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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

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ABSTRACT

The purpose of this study was to document the influence of chronic obstructive pulmonary diseases (COPD) on stage at diagnosis, treatment strategy, and survival for unselected cancer patients (35 years and older) diagnosed between 1995 and 2004 in the Eindhoven Cancer Registry. Follow-up of all patients was complete up to January 1st, 2006.

Twelve percent of all cancer patients had COPD at the time of cancer diagnosis, being about 15% in elderly patients (65+) and up to 30% among lung cancer patients, middle-aged males and all females with oesophageal and laryngeal cancer, and middle-aged women with renal cancer. Stage at diagnoses was not significantly different between cancer patients with or without COPD, except for lung cancer patients who were diagnosed at an earlier stage. Nevertheless, non-small cell lung cancer (NSCLC) patients with COPD less frequently underwent surgery, and chemotherapy, and more often radiotherapy. In the presence of COPD, women with oesophageal cancer underwent surgery less often, and patients with laryngeal cancer received radiotherapy more often. The effect of COPD on the type of oncological treatment was not different for middle-aged (35–64 years) and elderly cancer patients. In a multivariate Cox-regression model, COPD was associated with a significantly worse survival, especially for elderly patients with colon, rectum, larynx, prostate or urinary bladder cancer.

In conclusion, not surprisingly, COPD is related with age and smoking-associated tumours. Therapy of cancer patients with COPD was different for head and neck tumours and primary tumours in the chest organs (above the diaphragm), for whom radiotherapy, as an alternative treatment option, was available. As COPD, especially at older age, is frequently associated with a worse prognosis, further prospective investigation of interactions seems warranted. Further, closer involvement of pulmonologists and COPD nurses in elderly cancer patients might be warranted.

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1. Introduction

With the ageing of the population, the number of people who suffer from more than one chronic disease is increasing. Recent analyses of Eindhoven Cancer Registry data on co-morbidity at the time of diagnosis of cancer showed that about 60% of all new cancer patients older than 65 years suffered from at least one other serious disease.[1] Chronic obstructive pulmonary diseases (COPD) appeared to be one of the most common (17%) conditions in these newly diagnosed cancer patients.[1] The national institute for public health and the environment (RIVM) calculated the prevalence of COPD for the general Dutch population (2.0%, range 1.0 to 3.1 depending on the registration system).[2] The estimated prevalence for persons older than 65 was 13% for men and 6.4% for women.[2] COPD was listed as the sixth leading cause of death in the world in 1990, and further increases in prevalence and mortality are expected in the coming decades.[3]

Since smoking is an important risk factor for both COPD and lung cancer, an increased prevalence of COPD can be expected among lung cancer patients. The presence of impaired lung function might also be an independent risk factor for development of lung cancer.[4,5] The impaired lung function could be an indicator of underlying conditions that increase the risk of lung cancer, for example through inflammation.[6,7] Furthermore, decreased lung function results in reduced effective lung clearance mechanisms[8] which enlarges the exposure of carcinogens to the lung. The presence of COPD might also be related to stage at cancer diagnosis. In addition to the relationship with cancer development and detection, presence of COPD might lead to less agressive cancer treatment and should affect the life expectancy of cancer patients.

Since both elderly cancer patients and patients with relevant comorbidity are usually excluded from clinical trials, little is known about patient care and survival of those with both COPD and cancer. In this population-based study we investigated the prevalence of COPD among newly diagnosed cancer patients. Furthermore, we assessed whether such patients had a different stage at diagnosis, were treated differently, and to what extent they had a different outcome compared to newly diagnosed cancer patients without COPD.

2. Methods

2.1. Study population and data collection

The Eindhoven Cancer Registry records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.3 million inhabitants, ten general hospitals and two large radiotherapy institutes.[9] Trained registration clerks actively collect data on diagnosis, topography, histology, stage (TNM) and detailed information about initial treatment (delivered within 6 months from diagnosis) from hospital medical records. The medical record is generally regarded as the most complete source of information on the patient's past and current health status.[10]

Since 1993 the Eindhoven Cancer Registry registers the presence of serious comorbidity with prognostic impact at the time of cancer diagnosis. A slightly modified version of the widely used Charlson comorbidity index[11] is used for recording comorbidity.[1] COPD was registered as a dichotomous variable (yes/no), according to the medical history of the patient, use of relevant drugs and diagnostic work-up. Since COPD is associated with a high prevalence of cardiovascular disease (CVD) we adjusted our analyses for CVD. CVD included myocardial infarction, cardiac insufficiency, angina pectoris, coronary artery bypass graft, peripheral arterial disease and cerebrovascular diseases.

