Respiratory Medicine (2012) **106**, 845–852

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Chronic obstructive pulmonary disease and cancer risk: A Danish nationwide cohort study

Jette Brommann Kornum [a], Claus Sværke [a], Reimar Wernich Thomsen [a,*], Peter Lange [b], Henrik Toft Sørensen [a]

[a] *Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University Hospital, Aarhus N DK-8200, Denmark*

[b] *Department of Cardiology and Respiratory Medicine, University Hospital of Copenhagen, DK-2650 Hvidovre, Denmark*

Received 22 October 2011; accepted 12 December 2011
Available online 2 January 2012

KEYWORDS
Cohort study;
Chronic obstructive pulmonary disease;
Neoplasms;
Smoking;
Risk

Summary
Introduction: Little is known about the risk of cancer in patients with chronic obstructive pulmonary disease (COPD), including which cancer sites are most affected. We examined the short- and long-term risk of lung and extrapulmonary cancer in a nationwide cohort of COPD patients.
Methods: We linked the Danish National Registry of Patients and the nationwide cancer registry, and examined the incidence of various cancers in 236,494 individuals with a first incident hospital contact with COPD during 1980–2008. The observed cancer incidence in this cohort was compared with the expected incidence in the general population on the basis of national age-, sex-, and site-specific incidence rates.
Results: Median follow-up was 3.5 years. During the first year of follow-up, 9434 cancers were diagnosed in COPD patients [standardized incidence ratio (SIR) = 3.1; 95% CI 3.0 to 3.2]. The 1-year SIR was 8.5 (8.2–8.9) for lung cancer, 5.1 (5.0–5.2) for all tobacco-related cancers, and 1.9 (1.9–2.0) for other cancers. In the following years, cancer incidence was increased 1.4-fold (1.4–1.5) in COPD patients. These patients had an increased risk of developing tobacco-related cancers (SIR = 2.1; 95% CI 2.0–2.1), including cancers of the lung, larynx, tongue, oral cavity, pharynx, esophagus, stomach, liver, pancreas, cervix uteri, and urinary tract (with SIRs ranging between 1.3 and 2.8).

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DCR, Danish Cancer Registry; DNRP, Danish National Registry of Patients; SIR, Standardized incidence ratio.

* Corresponding author. Department of Clinical Epidemiology, Aarhus University Hospital, Sdr. Skovvej 15, DK-9000 Aalborg, Denmark. Tel.: +45 9932 6904; fax: +45 9932 6914.
E-mail addresses: rwt@dce.au.dk, r.thomsen@rn.dk (R.W. Thomsen).

0954-6111/$ - see front matter
doi:10.1016/j.rmed.2011.12.009

Conclusions: Patients with first-time hospital-diagnosed COPD are at considerably increased risk of developing both lung cancer and extrapulmonary cancers. Physicians should be aware of cancer in COPD patients.

Introduction

Chronic obstructive pulmonary disease (COPD) is currently the fourth most frequent cause of death in the world and a major cause of hospitalizations.[1,2] In Europe and North America, the prevalence of COPD is at least 10% among adults aged 40 years and older.[3–6] The prevalence is increasing, due to population aging and a decline in all-cause mortality.[5]

It has been known for many decades that COPD and lung cancer often occur together.[7–9] There is evidence that the risk of developing lung cancer is substantially increased in individuals with COPD and may be associated with the severity of lung function impairment and with chronic mucus hypersecretion.[10–14] Given the systemic inflammation accompanying COPD and shared risk factors for many cancers (*e.g.*, smoking), it is also plausible that COPD is associated with an increased risk of extrapulmonary cancers.[15–17] Available evidence for such association is limited. In a Dutch cohort study, COPD was linked with 1.4-fold increased mortality from extrapulmonary cancers.[15] In a Swedish study of male construction workers, those with moderate or severe COPD had a 1.6-fold [95% confidence interval (CI) 1.4 to 2.0] increased risk of any extrapulmonary tobacco-related cancer.[12] A Japanese cohort study including 127 COPD patients found a 2.3-fold (1.2–4.3) greater risk of developing any cancer as compared with patients with "benign respiratory disease".[18] To our knowledge no previous large-scale studies have examined the magnitude and period of increased risk of specific cancer sites associated with COPD, or addressed the impact of comorbidity on cancer risk.

