# Use of inhaled corticosteroids and the risk of lung cancer, the HUNT study

Kirsti Sørli [*,1], Stine Marie Thorvaldsen[*,1], Peter Hatlen[2,3]

* These authors share first authorship

1. The Faculty of Medicine and Health Sciences, NTNU, 7006 Trondheim Norway
2. Dept. of Pulmonology, St. Olavs hospital HF, 7006 Trondheim Norway
3. Dept. of Circulation and Medical Imaging (ISB), Faculty of Medicine and Health Sciences, NTNU 7489 Trondheim

## Abstract

**Background**: Inflammation plays a central role in COPD and lung cancer carcinogenesis. Inhaled corticosteroids (ICS) reduce inflammation. This study has investigated whether ICS use are associated with a lower risk of lung cancer.

**Material and methods**: Data from the Nord-Trøndelag Health Study (HUNT2 Survey, 1995-1997) were merged with The Cancer Registry of Norway and Norwegian Cause of Death Registry. From a total of 65215 participants, those with chronic airway inflammation, defined by FEV1%<70 and/or chronic cough and expectorate phlegm, were included (N=4136). Of these, 3041 individuals reported regarding ICS use and were observed for a period of 12 years. Cox regression models were used to calculate the risk of lung cancer with a 95% confidence interval (CI) with sex, age, smoking pack years and FEV1%<70 as known confounders.

**Results**: Among ICS users (N=1095) we found a higher, but not significant, incidence of lung cancer N=39 (3.6%), compared to non-users (N=1946) with N=65 (3.3%) cases. Age and smoking was associated with a higher risk, while sex and lung function was not. After adjusting for confounders, ICS use did not change the risk of lung cancer, hazard ratio (HR) = 0.968, (95% CI, 0.608–1.540) and p-value 0.890.

**Conclusion**: ICS use are not associated with a reduced risk of lung cancer in our study population.

# Introduction

Globally, lung cancer is the most frequently occurring type of cancer, with more than 1.8 million new cases, causing almost 1.6 million deaths as estimated in 2012. It has the highest incidence (34.2 per 100 000) among men, and rated third (13.6 per 100 000) among women (1). With a total of 3191 new cases reported in 2015, lung cancer has the third highest incidence in Norway following cancer prostate and cancer mammae (2)

Treatment options have been improved, but the five year overall survival rate is still poor (10-15%) (1). At the time of diagnosis, the disease is often in an advanced stage and curation is therefore not possible. Considering the fatal outcome, prevention is a much better approach to avoid new cases (3).

Cancer-related inflammation comprises of both inflammatory mediators and cells, as seen in chronic inflammatory responses and tissue repair (4). Chronic inflammation can contribute to unrestricted cell proliferation and invasion, inducing angiogenesis and increasing mutagenesis (3).

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease and consist of emphysema, chronic bronchitis or these in combination. Several pathophysiological mechanisms may link COPD and lung cancer. Factors as inflammation, smoking, presence of specific proteinases, genetic and epigenetic changes are associated with COPD and may potentially be linked to the development of lung cancer (5).

The pathological structural changes and the chronic inflammation, remain despite smoking cessation and increase with COPD severity (6). Young et al. concluded that COPD is both a common and important independent risk factor associated with the development of lung cancer (7). Smokers with COPD have five times higher risk of developing lung cancer compared to smokers with normal lung function (8). In addition to smoking and COPD, other known risk factors for developing lung cancer are sex and age (9-11).

By suppressing the inflammatory process with corticosteroids there exist a potential for reducing the tumor-promoting effect, by increasing or decreasing transcription of genes involved in the inflammatory process (12, 13).

There are only a few studies investigating the connection between the incidence of lung cancer and the effect of inhaled corticosteroids (ICS) in patients with chronic airway inflammation. These studies present conflicting results. Observational studies have shown a decreased risk of lung cancer with use of ICS, on the contrary there were no association in several randomized controlled trials (RCTs) (14-19). The studies have some limitations, such

as their study population and follow-up time. The follow-up time varied from 6 months to 4.5 years, and considering the prolonged latency period in lung cancer, this may be too short to conclude whether there is an association or not (14, 15, 17-19).

In summary, the research question remains unanswered, and a population-based cohort study, the Nord-Trøndelag Health Study (HUNT), with a long follow-up period can contribute to answer this question. In this study, we have tested the hypothesis suggesting that treatment with ICS reduces chronic inflammation and further decrease the incidence of lung cancer.

