Lung Cancer Mortality in Relation to Age, Duration of Smoking, and Daily Cigarette Consumption: Results from Cancer Prevention Study II[1]

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ABSTRACT

The magnitude of the effect of smoking duration on lung cancer mortality relative to that of intensity (cigarettes/day) has practical implications for both tobacco control policy and research. This issue was addressed by R. Doll and R. Peto (J. Epidemiol. Commun. Health, *32:* 303–313, 1978) in their historic analysis of one of the few large cohort studies in which intensity and duration were estimated separately. Their findings have been interpreted to mean that smoking duration is much more important than smoking intensity in causing lung cancer. The separate contributions of smoking duration and intensity to lung cancer risk have not been evaluated in other large prospective studies.

We studied participants in the Cancer Prevention Study II, followed from 1982 through 1988. After restricting to people 40–79 years old who smoked ≤40 cigarettes per day at enrollment, we fit Poisson models for four age groups and evaluated lung cancer mortality (M) in relation to smoking duration (D) and intensity (I) on a double-log scale, as suggested by the Armitage-Doll multistage carcinogenesis model.

The age-specific mortality estimates for men (M_m) and for women (M_w), when transformed to the original scale, were:

ages 40–49: $\hat{M}_m = e^{-17.9} \times D^{1.9} \times I^{0.95}$, $\hat{M}_w = e^{-20.2} \times D^{2.8} \times I^{0.96}$;
ages 50–59: $\hat{M}_m = e^{-17.4} \times D^{2.6} \times I^{0.52}$, $\hat{M}_m = e^{-17.2} \times D^{2.2} \times I^{0.75}$;
ages 60–69: $\hat{M}_m = e^{-15.7} \times D^{2.4} \times I^{0.37}$, $\hat{M}_m = e^{-14.1} \times D^{1.5} \times I^{0.78}$;
ages 70–79: $\hat{M}_m = e^{-13.0} \times D^{1.8} \times I^{0.39}$, $\hat{M}_m = e^{-13.2} \times D^{1.3} \times I^{0.95}$.

Our study confirms that years of cigarette smoking is far more important than the number of cigarettes smoked per day in predicting lung cancer risk in United States men, regardless of age, and provides new evidence that a qualitatively similar pattern holds for women. The results support measures to prevent the uptake of smoking by adolescents and increase cessation. We discuss reasons why the associations we observe are lower than those reported by R. Doll and R. Peto (J. Epidemiol. Commun. Health, *32:* 303–313, 1978).

INTRODUCTION

The relative impact on lung cancer mortality of smoking duration compared with the effect of intensity (cigarettes/day) has practical implications for both tobacco control policy and for research. For example, if the intensity of smoking is largely overshadowed by the duration of smoking as a determinant of lung cancer, then even effective measures to reduce the "tar yield" of cigarettes could have less impact on lung cancer risk than would equivalently effective measures to reduce the duration of smoking. Research studies on tobacco that combine the duration and intensity of smoking into a single variable, such as pack years, provide little or no information about the relative importance of duration *versus* intensity.

Doll and Peto (1) addressed this issue in their historic analysis of one of the few large cohort studies in which the effects of intensity and duration have been estimated separately. They modeled the relationship between incidence of lung cancer and cigarette smoking duration and intensity by using data from the 20-year follow-up of male British physicians, and they concluded that incidence was proportional to approximately the fourth or fifth power of smoking duration (as measured by age) and to the second power of smoking intensity (measured as cigarettes/day). The findings of their research have been widely interpreted to mean that smoking duration is much more important than smoking intensity in causing lung cancer and that the development of lung cancer may be a five- or six-step process.

Some have attempted to interpret these patterns of risk theoretically in terms of the stages of lung cancer development. According to the multistage theory of carcinogenesis (2–5), an ordered sequence of discrete cellular changes that are heritable when somatic cells divide is needed to transform a normal epithelial cell into a progenitor of a carcinoma (1, 5). If we denote the incidence of a specific carcinoma after t years of exposure to an environmental carcinogen as I_t, then a simple multistage theory predicts that

$$I_t \propto t^{n-1}, \tag{A}$$

where n is the number of stages it takes for a normal epithelial cell to be transformed into a carcinoma that can be clinically diagnosed (2, 5). Equation A implies a log-log linear relationship between incidence I_t and duration of exposure t (*i.e.*, a plot of log I_t *versus* log t would yield an approximately straight line with slope $n - 1$; Ref. 5, 6). For lung cancer, I_t can be approximated by the mortality rate (M_t), because death is very likely and usually happens within 6 months after clinical diagnosis (7). Hence, if we substitute M_t for I_t in Equation A, the relationship should still hold approximately.

