Effect of Smoking Reduction on Lung Cancer Risk

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Context Many smokers are unable or unwilling to completely quit smoking. A proposed means of harm reduction is to reduce the number of cigarettes smoked per day. However, it is not clear whether this strategy decreases the risk for tobacco-related diseases.

Objective To assess the effects of smoking reduction on lung cancer incidence.

Design, Setting, and Participants Observational population-based cohort study with up to 31 years of follow-up from the Copenhagen Centre for Prospective Population Studies, which administrates data from 3 longitudinal studies conducted in Copenhagen and suburbs, the Copenhagen City Heart Study, the Copenhagen Male Study, and the Glostrup Population Studies, Denmark. Participants were 11 151 men and 8563 women (N=19 714) aged 20 to 93 years, who attended 2 consecutive examinations with a 5- to 10-year interval between 1964 and 1988. Participants underwent a physical examination and completed self-filled questionnaires about lifestyle habits. The study population was divided into 6 groups according to smoking habits: continued heavy smokers (≥15 cigarettes/d), reducers (reduced from ≥15 cigarettes/d by minimum of 50% without quitting), continued light smokers (1-14 cigarettes/d), quitters (stopped between first and second examination), stable ex-smokers, and never smokers.

Main Outcome Measure Incident primary lung cancer cases assessed by record linkage with the National Cancer Registry until December 31, 2003.

Results There were 864 incident lung cancers during follow-up. Using Cox regression, the adjusted hazard ratio (HR) for lung cancer in reducers was 0.73 (95% confidence interval [CI], 0.54-0.98) compared with persistent heavy smokers. The HR for light smokers was 0.44 (95% CI, 0.35-0.56); for quitters, HR 0.50 (95% CI, 0.36-0.69), for stable ex-smokers, HR 0.17 (95% CI, 0.13-0.23), and for never smokers, HR 0.09 (95% CI, 0.06-0.13).

Conclusion Among individuals who smoke 15 or more cigarettes per day, smoking reduction by 50% significantly reduces the risk of lung cancer.

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LUNG CANCER REMAINS THE LEADing cause of death from cancer worldwide with an estimated 90% of the cases being tobacco related. Consequently, efforts to prevent smoking uptake and to encourage smoking cessation are crucial in cancer control. However, the overall prevalence of cigarette smoking is still high, and the efficacy of smoking cessation intervention is limited.[1-3] This has led tobacco researchers to investigate possible alternative methods for diminishing the harmful effects of smoking, so-called harm reduction. One element in harm reduction, which is gaining increasing attention, concerns reducing the number of cigarettes smoked per day.

Despite comprehensive reviews on the issue,[4,5] there are limited data in the literature on the effects of smoking reduction with respect to end points such as morbidity and mortality from tobacco-related diseases. We have previously shown that heavy smokers (>15 cigarettes/d) who reduce their tobacco intake by at least 50% do not decrease their risk of fatal or nonfatal myocardial infarction, hospitalization for chronic obstructive pulmonary disease (COPD), or all-cause mortality compared with heavy smokers who do not change smoking habits.[6-8] Compensatory smoking, ie, increasing the puff volume per cigarette, is a possible explanation for the lack of benefit.

See also pp 1493 and 1550.

Evidence regarding changes in smoking habits and lung cancer incidence is—with the exception of the impact of smoking cessation—also sparse. Whether shifting to low-tar and low-nicotine yield cigarettes decreases lung cancer risk is still controversial, as is the issue concerning the effect of smoking other tobacco types than cigarettes (cigar and/or pipe; dark vs blond tobacco).[9-20] The general tendency in the numerous case-control studies is toward a more favorable risk profile from low-tar cigarettes and smoking of a cigar or pipe, whereas most cohort studies have not found any substantial reductions in risk. This can probably be

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Table 1. Overview of the Study Population (N = 19 714)

Cohort of Origin	Years of Examinations	No. of Men (n = 11 151)	No. of Women (n = 8563)	Age at Examinations, y	No. of Lung Cancer Cases
Copenhagen City Heart Study	1976, 1983	4776	6212	20-93	468
Glostrup Population Studies, 1897 birth cohort	1967, 1977	84	112	70-80	7
Glostrup Population Studies, 1914 birth cohort	1964, 1974	335	286	50-60	35
Glostrup Population Studies, 1936 birth cohort	1976, 1981	455	500	40-45	19
Glostrup Population Studies, MONICA I*	1981, 1988	1497	1453	30-65	65
Copenhagen Male Study	1970, 1976	4004	0	39-65	270

*The MONICA project is an international study conducted by the World Health Organization to monitor trends in and determinants of mortality from cardiovascular disease.

attributed to differences in adjustment for inhalation habits and smoking intensity and selection bias in the case-control design.

