Sex differences in risk of smoking-associated lung cancer: results from a cohort of 600,000 Norwegians

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Funding: PhD student Merethe Selnes Hansen was funded by Northern Norway Health Authority (SFP 1227-15). Postdoc Idlir Licaj was funded by grants from Norwegian Cancer Society. Grant agreement number: 4510766-2013.

Conflict of interest: No potential conflicts of interest were disclosed

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Abbrevations:
BMI (body mass index)
ICD (International Classification of Disease)
HRs (hazard ratios)
CI (confidence intervals)
CONOR (Cohort of Norway (CONOR) Study

ABSTRACT

Whether women are more susceptible than men to smoking-related lung cancer has been a topic of controversy. To address this question we compared risk of lung cancer associated with smoking by sex. Altogether 585,583 participants from three Norwegian cohorts (Norwegian Counties Study, 40 Years Study and CONOR) were followed until 31 December 2013 through linkage of data to national registries. We used Cox proportional hazards models and 95% confidence intervals (CIs). During nearly 12 million person-years of follow-up, 6534 participants (43% women) were diagnosed with lung cancer. More men than women were heavier smokers. Compared with never smokers men and women current smokers who smoked ≥ 16 pack-years had a hazard ratio for lung cancer of 27.24 (95%CI: 22.42, 33.09) and 23.90 (95%CI: 20.57, 27.76) respectively, ($P_{heterogeneity}$ = 0.30). In contrast, for current smokers, in the model of pack-years measured continuously, men had a hazard ratio of 1.43 (95%CI: 1.39, 1.48***)*** and women a hazard ratio of 1.64 (95%CI: 1.57, 1.71) for each 10 pack-years increment, ($P_{heterogeneity}$ <0.01). Our results suggest that women have an increased susceptibility to lung cancer compared to men, given the same lifetime smoking exposure.

Key words: Cohort study, CONOR, histology, lung neoplasms, sex differences, smoking

Tobacco smoking is the predominant cause of lung cancer, one of the most lethal human cancers, with a 5-year survival of only 10-15%. Lung cancer is the most common cancer in men and the third most common cancer in women worldwide (1). In Norway, lung cancer is the second and third most frequent cancer among men and women, respectively. Lung cancer incidence in Norway increased in both sexes until 2012, when it started to plateau for men, but continued to increase for women (2). The prevalence of daily smoking in Norwegian men

peaked at 65% during the late 1950s, while in women the peak was at 37% around 1970 (3). In 2013, the prevalence was 15% for both sexes (4). As of today, the majority of adults in Norway are ever, i.e., current or former, smokers.

The continuing rising incidence of lung cancer in women globally, has raised the possibility of a sex difference in the association of smoking with lung cancer. For women, a higher proportion are diagnosed at a younger age, at an earlier stage and with adenocarcinoma, compared to men (1). While there are conflicting findings from case-control studies (5-7), results from five recent cohort studies showed similar lung cancer incidence rates among men and women with comparable smoking histories (8-12).

Neither the most recent World Cancer Report (1) nor the United States Surgeon General Report (13) discusses a possible sex difference in the risk of smoking related cancer.

The purpose of this study was to examine by sex, the association between different measures of smoking exposure and risk of lung cancer overall, and by histological subtypes, in a large Norwegian cohort.

MATERIAL AND METHODS

Study sample

The study population included 635,840 men and women, born between 1897 and 1975, recruited from different Norwegian Health Screening Surveys (NHHS) conducted by The National Health Screening Service (now included in the Norwegian Institute of Public Health): the Norwegian Counties Study, the 40 Years Study, and the Cohort of Norway (CONOR) Study.

The Norwegian Counties Study took place between 1974 and 1978. Everyone aged 35-49 years and a 10% random sample of individuals aged 20-34 years residing in 3 rural Norwegian counties (Finnmark, Sogn og Fjordane, and Oppland), were invited to regular screening examinations for cardiovascular disease. The participation rate was 88% (14-16).

In the 40 Years Study, men and women aged 40-42 years, from all counties in Norway were invited to participate in a health survey during 1985-1999. In some counties broader age groups were invited. These surveys included 420,000 Norwegians. The participation rate was 69% (17, 18).

The CONOR Study consists of 10 surveys (Tromsø health study IV, The second Nord-Trøndelag Health Study, Hordaland Health Study, Oslo Study II, The Oslo Health Study, Oppland and Hedmark Health Study, Tromsø Health Study V, The Oslo Immigrant Health Study, Troms and Finnmark Health Study and The second Romsås in Motion Study) from different regions in Norway, including different age groups from 20-103 years. These surveys were conducted in 1994-2003. The overall participation rate for the CONOR study was 58% (14, 19, 20).

