Estimating Lung Cancer Risk with Exposure to Environmental Tobacco Smoke

Jay H. Lubin

Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland USA

Estimates of lung cancer in nonsmokers due to exposure to environmental tobacco smoke (ETS) in the workplace or in the home may be developed in several ways. Estimates may be based on *a*) models developed using the full range of data in smokers; *b*) models developed using data restricted to smokers with a low smoking rate, for example, ≤ 10 cigarettes per day; *c*) models developed using data from studies of residential exposure to ETS of nonsmokers, with exposures based on smoking rates of spouses; and *d*) models using data from studies of occupational exposure to ETS of nonsmokers. Methods *a* and *b* require an estimate of cigarette equivalent exposure for ETS as well as assumptions on the cigarette equivalent dose to target cells from ETS and on the comparability of lung cancer risk per unit dose from smokers and nonsmokers. Summary relative risks (RRs) and 95% confidence intervals (CI) from ETS studies of nonsmokers with exposures based on smoking patterns of spouses are 1.24 (1.1, 1.4) for females and 1.34 (1.0, 1.8) for males, whereas the RR estimate for occupational ETS exposure and its 95% CI is 1.39 (1.2, 1.7). Using RR estimates for ETS exposure, cigarette equivalents for ETS range from 0.1 to 1.0, based on a range of descriptive and biologically motivated models in active smokers; a cigarette equivalent is 0.2 based on a comparison of log-linear trends in RR with number of cigarettes smoked per day in active smokers and in spouses of nonsmokers. *Key words*: epidemiology, lung cancer, meta-analysis, passive smoking, relative risk. — *Environ Health Perspect* 107(suppl 6):879–883 (1999). *http://ehpnet1.niehs.nih.gov/docs/1999/suppl-6/879-873lubin/abstract.html*

Models are used to synthesize complex patterns of associations within data. In the case of lung cancer risk with exposure to environmental tobacco smoke (ETS) among nonsmokers or with duration and rate of cigarette use among smokers, models bridge the gap between the needs of risk estimation and the availability of data, as often there are insufficient data to estimate with precision relative risks (RRs) for every exposed subgroup of interest.

Two types of modeling approaches have been applied (*1*). In the descriptive approach, statistical models are applied to epidemiologic data and used to summarize lung cancer rates as a function of smoking characteristics and other covariates. For example, investigators find that the RR of lung cancer increases with duration and rate (number of cigarettes smoked) of cigarette use and decreases with time since cessation of smoking (of the individual, or in the case of ETS, of the spouse or co-workers). In addition to those factors, other potential risk factors include age at start of smoking, age at risk, other lung diseases, occupation, diet, and sex. Descriptive models allow the evaluation of a diverse set of potential risk factors with few a priori assumptions about the form of the functional relationship between risk and the covariates. Descriptive models are developed one step at a time, with the addition of covariates and the specification of their functional forms based on formal statistical tests. Descriptive models are sufficiently flexible that expected biologic effects of exposure can be qualitatively or quantitatively incorporated into the modeling. The validity of the elements of a model and the inclusion of specific covariates can be directly evaluated within the data. However, with limitations in the amount and range of data, descriptive models are often rather crude, yielding at best a rough characterization of disease rates.

Biologically motivated models seek to provide a link between disease risk and underlying biologic processes. The estimated parameters are then interpretable within the mechanistic framework and may provide meaningful biologic insights. Two biologically motivated models that have been applied to lung cancer data are the Armitage-Doll multistage model (*2*) and the Moolgavkar-Knudsen two-stage clonal expansion model (*3*). Although biologically motivated models may provide a link to disease processes, the biologic basis of the model cannot be validated within the epidemiologic data. Both descriptive and biologically motivated models permit estimation of lung cancer risks over a broad range of smoking rates and durations, in particular at levels of exposure comparable with ETS exposure in nonsmokers.