We included all cancer patients (35 years and older), newly diagnosed between 1995 and 2004. We analysed gender-specific prevalence of COPD and its association with age, stage, treatment and prognosis for each of the following tumours: oesophagus, stomach, colon, rectum, larynx, lung, breast, corpus uteri, cervix, ovary, prostate, kidney, urinary bladder and non-Hodgkin's lymphoma (NHL). These tumours were selected because of the high prevalence or because of a possible correlation with smoking.

Pathological tumour stage was classified in four categories based on the pathological/post-operative TNM classification. Clinical TNM was used when pathological TNM classification was not available. Oncological treatment was defined as surgery, radiotherapy, chemotherapy and/or hormonal therapy (including adjuvant therapy) for primary disease. Surgery did not comprise diagnostic operations. Postal codes of residential area were used to establish the socio economic status (SES) of diagnosed cancer patients. At the six-position level of postal code, data on household income and economical value of the house are available from fiscal data.[12] This information was transformed into four categories: low, medium and high socio economic status, and patients who lived in a home (such as a retirement home).

Follow-up of vital status of all patients was complete up to January 1st, 2006. In addition to passive follow-up via the hospitals, this information was actively obtained from the municipal personal records database (GBA).

2.2. Statistical analysis

The prevalence of COPD for each tumour type was calculated separately for men and women and for patients younger and older than 65 years. To compare treatment between cancer patients with and without COPD we used regression analysis. For each tumour type, models were fitted with 'receiving therapy' (either surgery, radiotherapy, chemotherapy or hormonal therapy when appropriate) as dependent variable, and age, gender, tumour stage, socio-economic status, having CVD and/or COPD as independent variables. We used the *clinical* TNM stage when surgery was the dependent variable, because surgical decisions are based on this tumour stage. For the other models the *pathological* tumour stage was used. Treatment and survival could be different per tumour stage. Therefore, interaction was investigated between COPD and other dependent variables (especially stage), and the results were stratified per variable outcome when interaction was found.

Survival time was defined as the time from diagnosis to death or January 1st, 2006, for the patients who were still alive. The independent prognostic effect of COPD versus no COPD stratified by age (middle-aged (36–64) and elderly (65+)) was estimated using Cox regression models. The

proportional hazard assumption of COPD was evaluated by applying Kaplan–Meier curves. The effect of COPD over time satisfied the assumption of proportionality since the graphs of the log(-log(survival)) versus log of survival time resulted in graphs with parallel lines. The hazard rates for death (model A, unadjusted) were adjusted for age, gender, socio economic status and pathological stage (model B) and also for treatment (model C). Correction was made for variables which influence survival, and are distributed differently between patients with and without COPD. In addition, we adjusted for CVD excess mortality (model D) in order to analyse whether the prognostic effect of COPD could be explained by death due to CVD. Hazard ratios with 95% confidence intervals were calculated.

The SAS computer package (version 8.2) was used for all statistical analyses (SAS Institute Inc., Cary, North Carolina, USA, 1999).

3. Results

3.1. *Prevalence of COPD among cancer patients*

During the period 1995 to 2004, 8651 (12%) of the newly diagnosed cancer patients aged 35 years and older also had COPD, and 64,604 did not (88%). The prevalence of COPD was higher at older (65+) than at middle-age (35–65 years) (15% versus 7.4%), and higher among males as compared to females (15% versus 7.6%). A relatively higher prevalence of COPD was found among patients with lung cancer, middle-aged male and all female patients with oesophageal cancer, female patients with laryngeal cancer, and middle-aged women with renal cancer (Table 1). The prevalence of COPD was significantly higher for squamous cell lung carcinoma (29%) compared to adenocarinoma (22%) and small cell lung cancer (24%) ($p < 0.0001$). Stage at diagnosis was not significantly different between cancer patients with or without COPD, except for lung cancer patients: those with COPD were diagnosed at an earlier stage of cancer compared to those without COPD (stage I: 31% versus 19%, stage II: 7% both, stage III: 37% versus 39% and stage IV: 25% versus 35%). This was comparable in the middle-aged and elderly patients. The proportion of cancer patients with COPD who also suffered from CVD was higher compared to those without COPD, especially among elderly patients (middle-aged: range 9–31%, and 4–22%, respectively. Elderly: 28–52% and 21–39%, respectively). A low socioeconomic status (SES) was more frequent among those with COPD (38%) compared to those without COPD (27% $p < 0.0001$). Elderly patients also had a more deprived SES (33%), compared to the middle-aged patients (22%).