For two decades, no data from other large, prospective studies have been evaluated to verify these findings. In our study, we used data from the first 6 years of follow-up of the American Cancer Society CPS-II[4] to examine lung cancer mortality in relation to cigarette smoking duration and intensity, and especially to evaluate the double-log linear relationship suggested by the multistage theory of carcinogenesis of Armitage and Doll (2–5). We used the smoking duration reported by respondents rather than age (less some constant), as did Doll and Peto (1). Our analyses also considered women as well as men. Additionally, to separate the effect of duration of exposure to cigarette smoke from that of age, we stratified the data by age and examined the relationship among the different age groups.

MATERIALS AND METHODS

CPS-II was begun by the American Cancer Society in 1982. It is the largest and most recent prospective study on smoking and lung cancer (8–11). Subjects were recruited in 1982 from among the friends, neighbors, and acquaintances of volunteers for the American Cancer Society. Enrollment was by household. Volunteers sought to enroll all household members 30 years or older if at least one family member was at least 45 years old. Participants were from all 50 states, the District of Columbia, Puerto Rico, and Guam. Compared

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[4] The abbreviation used is: CPS-II, Cancer Prevention Study II.

with the general United States population, participants of CPS-II were older, more educated, and more frequently married and middle class (8, 9). Whites made up 93% of CPS-II participants. At enrollment, participants completed a questionnaire that asked the question: "Do you now or have you ever smoked cigarettes at least one a day for one year's time?" For men, this question also mentioned cigars and pipes. Current smokers were asked to complete separate sections on the average number of cigarettes smoked per day, years of smoking, age of starting to smoke, and depth of inhalation. During the first 6 years of follow-up, the volunteers tracked, by personal inquiry, whether the participants died. Current analyses are based on 6 years of follow-up, for reasons discussed below. Follow-up was 98.2% complete, and death certificates were obtained for 96.5% of deceased subjects. The underlying cause of death was coded according to abbreviated versions of the ninth revision of the International Classification of Disease (12).

In this study, we defined current smokers as persons who reported having smoked at least one cigarette per day for at least 1 year, who were currently smoking cigarettes only, and who had never smoked pipes or cigars. Our analyses, like those of Doll and Peto (1), excluded former smokers. We also excluded persons who had smoked other tobacco products besides cigarettes and persons with incomplete or implausible data on amount or duration of smoking. We restricted our analysis to persons 40–79 years of age, to facilitate comparisons with the results of Doll and Peto (1) and because relatively few lung cancer deaths had occurred before age 40 or after age 79. To allow for latency in lung cancer development, we restricted our analyses to follow-up of people who had smoked at least 10 years. We excluded those who smoked more than 40 cigarettes per day, reported lung cancer at enrollment, or started smoking before age 10. Our analyses included the 93,215 currently smoking men and the 24,159 currently smoking women in CPS-II who met eligibility criteria (Table 1). In sensitivity analyses, we also included the 127,162 nonsmoking men and 355,363 nonsmoking women who met eligibility criteria (Table 1). The intensity of smoking was defined as the self-reported average number of cigarettes smoked per day, and duration of smoking was defined as the self-reported total number of years of smoking (or, if those data were missing, the difference between age of initiation and age). We advanced age and duration of smoking as follow-up progressed, assuming that smokers continued to smoke. For example, during the first and second year of follow-up, a 59-year-old who had smoked for 20 years at enrollment was considered to be 60 and 61 years old in these years, respectively, and to have smoked for 21 and 22 years.

We summarized person-time and deaths stratified by attained age, duration, and cigarettes per day. For attained age, we used four strata (40–49, 50–59, 60–69, and 70–79 years) and analyzed men and women separately. For each age group and gender, we fit Poisson regression models that contained both smoking duration and intensity variables. In fitting the Poisson models, we categorized years of smoking into five groups (10–19, 20–29, 30–39, 40–49, and ≥50 years) and assigned a score corresponding to the observed mean for each category (15.6, 25.7, 35.3, 44.4, and 53.6 years, for men and 15.2, 25.6, 34.8, 44.0, and 53.4 years for women, respectively).

Similarly, we classified intensity of smoking into five categories of cigarettes per day (1–9, 10–19, 20–29, 30–39, and 40) and assigned a score corresponding to the observed mean for each category (4.5, 12.8, 20.8, 30.6, and 40 cigarettes per day for men and 5.0, 12.5, 20.6, 30.5, and 40 cigarettes per day per day for women, respectively). We used a log link function and log-transformed the duration and intensity, so that the modeled relationship between lung cancer mortality ($\hat{M}_m$) and cigarette smoking duration (D_k) and intensity (I_k) for the age group k could be expressed as

$$\hat{M}_m = e^{\hat{\beta}_{0k}} (D_k)^{\hat{\beta}_{Dk}} (I_k)^{\hat{\beta}_{Ik}} \text{ (B)}$$

where $\hat{\beta}_{0k}$ is the intercept estimate for age group k and $\hat{\beta}_{Dk}$ and $\hat{\beta}_{Ik}$ are parameter estimates for duration and intensity of smoking, respectively. To examine graphically the association between lung cancer mortality and smoking behavior, we fit Poisson regression models separately for smoking duration and then for intensity for each age- and sex-specific group.

