Cancer risk in patients with chronic obstructive pulmonary disease

Cornelia Schneider¹
Susan S Jick²
Ulrich Bothner³
Christoph R Meier¹

¹Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department Pharmaceutical Sciences, University Basel, Basel, Switzerland; ²Boston Collaborative Drug Surveillance Program, Boston University Medical Center, Lexington, MA, USA; ³Nycomed AG, Konstanz, Germany

Purpose: The goal of this study was to compare the risk of developing cancer between patients with or without chronic obstructive pulmonary disease (COPD), and to assess the role of gender as well as the use of respiratory medication on the risk of developing lung cancer in COPD patients.

Patients and methods: We used the UK-based General Practice Research Database to conduct a follow-up study with a nested case-control analysis. We identified all patients with a first-time COPD diagnosis aged 40–79 years between 1995 and 2005 and a matched COPD-free comparison group. We then identified all patients who received an incident cancer diagnosis during follow-up.

Results: Among 35,772 COPD patients and 35,772 COPD-free patients, we identified 4506 patients with an incident cancer diagnosis, of whom 2585 (57.4%) had a previous COPD diagnosis, yielding a crude incidence rate ratio of 1.64 (95% CI 1.55–1.74). The increased risk was mainly driven by a high lung cancer risk among COPD patients, while other cancers not associated with smoking were not statistically significantly associated with an altered COPD risk. In the nested case-control analysis, the odds ratio (OR) for lung cancer associated with COPD was higher for women (OR 5.26, 95% CI 3.64–7.61) than for men (OR 2.10, 95% CI 1.70–2.60). In the nested case-control analysis, none of the respiratory drugs were associated with a substantially altered risk of developing lung cancer among COPD patients.

Conclusion: Our findings provide further evidence that COPD is associated with an elevated lung cancer risk, and that women with COPD may be more susceptible to developing lung cancer than men. Overall, respiratory medication did not have an influence on cancer risk.

Keywords: COPD, cancer, GPRD, gender

Introduction

According to the Global Initiative for Obstructive Lung Diseases (GOLD), chronic obstructive pulmonary disease (COPD) is associated with an abnormal inflammatory response of the lungs, which is accompanied by a not fully reversible airflow limitation. The pronounced chronic inflammatory process is thought to increase the risk for lung cancer due to constant tissue damage and exposure to substances with mutagenic potential such as reactive oxygen species. For other organ systems, similar associations between chronic inflammation and cancer have been discussed, such as chronic hepatitis and liver cancer. Asthma is another major obstructive lung disease with substantial inflammation; although studies on the association between asthma and lung cancer reported conflicting results, pooled estimates did not provide evidence for an association between asthma and an increased cancer risk.
Previous studies on the association between COPD and cancer risk mainly focused on lung cancer, suggesting that COPD increases the risk for lung cancer materially.16–10 COPD patients and lung cancer patients share an important risk factor, which is smoking. Men have been reported to have higher COPD rates than females, which may be attributed to higher smoking rates in males compared with females in the past, but smoking rates as well as COPD rates in females have been reported to rise.11 In addition, studies indicated that female smokers might be more susceptible to developing COPD than male smokers, as women with COPD tended to suffer from a greater reduction in forced expiratory volume in one second (FEV1).12

In vitro and in vivo studies have explored potential carcinogenic effects of respiratory drugs, but clinical and epidemiological data are scarce. Theophylline and rolipram— a more selective phosphodiesterase (PDE) inhibitor—are thought to mediate antiapoptotic effects by inhibition of the anti-apoptotic Bcl2 protein and by induction of the pro-apoptotic Bax protein in cultured H1299 non-small lung carcinoma cells (NSCLC) and in B-cells from chronic lymphocytic leukemia (CLL) patients.13,14 Positive effects were also seen in CLL patients receiving theophylline alone or in combination with chlorambucil.13,16 Systemic corticosteroid use, on the other hand, has been reported to increase the risk for skin cancer, but no such association was seen with inhaled steroids.17 In vivo studies, however, suggested anti-proliferative effects of glucocorticoids potentially inhibiting the growth of lung cancer.15–20 The authors of a recent study reported a reduced lung cancer risk in US veterans exposed to high doses of inhaled steroids.21 Another study that investigated the role of antiasthmatic drug use and cancer risk in asthma patients did not find an association between use of inhaled bronchodilators and lung cancer risk, and only a slight increase in risk associated with use of oral steroids.22

In this study we explored the association between COPD and the risk of developing cancer, and we investigated whether the lung cancer risk is associated with use of respiratory drugs among patients with COPD.

