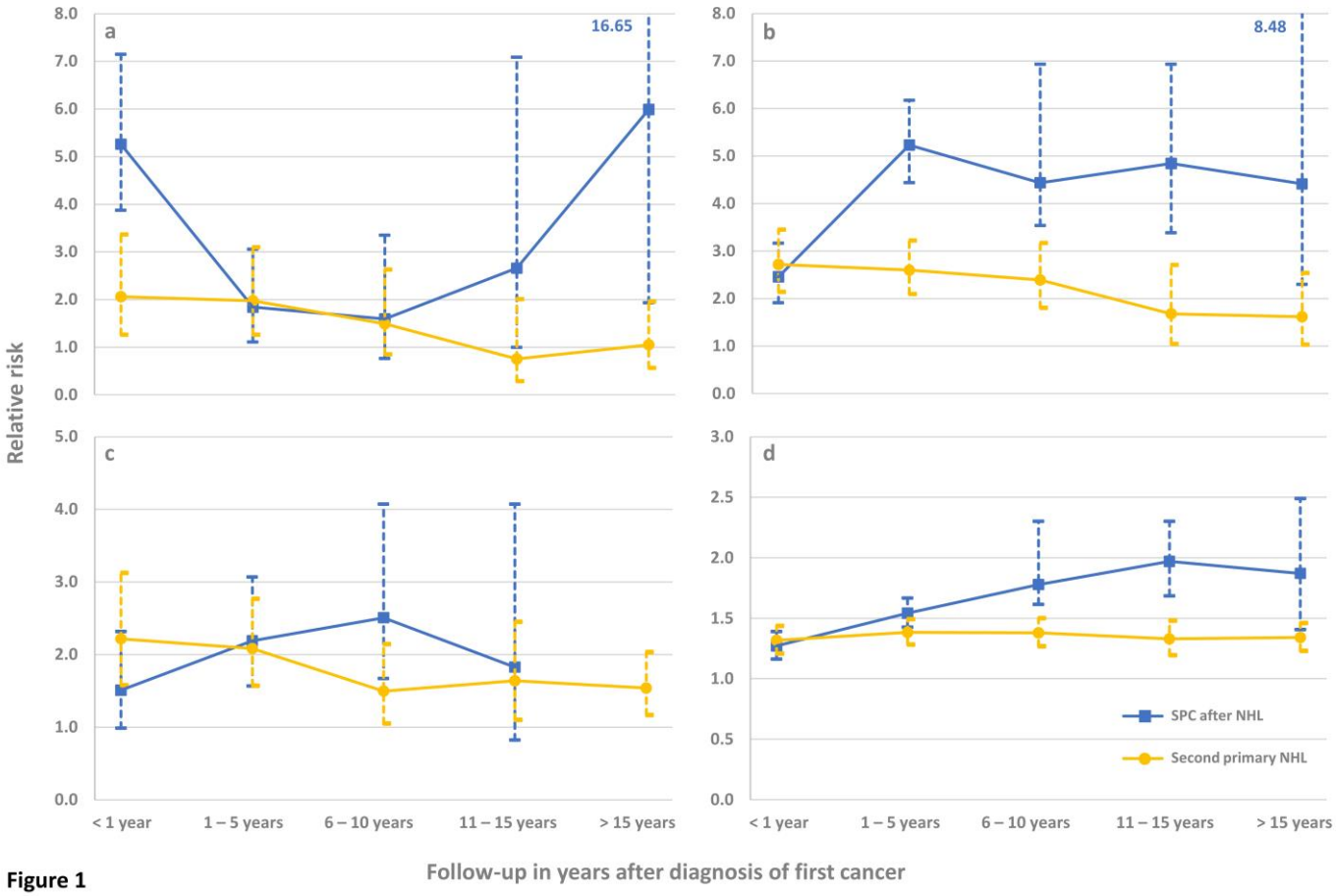

Figure 1

Table 1. Summary of the cohort

Total number of individuals followed		12,244,473
Summary of cases		
I. Number of first primary cancer (except NHL)		940,811
a. Males		491,412 (52.2) [a]
b. Females		449,399 (47.8)
II. Number of first primary NHL		19,833
a. Males		11,096 (55.9)
b. Females		8,737 (44.1)
III. Number of SPCs in NHL survivors		1,731
IV. Number of second primary NHLs after other primary cancer		2,571
Summary of age		
V. Median age at first primary NHL (years)		69 [58 - 77] [b]
VI. Median follow-up time until SPC (years)		4 [1 - 7]
VII. Median age at second primary NHL (years)		76 [69 - 82]
VIII. Median follow-up time until second primary NHL (years)		6 [2 - 13]
Summary of NHL subtype		
	No. of SPCs in patients with NHL	**No. of second primary NHLs in other cancer survivors**
1. Diffuse large B-cell lymphoma	537	1,094
2. Follicular lymphoma	584	587
3. Lymphoplasmacytic lymphoma	261	282
4. Mantle cell lymphoma	123	237
5. Marginal zone lymphoma	57	62
6. Small lymphocytic lymphoma	40	112
7. Burkitt lymphoma	10	22
8. Mature T-cell lymphoma	49	97
9. Cutaneous T-cell lymphoma	47	55
10. Anaplastic T-cell lymphoma	23	23

Abbreviation:
SCC, squamous cell carcinoma; SPC, second primary cancer;
a Percentages in parentheses
b Inter-quartile distance shown in square brackets

Table 2. Risk of second primary cancer after diagnosis of non-Hodgkin lymphoma (A) and risk of non-Hodgkin lymphoma after diagnosis of non-NHL cancer (B).

Cancer	A. Risk of non-NHL cancer after diagnosis of NHL					B. Risk of NHL after diagnosis of non-NHL cancer				
	N	RR	CI_{lower}	CI_{upper}	*P*	N	RR	CI_{lower}	CI_{upper}	*P*
UAT	**40**	**1.96**	**1.44**	**2.68**	**<.0001**	**66**	**1.71**	**1.34**	**2.17**	**<.0001**
Esophagus	9	0.94	0.51	1.75	0.85	3	0.73	0.28	1.96	0.5363
Stomach	**34**	**1.52**	**1.08**	**2.13**	**0.015**	21	1.01	0.66	1.56	0.947
Small intestine	3	0.60	0.19	1.87	0.382	6	0.88	0.39	1.95	0.7451
Colorectum	**182**	**1.35**	**1.16**	**1.56**	**<.0001**	**269**	**1.28**	**1.13**	**1.44**	**<.0001**