Several methods are used to estimate lung cancer risks with ETS exposure (Table 1). Estimates of risk from ETS exposure in nonsmokers may be based on models developed using the full range of smoking data or from data on low-exposed smokers, for example, those smoking ≤ 10 cigarettes per day. The restricted data are more directly relevant to the range of ETS exposure encountered by nonsmokers. Applicability of risk estimates from models based on active smokers requires that there is an estimate of cigarette equivalent exposure in active smokers that is related to ETS exposure, and the consequences of exposure from one cigarette equivalent are the same in active smokers and in those exposed to ETS. Puntoni et al. (*4*) estimated an empirical, risk-based cigarette equivalent by equating RRs in studies of smokers with RRs in studies of ETS exposure, specifically the results of Saracci and Riboli (RR = 1.37 with 95% confidence interval [CI] 1.20, 1.53) (*5*) and Tweedie and Mengersen (RR = 1.17 with 95% CI 1.06, 1.28) (*6*). Puntoni et al. fitted six different mathematical models to summary data on smokers from nine cohort studies, then equated the predicted risk from the models to the estimated RR for ETS exposure to obtain estimates of cigarette equivalents. The models include the biologically motivated one-hit model, the two-stage Moolgavkar-Knudsen model, the Armitage-Doll multistage model, and the logit, probit, and Weibull probability models. These risk-based estimates suggest that average ETS exposure is equivalent to exposure of an active smoker to 0.21–0.43 cigarettes per day.

A number of reports tabulate the constituents of ETS derived from sidestream smoke and exhaled mainstream smoke (MS) and the MS that is directly inhaled by the smoker (*7,8*). The components of ETS are qualitatively similar to those of inhaled MS, although there are quantitative differences. On the basis of biochemical markers, ETS exposure in nonsmokers is estimated to be equivalent to active smokers consuming from 0.1 to as many as two cigarettes per day (*8*). Whether this biologically equivalent exposure in active smokers and in nonsmokers exposed to ETS reflects an equal lung dose and thereby an equal increment of lung cancer risk is unclear.

Lung cancer risk can also be estimated directly from studies of ETS exposure. Even though many of the epidemiologic studies of ETS consist of female nonsmokers, with exposure based on smoking characteristics of

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Address correspondence to J.H. Lubin, Division of Cancer Epidemiology and Genetics, NCI, 6120 Executive Blvd., EPS/8042, Bethesda, MD 20892-7244. Telephone: (301) 496-4153. Fax: (301) 402-0081. E-mail: lubinj@exchange.nih.gov

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Table 1. Methods and sources of data for estimating lung cancer risk from the exposure to ETS of nonsmokers.

Method	Sources of data	Comment
Modeling risks in current and former smokers	Studies of current and former smokers and nonsmokers	Models include the full range of data from ever smokers. Relevance of RRs for ETS exposure depends on adjustment of baseline RR in nonsmokers for ETS exposure, low-dose extrapolation and on validity of cigarette equivalents.
Modeling RRs in low-exposure smokers	Studies of smokers with low smoking rate, e.g., ≤ 10 cigarettes per day	More directly applicable to the range of ETS exposures. Relevance depends on adjustment of baseline RR in nonsmokers for ETS exposure and on validity of cigarette equivalents for ETS exposure.
Modeling RRs for residential ETS of nonsmokers	Studies of nonsmokers exposed to ETS	Range of data directly applicable to ETS exposure. Majority of data derived from studies of nonsmoking females, with ETS exposure defined by smoking habits in the spouse. Estimates require adjustment of baseline RR for other ETS exposure and for inclusion of smokers who claim to be nonsmokers.
Modeling RRs for occupational ETS exposure	Studies of nonsmokers occupationally exposed to ETS	Range of data directly applicable to ETS exposure. Estimates require adjustment for the inclusion of smokers who claim to be nonsmokers and for the assessment of occupational exposures over time.