Methods

Data source

We used the UK-based General Practice Research Database (GPRD) to conduct a follow-up study with a nested case-control analysis. The GPRD has been described in detail elsewhere.23 It is a large primary care database established in 1987 that encompasses some five million patients who are enrolled with selected general practitioners (GPs) throughout the UK. The GPs, who contribute data to the GPRD, have been trained to record medical information in a standard manner and to supply it anonymously. The recorded information includes demographics, medical diagnoses, and virtually all drug prescriptions. The patients enrolled in the GPRD are representative of the UK population in respect of age, sex, and geographical distribution.22 The GPRD has been used before for studies of COPD and cancer.22

The GPRD is managed by the Medicines and Healthcare products Regulatory Agency (MHRA), and the study protocol was approved by the Independent Scientific Advisory Committee for MHRA database research (ISAC). The investigators only had access to anonymized information.

Study population

We identified in the GPRD all patients with a first-time diagnosis of COPD (based on medical Read or OXMIS codes) between January 1, 1995 and December 31, 2005 at age 40–79 years. We excluded patients with less than 3 years of active recording history prior to the date of the first COPD diagnosis. In addition, we identified at random from the GPRD one comparison subject without COPD for each COPD patient, matched 1:1 on age (same year of birth), sex, general practice, and calendar time (ie, the date of the first COPD diagnosis of the COPD patient). We applied the same exclusion criteria to the comparison group as to the COPD patients.

Follow-up analysis

We excluded all patients from the COPD and the COPD-free comparison group with a recorded history of cancer (excluding non-melanoma skin cancer), HIV, drug abuse, or alcoholism prior to the COPD diagnosis (or the corresponding date in the COPD-free group). We then followed all remaining patients from the start of follow-up (ie, the COPD diagnosis date or the corresponding date in the comparison group) and assessed the person-time for each patient until he or she developed an incident diagnosis of cancer, left the database, died, or reached the end of the study (December 31, 2005), whatever came first. We estimated incidence rates with 95% confidence intervals (CI) separately for COPD patients and COPD-free patients and stratified by age and gender.

Nested case-control analysis

We conducted a nested case-control analysis to further analyze the impact of COPD, respiratory drugs, and various potential confounders on the risk of developing cancer. For this purpose we identified for each case with an incident
cancer diagnosis four control patients selected at random from the study population (ie, patients with or without COPD who did not develop cancer during follow-up). These controls were matched to cases on age, sex, practice, and index date (ie, the date when the case had the incident cancer diagnosis). We compared the prevalence of COPD in patients with cancer and controls using conditional logistic regression analyses.

We provided the risk estimates stratified for different cancer sites and adjusted for patient characteristics such as body mass index (BMI <18.5, 18.5–25, 25–29.9, 30–60 kg/m², or unknown), smoking history (no, current, past, unknown), as well as for various cancer type specific confounders (breast cancer: contraceptive use, hormone replacement therapy use, benign neoplasms, non-melanoma skin cancer, and NSAID use; lymphoma: benign neoplasms, use of carcinogenic drugs; gastro-esophageal cancer: gastro-esophageal reflux disease, benign neoplasms, non-melanoma skin cancer; colorectal cancer: NSAID use, constipation, benign neoplasms, non-melanoma skin cancer; female reproductive system cancer: contraceptive use, hormone replacement therapy use, benign neoplasm, non-melanoma skin cancer, NSAID use; urinary system cancers: hypertension, benign neoplasms, use of diuretics, use of carcinogenic drugs, urinary dysfunction).

Drug exposure
To analyze the association between respiratory medication and lung cancer risk we stratified patients into ‘non-users’, ‘current users’, or ‘past users’. Current users were patients who received their last prescription within 180 days prior to the lung cancer diagnosis, and past users were all the patients who had prescriptions for the drugs of interest recorded >180 days prior to the lung cancer diagnosis. We further subdivided ‘current use’ into ‘current short-term use’ of less than a year (ie, patients have had their first drug prescription within a year prior to the diagnosis), of 1–3 years, or of >3 years. We also divided current and past users into ‘regular’ or ‘intermittent’ user; in order to be a ‘regular user’, patients had to have at least one prescription recorded every 100 days, and if a patient was a current user with less than one prescription every 100 days, the patient was an ‘intermittent user’.

Statistical analyses were performed with the statistical software SAS (release 9.1, SAS Institute, Inc, Cary, NC, USA).