We assumed that smoking duration advanced during the 6-year follow-up, because no information on smoking was collected after enrollment. We ignored the lag time between malignant transformation and clinical diagnosis of lung cancer, which other researchers have assumed to be 3.5 years (1, 13). Sensitivity analyses suggested the potential biases resulting from these simplifications to be small (data not shown). We also assessed why our results differed quantitatively, although not qualitatively, from those of Doll and Peto (1) by sequentially making changes, so that our method of analysis more closely approximated theirs. First, we reanalyzed our data (model 2) using age minus 22.5 as a surrogate for duration of smoking in the model, but otherwise ignored age and used the reported intensity +6, rather than intensity itself, changes that reflect how Doll and Peto (1) modeled duration and intensity. Finally, we further modified our analyses by including nonsmokers (model 3), an approach also used by Doll and Peto (1). We used PROC GENMOD of SAS (14, 15) to fit the Poisson models. We evaluated the goodness-of-fit of the models by using both the deviance statistic and residuals (14, 16, 17). Final models fit well for all age groups. In sensitivity analyses, we reanalyzed data after dividing each age group at the midpoint. The model continued to fit well, although control for age was required for adequate fit among 60- to 69-year-old men (results not shown).

RESULTS

Description of Study Cohort. The mean number of cigarettes smoked per day by age decreased with age, especially after age 60 (Table 1), and was somewhat lower for women than men (11). Smokers age 70–79 at baseline smoked about three to five fewer cigarettes per day than those age 40–49 years. Older persons tended to have smoker longer but to have begun at older ages. As expected, lung cancer risk increased as age advanced, with the lung cancer death rate 30–40 times higher for smokers 70–79 years of age than for smokers 40–49 years of age.

Graphical Representation of Lung Cancer Mortality by Duration and by Intensity of Cigarette Smoking. When we plotted lung cancer mortality by duration (Fig. 1 for men and Fig. 3 for women) and intensity of cigarette smoking (Fig. 2 for men and Fig. 4 for women) on a log-log scale, the straight-line model fit the data well for all age groups and did not depart substantially from a linear relation, although the slopes and intercepts of the fitted lines differed between gender and age groups. Middle-aged men and women tended to have slightly greater proportionate increases in mortality with amount smoked demonstrated by slightly steeper slopes for both intensity and duration, and greater negative intercepts, whereas older men and women usually had more gradual increases. Consequently, the difference in lung cancer mortality between the younger and older age groups, as shown on a log-log scale, tended to diminish slightly with heavier and more prolonged smoking.

Poisson Regression Models of Log Lung Cancer Mortality and Smoking Duration and Intensity. When we used the Poisson models to evaluate the relationship between lung cancer mortality, cigarette smoking duration, and cigarette smoking intensity on a log-log

Table 1 *Average intensity and duration of smoking among current smokers, by age*

Age group and gender	Deaths (person-years)	Average intensity (cigarettes/day)[a]	Average duration (years)[b]	Lung cancer mortality (deaths/100,000 persons)
40–49				
Men	18 (75,938)	25	29	24
Women	40 (138,275)	20	27	29
50–59				
Men	326 (221,677)	23	36	147
Women	249 (278,591)	20	33	89
60–69				
Men	699 (161,945)	23	44	432
Women	435 (197,527)	19	40	220
70–79				
Men	470 (50,371)	20	51	933
Women	217 (63,636)	17	46	341

[a] The intensity of smoking reflects the number of cigarettes smoked per day, as reported at baseline; excludes nonsmokers.