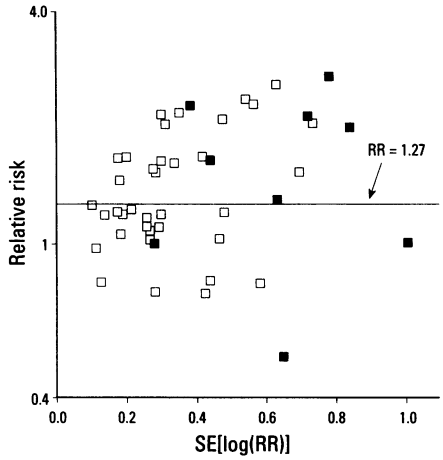

Figure 1. Funnel plot of environmental tobacco smoke studies. Studies of nonsmoking females and males with smoking spouses shown with open and solid squares, respectively. Data from Hackshaw et al. (*11*).

spouses, there are also relevant data for males and for occupational ETS exposure (*9*).

Estimating Lung Cancer Risk from ETS Using Data from ETS Studies

Epidemiologic studies that directly evaluate excess lung cancer risk from ETS exposure have two principal limitations: the excess risks under investigation are small, on the order of 10–50%, and exposures are determined with substantial misclassification, tending to reduce RRs and study power. These limitations suggest that definitive results from a single study, even a large study, are unlikely. Thus, the aggregation of results from multiple studies is needed to have sufficient power to characterize the risk from ETS exposure precisely.

Data from multiple studies can be combined by pooling or by meta-analysis. The former approach involves acquiring data on individuals from each study, with the individual as the unit of analysis. The latter approach uses summary results, e.g., RRs and 95% CIs, from published papers. Pooled analyses offer greater flexibility for assessing confounding factors and heterogeneity of RRs within subgroups and across study populations. Additional factors and subtle variations in effects that cannot be evaluated in individual studies can be analyzed in pooled data. The pooling of diverse data sets, including studies with potentially very different design protocols, is a complex undertaking and to date no large-scale pooling of ETS studies has been published. Meta-analysis is generally easier to carry out than data pooling, since data are limited to published results, although the ability to analyze additional factors within studies is limited. In the absence of uncontrolled confounding, meta-analyses provide unbiased estimates of association.

Meta-Analysis of ETS Exposure Studies

A number of meta-analyses of ETS exposure and lung cancer risk have been conducted (*7,8,10–12*). A recent review lists 37 ETS studies of lung cancer, including 4 cohort studies and 33 case–control studies (*11*). These studies were conducted in nonsmoking women whose spouses smoked; 9 of the 37 studies also include nonsmoking males with smoking spouses. [Hackshaw et al. (*11*) list two additional studies with results only for females and males combined.] The studies include a total of 4,900 lung cancer cases (5,095 cases in all 39 studies). The 1997 meta-analysis by Hackshaw and colleagues is the largest to date. For nonsmokers married to smokers compared to nonsmokers married to nonsmokers, the estimated RRs and 95% CIs are 1.24 (1.13, 1.36) for females and 1.34 (0.97, 1.84) for males, and 1.27 (1.17, 1.38) combined. Results are consistent across the various studies in the meta-analysis, and overall RRs are homogeneous. There is concern that study results may vary over time because of population drift or publication bias. A plot of the summary RR by calendar year reveals no variation of results with calendar time (*11*).

Hackshaw et al. (*11*) report on a dose–response analysis for studies with available data. Sixteen studies of nonsmoking females with a smoking spouse provide RRs by number of cigarettes smoked per day by the spouse. Eleven studies report RRs by categories of number of years a women lived with a smoking spouse. For both exposure measures, RRs increase approximately log-linearly with number of cigarettes smoked per day and with duration of exposure.

Hackshaw and colleagues (*11*) also consider the problem of the effects of various types of bias on the summary estimate of RR for ETS exposure. They consider *a*) misclassification bias from including current or former smokers as nonsmokers; *b*) exposure to ETS from other, nonspouse sources in the referent group of nonexposed; and *c*) confounding by low fruit and vegetable consumption. They conclude that the effects of bias from overestimation of RR from *a* and the underestimation of RR from *b* are likely to balance, and that any possible confounding from *c* is minimal. Their adjustments result in little practical change in the overall estimated summary RR from ETS exposure.