Results
The study population consisted of 35,772 COPD patients and the same number of matched COPD-free patients, 51.3% of them being male.

Within the study population, we identified a total of 4506 cancer cases during follow-up, 2585 among the COPD patients and 1921 among the COPD-free patients. Sixty-one percent of all cancer cases were men (Table 1). The incidence rates (IRs) were 27.8/1000 person-years (py) among COPD-patients, and 16.8/1000 py among COPD-free patients (Table 2). IRs were higher among men than among women, but the incidence rate ratio (IRR) associated with COPD was slightly higher in females than in males. The cancer IR increased with age.

In the nested case-control analysis we explored the association between a history of COPD and the risk of developing various types of cancer, stratified by gender (Tables 3 and 4). The relative risk was highest for developing lung cancer, and it was particularly high in women; OR 5.26 (95% CI 3.64–7.61), compared with men: OR 2.10 (95% CI 1.70–2.60) (likelihood ratio test \( P < 0.001 \)). The crude risk of developing urinary/kidney cancer (in both men and women) was also increased, but after adjustment for potential confounders the ORs were no longer statistically significantly increased. The relative risk of developing one of the other cancer types was not or only marginally altered in association with a previous COPD diagnosis.

To further analyze the association between COPD and lung cancer we did an analysis stratified by smoking status. The presence of COPD increased the risk of being diagnosed with lung cancer in non-smokers (OR 4.21, 95% CI 2.65–6.69) (Table 5).

| Table 1 Characteristics of cancer cases and controls |
|---|---|---|---|---|
| Age | COPD | COPD-free | COPD | COPD-free |
| 40–49 | 26 | 19 | 89 | 94 |
| 50–59 | 217 | 139 | 706 | 788 |
| 60–69 | 743 | 496 | 2357 | 2612 |
| 70–79 | 1329 | 992 | 4343 | 4775 |
| 80+ | 270 | 275 | 727 | 899 |
| Men | 1526 | 1207 | 5008 | 5521 |
| Smoking status | Non-smoker | Current smoker | Ex-smoker | Unknown |
| 432 | 896 | 1915 | 4673 |
| 1049 | 355 | 2713 | 1350 |
| 926 | 490 | 3016 | 2144 |
| 178 | 180 | 578 | 1001 |
| BMI | 15–18.4 | 126 | 28 | 326 | 87 |
| 18.5–24.9 | 930 | 593 | 2750 | 2791 |
| 25.0–29.9 | 699 | 696 | 2399 | 3161 |
| 30.0–60.0 | 380 | 282 | 1332 | 1470 |
| Unknown | 450 | 322 | 1414 | 1660 |
| Asthma | 1266 | 242 | 4204 | 861 |
In a second sensitivity analysis on the association between COPD and lung cancer we assessed respiratory drug use in detail among COPD patients (Table 6). The exposure prevalence to these drugs was high; short-acting beta agonists were used by 70%–80%, short-acting anticholinergic drugs by 30%–40%, and inhaled corticosteroids by more than 50% of COPD patients. For most drugs the proportion of lung cancer cases and controls using respiratory drugs on a longer-term basis was similar, yielding relative risk estimates around one. There was a tendency towards increased relative cancer risks associated with short-term current use of most respiratory drugs, which can be explained by a worsening of COPD symptoms prior to the lung cancer diagnosis. This effect was particularly strong for short-term current oxygen users with an OR of 5.06 (95% CI 2.87–8.90), and there was also a suggestion of an increased lung cancer risk associated with current long-term theophylline use (adjusted OR 2.37, 95% CI 1.05–5.35).

**Discussion**

In this large population-based study, the overall cancer risk was increased in COPD patients as compared with COPD-free patients. This increased risk was mainly driven by the increased lung cancer risk. There was also a suggestion of an increased cancer risk for cancers of the urinary and gastrointestinal tract, but after adjusting for smoking and other covariates the risk estimates no longer reached statistical significance. Smoking is the most important risk factor for both COPD and lung cancer, and it is likely that most of the observed lung cancer risk is due to smoking. However, stratification by smoking status showed that COPD increased the risk in non-smokers when comparing non-smoking COPD patients with non-smoking patients without COPD, which indicates an independent contribution of COPD on the lung cancer risk. This proposition is consistent with findings from previous studies reporting risk estimates ranging from 1.5 to 2.7 for various levels of COPD severity. Based on our findings from an observational study we cannot tell whether the substantially increased OR of 4.21 (95% CI 2.65–6.69) for lung cancer among non-smoking COPD patients points to a smoking-independent association between COPD and lung cancer risk, or whether it is the result of residual confounding or smoking misclassification; we cannot rule out that the result is driven to some degree by misclassification of tobacco exposure, ie, a patient being recorded as a non-smoker despite a previous history of smoking. Furthermore, a COPD diagnosis may be made by mistake because someone is presenting with lung cancer symptoms.