All studies had a baseline questionnaire including detailed assessments of smoking habits, and other lifestyle factors. Height and weight were measured at the screening facility by trained nurses and were used to calculate body mass index (BMI; weight in kilograms divided by height in squared meters). We excluded participants who emigrated or died before the start of follow-up (n=647), those with prevalent cancer (n=11,321), and those with missing information on vital status (n=190), measures of smoking exposure (6303), or any of the

covariates (body mass index, education, physical activity; n=31,796). Altogether 50,257 participants were excluded, leaving 585,583 (52% women) in the analytical cohort.

The present study was approved by the Regional Committee for Medical Research Ethics South-East, Norway, and the National Data Inspectorate. More details about our study population may be found elsewhere (21-23).

Exposure information

Information on current and former daily smoking, smoking duration in years, and number of cigarettes smoked per day was collected from questionnaires. Former smokers were also asked about time (years and/or months) since quitting. Only the CONOR Study asked about age at smoking initiation. In the other studies, we calculated this variable for both current (age at enrollment minus years of smoking) and former (age at enrollment minus years since quitting and duration of smoking) smokers.

Among the 367,046 ever smokers, the proportion of missing values was for cigarette consumption <2% (n=6552), for smoking duration <1% (n=3051), pack-years (i.e., number of cigarettes smoked per day, divided by 20, multiplied by the smoking duration in years) <3% (n=8280), and age at smoking initiation 21.6% (n=79,226).

In addition 56% (n=77,323) of the former smokers had missing values for years since quit smoking, and age at smoking initiation.

We categorized ever smokers according to age at smoking initiation (<16, 16-20, ≥21 years), number of cigarettes smoked per day (1-10, 11-20, >20), smoking duration in years (1-9, 10-

19, 20-29, ≥30), and number of pack-years (1-5, 6-15, ≥16). Former smokers were categorized by years since smoking cessation (0-4, 5-9, ≥10).

We adjusted for physical activity: [sedentary (reading, watching television, and sedentary activity), moderate (walking, bicycling, and/or similar activities ≥4 hours per week), and heavy (light sports or heavy gardening ≥4 hours per week, heavy exercise, or daily competitive sports)]; and body mass index, both at study enrollment. We merged group 1 (BMI <18.50) and group 2 (BMI 18.50-24.99) in the World Health Organization`s classification, and retained group 3 (BMI ≥25.00) and group 4 (BMI≥30.00) (24). We used the most recent information regarding duration of education obtained from Statistics Norway, to classify subjects in three categories: <10, 10-12, and ≥13 years of education.

Follow-up and endpoints

We used the unique 11-digit personal identification number to follow all participants for 1) cancer through linkage to the Cancer Registry of Norway; and 2) emigration or death through linkage to the Central Population Register. These national registries are both accurate and virtually complete (25). Person-years were calculated from age at enrollment to age at lung cancer diagnosis, any incident cancer diagnosis (except basal cell carcinoma), emigration, death, or the end of follow-up (December 31, 2013), whichever occurred first.

Cancer sites were identified by the anatomical sites and histological codes in the International Classification of Disease of Oncology (ICD-O) (26). All primary incident carcinomas of the trachea, bronchus, and lung (International Classification of Disease-7 code 162 or corresponding codes from International Classification of Disease-9 and International Classification of Disease-10) were considered. Lung cancers were classified into 6 histological subtypes (squamous cell, adenocarcinoma, large cell, other not specified non-small cell carcinoma, small-cell carcinoma, other carcinoma) according to the World Health

Organization's International Histological Classification. We present results on the risk for lung cancer overall and, separately for adenocarcinoma, squamous cell carcinoma, and small-cell carcinoma, which were the most frequent histological subtypes of lung cancer.

Statistical analysis

We calculated the age standardized (US 2000) incidence rate of lung cancer overall by sex and smoking status. All analyses were sex-specific unless otherwise noted.

We used cohort study and birth cohort (≤1950 and >1950) to overcome the heterogeneity for these variables in the stratified Cox proportional hazards model with attained age as the underlying time scale to estimate the multivariate-adjusted hazard ratios (HRs) with 95% confidence intervals (CI), for the associations between different measures of smoking exposure and the risk of lung cancer overall and by histological subtypes. The a priori selected covariates, included in the final models were; level of physical activity, body mass index (27), and years of education (<10, 10-12, ≥13), all at enrollment. Never smokers were used as the reference group in all categorical smoking analyses, except for the association between years since cessation and lung cancer risk, where we used current smokers as the reference group.

We estimated dose–response associations between the following continuous variables; smoking duration in 10 years, number of 10 cigarettes smoked per day, number of 10 pack-years, age at smoking initiation and lung cancer overall, for former, current and ever smokers. We evaluated the association between each 10 years since smoking cessation and lung cancer risk for former smokers only. In contrast to the categorical analyses never smokers are excluded in the continuous analyses.

