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Risk of cancer in patients with epistaxis and haemoptysis

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Background: Respiratory tract bleeding may be a marker of cancer. We quantified the risk of specific cancer types among patients with hospital-based diagnoses of epistaxis and haemoptysis relative to risk in the general population.

Methods: We used Danish, nationwide databases to conduct a population-based cohort study of 80460 patients diagnosed with epistaxis and 18487 patients presenting with haemoptysis (1995 – 2013). We followed patients until a cancer diagnosis, emigration, death, or 31 December 2013, whichever came first. As a measure of the relative risk, we computed standardised incidence ratios (SIRs), as the observed to expected number of cancers based on national cancer incidence rates.

Results: The 90-day absolute risk of any cancer was 0.59% in the epistaxis cohort and 3.78% in the haemoptysis cohort. The corresponding SIRs were 1.85 (95% confidence interval (CI) 1.69, 2.02) and 14.6 (95% CI 13.5, 15.7), respectively. The 90-day SIRs were highest for haematological cancers following epistaxis (5.78 (95% CI 4.62, 7.14)), and for smoking and alcohol-related cancers following haemoptysis (36.3 (95% CI 33.5, 39.3)). The cancer risk decreased steadily over time, but persisted beyond 5 years of follow-up after both conditions.

Conclusions: Epistaxis and particular haemoptysis may be markers of cancer at several sites.

The association between cancer, clotting, and bleeding has been known for more than a century (Ay *et al*, 2016). Cancer-associated bleeding may be caused by tumour compression or invasion of blood vessels, or by haematological conditions such as disseminated intravascular coagulopathy, thrombocytopenia, or platelet abnormalities (Pereira and Phan, 2004). At the same time, cancer may also be associated with a hypercoagulable state through activation of the coagulation system (Rickles and Edwards, 1983).

Epistaxis is a common condition (Bidwell and Pachner, 2005; Viehweg *et al*, 2006). It accounted for 33% of all ear-, nose-, and throat-related emergency room visits in Scotland during 1995 – 2004 (Walker *et al*, 2007). Haemoptysis is also frequent and varies from blood-streaked sputum to coughing up large amounts of pure blood (Bidwell and Pachner, 2005). Ninety percent of massive haemoptysis originates from bronchial arteries, while five percent originates from pulmonary arteries (Jean-Baptiste, 2000). Causes include malignancy, pulmonary embolism and other vascular causes, trauma, inflammation, infection, and bronchiectasis (Santiago *et al*, 1991; Uzun *et al*, 2010).

Epistaxis and haemoptysis may be markers of occult cancer in the respiratory tract or at other sites, but the evidence is sparse (Herth *et al*, 2001). Cancer associated with epistaxis or haemoptysis at sites other than the respiratory tract has been reported only in small studies or case reports (Vokes *et al*, 1993; Goldenberg *et al*, 2001; Fidan *et al*, 2002; Pritchyk *et al*, 2002; Lee *et al*, 2005; Uzun *et al*, 2010; Fyrmpas *et al*, 2011; Singh *et al*, 2014; Archer *et al*, 2015; Azoury *et al*, 2015). To address this gap in knowledge, we quantified the cancer risk of specific cancer sites in patients with a first-time hospital-based diagnosis of epistaxis or haemoptysis compared with the general population.

METHODS

Setting. This study was conducted using Danish national registries, covering a cumulative population of 7.2 million inhabitants during the 1995–2013 period (Frank, 2000). Danish registries record individual-level data on healthcare utilisation and

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vital status. All registries can be linked accurately and unambiguously using the unique personal identification number assigned by law to all Danish residents at birth or upon immigration (Schmidt *et al*, 2014).

Denmark's universal health care system provides free tax-supported access to primary and secondary health care (Frank, 2000). General practitioners function as gatekeepers to the secondary health care system, referring patients for inpatient and outpatient hospital treatment (Pedersen *et al*, 2012).

The Danish National Patient Registry (DNPR) has recorded all Danish non-psychiatric inpatient hospitalisations since 1977, and all outpatient visits, emergency room visits, and hospital-based outpatient clinic visits since 1995 (Schmidt *et al*, 2015). Diseases are classified according to the International Classification of Diseases (ICD), Eighth Revision through 1993 and Tenth Revision thereafter (Schmidt *et al*, 2015). Diagnosis codes used in the study are provided in the online data Supplementary Table E1.