Data on these topics could provide insight into the clinical course of patients with COPD and may have implications for the clinical follow-up of this large patient group, potentially including surveillance for cancer. We therefore examined short- and long-term cancer risk by site after a first hospital contact with COPD in Denmark, using data from the Danish Cancer Registry and a nationwide hospital registry.

Materials and methods

The Danish healthcare system provides tax-supported healthcare services to all residents, guaranteeing free access to hospitals and primary medical care. The civil registration number, a unique identifier assigned to every Danish citizen, allowed for accurate linkage among the databases used in this study.[19]

Identification of patients with COPD

We used the Danish National Registry of Patients (DNRP), covering all Danish hospitals,[20] to identify all patients aged 40 years or older with COPD, defined by a first-time inpatient hospitalization or hospital outpatient clinic or emergency room visit with a diagnosis of COPD (ICD-8 codes: 491–492; ICD-10 codes: J41-J44) between 1980 and 2008.[21]

Data on comorbidity and alcoholism-related conditions

For supplemental analyses, we retrieved data on comorbidities included in the Charlson Comorbidity Index, identified as conditions recorded in the DNRP before each patient's first hospital contact with COPD[22]: previous myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, renal disease, any solid malignancy, leukemia, lymphoma, metastatic cancer, and AIDS. Three comorbidity levels were defined: low (score of 0), medium (score of 1–2), and high (score of $\geq$3). We also identified persons with a history of alcoholism-related conditions not included in the CCI, by retrieving ICD codes for any mental or behavioural disorders due to alcohol use (including acute intoxication, dependence, psychotic or amnestic disorders), and codes for alcoholic organ damage other than liver disease (including alcohol-related neuropathy, myopathy, cardiomyopathy, gastritis, and pancreatitis).[21]

Identification of cancer

We obtained information on all cancer diagnoses (except non-melanoma skin cancers) from the Danish Cancer Registry (DCR). The DCR stores data on cancer incidence in entire Denmark and is 95%–98% complete and valid.[23] We excluded patients with a cancer diagnosis other than non-melanoma skin cancer preceding the first hospital contact with COPD.

Statistical analysis

We followed COPD patients to detect any occurrence of cancer from the date of first hospital contact with COPD until the date of death, emigration, or Dec 31, 2008, whichever came first.

The standardized incidence ratio (SIR) of cancer was computed as the observed number of cancers divided by the expected number of cancers. The expected number was obtained by multiplying the number of person-years at risk in our cohort by national cancer incidence rates according to sex, age, and year of diagnosis in 5-year intervals.[24] Because a hospital contact with COPD may be related to undiagnosed pulmonary and other cancer, we computed SIRs separately for early (first year) and longer-term (subsequent years)

follow-up. SIRs with 95% CIs assuming a Poisson distribution were computed for any cancer, for site-specific cancers, and for the following malignancy subgroups: tobacco-related cancers,[25] non-tobacco-related cancers, alcohol-related cancers,[26] cancers associated with immunosuppression,[27] and hematological cancers (for ICD-10 codes see Tables 1–4 in the Results section).

The SIR for cancer was computed separately for inpatient or outpatient diagnoses of COPD, and stratified by sex and age group (40–49, 50–69, and 70 + years) and by calendar time periods. We also computed SIRs for cancer separately for COPD patients with and without an alcoholism-related condition and for COPD patients with different levels of CCI scores. Finally, to summarize time-to-events, we calculated the cumulative incidence of cancer, treating death as a competing risk. We used SAS software (version 9.2, SAS Institute, Cary, NC). The Danish Registry Board approved the study. According to Danish law, this purely registry-based project needed no further IRB approval.

Results

We identified 236,494 patients (107,150 women and 129,344 men) with a first hospital contact with COPD between 1980 and 2008 (Table 1). The median age was 70 years (range 40–90 years) and median follow-up time was 3.5 years (IQR: 1.1–7.3 years).

