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Smoking and Deaths between 40 and 70 Years of Age in Women and Men

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Background: The vast scientific literature on smoking and health contains few large studies with direct estimates of long-term mortality by smoking habits. Data have been lacking, particularly for women.

Objective: To study smoking and deaths and causes of death in women and men of middle age (40 to 70 years of age).

Design: Population-based cohort study.

Setting: Norway (the Norwegian Counties Study).

Participants: 24 505 women and 25 034 men who were born between 1925 and 1941.

Measurements: Initial information on smoking habits was collected between 1974 and 1978. Smoking status was also assessed about 5 years and 10 years after the first examination. Death during 1974 to 2000 was studied by using death certificate information.

Results: During follow-up, 2333 women and 4680 men died in middle age. Among women and men, 9% and 14% of never smokers, respectively, and 26% and 41% of continuing heavy smokers (≥20 cigarettes per day), respectively, died in middle age. Years of life lost among heavy smokers between 40 and 70 years of age were 1.4 years in women and 2.7 years in men, compared with never smokers. Rates of smoking-associated lung cancer were similar in women and men, while lower cardiovascular mortality rates in women explained most of the difference in smoking-associated all-cause mortality between men and women.

Limitations: Data on changes in smoking habits after the baseline examination were not available for all participants and for the last 15 years of follow-up. Mortality levels in middle age may not apply to non-Norwegian populations.

Conclusions: Continuing smoking strongly increased and smoking cessation decreased the risk for death between 40 and 70 years of age for both women and men. Despite similar rates for lung cancer death, women who smoked had lower mortality rates in middle age than men with similar smoking histories due to fewer cardiovascular deaths in women.

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An early report on smoking and longevity appeared more than 60 years ago (1), and it suggested a clear survival advantage of nonsmokers over heavy smokers in midlife. More than a half century later, another report presented precise survival curves for men by smoking habits (2). In the time between these reports, the historic dimension of the health consequences of smoking was increasingly realized (3–9).

The World Health Organization now recognizes tobacco use as the major preventable cause of adult death, and about 5 million deaths worldwide each year (8.8% of all deaths annually) are attributed to smoking (10). More than half of smoking-attributable deaths worldwide (56%) occur in people younger than 70 years of age and account for 13% of deaths in people 30 to 69 years of age (9). On a global scale, the death toll from tobacco use is increasing (9, 11), and accurately quantifying and updating the number of premature deaths due to smoking is an important task. Estimated numbers of deaths caused by smoking on a national, international, or global level have been calculated by combining relative risks for smokers versus nonsmokers for different causes of death from the second large prospective American Cancer Society Cancer Prevention Study (CPS-II) (12, 13) with direct or indirect (via lung cancer mortality rates) estimates of smoking histories and national mortality statistics (6, 9, 14–17).

However, estimating the number of smoking-attributable deaths that occur in a population in a given year depends on the maturity of the smoking epidemic and will predict the lifetime mortality experience of smoking men and women only under certain conditions (18). To predict individual risks precisely, follow-up studies of individuals through their lifetime are needed. Such studies are rare and have not always estimated direct long-term risk for death. Among studies of survival and smoking (1, 19, 20), the British doctors' study (2, 21) has provided the longest follow-up (50 years) and has allowed for direct and precise calculation of survival of men through middle age and beyond.

Using data from nearly 50 000 Norwegian adults who were born in the second quarter of the 20th century and were followed in the last quarter, we studied smoking, death in middle age (40 to 70 years of age), and causes of death in both women and men.

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Context

The best way to estimate deaths from smoking is to observe people over many decades, as done in a 50-year study of male British physicians. No such study exists for women.

Content

A 25-year study of residents of rural Norway included 24 505 women. Of these women, 2333 women died at age 40 to 70 years (9.4% of never smokers and 18.7% of continuing smokers), mostly from cardiovascular disease and cancer. Continuing heavy smokers survived 1.4 fewer years than never smokers. Mortality rates in smokers and nonsmokers were lower in women than in men.

Cautions

Participants were white and lived in rural areas.

Implications

Active smoking has a large effect on women's longevity in middle age.

—The Editors

METHODS

Study Sample

Between 1974 and 1978, all men and women 35 to 49 years of age who were residing in the 3 rural Norwegian counties of Oppland, Sogn og Fjordane, and Finnmark were invited to a cardiovascular health screening examination. Excluding 783 men and 215 women who were temporarily absent from their residence, 91.4% of the men and 94.2% of the women gave a self-report of their past and current smoking habits and were screened for cardiovascular risk factors (22, 23). Thus, our report is based on mortality follow-up between 40 and 70 years of age (middle age) of 24 505 women and 25 034 men (who were born between 1925 and 1941). Approximately 92% of the respondents attended a second survey and 65% attended a third survey about 5 years and 10 years after the first examination, respectively. We grouped participants into never smokers (no report of smoking at any examination); former smokers; or continuing smokers of 1 to 9 cigarettes, 10 to 19 cigarettes, or 20 or more cigarettes per day (heavy smokers). As a supplementary analysis to facilitate comparison with the 40-year follow-up of the British doctors' study (2), we also studied men who reported smoking 25 or more cigarettes daily. We classified persons as continuing smokers on the basis of the information from the last of up to 3 examinations. On the basis of information given about time since smoking cessation and changes among the 3 examinations, we separated the former smokers into 3 groups on the basis of their age when they stopped smoking (<40 years, 40 to 49 years, or 50 to 59 years).