Our findings were also similar to the ones in a previous analysis on lung diseases and cancer risk on the same database that covered the period from 1994 to 2001 and encompassed only some 9000 subjects with COPD; our study was done between 1995 and 2005 and involved some 35,000 COPD patients. Furthermore, we stratified the results of the nested case-control analysis by gender, which was not done in the previous study.

Overall, the distribution of various cancer types in the current study population reflects what is known from cancer

| Sex | No. of cases | Person-years (py) | IR per 1000 py | 95% CI | IRR | 95% CI |
|-----|-------------|------------------|----------------|-------|-----|-------|
| Male | NC | 1207 | 56919.3 | 21.2 | 20.1–22.4 | 1.00 | ref |
|     | C  | 1526 | 45642.3 | 33.4 | 31.8–35.1 | 1.56 | 1.45–1.68 |
| Female | NC | 714 | 57522.1 | 12.4 | 11.5–13.4 | 1.00 | ref |
|      | C  | 1059 | 47281.7 | 22.4 | 21.1–23.8 | 1.79 | 1.63–1.96 |

**Table 2** Incidence rate and rate ratio: all cancers by age, gender, and COPD status

| Age, yrs | No. of cases | Person-years (py) | IR per 1000 py | 95% CI | IRR | 95% CI |
|---------|-------------|------------------|----------------|-------|-----|-------|
| <50     | NC | 19 | 5133.0 | 3.7 | 2.4–5.8 | 1.00 | ref |
|         | C  | 26 | 4672.2 | 5.6 | 3.8–8.1 | 1.50 | 0.84–2.69 |
| 50–59   | NC | 139 | 19374.0 | 7.2 | 6.1–8.5 | 1.00 | ref |
|         | C  | 217 | 17462.4 | 12.4 | 10.9–14.2 | 1.72 | 1.40–2.12 |
| 60–69   | NC | 496 | 36029.7 | 13.8 | 12.6–15.0 | 1.00 | ref |
|         | C  | 743 | 30570.8 | 24.3 | 22.6–26.1 | 1.75 | 1.56–1.95 |
| 70–79   | NC | 992 | 44520.8 | 22.3 | 21.0–23.7 | 1.00 | ref |
|         | C  | 1329 | 34239.1 | 38.8 | 36.8–40.9 | 1.71 | 1.58–1.82 |
| ≥ 80    | NC | 275 | 9383.9 | 29.3 | 26.1–32.9 | 1.00 | ref |
|         | C  | 270 | 5979.5 | 45.2 | 40.2–50.7 | 1.52 | 1.28–1.80 |

Abbreviations: C, COPD; CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio; NC, no COPD; py, person-years; ref, reference category; y, years.
### Table 3 Cancer risk in women

| Cases (N = 1007) | Controls (N = 4028) | OR (95% CI) | Adjusted OR (95% CI) |
|-----------------|---------------------|-------------|---------------------|
| **Gastro-esophageal cancers** | | | |
| No COPD | 19 | 93 | 1.0 | 1.0 |
| COPD | 26 | 87 | 1.44 (0.75–2.76) | 0.92 (0.43–1.98) |
| **Intestinal cancers** | | | |
| No COPD | 51 | 233 | 1.0 | 1.0 |
| COPD | 63 | 223 | 1.28 (0.85–1.91) | 1.14 (0.73–1.77) |
| **Lymphoma** | | | |
| No COPD | 24 | 89 | 1.0 | 1.0 |
| COPD | 18 | 79 | 0.86 (0.45–1.65) | 0.86 (0.45–1.65) |
| **Breast cancer** | | | |
| No COPD | 170 | 687 | 1.0 | 1.0 |
| COPD | 167 | 661 | 1.02 (0.81–1.28) | 1.06 (0.82–1.38) |
| **Female genital cancers** | | | |
| No COPD | 53 | 184 | 1.0 | 1.0 |
| COPD | 35 | 168 | 0.74 (0.47–1.17) | 0.82 (0.48–1.37) |
| **Urinary/Kidney cancers** | | | |
| No COPD | 22 | 125 | 1.0 | 1.0 |
| COPD | 38 | 115 | 1.86 (1.04–3.33) | 1.88 (0.83–4.27) |
| **Lung cancer** | | | |
| No COPD | 41 | 733 | 1.0 | 1.0 |
| COPD | 280 | 551 | 8.35 (5.90–11.8) | 5.26 (3.64–7.61) |