Any cancer

COPD patients had a substantially higher risk of cancer than persons in the general population. In the first year of follow-up, 9434 cancers were identified among COPD patients, yielding an SIR for any cancer of 3.1 (95% CI 3.0–3.2) (Table 1). This result was similar for men and women. Individuals aged 70 years or older had the lowest relative risk of cancer in the first year of follow-up (SIR = 2.7; 95% CI 2.6–2.8), while 1-year relative risks were elevated approximately fourfold among those aged 40–69 years. One-year SIRs decreased from 3.9 to 2.6 between 1980 and 1999, and then rose slightly to 2.9 in 2005–2008. The relative risk for cancer during the first year was lower among COPD patients whose first hospital contact was as an outpatient (SIR = 2.4; 95% CI 2.3–2.5). Presence of an alcoholism-related diagnosis increased the relative cancer risk (SIR = 3.9; 95% CI 3.6–4.2) (Table 2), while the overall level of comorbidity had little influence on relative risk (Table 3).

After the first year of follow-up, 22,759 cancers were diagnosed in the COPD cohort (SIR = 1.4; 95% CI 1.4–1.5) (Table 1). COPD patients aged less than 70 years continued to have higher relative risk increase for cancer than elderly COPD patients. The longer-term cancer SIRs remained stable at 1.4–1.5 in each calendar period examined, and were similar regardless of inpatient or outpatient COPD status (Table 1) or level of comorbidity (Table 3). The SIR was 2.1 (2.0–2.2) among COPD patients who also had an alcoholism-related diagnosis (Table 2). Fig. 1 summarizes overall cancer risk by length of follow-up time. After the first year of follow-up, the SIRs remained rather stable yet with a slight decline over the next nine years.

Tobacco-related cancers

In the first year of follow-up, the SIR for tobacco-related cancer in COPD patients was 5.1 (5.0–5.2) (Table S1, see online data supplement). During that period, we found a particularly high risk for cancers of the lung, bronchus, and trachea (SIR = 8.5; 95% CI 8.2–8.8). SIRs were also 2 or greater for most other tobacco-related cancers, including cancers of the oral cavity, esophagus, stomach, liver, pancreas, larynx, kidney, renal pelvis, urinary bladder, and myeloid leukemia (Table S1).

After the first year of follow-up, the SIR for tobacco-related cancer was 2.1 (2.0–2.1) (Table S2, see online data supplement). Patients had a substantially raised risk of cancers of the lung, bronchus, and trachea (SIR = 2.8; 95% CI: 2.7–2.8), but we also found elevated SIRs (1.3 or higher) for cancers of the tongue, oral cavity, pharynx, esophagus, stomach, liver, pancreas, larynx, cervix uteri, and urinary tract (Table S2). The relative risk for cancers of the lung, bronchus, and trachea remained elevated after more than 10 years of follow-up (SIR = 2.5; 95% CI: 2.3–2.6).

The cumulative risk for lung cancer in the COPD cohort after 1, 5 and 10 years was 1.8% (1.7%–1.9%), 3.6% (95% CI 3.6%–3.7%) and 4.9% (4.9%–5.0), respectively (Table 4). The corresponding risks for other tobacco-related cancers were 0.6% (0.6%–0.7%), 1.8% (1.8%–1.9%) and 2.7% (2.6%–2.8%). For any cancer, the 10-year incidence reached 14.2%.

Alcohol-related cancers

The SIR for alcohol-related cancers was 1.7 (1.6–1.8) in the first year of follow-up (Table S1) and 1.2 (1.1–1.2) in subsequent years (Table S2). In the later period, SIRs were elevated mainly for cancers that were also classified as tobacco-related cancers (cancers of the oral cavity, pharynx, esophagus, larynx, and liver). The 10-year incidence of alcohol-related cancers was 3.2% (3.1%–3.2%) (Table 4).

Immune-related and hematological cancers

In the first year of follow-up, the SIR for immune-related cancers was 1.9 (1.7–2.1), while the SIR for hematological cancers was 2.7 (2.5–2.9). We found a particularly high risk for Hodgkin's lymphoma (SIR = 5.0; 95% CI 3.4–7.1). In subsequent years of follow-up, the SIR for both immune-related cancers and hematological cancers was 1.1 (1.0–1.1).

The SIRs for other cancers are also shown in Tables S1 and S2.

Discussion

In our cohort of more than 236,000 patients followed after an initial hospital contact with COPD, cancer risk was clearly higher than among the general Danish population of comparable age. In addition to lung and other tobacco-related cancers, we also found a high relative risk of alcohol- and immune-related cancers, hematological

Table 1 Standardized incidence ratio for subsequent diagnosis of any cancer among 236,494 individuals with a first incident hospital contact (hospitalization or outpatient visit) with COPD according to sex, age, year of diagnosis, and in-/outpatient status.