Patient population. We used the DNPR to identify patients with a first-time primary or secondary hospital-based diagnosis of epistaxis or haemoptysis between 1 January 1995 and 31 December 2013. Patients were classified according to the first recorded bleeding event as either epistaxis or haemoptysis. There were 50 patients diagnosed with both epistaxis and haemoptysis during the same hospital visit. We included all inpatient, outpatient clinic, and emergency room diagnoses. The discharge date for epistaxis or haemoptysis defined the index date. Patients diagnosed with any cancer, benign tumours before or on the index date were not included in the study.

Cancer diagnoses. We used the Danish Cancer Registry (DCR) to identify all incident cancers diagnosed after the index date. The DCR has recorded all incident cancer cases in Denmark since 1943, including information on morphology, histology, and stage at diagnosis (Gjerstorff, 2011). Diagnoses are coded according to the ICD-10. We categorised cancers as haematological, immune-related, smoking and alcohol related, and cancers at all other sites, as shown in detail in the online data Supplementary Table E1.

Follow-up. We computed the number of person-years of observation as the time between the index diagnosis date of epistaxis or haemoptysis and date of incident cancer diagnosis, death, emigration, or 31 December 2013, whichever came first. These dates were determined through linkage to the DCR and to the Danish Civil Registration System, which updates information on vital status and emigration on a daily basis for the entire Danish population (Gjerstorff, 2011; Schmidt *et al*, 2014).

Analytic variables. We categorised patients with epistaxis or haemoptysis according to location of diagnosis (inpatient department, outpatient clinic, or emergency room) and type of diagnosis (primary *vs* secondary diagnosis), sex, age group (0–30 years, 31–55 years, 56–65 years, 66–75 years, 76–85 years, and $\geq$85 years), and calendar period of diagnosis (1995–1999, 2000–2004, 2005–2009, and 2010–2013). We also obtained a complete hospital history of comorbidities from the DNPR as of the index date and categorised conditions as present or absent. Comorbidity was categorised using the Charlson comorbidity index (CCI) (Charlson *et al*, 1987). We excluded cancer from the CCI and categorised the patients by comorbidity level (CCI score = 0, CCI score $\geq$1). We also ascertained diagnoses of pneumonia, tuberculosis, abscess, bronchiectasis, and deep venous thrombosis and pulmonary embolism as of the index date, using the entire medical history available in the DNPR. For inpatients diagnosed with epistaxis or haemoptysis in 2002 or later, we included information from the index hospital contact on epistaxis-related procedures or surgery and on endoscopy of the upper airways or bronchoscopy.

Statistical analysis. We characterised patients according to type of bleeding diagnosis, sex, age group, calendar period of the bleeding diagnosis, comorbidity history, and hospital-based procedures/surgery. Absolute risk of cancer was calculated overall and by categories of follow-up time (0–90 days, 91–365 days, >1–5 years, and >5 years), treating death as a competing risk. The expected cancer rate among persons with bleeding was calculated assuming that their expected risk would be the same as that of the general

Table 1. Characteristics of patients with a diagnosis of epistaxis or haemoptysis, Denmark 1995–2013