Anus	**7**	**2.65**	**1.26**	**5.58**	**0.01**	3	0.68	0.22	2.12	0.511
Liver	30	1.29	0.91	1.83	0.159	10	0.89	0.48	1.66	0.7204
Pancreas	25	0.95	0.64	1.40	0.779	5	0.53	0.22	1.29	0.1617
Nose	3	2.25	0.72	7.00	0.161	3	1.24	0.40	3.84	0.7099
Lung	**126**	**1.48**	**1.25**	**1.77**	**<.0001**	42	0.88	0.65	1.20	0.4216
Breast	93	0.88	0.72	1.08	0.221	**377**	**1.28**	**1.16**	**1.42**	**<.0001**
Cervix	1	0.19	0.03	1.36	0.099	**53**	**1.81**	**1.38**	**2.37**	**<.0001**
Endometrium	20	0.74	0.48	1.14	0.175	**111**	**1.36**	**1.13**	**1.65**	**0.0012**
Ovary	9	0.65	0.34	1.25	0.193	37	1.14	0.83	1.58	0.4225
Other female genitals	4	0.91	0.34	2.42	0.844	9	1.34	0.70	2.57	0.3835
Prostate	265	0.89	0.79	1.01	0.068	**576**	**1.14**	**1.05**	**1.24**	**0.0027**
Testis	0					**28**	**2.29**	**1.58**	**3.32**	**<.0001**
Other male genitals	4	1.71	0.64	4.56	0.286	2	0.41	0.10	1.65	0.2097
Kidney	**70**	**3.10**	**2.45**	**3.92**	**<.0001**	**61**	**1.57**	**1.22**	**2.02**	**0.0004**
Urinary bladder	**83**	**1.54**	**1.24**	**1.91**	**<.0001**	**128**	**1.29**	**1.09**	**1.54**	**0.0037**
Melanoma	**83**	**1.98**	**1.60**	**2.44**	**<.0001**	**185**	**1.80**	**1.56**	**2.08**	**<.0001**
Skin (SCC)	**314**	**4.12**	**3.69**	**4.60**	**<.0001**	**237**	**2.44**	**2.14**	**2.77**	**<.0001**
Eye	2	0.85	0.21	3.41	0.822	9	1.70	0.92	3.17	0.0918
Nervous system	24	1.14	0.76	1.70	0.525	46	0.96	0.72	1.29	0.8004
Thyroid gland	**10**	**2.14**	**1.15**	**3.98**	**0.017**	18	0.92	0.58	1.46	0.7152
Endocrine glands	14	1.16	0.70	1.92	0.576	**70**	**1.37**	**1.08**	**1.73**	**0.009**
Bone	1	1.30	0.18	9.25	0.793	6	2.01	0.90	4.47	0.0881
Connective tissue	9	1.67	0.87	3.21	0.125	18	1.58	0.99	2.50	0.0535
Hodgkin lymphoma	**15**	**9.38**	**5.81**	**15.15**	**<.0001**	**46**	**7.29**	**5.46**	**9.73**	**<.0001**
Multiple myeloma	14	0.89	0.52	1.50	0.648	**24**	**1.54**	**1.03**	**2.30**	**0.034**
Leukemia	**94**	**2.90**	**2.36**	**3.56**	**<.0001**	2	1.75	0.44	7.01	0.4269
CUP	48	1.31	0.99	1.74	0.061	12	0.67	0.38	1.19	0.1719
*All	**1731**	**1.53**	**1.46**	**1.61**	**<.0001**	**2571**	**1.40**	**1.34**	**1.46**	**<.0001**