3.2. *Influence of COPD on primary treatment of cancer*

In univariate and multivariate analyses COPD did not affect choice of treatment for cancer of the stomach, cervix, corpus uteri, ovary, kidney, urinary bladder, SCLC or NHL (Table 2). After adjustment for age, gender, tumour stage, socioeconomic status and CVD, the effect of COPD on primary treatment strategy disappeared for colon, rectal, breast and prostate cancer patients. Non-small cell lung cancer (NSCLC) patients with COPD received radiotherapy more often, but underwent surgery and chemotherapy less frequently. Women with oesophageal cancer underwent surgery less often when COPD was present, which was only visible after adjustment for other prognostic factors. Patients with laryngeal

Table 1 – Prevalence of COPD (%) in cancer patients in the Eindhoven Cancer Registry, diagnosed in the period 1995–2004

	Men		Women	
	35–64 years (*N* = 10859) % (*N*)	65+ years (*N* = 18749) % (*N*)	35–64 years (*N* = 12960) % (*N*)	65+ years (*N* = 13795) % (*N*)
All cancers	9.5 (1113)	19 (3806)	6.0 (901)	9.2 (1350)
Oesophagus	12 (46)	18 (84)	15 (18)	12 (26)
SCC	14 (22)	18 (30)	15 (12)	12 (11)
AC	11 (24)	17 (47)	17 (6)	11 (11)
Stomach	7.1 (39)	16 (165)	6.0 (15)	9.0 (57)
Colon	5.7 (61)	16 (359)	5.8 (56)	8.7 (202)
Rectum	6.0 (58)	16 (223)	5.2 (30)	8.6 (86)
Larynx	8.6 (28)	20 (78)	14 (11)	19 (11)
Lung	19 (573)	30 (1534)	19 (284)	25 (288)
NSCLC	20 (473)	30 (1291)	20 (230)	25 (203)
SCC	23 (235)	32 (714)	27 (76)	30 (86)
AC	17 (109)	28 (256)	19 (84)	17 (47)
SCLC	18 (98)	29 (248)	16 (52)	28 (85)
Breast	–	–	4.1 (304)	7.6 (352)
Cervix	–	–	4.3 (16)	5.8 (10)
Corpus uteri	–	–	3.3 (27)	6.2 (52)
Ovary	–	–	4.6 (34)	7.4 (48)
Prostate	6.3 (117)	13 (751)	–	–
Kidney	5.0 (22)	13 (57)	9.0 (23)	6.7 (21)
Urinary bladder	7.3 (21)	19 (145)	7.1 (7)	8.9 (22)
Non-Hodgkin lymphoma	6.0 (36)	14 (84)	3.0 (13)	7.1 (39)

SCC = Squamous cell carcinoma, AC = Adenocarcinoma, NSCLC = Non-small cell lung cancer, SCLC = Small cell lung cancer.

Table 2 – The relative risk of receiving primary treatment in the presence of COPD in the period 1995–2004

Tumour		Surgery RR (95% CI)	Radiotherapy RR (95% CI)	Chemotherapy RR (95% CI)	Hormonal therapy RR (95% CI)
Oesophagus Men	U	0.8 (0.6–1.2)	0.9 (0.7–1.1)		
	A	1.4 (0.9–2.2)	0.8 (0.6–1.1)		
Oesophagus Women	U	0.7 (0.4–1.3)	1.4 (1.0–1.8)		
	A	0.3 (0.1–0.9)*	1.4 (0.9–2.1)		
Stomach	U	1.0 (0.8-1.1)			
	A	0.9 (0.6–1.3)			
Colon	U	1.0 (1.0–1.0)		0.7 (0.6–0.9)*	
	A	1.0 (1.0–1.1)		1.0 (0.9–1.2)	
Rectum	U	1.0 (0.9–1.0)	0.9 (0.9–1.1)	0.6 (0.5–0.8)*	
	A	1.0 (0.8–1.1)	1.0 (0.9–1.1)	1.0 (0.7–1.2)	
Larynx	U	1.2 (0.8–1.8)	1.2(1.1–1.3)*		
	A	1.1 (0.7–1.6)	1.2 (1.1–1.3)*		
NSCLC Localised	U	0.8 (0.7–0.8)*	1.8 (1.5–2.0)*		
	A	0.8 (0.7–0.9)*	1.6 (1.4–1.9)*		
NSCLC Non-local	U		1.2 (0.1–1.3)	0.7 (0.6–0.8)*	
	A		1.2 (1.1–1.3)*	0.8 (0.7–0.9)*	
SCLC	U		0.9 (0.7–1.0)	1.0 (0.9–1.1)	
	A		0.9 (0.7–1.0)	1.1 (1.0–1.1)	
Breast	U	1.0 (1.0–1.0)	0.9 (0.8–0.9)*	0.7 (0.6–0.9)*	1.1 (1.0–1.3)
	A	1.0 (1.0–1.0)	0.9 (0.9–1.0)	1.0 (0.9–1.1)	1.0 (1.0–1.1)
Cervix	U	1.1 (0.8–1.4)	1.3 (0.9–1.7)		
	A	1.2 (1.0–1.5)	1.3 (1.0–1.8)		
Corpus uteri	U	1.0 (1.0–1.1)	1.0 (0.8–1.4)		
	A	1.0 (0.9–1.2)	1.0 (0.7–1.4)		
Ovary	U	0.9 (0.8–1.1)		1.0 (0.8–1.2)	
	A	1.1 (1.0–1.2)		1.0 (0.9–1.2)	
Prostate	U	0.5 (0.4–0.6)*	0.9 (0.8–1.0)		1.1 (1.0–1.2)
	A	0.8 (0.6–1.0)	1.0 (1.0–1.1)		1.0 (1.0–1.1)
Kidney	U	0.9 (0.8–1.0)			
	A	1.1 (1.0–1.1)			
Urinary bladder	U	0.8 (0.6–1.1)	1.0 (0.9–1.2)		
	A	1.0 (0.8–1.3)	1.0 (0.8–1.2)		
Non-Hodgkin lymphoma	U		1.1 (0.8–1.4)	1.1 (0.9–1.2)	
	A		1.1 (0.9–1.4)	1.0 (0.9–1.2)	