We used fractional polynomials to determine the function of the different smoking exposures that best fitted the data (28). We entered the continuous variables into the multivariate Cox

regression models via a set of defined transformations [$x-2$, $x-1$, $x-0.5$, $x0.5$, $x1$, $x2$, $x3$ and $\log(x)$], allowing for a maximum of two terms in the model. We found, as a result of these analyses, that the log-transformed model best fitted our data. We then compared the log-transformed effect of each smoking exposure for men and women, and found similar sex differences.

We tested for trend across categories of measures of smoking for ever-smokers based on the median values in each category with the lowest category of each smoking exposure as reference. We used Wald test and tested for heterogeneity by sex for the measures of smoking exposure and the risk of lung cancer.

We tested and found that the criteria for the proportional hazards assumption were met using Schoenfeld residuals (data not shown).

We performed the similar analyses after excluding participants who were diagnosed with lung cancer within 2 years of enrollment.

We assessed possible interactions between smoking status and, education (three categories), BMI (three categories), physical activities (three categories).

We collapsed men and women when we analyzed the small-cell carcinomas due to small number of cases among never smokers.

We performed the analyses using STATA version 14.0 (Stata Corp, College Statistics, TX, USA) and considered two-sided *P*-values of <0.05 as statistically significant.

RESULTS

At enrollment, the proportions of never, former and current smokers were 34%, 26% and 40% in men and 41%, 21% and 38% in women. During nearly 12 million person-years of follow-

up, 6,534 participants (43% women) were diagnosed with lung cancer. For men the age-standardized incidence rate for lung cancer among never, former and current smokers was 9.2, 61.3 and 275.2 per 100,000 person-years respectively. For women the corresponding numbers were 17.6, 42.2 and 207.7. Adenocarcinomas were the most common tumor type for both sexes with 33% in men and 41% in women. During follow-up 14% of men and 9% of women died from all causes.

Table 1 shows that in the Norwegian Counties Study 51% of men and 40% of women were current smokers at enrollment. In CONOR, the most recent study these numbers were 31% for men and 32% for women. Stratified by birth cohort, 43% of men and 37% of women born in or before 1950 were current smokers. For those born after 1950, 37% of men and 39% of women were current smokers. Altogether 18% of men and 8% of women had smoked for 30 years or more. Thirty two % of men and 45% of women started to smoke after age 20. Age at enrollment increased from the earliest study (the Norwegian Counties Study) to the most recent study (CONOR), while years of follow-up decreased for both sexes (data not shown). The mean age at lung cancer diagnosis was for men 64 years and for women 63 years (Web Table 1).

Table 2 shows that the overall incidence rates for men were in the Norwegian Counties Study, the 40 Years Study and CONOR 102.4, 50.4, 83.2 per 100,000 person-years respectively, and for women 59.4, 42.0, and 51.5.

Table 3 shows that compared with their never smoker counterparts, men (HR=19.12, 95%CI: 15.78, 23.18) and women (HR=13.63, 95%CI: 11.83, 15.70) who were current smokers at baseline had a significantly increased risk of lung cancer overall. For both sexes, former and current smokers, showed significant associations with lung cancer risk for smoking duration,

number of cigarettes smoked daily, pack-years of smoking, and age at smoking initiation, (all *P* trend < 0.01). The heterogeneity test for both former and current smokers and lung cancer overall risk showed that these associations were stronger for men than for women (both $P_{heterogeneity} = 0.01$).

For men, Table 3 shows that, compared with never smokers, current smokers who smoked ≥ 16 pack-years had a hazard ratio of 27.24 (95%CI: 22.42, 33.09), and women current smokers a hazard ratio of 23.90 (95%CI: 20.57, 27.76) for lung cancer ($P_{heterogeneity} = 0.30$). Table 3 further shows that, for current smokers, the test for heterogeneity by sex for each variable category compared to never smokers was statistically significant only for duration of smoking (all $P_{heterogeneity} <0.05$) but was not significant for the upper category (≥30 years of smoking) and for the other variables: (number of cigarettes smoked per day, age at smoking initiation and pack-years) [except for the lowest category (1-5 pack-years)]. Also, for former smokers the test for heterogeneity by sex was not significant for any of the smoking variables.

For current smokers, the increase in lung cancer risk was significantly greater in women than men when we examined the various measures of smoking exposures as continuous variables; for each 10 pack-years increment, male (HR=1.43, 95%CI:1.39, 1.48) and female (HR=1.64, 95%CI: 1.57, 1.71), ($P_{heterogeneity} <0.01$), (Table 3). The test for heterogeneity was significant for increments (as continuous measures) of 10 years of smoking duration and 10 cigarettes per day, with a higher risk for women compared to men, who are current smokers (both $P_{heterogeneity}$ values <0.01). When we examined the various measures of smoking exposures as continuous variables in former smokers, the heterogeneity test was significant by sex for 10 pack-years with a higher increased risk of lung cancer per increment for women compared to men ($P_{heterogeneity} <0.01$).