Abbreviations:
N, frequency; RR, relative risk; CI, 95% confidence interval; P, probability; UAT, upper aerodigestive tract; SCC, squamous cell carcinoma; CUP, cancer of unknown primary;
Bolding indicates statistical significance at 0.05 level

Table 3. Risk of second primary cancers among survivors of five frequent subtypes of non-Hodgkin lymphoma.

Second cancers	Diffuse large B-cell lymphoma				Follicular lymphoma				Lymphoplasmacytic lymphoma				Mantle cell lymphoma				Marginal zone lymphoma			
	N	**RR**	**95% CI**	***P***	**N**	**RR**	**95% CI**	***P***	**N**	**RR**	**95% CI**	***P***	**N**	**RR**	**95% CI**	***P***	**N**	**RR**	**95% CI**	***P***
UAT	**14**	**1.89**	**1.12 - 3.20**	**0.017**	**13**	**2.06**	**1.19 - 3.54**	**0.0094**	**7**	**2.53**	**1.21 - 5.31**	**0.0141**	3	2.33	0.75 - 7.22	0.1435	1	1.66	0.23 - 11.77	0.613
Stomach	10	0.98	0.52 - 1.81	0.9382	11	1.31	0.72 - 2.36	0.3748	5	1.21	0.50 - 2.91	0.6666	3	1.76	0.57 - 5.45	0.3292	**3**	**3.91**	**1.26 - 12.14**	**0.0181**
Colorectum	**65**	**1.31**	**1.03 - 1.67**	**0.03**	52	1.27	0.97 - 1.67	0.0806	**32**	**1.65**	**1.16 - 2.33**	**0.0049**	11	1.31	0.72 - 2.36	0.3766	**8**	**1.99**	**1.00 - 3.99**	**0.049**
Anus	1	1.09	0.15 - 7.73	0.9326	**5**	**6.34**	**2.63 - 15.25**	**<0.0001**	1	2.90	0.41 - 20.62	0.2867								
Liver	15	1.56	0.94 - 2.59	0.085	6	0.75	0.34 - 1.67	0.4833	3	0.77	0.25 - 2.39	0.6511					**3**	**3.91**	**1.26 - 12.14**	**0.0181**
Nose	2	3.89	0.97 - 15.59	0.0549																
Lung	28	0.94	0.65 - 1.36	0.7511	**51**	**1.93**	**1.46 - 2.53**	**<0.0001**	**19**	**1.68**	**1.07 - 2.63**	**0.0241**	**10**	**1.89**	**1.02 --3.52**	**0.0436**	**6**	**2.41**	**1.08 - 5.37**	**0.0311**
Breast	32	0.86	0.61 - 1.22	0.4051	39	1.01	0.74 - 1.38	0.9593	12	0.96	0.55 - 1.70	0.8981	3	0.79	0.25 - 2.44	0.6803	2	0.54	0.14 - 2.18	0.3893
Cervix					1	0.50	0.07 - 3.53	0.4853												
Endometrium	11	1.27	0.70 - 2.30	0.4245	6	0.65	0.29 - 1.45	0.2927	2	0.68	0.17 - 2.74	0.5912								
Ovary	1	0.20	0.03 - 1.43	0.1098	5	0.92	0.38 - 2.21	0.8504	3	1.79	0.58 - 5.54	0.315								
Prostate	**77**	**0.72**	**0.58 - 0.90**	**0.0044**	82	1.10	0.89 - 1.37	0.3781	52	1.13	0.86 - 1.48	0.3796	18	0.72	0.45 - 1.14	0.1608	1	0.15	0.02 - 1.05	0.056