NSCLC = Non-small cell lung cancer, SCLC = Small cell lung cancer, RR = Relative risk, 95% CI = 95% Confidence interval.
Per tumour, the upper relative risk (RR) shows the unadjusted analysis (U) between having COPD and the chance of receiving the treatment, whereas the lower RR is adjusted (A) for the effect of gender, age, tumour stage (based on clinical TNM stage for surgery and based on post-operative TNM stage for the other treatments), socio economic status and the prevalence of cardiovascular disease.
* Significant at 0.05 level.

cancer and COPD received radiotherapy more often compared to those without COPD. Stratified analyses of middle-aged and elderly cancer patients showed that the effect of COPD on the type of oncological treatment was not different in both groups (Tables not shown).

3.3. *Influence of COPD on survival of cancer patients*

Unadjusted analyses showed that the overall mortality for middle-aged cancer patients with COPD compared to those without COPD was significantly higher for oesophagus, breast, prostate and urinary bladder and lower for lung cancer (Table 3a, model A). For elderly patients the overall mortality for those with COPD was significantly higher for colon, rectum, larynx, breast, cervix, prostate and kidney cancer (Table 3b, model A). The effect of COPD on survival disappeared after adjustment for age, gender, SES and pathological stage (model B) for oesophagus and lung cancer in middle-aged patients and for cervix and kidney cancer in the elderly. A decreased survival of elderly endometrial and urinary bladder cancer patients with COPD compared to patients without COPD was only visible after adjustment in model B. The hazard ratios (HR) for the effect of COPD did not change after additional adjustment for treatment (model C), except for endometrial cancer. Cardiovascular disease only affected the HR for the effect of COPD (model D) in elderly breast cancer patients. Fig. 1A–F show crude life table survival curves for tumours who showed a significant effect of COPD on survival in multivariate analyses, stratified according to age and COPD.

4. Discussion

4.1. *Prevalence of COPD among cancer patients*

This population-based study revealed that the prevalence of COPD among cancer patients over age 35 was 12% and that the prevalence of COPD was higher among men than women and patients over 65 years. The Dutch national institute for

Table 3a – Hazard ratio of dying for patients (age 35–64 years) with cancer and COPD compared to those without COPD, according to tumour site

Tumour	Model A HR (95% CI)	Model B Adjusted HR (95% CI)	Model C Adjusted HR (95% CI)	Model D Adjusted HR (95% CI)
Oesophagus	1.4 (1.1–1.9)*	1.2 (0.9–1.7)	1.2 (0.8–1.6)	1.2 (0.8–1.6)
SCC	1.4 (1.0–2.1)	1.3 (0.8–2.0)	1.3 (0.8–2.0)	1.3 (0.8–2.0)
AC	1.4 (0.9–2.1)	1.2 (0.7–1.9)	1.1 (0.7–1.8)	1.1 (0.7–1.8)
Stomach	1.2 (0.9–1.6)	1.3 (0.9–1.7)	1.1 (0.8–1.5)	1.1 (0.8–1.5)
Colon	1.0 (0.8–1.4)	1.1 (0.8–1.4)	1.1 (0.8–1.5)	1.1 (0.9–1.5)
Rectum	1.1 (0.8–1.5)	1.1 (0.7–1.5)	1.1 (0.8–1.6)	1.1 (0.8–1.6)
Larynx	1.7 (1.0–2.7)	1.4 (0.8–2.4)	1.4 (0.8–2.4)	1.4 (0.8–2.5)
Lung	0.9 (0.8–0.9)*	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.0 (0.9–1.1)
NSCLC	0.8 (0.8–0.9)*	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.0 (0.9–1.1)
SCLC	1.0 (0.8–1.2)	1.1 (0.9–1.4)	1.2 (0.9–1.4)	1.2 (0.9–1.4)
Breast	1.6 (1.2–2.0)*	1.6 (1.2–2.0)*	1.6 (1.2–2.0)*	1.6 (1.2–2.0)*
Cervix	1.0 (0.4–2.4)	0.5 (0.2–1.4)	0.5 (0.2–1.7)	0.6 (0.2–1.7)
Corpus uteri	1.0 (0.4–2.6)	1.3 (0.5–3.5)	1.5 (0.5–4.1)	1.5 (0.5–4.0)
Ovary	1.1 (0.7–1.8)	0.8 (0.5–1.4)	0.9 (0.5–1.5)	0.9 (0.5–1.5)
Prostate	1.5 (1.1–2.2)*	1.8 (1.2–2.6)*	1.8 (1.2–2.6)*	1.7 (1.2–2.5)*
Kidney	1.3 (0.9–1.8)	1.4 (0.9–2.1)	1.6 (1.0–2.4)	1.5 (1.0–2.3)
Urinary bladder	1.8 (1.1–2.8)*	1.9 (1.2–3.1)*	2.0 (1.2–3.1)*	1.9 (1.2–3.0)
Non-Hodgkin lymphoma	1.1 (0.7–1.7)	1.0 (0.6–1.7)	1.0 (0.6–1.7)	0.9 (0.6–1.6)*