Mortality Follow-up

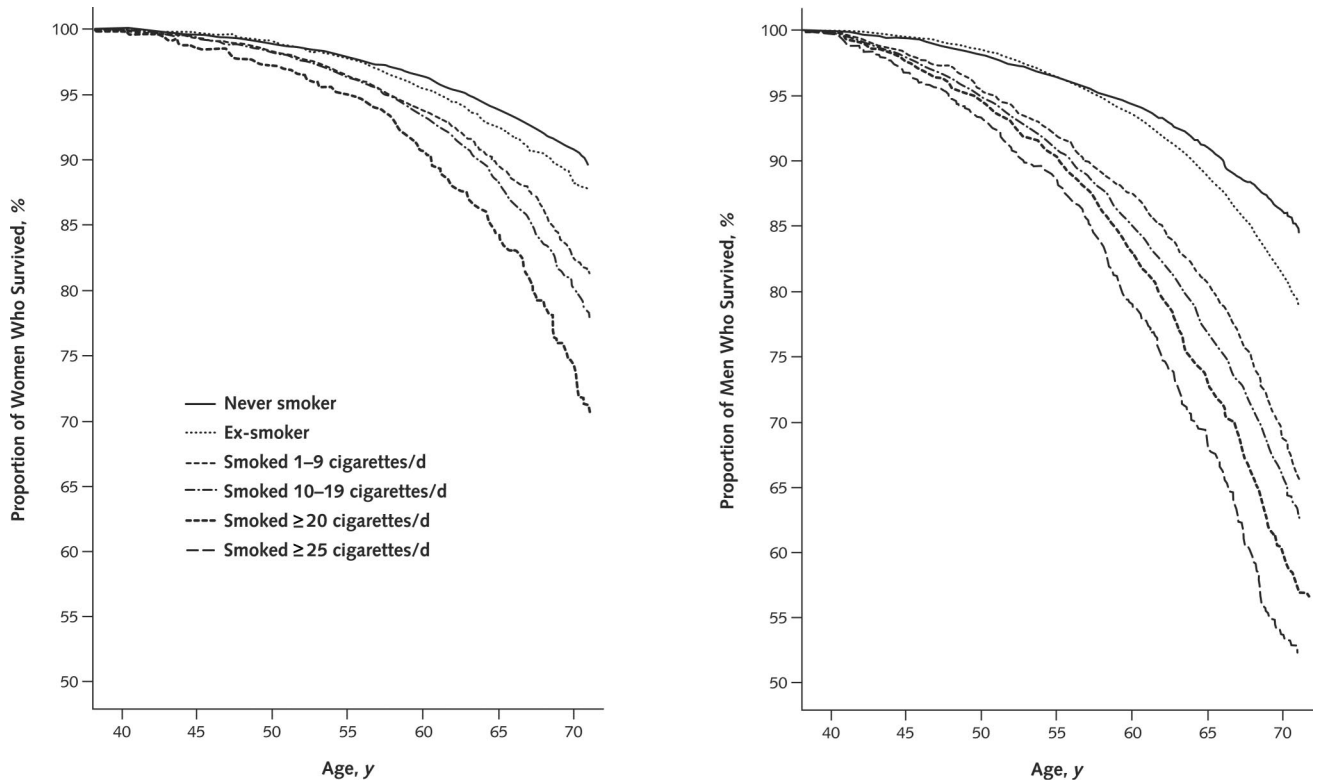
We performed mortality follow-up by record linkage using the Norwegian 11-digit birth number (date of birth plus a 5-digit identifier), which is unique to each person residing in Norway, to obtain the date and underlying cause of death kept by Statistics Norway. Loss to follow-up was due only to emigration, and we censored 93 men and 99 women (0.4%) on their registered date of taking resi-

Table 1. **Baseline Characteristics by Smoking Habit of the 24 505 Women and 25 034 Men Who Were Born between 1925 and 1941 and Were Recruited in Three Norwegian Counties, 1974–1978***