For ever smokers, the increase in risk of lung cancer overall differed significantly by sex, with a greater increased risk in women for increments of 10 years of smoking, 10 cigarettes per day and 10 pack-years (all $P_{\text{heterogeneity}}$ values<0.01) (Table 4). We observed similar significant differences by sex for squamous cell carcinomas, and for adenocarcinomas for increments of 10 cigarettes per day and 10 pack-years, (Table 4). The log-transformed models in ever smokers and by cell-types showed similar differences by sex (data not shown). Due to few cases of small-cell carcinoma, especially among never smokers, we did not stratify by sex when we examined this subtype. We found significant dose response association between smoking duration and risk of small-cell carcinoma (results not shown).

Neither body mass index, nor physical activity or education of the interactions tested was statistically significant for any of the outcomes investigated (data not shown).

The overall results stayed materially the same, when we excluded subjects with lung cancer diagnosed within 2 years after enrollment (data not shown).

Web Table 2 shows that for men current smokers, the overall lung cancer risk differed significantly between the 40 Years Study and the CONOR Study, with a greater risk in the more recent study (CONOR). For female current smokers, the risk of lung cancer differed significantly between all three studies with the highest risk in the earliest study (The Norwegian Counties Study).

Web Table 3 shows that men current smokers born in or before 1950 had a hazard ratio of 23.11 (95%CI: 18.30, 29.20) and the corresponding risk for men born after 1950 was (HR=

10.75, 95%CI:7.62, 15.16), ($P_{heterogeneity}$ <0.01). Also in women the risk of lung cancer was greatest in the oldest birth cohort (born ≤1950).

DISCUSSION

In this large prospective study, we found that compared to women, more men were ever and heavier smokers. More women than men never smokers were diagnosed with lung cancer during follow-up. The age-standardized incidence rate for lung cancer in men was more than six-fold greater among former smokers and 30-fold greater among current smokers, compared with never smokers. The corresponding rates for lung cancer in women was more than doubled in former and more than tenfold greater in current smokers, compared with never smokers.

When we analyzed smoking exposure according to categorical groups (smoking status) we did not detect a difference between men and women. However, when we analyzed the smoking exposure as a continuous variable, women current smokers had a significantly higher risk of lung cancer compared to men current smokers for increments of pack-years, cigarettes per day and smoking duration. The pattern of a greater risk of lung cancer for women compared to men remained after excluding subjects diagnosed with lung cancer within the first two years after enrollment.

Five cohort studies published between 2004 and 2015, including from 470 to 17,670 lung cancer cases did not find a sex difference in susceptibility to the carcinogenic effects of cigarette smoke (9, 11, 29-31). These cohorts analyzed the lung cancer risk according to fixed smoking exposure categories. Our results are in accordance with theirs when we analyze the

data this way. The increased risk for lung cancer among women that we found when we analyzed the data continuously is most likely concealed when the smoking exposure data are categorized. Since men are heavier smokers than women, within each category, they are most likely to be more heavily exposed than women smokers. Furthermore the reference group for women comprises more lung cancer cases than that of men. This will also inflate the lung cancer risk for smoking men, and attenuate that for women. The higher incidence rates for lung cancer for women compared to men never smokers, is likely explained by more women than men being exposed to passive smoking. This is also what was found in a recent review (32).

In Norway, men in every age group, have a higher death rate than women from cardiovascular disease (33), this was also found in this study, and could support the explanation for our finding of a sex difference in risk of lung cancer. A recent study from the European prospective Investigation into Cancer and nutrition (EPIC) revealed lower relative risks for lung cancer in women compared to men current smokers. However, this could be explained by a much heavier smoking burden among men compared to women in countries like Italy, Spain and Greece included in the European prospective Investigation into Cancer and nutrition studies (EPIC) (34).

Our results towards lower relative risks of lung cancer in the most recent birth cohorts are not in accordance with findings observed in the United States and United Kingdom respectively, whose changes were towards higher relative risks (11, 35). The difference observed by birth cohort between our study and the United States study is mainly because we stratified by birth cohort in or before 1950 or after 1950, while the two most recent time periods (1982-1988 and 2000-2010) from the United States study were closer in time and had shorter duration of

follow-up (6-10 years). Likewise an explanation for the change towards lower relative risk in the most recent birth cohort in our study, is that the proportion of lung cancer among those younger than 50 years is only 10% in Norway (2).

Our study has several major strengths. It is based on a large, prospective Norwegian cohort, comprising a high proportion of men and women ever smokers, with long, virtually complete follow-up due to the national registries. Another major strength is that the questions about smoking duration in years and number of cigarettes per day, were open instead of fixed categories. Moreover, we had more than 6500 cases, giving us more stable risk estimates and results that are less prone to chance. We were also able to examine the association between smoking and lung cancer according to histological subtypes and according to different measures of smoking exposure.