Characteristic	Epistaxis	Haemoptysis
Number of patient	80 460	18 487
Median follow-up time, years (25th–75th percentiles)	6.4 (2.8, 11)	5.7 (2.3, 10)
Location of diagnosis		
In patient	7760 (9.6)	5221 (28)
Out patient visit	8066 (10)	11 235 (61)
Emergency room	64 634 (80)	2031 (11)
Type of diagnosis		
Primary diagnosis	74 356 (92)	15 964 (86)
Secondary diagnosis	6104 (7.6)	2523 (14)
Sex		
Female	31 737 (39)	7 029 (38)
Male	48 723 (61)	11 458 (62)
Age at diagnosis, years (25th–75th percentiles)	59 (32, 73)	55 (42, 67)
Age group at diagnosis (years)		
0–30	19 159 (24)	2021 (11)
31 – 55	16 135 (20)	7186 (39)
56 – 65	13 494 (17)	4028 (22)
66 – 75	14 185 (18)	3164 (17)
76 – 85	12 261 (15)	1741 (9.4)
⩾85	5226 (6.5)	347 (1.9)
Calendar period of diagnosis		
1995 – 1999	23 023 (29)	3679 (20)
2000 – 2004	22 222 (28)	5196 (28)
2005 – 2009	20 468 (25)	5304 (29)
2010 – 2013	14 747 (18)	4308 (23)
Charlson Comorbidity Index score category		
0	54 416 (68)	11 854 (64)
⩾1	26 044 (32)	6 633 (36)
Charlson Comorbidity Index diseases		
Myocardial infarction	5372 (6.7)	1097 (5.9)
Congestive heart failure	4982 (6.2)	887 (4.8)
Peripheral vascular disease	3618 (4.5)	926 (5.0)
Cerebrovascular disease	7544 (9.4)	1171 (6.3)
Dementia	843 (1.1)	108 (0.58)
Chronic pulmonary disease	6505 (8.1)	2882 (16)
Connective tissue disease	2110 (2.6)	577 (3.1)
Ulcer disease	3518 (4.4)	1030 (5.6)
Mild liver disease	1356 (1.7)	439 (2.4)
Diabetes type 1 and 2	3962 (4.9)	871 (4.7)
Hemiplegia	226 (0.28)	49 (0.27)
Moderate to severe renal disease	1826 (2.3)	316 (1.7)
Diabetes with end-organ damage	1982 (2.5)	440 (2.4)
Moderate to severe liver disease	447 (0.56)	115 (0.62)
Acquired immunodeficiency syndrome	38 (0.05)	24 (0.13)
Other comorbidities		
Pneumonia	6978 (8.7)	2534 (14)
Tuberculosis	259 (0.32)	354 (1.9)
Abscess	3834 (4.8)	1345 (7.3)
Bronchiectasis	101 (0.13)	134 (0.72)
Pulmonary embolism	900 (1.1)	317 (1.7)
Deep venous thrombosis	21 145 (26)	5163 (28)
Inpatient procedures[a]		
Endoscopy of upper airways or bronchoscopy	1950 (4.0)	1892 (15)
Procedure or surgery for epistaxis	8029 (17)	13 (1)

Data are numbers (percentages) unless otherwise indicated.
[a]For inpatients starting in 2002.

Danish population. We multiplied the number of person-years of observation by Danish national cancer incidence rates across single-year age groups, sex, and single-year periods of diagnosis year to obtain the expected number of incident cancers. As a measure of relative risk, we then computed standardised incidence ratios (SIRs) as the ratio of observed to expected numbers of cancers. Associated 95% confidence intervals (CIs) were derived using Byar's approximation, assuming that the observed number of cases in a specific category followed a Poisson distribution. We used exact 95% CIs when the observed number of cancers was less than ten. We performed analyses for all cancer types combined, for subgroups of cancer types, and for individual cancer sites.

All analyses were separately for epistaxis and haemoptysis and stratified by categories of follow-up time (0–90 days, 91–365 days, >1–5 years, and >5 years) and by comorbidities. For inpatients, analyses also were stratified by presence or absence of epistaxis requiring a procedure, surgery, or endoscopy of upper airways or bronchoscopy (reflecting more advanced disease severity).

In a sensitivity analysis, we followed inpatients from their admission date instead of their discharge date, to capture any additional cancers diagnosed during admission.

All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

The study was approved by the Danish Data Protection Agency (record number 1-16-02-1-08). Danish law does not require ethical review board approval or informed consent from patients for registry-based studies.

RESULTS

Descriptive characteristics. We identified 80,460 patients with epistaxis and 18,487 patients with haemoptysis (Table 1). Ninety-two per cent of patients with epistaxis were coded as a primary diagnosis whereas 86% of patients with haemoptysis were coded ad a primary diagnosis. Among patients with epistaxis, 80% were diagnosed during emergency room visits 10% during an outpatient visit, and nine percent during an inpatient admission. Following the outpatient visit, 19% of epistaxis patients were hospitalised with the same diagnosis. In patients with haemoptysis, 28% were diagnosed during an inpatient admission, 11% during an emergency room visit, 61% were diagnosed during an outpatient visit, and 2.9% of these patients were then hospitalised with the same diagnosis.

