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Effect Modification of the Association of Cumulative Exposure and Cancer Risk by Intensity of Exposure and Time Since Exposure Cessation: A Flexible Method Applied to Cigarette Smoking and Lung Cancer in the SYNERGY Study

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The indiscriminate use of the cumulative exposure metric (the product of intensity and duration of exposure) might bias reported associations between exposure to hazardous agents and cancer risk. To assess the independent effects of duration and intensity of exposure on cancer risk, we explored effect modification of the association of cumulative exposure and cancer risk by intensity of exposure. We applied a flexible excess odds ratio model that is linear in cumulative exposure but potentially nonlinear in intensity of exposure to 15 case-control studies of cigarette smoking and lung cancer (1985–2009). Our model accommodated modification of the excess odds ratio per pack-year of cigarette smoking by time since smoking cessation among former smokers. We observed negative effect modifi-cation of the association of pack-years of cigarette smoking and lung cancer by intensity of cigarette smoke for persons who smoked more than 20–30 cigarettes per day. Patterns of effect modification were similar across individual studies and across major lung cancer subtypes. We observed strong negative effect modification by time since smok-ing cessation. Application of our method in this example of cigarette smoking and lung cancer demonstrated that reducing a complex exposure history to a metric such as cumulative exposure is too restrictive.

Cumulative exposure (the product of average daily expo-sure intensity and duration of exposure) is often the default exposure metric used in epidemiologic cancer studies. How-ever, the assumptions on which the use of cumulative expo-sure is based, namely that the cumulative probability of developing a disease is proportional to the sum of the daily probabilities of developing a disease, the daily probability of developing a disease increases monotonically with the concentration in the target tissue, the concentration in the tar-get tissue is linearly related to the external exposure (1), are not always justified.

Pack-years of cigarette smoking (PCS) are calculated as the average number of packs of cigarettes smoked per day multi-plied by the cumulative number of years during which a person smoked. This example of the cumulative exposure metric is often used to evaluate smoking behavior in epidemiologic analyses. There is considerable evidence that with a straightfor-ward inclusion of PCS in epidemiologic analyses of chronic health effects, not all intensity- and duration-related aspects of smoking behavior are optimally characterized (2). For ex-ample, Doll and Peto (3) demonstrated that the absolute excess rate of lung cancer among smokers was related to at least the fourth power of smoking duration and only to the second power of smoking intensity. Because both smoking duration and baseline lung cancer rates vary with age, the relationships be-tween the excess relative risk and duration and intensity of smoking are likely to be more complex.

One way to assess the independent effects of duration and intensity of cigarette smoking on lung cancer risk is to ex-plore effect modification of the association between PCS and lung cancer by intensity of cigarette smoking (4). Excess relative risk or excess odds ratio (EOR) models that are linear in total exposure and exponential in the intensity of exposure have been applied successfully to explore effect modification of cumulative exposure by intensity of exposure for a number of exposures (4–10). Such models have a general form of $OR(d) = 1 + \beta_1 d \times \exp(\beta_2 (n))$, where β_1 represents the EOR per unit of total exposure (d) (i.e., the EOR of disease changes in an additive fashion with total exposure) and β_2 represents the (multiplicative) modifying effect of intensity of exposure (n). In the past, fitting these models required the use of specialized software, but they can now be fitted in stan-dard software packages with relative ease (11).

We explored the modification of the effect of PCS on the EOR for lung cancer by lifetime average intensity of cigarette smoking (ICS). For our analysis, we modified a previously developed approach to model total exposure and exposure in-tensity (4). Our analysis is unique in that we were able to apply this model in a large data set of 15 independently de-signed case-control studies with detailed smoking informa-tion (the SYNERGY pooling project, a pooled analysis of case-control studies on the joint effects of occupational car-cinogens in the development of lung cancer) (12–14). Fur-thermore, our approach differs from previous applications by including a direct assessment of the modification of the EOR per PCS by the time since smoking cessation (TSC), which is a strong predictor of lung cancer risk in former smokers (15), in the regression model, and we included a 3-knot restricted cubic spline function for both ICS and TSC to allow a more flexible assessment of the shape of the modification of the EOR per PCS.

METHODS

SYNERGY data set

We used data from the SYNERGY project (12–14). Our data set included data from 14 case-control studies from Canada (n = 2), France (n = 3), Germany (n = 2), Italy (n = 3), New Zealand (n = 1), Spain (n = 1), Sweden (n = 1), and The Netherlands (n = 1), as well as a multicenter study conducted in Central and Eastern Europe and the United Kingdom (16). Controls were individually or frequency-matched to cases by sex and age and recruited from the general population (82%) or hospitals (18%). Smoking information was predominantly collected through interviews with the subjects themselves (92% of cases, 94% of controls). Lung cancer subtypes were classified according to World Health Organization guidelines by the pathologists associated with the participat-ing hospitals. The ethics committees of the individual studies approved the conduct of the study, as did the institutional re-view board at the International Agency for Research on Can-cer. We provide an overview of the characteristics of the studies included in the analysis in Web Table 1, available at http://aje.oxfordjournals.org/.