**Notes:** OR adjusted for BMI, smoking, and various cancer type specific confounders. Breast cancer: contraceptive use, hormone replacement therapy use, benign neoplasms, non-melanoma skin cancer, and NSAID use; lymphoma: benign neoplasms, use of carcinogenic drugs; gastro-esophageal cancer: gastro-esophageal reflux disease, benign neoplasms, non-melanoma skin cancer; colorectal cancer: NSAID use, constipation, benign neoplasms, non-melanoma skin cancer; female reproductive system cancer: contraceptive use, hormone replacement therapy use, benign neoplasm, non-melanoma skin cancer, NSAID use; urinary system cancers: hypertension, benign neoplasms, use of diuretics, use of carcinogenic drugs, urinary dysfunction.

**Abbreviations:** CI, confidence interval; OR, odds ratio.

---

### Table 4 Cancer risk in men

| Cases (N = 1643) | Controls (N = 6572) | OR (95% CI) | Adjusted OR (95% CI) |
|-----------------|---------------------|-------------|---------------------|
| **Gastro-esophageal cancers** | | | |
| No COPD | 63 | 264 | 1.0 | 1.0 |
| COPD | 58 | 220 | 1.09 (0.75–1.60) | 1.03 (0.69–1.54) |
| **Intestinal cancers** | | | |
| No COPD | 90 | 390 | 1.0 | 1.0 |
| COPD | 93 | 342 | 1.17 (0.85–1.60) | 1.24 (0.88–1.74) |
| **Lymphoma** | | | |
| No COPD | 34 | 137 | 1.0 | 1.0 |
| COPD | 38 | 151 | 1.01 (0.61–1.68) | 1.01 (0.61–1.68) |
| **Male genital cancers** | | | |
| No COPD | 270 | 1066 | 1.0 | 1.0 |
| COPD | 231 | 938 | 0.97 (0.81–1.18) | 1.01 (0.83–1.24) |
| **Urinary/Kidney cancers** | | | |
| No COPD | 95 | 444 | 1.0 | 1.0 |
| COPD | 121 | 420 | 1.34 (0.99–1.80) | 1.08 (0.75–1.57) |
| **Lung cancer** | | | |
| No COPD | 146 | 1172 | 1.0 | 1.0 |
| COPD | 404 | 1028 | 2.93 (2.40–3.59) | 2.10 (1.70–2.60) |

**Notes:** OR adjusted for BMI, smoking, and various cancer type specific confounders. Lymphoma: benign neoplasms, use of carcinogenic drugs; gastro-esophageal cancer: gastro-esophageal reflux disease, benign neoplasms, non-melanoma skin cancer; colorectal cancer: NSAID use, constipation, benign neoplasms, non-melanoma skin cancer; urinary system cancers: hypertension, benign neoplasms, use of diuretics, use of carcinogenic drugs, urinary dysfunction.

**Abbreviations:** CI, confidence interval; OR, odds ratio.

---

statistics: in men, lung cancer and cancer of the reproductive system (mainly prostate cancer) are the most frequent cancer types, followed by colorectal cancer; in women, lung, breast, and colorectal cancer are the most common malignancies. We observed higher relative lung cancer risk estimates associated with a history of COPD for women than for men; whether this points towards a greater susceptibility for women, or whether it is due to other factors and needs to be further...
explored, is unknown and controversially discussed. Women outnumber men in the population of non-smoking COPD patients.

We did not find much evidence for an altered lung cancer risk in association with long-term use of various respiratory drugs. The increased relative risk seen for short-term current drug users is most likely due to the fact that respiratory function decreased shortly prior to the lung cancer diagnosis, which led to the initiation of a new drug treatment. This finding indicates that COPD patients with an acute deterioration of their lung function need careful evaluation because one of several reasons for the worsening clinical situation might be the first manifestation of lung cancer. There was a suggestion of an increased risk of developing lung cancer associated with long-term theophylline use, but this finding was based on a relatively small number of exposed cases and controls and may be a chance finding; this cannot be ruled out, particularly if a substantial number of exposure categories are tested in the model. It may also reflect a more advanced and severe stage of COPD and thereby be the result of confounding by indication.

