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
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, and ≥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 ≥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.

### 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 | 6650 (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 | 1992 (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 | | |
| 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. *For inpatients starting in 2002.

**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 population.
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 as 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, 16.81)), 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).
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 nationwide 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

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

ACKNOWLEDGEMENTS

This work was supported by the Program for Clinical Research Infrastructure (PROCRIN), established by the Lundbeck Foundation and the Novo Nordisk Foundation, and the Danish Cancer Society. The funding sources had no role in study design, data collection, data analysis, or interpretation of data; in writing the report; or in the decision to publish. The corresponding author had full access to all data used in the study and had final responsibility for the decision to submit for publication. The authors report no personal disclosures. The Department of Clinical Epidemiology at Aarhus University is, however, involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study.

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.

REFERENCES

Archer KA, Goyal P, Mortelliti AJ (2015) Nasal obstruction and epistaxis. Nasal alveolar soft part sarcoma. JAMA Otolaryngol 141(5): 479–480.
Ay C, Pabinger I, Cohen AT (2016) Cancer-associated venous thromboembolism: burden, mechanisms, and management. Thromb Haemost 117(2pp): 219–230.
Azoury SC, Crompton JG, Straughan DM, Klemen ND, Reardon ES, Beresnev TH, Hughes MS (2015) Unknown primary nasopharyngeal melanoma presenting as severe recurrent epistaxis and hearing loss following treatment and remission of metastatic disease: a case report and literature review. Int J Surg Case Rep 10: 232–235.
Bidwell JL, Pachner RW (2005) Hemoptysis: diagnosis and management. Am Fam Phys 72(7): 1253–1260.
Charlson ME, Pompei P, Ales KL, Mackenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40(5): 373–383.
Fidan A, Ozdogan S, Oruc O, Salepci B, Ocak Z, Caglayan B (2002) Hemoptysis: a retrospective analysis of 108 cases. Respir Med 96(9): 677–680.
Frank I (2000) Epidemiology. When an entire country is a cohort. Science 287(5462): 2398–2399.
Fyrmpas G, Adeniyi A, Baer S (2011) Occult renal cell carcinoma manifesting with epistaxis in a woman: a case report. J Med Case Rep 5: 1947–5–79.
Gjerstorff ML (2011) The Danish Cancer Registry. Scand J Public Health 39(7 Suppl): 42–45.
Goldenberg D, Golz A, Fradis M, Martu D, Ocal Z, Joachims HZ (2001) Malignant tumors of the nose and paranasal sinuses: a retrospective review of 291 cases. Ear Nose Throat J 80(4): 272–277.
Guarisco JL, Graham 3RD HD (1989) Epistaxis in children: causes, diagnosis, and treatment. Ear Nose Throat J 68(7): 522 528–30, 532 passim.
Herth F, Ernst A, Becker HD (2001) Long-term outcome and lung cancer incidence in patients with hemoptysis of unknown origin. Chest 120(5): 1592–1594.
Holst J, Koskela O, Von Schoutz B (1983) Endometrial findings according to age and indications. Ann Chir Gynaecol 72(5): 274–277.
Jean-Baptiste E (2000) Clinical assessment and management of massive hemoptysis. Arch Intern Med 160(4): 308–311.
Pedersen KM, Andersen JS, Søndergaard J (2012) General practice and primary health care in Denmark. J Am Board Fam Med 25(Suppl 1): S34–S38.
Pereira J, Phan T (2004) Management of bleeding in patients with advanced cancer. Oncologist 9(5): 561–570.
Pritchky KM, Schiff BA, Newkirk KA, Krowiak E, Deeb ZE (2002) Metastatic renal cell carcinoma to the head and neck. Laryngoscope 112(9): 1598–1602.
Rickles FR, Edwards RL (1983) Activation of blood coagulation in cancer: Trousseau’s syndrome revisited. Blood 62(1): 14–31.
Santiago S, Tobias J, Williams AJ (1991) A reappraisal of the causes of hemoptysis. Arch Intern Med 151(12): 2449–2451.
Schmidt M, Pedersen L, Sorensen HT (2014) The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 29(8): 541–549.

Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT (2015) The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 7: 449–490.

Singh J, Baheti V, Yadav SS, Mathur R (2014) Occult renal cell carcinoma manifesting as nasal mass and epistaxis. *Rev Urol* 16(3): 145–148.

Uzun O, Atasoy Y, Findik S, Atici AG, Erkan L (2010) A prospective evaluation of hemoptysis cases in a tertiary referral hospital. *Clin Respir J* 4(3): 131–138.

Viehweg TL, Roberson JB, Hudson JW (2006) Epistaxis: diagnosis and treatment. *J Oral Maxillofac Surg* 64(3pp): 511–518.

Vokes EE, Weichselbaum RR, Lippman SM, Hong WK (1993) Head and neck cancer. *N Engl J Med* 328(3pp): 184–194.

Walker TW, Macfarlane TV, Mcquarry GW (2007) The epidemiology and chronobiology of epistaxis: an investigation of Scottish hospital admissions 1995-2004. *Clin Otolaryngol* 32(5): 361–365.

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Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)