[b] Age and the duration of smoking increase with each year of follow-up on the assumption that current smokers continue to smoke.
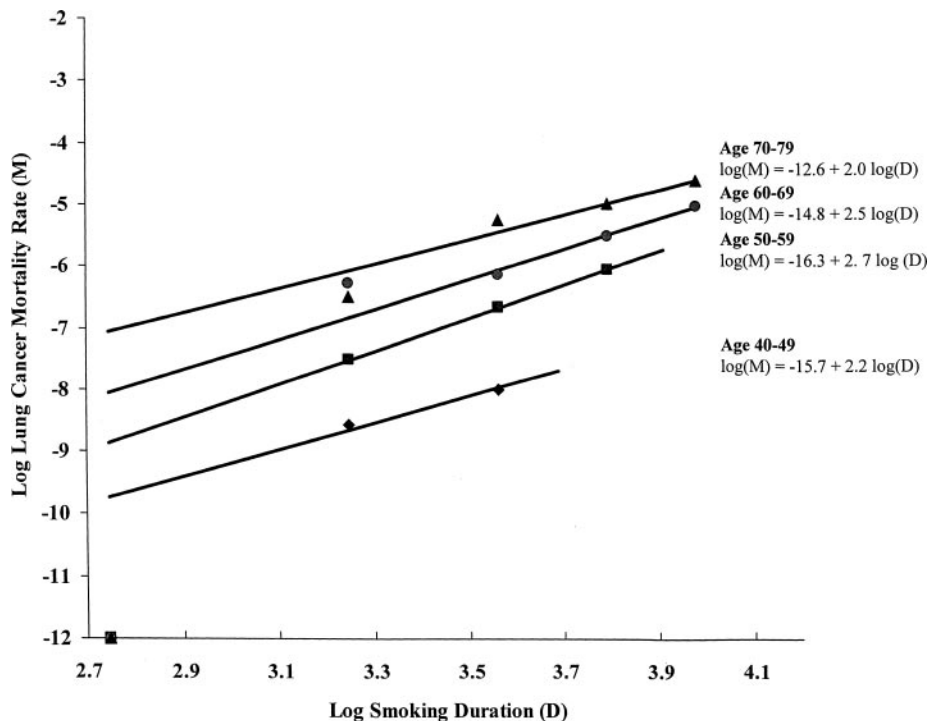
Fig. 1. Logarithm of lung cancer mortality among currently smoking men by logarithm of duration of smoking, by age, CPS II 1982–1988.

Age 70-79
$\log(M) = -12.6 + 2.0 \log(D)$
Age 60-69
$\log(M) = -14.8 + 2.5 \log(D)$
Age 50-59
$\log(M) = -16.3 + 2.7 \log(D)$

Age 40-49
$\log(M) = -15.7 + 2.2 \log(D)$

Note: Categories with 0 deaths are plotted as though the log (mortality rate) were -12.

scale, we found that the association of mortality with cigarette smoking, especially with intensity, tended to decrease with increasing age, (Table 2). For both men and women 40–49 years of age, mortality increased roughly in proportion to the second power of smoking duration and to the first power of intensity. For men 70–79 years of age, mortality increased roughly in proportion to the second power of smoking duration and the square root of intensity. The increases for women depended somewhat more strongly on intensity than they did for men, and perhaps slightly less strongly on duration, although the overall patterns were similar. For equivalent duration and intensity of smoking, the estimated absolute risk of lung cancer was higher for older smokers than for younger smokers, reflecting a rapid increase with age in the baseline rates. These results are consistent with the graphical representation of lung cancer mortality and smoking described previously (Figs. 1–4). Results were similar when we excluded men who first started to smoke at age 40 or older, or when we
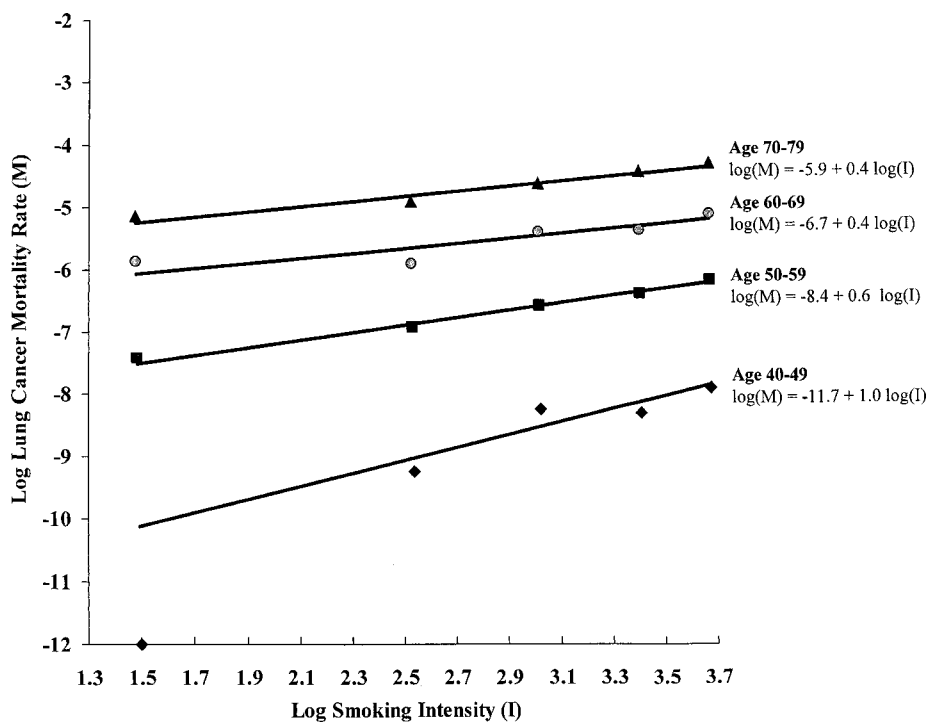

Fig. 2. Logarithm of lung cancer mortality among currently smoking men by logarithm of intensity of smoking, by age, CPS II 1982–1988.