Parimon et al reported that high doses of inhaled corticosteroids (>1200 mcg/d) reduced the risk of a lung cancer diagnosis significantly when compared with non-users. Kiri et al also reported a reduced lung cancer risk in patients using inhaled corticosteroids alone or in combination with long-acting beta agonists when compared with patients using short-acting beta agonists. In our study population, we did not see a significant association between corticosteroid use and the risk of lung cancer. In women with a cancer diagnosis, there was a tendency towards a decreased exposure history to inhaled corticosteroids as compared with cancer-free controls, but the adjusted analysis did not yield a statistically reduced risk estimate (data not shown). There was no such effect seen in men. In a study involving asthma patients, use of oral corticosteroids was associated with an increased cancer risk.

An important limitation of this study is the limited follow-up time between the first COPD diagnosis and the incident cancer diagnosis. Both COPD and cancer are chronic diseases that develop and are present for some time before first symptoms become clinically manifest. Thus, we may have missed a certain proportion of patients with mild COPD who had not yet been diagnosed by the GP. Further, the proportion of patients with severe COPD may be small due to limited follow-up. Thus, the current study population may reflect a patient population with a relatively high proportion of moderate COPD. In addition, it would have been desirable to have more information on certain potential risk factors (eg, human papilloma virus infections) or protective factors (eg, former use of oral contraceptives (OCs)) for various gynecological cancers. We assessed OC use prior to the index date for women in the nested case-control analysis and adjusted the analyses for this parameter, but for elderly women the likelihood of having previous OC use recorded on computer was low. By matching cancer cases and controls in practice, we made an attempt to take socioeconomic status into account to some degree, as social deprivation shows a geographical pattern and therefore people from the same neighborhood are more likely to see the same GP. We adjusted all our analyses for smoking status; however, we cannot exclude residual confounding by environmental tobacco exposure or smoking intensity.

A strength of this study is that the GPRD is a well-validated data source with a high validity of recorded drug exposure. In addition, all drug use was recorded prior to these analyses and in the absence of any study hypothesis. Further, we classified drug use in all patients (ie, cases or controls, or patients with or without COPD) in the same way so that any exposure misclassification should be non-differentially distributed across users of various COPD medications.

In summary, this observational study provides further evidence that COPD is only marginally or not at all associated
### Table 6 Lung cancer stratified risk by medication use