All cancer	Number of patients with COPD	Within first year					Within subsequent years				
		Number of cancers observed	Person-years of follow-up	Number of cancers expected	Incidence rate per 100,000 person years	Standardized incidence ratio (95% CI)	Number of cancers observed	Person-years of follow-up	Number of cancers expected	Incidence rate per 100,000 person years	Standardized incidence ratio (95% CI)
Overall											
All patients	236,494	9434	198,584.8	3060.6	4751	3.1 (3.0–3.2)	22,759	975,255.7	15,847.0	2334	1.4 (1.4–1.5)
Sex											
Women	107,150	3488	92,166.2	1183.6	3784	3.0 (2.9–3.1)	9470	469,371.6	6398.8	2018	1.5 (1.5–1.5)
Men	129,344	5946	106,418.6	1877.0	5587	3.2 (3.1–3.3)	13,289	505,884.0	9448.2	2627	1.4 (1.4–1.4)
Age (yrs)											
40–49	14,646	174	13,918.5	41.6	1250	4.2 (3.6–4.9)	1172	116,884.6	707.2	1003	1.7 (1.6–1.8)
50–69	102,733	3781	91,611.6	990.0	4127	3.8 (3.7–3.9)	12,385	545,196.7	8059.6	2272	1.5 (1.5–1.6)
70+	119,115	5479	93,054.7	2029.0	5888	2.7 (2.6–2.8)	9202	313,174.4	7080.2	2938	1.3 (1.3–1.3)
Year of diagnosis											
1980–1984	34,545	1614	28,538.3	410.2	5656	3.9 (3.7–4.1)	4612	199,371.4	3191.0	2313	1.4 (1.4–1.5)
1985–1989	31,587	1417	25,894.4	394.0	5472	3.6 (3.4–3.8)	3806	162,997.1	2684.3	2335	1.4 (1.4–1.5)
1990–1994	34,616	1353	29,126.8	443.8	4645	3.1 (2.9–3.2)	4125	173,186.7	2838.9	2382	1.5 (1.4–1.5)
1995–1999	46,584	1616	40,718.5	620.2	3969	2.6 (2.5–2.7)	5348	233,503.5	3728.7	2290	1.4 (1.4–1.5)
2000–2004	50,635	1987	44,362.3	701.1	4479	2.8 (2.7–3.0)	4102	172,523.7	2848.0	2378	1.4 (1.4–1.5)
2005–2008	38,527	1447	29,944.5	491.4	4832	2.9 (2.8–3.1)	766	33,673.3	556.1	2275	1.4 (1.3–1.5)
Patient type											
Outpatients	52,239	1557	48,541.3	647.7	3208	2.4 (2.3–2.5)	4993	235,451.1	3387.4	2121	1.5 (1.4–1.5)
Inpatients	184,255	7877	150,043.5	2412.9	5250	3.3 (3.2–3.3)	17,766	739,804.5	12,459.6	2401	1.4 (1.4–1.5)

Table 2 Standardized incidence ratios (SIRs) for cancer among COPD patients with and without an alcoholism-related diagnosis before the time of their first hospital contact with COPD.

Cancer grouping	Alcoholism-related diagnosis present (n = 15,274)		Alcoholism-related diagnosis absent (n = 221,220)	
	Observed	SIR (95% CI)	Observed	SIR (95% CI)
Any cancer				
Follow-up 0–12 months	538	3.9 (3.6–4.2)	8896	3.0 (3.0–3.1)
Follow-up >12 months	1338	2.1 (2.0–2.2)	21,421	1.4 (1.4–1.4)
Tobacco-related cancers				
Follow-up 0–12 months	390	7.4 (6.7–8.2)	5320	5.0 (4.9–5.1)
Follow-up >12 months	822	3.5 (3.2–3.7)	10,698	2.0 (2.0–2.0)
Non-tobacco-related cancers				
Follow-up 0–12 months	148	1.7 (1.5–2.0)	3576	1.9 (1.9–2.0)
Follow-up >12 months	516	1.3 (1.2–1.4)	10,723	1.1 (1.1–1.1)
Alcohol-related cancers				
Follow-up 0–12 months	123	3.1 (2.6–3.7)	1420	1.6 (1.6–1.7)
Follow-up >12 months	389	2.1 (1.9–2.4)	5202	1.1 (1.1–1.2)
Immune–related cancers				
Follow-up 0–12 months	40	3.6 (2.6–4.9)	373	1.8 (1.6–2.0)
Follow-up >12 months	78	1.6 (1.2–1.9)	1125	1.0 (1.0–1.1)
Hematological cancers				
Follow-up 0–12 months	16	1.6 (0.9–2.6)	569	2.8 (2.5–3.0)
Follow-up >12 months	47	1.0 (0.8–1.4)	1139	1.1 (1.0–1.1)