SCC = Squamous-cell carcinoma, AC=Adenoma carcinoma, NSCLC = Non-small cell lung cancer, SCLC = Small cell lung cancer, HR = Hazard ratio, 95% CI = 95% Confidence interval.
Model A: unadjusted hazard ratio.
Model B: adjusted for gender, socio economic status (SES) and stage.
Model C: adjusted for gender, SES, stage and treatment.
Model D: adjusted for gender, SES, stage, treatment and cardiovascular disease.
* Significant at 0.05 level.

Table 3b – Hazard ratio of dying for patients (age 65 years and older) with cancer and COPD compared to those without COPD, according to tumour site

Tumour	Model A HR (95% CI)	Model B Adjusted HR (95% CI)	Model C Adjusted HR (95% CI)	Model D Adjusted HR (95% CI)
Oesophagus	1.0 (0.8–1.2)	1.0 (0.7–1.3)	0.9 (0.7–1.2)	0.9 (0.7–1.2)
SCC	1.0 (0.7–1.4)	1.1 (0.7–1.7)	1.1 (0.7–1.7)	1.1 (0.7–1.7)
AC	0.9 (0.7–1.3)	0.9 (0.5–1.4)	0.9 (0.5–1.4)	0.8 (0.5–1.4)
Stomach	1.1 (0.9–1.2)	1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.1 (0.9–1.3)
Colon	1.3 (1.2–1.4)*	1.4 (1.3–1.6)*	1.5 (1.3–1.6)*	1.4 (1.3–1.6)*
Rectum	1.4 (1.2–1.6)*	1.3 (1.1–1.6)*	1.4 (1.2–1.6)*	1.4 (1.2–1.6)*
Larynx	2.0 (1.5–2.7)*	1.8 (1.4–2.5)*	2.0 (1.5–2.8)*	2.1 (1.5–2.9)*
Lung	0.9 (0.9–1.0)	1.1 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)
NSCLC	0.9 (0.9–1.0)	1.0 (1.0–1.1)	1.0 (0.9–1.1)	1.0 (0.9–1.1)
SCLC	1.1 (0.9–1.2)	1.0 (0.9–1.2)	1.1 (1.0–1.3)	1.1 (1.0–1.3)
Breast	1.4 (1.2–1.6)*	1.4 (1.2–1.6)*	1.3 (1.1–1.6)*	1.2 (1.0–1.5)
Cervix	2.5 (1.3–4.9)*	1.8 (0.9–3.7)	2.1 (1.0–4.5)	2.1 (1.0–4.5)
Corpus uteri	1.5 (1.0–2.1)	1.6 (1.1–2.3)*	1.5 (1.0–2.6)	1.5 (1.0–2.3)
Ovary	1.2 (0.9–1.6)	1.3 (0.9–1.8)	1.2 (0.9–1.8)	1.2 (0.9–1.7)
Prostate	1.5 (1.3–1.7)*	1.4 (1.2–1.5)*	1.4 (1.2–1.5)*	1.4 (1.2–1.5)*
Kidney	1.3 (1.1–1.7)*	0.9 (0.7–1.3)	1.1 (0.7–1.3)	0.9 (0.7–1.3)
Urinary bladder	1.2 (1.0–1.5)	1.3 (1.1–1.6)*	1.4 (1.1–1.7)*	1.4 (1.1–1.6)*
Non-Hodgkin lymphoma	1.1 (0.9–1.4)	1.1 (0.8–1.4)	1.1 (0.9–1.4)	1.1 (0.8–1.4)