The sex distribution was similar in the two patient groups: 61% of patients with epistaxis and 62% of those with haemoptysis were male. Median age at bleeding diagnosis was 59 years (25th and 75th percentiles: 32, 73 years) among patients with epistaxis and 55 years (IQR 42, 67 years) among patients with haemoptysis. Comorbidity was classified as none (CCI score = 0) in 68% of patients with epistaxis and in 64% of patients with haemoptysis. Cardiovascular diseases and chronic pulmonary disease were the most prevalent comorbidities among patients with epistaxis, while chronic pulmonary disease and pneumonia, followed by cardiovascular diseases, were the most prevalent comorbidities among patients with haemoptysis. Patients with epistaxis were followed for a median of 6 years (25th and 75th percentile: 2.8, 11 years) and patients with haemoptysis for five years (25th and 75th percentile: 2.3, 10 years).

Cancer risk. We observed 9173 cancers compared with 7737 expected among patients with epistaxis, and 2582 cancers compared with 1540 expected among patients with haemoptysis.

During the first 90 days after diagnosis with epistaxis, the absolute risk was 0.59% (95% CI 0.54%, 0.65%) for any cancer, 0.11% (95% CI 0.09%, 0.13%) for a haematological cancer, 0.11% (95% CI 0.09%, 0.13%) for an immune-related cancer, 0.19% (95% CI 0.16%, 0.22%) for smoking- and alcohol-related cancers, and 0.19% (95% CI 0.16%, 0.22%) for cancers at all other sites.

During the first 90 days after diagnosis with haemoptysis, the corresponding risks were 3.78% (95% CI 3.51%, 4.06%) for any cancer, 0.10% (95% CI 0.06%, 0.16%) for haematological cancers, 0.05% (95% CI 0.02%, 0.09%) for an immune-related cancer, 3.32% (95% CI 3.07%, 3.58%) for smoking and alcohol-related cancers, and 0.30% (95% CI 0.23%, 0.39%) for cancers at all other sites. Absolute risks for specific cancer types are presented in Table 2.

As presented in Table 3, the overall SIR was 1.19 (95% CI 1.16, 1.21) for epistaxis and 1.68 (95% CI 1.61, 1.74) for haemoptysis. The SIRs were 1.85 (95% CI 1.69, 2.02) during the first 90 days following an epistaxis diagnosis and 14.6 (95% CI 13.5, 15.7) during the first 90 days following a haemoptysis diagnosis. The relative risk decreased during follow-up, but was consistently elevated after 5 years of follow-up (1.14 (95% CI 1.10, 1.17) after epistaxis and 1.19 (95% CI 1.11, 1.27) after haemoptysis). The strength of the association varied by type of cancer. The SIR of haematological cancer was high for patients with epistaxis (5.78 (95% CI 4.62, 7.14) after 90 days of follow-up), while the SIR of smoking and alcohol-related cancers was particularly high after 90 days of follow-up for patients with haemoptysis (36.3 (95% CI 33.5, 39.3)) (Table 3). Selected site-specific results for the overall follow-up period are shown in Table 4.

Except for a high one-year SIR for cancer in patients aged 0-30 years at time of haemoptysis (8.17 (95% CI 3.28, 16.8)), results were broadly unchanged in subgroups of patients stratified by sex, age, location of hospital diagnosis, type of hospital diagnosis, use of endoscopy/bronchoscopy or procedures for epistaxis, or presence/absence of comorbidity (online data Supplementary Table E2).

Table 2. Absolute risk of cancer and 95% CIs for a cancer diagnosis among patients with a diagnosis of epistaxis or haemoptysis, by follow-up time, Denmark 1995–2013