A limitation of our study is the lack of updated information on smoking status during follow-up. In Norway, the proportion of daily smokers has decreased steadily with a steeper reduction in men, and the protection from passive smoking has increased, especially during the last decade of our follow-up period. This may explain some of the heterogeneity across birth and study cohorts. As more men than women have quit smoking, this could explain some of the differences in lung cancer risk by sex that we found. We lack information about passive smoking from the majority of the participants. Our reference group is therefore most likely contaminated with passive smokers. Since more men than women were smokers in our population, it is likely that more women than men never smokers were exposed to passive smoking. For women, this will attenuate our observed risk for lung cancer among ever smokers. For men, this will increase our observed risk for lung cancer among ever smokers.

Around 10% of the Norwegian population reported to be occasional smokers in our follow-up (36). Some of these occasional smokers may have been excluded from our analytical sample due to insufficient smoking information, whereas others may have been included in the reference group, together with women exposed to passive smoking. This misclassification would most likely have attenuated the revealed associations between smoking and lung cancer.

We also lack information on possible confounders such as radon-, and occupational, outdoor- and indoor exposures (1). We cannot rule out the possibility of residual confounding due to the above described factors, or other factors we did not measure.

In conclusion, our results suggest that women are more susceptible than men to lung cancer given the same smoking exposure. Future efforts to eliminate smoking in both sexes should continue.

Disclosure of potential Conflicts of interest

No potential conflicts of interest were disclosed.

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3) Phd student Merethe Selnes Hansen was supported by Northern Norway Health Authority (SFP1227-15). Postdoc Idlir Licaj was supported by grants from Norwegian Cancer Society. Grant agreement number: 4510766-2013.

4) Also, we would like to acknowledge the services of Cohort of Norway (CONOR) study and the contributing research centers delivering data to CONOR.

5) No potential conflicts of interest were disclosed

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Tables

Table 1. Selected Characteristics of the Participants at Enrollment by Sex and Smoking Status, the Norwegian Health Screening Surveys, 1974-2003, (N=585,583)

Selected characteristics	Total	Men n=282,637						Women n=302,946					
Smoking status		Current		Former		Never		Current		Former		Never	
Number and %		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Smoking status	585,583	113,033	40	74,639	26	94,965	34	115,350	38	64,024	21	123,572	41
Norwegian counties study	83,500	21,416	51	9,599	23	10,898	26	16,501	40	6,054	14	19,032	46
40 years study	384,864	74,325	40	47,919	26	62,863	34	79,214	40	43,267	21	77,276	39
CONOR study	117,219	17,292	31	17,121	31	21,204	38	19,635	32	14,703	24	27,264	44
Born ≤1950	294,280	62,008	43	42,182	29	40,698	28	55,898	37	28,262	19	65,232	44
Born > 1950	291,303	51,025	37	32,457	24	54,267	39	59,452	39	35,762	23	58,340	38
Age at enrollment[a]	43 (8)	42 (7)		45 (10)		42 (8)		42 (7)		43 (8)		44 (10)	
Person-years	11,553,611	2,282,012		1,446,049		1,847,649		2,289,524		1,211,302		2,477,075	
Age at diagnosis[a]	64 (10)	64	10	69	11	61	12	62	9	65	12	66	12
Lung cancer overall	5,514	3147	85	458	12	109	3	2367	84	232	8	221	8
Adenocarcinoma	1,384	957	26	172	5	63	2	900	32	130	5	119	4
Squamous cell carcinoma	1,293	811	22	99	3	9	<1	346	12	20	<1	8	<1
Small-cell carcinoma	1,161	561	15	49	1	2	<1	516	18	21	<1	12	<1

Education, years												
<10	23		30		22		13	32			21	20
10-12	55		56		55		52	57			57	52
≥ 13	22		14		23		35	11			22	28
Physical activity level[c]												
Sedentary	21		25		19		17	25			20	20
Moderate	51		46		45		41	57			56	58
High	28		29		36		42	18			24	22
BMI[a,d]	25 (4)	25 (3)		26 (3)		26 (3)		24 (4)		25 (4)		25 (4)
Smoking duration years												
1-9	16		5		28			7			41	
10-19	28		17		42			24			40	
20-29	47		67		23			63			15	
≥30	6		11		7			5			3	
Number of cigarettes per day												
1-10	51		37		49			55			72	
11-20	41		52		39			42			24	
>20	5		9		10			3			2	
Pack-years ≥16	28		45		21			27			8	
Age at smoking initiation												
≥21	22		27		5			38			7	
16-20	43		55		26			50			30	

<16	12		18		10			12			10		
Years since quit smoking[c] 0-4 years	12				24						23		

[a]Age at enrollment, age at diagnosis (both in years) and BMI are expressed as mean (standard deviation).