Age 70-79
$\log(M) = -5.9 + 0.4 \log(I)$
Age 60-69
$\log(M) = -6.7 + 0.4 \log(I)$
Age 50-59
$\log(M) = -8.4 + 0.6 \log(I)$

Age 40-49
$\log(M) = -11.7 + 1.0 \log(I)$

Note: Categories with 0 deaths are plotted as though the log (mortality rate) were -12.

Table 2 *Age-specific associations of lung cancer mortality with duration and intensity among current smokers*

Age group and gender	Intensity β_{Ik} (RR: 95% CI)[a]	Duration β_{Dk} (RR: 95% CI)[b]	Deviance/df[c]
40–49			
Men	0.95 (2.6: 0.8–3.1)	1.9 (6.7: 0.5–94)	0.75
Women	0.96 (2.6: 1.3, 3.7)	2.8 (16: 2.7, 95)	1.27
50–59			
Men	0.52 (1.7: 1.3–2.1)	2.6 (13: 6.2–29)	0.57
Women	0.75 (2.1: 1.6, 2.7)	2.2 (9.4: 4.3, 21)	0.81
60–69			
Men	0.37 (1.4: 1.3–1.7)	2.4 (11: 6.0–20)	1.18
Women	0.78 (2.2: 1.8, 2.6)	1.5 (4.7: 2.7, 8.1)	1.09
70–79			
Men	0.39 (1.5: 1.3–1.7)	1.8 (6.0: 2.2–16)	0.58
Women	0.95 (2.6: 2.0, 3.4)	1.3 (3.5: 1.7, 7.2)	1.04

[a] The intensity of smoking reflects the number of cigarettes smoked per day, as reported at baseline, and was modeled as the logarithm of intensity; analyses exclude nonsmokers and former smokers. $\hat{\beta}_{Ik}$ is log of age-specific hazard ratio for log-intensity; RR is the hazard ratio, followed by associated 95% confidence intervals.

[b] Age and the duration of smoking increase with each year of follow-up, assuming that current smokers continue to smoke; duration was modeled as the logarithm of duration. $\hat{\beta}_{Dk}$ is log of age-specific hazard ratio for log-duration; RR is the hazard ratio, followed by associated 95% confidence intervals.

[c] df, degrees of freedom.

included men who reported that they had started to smoke before age 10 (data not shown).

When we compared the estimates of association between lung cancer mortality and either smoking duration or intensity, we found that, in each age group, the estimated increase in mortality associated with duration measured in years was much larger than that for intensity measured in cigarettes per day (Table 2), for both men and women. The ratios of the two exponents $(\hat{\beta}_{Dk}/\hat{\beta}_{Ik})$ for men, were 2.0, 4.6, 6.5, and 4.6 for persons 40–49, 50–59, 60–69, and 70–79 years of age, respectively. For women, the corresponding ratios were: 2.9, 2.9, 1.9, and 1.4, respectively.

Comparison with Results of Doll and Peto. We repeated the analyses using alternative statistical models to determine why our results differed quantitatively from those of Doll and Peto (Ref. 1;

Table 3). These analyses, like those of Doll and Peto (1), are restricted to men. Results of our main analysis (Table 3, model 1) showed that lung cancer mortality among men increased in proportion to the square root of intensity ($\beta \approx 0.4$), whereas Doll and Peto (1) estimated that the increase (in incidence) was proportional to the intensity squared ($\beta \approx 2$). We found that the increase in lung cancer was proportional to duration raised to the 2.3 power, whereas Doll and Peto (1) estimated the it as duration raised to the 4.5 power.

We then changed this model in two ways. First, we used age minus 22.5 as a surrogate for duration of smoking in the model, but otherwise ignored age, and modeled intensity as the reported intensity +6, rather than the reported intensity itself. These modifications reflect how Doll and Peto (1) modeled duration and intensity, so that our modified model 2 more closely approximates their analyses. [Doll and Peto (1) used age minus 22.5 as a measure of duration at onset of cancer, because men in their study had started to smoke at approximately age 19 and to allow for several years for a lung cancer to become clinically evident. They used intensity +6 for intensity, based on consideration of the best fitting model.] With these changes, we found that the estimated mortality was proportional to intensity raised to the 0.69 power and to duration raised to the 4.4 power. Finally, we further modified our analyses (model 3) by including nonsmokers, an approach also used by Doll and Peto (1). With this approach, mortality increased in proportion to intensity raised to the 1.6 power and to duration to the 4.6 power, similar to the results of Doll and Peto (1), but with a poor fit.