SCC = Squamous-cell carcinoma, AC = Adenoma carcinoma, NSCLC = Non-small cell lung cancer, SCLC = Small cell lung cancer, HR = Hazard ratio, 95% CI = 95% Confidence interval.
Model A: unadjusted hazard ratio.
Model B: adjusted for gender, socio economic status (SES) and stage.
Model C: adjusted for gender, SES, stage and treatment.
Model D: adjusted for gender, SES, stage, treatment and cardiovascular disease.
* Significant at 0.05 level.

public health and the environment (RIVM) calculated the prevalence of COPD for the general Dutch population (2.0%, range 1.0 to 3.1 depending on the registration system).[2] The prevalence of COPD for the Dutch population was also higher among men than women and increased with age (men age 35–64: 2.0%, women age 35–64: 1.7%, men age 65+: 13% and

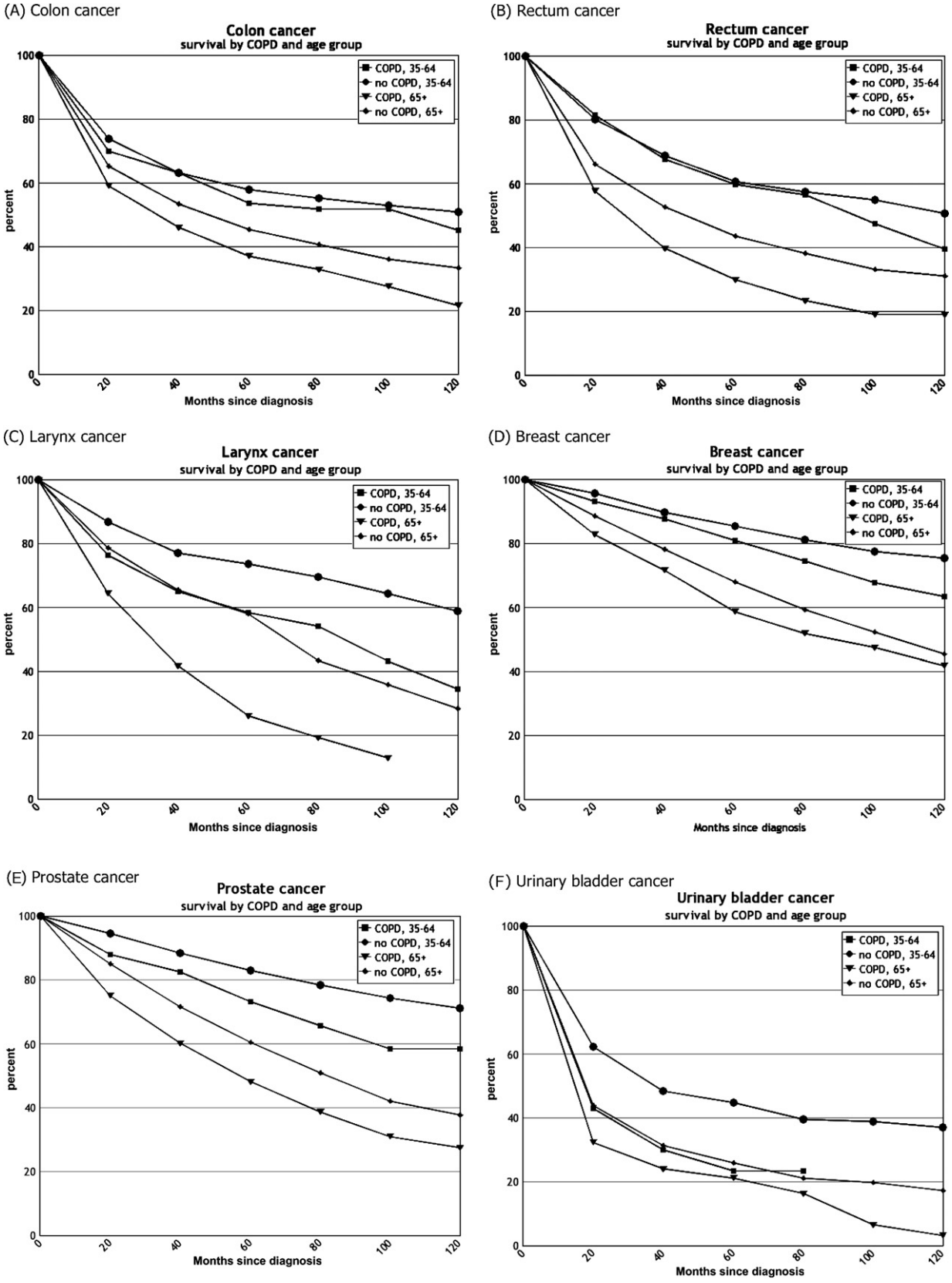

Fig. 1 – Crude survival rates stratified according to age group and COPD.