Smoking Habit†	Participants, *n (%)*	Median Age When Smoking Started, *y*	Physically Active, %‡	Higher Education, %§	Married, %
Women	24 505 (100)		10.2	9.8	89.5
Never smokers	11 823 (48)	NA	10.9	11.6	89.6
Former smokers	4299 (18)	–	10.8	11.7	90.5
Continuing smokers	8383 (34)	23.2	9.0	6.1	88.7
1–9 cigarettes/d	2984 (12)	25.9	10.5	5.0	89.7
10–19 cigarettes/d	4458 (18)	22.3	8.2	6.0	89.0
≥20 cigarettes/d	919 (4)	20.9	8.1	10.0	84.3
Pipe or cigar only	22 (0.1)	27.4	13.6	13.6	77.3
Men	25 034 (100)		28.3	16.6	83.3
Never smokers	5348 (21)	NA	35.9	24.2	80.5
Former smokers	8293 (33)	–	28.1	17.4	87.3
Continuing smokers	11 393 (46)	19.2	24.3	12.4	81.7
1–9 cigarettes/d	2236 (9)	20.2	27.8	10.3	80.7
10–19 cigarettes/d	5793 (23)	19.2	24.8	11.5	82.2
≥20 cigarettes/d	2687 (11)	18.5	19.8	16.1	81.0
Pipe or cigar only	677 (3)	19.2	27.2	12.0	83.4

* Dashes denote data that were not available. NA = not applicable.
† Smoking classification was based on the last of up to 3 examinations.
‡ Intermediate or intensive physical activity in leisure time (upper 2 of 4 categories).
§ Duration of education ≥11 y.

Figure 1. **Survival from 40 to 70 years of age in women and men by smoking habit.**



Kaplan–Meier survival curves show the percentage of women (*left*) and men (*right*) who are alive in the age range of 40 years to 70 years by smoking habit. The curves are based on 2333 deaths in middle age among the 24 505 women and 4680 deaths among the 25 034 men during follow-up from 1974–1978 to 2000. We have shown a separate survival curve for men who reported smoking ≥25 cigarettes/d. These men are also included in the ≥20 cigarettes/d group.

dence abroad. Our report is based on mortality follow-up through the year 2000. We classified the 7013 deaths in middle age into 7 groups on the basis of the underlying cause of death coded at Statistics Norway by using the 8th, 9th, or 10th revisions of the International Classification of Diseases (ICD) and European shortlist categories (24). The groups were deaths due to 1) lung cancer (151 deaths in women and 316 deaths in men); 2) other types of smoking-related cancer, including cancer of the lip, oral cavity, pharynx, larynx, esophagus, stomach, liver, pancreas, cervix uteri, kidney, bladder, and acute myelogenous leukemia (262 deaths in women and 386 deaths in men); 3) other types of cancer (796 deaths in women and 648 deaths in men); 4) cardiovascular disease, including sudden death (624 deaths in women and 2252 deaths in men); 5) other medical causes (358 deaths in women and 505 deaths in men); 6) alcohol abuse and chronic liver disease (20 deaths in women and 115 deaths in men); and 7) accidents and violence (122 deaths in women and 458 deaths in men). Types of smoking-related cancer were those reported to be associated with smoking in the 2004 U.S. Surgeon General report (25).

Statistical Analysis

We estimated Kaplan–Meier survival curves from 40 to 70 years of age separately for men and women, and for the various smoking categories, using age as the time scale. We performed computations with the survfit function of S-PLUS, version 6.1 (Insightful Corp., Seattle, Washington). The limited number of individuals who were recruited before 40 years of age led to unstable survival estimates. For this reason, we calibrated all survival analyses to start at 100% at age 40 years.

We estimated mortality hazard (rate) ratios comparing the persons in various smoking categories with never smokers by using the Cox proportional hazards model with age as the time scale and calculated with and without adjustment for potential confounding. The confounders were the following variables, which were all registered at the first examination: marital status (not married or married), duration of education (0 to 9 years, 10 years, 11 to 12 years, or ≥13 years), county of residence, and physical activity in leisure time (sedentary, moderate, intermediate, or intensive). We also used the Cox model to estimate women–men mortality hazard ratios overall and with the different

Table 2. **Mortality in Middle Age by Smoking Habit of 24 505 Women and 25 034 Men Who Were Followed from 1974–1978 to 2000**