Critics raise the possibility that results may be influenced by publication bias, where studies with null results or negative results are less likely to be published. Figure 1 shows a funnel plot of the study-specific RRs for ETS exposure on a log scale by the standard error of ln(RR). Variation in study estimates due to random statistical error results in a funnel pattern with an increasing spread of points with increasing standard error. The figure provides little evidence of a publication bias, although there is some suggestion of a dearth of estimates from smaller or less powerful studies (large standard errors) with null results.

In the meta-analysis of Hackshaw et al., there is no overall statistically significant heterogeneity in the results from the ETS studies. The radial plot, where standardized coefficients are plotted against their inverse standard errors, illustrates study variability (*13*). Estimates from ETS and lung cancer studies are shown in Figure 2. Points nearer the origin are measured with greater uncertainty [the inverse standard error is small, and the standardized ln(RR) is small], whereas points away from the origin are estimated with greater confidence. The solid line represents the weighted estimate of the

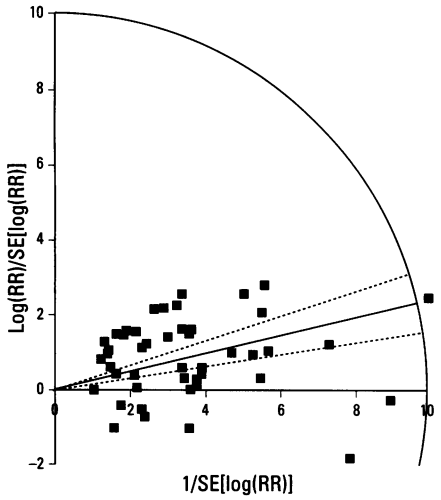

Figure 2. Radial plot of results from environmental tobacco smoke studies of nonsmokers with smoking spouses. Summary relative risks (solid line) and 95% confidence intervals (dotted lines) are 1.27 (1.1, 1.4) and are equal to the slopes of the lines. Data from Hackshaw et al. (*11*).

summary ln(RR) and the dotted lines its 95% CI. Points markedly outside the area between the dotted lines are outliers relative to the summary estimate. The plot suggests substantial variability in the studies over the entire range of study weights. This variability may be due to differences among studies in the level of ETS exposure, and hence the observed RRs; large variations within study, due perhaps to limited ranges of exposure; and exposure misclassification. Using a random effects model (*1*), a random effects adjustment for the individual RR estimates results in extreme shrinkage of the study-specific RRs toward the overall weighted mean (not shown), which again suggests large variability among studies.

Assumptions are needed to use results from ETS studies of nonsmokers (mainly females) with smoking spouses to estimate risks for occupational ETS exposure. Although there is little reason to suspect fundamental differences in the composition of ETS exposure at the workplace, assumptions are needed to relate the amount of ETS exposure at home and at the workplace. Alternatively, RR estimates of lung cancer can be based on studies of occupational ETS exposure directly, such as those provided in a recent meta-analysis of 14 occupational ETS studies (*12*).

There are 14 published studies with useful information (*12*). Wells argues that exposure assessments in studies of occupational ETS are subject to uncertainties not affecting the spousal studies (job mobility, variation in occupational environment due to worker turnover, workplace changes over time, the inability of surrogate respondents to recall accurately the ETS environment of deceased subjects), and therefore studies should satisfy strict inclusion criteria before acceptance into any meta-analysis. Wells specifies the following criteria for inclusion of studies: *a*) availability of a minimum exposure history; *b*) no more than 50% surrogate response; *c*) some level of exposure quantification beyond little or minimal ETS exposure; *d*) no large nonenvironmental exposure to tobacco smoke; *e*) for cohort studies, results only from nonsmokers; and *f*) some check on the CIs of RRs. Of the 14 studies, only 5 studies satisfy the eligibility criteria. Reasons for rejecting studies include a high percentage of surrogate responders, current exposures only, inclusion of former smokers, and the presence of heavy exposure from coal-heating fumes. In the 5 studies there are 835 lung cancer cases, 794 females and 41 males. The combined RR and 95% CI are 1.39 (1.15, 1.68) for all studies and 1.43 (1.15, 1.78) for U.S. studies. Wells also examines results by categories of duration of workplace ETS exposure. He finds a statistically significant increasing trend with duration ($p < 0.001$). Relative to no occupational ETS, RRs are 1.46, 1.55, and 2.08 for 1–15, 15–30, and > 30 years of exposure.