women age 65+: 6.4%).[2] Mannino[13] showed that the prevalence of COPD in the general American population ranged between 2.9 and 14.3%, depending on the definition and method of estimation. The European Respiratory Society's (ERS) definition of COPD and the Global initiative for chronic Obstructive Lung Disease's (GOLD) definition of COPD were

responsible for high prevalence scores in the Third National Health and Nutrition Examination Survey (NAHES III) data (14.3% and 13.9% of the adult population) while the American Thoracic Society's (ATS) definition of COPD resulted in low prevalence scores (2.9% of the adult population).[13] In our study the prevalence of COPD was based on COPD diagnosis recorded in medical records. The definition used is thus unknown and might differ between patients and medical specialists. Subsequently, it is shown that almost two-thirds of all people who have impaired lung function (according to lung function tests) have not been diagnosed with COPD by their physician.[2,14–16] Therefore, the real prevalence of impaired lung function is underestimated in our study population, but we probably discovered the more severe cases of COPD.

In our study, a relatively higher prevalence of COPD was found among patients with lung cancer, middle-aged male and all female patients with oesophageal cancer, female patients with laryngeal cancer, and middle-aged women with renal cancer. Smoking is a predominant risk factor for both COPD and lung cancer, and also, to a lesser extent, for oesophageal, laryngeal and renal cancer.[17,18] Therefore, it is difficult to demonstrate an independent effect of COPD on cancer risk. Tumours associated with smoking are also associated with COPD; when confounding by smoking is an important factor. Analyses stratified according to lung cancer histology can offer insight into the relationship between COPD and lung cancer, given the well-established finding that smoking is a stronger risk factor for squamous cell and small cell carcinoma than for adenocarcinoma of the lung.[18,19] Purdue and colleagues[5] reported that COPD followed a similar pattern. In our study, we found that the prevalence of COPD was higher for squamous cell carcinoma compared to adenocarinoma, but equal in adenocarcinoma and small cell carcinoma.

4.2. *Association of COPD with stage at cancer diagnosis*

COPD had no influence on stage at diagnosis of most tumour types, except for lung cancer. When COPD was present the latter tumours were detected at an earlier stage. Patients with COPD are regularly checked which could lead to earlier detection of lung cancer signs. It is also possible that COPD patients undergo fewer staging procedures, because of their worse functional status. This leads to clinical staging instead of pathological staging and more patients with an unknown stage. This was demonstrated in a study[20] of elderly breast cancer patients with or without co-morbidity. Cancer patients with an early stage of disease and thus candidates for surgery usually undergo a number of preoperative diagnostic tests. It is also possible that in this way COPD is more often detected, and thus leads to more COPD in patients with a resectable cancer. We found no evidence in this study that COPD masked cancer symptoms and led to a more advanced stage at cancer diagnosis.

4.3. *Influence of COPD on primary treatment of cancer*

The oncological treatment of most tumour types did not seem to be affected by COPD, except for lung, laryngeal and oesophageal cancer (all tumours located above the diaphragm). In the latter tumour types, surgery was performed less often and potential chemotherapy administered less frequently. As an alternative (second best) therapy, radiotherapy was more often given. For example, patients with NSCLC and COPD underwent surgery and chemotherapy less often than those without COPD. The increased chance of receiving radiotherapy is likely a consequence from not being considered suitable for chemotherapy or high risk surgery. Earlier studies showed that the chance of receiving treatment for lung cancer was associated with the smoking history.[21] This could also be a factor in the treatment differences between cancers patients with and without COPD. Age was not an important factor in the effect of COPD on the type of oncological treatment.

4.4. *Influence of COPD on survival of cancer patients*

We found COPD to be associated with reduced survival in breast, prostate, and urinary bladder cancer in middle-aged patients, and in colon, rectum, larynx, prostate and urinary bladder cancer in elderly patients. This was observed after adjustment for age, gender, SES, stage, and even primary treatment and CVD. A logical explanation for the lower survival of COPD patients would be that those patients received a different treatment because of their reduced performance status. However, our earlier analyses showed that most tumours did not have an altered treatment when COPD was present. Furthermore, the risks of death were adjusted for treatment in models C and D, implying that deviation from standard treatment could not fully explain the prognostic effects of COPD.

Another explanation for the decreased survival in cancer patients with COPD might be that cancer treatment in the presence of COPD causes extra treatment complications and therefore decreases survival chances. Furthermore, it is not known to what extent cancer treatment might affect the severity of COPD and cause excess mortality of COPD.