DISCUSSION

Our principal finding is that the lung cancer death rate increased far more strongly with each additional year of smoking duration than with each additional cigarette per day, among United States men enrolled in CPS-II, regardless of age. A similar pattern held for women, in that the increase with each additional year of smoking duration was greater than that for each additional cigarette per day, but the relative de-
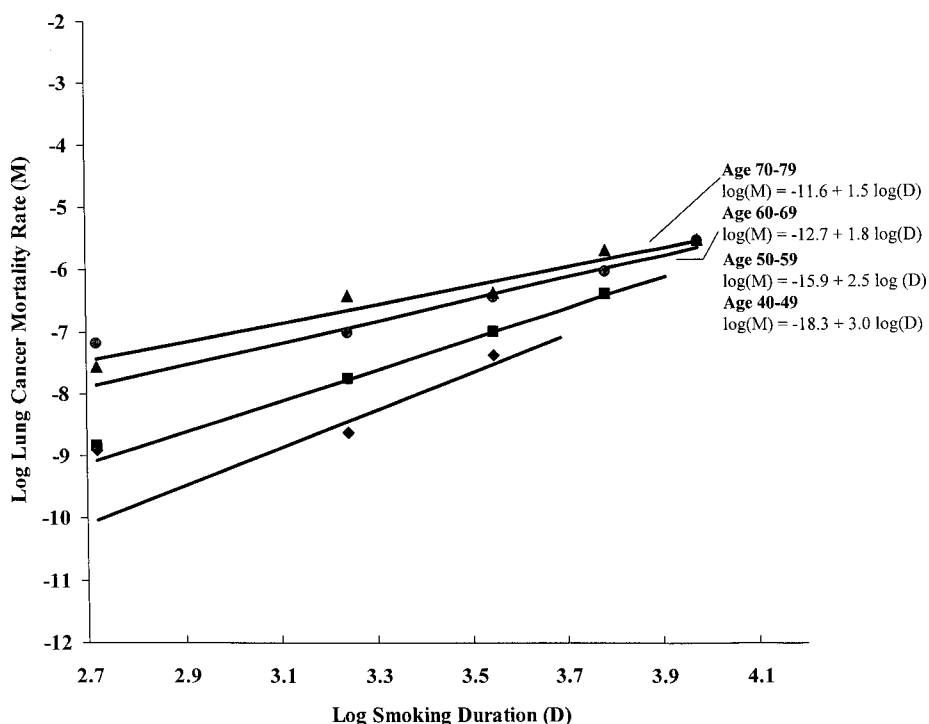

Fig. 3. Logarithm of lung cancer mortality among currently smoking women by logarithm of duration of smoking, by age, CPS II 1982–1988.

Age 70-79
log(M) = -11.6 + 1.5 log(D)
Age 60-69
log(M) = -12.7 + 1.8 log(D)
Age 50-59
log(M) = -15.9 + 2.5 log (D)
Age 40-49
log(M) = -18.3 + 3.0 log(D)

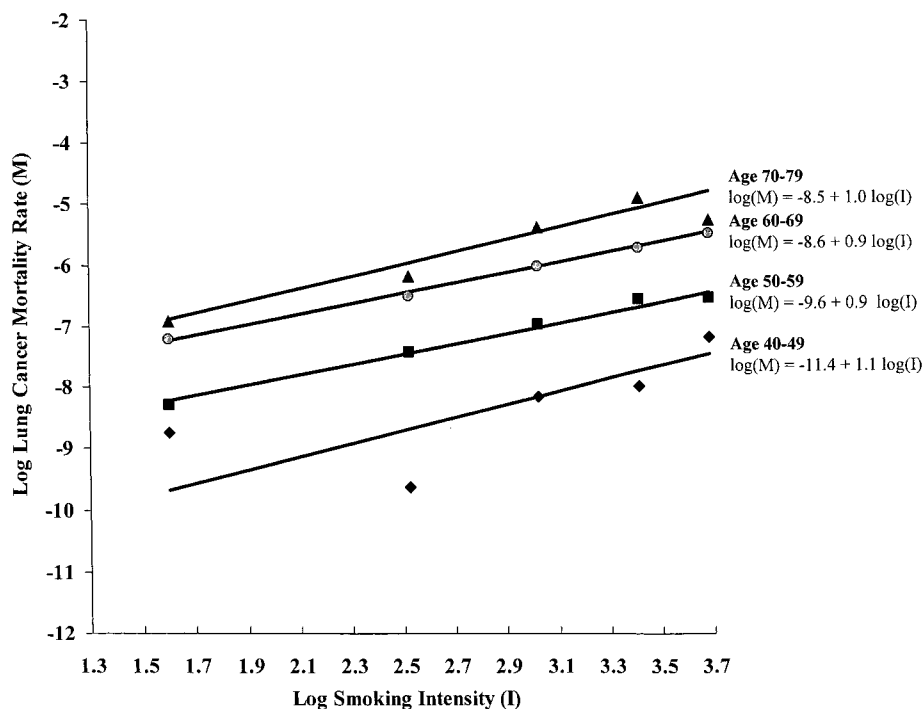Note: Categories with 0 deaths are plotted as though the log (mortality rate) were -12.

