



Smoking, alcohol, and nutritional status in relation to one-year mortality in Danish stage I lung cancer patients

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ABSTRACT

Introduction: In addition to the highest incidence rate of lung cancer among the Nordic countries, Denmark has the highest mortality rate. Moreover, rates of tobacco and alcohol consumption are among the highest in these countries.

Method: In a population-based matched case/control study, we aimed to assess the association between one-year all-cause mortality and a number of smoking-related parameters, high-risk alcohol intake, and nutritional status in clinical stage I lung cancer patients.

Results: We included 221 patients who died within one year after diagnosis (early death) and 410 matched controls who survived more than one year (survivor). The odds ratio (OR) for early death among never-smokers was 0.3 (CI 95%: 0.1–0.9). There was no significant difference between patients who died early and survivors in proportions of current smokers (49 vs. 45%), number of cumulated pack-years (45 vs. 46), daily tobacco consumption (15 vs. 14 cigarettes/day), patients who quit smoking after diagnosis (25 vs. 40%) and the prevalence of chronic obstructive pulmonary disease (COPD) (43 vs. 38%). Patients that died early received more medications for COPD ($p = 0.03$) and smoked more after diagnosis, 14 vs. 10 cigarettes per day ($p = 0.03$). The unadjusted OR for high-risk alcohol intake was 2.2 (CI 95% 1.3–3.7) in the early death group vs. the survivors. However, in a treatment-stratified analysis this was observed only for surgically treated patients (OR, 3.2; CI 95% 1.7–6.1). Low nutritional status was associated with early death, unadjusted (OR 2.3; CI 95% 1.4–3.7), while OR was 1.8 (95% CI 1.0–2.3) adjusted for high-risk alcohol intake and COPD. Treatment selection according to and interventions against these factors before and after lung cancer diagnosis may improve outcomes.

1. Introduction

Primarily due to tobacco smoking and excessive alcohol consumption, Denmark ranks as the unhealthiest among the Nordic countries [1] and the average lifespan is also the lowest (2015) [2]. Furthermore, Denmark has the highest incidence of lung cancer. There is a growing body of evidence indicating that continued smoking after the diagnosis of lung cancer is related to an adverse outcome and that Danish lung cancer patients also have the highest mortality rate (2015) [3–7]. Since 2006, evidence supporting the effectiveness of the current smoking cessation therapy has been solidified [8–10]. However, in contrast to other Nordic countries, the Danish lung cancer guidelines place little emphasis on smoking cessation and have not included treatment

algorithms against tobacco smoking [11]. The Danish follow-up algorithm, with regular short-interval visits, allows for structured long-term interventions against risk factors, e.g. continued smoking, for recurrence and mortality. However, to our knowledge, no study has evaluated the extent of smoking cessation initiatives by physicians in relation to the treatment of or follow-up on lung cancer patients in a Danish setting.

Alcohol is a risk factor for several types of cancer, but appears to be only vaguely related to the development of lung cancer, and, in fact, both protective and oncogenic mechanisms from alcohol have been described [12–14]. How high alcohol intake affects the prognosis after lung cancer is not well established, even though a register-based study did find a negative association between alcohol abuse at diagnosis and

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one-year mortality in a surgical cohort [15], These findings need to be confirmed in a more recent data material.

Nutritional status is most likely not a risk factor per se for lung cancer [16]. As it is an indicator of a systemic inflammatory response to the tumor and increases the patient's susceptibility to treatment complications, low nutritional status is, however, considered an established risk factor for adverse outcome in lung cancer patients [17–19]. Since low nutritional status could also be related to severe comorbidity or alcohol abuse it may confound associations between these factors and lung cancer mortality.

In a Danish population-based setting, we sought to establish how these lifestyle factors and nutritional status were associated with short-term prognosis, as measured by all-cause one-year mortality in stage I lung cancer patients (TNM 7th edition) [20]. Moreover, we aimed to establish the extent of smoking cessation guidance and medical treatment against nicotine dependency provided during the follow-up program.

2. Materials and method

The study was designed as a population-based matched case/control study.

We identified patients registered in the Danish lung Cancer Registry (DLCR) with clinical stage I lung cancer, diagnosed between January 1, 2011 and December 31, 2014, who died from any cause within the first year after diagnosis (early death group) and for whom we had a treatment registration. These patients were then matched with similar patients according to stage (IA/IB), age, gender, same or previous year of diagnosis who survived more than one year (one-year survivors).