[b]The numbers of lung cancer subtypes of adenocarcinomas, squamous cell carcinomas and small-cell carcinomas do not sum up to the numbers in the lung cancer overall groups because only the main subgroups are in the table.

[c]Physical activity level;sedentary (reading, watching television, and sedentary activity), moderate (walking, bicycling, or similar activities ≥4 hours/wk, and heavy (light sports or heavy gardening ≥4 hours/wk, heavy exercise or daily competitive sports).

[d]BMI (Weight in kilogram divided by height in squared meters)

[e]The sum of percentages in columns of smoking duration, number of cigarettes per day and age at smoking initiation do not sum up to 100% because of missing values.

Table 2. Incidence Rates[a] by Subcohorts, Sex and Smoking Status, the Norwegian Health Screening Surveys, 1974-2003, (N=585,583)

Smoking status	Norwegian Counties Study (1974-1978)		40 Years Study (1985-1989)		The CONOR Study (1994-2003)	
	Men	Women	Men	Women	Men	Women
Overall[b]	102.4	59.4	50.4	42.0	83.2	51.5
Never smokers	7.7	7.5	5.7	8.2	4.5	14.0
Former	28.3	25.3	21.5	13.6	76.1	35.1
Current	188.7	135.2	107.0	90.8	189.7	114.4

[a]Incidence rates per 100,000 personyears

[b]Never, former and current smokers together

Table 3. Multivariate[a]-Adjusted Hazard Ratios for Lung Cancer by sex and Measures of Smoking, the Norwegian Health Screening Surveys, 1974-2003, (N=585,583)

Smoking status	Men Multivariate[a]-adjusted HRs (95% CI)			Women Multivariate[a]-adjusted HRs (95% CI)			Heterogeneity test for women versus men
	No.	HRs	95% CI	No.	HRs	95% CI	
Never	109	1.00	Referent	221	1.00	Referent	
Former	458	3.64	2.95, 4.49	232	2.51	2.08, 3.02	0.01
Current	3147	19.12	15.78, 23.18	2,367	13.63	11.83, 15.70	0.01
Former years smoking							
1-9	23	0.96	0.61, 1.51	42	1.21	0.86, 1.69	0.43
10-19	85	1.95	1.46, 2.60	77	2.11	1.62, 2.75	0.69
20-29	167	5.89	4.59, 7.57	65	4.26	3.22, 5.64	0.09
≥30	177	11.41	8.48, 15.36	43	7.19	5.01, 10.32	0.05
P-trend[d]		0.00			0.00		
Linear[e]		1.83	1.67, 2.00		1.76	1.54, 2.02	0.68
Current years smoking							
1-9	34	6.23	4.12, 9.43	43	3.02	2.12, 4.31	0.01

10-19	274	11.35	9.06, 14.21	351	8.03	6.75, 9.55	0.02
20-29	1971	19.89	16.35, 24.20	1589	15.02	12.94, 17.42	0.02
≥30	858	23.19	18.79, 28.61	368	21.92	18.08, 26.56	0.70
P-trend[d]		0.00			0.00		
Linear[e]		1.37	1.30, 1.45		1.69	1.58, 1.81	<0.01
Former cigarettes/day							
1-10	150	2.23	1.73, 2.87	139	2.00	1.62, 2.4	0.53
11-20	206	4.55	3.60, 5.76	80	4.29	3.30, 5.58	0.74
> 20	77	6.14	4.56, 8.26	10	5.67	3.00, 10.73	0.83
P-trend[d]		0.05			0.43		
Linear[e]		1.34	1.23, 1.46		1.54	1.33, 1.80	0.11
Current cigarettes/day							
1-10	763	11.53	9.42, 14.11	956	9.57	8.24, 11.11	0.15
11-20	1783	22.95	18.88, 27.89	1262	19.73	16.99, 22.90	0.23
>20	507	39.84	32.32, 49.12	140	34.46	27.74, 42.81	0.35
P-trend[d]		0.00			0.00		

Linear[e]		1.54	1.49, 1.60		1.76	1.67, 1.86	<0.01
Former pack-years[b]							
1-5	33	0.95	0.64, 1.40	79	1.49	1.15, 1.93	0.06
6-15	145	2.97	2.30, 3.82	86	3.05	2.37, 3.93	0.88
≥ 16	253	7.98	6.29, 10.13	60	7.43	5.54, 9.97	0.71
P-trend[d]		0.00			0.01		
Linear[e]		1.52	1.43, 1.62		1.85	1.65, 2.07	<0.01
Current pack-years[b]							
1-5	88	5.73	4.31, 7.61	142	3.84	3.09, 4.76	0.03
6-15	906	13.54	11.08, 16.55	1133	12.67	10.92, 14.69	0.60
≥ 16	2052	27.24	22.42, 33.09	1072	23.90	20.57, 27.76	0.30
P-trend[d]		0.00			0.00		
Linear[e]		1.43	1.39, 1.48		1.64	1.57, 1.71	<0.01
Former age at smoking initiation							
≥ 21	22	2.57	1.50, 4.39	29	2.78	1.80, 4.30	0.82
16-20	124	4.26	2.94, 6.18	54	2.95	2.04, 4.25	0.17