Only 1 cohort study and 1 case-control study have actually investigated individual changes in smoking behavior and subsequent lung cancer risk.[19,21] In the former, switching from cigarette smoking to pipes or cigars decreased lung cancer mortality by 46% compared with continuing cigarette smokers, while the case-control study showed nonsignificantly decreased lung cancer risks with change in cigarette type or a reduction in cigarettes per day by more than 25%. Our observational study of smoking reduction and mortality indicated a nonsignificant trend toward a reduced risk of mortality from tobacco-related cancer.[6] From a public health perspective, the recent results from the California tobacco control program support that extensive smoking restrictions are followed by a decline in lung cancer incidence.[22] A newly published intervention study has investigated the relationship between short-term (up to 26 weeks) smoking reduction and a tobacco-specific lung carcinogen.[23] The uptake in urine of the metabolites of the lung carcinogen was significantly reduced in participants who reduced smoking; however, the percentage reduction in levels of the metabolites was modest and did not correspond with the percentage decrease in cigarettes per day.

The objective of the present cohort study was to analyze the association between smoking reduction and incidence of the major histologic subtypes of primary lung cancer.

METHODS

Study Population

The Copenhagen Centre for Prospective Population Studies contains pooled data from 3 longitudinal population-based studies carried out in Copenhagen, Denmark and its vicinity during 1964 through 1993. A total of 30 911 persons participated at least once in 1 of the substudies, and the majority of participants were examined on 3 occasions with 1- to 10-year intervals. Mean response rate was 77%. The studies were approved by local ethics committees and all participants signed an informed consent prior to participation. All studies have been previously described.[24-26]

In the present study of changes in smoking habits, we required complete information on smoking habits in at least 2 consecutive examinations, preferably the first (baseline) and the second (follow-up). Thus, the present population was composed of 19 714 study participants (8563 women and 11 151 men). Participants were observed by use of a central personal registration number from the second examination until 2004, ie, up to 31 years of follow-up with a mean of 18 years. Follow-up was complete for all participants except those who emigrated or disappeared (<1%). TABLE 1 shows the distribution of the population on substudy, age, and years of examination.

Smoking Reduction and Covariates

Smoking status and changes in smoking habits in this study are based on self-reports. At each examination, participants were asked whether they smoked or not and if affirmative, about amount, duration, inhalation, and preferred type of tobacco. Ex-smokers were asked about years of active smoking and participants from the Copenhagen City Heart Study were asked about time since quitting (>5 years or <5 years prior to examination). For standardization of the tobacco variables in the pooled population, participants were categorized as heavy smokers (≥15 g/d), light smokers (1-14 g/d), ex-smokers, and never smokers. Tobacco consumption was calculated by equating a cigarette to 1 g of tobacco, a cheroot to 3 g, and a cigar to 5 g. Pack-years of smoking were calculated at the baseline examination as number of cigarettes per day multiplied by number of years of smoking divided by 20. Due to the imprecise information on exact dates for changes in smoking (quitting or reducing), it was not possible to calculate pack-years at follow-up.

Our definition of smoking reduction is in accordance with the clinical studies of heavy smokers who reduce, in which a chosen set point of 50% reduction or more in the amount smoked is sought and achieved.[27-29] It is well known that the heavier smokers are generally more addicted to nicotine than light smokers, and hence, find it more difficult to quit. To measure a substantial reduction in tobacco consumption, we only considered participants who were heavy smokers at first examination. Smoking reduction was then defined as smokers of 15 g of tobacco or more per day at first examination, who at the second examination reported a decrease of 50% or more without quitting. We also categorized 2 groups of former smokers: those who were ex-smokers both at baseline and

Table 2. Background Characteristics According to Smoking Status at Second Examination for the Pooled Study Population