# Materials and methods

## Source of data

Data applied in this study were obtained from the HUNT Study, a large population-based cohort study (20). It is a collaboration between the Faculty of Medicine and Health Sciences, the Norwegian University of Science and Technology (NTNU), the Norwegian Institute of Public Health and Nord-Trøndelag County Council. Three surveys have been performed, the HUNT1 (1984-1986), the HUNT2 (1995-1997) and the HUNT3 (2006-2008). All inhabitants of the Nord-Trøndelag County, older than 20 years have been invited to participate in the study. In total 77212 (89.4%), 65215 (69.5%) and 50807 (54.1%) individuals have participated in HUNT1, 2 and 3, respectively.

## Study population

The current study includes only participants from the HUNT2 Survey (N=65215). The observational period went from the day of inclusion in the HUNT2 Survey until the diagnosis of lung cancer, death or at the end of the study in December 2008, whichever occurred first. In our study only participants with chronic inflammation were included (N=4136). Chronic airway inflammation was defined either by reduced forced expiratory volume in 1 second/forced vital capacity (FEV1%) (lower than 70%), and/or participants that answered "yes" to the question whether they have had "persistent cough and expectorate phlegm in the morning at least three months the last two years" or not. Among the participants that filled the criteria mentioned above, 3041 individuals answered the question regarding ICS treatment. This population was divided into two groups, ICS users versus non-users (figure 1). All patients diagnosed with lung cancer prior to 2002 were excluded, in order to avoid a possible selection bias.

The data derived from the HUNT Study were matched with data from the Cancer Registry of Norway (CRN) and the Norwegian Cause of Death Registry at Statistics Norway (2).

**Fig. 1.** Selection of the study population

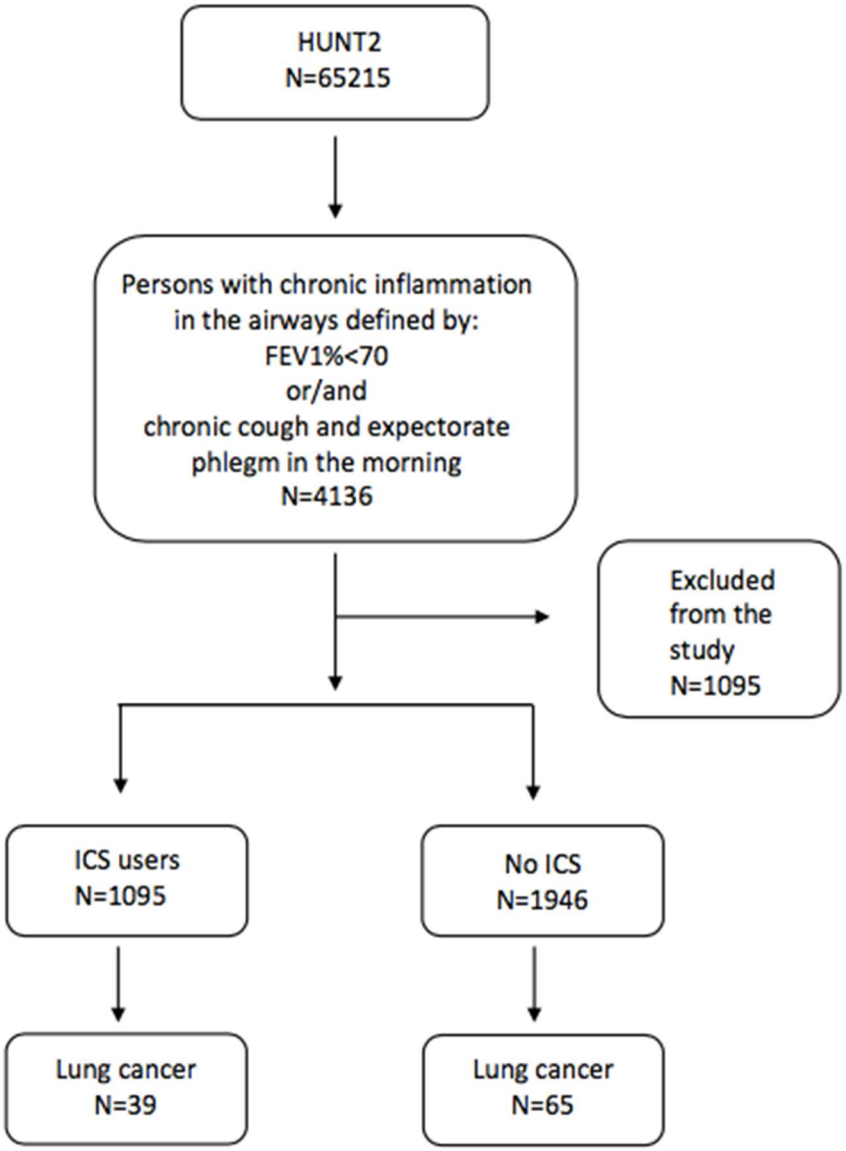


Figure 1. HUNT2, The Nord-Trøndelag Health Study; N, numbers; FEV1%, forced expiratory volume in 1 sec/forced vital capacity FEV1/FVC; ICS, inhaled corticosteroids.