COPD affected treatment in patients with oesophageal or lung cancer but not prognosis (which is of course poor for these patients), implying that many patients die from the cancer before they become at risk of dying from the COPD. In another study the presence of co-morbidity did not have any impact on lung cancer survival.[19] However, retrospective analysis demonstrated that preoperative FEV1 below a threshold of 60% carried a two to threefold increased risk for surgical mortality and respiratory complications after resection for lung cancer.[22] Also, in earlier studies, co-morbidity was shown to be an important prognostic factor for (lung) cancer patients.[23,24] Although the number of concomitant conditions and the Charlson index were significant predictors of lung cancer survival, it only explained 2.5% and 2.0% of the survival variation, respectively.[24] The differences between the previous studies on the effect of COPD on lung cancer survival could be explained by different underlying risks of smoking and different classification systems for other co-morbidities in these studies.[19,21,22,24,25] We adjusted for the presence of CVD but could not adjust our data for smoking and postoperative complications, since the latter were not recorded routinely in the Eindhoven Cancer Registry.

The other tumour for which treatment was affected by COPD was laryngeal cancer. These patients received radiotherapy more often when COPD was present, and survival was also worse in elderly with COPD, both before and after adjust-

ment for treatment. There are several reasons for that; as all laryngeal cancer patients are or were smokers, either sticking with the smoking habit or being depressed after smoking cessation offer some explanations, besides a wider indication to radiotherapy for the glottic tumours. A retrospective cohort study in the United Kingdom showed moderate and severe co-morbidity to have a greater and statistically significant impact on survival of laryngeal cancer than the TNM stage.[29]

In an American study a substantial proportion of deaths of colorectal cancer patients could be attributed to comorbidity, and COPD was second in the list of attributable deaths.[26] This is in line with our study demonstrating that elderly colorectal cancer patients with COPD had a lower chance of survival than those without COPD. A previous study among colorectal cancer patients showed that comorbidity increased the complexity of cancer management and therefore affected duration of survival.[27] Development of complications among colorectal cancer patients undergoing surgery (high-risk and often inevitable) was especially predicted by presence of COPD and deep vein thrombosis.[28]

In previous studies breast cancer mortality was reported to be related to age, stage and several co-morbidities (renal failure, liver disease, stroke/transient ischemic attack, asthma, diabetes, a previous malignant tumour, smoking and COPD).[20,23,30] The relationship between COPD and breast cancer survival can probably be explained by the fact that smoking is also associated with breast cancer mortality. Possible explanations[31] are that smoking influences the immune system or the development of the tumour or that smoking is associated with lower SES and higher fat intake in Sweden. Since surgery for breast cancer is low-specific risk surgery, the risk of developing any postoperative complication was not significantly related to COPD.[32]

In our study, COPD was an important independent predictor of death among patients with prostate cancer. In other studies, it has also been observed that these patients have an increased chance of dying *with* prostate cancer rather than dying *from* prostate cancer.[33,34,36]

In the literature we could not find a confirmation or explanation for the higher mortality for urinary bladder cancer patients with COPD, compared to those without COPD. Urinary bladder cancer mortality is, like breast cancer mortality, associated with smoking.[31,35] This could interfere with the survival of urinary bladder in patients with COPD, as shown for breast cancer.

Although the presence of COPD was assessed from medical records, which is more clinically precise than self-reported or administrative databases, no information was available about the severity and duration of COPD, exacerbation or outcome of COPD in relation to primary therapy, physical functioning of the patient and co-morbidity developing after the cancer diagnosis. If we missed COPD cases, they are likely to be less severe. The strength of this large population-based study is that cancer and its treatment are registered in a quality-controlled cancer registry system. Furthermore, the sample size was sufficient to explore the confounding effects of age, CVD and several other prognostic factors on survival. In addition, we have shown the influence of COPD on treatment of cancer and outcome. However, choice of cancer treatment may also be related to exacerbation or outcome of COPD. Unfortunately, we had no information on exacerbation or outcome of COPD.

Given the high prevalence of cancer among the elderly, who often also have other health problems, research on the necessity to adapt oncological standard treatment is warranted. Both COPD and cancer prevalences are expected to increase in the future (especially in women), because they are associated with smoking and ageing of the population. Therefore, the number of patients with both diseases will also increase.

In conclusion, we found that COPD more frequently occurred in elderly cancer patients (in about 15%) and treatment modifications were manifest in case of a head/neck, lung and oesophageal cancer for which radiotherapy as alternative treatment option was available. Several tumour types showed a decreased survival when COPD was present, especially in the elderly. Since COPD often occurs in combination with other (smoking-related) co-morbidity and (combinations of) treatment depends on tumour stage, further in depth studies are necessary to explore our findings. With this information, specific subgroups might be selected for prospective studies on treatment and treatment outcome. Therefore, co-morbidity should be registered prospectively with uniform definitions of COPD or objective figures, like FEV1 values. Besides further investigation of determinants of critical clinical situations to evaluate these findings, closer involvement of pulmonologists and COPD nurses in elderly cancer patients is warranted.

Conflict of interest statement

None declared.

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