Smoking Habit	Deaths between 40 and 70 Years of Age, *n*	Proportion Who Died between 40 and 70 Years of Age, %		Years of Life Lost between 40 and 70 Years of Age, *y*		Hazard Ratio for Mortality in Middle Age (95% CI)	
		Unadjusted (95% CI)	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted†
Women	2333	13.0 (12.5–13.5)	12.9	1.18	1.18		
Never smokers	823	9.2 (8.6–9.8)	9.4	0.88	0.90	1.00	1.00
Former smokers	368	11.7 (10.5–12.9)	11.7	1.04	1.04	1.28 (1.13–1.45)	1.25 (1.11–1.42)
Continuing smokers	1142	19.4 (18.3–20.5)	18.7	1.68	1.62	2.12 (1.94–2.32)	2.00 (1.83–2.19)
1–9 cigarettes/d	382	17.5 (15.8–19.2)	17.0	1.50	1.47	1.88 (1.67–2.13)	1.80 (1.59–2.04)
10–19 cigarettes/d	602	19.7 (18.1–21.3)	19.0	1.67	1.62	2.14 (1.93–2.38)	2.03 (1.82–2.26)
≥20 cigarettes/d	155	25.6 (21.5–29.6)	24.0	2.29	2.10	2.89 (2.43–3.43)	2.62 (2.20–3.12)
Pipe or cigar only	3						
Men	4680	25.3 (24.6–26.0)	25.2	2.42	2.41		
Never smokers	525	13.8 (12.6–15.0)	14.2	1.36	1.42	1.00	1.00
Former smokers	1159	18.9 (17.9–20.0)	19.2	1.58	1.61	1.34 (1.21–1.49)	1.31 (1.18–1.46)
Continuing smokers	2996	34.7 (33.6–35.8)	33.7	3.51	3.39	2.77 (2.52–3.04)	2.58 (2.35–2.83)
1–9 cigarettes/d	534	31.4 (29.0–33.7)	30.7	3.06	3.00	2.39 (2.12–2.69)	2.24 (1.99–2.53)
10–19 cigarettes/d	1504	34.5 (33.0–36.1)	33.6	3.51	3.42	2.77 (2.51–3.06)	2.60 (2.35–2.87)
≥20 cigarettes/d‡	802	40.5 (38.0–42.9)	38.3	4.04	3.82	3.37 (3.02–3.76)	3.04 (2.71–3.40)
Pipe or cigar only	156	27.2 (23.3–30.9)	27.4	2.69	2.71	2.10 (1.75–2.51)	2.04 (1.70–2.44)
≥25 cigarettes/d	286	46.5 (41.9–50.8)	42.9	4.87	4.48	4.11 (3.56–4.75)	3.59 (3.10–4.15)
Sex interaction§							
Female trend coefficient						1.30 (1.26–1.34)‖	1.27 (1.24–1.31)¶
Male trend coefficient						1.37 (1.34–1.40)‖	1.34 (1.31–1.37)¶

* Adjusted for county, education, marital status, and physical activity by averaging individual survival estimates for all observed covariate combinations.
† Adjusted for county, education, marital status, and physical activity in a Cox proportional hazards model.
‡ Smokers of ≥20 cigarettes/d are denoted as heavy smokers and include the ≥25 cigarettes/d group.
§ Test for sex difference in smoking–mortality trends (equally spaced integer scores for never smokers, former smokers, and the 3 continuing smokers categories). Additional adjustment for age when smoking began yielded a *P* value for interaction of 0.39.
‖ *P* value for interaction = 0.004.
¶ *P* value for interaction = 0.006.

cause-of-death groups as outcomes. We performed these analyses for never smokers and for continuing smokers with additional adjustment for age when smokers began smoking and for number of cigarettes smoked per day. We performed tests for difference in regression coefficients between men and women and between smokers and nonsmokers (interaction tests), with the variance estimated as the sum of each coefficient's variance.

We calculated adjusted survival first by predicting survival probabilities for each individual from the Cox model with confounders and then by averaging over all individuals in the sample (26, 27). We did this separately for women and men. We computed the average number of years of life lost between 40 and 70 years of age by summing person-time lost over the survival curves.

To compute cause-specific mortality probabilities for the interval of 40 to 70 years of age, we analyzed the different cause-of-death groups in a competing risk framework. Again, we performed the computations separately for men and women and for the different smoking categories. Let P_{xj} be the probability of death of cause j between 40 and 70 years of age for a person in smoking group x. This probability can be estimated from the following formula:

$$P_{xj} = \int_{40}^{70} S_x(s-)d\Lambda_{xj}(s)$$

where $S_x(t)$ is the Kaplan–Meier estimate of all-cause survival in smoking group x and $\Lambda_{xj}(t)$ is the Nelson–Aalen estimator of cumulative cause-specific hazard, which is computed by using cause j as the outcome and treating all other causes as censoring (28). Note that the probabilities P_{xj} sum to P_x, the all-cause probability of dying between 40 and 70 years of age for a person in smoking group x. The Nelson–Aalen estimator is used rather than the Kaplan–Meier, since cause-specific Kaplan–Meier estimates do not correctly account for deaths from other causes.