Demographics	Heavy Smokers (n = 7351)	Reducers (n = 832)	Light Smokers (n = 3189)	Quitters (n = 1455)	Ex-Smokers (n = 2881)	Never Smokers (n = 4006)	*P* Value*
No. of lung cancer cases	576	52	104	52	52	28	
Men, No. (%)	4896 (66.6)	600 (72.1)	1516 (47.5)	891 (61.2)	1897 (65.9)	1351 (33.7)	.001
Age, mean (SD), y	52.4 (9.8)	55.1 (11.2)	54.8 (11.0)	55.0 (11.6)	55.8 (10.9)	54.5 (12.3)	<.001†
Tobacco consumption, mean (SD), g/d							
At baseline	19.8 (8.7)	22.2 (12.3)	9.0 (4.3)	14.5 (12.1)			.001†
At follow-up	20.2 (8.9)	8.5 (5.5)	9.3 (4.2)				<.001†
Pack-years of smoking at baseline, mean (SD)	31.2 (20.0)	27.1 (21.0)	14.2 (8.5)	19.5 (18.1)	14.6 (16.2)		<.001†
Inhalers, %	5771 (78.5)	553 (66.5)	2073 (65.0)				<.001
Type of tobacco smoked, %							
Cigarettes only	4278 (58.2)	351 (42.2)	2341 (73.4)				<.001
Cigars, cheroots, pipe, or mixed	3073 (41.8)	481 (57.8)	848 (26.6)				<.001
Duration of smoking, mean (SD), y	33.1 (11.9)	34.4 (13.6)	31.1 (13.8)	28.8 (14.3)			.006†

**P* values represent differences between the reducers and the continuous heavy smokers.
†Two-sample *t* tests. All other are χ^2 tests with 2-tailed *P* values.

follow-up and those who were smokers at baseline but had stopped smoking at follow-up. The study population as a whole was then divided into the following categories: continued heavy smokers, reducers, continued light smokers, quitters, continued ex-smokers, and never smokers.

Outcome Measures

New cases of lung cancer from study entry, ie, date of second examination until December 31, 2003, were identified by record linkage with the Danish National Cancer Registry. In validation studies, the cancer registry has been found to register more than 95% of all cancers with a nearly 100% accuracy for cancers with a high mortality rate such as lung cancer.[30] We obtained the year and month of diagnosis and included the following histologic types: squamous cell carcinoma, adenocarcinoma, anaplastic carcinoma (small cell lung cancer), and primary lung cancer with unspecified histology.

Statistical Analysis

Multivariate Cox proportional hazards regression models were applied to study the association between smoking reduction, smoking cessation, no change in smoking habits, and lung cancer incidence. Age was chosen as the underlying timescale, thus allowing for delayed entry. Factors such as education, alcohol consumption, and body mass index (calculated as weight in kilograms divided by the square of height in meters) did not differ between the 2 main smoking groups of interest (reducers and sustained heavy smokers), and were therefore, not included in the analyses. We included the following confounders in the model: cohort of origin, sex, duration of smoking, inhalation habits, and type of tobacco smoked. Pack-years of smoking were not included because of the method our dependent variable was constructed (the 6 smoking groups), which would have resulted in over-adjustment. Tests of interaction mainly between sex and baseline smoking habits were performed. The assumption of proportional hazards was tested graphically and with a formal statistical test as proposed by Grambsch and Therneau.[31] All analyses were performed using Stata software version 7.0 (Stata Corp, College Station, Tex).

RESULTS

The demographic and smoking characteristics by smoking group are shown in TABLE 2. Reducers decreased their tobacco consumption from a mean of 22.2 g per day to a mean of 8.5 g per day, stable heavy smokers consumed approximately 20 cigarettes per day at both examinations, quitters consumed an average of 14.5 g of tobacco per day at baseline, and stable light smokers consumed 9 g of tobacco per day at both examinations. Compared with continued heavy smokers, the reducers were significantly older, a larger proportion were men, and they had smoked slightly more and longer; however, number of pack-years was significantly smaller (27 vs 31). Furthermore, a smaller proportion of reducers inhaled and were less likely to smoke cigarettes only.

During follow-up, 864 participants were diagnosed with primary lung cancer: 360 cases were among women and 504 were among men. TABLE 3 shows the distribution of cancer type among the smoking groups. There were 229 cases of squamous cell carcinoma, 234 cases of adenocarcinoma, 179 cases of small cell lung cancer, and 222 lung cancers with unspecified histology. Overall, the cancers are evenly distributed among the groups of current smokers with a tendency of a larger proportion of small cell lung cancer with increasing tobacco exposure. The age-standardized incidence rates of lung cancer according to the smoking groups of interest for men and women are shown in the FIGURE. Overall, the rates are higher for men than for women except in never smokers. There is a dose response relationship between increasing smoking intensity and lung cancer incidence rates except in male quitters, whose rates are