There have been several previous meta-analyses of occupational ETS exposure, with results that fail to identify an excess risk from occupational ETS exposure (*14–17*). Wells argues that these authors failed to consider important errors in the studies. These errors include the misspecification of CIs in one study because of an analytic or a publication error that resulted in the (negative) study receiving too much weight, and an erroneous RR that changed an estimate from 1.1 to 1.2. Wells claims that correcting these errors largely explains the discrepancies between the previous meta-analyses and his own.

Risk Models for Lung Cancer with ETS Exposure

There has been little fitting of risk models directly to data from studies of ETS. As described above, Hackshaw and colleagues examined the RR relationship by categories of spouses' smoking rate and duration of exposure (*11*). They found an increasing RR trend with both factors. For the log-linear model $RR(x) = \exp(\beta x)$, they estimate β as 0.021, or a RR of 1.23 for exposure to 10 cigarettes per day. Because there has been little quantitative modeling of ETS data in houses or in the workplace, there has been little or no assessment of factors that might modify the ETS lung cancer association, which could be compared to results in smokers. Factors that could be evaluated include rate and duration of ETS exposure, age at exposure, age at risk, time since cessation of ETS exposure, and sex.

Estimating Lung Cancer Risk from ETS Using Data from Cigarette Smokers

Regression models developed using the full range of exposures in active smokers or using only data restricted to low-exposure rates, for example, 1–10 cigarettes per day, can provide risk estimates from ETS exposure in nonsmokers. If ETS exposure is properly expressed through cigarette equivalents, and if the health consequences of a cigarette equivalent are the same for those exposed to ETS and for active smokers, than the observed RRs for low-exposure-rate smokers estimate the consequences of ETS in exposed nonsmokers.

Estimating Risk of Lung Cancer from Low-Exposure Data in Smokers

Table 2 and Figure 3 summarize results from studies with RRs for active smokers for categories at or below 10 cigarettes per day relative to those of nonsmokers. Nearly all estimated RRs for low exposures are above one, and there is no evidence of a threshold below which exposures do not increase risk of lung cancer. These RRs are generally considered to underestimate effects relative to effects for those who were truly nonexposed, as the referent group for the RRs includes persons with some ETS exposure. Sources of potential bias include smokers who incorrectly claim to be nonsmokers (increasing the baseline odds and decreasing the RRs), and nonsmokers who are exposed to substantial amounts of unmeasured ETS exposure (increasing the apparent effects of their exposure). Using arguments similar to those in Hackshaw et al. (*11*), approximations of the degree of bias could be obtained.

The studies in Table 2 do not always provide information on standard errors of the RR or on category-specific CIs, so the following weighted regression analysis uses numbers of lung cancer cases, when available, or expected numbers of cases based on the British doctors' study as weights. A linear model, $RR(x) = 1 + \beta x$, and log-linear model $RR(x) = \exp(\beta x)$ were fitted to the data (Figure 3).

Estimating Risk of Lung Cancer in Cigarette Smokers: Descriptive Models

For developing descriptive models, analyses of data in smokers generally focus on smoking history without considering other lung cancer risk factors. Analyses find an increase in RRs with duration and rate of cigarette use and a decline in RRs with years since cessation of smoking (*18*). Analyses also evaluate the risk associated with other aspects of smoking, such as nonfiltered/filtered cigarettes, high-tar/low-tar cigarettes, the effects of switching from nonfiltered/high-tar cigarettes to filtered/low-tar cigarettes, types of tobacco, and depth and frequency of inhalation of tobacco smoke.