Follow-up time	All cancers	Haematological cancers	Immune-related cancers	Smoking- and alcohol-related cancers	All other sites
Epistaxis					
0–90 days	0.59 (0.54, 0.65)	0.11 (0.09, 0.13)	0.11 (0.09, 0.13)	0.19 (0.16, 0.22)	0.19 (0.16, 0.22)
91–365 days	1.73 (1.64, 1.83)	0.20 (0.17, 0.24)	0.41 (0.37, 0.46)	0.62 (0.56, 0.67)	0.50 (0.46, 0.56)
>1–5 years	7.00 (6.82, 7.19)	0.50 (0.45, 0.55)	1.78 (1.69, 1.88)	2.67 (2.55, 2.79)	2.06 (1.95, 2.16)
>5–14 years	19.1 (18.6, 19.6)	1.12 (0.98, 1.27)	5.45 (5.14, 5.78)	7.04 (6.73, 7.36)	5.50 (5.22, 5.79)
Haemoptysis					
0–90 days	3.78 (3.51, 4.06)	0.10 (0.06, 0.16)	0.05 (0.02, 0.09)	3.32 (3.07, 3.58)	0.30 (0.23, 0.39)
91–365 days	5.08 (4.77, 5.41)	0.18 (0.13, 0.25)	0.29 (0.22, 0.37)	4.04 (3.77, 4.34)	0.57 (0.47, 0.69)
>1–5 years	10.1 (9.60, 10.5)	0.42 (0.33, 0.53)	1.56 (1.37, 1.77)	6.14 (5.79, 6.51)	1.93 (1.72, 2.15)
>5–14 years	24.9 (23.5, 26.4)	1.40 (1.09, 1.78)	5.24 (4.59, 5.95)	12.89 (11.80, 14.02)	5.39 (4.79, 6.04)

Abbreviation: CI=confidence interval.

Table 3. SIRs and 95% CIs for a cancer diagnosis among patients with a diagnosis of epistaxis or haemoptysis, Denmark 1995–2013.

Follow-up time	All cancers		Haematological cancers		Immune-related cancers		Smoking and alcohol-related cancers		All other sites	
	Obs/exp	SIR (95% CI)	Obs/exp	SIR (95% CI)	Obs/exp	SIR (95% CI)	Obs/exp	SIR (95% CI)	Obs/exp	SIR (95% CI)
Epistaxis										
Overall	9173/7737	1.19 (1.16, 1.21)	573/436	1.31 (1.21, 1.42)	2460/2313	1.06 (0.02, 1.11)	3500/2706	1.29 (1.25, 1.34)	2640/2282	1.16 (1.11, 1.20)
0 –90 days	743/155	1.85 (1.69, 2.02)	86/15	5.78 (4.62, 7.14)	86/71	1.21 (0.97, 1.49)	148/94	1.58 (1.34, 1.86)	153/76	2.01 (1.70, 2.36)
91 – 365 days	893/736	1.21 (1.13, 1.29)	74/43	1.73 (1.36, 2.17)	237/206	1.15 (1.01, 1.31)	337/269	1.25 (1.12, 1.39)	245/219	1.12 (0.98, 1.27)
>1–5 years	3642/3085	1.18 (1.14, 1.22)	207/176	1.17 (1.02, 1.35)	950/885	1.07 (1.01, 1.14)	1415/1106	1.28 (1.21, 1.35)	1070/917	1.17 (1.10, 1.24)
>5–14 years	4165/3660	1.14 (1.10, 1.17)	206/203	1.02 (0.88, 1.17)	1187/1150	1.03 (0.97, 1.09)	1600/1237	1.29 (1.23, 1.36)	1172/1070	1.10 (1.03, 1.16)
Haemoptysis										
Overall	2582/1540	1.68 (1.61, 1.74)	127/84	1.51 (1.26, 1.79)	483/466	1.04 (0.95, 1.13)	1449/521	2.78 (2.64, 2.93)	523/468	1.12 (1.02, 1.22)
0 –90 days	695/48	14.6 (13.5, 15.7)	19/3	7.03 (4.23, 11.0)	9/14	0.66 (0.30, 1.26)	611/17	36.3 (33.5, 39.3)	56/15	3.86 (2.91, 5.01)
91 – 365 days	232/136	1.70 (1.49, 1.94)	14/8	1.82 (0.99, 3.05)	42/39	1.08 (0.78, 1.46)	129/48	2.69 (2.25, 3.20)	47/42	1.13 (0.83, 1.50)
>1 to 5 years	750/596	1.26 (1.17, 1.35)	37/33	1.11 (0.78, 1.54)	191/175	1.09 (0.94, 1.26)	318/206	1.54 (1.38, 1.72)	204/182	1.12 (0.97, 1.28)
>5–14 years	905/760	1.19 (1.11, 1.27)	57/41	1.40 (1.06, 1.82)	241/239	1.01 (0.88, 1.14)	391/251	1.56 (1.41, 1.72)	216/229	0.94 (0.82, 1.08)

Abbreviations: CI = confidence interval; Obs/exp = observed number/expected number; SIR = standardised incidence ratios.