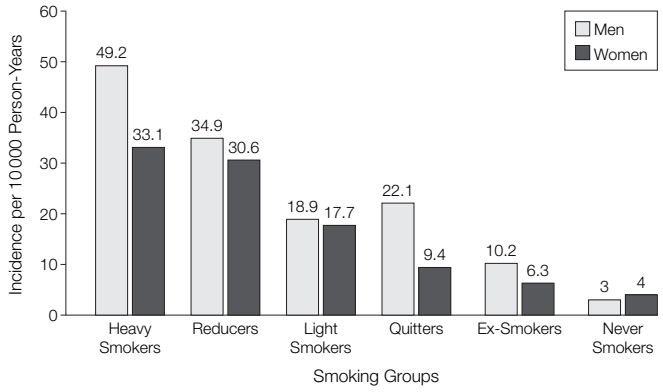
slightly higher than continued light smoking men.

Results of the Cox regression analyses are shown in TABLE 4. Reducing tobacco consumption from approximately 20 cigarettes per day to less than 10 was associated with a 27% (95% confidence interval [CI], 2%-46%) reduction in lung cancer risk compared with unchanged heavy smoking. Participants who were continued light smokers or who quit smoking between baseline and follow-up reduced their lung cancer risk by 56% and 50%, respectively, compared with persistent heavy smokers. Risk of lung cancer among the stable ex-smokers was 83% lower than among the heavy smokers, but still significantly higher than among the never smokers. Omitting the first 2 years after follow-up in the analyses to control for any possible ill-quitter or ill-reducer effect did not significantly change results, neither did omission of participants according to a chronic baseline disease index based on self-reported chronic respiratory conditions or hospital admission for lung disease before study entrance. We also performed analyses confined to cigarette smokers, thus excluding smokers of any other tobacco product, but this did not change the associations. In the multivariate analyses, inhaling the smoke, longer duration of smoking, and being of male sex were independent risk factors for lung cancer, whereas smoking other types of tobacco than cigarettes (or mixed), and cohort of origin were not.

Table 3. Number of Primary Lung Cancers by Histologic Subtyping and Smoking Status

	Smoking Category, No. (%)					
Type of Cancer	Heavy Smokers	Reducers	Light Smokers	Quitters	Ex-Smokers	Never Smokers
Squamous cell (n = 229)	157 (27)	15 (29)	23 (22)	16 (31)	12 (23)	6 (22)
Adenocarcinoma (n = 234)	151 (26)	12 (23)	25 (24)	11 (21)	22 (42)	13 (46)
Small cell (n = 179)	132 (23)	9 (17)	25 (24)	10 (19)	3 (6)	0
Unspecified (n = 222)	136 (24)	16 (31)	31 (30)	15 (29)	15 (29)	9 (32)

Figure. Age-Standardized Incidence Rates of Lung Cancer



Incidence rates are based on the second examination in 11 151 men and 8563 women from Copenhagen, Denmark.

COMMENT

In this large, population-based study with extensive follow-up, we found that reporting a large reduction in tobacco consumption between baseline and follow-up was associated with a decreased risk of subsequent lung cancer. However, a mean decrease of 62% in the amount smoked corresponded with a 27% reduction in risk of lung cancer, whereas participants who were light smokers throughout the study or who stopped smoking had considerably lower risk. This indicates that risk reduction is disproportionally smaller than the corresponding smoking reduction.

Undoubtedly, smoking cessation decreases the risk of lung and other tobacco-related cancers,[32,33] and our study also demonstrates that participants who were already ex-smokers when enrolled in the study had a much lower lung cancer risk than those who reported quitting between baseline and follow-up. Recently, Peto et al[34] showed that cessation of smoking before middle age is associated with a more than 90% reduction in tobacco-attributable cancer risk. Regarding smoking reduction and tobacco-related cancer, there are no data from other population-based studies. Results from 2 intervention studies examining carcinogenic biomarkers[23,35] and other short-term

Table 4. Lung Cancer Risk by Smoking Status at the Second Examination*

	Smoking Category					
	Heavy Smokers	Reducers	Light Smokers	Quitters	Ex-Smokers	Never Smokers
No. of cases	576	52	104	52	52	28
Crude hazard ratio (95% CI)†	1.00	0.68 (0.50-0.91)	0.40 (0.32-0.50)	0.36 (0.27-0.49)	0.17 (0.13-0.23)	0.09 (0.06-0.13)
Adjusted hazard ratio (95% CI)‡	1.00	0.73 (0.54-0.98)	0.44 (0.35-0.56)	0.50 (0.36-0.69)	0.17 (0.13-0.23)	0.09 (0.06-0.13)