Fig. 4. Logarithm of lung cancer mortality among currently smoking women by logarithm of intensity of smoking, by age, CPS II 1982–1988.

Note: Categories with 0 deaths are plotted as though the log (mortality rate) were -12.

pendency on intensity was greater for women than for men. Specifically, in every age stratum, lung cancer mortality among men increased approximately in proportion to duration squared and increased approximately in proportion to the square root of intensity. Among women, lung cancer mortality increased approximately in proportion to duration to the first or second power and increased approximately in proportion to intensity. Qualitatively similar results were observed by Doll and Peto (1) among male British physicians. These authors estimated that lung cancer incidence was proportional to the fourth or fifth power of smoking duration as measured by (age minus 22.5) and to the second power of smoking intensity (1). In a separate analysis of the study of British physicians, Whittemore and Altshuler (18) also observed a linear relationship between lung cancer incidence and daily cigarette consumption.

The quantitative differences between our findings and those of Doll and Peto (1) are largely attributable to three differences in the specification of age, duration, and intensity in the statistical model and to whether nonsmokers are included in the analysis. Our primary analyses directly considered age in estimating the association between lung cancer mortality and duration and intensity of smoking. Doll and Peto (1), in contrast, studied a much smaller cohort and used age as a

surrogate for duration. Therefore, their approach effectively precluded the separation of years of smoking from attained age. When we repeated our analyses using age minus 22.5 as a proxy for duration and adding 6 to the reported number of cigarettes per day, paralleling the approach of Doll and Peto (1), the association between lung cancer mortality and duration increased to 4.4, the same as reported by Doll and Peto. Furthermore, after these modifications, the association between lung cancer mortality and intensity increased from 0.41 to 0.69. Doll and Peto (1) found a stronger association with intensity (exponent ≈ 2.0) but noted that the estimated exponent for duration of smoking depended on the constant chosen to be subtracted from age. Finally, we included nonsmokers in our analyses to replicate even more closely the approach of Doll and Peto (1). With the inclusion of nonsmokers, our estimates are similar to those of Doll and Peto (1.6 *versus* 2 for intensity; 4.6 *versus* 4.5 for duration). Doll and Peto (1) noted that had they used (cigarettes/day +1) instead, the estimated exponent for smoking intensity would also have been approximately one. The rationale for adding a constant to duration and intensity was presumably because the logarithm of duration and intensity would otherwise have been undefined in nonsmokers. The residual, relatively small differences between our results and those of Doll and Peto

Table 3 *Estimated association of lung cancer mortality with duration and intensity, using alternative models*

Model	Model no.	Intensity $\hat{\beta}_{Ik}$ (RR: 95% CI)[a]	Duration $\hat{\beta}_{Dk}$ (RR: 95% CI)[b]	Deviance/df[c]
Baseline—reported duration and intensity; adjusted for age	1	0.41 (1.5: 1.4–1.7)	2.3 (10: 6.5–15)	0.96
Duration = age − 22.5; intensity = intensity + 6[d]	2	0.69 (2.0: 1.7–2.3)	4.4 (81: 62–110)	1.24
Duration = age − 22.5; intensity = intensity + 6[d] include nonsmokers	3	1.6 (4.9: 4.6–5.4)	4.6 (99: 76–130)	2.39

[a] The intensity of smoking reflects the number of cigarettes smoked per day, as reported at baseline, and was modeled as the logarithm of intensity; analyses exclude nonsmokers and former smokers. $\hat{\beta}_{Ik}$ is log of of the hazard ratio for log-intensity; RR is the hazard ratio, followed by associated 95% confidence intervals.

[b] Age and the duration of smoking increase with each year of follow-up, assuming that current smokers continue to smoke; duration was modeled as the logarithm of duration. $\hat{\beta}_{Dk}$ is log of the hazard ratio for log-duration; RR is the hazard ratio, followed by associated 95% confidence intervals.

[c] df, degrees of freedom.

[d] All models that use age − 22.5 as surrogate for duration include no adjustment or modeling of age.

(1) may be attributable to chance or to other differences in design between the studies. For example, the CPS-II cohort was larger, more heterogeneous, and were followed for a shorter time.

Our analyses considered only the first 6 years of follow-up to minimize misclassification of smoking during follow-up. This approach was necessary because smoking histories were obtained only at baseline, and many current smokers would have quit during more prolonged follow-up.