We estimated the probability of dying between 40 and 70 years of age as a function of age when smoking began. We calculated these probabilities separately for men and women and for the 3 smoking categories (1 to 9 cigarettes per day, 10 to 19 cigarettes per day, and ≥20 cigarettes per day). We obtained the estimates by fitting a Cox model with a P-spline function (pspline function of S-PLUS) (29) to show the effect of age when smoking began. The P-spline allows for a flexible effect estimation, avoiding the need to assume a prespecified functional relationship be-

tween exposure and outcome, such as linear or polynomial (30). We then estimated the predicted survival from 40 to 70 years of age by using the S-PLUS survfit function for a set of values of ages when smoking began. We plotted the estimated relationships from the 20th to the 80th percentile of age when smoking began in each sex and smoking category.

Role of the Funding Source

No funding was received for this study.

RESULTS

Table 1 shows the baseline characteristics of the participating men and women who were 35 to 49 years of age at the first health screening examination. Marital status, physical activity, and educational level differed between men and women and among the smoking categories.

On the basis of 7013 deaths in middle age during 25 years of follow-up, we estimated that 13% of women and 25% of men died in middle age (**Figure 1** and **Table 2**). Furthermore, 9% of women and 14% of men who had never smoked died, while 26% of women and 41% of men who were heavy smokers (≥20 cigarettes per day) died.

We also computed years of life lost before 70 years of age (**Table 2**). The difference in years of life lost between heavy smokers and never smokers was larger in men (2.7 years) than in women (1.4 years). Years of life lost among those who died showed little variation across smoking categories (including nonsmokers) and were 9.1 years for women and 9.6 years for men.

Table 2 also provides mortality hazard ratios comparing the various smoking groups with never smokers. For both women and men, former smokers had a greater mortality hazard than never smokers, and the hazards increased progressively with increasing consumption. Confounding adjustment only moderately reduced the risk estimates. The smoking–mortality association was stronger in men than in women, but the interaction was weakened and was no longer statistically significant after adjustment of age when smoking began.

We studied risks for death by cause of death. **Table 3** shows the contribution of the 7 cause-of-death groups to the risk for death in middle age in various smoking categories. Lung cancer mortality in middle age was low in never smokers: 1.0 death per 1000 women and 1.3 deaths per 1000 men, compared with 8.3 deaths per 1000 women overall and 18 deaths per 1000 men overall. Among women and men who smoked 20 or more cigarettes daily, 41 lung cancer deaths per 1000 women and 43 lung cancer deaths per 1000 men occurred in middle age, constituting 16% and 11% of the deaths, respectively. The major sex difference in cause-specific risks for death was deaths due to cardiovascular disease, which accounted for 23% and 46% of deaths in heavy-smoking women and men, respectively.

We studied smoking and the risk for death by decade of age (**Table 4**). Overall, about 60% of mortality occurred in the third decade of middle age (60 to 69 years of age), and risks for death were 5 to 6 times higher for men and women in their 60s compared with those in their 40s. In all decades, the risk for death strongly increased with increasing smoking. We also studied former smokers by the age when they stopped smoking (up to 60 years of age). For both men and women, in all 3 decades of middle age, we observed lower risk for death among those who stopped

Table 3. **Proportion of Women and Men Who Died between 40 and 70 Years of Age by Smoking Habit and Cause of Death***

Smoking Habit	Cause of Death, %							
	Any Cause	Lung Cancer	Other Type of Smoking-Related Cancer*	Other Type of Cancer	Cardiovascular	Other Medical Condition	Alcohol-Related Cause and Chronic Liver Disease	Accidents and Violent Deaths
Women	12.99	0.83	1.44	4.33	3.57	2.10	0.11	0.61
Never smokers	9.19	0.10	1.01	4.15	2.03	1.44	0.04	0.42
Former smokers	11.69	0.48	1.13	4.62	2.86	1.92	0.07	0.60
Continuing smokers	19.44	2.11	2.23	4.47	6.28	3.23	0.24	0.88
1–9 cigarettes/d	17.47	1.42	1.82	4.45	6.32	2.75	0.16	0.56
10–19 cigarettes/d	19.70	2.23	2.37	4.21	6.25	3.40	0.29	0.94
≥20 cigarettes/d	25.62	4.11	2.89	6.19	5.89	4.74	0.16	1.64
Men	25.32	1.75	2.09	3.60	12.18	2.81	0.59	2.29
Never smokers	13.80	0.13	0.94	3.33	5.97	1.45	0.20	1.77
Former smokers	18.93	0.61	1.50	3.59	9.03	2.25	0.28	1.67
Continuing smokers	34.71	3.23	2.97	3.68	17.05	3.78	0.99	3.01
1–9 cigarettes/d	31.37	1.82	2.15	3.85	17.07	3.56	0.46	2.45
10–19 cigarettes/d	34.52	3.46	2.86	3.59	16.85	3.65	0.96	3.17
≥20 cigarettes/d	40.51	4.30	4.17	3.99	18.82	4.38	1.61	3.25
≥25 cigarettes/d	46.52	5.84	5.56	3.36	19.05	5.69	3.13	3.90

* Other types of smoking-related cancer include cancer of the lip, oral cavity, pharynx, larynx, esophagus, stomach, liver, pancreas, cervix uteri, kidney, and bladder and acute myelogenous leukemia (25).