In the sensitivity analysis that used the inpatient admission date, rather than the discharge date, as the index date, the SIR for cancer overall was largely unchanged for patients with epistaxis (SIR 1.19 (95% CI 1.16, 1.21)), but was slightly increased in patients with haemoptysis (SIR 1.72 (95% CI 1.65, 1.78)).

DISCUSSION

In this nation-wide cohort study, patients with a hospital-based diagnosis of epistaxis or haemoptysis were at increased risk of a subsequent cancer diagnosis compared with the general population. The 90-day absolute risk was 0.59% following epistaxis and higher (3.78%) following haemoptysis. Relative risks were particularly high for haematological cancers after epistaxis and for smoking and alcohol-related cancers after haemoptysis. The 90-day relative risks of cancer were 2-fold increased after epistaxis and 15-fold increased after haemoptysis.

For decades, the association between localised occult or visible bleeding and presence of organ-specific tumours has been recognised. Examples include gastrointestinal cancer associated with rectal bleeding and uterine cancer associated with vaginal bleeding in postmenopausal women (Pacheco and Kempers, 1968; Holst *et al*, 1983). Our study adds to the existing literature by quantifying cancer risk at specific cancer sites for patients presenting with epistaxis or haemoptysis. Several case reports have described metastatic renal cancer manifesting as epistaxis, while other small studies have associated epistaxis with melanoma and head and neck cancer and haemoptysis with lung cancer (Vokes *et al*, 1993; Goldenberg *et al*, 2001; Herth *et al*, 2001; Fidan *et al*, 2002; Pritchyk *et al*, 2002; Pereira and Phan, 2004;Lee *et al*, 2005; Uzun *et al*, 2010; Fyrmpas *et al*, 2011; Singh *et al*, 2014; Archer *et al*, 2015; Azoury *et al*, 2015). In a US single-centre study of 722 patients referred to a pulmonary department for evaluation of haemoptysis, the underlying cause determined at initial endoscopic examination was lung cancer or metastatic cancer with lung involvement in 40% of patients (9). A single-centre study of 178 patients in Turkey reported this finding for 30% of patients (Herth *et al*, 2001; Uzun *et al*, 2010). The absolute risks found in our study were markedly lower than those previously reported, which may reflect differences in health care systems and our inclusion of patients with any hospital contact for haemoptysis. The etiology of haemoptysis also may vary by geographic location and by birth cohort (Santiago *et al*, 1991). In developed countries, causes of haemoptysis have transitioned from tuberculosis to lung cancer, which has become a disease epidemic (Santiago *et al*, 1991).

Several mechanisms may underlie our findings. We found increased risks for cancers of the lung, bronchus, trachea, larynx, pharynx, tongue, and tonsils, likely caused by tumour invasion or compression of blood vessels (Pereira and Phan, 2004). Haematological disorders also can lead to bleeding (Pereira and Phan, 2004), consistent with the observed increased risk of haematological cancers. At the same time, some of the excess risk observed in the initial 90 days after haemoptysis may have been due to early detection through diagnostic imaging of the thorax.

As the risk of cancer was high for patients with haemoptysis, particularly for smoking- and alcohol-related cancer, it may be reasonable to offer them an extensive diagnostic work-up for cancer. Unfortunately, we lacked information on whether such a work-up would detect more occult cancers, shorten time to cancer diagnosis, and reduce cancer-related mortality. For the last many years, it has been recommended that all patients in Denmark with haemoptysis should be referred to a hospital for a diagnostic cancer work-up (National Board of Health, 2005). Further research in a potential benefit of extended cancer work-up in patients with airway bleeding is warranted.