<16	46	5.36	3.47, 8.27	11	3.38	1.73, 6.59	0.26
P-trend[d]		0.01			0.14		
Linear[f]		0.92	0.88, 0.96		0.97	0.93, 1.01	0.12
Current age at smoking initiation							
≥ 21	641	12.01	9.79, 14.73	857	9.70	8.34, 11.28	0.10
16-20	1819	20.92	17.22, 25.43	1239	18.83	16.19, 21.89	0.40
<16	682	29.28	23.85, 35.93	261	28.50	23.54, 34.51	0.85
P-trend[d]		0.00			0.00		
Linear[f]		0.92	0.91, 0.93		0.91	0.91, 0.92	0.20
Former smokers years since cessation[c]							
Current smokers		1.00	Referent		1.00	Referent	
0-4	61	0.44	0.34, 0.57	31	0.36	0.25, 0.51	0.38
5-9	34	0.35	0.25, 0.49	14	0.25	0.14, 0.42	0.28
≥ 10	92	0.16	0.13, 0.20	44	0.17	0.12, 0.23	0.77
P-trend[d]		0.00			0.00		
Linear[e]		0.57	0.49, 0.66		0.66	0.53, 0.83	0.26

[a] Adjusted for age, body mass index, physical activity level, all at enrollment, and duration of education.

[b]Pack-years were calculated as numbers of cigarettes smoked per day, divided by 20 and multiplied by smoking duration in years.
[c] For smoking cessation current smokers were the reference
[d]Trend test without never smokers included.
[e] Per 10 year respectively for smoking duration, per 10 cigarettes per day, per 10 pack-years in former and current smokers, and per 10 years since smoking cessation in former smokers, for lung cancer overall
[f]Per year for age at smoking initiation in former and current smokers, for lung cancer overall

Table 4. Multivariate[a]-Adjusted Hazard Ratios for Lung Cancer by Sex, Measures of Smoking and Histological Subtypes, the Norwegian Health Screening Surveys, 1974-2003, (N=585,583)

Smoking status	Men Multivariate[a]-adjusted HRs (95% CI)			Women Multivariate[a]-adjusted HRs (95% CI)			Heterogeneity test for men versus women
	No.	HRs	95% CI	No.	HRs	95% CI	
Lung cancer overall							
Never	109	1.00	Referent	221	1.00	Referent	
Former	458	3.64	2.95, 4.49	232	2.51	2.08, 3.02	0.01
Current	3147	19.12	15.78, 23.18	2367	13.63	11.83, 15.70	0.01
Smoking duration							
1-9	57	1.78	1.29, 2.47	85	1.63	1.26, 2.11	0.68
10-19	359	5.12	4.12, 6.34	428	5.09	4.32, 5.99	0.97
20-29	2138	16.04	13.21, 19.48	1 654	13.05	11.29, 15.08	0.10
≥30	1035	24.50	19.92, 30.13	411	21.47	17.84, 25.84	0.35
P-trend[c]		0.00			0.00		
Linear[d]		1.90	1.82, 1.98		2.11	2.00, 2.23	<0.01
Cigarettes smoked/day							
1-10	913	6.93	5.68, 8.46	1 095	6.25	5.40, 7.24	0.42
11-20	1989	15.52	12.78, 18.83	1 342	15.53	13.41, 17.97	1.00
>20	584	23.03	18.75, 28.29	150	24.85	20.13, 30.69	0.61
P-trend[c]		0.00			0.00		
Linear[d]		1.44	1.40, 1.49		1.82	1.74, 1.91	<0.01
Pack-years[b]							
1-5	121	2.34	1.80, 3.03	221	2.40	1.99, 2.90	0.87
6-15	1051	8.86	7.27, 10.81	1 219	10.03	8.67, 11.61	0.32
≥16	2305	22.12	18.22, 26.84	1 132	21.27	18.34, 24.66	0.75
P-trend[c]		0.00			0.00		
Linear[d]		1.57	1.53, 1.61		1.84	1.78, 1.91	<0.01
Age at smoking initiation							
≥21	663	10.70	8.73, 13.11	886	8.76	7.54, 0.17	0.12