## Outcome and exposure variable

Lung cancer diagnosis was defined as the outcome variable, and is based on the classification released by the World Health Organization (WHO) (21). All histological types of lung cancer were included in our study, both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) with all subtypes. ICS use was defined as the exposure variable. The participants were classified as ICS users by answering "yes" to the following question: "Have you ever regularly used medicines like becotide (beclomethasone), flutide (fluticasone), pulmicort (budesonide) or viarox (beclomethasone)?". Age at the time of inclusion, sex, smoking pack years and FEV1%<70 were variables included in the statistical model as confounders.

## Statistical analysis

The statistical analysis was performed using PASW version 22 (Predictive Analytics Soft Ware, IBM Corporation, New York 10589, USA). First, we divided our study population, consisting of participants with chronic inflammation (N=4136), into ICS users (N=1095) and non-users (N=1946). Second, by using the chi-square test, we investigated the differences in known prognostic factors between the two study groups. Third, applying the cox regression model, we estimated the hazard ratio (HR) with a 95% confidence interval for developing lung cancer, stratified by known potential confounders like sex, smoking pack years, FEV1%<70 and age in both the univariate and multivariate analysis. All participants in the period from 1996 to 2008 were included. Both smoking pack years and age were tested for linearity and thus used as continuous variables in the analysis. Fourth, we performed a sensitivity analysis with cox regression including only participants using ICS in HUNT2 and that were still using ICS in 2008. Furthermore, we acquired a long follow-up period (12 years) which made it possible to compare these results with the results derived from the overall analysis. Two-sided tests were used in all analysis, and the statistical significance was defined as $p<0.05$.

## Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics (2015/1801/REK midt).

# Results

## Participant characteristics

Non-users were in mean three years younger, and had a better lung function, measured in FEV1<70%, than the registered ICS users. There were more men in both groups, however the burden of smoking was similar. Participant characteristics are presented in Table 1. Of those using ICS; 60% had used ICS up to 4 years, while the rest more than 4 years. In the ICS user group, we found 39 (3.6%) cases of lung cancer, and in the non-user group 65 (3.3%) cases. However, there was no difference in the incidence (p=0.747). The mean age at diagnosis was 70 years (49-90) in the ICS user group and 72 years (44-92) in the non-user group (p=0.742).

**Tbl 1.** Participant characteristics

| | Cohort (N = 3041) | | |
|---|---|---|---|
| | ICS users (N = 1095) | No ICS (N = 1946) | P-value |
| Age, mean, yr | 61 | 58 | 0.004 |
| Sex, N (%) | | | |
| Female | 516 (47%) | 839 (43%) | 0.033 |
| Male | 579 (53%) | 1107 (57%) | 0.033 |
| PY, mean | 21 | 22 | 0.667 |
| FEV1%<70 | 876 (80) | 1466 (75) | 0.002 |

N, numbers; ICS, inhaled corticosteroids; yr, years; PY, pack years; FEV1%, forced expiratory volume in 1 sec/forced vital capacity (FEV1/FVC).

## Univariate and multivariate analysis

**Tbl 2.** Univariate and multivariate analysis of risk factors affecting incidence of lung cancer

| | Unadjusted | | | Adjusted | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P-value | HR | 95% CI | P-value |
| Sex | 1.490 | 1.025-2.166 | 0.037 | 0.715 | 0.444-1.151 | 0.167 |
| Age | 1.026 | 1.014-1.039 | <0.001 | 1.028 | 1.008-1.049 | 0.006 |
| PY | 1.029 | 1.020-1.039 | <0.001 | 1.027 | 1.016-1.039 | <0.001 |
| FEV1%<70 | 2.583 | 1.342-4.971 | 0.005 | 1.661 | 0.782-3.528 | 0.187 |
| ICS use | 1.022 | 0.671-1.557 | 0.920 | 0.968 | 0.608-1.540 | 0.890 |

HR, hazard ratio; CI, confidence interval; PY, pack years; ICS, inhaled corticosteroids; FEV1%, forced expiratory volume in 1 sec/forced vital capacity (FEV1/FVC)

The unadjusted analysis identified male sex, higher age, smoking pack years and FEV1%<70 as the factors increasing the risk of lung cancer. In the multivariate analysis, as shown in table 2, only age and smoking pack years increased the risk of lung cancer. ICS use did not decrease the risk, neither unadjusted or adjusted.