Our study has several strengths. All Danish hospitals report inpatient, outpatient and emergency discharge diagnoses to the DNPR (Schmidt *et al*, 2015). Our ability to (1) identify patients using this comprehensive hospital-based registry, in a national setting with

Table 4. Selected site–specific SIRs and 95% CIs of a cancer diagnosis among patients with a hospital diagnosis of epistaxis or haemoptysis, Denmark 1995–2013

	Epistaxis			Haemoptysis		
Cancer site	**Obs**	**Exp**	**SIR (95% CI)**	**Obs**	**Exp**	**SIR (95% CI)**
All malignant neoplasms	9173	7737	1.19 (1.16, 1.21)	2582	1540	1.68 (1.61, 1.74)
Hodgkin's lymphoma	9	16	0.57 (0.26, 1.08)	6	3	1.82 (0.67, 3.97)
Non-Hodgkin's lymphoma	240	188	1.28 (1.12, 1.45)	52	38	1.37 (1.03, 1.80)
Multiple myeloma	97	71	1.36 (1.10, 1.66)	26	14	1.89 (1.23, 2.77)
Leukaemia	224	160	1.40 (1.22, 1.59)	41	29	1.40 (1.01, 1.90)
Liver	146	68	2.16 (1.82, 2.54)	39	13	2.92 (2.07, 3.99)
Malignant melanoma	204	202	1.01 (0.88, 1.16)	31	47	0.66 (0.45, 0.93)
Non-melanoma skin cancer	2165	2049	1.06 (1.01, 1.10)	442	405	1.09 (0.99, 1.20)
Cervix	61	33	1.83 (1.40, 2.35)	NA		
Anus and anal canal excluding malignant melanomas	12	15	0.82 (0.42, 1.43)	NA		
External female genitals excluding basal cell carcinomas	17	14	1.21 (0.70, 1.93)	NA		
Lip	12	12	1.03 (0.53, 1.80)	5	2	2.62 (0.85, 6.10)
Tongue	50	22	2.27 (1.69, 3.00)	17	5	3.30 (1.92, 5.29)
Mouth	86	37	2.32 (1.86, 2.87)	12	8	1.47 (0.76, 2.58)
Tonsil and pharynx	142	53	2.70 (2.28, 3.18)	35	14	2.56 (1.78, 3.56)
Other and poorly specified location in lip, oral cavity, or pharynx	NA			26	11	2.30 (1.50, 3.36)
Larynx	77	52	1.47 (1.16, 1.84)	NA		
Oesophagus	123	94	1.31 (1.09, 1.56)	28	19	1.51 (1.00, 2.18)
Stomach	121	118	1.02 (0.85, 1.22)	26	22	1.18 (0.77. 1.73)
Colon including rectosigmoid junction	641	592	1.08 (1.00, 1.17)	118	105	1.12 (0.93. 1.34)
Rectum	289	301	0.96 (0.85, 1.08)	52	58	0.90 (0.68. 1.19)
Pancreas	204	184	1.11 (0.96, 1.27)	49	35	1.42 (1.05. 1.87)
Lung, bronchus, and trachea	1183	815	1.45 (1.37, 1.54)	958	163	5.87 (5.51. 6.26)
Kidney	188	117	1.60 (1.38, 1.85)	45	25	1.81 (1.32. 2.42)
Renal pelvis	15	15	1.02 (0.57, 1.68)	NA		
Ureter	6	5	1.27 (0.46, 2.76)	NA		
Urinary bladder	214	220	0.97 (0.84, 1.11)	33	38	0.86 (0.59, 1.21)
Salivary gland	12	9	1.28 (0.66, 2.23)	NA		
Small intestine	20	16	1.23 (0.75, 1.90)	6	4	1.71 (0.63, 3.74)
Gallbladder and bile ducts	50	41	1.22 (0.91, 1.61)	14	7	1.91 (1.04, 3.20)
Nasal cavity, middle ear, and accessory sinuses	55	13	4.28 (3.23, 5.57)	NA		
Pleura including mesothelioma pleura	16	24	0.67 (0.38, 1.09)	8	5	1.70 (0.73, 3.34)
Bone and articular cartilage	9	6	1.58 (0.72, 3.00)	NA		
Retroperitoneum and peritoneum, and malignant neoplasm of other connective and soft tissue	35	34	1.03 (0.71, 1.43)	9	7	1.25 (0.57, 2.37)
Breast	645	559	1.15 (1.07, 1.25)	136	137	0.99 (0.83, 1.18)
Uterus	111	108	1.03 (0.85, 1.24)	16	25	0.65 (0.37, 1.06)
Ovary and fallopian tube	68	77	0.88 (0.68, 1.12)	18	17	1.04 (0.61, 1.64)
Penis excluding basal cell carcinomas	13	13	1.02 (0.54, 1.75)	3	2	1.25 (0.26, 3.66)
Prostate	1137	1002	1.13 (1.07, 1.20)	200	187	1.07 (0.92, 1.23)
Testis	29	31	0.95 (0.63, 1.36)	5	8	0.66 (0.21, 1.54)
Eye and adnexa	12	12	0.97 (0.50, 1.69)	NA		
Brain including hypophysis, corpus pineale, and ductus craniopharyngealis	79	74	1.07 (0.85, 1.34)	21	16	1.31 (0.81, 2.01)
Endocrine glands and related structure	27	23	1.15 (0.76, 1.67)	14	6	2.37 (1.30, 3.98)
Metastasis and unspecified cancer in lymph nodes	204	159	1.28 (1.11, 1.47)	42	26	1.59 (1.15, 2.15)
Malignant neoplasm of other, ill-defined, or unspecified sites	98	61	1.60 (1.30, 1.95)	18	9	1.94 (1.15, 3.06)