| Medication Type                 | Cases (%) (N = 684) | Controls (%) (N = 1579) | Adjusted OR | 95% CI       |
|--------------------------------|----------------------|-------------------------|-------------|--------------|
| **Short-acting beta agonists**  |                      |                         |             |              |
| No use                          | 161 (23.5)           | 379 (24.0)              | ref         | ref          |
| Current < 1y                    | 87 (12.7)            | 133 (8.4)               | 1.37        | 0.94–1.99    |
| Current 1–3y                    | 55 (8.0)             | 112 (7.1)               | 1.15        | 0.74–1.77    |
| Current > 3y                    | 149 (21.8)           | 365 (23.1)              | 1.00        | 0.69–1.43    |
| Current few                     | 120 (17.5)           | 246 (15.6)              | 1.33        | 0.95–1.87    |
| Past regularly                  | 68 (9.9)             | 203 (12.9)              | 0.90        | 0.63–1.30    |
| Past few                        | 44 (6.4)             | 141 (8.9)               | 0.87        | 0.56–1.34    |
| **Long-acting beta agonists**   |                      |                         |             |              |
| No use                          | 549 (80.3)           | 1197 (75.8)             | ref         | ref          |
| Current < 1y                    | 33 (4.8)             | 88 (5.6)                | 0.64        | 0.41–1.02    |
| Current 1–3y                    | 24 (3.5)             | 63 (4.0)                | 0.80        | 0.46–1.40    |
| Current > 3y                    | 22 (3.2)             | 61 (3.9)                | 0.92        | 0.52–1.65    |
| Current few                     | 10 (1.5)             | 21 (1.3)                | 1.28        | 0.55–3.00    |
| Past regularly                  | 39 (5.7)             | 125 (7.9)               | 0.69        | 0.45–1.08    |
| Past few                        | 7 (1.0)              | 24 (1.5)                | 0.75        | 0.28–2.01    |
| **Short-acting anticholinergics**|                    |                         |             |              |
| No use                          | 450 (65.8)           | 1084 (68.7)             | ref         | ref          |
| Current < 1y                    | 76 (11.1)            | 109 (6.9)               | 1.33        | 0.93–1.90    |
| Current 1–3y                    | 23 (3.4)             | 64 (4.1)                | 0.81        | 0.46–1.41    |
| Current > 3y                    | 41 (6.0)             | 87 (5.5)                | 1.38        | 0.87–2.20    |
| Current few                     | 18 (2.6)             | 25 (1.6)                | 2.00        | 0.99–4.04    |
| Past regularly                  | 61 (8.9)             | 176 (11.2)              | 0.86        | 0.60–1.23    |
| Past few                        | 15 (2.2)             | 34 (2.2)                | 1.35        | 0.68–2.68    |
| **Tiotropium**                  |                      |                         |             |              |
| No use                          | 633 (92.5)           | 1512 (95.8)             | ref         | ref          |
| Current < 1y                    | 36 (5.3)             | 46 (2.9)                | 1.70        | 0.98–2.95    |
| Current 1–3y                    | 7 (1.0)              | 15 (1.0)                | 1.24        | 0.44–3.49    |
| Current > 3y                    | –                    | –                      | –           | –            |
| Current few                     | –                    | –                      | –           | –            |
| Past regularly                  | 8 (1.2)              | 6 (0.4)                 | 3.31        | 1.05–10.45   |
| Past few                        | –                    | –                      | –           | –            |
| **Inhaled corticosteroids**     |                      |                         |             |              |
| No use                          | 309 (45.2)           | 667 (42.2)              | ref         | ref          |
| Current < 1y                    | 78 (11.4)            | 121 (7.7)               | 1.23        | 0.85–1.78    |
| Current 1–3y                    | 46 (6.7)             | 11 (7.0)                | 0.80        | 0.52–1.25    |
| Current > 3y                    | 121 (17.7)           | 341 (21.6)              | 0.83        | 0.59–1.17    |
| Current few                     | 67 (9.8)             | 158 (10.0)              | 0.56        | 0.59–1.25    |
| Past regularly                  | 45 (6.6)             | 114 (7.2)               | 0.91        | 0.59–1.39    |
| Past few                        | 18 (2.6)             | 67 (4.2)                | 0.68        | 0.37–1.26    |
| **Theophylline**                |                      |                         |             |              |
| No use                          | 611 (89.3)           | 1434 (90.8)             | ref         | ref          |
| Current < 1y                    | 7 (1.0)              | 16 (1.0)                | 1.29        | 0.47–3.50    |
| Current 1–3y                    | 4 (0.6)              | 11 (0.7)                | 0.85        | 0.23–3.12    |
| Current > 3y                    | 13 (1.9)             | 17 (1.1)                | 2.37        | 1.05–5.35    |
| Current few                     | 2 (0.3)              | 11 (0.7)                | 0.57        | 0.12–2.77    |
| Past regularly                  | 34 (5.0)             | 63 (4.0)                | 1.38        | 0.83–2.29    |
| Past few                        | 13 (1.9)             | 27 (1.7)                | 1.47        | 0.65–3.33    |
| **Other xanthines**             |                      |                         |             |              |
| No use                          | 628 (91.8)           | 1443 (91.4)             | ref         | ref          |
| Current < 1y                    | 13 (1.9)             | 9 (0.6)                 | 5.05        | 1.86–13.72   |
| Current 1–3y                    | 6 (0.9)              | 8 (0.5)                 | 1.52        | 0.48–4.82    |
| Current > 3y                    | 11 (4.6)             | 29 (1.8)                | 0.82        | 0.36–1.86    |

(Continued)
with most cancers except lung cancer. The risk of developing lung cancer is substantially increased for COPD patients, which can in part be explained by smoking as a major common underlying risk factor, but an independent association between chronic lung inflammation due to COPD and an increased cancer risk beyond the effect of smoking is also possible. In our study population, the risk of developing lung cancer in association with COPD was higher in women than in men.

Acknowledgment
This study was funded by an unconditional grant by Nycomed GmbH.

Disclosure
Doctors Meier, Jick, and Schneider have no conflicts of interest to disclose. Dr Bothner was employed by Nycomed GmbH at that time.