**Sensitivity analysis**

First, we estimated the risk of lung cancer among participants using ICS over 12 years, in the period between 1996-2008. Still ICS use did not decrease the risk of lung cancer, HR 0.750 (95% CI, 0.120-4.67) and p-value 0.758. Secondly, we excluded all patients diagnosed with lung cancer prior to 2002, in order to avoid selection bias. The results did not indicate that patients using ICS had a decreased risk of lung cancer with HR 0.909 (95% CI, 0.543-1.521) and p-value 0.716 in patients using ICS.

# Discussion

In contrast to the hypothesis, this study did not find a decreased incidence of lung cancer in patients with COPD using ICS. Of the variables included in our study, in both the univariate and multivariate analysis, smoking pack years and higher age were found to be the variables associated with increased risk of lung cancer. Alberg et al. showed that lifetime smokers have a 20-fold increased risk, compared with lifetime non-smokers (22). The carcinogenesis induced by smoking is a cumulative process that takes place over several decades. Consequently, lung cancer peaks in the elderly population, and is seldom found with individuals younger than the age of 30 (23). As listed in the univariate analysis, both male sex and FEV1%<70 increased the risk in this study. In our population of ICS users and non-users, we found with a chi-squared test a higher incidence of lung cancer in men. This is consistent with data worldwide. Compared to those with preserved lung function, patients with the lowest pulmonary function have the highest risk. This correlation is alinear, meaning that a small disparity in FEV1 increases the risk of lung cancer even though it is considered within normal range (24).

Several studies have shown that chronic inflammation promote susceptibility to occurrence of a variety of cancers. A chronic inflammatory environment with inflammatory cells, chemokines and cytokines can trigger transcription of proto-oncogenes, suppressor oncogenes and epigenetic mechanisms that promote carcinogenesis. This process may be activated by several conditions and mechanisms, such as autoimmune diseases and microbial

infections. For instance, colon cancer is associated with inflammatory bowel disease, and gastric cancer is related to helicobacter pylori infection. The risk of cancer and mortality rate decrease with the use of non-steroidal anti-inflammatory drugs, as observed with both colon cancer and breast cancer (4). This further support the association of inflammation and cancer.

A systematic review investigated ICS therapy among COPD patients and the correlation with lung cancer risk (25). It is based on four RCTs and two observational studies. These studies included COPD patients at age 40 and older, treatment with ICS alone and ICS in combination with β-agonists. The primary or secondary outcome was either lung cancer diagnosis or mortality. In one of the observational studies included, Parimon et al. followed 10474 patients in a median of 3.8 years, and proved that ICS use was effective. They found a risk reduction when using higher doses of ICS, suggesting a dose-dependent relationship. As opposed to our study, their study population mainly consisted of males (97%) (17). This fact makes it difficult to generalize to a typical COPD population.

It is known that the latency period in lung cancer is prolonged. This was considered in this study by excluding participants that reported to have lung cancer until 2002 in a sensitivity analysis. Parimon et al. had a much shorter observational time and did not include this latency period. They excluded patients with lung cancer the first year after inclusion. In comparison, we excluded the same group the first six years of the study (17).

Kiri et al. used a case-control study, and the cohort included 7079 patients. Their study showed that regular use of ICS in monotherapy and ICS in combination with LABA, reduced the risk of lung cancer with 36% and 50%, respectively. The risk was further reduced with the use of higher doses, as presented by Parimon et al. In Kiris' population only former smokers were included, thereby their study may lack some transmissibility (16, 17). Despite suffering from either mild or serious COPD, many do not accomplish tobacco smoking cessation, and need help in order to do so (26). Tobacco smoking cessation is essential in lung cancer control. If smokers of 15 cigarettes or more per day reduce their intake by 50%, they will reduce the risk of lung cancer significantly (27). Kiri et al. included only 30% women, in comparison to 45% female participants in our study (16). Despite the fact that previous studies have reported men to have higher prevalence and mortality of COPD than women, new evidence suggest a rather balanced gender distribution (6).