Alcoholism-related diagnoses include mental or behavioural disorders due to alcohol use, and alcoholic organ damage, see text.

cancers, and cancers of the pleura, tonsil, small intestine, thyroid gland, retroperitoneum, and peritoneum. A 40% increased risk for cancer of any sites persisted after the first year of follow-up, with COPD continuing to be a strong predictor for tobacco-related cancers.

Our estimates agree with previous observations of high risk of in particular lung cancer in COPD. In the Swedish study of 176,997 male construction workers, those with moderate/severe COPD had a 2.2-fold (95% CI: 1.8–2.7) increased risk of lung cancer and a 1.6-fold (95% CI 1.4–2.0) increased risk of extrapulmonary tobacco-related cancers compared with men with normal lung function.[12] Mild COPD was associated with a 1.5-fold (95% CI: 1.2–1.9) increased risk of lung cancer, but not with non-lung tobacco-related cancer or other cancers. Similarly, an earlier Danish study reported a "dose-response" relationship between COPD severity and lung cancer, with a particular high risk if patients reported chronic mucus hypersecretion, a sign of on-going inflammation in the large airways.[14] A recent Dutch cohort mortality study found that COPD was associated with increased lung cancer mortality (hazard ratio = 2.1; 95% CI: 1.3–3.2) and extrapulmonary cancer mortality (hazard ratio = 1.4; 95% CI: 1.1–1.9) in a cohort of 3371 patients with peripheral arterial disease who underwent vascular surgery.[15] A Dutch cross-sectional study of 73,255 newly diagnosed cancer patients found that 12% of patients had COPD at the time of diagnosis,[28] while up to 50% of patients with lung cancer reportedly have spirometric evidence of COPD.[29]

Several mechanisms may underlie the observed association between hospital-diagnosed COPD and cancer. Heightened diagnostic surveillance and presence of undiagnosed cancer at the time of the first COPD hospital contact may explain much of the strong short-term association, but is less likely to explain the markedly increased cancer risk in subsequent years. Initial false diagnosis of COPD might also partly explain the high early rates of lung cancer diagnoses, but such misclassification is unlikely to explain the highly increased lung cancer risk after 5–10 years of follow-up. The observed high SIR for lymphomas during the first year of follow-up is probably due to diagnostic bias, since the SIR was 1 in following years.

A plausible explanation for the association between hospital-diagnosed COPD and cancer is the sharing of risk factors like smoking, poor diet, low level of physical activity, and high alcohol consumption. Smoking is the predominant risk factor for COPD and an important risk factor for pulmonary but also other cancer, potentially caused by circulating systemic tobacco carcinogens. Among 11,580 COPD patients seen at hospital outpatient clinics in Denmark during 2010, 32% reported to be current smokers and 65% were former smokers (unpublished data).[30] Thus, we believe smoking may explain much of the observed long-term cancer risk increase associated with COPD. However, local lung inflammation *per se* may predispose to lung cancer,[10,12,14,15] consistent with a very high incidence of lung cancer in patients with idiopathic pulmonary fibrosis.[31] Unfortunately, we lacked the data necessary to examine

Table 3 Standardized incidence ratios (SIRs) for cancer among COPD patients with different levels of comorbidity before the time of their first hospital contact with COPD.