Abbreviations: CI = confidence interval; Exp = expected number; NA = not available; Obs = observed number; SIR=standardised incidence ratios. Only cancer with at least five observed cases are presented. NA indicates less than five cancer cases.

free access to healthcare, and (2) track patients by means of the Civil Registration System permitted unselected patient inclusion and complete follow-up (Schmidt *et al*, 2014; Schmidt *et al*, 2015). Cancers were most often histologically verified in the DCR, which is nearly complete and valid due to mandatory reporting throughout the Danish health care system (Gjerstorff, 2011).

Our study population only included patients with epistaxis or haemoptysis managed in a hospital. Most persons with epistaxis are likely not in contact with the health care system. Some of them will receive treatment by general practitioner; and a small proportion of persons are seen at a hospital or outpatient hospital clinic. However haemoptysis and particular recurrent haemoptysis may to a larger extent than for epistaxis lead to consultation with a general practitioner who likely will refer the patient to an X-ray and/or a hospital or outpatient specialist clinic. The positive predictive values of epistaxis and haemoptysis recorded in the DNPR are probably high, but any misclassification would have produced conservative relative effect measures.

We lacked information on lifestyle factors such as smoking and alcohol consumption, Factor V Leiden mutations, and medications including anticoagulant treatment. We also did not have information on the origin and type of epistaxis or haemoptysis, although more than 90% of epistaxis episodes occur anteriorly and are likely venous bleeds (Guarisco and Graham, 1989; Padgham, 1990). However, subanalyses of inpatients who underwent upper airway endoscopy or bronchoscopy, as well as subanalyses of inpatients with epistaxis requiring a procedure or surgery, yielded results similar to those in the main analysis.

Heightened diagnostic effort and the effects of occult cancer probably explain most of the associations in the short term. However, we observed that the increased risk of cancer in patients with epistaxis or haemoptysis persisted for more than 5 years. In case of detection bias, the period of increased cancer diagnosis would be followed by a compensatory deficit, which was not apparent from our analysis.

As well, the SIRs for common cancers, such as colon, prostate, and breast cancer, were not notably increased in patients with bleeding, indicating that detection bias cannot explain our findings.

In conclusion, we found that patients with a hospital diagnosis of epistaxis and particularly haemoptysis were at increased risk of cancer compared with the Danish general population. The relative risks were particularly high for haematological cancer after epistaxis, and of smoking and alcohol- related cancers after haemoptysis. The association with cancer persisted for more than 5 years after the initial bleeding event.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

AGO, KV, and HTS had had full access to all data used in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Data responsible: HTS. Study concept and design: AGO, DKF, and HTS. Statistical analysis: KV and DKF. Interpretation of data: All authors. Drafting of manuscript: AGO. Critical revision of the manuscript for important intellectual content: All authors. Obtained funding: HTS. Study supervision: HTS.

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