Kidney	**20**	**2.33**	**1.51 - 3.62**	**0.0002**	**25**	**3.36**	**2.27 - 4.97**	**<0.0001**	6	1.90	0.85 - 4.23	0.1163	**6**	**3.97**	**1.79 - 8.85**	**0.0007**	**4**	**5.99**	**2.25 - 15.96**	**0.0003**
Urinary bladder	**30**	**1.53**	**1.07 - 2.19**	**0.0198**	**29**	**1.79**	**1.24 - 2.58**	**0.0017**	8	1.06	0.53 - 2.12	0.8681	**9**	**2.64**	**1.38 - 5.08**	**0.0035**	1	0.63	0.09 - 4.49	0.6462
Melanoma	**23**	**1.58**	**1.05 - 2.37**	**0.029**	**28**	**2.28**	**1.57 - 3.30**	**<0.0001**	**10**	**2.04**	**1.10 - 3.79**	**0.0245**	**7**	**2.84**	**1.36 - 5.97**	**0.0057**	**7**	**5.85**	**2.79 - 12.28**	**<0.0001**
Skin (SCC)	**108**	**3.90**	**3.23 - 4.72**	**<0.0001**	**87**	**4.30**	**3.48 - 5.31**	**<0.0001**	**51**	**4.78**	**3.64 - 6.30**	**<0.0001**	**27**	**6.20**	**4.25 - 9.04**	**<0.0001**	**11**	**4.75**	**2.63 - 8.58**	**<0.0001**
Eye	1	1.20	0.17 - 8.54	0.8542	1	1.38	0.19 - 9.80	0.7479												
Nervous system	9	1.18	0.62 - 2.28	0.6114	6	0.87	0.39 - 1.94	0.7378	3	1.15	0.37 - 3.55	0.8143	1	0.76	0.11 - 5.41	0.7855	1	1.70	0.24 - 12.08	0.5949
Thyroid gland	2	1.08	0.27 - 4.31	0.9154	1	0.65	0.09 - 4.61	0.6651	1	1.57	0.22 - 11.14	0.6526	1	3.43	0.48 - 24.37	0.2175				
Endocrine glands	4	0.90	0.34 - 2.40	0.8351	6	1.50	0.67 - 3.33	0.3248	2	1.29	0.32 - 5.16	0.7189					1	2.80	0.39 - 19.90	0.3029
Bone					1	3.91	0.55 - 27.83	0.1726												
Connective tissue	2	1.00	0.25 - 3.99	0.9967	3	1.78	0.57 - 5.53	0.3176	2	2.72	0.68 - 10.87	0.1577	1	2.84	0.40 - 20.17	0.2966	1	6.59	0.93 - 46.83	0.0593
Hodgkin lymphoma	**4**	**4.64**	**1.74 - 12.37**	**0.0022**	**7**	**9.64**	**4.59 - 20.25**	**<0.0001**	1	3.33	0.47 - 23.63	0.2294	**1**	**7.21**	**1.01 - 51.20**	**0.0483**				
Multiple myeloma	2	0.35	0.09 - 1.39	0.1343	4	0.82	0.31 - 2.19	0.6927	**6**	**2.69**	**1.21 - 5.98**	**0.0156**	2	1.97	0.49 - 7.87	0.3385				
Leukemia	**30**	**2.68**	**1.87 - 3.83**	**<0.0001**	**34**	**3.66**	**2.61 - 5.12**	**<0.0001**	8	1.91	0.96 - 3.82	0.0668	**12**	**6.20**	**3.52 - 10.91**	**<0.0001**	1	1.13	0.16 - 8.00	0.9049
CUP	13	0.99	0.58 - 1.71	0.9837	**20**	**1.79**	**1.16 - 2.78**	**0.0092**	7	1.30	0.62 - 2.73	0.4866	4	1.79	0.67 - 4.76	0.2453	1	1.00	0.14 - 7.06	0.996
All	**537**	**1.33**	**1.22 - 1.45**	**<0.0001**	**584**	**1.69**	**1.56 - 1.83**	**<0.0001**	**261**	**1.64**	**1.45 - 1.85**	**<0.0001**	**123**	**1.78**	**1.49 - 2.12**	**<0.0001**	**57**	**1.70**	**1.31 - 2.20**	**<0.0001**