Abbreviation: CI, confidence interval.
*Results from Cox proportional hazards regression analysis with age as underlying time scale.
†Cox regression model adjusted for sex and cohort of origin.
‡Multivariate analysis adjusted for sex, cohort of origin, inhalation habits (yes/no), tobacco type (cigarettes, cigars/pipe/cheroots, mixed), and years as smokers (continuous).

smoking-reduction studies using nicotine replacement therapy[36,37] clearly demonstrate the major problems in harm reduction. Only a minority of the smokers are actually able to achieve and sustain a considerable reduction in cigarettes per day, and equally important, even with *ad libitum* nicotine replacement therapy, substantial compensatory smoking occurs as measured by the most common biomarkers of tobacco exposure. Our results are in accordance with these studies.

In our study, we did not have repeated measurements of biomarkers of smoking. Carbon monoxide in expired air was measured in the Copenhagen City Heart Study III (1991-1993) in approximately 10 000 participants, and serum cotinine was obtained from 3300 participants in the Copenhagen Male Study in 1985. In this subset of smokers, we found that the reducers had significantly decreased levels of carbon monoxide and cotinine, respectively, compared with the heavy smokers but still higher than the stable light smokers, despite similar exposure in these 2 groups. This indicates that in observational studies not using nicotine replacement therapy, compensatory mechanisms occur. Furthermore, our results could be biased from differential misclassification especially if the reducers tended to underreport their consumption or changed their smoking habits during follow-up. However, due to the study design and our biomarker results, we do not believe this to be of major importance. Data on smoking behavior from the second examination to the third indicate that approximately 50% have continued as light smokers, 20% have quit entirely, and the remaining 30% have relapsed to heavy smoking. Hence, misclassification of smokers is likely to affect results in both directions (underestimation and overestimation of associations). However, also a proportion of the reference group has presumably reduced or quit smoking during follow-up leading to an underestimation of the effect of smoking reduction.

We have previously investigated the end points all-cause and cause-specific mortality, fatal or nonfatal myocardial infarction, and a first hospitalization for COPD in this cohort, and as mentioned earlier, we did not find any risk reduction with smoking reduction compared with continued heavy smoking. However, there was a trend toward a declining risk of lung cancer deaths following reduced smoking.[6] It is likely that lung cancer, which in particular demonstrates a dose-response relationship with smoking amount, will develop to a lesser extent after smoking reduction in contrast with other tobacco-related disorders due to DNA repair. On the other hand, given the long duration of excess lung cancer risk in former smokers, a rapid decline in risk for the reducers to the level of light smokers would not have been expected even if there were no signs of compensatory smoking as discussed previously.

This study has the advantages of a reasonably large size, a large proportion of smokers at baseline, and a long, up-to-date and almost 100% complete follow-up of participants. When studying changes in risk factors in an observational setting, the question of unmeasured confounding becomes relevant. We have focused on the comparison between the reducers and the sustained heavy smokers, but our study design does not enable us to examine reasons for this change in smoking behavior. For instance, we do not know if this group actually comprises the participants who are unable or unwilling to quit altogether. We have previously shown from the Copenhagen City Heart Study[38] that heavy smokers who reduce their smoking generally have a less healthy lifestyle than continued heavy smokers. However, these differences were not as pronounced in the pooled study population and we also used another definition of smoking reduction in the present study.

In conclusion, smoking reduction from an average of 20 cigarettes per day to less than 10 cigarettes per day reduced the lung cancer risk by approximately 25%. Presumably, the discrepancy between reported amount of reduction and calculated risk reduction can be largely explained by compensatory smoking. More data from long-term studies of smoking reduction are warranted, but for the present, smoking cessation and not smoking reduction should still be advocated as the ultimate method of reducing harm from smoking, especially since diseases such as COPD and myocardial infarction, which have a larger public health effect than lung cancer, have not shown any reductions in risks after smoking reduction.

Author Contributions: Dr Godtfredsen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Godtfredsen, Prescott, Osler.
Acquisition of data: Godtfredsen.
Analysis and interpretation of data: Godtfredsen, Prescott, Osler.
Drafting of the manuscript: Godtfredsen.
Critical revision of the manuscript for important intellectual content: Prescott, Osler.
Statistical analysis: Godtfredsen.
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Study supervision: Prescott, Osler.
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