Table 2. Relative risks for men and women by number of cigarettes smoked per day for studies with low-exposure categories (≤ 10 cigarettes per day).[a]

Study population	Cigarettes/day	Relative risk	
		Males	Females
ACS 25-state study (*27*)	0	1.00	1.00
	1–9	4.62	1.3
British doctors' study (*28*)	0	1.00	1.00
	1–14	7.80	1.28
Swedish study (*29*)	0	1.00	1.00
	1–7	2.30	1.80
	8–15	8.80	11.3
U.S. veterans study (*30*)	0	1.00	
	1–9	3.89	
ACS nine-state study (*31*)	0	1.00	
	1–9	8.00	
Canadian veterans study (*32*)	0	1.00	
	1–9	9.50	
European case–control study (*33*)	1–4	2.03	0.87
	5–9	2.90	2.29
Cuba (*34*)	0	1.00	1.00
	1–9	5.40	4.70

ACS, American Cancer Society. [a]Data adapted from U.S. Environmental Protection Agency (*8*).

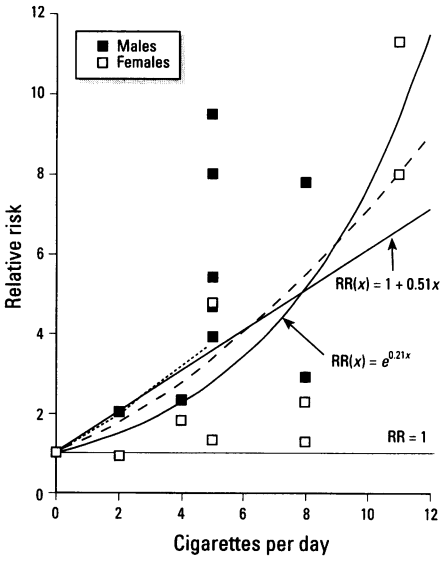

Figure 3. Relative risks by number of cigarettes per day, together with estimated linear and log-linear models, and predictions from Doll and Peto (*19*) (dashed line) and Darby and Pike (*22*) (dotted line).

Table 3. Estimated relative increase in cellular event rates for multistage model applied to relative risks of lung cancer among cigarette smokers.[a]

Cigarettes/day	Relative increase due to smoking	
	First stage	Penultimate stage
1–10	0.7	2.8
11–20	2.5	5.0
21–30	3.5	6.3
>30	4.0	7.0

[a]Data from Brown and Chu (*23*).

However, a single, broad-based descriptive model for lung cancer risk that includes a comprehensive, quantitative characterization of all of these diverse smoking-related risk factors, and other factors such as sex and occupational exposures, has not been developed.

Using 20 years of data from the British doctors' study, Doll and Peto fit various models to data from lifelong nonsmokers and from continuing, cigarette-only smokers who maintained an approximately constant exposure rate (*19*). Although the authors are guided by the multistage model for lung cancer, their approach is essentially descriptive, concentrating on lung cancer rates for ages 40–79 years. Standardizing for age, the incidence of lung cancer increases with approximately the square of exposure rate. Standardizing for exposure rate, the incidence increases with duration of smoking, characterized as age minus 22.5, to the 4.5th power. The authors note that the fit for the duration models is similar regardless of the number of years between 0 and 34 that are subtracted from age. The model selected to represent the annual incidence of lung cancer for the British doctors is:

$$0.273 \times 10^{-12}\,(\text{cigarettes/day} + 6)^2\,(\text{age } 22.5)^{4.5}$$

This model suggests that for a fixed age at risk, the RR as a function of number of cigarettes smoked per day (x) and relative to nonsmokers is described by $RR(x) = (x + 6)^2/36$. This curve fits the RRs for low exposures quite well (Figure 3).