16-20	1943	18.59	15.30, 22.58	1 293	16.23	13.99, 18.83	0.28
<16	728	26.86	21.10, 31.71	278	24.38	20.19, 29.44	0.68
P-trend[c]			0.00			0.00	
Linear[e]		0.92	0.91, 0.93		0.92	0.91, 0.93	0.51
Adenocarcinoma							
Smoking status							
Never	63	1.00	Referent	119	1.00	Referent	
Former	172	2.65	1.98, 3.55	130	2.45	1.91, 3.15	0.93
Current	957	10.33	7.98, 13.37	900	8.52	7.00, 10.36	0.23
Smoking duration							
1-9	26	1.41	0.89, 2.25	44	1.48	1.04, 2.11	0.88
10-19	114	2.94	2.16, 4.01	190	3.99	3.17, 5.04	0.12
20-29	730	9.60	7.39, 12.46	666	8.96	7.32, 10.96	0.68
≥30	253	13.67	10.13, 18.44	128	12.51	9.37, 16.71	0.68
P-trend[c]			0.00			0.00	
Linear[d]		1.83	1.69, 1.98		1.91	1.75, 2.08	0.47
Cigarettes smoked/day							
1-10	272	3.92	2.97, 5.16	448	4.42	3.60, 5.42	0.49
11-20	652	9.07	6.99, 11.77	521	9.84	8.02, 12.09	0.63
>20	166	11.83	8.83, 15.86	60	16.51	12.04, 22.63	0.13
P-trend[c]			0.00			0.00	
Linear[d]		1.38	1.30, 1.47		1.69	1.57, 1.83	<0.01
Pack-years[b]							
1-5	49	1.68	1.15, 2.44	118	2.23	1.73, 2.89	0.22
6-15	344	5.32	4.05, 6.97	490	6.83	5.57, 8.37	0.15
≥16	695	12.41	9.55, 16.12	419	13.17	10.67, 16.25	0.73
P-trend[c]			0.00			0.00	
Linear[d]		1.51	1.44, 1.58		1.76	1.66, 1.87	<0.01
Age at smoking initiation							
≥21	186	5.52	4.14, 7.36	336	5.83	4.72, 7.20	0.76
16-20	582	10.18	7.82, 13.25	484	9.70	7.87, 11.96	0.78
<16	248	16.18	12.20, 21.45	123	16.38	12.51, 21.45	0.95
P-trend[c]			0.00			0.00	
Linear[e]		0.91	0.90, 0.93		0.92	0.90, 0.93	0.61
Squamous cell carcinoma							
Smoking status							
Never	9	1.00	Referent	8	1.00	Referent	

Former	99	9.01	4.55, 17.85	20	6.64	2.91, 15.13	0.87
Current	811	57.49	29.76, 111.05	346	61.63	30.10, 126.20	1.00
Smoking duration							
1-9	14	5.39	2.31, 12.57	7	3.86	1.37, 10.92	0.63
10-19	94	15.50	7.81, 30.74	53	17.55	8.32, 37.02	0.81
20-29	512	44.95	23.21, 87.05	234	54.72	26.87, 111.42	0.62
≥30	289	70.28	35.83, 137.84	67	110.35	51.17, 237.97	0.39
P-trend[c]		0.00			0.00		
Linear[d]		1.90	1.75, 2.07		2.45	2.11, 2.84	<0.01
Cigarettes smoked/day							
1-10	215	18.46	9.47, 35.99	149	24.35	11.93, 49.70	0.58
11-20	480	44.01	22.74, 85.17	191	69.06	33.84, 140.96	0.36
>20	184	85.98	43.98, 168.09	25	131.74	58.98, 294.25	0.42
P-trend[c]		0.00			0.00		
Linear[d]		1.57	1.48, 1.67		2.02	1.79, 2.27	<0.01
Pack-years[b]							
1-5	27	6.14	2.89, 13.08	18	5.59	2.42, 12.93	0.87
6-15	250	24.07	12.37, 46.86	175	42.50	20.83, 86.69	0.25
≥16	601	66.72	34.49, 129.07	168	102.56	50.08, 210.02	0.39
P-trend[c]		0.00			0.00		
Linear[d]		1.69	1.61, 1.77		1.99	1.82, 2.19	<0.01
Age at smoking initiation							
≥21	181	33.58	17.18, 65.63	137	37.54	18.36, 76.80	0.82
16-20	486	55.06	28.42, 106.65	183	71.94	35.09, 147.49	0.59
<16	187	79.03	40.37, 154.69	32	101.15	45.75, 223.64	0.64
P-trend[c]		0.00			0.00		
Linear[e]		0.93	0.91, 0.94		0.91	0.89, 0.94	0.28

[a]Adjusted for age, body mass index, physical activity level, all at enrollment, and duration of education.
[b]Pack-years were calculated as numbers of cigarettes smoked per day, divided by 20 and multiplied by smoking duration in years.
[c]Trend test without never smokers included.
[d]Per 10 year respectively for smoking duration, per 10 cigarettes per day, and per 10 pack-years, among ever smokers, for lung cancer overall, adenocarcinoma and squamous cell carcinoma
[e]Per year for age at smoking initiation, among ever smokers , for lung cancer overall, adenocarcinoma and squamous cell carcinoma