Cancer grouping	Low comorbidity (n = 149,995)		Medium comorbidity (n = 74,196)		High comorbidity (n = 12,303)	
	Observed	SIR (95% CI)	Observed	SIR (95% CI)	Observed	SIR (95% CI)
All cancers						
Follow-up 0–12 months	6344	3.3 (3.2–3.4)	2671	2.7 (2.6–2.8)	419	2.6 (2.4–2.9)
Follow-up >12 months	16,243	1.4 (1.4–1.5)	5894	1.5 (1.4–1.5)	622	1.6 (1.5–1.7)
Tobacco-related cancers						
Follow-up 0–12 months	3894	5.5 (5.3–5.7)	1587	4.5 (4.2–4.7)	229	4.1 (3.5–4.6)
Follow-up >12 months	8233	2.0 (2.0–2.1)	2961	2.1 (2.0–2.2)	326	2.4 (2.1–2.7)
Non-tobacco-related cancers						
Follow-up 0–12 months	2450	2.0 (2.0–2.1)	1084	1.7 (1.6–1.8)	190	1.9 (1.6–2.2)
Follow-up >12 months	8010	1.1 (1.1–1.1)	2933	1.1 (1.1–1.2)	296	1.2 (1.0–1.3)
Alcohol-related cancers						
Follow-up 0–12 months	999	1.8 (1.7–1.9)	460	1.6 (1.4–1.7)	84	1.8 (1.5–2.3)
Follow-up >12 months	3928	1.1 (1.1–1.2)	1507	1.2 (1.2–1.3)	156	1.4 (1.2–1.6)
Immune–related cancers						
Follow-up 0–12 months	250	1.8 (1.6–2.1)	130	1.8 (1.5–2.2)	33	2.9 (2.0–4.1)
Follow-up >12 months	845	1.0 (1.0–1.1)	308	1.0 (0.9–1.2)	50	1.8 (1.3–2.3)
Hematological cancers						
Follow-up 0–12 months	391	2.9 (2.6–3.2)	175	2.5 (2.1–2.9)	19	1.6 (1.0–2.6)
Follow-up >12 months	841	1.0 (1.0–1.1)	312	1.1 (1.0–1.2)	33	1.2 (0.8–1.6)

Level of comorbidity categorized as low (Charlson comorbidity index score of 0), medium (score of 1–2), and high (score of ≥3), see text.

the role of smoking in our study. Confounding by alcohol overuse may also affect the observed association between COPD and certain tobacco-related cancers, such as cancer of the oral cavity, pharynx, larynx, esophagus, and liver. However, we observed a twofold increased long-term risk of tobacco-related cancers even among COPD patients without an alcohol-related diagnosis.

Other comorbidities might partially explain the increased cancer risk associated with hospital-diagnosed COPD, but we observed a 40% increased long-term risk even in COPD patients without any previously recorded comorbidity. In recent years there has been substantial interest in the low-grade systemic inflammation associated with COPD[17,32,33] and an increased risk of cancer has been mentioned as a possible consequence of this systemic inflammatory process.[17] It is also possible that genetic differences in inflammatory responses may contribute to both COPD and cancer development.

The strengths of our study include its long and complete follow-up, the non-differential ascertainment of outcomes

Table 4 Absolute risks for cancer in 236,494 individuals with a first incident hospital contact with COPD.

	No. cancers observed within first year	1-year cancer risk in percent (95% CI)	No. cancers observed within first 5 years	5-year cancer risk in percent (95% CI)	No. cancers observed within first 10 years	10-year cancer risk in percent (95% CI)
Any cancer	9434	4.0% (4.0–4.1%)	21,615	9.9% (9.8–10.0%)	28,456	14.2% (14.1–14.4%)
Lung cancer	4209	1.8% (1.7–1.9%)	8051	3.6% (3.6–3.7%)	10,118	4.9% (4.9–5.0%)
Tobacco-related cancers other than lung cancer	1501	0.6% (0.6–0.7%)	3994	1.8% (1.8–1.9%)	5327	2.7% (2.6–2.8%)
Alcohol-related cancers	1543	0.7% (0.6–0.7%)	4438	2.1% (2.0–2.1%)	6167	3.2% (3.1–3.2%)

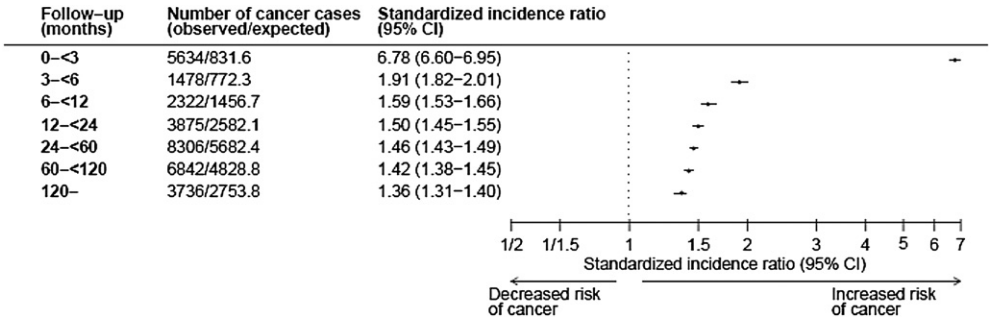

Figure 1 Standardized incidence ratio for diagnosis of any cancer among individuals with a first incident hospital contact with COPD.