Estimating Risk of Lung Cancer in Cigarette Smokers: Biologically Motivated Models

The Armitage-Doll multistage model assumes that a single cell generates a malignant tumor after undergoing k, distinct, ordered, heritable transformations (*2,20,21*). As a consequence of the multistage model, the background incidence rate at age t is proportional to t^{k-1}, and a plot of log–incidence against log–age results in a linear function with slope k–1. Based on data from nonsmokers, the incidence rate increases approximately with the 4th power of age, suggesting five stages in the carcinogenic process (*22*). Among smokers, incidence increases more rapidly with age; however, when incidence is plotted against duration of exposure, incidence increases again with approximately the 4th power. The relationship between incidence and the square of smoking rate is interpreted as evidence that smoking affects more than one stage of the carcinogenesis process (*22*).

Using the Armitage-Doll model, Day and Brown formally describe how observed patterns of excess risk by age at first exposure, duration of exposure, and time since exposure are related to stage of action. In particular, they present equations for excess risk patterns associated with exposure that acts at the first stage and/or the penultimate stage of the carcinogenic process (*20*). Brown and Chu apply these equations in an analysis of a large European case–control study of lung cancer to show that smoking acts as both an early-stage and a late-stage carcinogen (*23*). They consider two RR patterns: variation of the RRs with age started smoking among continuing smokers, and variation of the RRs with time since cessation of smoking among former smokers. In nonsmokers and continuing smokers, RRs decline with age started smoking, after adjusting for age at interview, smoking rate, filtered and nonfiltered cigarette use, and other factors. This pattern is indicative of a carcinogen that acts at an early stage of a multistage process. Among continuing and former cigarette smokers, RRs decrease with time since cessation of smoking, after adjusting for age at interview, smoking rate, duration of smoking, filtered and nonfiltered cigarette use, and other factors. This pattern is indicative of a carcinogen that acts at a late stage. Brown and Chu also note that RRs with time since cessation of smoking stop declining after about 20 years and maintain a plateau. This pattern suggests that smoking affects both early and late stages, with the decline reflecting late-stage effects and the leveling off reflecting residual first-stage effects. Table 3 shows that at low smoking rates, smoking plays a relatively greater role as a penultimate-stage carcinogen than as a first-stage carcinogen. There has been no application of the Armitage-Doll model directly to data on ETS exposures to evaluate the ETS exposure as an early-stage and/or late-stage carcinogen. Nonetheless, Brown and Chu's analysis suggests that ETS exposure as a late-stage promoter may have an enhanced impact in occupational settings where other lung carcinogens are present.

Results similar to those of Brown and Chu (*23*) are obtained by Darby and Pike (*22*) in their fitting of the Armitage-Doll model to the British doctors' data. Darby and Pike use their derived model to estimate RRs for various levels of cigarettes per day (Table 4). Note that these estimates are not adjusted for the possible effects of ETS exposure among nonsmokers. The predicted RRs in the table suggest a substantial level of lung cancer risk from ETS exposure. In addition, whereas duration of exposure is a potent factor in determining risks among smokers (e.g., risk increases with the 4th power of duration), the impact of duration of ETS exposure is relatively less at low exposure rates. The RR with exposure to 1 cigarette per day increases from 1.46 to 1.77 with 20 years' additional exposure (Table 4). In contrast, based on the Armitage-Doll

Table 4. Relative risk of lung cancer at 65 years of age for ETS exposure in cigarette equivalents per day.[a]

Equivalent cigarettes per day	Exposed (0–65 years of age)	Exposed (20–65 years of age)	Exposed (0–20 years of age)
0.00	1.00	1.00	1.00
0.10	1.07	1.04	1.02
0.20	1.14	1.09	1.05
0.25	1.17	1.11	1.06
0.50	1.36	1.22	1.11
1.00	1.77	1.46	1.23
1.50	2.23	1.71	1.34
2.00	2.75	1.97	1.46
3.00	3.95	2.52	1.69
4.00	5.36	3.13	1.93
5.00	6.98	3.78	21.6

[a]Data based on the Armitage-Doll model fitted to the British doctors' data (*22*).