Table 4. **Proportion of Women and Men Who Died by Decade of Middle Age and by Age at Smoking Cessation***

Smoking Habit	Participants, *n*	Decade of Death in Middle Age, %			Dying in Middle Age (40–70 y), %
		40–49 y	50–59 y	60–69 y	
Women	24 505	1.3	3.6	8.1	13.0
Never smokers	11 823	1.0	2.6	5.6	9.2
Former smokers	4299	0.8	3.6	7.2	11.7
Stopped at age <40 y	1812	1.0	3.1	5.3	9.4
Stopped at age 40–49 y	1888	NA	4.5	7.6	NA
Stopped at age 50–59 y	581	NA	NA	8.3	NA
Continuing smokers	8383	1.8	5.0	12.6	19.4
1–9 cigarettes/d	2984	1.6	4.6	11.3	17.5
10–19 cigarettes/d	4458	1.7	5.0	13.0	19.7
≥20 cigarettes/d	919	2.8	6.4	16.4	25.6
Men	25 034	3.2	6.9	15.2	25.3
Never smokers	5348	1.8	3.8	8.1	13.8
Former smokers	8293	1.5	4.9	12.5	18.9
Stopped at age <40 y	3000	1.4	3.6	10.5	15.5
Stopped at age 40–49 y	4161	NA	5.8	11.7	NA
Stopped at age 50–59 y	1099	NA	NA	16.1	NA
Continuing smokers	11 393	5.1	9.8	19.8	34.7
1–9 cigarettes/d	2236	4.6	7.9	18.9	31.4
10–19 cigarettes/d	5793	5.1	9.8	19.6	34.5
≥20 cigarettes/d	2687	5.5	11.7	23.3	40.5

* NA = not applicable.

smoking compared with those who continued smoking. The benefit was stronger the earlier the person stopped smoking, but it was also clearly present for those who stopped smoking between 50 and 60 years of age (**Table 4**).

The women in our cohort started to smoke at a later age than the men, and both female heavy smokers and male heavy smokers started smoking at an earlier age than moderate or light smokers (**Table 1**). The shorter history of past smoking in female smokers would tend to exaggerate the survival advantage of female smokers over male smokers. To address this issue, we calculated the probability of death in middle age as a function of the age when smoking began (**Figure 2**). In all smoking groups, women were always at lower risk than men, with a difference between the sexes of 8 percentage points to 15 percentage points.

To further study the sex difference, we estimated the women–men mortality hazard ratios in middle age among never smokers and continuing smokers separately (**Table 5**). We calculated these with adjustment for confounding and among continuing smokers with additional adjustment for numbers of cigarettes smoked per day and age when smoking began. After adjustment, all-cause mortality hazards were about 40% lower in women. The women–men all-cause mortality hazard ratios were similar (P for interaction = 0.14) among continuing smokers (hazard ratio, 0.59 [95% CI, 0.54 to 0.64]) and never smokers (hazard ratio, 0.64 [CI, 0.57 to 0.71]). The lower mortality rates during middle age in women (both continuing smokers and never smokers) were due to lower rates of cardiovascular deaths, alcohol-related deaths, and deaths from accidents and violence. With the exception of a 28% increased risk for death from non–smoking-related cancer in female never smokers ($P = 0.02$), we did not observe any statistically significant differences between men and women for deaths due to lung cancer, other types of smoking-related cancer, or other medical conditions in smokers or never smokers.

Discussion

Our study shows that smoking strongly reduces the chances of surviving from 40 to 70 years of age. The detrimental effect is strongest for high cigarette consumption and early age when smoking began. Smoking cessation increases the chances of survival through middle age. The beneficial effect of smoking cessation is stronger at earlier ages but is also clearly present in the oldest group of quitters (50 to 60 years of age). These findings hold for both women and men, but on an absolute scale, the increased risk for death in middle age is more pronounced for men who smoke than for women with similar smoking histories.