Unlike the observational studies, the four RCTs from the systematic review did not indicate a statistically significant effect of ICS use. This result corresponds well with the results obtained in our study. The CIs have a large width, which illustrates the uncertainty of

the relative risks. The study populations contain few lung cancer diagnosis and deaths, making these studies more prone to type II error ("false negative"). The prolonged latency period with lung cancer requires a long follow-up period, to identify a significant effect of ICS use in either direction (25). Due to the population size and the follow-up, those studies are underpowered to detect an effect.

For an optimal ICS treatment, patients need to adhere to a proper treatment regimen and use the inhaler correctly. In a systematic review based on data derived from 144 articles, covering 54354 subjects completing 59584 observed tests of technique, Sanchis et al. found that inadequate inhaler technique is alarmingly frequent. The most regular errors in inhaler use have not improved over the last 40 years (28). In a study at a tertiary care hospital in British Colombia, 37 COPD patients were observed as they demonstrated their inhalation technique. The results showed that N=22 (59%) did critical errors during the observed demonstration. The patients who used metered-dose inhalers made more critical errors than patients using other inhalers (29). We do not have information concerning inhalation technique and devices used in our study. It is crucial in both future studies as well as in the clinical setting to ensure that the correct technique is achieved by patient groups. Simple measures will increase the value of studies and especially optimize the treatment of patients.

Considering the clinical complexity of COPD, it is now clear that these patients derive from a heterogeneous group with different associated subgroups. With that in mind, it is possible that the effect of ICS use depends on which phenotype the patient belong to and is influenced by genetic involvement (5). In order to improve clinical outcomes, it will be valuable to provide individualized treatment (30).

All histological types of lung cancer were included in our study. None of the studies included in the systematic review differentiated between SCLC and NSCLC with all subtypes, neither did we. This study is therefore not suitable to unveil whether ICS use had a chemoprotective effect in any of the histological types individually, and consequently a lower incidence of lung cancer. In our study participants with chronic airway inflammation are defined by FEV1%<70 and/or chronic cough and expectorate phlegm in the morning. It would be preferable with spirometry results of all participants to identify the diagnosis of COPD. Compared to Parimon et al. which had not spirometry of any of their participants, we received results from half of the population (17). To ensure that the majority of COPD patients were incorporated in this study, we also included the question concerning chronic cough.

Most of our data is based on a questionnaire, this may have given both an underestimate as well as an overestimate of our results. For example, 1095 participants did not answer the question regarding ICS use.

The data material utilized in this study is based on the HUNT Study which has several strengths. The data set represents a large database with high participation, and includes different known risk factors for developing lung cancer. The region in the population-based prospective cohort study consist of both coastal, and inland municipalities with a population aged 20 years and older. Thereby providing a group with relatively diverse exposures (20). The prevalence of lung cancer and the median age of 71 years, is in line with other studies, indicating high validity of our study. Since we have a population-based study our results have great transmissibility. The main features of the population in HUNT is typical of the Norwegian population (31). Additionally, the population has remained stable throughout the study. All data are individually connected to The Cancer Registry of Norway and Norwegian Cause of Death Registry, increasing the validity and reliability of the study (20). Compared with other similar studies, our study had the longest follow-up period as well as a large population size.

This study contains several potential limitations. Firstly, diseases and risk factors concerning health can be related to socioeconomic status. Since participants in population-based studies compared to nonparticipants have a higher socioeconomic status, this can contribute to selection bias (32). The region, Nord Trøndelag, does not include large cities, and it has generally a lower socioeconomic status compared to the rest of the country. Furthermore, the inhabitants of Nord-Trøndelag are found to be smoking less than the average population in Norway. This may ultimately influence the results of our study (33-35).

Unfortunately, the current data set contains no information concerning the participants daily dose of ICS. Parimon et al. found in their study a dose-dependent decreased risk with a cut off value of ≥1200 μg/day adjusted HR 0.39 (CI 0.67-1.90) (17). The lack of dosage-based segmentation in our group of ICS users may have influenced our results.

**Conclusion**

We found no protective effect of ICS use on the incidence of lung cancer. However, high doses of ICS may have a protective effect. A large prospective population-based study including the dose of ICS use is needed to further answer the question definitively.

## Conflict of interest statement

The authors declare that they have no conflicts of interest.

## Acknowledgements

The authors would like to thank Professor Peter Hatlen for his scientific contributions and important counseling. We also acknowledge Professor Tore Amundsen for his contributions. We would like to thank the Norwegian Institute of Public Health and The Nord-Trøndelag Health Study (The HUNT Study) that has granted us access to the data utilized in this study. HUNT is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology NTNU), Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian Institute of Public Health.

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