Table 5. Estimates of cigarette equivalents.

Source	Range
Doll and Peto (*19*)	0.5–1.0[a]
Darby and Pike (*22*)	0.4–0.8[a]
Puntoni et al. (*4*)	0.2–0.4[a]
Hackshaw et al. (*11*)	0.2–0.3[b]
U.S. EPA (*8*)	0.1–2.0[b]
Linear model for ≤ 10 cigarettes/day data	0.5–2.1[a,c]
Log–linear model for ≤ 10 cigarettes/day data	0.2–0.9[a,c]
Comparison of log–linear models	0.07–0.14[d]

U.S. EPA, U.S. Environmental Protection Agency. [a]Range derived from 95% CI for combined RR of ETS exposure. [b]Range based on biologic markers of cotinine/nicotine. [c]Range includes 95% CI of model parameter estimate. [d]Comparison of model parameters for cigarettes/day for active smokers (Figure 3) and ETS exposure [Hackshaw et al. (*11*)].

model, for 20 cigarettes per day the excess RRs for similar duration of exposures would predict a 4-fold increase (*22*). Figure 3 includes the Darby and Pike predictions (dotted line) and shows that the fitted estimates from the multistage model are similar to RRs for very low smoking rates from a variety of epidemiologic studies.

The Moolgavkar-Knudsen two-stage clonal expansion model incorporates two principal features: transition of target stem cells into cancer cells through an intermediate stage in two rate-limiting and heritable steps, and growth and differentiation of normal target and intermediate cells (*3,24*). This model differs from the Armitage-Doll model by allowing the clonal expansion of the intermediate cells. Moolgavkar and colleagues (*24*) apply the two-stage model to the British doctors' data, and confirm the earlier conclusion by Doll and Peto that lung cancer incidence increases approximately with the square of the smoking rate. However, Moolgavkar et al. dispute the conclusion that smoking duration is more important than smoking rate in determining level of risk. Under the two-stage model, the relative importance of smoking rate and smoking duration depends on the final model selected. With one set of parameter estimates and for ages over 45 years, predicted lung cancer risk for smoking 40 cigarettes per day for 10 years results in a greater risk than smoking 20 cigarettes per day for 20 years, suggesting that smoking rate is a more important determinant of risk than duration of smoking. For a second set of model parameter estimates, which fit the doctors' data equally well, the predicted risks are reversed, suggesting a greater role for duration of smoking. Thus, under the two-stage model, the British doctors' data are consistent with either smoking rate or smoking duration playing a dominant role. Moolgavkar et al. point out that Whittemore (*25*) fits a model to the doctors' data that includes cumulative exposure and finds that the model fits as well as a model that includes smoking rate and duration separately. Moolgavkar et al. conclude that because of limited data there is substantial indeterminancy in the doctors' data and a variety of interpretations are consistent with the data.

In a joint analysis of the British doctors' data and data from a cohort of Colorado Plateau uranium miners exposed underground to radioactive radon, Moolgavkar et al. (*26*) find that the smoking effects are similar in the two populations. They conclude that cigarette smoke affects the first-stage mutation rate and the kinetics of intermediate cell division.

Summary

There are several ways of deriving RR estimates due to ETS exposure. Based on a RR of 1.27 for exposure to ETS, estimates of cigarette equivalents are similar using *a*) a variety of descriptive models over the full range of data in smokers or in data restricted to low-exposed smokers, or *b*) biologically motivated models (Table 5). Estimates of cigarette equivalents range from 0.1 to 1.0 cigarettes per day. This range is consistent with a comparison of model-based estimates of RR of 8.17 for 10 cigarettes per day in active smokers and of 1.23 for ETS exposure to 10 cigarettes per day—a ratio of 0.2. The consistency of estimates using diverse sources of data and approaches provides confidence in the magnitude of the estimated ETS effects.

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