3. Study variables

3.1. Smoking status

According to the Danish guidelines, patients suspected of having lung cancer should have their full smoking history included in their medical record during the diagnostic work-up for lung cancer. We estimated the number of pack-years in cigarette equivalents. One pack-year was defined as 20 cigarette-equivalents per day for 365 days. For current smokers, the daily self-reported tobacco consumption was established (one cigarette = 1 g of tobacco, one cigar = 4 g, one pipe tobacco and cheroot = 3 g). Intervals were rounded to the lower whole number. Thus, a patient who had formerly smoked but had not smoked for at least six months was considered a former smoker. Those who had quit smoking within six months of the lung cancer diagnosis were registered as current smokers. For former smokers, the interval in years between smoking cessation and lung cancer diagnosis was established.

We also collected data on smoking habits after diagnosis. Data were collected in connection with the follow-up visits or from other hospital contacts until one year after treatment. Patients were divided into three categories. Nonsmoker, persistent smoker and quit after diagnosis. For persistent smokers, we assessed the difference in reported daily tobacco consumption before and after treatment (cigarette equivalents) by subtracting the post-treatment consumption from the pretreatment consumption.

3.2. Alcohol

In accordance with recommendations from the Danish Health Authority, we defined high-risk alcohol intake as above two and three units of alcohol/day on average for women and men respectively. Periodic alcohol abuse and a history of alcohol abuse were also considered as high-risk alcohol intake.

3.3. Nutritional status

As a part of the general assessment of the patient, nutritional status is typically registered in the medical record as either low (or poor), normal or above. If nutritional status was not mentioned and only the height and weight of the patient were available, the body mass index (BMI) was calculated and the nutritional status was registered as either low if BMI < 18.5, normal if BMI was 18.5–24.9 or as above if BMI > = 25. We did not register data on BMI.

3.4. Comorbidity and cause of death

We registered if a patient either had an existing diagnosis or had been diagnosed with chronic obstructive pulmonary disease (COPD) or cardiovascular disease (including cerebrovascular events and excluding arterial hypertension) in connection with the lung cancer diagnosis. We registered the types of daily medications for COPD (not including corticosteroids and/or antibiotics prescribed for an acute exacerbation or a complication in the diagnostic work-up (DWU)). In addition, we retrieved data on forced expiratory volume (liters) in one second (FEV1) from the DLCR.

Outcome in the present study was all-cause mortality. However, on the basis of the medical records, we also registered the primary cause of death. This was categorized as lung cancer, comorbidity, treatment complications, other (suicide, accidents, etc.), or unknown.

3.5. Statistical analysis

Categorical variables were compared by proportional and Pearson chi-squared distribution. The Mann-Whitney *U* test was used to assess differences in continuous variables between the two groups. Tests for associations of selected study variables between the two groups were performed using a conditional logistic regression model. Since age, gender, stage (Ia/Ib), and year were conditioned upon in the regression analyses, the analyses were unadjusted and unstratified unless otherwise stated. It is not mandatory to register normal findings in the medical records in Denmark. Thus, in the regression analysis, if there was no mention of either alcohol intake or nutritional status, these factors were categorized as low-risk alcohol intake and normal status, respectively.

Calculations were performed with SAS software (SAS system, SAS Institute, Cary, NC) and Stata software (StataCorp 4905 Lakeway Drive College Station, Texas 77,845 USA).

4. Results

We finally included 221 early death patients and 410 survivors. Baseline characteristics are given in [Table 1](#).

In the early death group, 31% died of lung cancer, 22% of comorbidity, 18% from treatment complications, and 5% from other causes while in 24% of the cases the cause of death was registered as unknown.

4.1. Lifestyle factors at diagnosis

There was a strong adverse association between never-smoked and death within one year (OR 0.3; CI 95%: 0.1–0.9), as compared to the survivor group. Aside from never-smoked, none of the smoking-related factors were associated with early death ([Table 2](#)).

There was a significant difference between early death and the survivor groups in the proportion of patients who had high-risk alcohol use prior to diagnosis (20 vs. 11%; *p* = 0.002) corresponding to an OR of 2.2 (CI 95% 1.4–3.5). When adjusted for nutritional status, smoking status, daily tobacco consumption, and cumulated pack-years the association was unchanged (adjusted OR of 2.2; CI 95% 1.3–3.7). When analyses were stratified by treatment type, the OR was 3.1 (95% CI,

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