Abbreviations:
N, frequency; RR, relative risk; CI, confidence interval; P, probability; UAT, upper aerodigestive tract; SCC, squamous cell carcinoma; CUP, cancer of unknown primary;
Bolding indicates statistical significance at 5% level

Table 4. Risk of five frequent subtypes of non-Hodgkin lymphoma as second primary cancer among survivors of other cancers.

First cancer	Diffuse large B-cell lymphoma				Follicular lymphoma				Lymphoplasmacytic lymphoma				Mantle cell lymphoma				Marginal zone lymphoma			
	N	**RR**	**95% CI**	***P***	**N**	**RR**	**95% CI**	***P***	**N**	**RR**	**95% CI**	***P***	**N**	**RR**	**95% CI**	***P***	**N**	**RR**	**95% CI**	***P***
UAT	**27**	**1.59**	**1.09 - 2.32**	**0.0164**	**15**	**1.67**	**1.01 - 2.78**	**0.0464**	**10**	**2.20**	**1.18 - 4.10**	**0.0129**	5	1.56	0.65 - 3.77	0.3181	3	3.10	0.99 - 9.66	0.0512
Stomach	11	1.19	0.66 - 2.15	0.5685	3	0.64	0.21 - 1.98	0.4373	1	0.38	0.05 - 2.69	0.3307	2	1.21	0.30 - 4.85	0.7862	1	2.16	0.30 - 15.36	0.4435
Colorectum	102	1.06	0.87 - 1.29	0.5534	**72**	**1.58**	**1.25 - 2.00**	**0.0001**	34	1.36	0.97 - 1.91	0.0767	**26**	**1.55**	**1.05 - 2.29**	**0.0275**	7	1.35	0.64 - 2.85	0.4385
Anus	1	0.52	0.07 - 3.66	0.5073	1	0.99	0.14 - 7.04	0.993	1	2.07	0.29 - 14.71	0.467								
Liver	7	1.43	0.68 - 3.00	0.3463	2	0.77	0.19 - 3.08	0.7114					1	1.11	0.16 - 7.89	0.9173				
Nose	1	0.93	0.13 - 6.61	0.9426									**2**	**10.09**	**2.52 - 40.40**	**0.0011**				
Lung	17	0.82	0.51 - 1.32	0.41	9	0.81	0.42 - 1.56	0.5346	7	1.31	0.62 - 2.74	0.4821	4	1.03	0.39 - 2.75	0.9557	1	0.78	0.11 - 5.53	0.8008
Breast	144	1.10	0.93 - 1.30	0.2754	**113**	**1.40**	**1.15 - 1.69**	**0.0006**	35	1.20	0.85 - 1.69	0.2956	**25**	**1.65**	**1.10 - 2.49**	**0.0162**	12	1.24	0.69 - 2.22	0.4704
Cervix	**25**	**1.97**	**1.33 - 2.92**	**0.0007**	14	1.64	0.97 - 2.78	0.0646	4	1.34	0.50 - 3.59	0.5569	**4**	**2.81**	**1.05 - 7.53**	**0.0402**	1	1.08	0.15 - 7.69	0.9402
Endometrium	47	1.26	0.94 - 1.68	0.1234	29	1.37	0.95 - 1.98	0.0921	**15**	**1.78**	**1.06 - 2.97**	**0.0279**	6	1.43	0.64 - 3.22	0.3848	3	1.16	0.37 - 3.62	0.8037
Ovary	17	1.19	0.74 - 1.92	0.4663	9	0.98	0.51 - 1.88	0.9451	3	0.90	0.29 - 2.80	0.8564	**5**	**3.01**	**1.25 - 7.30**	**0.0144**	1	0.97	0.14 - 6.91	0.9743
Prostate	237	1.06	0.92 - 1.21	0.4227	112	1.23	1.01 - 1.49	0.0404	68	1.04	0.81 - 1.34	0.7313	**79**	**1.47**	**1.16 - 1.86**	**0.0015**	13	1.17	0.66 - 2.08	0.5975