through population-based registries, the ability to examine cancer incidence rather than mortality, and the large sample size conferring relatively high statistical precision. Some coding errors may have occurred, but the positive predictive value of a hospital diagnosis of COPD (J44.x) in Denmark is 92% (95% CI: 91—93%), assessed based on medical history, clinical symptoms and findings, and spirometry results.[30] Another limitation was the lack of data on smoking and other lifestyle factors associated with both COPD and cancer risk, and the lack of data on the severity of COPD.[12] Since our patients were recruited exclusively in the hospital setting, the vast majority were likely to have severe or very severe COPD.[30] Based on recent population surveys,[3,6] Denmark (population 5.5 million) has an estimated COPD prevalence of 450.000 (8% of the total population, or approximately 15% among adults aged 40 + years) and Danish hospitals admitted 13.000 patients with a new first-time hospitalization with COPD in 2006.[34]

In conclusion, patients with newly hospital-diagnosed COPD are at considerably increased risk of developing lung cancer and cancers at other sites. The pattern of cancer sites indicates that much of the overall increased cancer risk is attributable to smoking. Since improvements in treatment are increasing the longevity of COPD patients, the cancer burden is likely to increase among this patient group. Further research is needed to determine whether the observed increased risk justifies a special surveillance program or a more active case-finding approach by treating physicians.

Acknowledgments

None.

Supplementary data

Supplementary material related to this article can be found online at doi:10.1016/j.rmed.2011.12.009.

Author contributions

HTS conceived the study idea. JBK, RWT, CS and HTS reviewed the literature and designed the study. CS and HTS collected the data. CS analyzed the data and JBK, RWT, PL and HTS interpreted the findings. JBK organized the writing and wrote the initial draft. All authors edited the manuscript and approved the final version. HTS is the guarantor.

Financial support

The study was supported by the Clinical Epidemiological Research Foundation at Aarhus University, Denmark. The funding source had no role in the design, conduct, analysis, or reporting of this study.

Conflict of interest

Peter Lange has received honoraria for speaking and consulting and/or financial support for attending meettings from AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Norpharma, Nycomed, Pfizer, and UCB. No funding has been provided for this article. None of the other authors received any fees, honoraria, grants or consultancies that would constitute a conflict of interest with the current study. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study.

References

1. World Health Organization. *World health statistics*. Geneva: WHO Press; 2008.
2. Mannino DM. COPD: epidemiology, prevalence, morbidity and mortality, and disease heterogeneity. *Chest* 2002;**121**:121S—6S.
3. Hansen JG, Pedersen L, Overvad K, Omland O, Jensen HK, Sorensen HT. The Prevalence of chronic obstructive pulmonary disease among Danes aged 45-84 years: population-based study. *COPD* 2008;**5**:347—52.
4. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007;**370**:741—50.
5. Gershon AS, Wang C, Wilton AS, Raut R, To T. Trends in chronic obstructive pulmonary disease prevalence, incidence, and mortality in Ontario, Canada, 1996 to 2007: a population-based study. *Arch Intern Med* 2010;**170**:560—5.