Strengths and Limitations

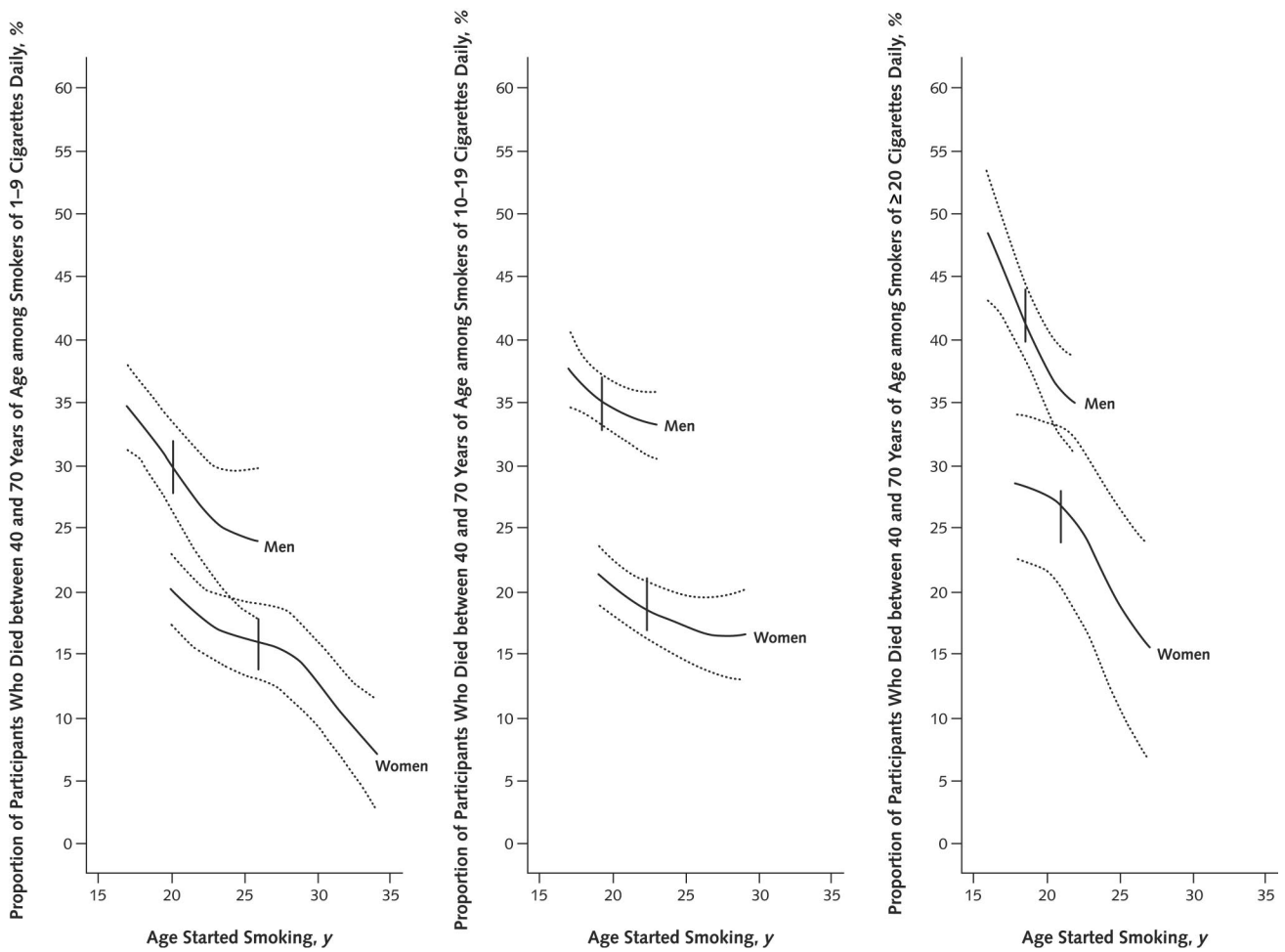
The strengths of our data include complete follow-up of a large cohort of both women and men who were recruited from a relatively recent and narrow range of birth years. More than 7000 deaths in middle age during the 25 years of follow-up allowed us to study main cause-of-death groups and to precisely estimate smoking-associated mortality in middle age in women. A weakness of our study is incomplete updating of smoking histories. From the first (1974–1978) to the last (1996–2000) 5-year periods of

the study, the percentage of adult men in Norway who smoked daily decreased from 48% to 31%, while the percentage of adult women in Norway who smoked daily was stable, decreasing from 33% to 32% (31). Smoking histories were collected about 5 years and 10 years after the initial examination but not during the last 15 years of follow-up. This means that we analyzed smokers who quit smoking during the latter period as continuing smokers, not as former smokers. The misclassification is probably more important for men and would underestimate the effects of continuing smoking on mortality.

Confounding

Higher alcohol consumption, certain personality traits, lower educational level, and a less healthy diet in smokers complicate the interpretation of the increased risk for death in smokers compared with nonsmokers. The issue is complex, and confounding might both inflate and deflate smoking–disease associations (7). Different confounding mechanisms are at play for different causes of death. For example, confounding is of minor importance in explaining the very strong smoking–lung cancer relationship, but it is likely to explain most of the association between smoking and deaths due to accidents, violence, alcohol abuse, and chronic liver disease. Therefore, in line with Peto and colleagues (6), we reported such deaths separately. For all-cause mortality, however, our results and those of other studies indicate that confounding is modest (32, 33). For example, Thun and colleagues (32) investigated confounding in CPS-II and concluded that multivariate adjustment for education, occupation, race, alcohol consumption, and dietary factors reduced the overall estimate of deaths due to smoking by approximately 1 percentage point. In our study, confounding adjustment for marital status, education, county, and physical activity typically reduced hazard ratios by 5% to 10% and had somewhat less effect on years of life lost and estimates of mortality in middle age.