The observation that the duration of smoking is such a strong determinant of lung cancer risk has important implications for public health. It supports efforts to prevent or delay the uptake of smoking among adolescents. Such measures include excise taxes to increase the price of cigarettes and counter-advertising (19, 20). It reinforces the need for more effective smoking cessation programs that motivate smokers to quit at earlier ages (21). Finally, it predicts a steep increase in lung cancer incidence and mortality over time in countries in which the tobacco epidemic has only recently begun, even though smokers in some of these countries smoke fewer cigarettes per day, on average, than in the United States or in the United Kingdom (22, 23).

Whether age plays an independent role in carcinogenesis, separate from its correlation with cumulative genetic damage, has been debated without clear resolution, partly because limited data from humans are available to examine this issue (24, 25). In our study, we stratified the analysis on age and found that the estimated exponents for both duration and intensity of smoking decreased with increasing age (Table 2). Moreover, the close correlation of age at initiation, attained age, and the duration of smoking effectively prevents us from studying the effects of age at initiation in current smokers (26, 27).

These findings should not be interpreted as implying that older smokers are at lower risk of dying from lung cancer. The opposite is true, in fact, because older smokers incur a greater absolute risk of lung cancer than younger smokers for the same duration and intensity of smoking. The reductions in the estimated exponents for relative risks signify only that the incidence rate ratios are smaller for older smokers than for younger smokers, given the same duration and intensity of smoking, as reported by Thun *et al.* (11).

Another point that warrants special attention is that when relating lung cancer mortality with duration and intensity of smoking on a double-log scale, a small slope in older age groups does not imply that increases in the duration or intensity of smoking have little effect on lung cancer risk of older smokers. Because the slope is positive, lung cancer risk increases exponentially with duration and intensity of smoking.

One hypothesis to explain the decrease in the association between lung cancer and the duration and intensity of cigarette smoking at older ages relates to the multistage model of carcinogenesis (2, 24, 25). For individuals who start smoking at a young age, cigarette smoke may be more essential to the accumulation of multiple genetic mutations than at older ages. At older ages, when smokers have already developed many partially altered cells and the absolute risk of developing lung cancer is higher, other factors may contribute to the progression of cells to invasive cancer.

A second factor that may explain the lower exponents associated with duration and intensity of cigarette smoking at older ages is that the declining exponents may reflect underreporting of exposure. For example, older persons may be more likely to misreport the number of years of cigarette smoking than are younger persons because of recall bias. Similarly, current daily cigarette consumption may be an inaccurate measure of lifetime smoking intensity (28). For example, it is unlikely that a person who currently smokes two packs a day has been smoking this amount ever since he or she started. Smokers may have changed their lifetime smoking behavior to compensate for the changing nicotine yields in manufactured cigarettes (29, 30). In any case,

the self-reported number of cigarettes smoked per day is only a crude measure of the "true" dose of cigarette smoke (1, 5, 30). Whether the lower exponents for duration and intensity of cigarette smoking at older ages reflect biological factors, underreporting, or misclassification of exposure at older ages is unknown and cannot be answered with our data.

The data both from the British doctors' study (1) and the data from CPS-II demonstrate a power relationship between lung cancer mortality and smoking duration. This finding accords with the multistage carcinogenesis theory (2, 3, 5, 32). Under the Armitage-Doll model (see Eq. A), if there were no misreporting of smoking duration by men 40–49 years of age (see previous discussion), then the exponent of three among men 40–49 years of age estimated in this study might suggest at least four critical stages of lung cancer development (*i.e.*, $\hat{\beta}_{Dk}$ in Eq. B is equivalent to $n - 1$ in Eq. A; because $\hat{\beta}_{Dk}$ is approximately 3, $n \approx 4$). However, the problem is likely more complex than that is represented in Equation A if one attempts to examine age, duration, and intensity simultaneously, even using a simplified multistage theory of carcinogenesis (32).

The underlying assumptions of the Armitage-Doll model have been criticized by some researchers. For example, the model does not take into account the selective growth advantage that early genetic mutations may confer over normal cells or factors that may complicate the kinetics of human epithelial cells (5, 33–35). Alternative multistage models, most with less restrictive assumptions, have been proposed (5, 34, 36–45). Most of these models predict a power relationship between the incidence rate of carcinoma and the duration of exposure to environmental carcinogens, although the interpretations of the exponents differ.

In summary, we found that cigarette smoking duration is a stronger predictor of lung cancer mortality than is cigarette smoking intensity, regardless of age in both men and women. Furthermore, we found that lung cancer risk was proportional to approximately the second or third power of cigarette smoking duration among men and women 40–49 years of age. This finding suggests, under the Armitage-Doll multistage model of carcinogenesis, that cigarette smoking affects at least four stages of lung cancer development. We also found that the estimated exponents for both the duration and intensity of cigarette smoking decrease with increasing age.

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