6. Fabricius P, Lokke A, Marott JL, Vestbo J, Lange P. Prevalence of COPD in Copenhagen. *Respir Med* 2011;**105**:410—7.
7. van der Wal AM, Huizinga E, Orie NG, Sluiter HJ, de VK. Cancer and chronic non-specific lung disease (C.N.S.L.D. *Scand J Respir Dis* 1966;**47**:161—72.
8. Rimington J. Smoking, chronic bronchitis, and lung cancer. *Br Med J* 1971;**2**:373—5.
9. Legge JS, Palmer KN. Pulmonary function in bronchial carcinoma. *Thorax* 1973;**28**:588—91.
10. Mannino DM, Aguayo SM, Petty TL, Redd SC. Low lung function and incident lung cancer in the United States: data From the First National Health and Nutrition Examination Survey follow-up. *Arch Intern Med* 2003;**163**:1475—80.
11. Koshiol J, Rotunno M, Consonni D, et al. Chronic obstructive pulmonary disease and altered risk of lung cancer in a population-based case-control study. *PLoS One* 2009;**4**: e7380.
12. Purdue MP, Gold L, Jarvholm B, Alavanja MC, Ward MH, Vermeulen R. Impaired lung function and lung cancer incidence in a cohort of Swedish construction workers. *Thorax* 2007;**62**:51—6.
13. Peto R, Speizer FE, Cochrane AL, et al. The relevance in adults of air-flow obstruction, but not of mucus hypersecretion, to mortality from chronic lung disease. Results from 20 years of prospective observation. *Am Rev Respir Dis* 1983;**128**: 491—500.
14. Lange P, Nyboe J, Appleyard M, Jensen G, Schnohr P. Ventilatory function and chronic mucus hypersecretion as predictors of death from lung cancer. *Am Rev Respir Dis* 1990; **141**:613—7.
15. van Gestel YR, Hoeks SE, Sin DD, et al. COPD and cancer mortality: the influence of statins. *Thorax* 2009;**64**:963—7.
16. Tkac J, Man SF, Sin DD. Systemic consequences of COPD. *Ther Adv Respir Dis* 2007;**1**:47—59.
17. Fabbri LM, Luppi F, Beghe B, Rabe KF. Complex chronic comorbidities of COPD. *Eur Respir J* 2008;**31**:204—12.
18. Nakayama M, Satoh H, Sekizawa K. Risk of cancers in COPD patients. *Chest* 2003;**123**:1775—6.
19. Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000;**287**:2398—9.
20. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;**46**:263—8.
21. Christensen S, Thomsen RW, Torring ML, Riis A, Norgaard M, Sorensen HT. Impact of COPD on outcome among patients with complicated peptic ulcer. *Chest* 2008;**133**:1360—6.
22. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373—83.
23. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry—history, content, quality and use. *Dan Med Bull* 1997;**44**:535—9.
24. Sorensen HT, Mellemkjaer L, Skriver MV, et al. Fever of unknown origin and cancer: a population-based study. *Lancet Oncol* 2005;**6**:851—5.
25. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *IARC monographs on the evaluation of carcinogenic risks to humans. tobacco smoke and involuntary smoking*. Lyon, France: IARCPress AND the World Health Organization Marketing and Dissemination; 2004. Report No. 83.
26. Baan R, Straif K, Grosse Y, et al. Carcinogenicity of alcoholic beverages. *Lancet Oncol* 2007;**8**:292—3.
27. Nasca PC. Immunity and cancer risk. In: Nasca PC, Patides H, editors. *Fundamentals of cancer epidemiology*. Gaithersburg: Aspen Publishers; 2001. p. 255—73.
28. van de Schans SA, Janssen-Heijnen ML, Biesma B, et al. COPD in cancer patients: higher prevalence in the elderly, a different treatment strategy in case of primary tumours above the diaphragm, and a worse overall survival in the elderly patient. *Eur J Cancer* 2007;**43**:2194—202.
29. Young RP, Hopkins RJ, Hay BA, Epton MJ, Black PN, Gamble GD. Lung cancer gene associated with COPD: triple whammy or possible confounding effect? *Eur Respir J* 2008;**32**:1158—64.
30. Thomsen RW, Lange P, Hellquist B, et al. Validity and underrecording of diagnosis of COPD in the Danish National Patient Registry. *Respir Med* 2011;**3**:85—9.
31. Turner-Warwick M, Lebowitz M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis and lung cancer. *Thorax* 1980;**35**: 496—9.
32. Agusti A. Systemic effects of COPD: just the tip of the iceberg. *COPD* 2008;**5**:205—6.
33. Decramer M, Rennard S, Troosters T, et al. COPD as a lung disease with systemic consequences—clinical impact, mechanisms, and potential for early intervention. *COPD* 2008;**5**:235—56.
34. Lash T, Johansen MB, Christensen S, et al. Hospitalization rates and survival associated with COPD: a nationwide Danish cohort study. *Lung* 2011;**189**:27—35.