Testis	6	1.15	0.52 - 2.57	0.7284	5	1.78	0.74 - 4.28	0.1988	**5**	**4.59**	**1.90 - 11.06**	**0.0007**	**6**	**5.27**	**2.36 - 11.77**	**<0.0001**				
Kidney	21	1.22	0.79 - 1.87	0.3628	**19**	**2.13**	**1.36 - 3.35**	**0.001**	7	1.54	0.73 - 3.23	0.2554	4	1.25	0.47 - 3.34	0.6533				
Urinary bladder	57	1.27	0.98 - 1.65	0.0724	26	1.21	0.82 - 1.78	0.3406	17	1.43	0.88 - 2.30	0.1459	10	1.19	0.64 - 2.22	0.585	2	0.84	0.21 - 3.37	0.8027
Melanoma	**68**	**1.50**	**1.18 - 1.91**	**0.0009**	**41**	**1.71**	**1.26 - 2.33**	**0.0006**	**18**	**1.64**	**1.03 - 2.62**	**0.0361**	**20**	**2.46**	**1.58 - 3.83**	**<0.0001**	**8**	**2.81**	**1.39 - 5.67**	**0.0039**
Skin (SCC)	**110**	**2.39**	**1.97 - 2.89**	**<0.0001**	**50**	**2.56**	**1.93 - 3.39**	**<0.0001**	**26**	**2.26**	**1.53 - 3.33**	**<0.0001**	**19**	**2.46**	**1.56 - 3.88**	**0.0001**	3	1.26	0.40 - 3.94	0.6913
Eye	**7**	**2.69**	**1.28 - 5.65**	**0.0088**					1	1.53	0.22 - 10.89	0.6695								
Nervous system	21	1.01	0.66 - 1.55	0.9557	9	0.77	0.40 - 1.49	0.4417	6	1.21	0.54 - 2.69	0.6439	2	0.55	0.14 - 2.22	0.4042	2	1.56	0.39 - 6.25	0.5317
Thyroid gland	9	1.06	0.55 - 2.04	0.8591	2	0.42	0.10 - 1.66	0.2148	2	0.97	0.24 - 3.87	0.9614	2	1.43	0.36 - 5.74	0.6115				
Endocrine glands	**34**	**1.51**	**1.07 - 2.11**	**0.0174**	**20**	**1.68**	**1.08 - 2.60**	**0.0213**	4	0.70	0.26 - 1.86	0.468	7	1.80	0.86 - 3.79	0.1206	2	1.47	0.37 - 5.89	0.5896
Bone	**4**	**3.09**	**1.16 - 8.22**	**0.0243**	1	1.36	0.19 - 9.62	0.7613					1	4.34	0.61 - 30.82	0.1425				
Connective tissue	3	0.60	0.19 - 1.85	0.3688	**6**	**2.24**	**1.01 - 4.99**	**0.0482**	2	1.57	0.39 - 6.28	0.5246	1	1.11	0.16 - 7.88	0.9178				
Hodgkin lymphoma	**37**	**13.76**	**9.96 - 19.02**	**<0.0001**	**6**	**3.72**	**1.67 - 8.30**	**0.0013**									1	6.02	0.84 - 42.82	0.0732
Multiple myeloma	**14**	**2.05**	**1.22 - 3.47**	**0.0072**	3	0.84	0.27 - 2.59	0.7559	**5**	**2.69**	**1.12 - 6.48**	**0.027**								
Leukemia	2	3.91	0.98 - 15.65	0.0538																
CUP	6	0.77	0.34 - 1.71	0.5136	2	0.48	0.12 - 1.93	0.3033	1	0.47	0.07 - 3.36	0.4545	1	0.72	0.10 - 5.14	0.746				
All	**1094**	**1.27**	**1.19 - 1.36**	**<0.0001**	**587**	**1.35**	**1.23 - 1.47**	**<0.0001**	**282**	**1.27**	**1.12 - 1.44**	**0.0003**	**237**	**1.53**	**1.32 - 1.76**	**<0.0001**	62	1.22	0.93 - 1.60	0.1597

Abbreviations:
N, frequency; RR, relative risk; CI, confidence interval; *P*, probability; UAT, upper aerodigestive tract; SCC, squamous cell carcinoma; CUP, cancer of unknown primary;
Bolding indicates statistical significance at 5% level