Figure 2. **Probability of death between 40 and 70 years by age when smoking began.**



For each of 3 groups of smokers (1 to 9 cigarettes per day [*left*], 10 to 19 cigarettes per day [*middle*], and ≥20 cigarettes per day [*right*]), the graphs show the percentage of women and men who die in middle age as a function of age when smoking began. The curves extend from the 20th to the 80th percentile of age when smoking began, with the median depicted with a vertical line.

Table 5. **Sex Ratio (Women–Men Mortality Hazard Ratio in Middle Age) for All Deaths and by Specific Causes in Continuing Cigarette Smokers and Women and Men Who Never Smoked***

Cause of Death	Continuing Smokers			Never Smokers			*P* Value for Interaction†
	Deaths, *n*	Women–Men Mortality Ratio (95% CI)	*P* Value	Deaths, *n*	Women–Men Mortality Ratio (95% CI)	*P* Value	
Any cause	3979	0.59 (0.55–0.64)	<0.001	1348	0.64 (0.57–0.71)	<0.001	0.139
Lung cancer	389	1.00 (0.80–1.26)	1.00	14	0.45 (0.15–1.39)	0.167	0.91
Other smoking-related cancer	377	0.87 (0.69–1.10)	0.25	131	0.85 (0.59–1.23)	0.39	0.55
Other cancer	564	1.16 (0.97–1.40)	0.105	499	1.28 (1.04–1.57)	0.019	0.25
Cardiovascular disease	1754	0.36 (0.32–0.41)	<0.001	401	0.33 (0.27–0.40)	<0.001	0.79
Other medical conditions	477	0.98 (0.80–1.19)	0.83	178	0.96 (0.70–1.31)	0.79	0.54
Alcohol-related or chronic liver disease	100	0.28 (0.15–0.51)	<0.001	12	0.20 (0.06–0.71)	0.013	0.68
Accidents and violence	318	0.35 (0.26–0.48)	<0.001	113	0.24 (0.16–0.36)	<0.001	0.92

* Estimated from the Cox proportional hazards model with adjustment for confounders and in continuing smokers with additional adjustment for age when smoking began and number of cigarettes smoked daily (former smokers and pipe or cigar smokers were not included in this analysis).
† Test for difference in women–men mortality ratios between continuing smokers and never smokers.

Women and Sex Difference

Data from a series of case–control studies have suggested that women are more susceptible to lung cancer from smoking than men (34). After correction for dose and duration of smoking, we did not observe a difference in lung cancer deaths during middle age between male and female continuing smokers. Thus, our results are in line with those of recent analyses from large U.S. cohort studies that conclude that women at equal smoking exposure as men have similar lung cancer risks (35). For all causes of death combined, however, we observed that women had about 36% to 41% lower mortality hazards in middle age compared with men. The lower mortality rates were similar in female never smokers and female continuing smokers and were largely explained by lower female cardiovascular mortality rates. Thus, the observation may not extend to areas of the world where coronary heart disease is less prevalent. Our observation that female mortality rates during middle age are doubled in smokers compared with never smokers is in agreement with major North American cohorts (8, 33) and Danish cohorts (36). Our directly estimated survival curves in middle age by smoking habits for women provide greater detail and higher precision than previous analyses (20).

British Doctors' Study

The 50-year follow-up report of the British doctors' study reported results by birth cohorts (21). This allowed us to compare the results for men who were born in the same time period. The difference in mortality during middle age in our cohort between male continuing smokers and never smokers, 21 percentage points, is somewhat lower than the difference of 28 percentage points observed among the youngest British physicians (born between 1920 and 1930). A likely explanation for this discrepancy is that the physicians smoked more than the men in our study, and as a group, the physicians were more similar to the Norwegian heavy smokers, who had a risk for death in middle age of 41% (27 percentage points higher than that of never smokers). We also noted good agreement between the difference in mortality during middle age between continuing smokers of 25 or more cigarettes daily and never smokers of 33 percentage points in our cohort and 30 percentage points in the British doctors' cohort (2).

Smoking Cessation

We observed substantially lower risk for death among those who quit smoking in all decades of middle age. The benefit was greater at earlier ages of smoking cessation. These results confirm and extend findings in randomized trials (37) and large cohorts of women (33) and men (21).

Conclusions

Our data should be a reminder of the historic dimension of the smoking epidemic that causes 2.3 million deaths and 0.4 million deaths among men and women, respectively, 35 to 69 years of age worldwide each year (9). Our results suggest that when women adopt the smoking habits of men, this sex gap in risk for smoking-associated death in middle age will narrow but will not disappear.

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