References
1. GOLD. Executive summary: global strategy for the diagnosis, management, and prevention of COPD. 2007 [updated 5 Mar 2009; cited 2007]. Available from: http://www.goldcopd.org/guidelineitem.asp?11=2&12=1&intId=996. Accessed 2010 Sep 26.
2. Sakai A, Nakanishi M, Yoshiyama K, Maki H. Impact of reactive oxygen species on spontaneous mutagenesis in Escherichia coli. Genes Cells. 2006;11(7):767–778.
3. Rahman I, Adcock IM. Oxidative stress and redox regulation of lung inflammation in COPD. Eur Respir J. 2006;28(1):219–242.
4. IARC. IARC monographs on the evaluation of carcinogenic risks to humans – hepatitis viruses. 1994 [updated 13 Feb 2007]. Available from: http://monographs.iarc.fr/ENG/Monographs/vol59/volume59.pdf. Accessed 2010 Sep 26.
5. Turner MC, Chen Y, Krewski D, Ghadirian P, Thun MJ, Calle EE. Cancer mortality among US men and women with asthma and hay fever. Am J Epidemiol. 2005;162(3):212–221.
6. Tennis P, Sherrill B, Fernandez C, Dolan C. Cancer risk in asthmatic populations. Ann Allergy Asthma Immunol. 2005;95(4):354–360.
7. Vesterinen E, Pukkala E, Timonen T, Aromaa A. Cancer incidence among 78,000 asthmatic patients. Int J Epidemiol. 1993;22(6):976–982.
8. Wasswa-Kintu S, Gan WQ, Man SF, Pare PD, Sin DD. Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis. Thorax. 2005;60(7):570–575.
9. 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(1):51–56.
10. Kiri VA, Soriano J, Visick G, Fabбри L. Recent trends in lung cancer and its association with COPD: an analysis using the UK GP Research Database. Prim Care Respir J. 2010;19(1):57–61.
11. Soriano JB, Maier WC, Egger P, et al. Recent trends in physician diagnosed COPD in women and men in the UK. Thorax. 2000;55(9):789–794.
12. Xu X, Weiss ST, Rijcken B, Schouten JP. Smoking, changes in smoking habits, and rate of decline in FEV1: new insight into gender differences. Eur Respir J. 1994;7(6):1056–1061.
13. Hirsh L, Dantes A, Suh BS, et al. Phosphodiesterase inhibitors as anticancer drugs. Biochem Pharmacol. 2004;68(6):981–988.
14. Siegmund B, Welsch J, Loher F, et al. Phosphodiesterase type 4 inhibitor suppresses expression of anti-apoptotic members of the Bcl-2 family in B-CLL cells and induces caspase-dependent apoptosis. Leukemia. 2001;15(10):1564–1571.
15. Wiernik PH, Paitetta E, Goloubeva O, et al. Phase II study of theophylline in chronic lymphocytic leukemia: a study of the Eastern Cooperative Oncology Group (E4998). Leukemia. 2004;18(10):1605–1610.
16. Mabed M, Aref S, Fouda M, El-Sharawy S. Chlorambucil plus theophylline vs chlorambucil alone as a front line therapy for B-cell chronic lymphatic leukemia. Leuk Lymphoma. 2004;18(10):1605–2035.
17. Karagas MR, Cushing GL Jr, Greenberg ER, Mott LA, Spencer SK, Nierenberg DW. Non-melanoma skin cancers and glucocorticoid therapy. Br J Cancer. 2001;85(5):683–686.
18. Wattenberg LW, Wiedmann TS, Estensen RD, et al. Chemoprevention of pulmonary carcinogenesis by brief exposures to aerosolized budesonide or beclomethasone dipropionate and by the combination of aerosolized budesonide and dietary myo-inositol. Carcinogenesis. 2000;21(2):179–182.
19. Greenberg AK, Hu J, Basu S, et al. Glucocorticoids inhibit lung cancer cell growth through both the extracellular signal-related kinase pathway and cell cycle regulators. Am J Respir Cell Mol Biol. 2002;27(3):320–328.
20. Wattenberg LW, Wiedmann TS, Estensen RD, Zimmerman CL, Steele VE, Kelloff GJ. Chemoprevention of pulmonary carcinogenesis by aerosolized budesonide in female A/J mice. Cancer Res. 1997;57(24):5489–5492.
21. Parimon T, Chien JW, Bryson CL, McDonell MB, Udris EM, Au DH. Inhaled corticosteroids and risk of lung cancer among patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007;175(7):712–719.

22. Gonzalez-Perez A, Fernandez-Vidaurre C, Rueda A, Rivero E, Garcia Rodriguez LA. Cancer incidence in a general population of asthma patients. *Pharmacoepidemiol Drug Saf*. 2006;15(2):131–138.

23. Wood L, Martinez C. The general practice research database: role in pharmacovigilance. *Drug Saf*. 2004;27(12):871–881.

24. 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(10):e7380.

25. Kiri VA, Fabbri LM, Davis KJ, Soriano JB. Inhaled corticosteroids and risk of lung cancer among COPD patients who quit smoking. *Respir Med*. 2009;103(1):85–90.