Smoking data

Information on cigarette smoking history included the number of cigarettes smoked per day in calendar-year periods and the age at smoking cessation for former smokers. We cal-culated continuous variables for duration of smoking, ICS, and PCS based on the smoking history. A current smoker was defined as someone who had smoked for more than 1 year and still smoked in the year of interview or in the year before. Former smokers were defined as persons who had smoked for at least 1 year but quit smoking at least 2 years before the date of the interview. Subjects who had smoked for less than 1 year were considered occasional smokers and were treated as never smokers in the analyses. All cases and controls for whom we had complete smoking data were in-cluded, without restriction on age or smoking status.

Statistical analysis

The model we used in this article provides a balance be-tween parsimony and model fit. The model falls within a more general framework for flexible modeling of exposure-time relations (17). Similar inferences were obtained using other model specifications within the more general frame-work (Web Appendix, Web Table 2, and Web Figure 1).

Below we provide a description of the models that we ap-plied in our study, with an emphasis on how they differed from the models used in the previously published study by Lubin and Caporaso (4). Our models are linear for PCS and exponential for ICS and TSC to force the modifying ef-fect to be non-negative. We used 2 approaches to model ICS (expressed as cigarettes smoked per day). The first approach defines I intensity categories and indicator variables, n_i i = 1, . . . , I, where n_i = 1 if a subject's intensity level occurs within the ith category and n_i = 0 otherwise.

The model is as follows:

$$\mathrm{OR}(d) = 1 + \beta d \times \exp\{\Sigma \theta_i n_i\}; \qquad \text{(A)}$$

where β represents the EOR for each PCS, d. The model spec-ifies a different slope for each intensity category. With θ_1 set to 0 for identifiability, θ_2, . . . , θ_i represent category-specific effects relative to the I = 1 level. Model A has been published before (4, 7, 8) and was fitted to a subset of the data that is restricted to current and never smokers 50–75 years of age to parallel the data sets used in previous publications.

We extended model A with a function for TSC to allow the inclusion of former smokers in our analysis, as follows:

$$\mathrm{OR}(d) = 1 + \beta d \times \exp[g_1(t)] \times \exp\{\Sigma \theta_i n_i\}; \qquad \text{(B)}$$

where $g_1(t)$ is a 3-knot restricted cubic spline function for TSC (knots located at the 20th, 50th, and 80th percentiles of the dis-tribution of TSC of all former smokers). The variation in EOR per PCS by continuous ICS (n) is assessed with 3 different models (models C, D, and E below). The first of those is:

$$\mathrm{OR}(d) = 1 + \beta d \times h(n); \qquad \text{(C)}$$

where h(n) has the functional form $h(n) = \exp(\Phi_1 \ln(n) + \Phi_2 \ln(n)^2)$. Φ_1 and Φ_2 are the parameters for the modifying function of continuous ICS. Model C has been published before (4, 7, 8).

We modified model C to include a flexible spline function for ICS, as shown:

$$\mathrm{OR}(d) = 1 + \beta d \times \exp\{g_1(n)\}: \qquad \text{(D)}$$

g_1 is a 3-knot restricted cubic spline function of continuous ICS (n) (knots located at the 20th, 50th, and 80th percentiles of the distribution of ICS of all smokers). Models C and D were fitted to a subset of the data that was restricted to current and never smokers who were 50–75 years of age.

Similar to model B, we extended model D with a function for TSC to allow the inclusion of former smokers in our anal-ysis, as follows:

$$\mathrm{OR}(d) = 1 + \beta d \times \exp(g_1(n) + g_2(t)); \qquad \text{(E)}$$

where g_1 and g_2 are 3-knot restricted cubic spline functions with knots located at the 20th, 50th, and 80th percentiles of the distribution of TSC of all former smokers. g_1 is a function of con-tinuous ICS (n) and g_2 is a function of continuous TSC (t).

All models were fitted using the NLMIXED procedure in SAS, version 9.2 (SAS Institute, Inc., Cary, North Carolina). Effects were adjusted for study center, age group (<45, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, ≥80 years), and sex by allowing for stratum-specific baseline odds. Anal-yses were also fully stratified by sex and study location and conducted for all lung cancer subtypes combined and for 3 major lung cancer subtypes separately: squamous cell carci-noma, small cell carcinoma, and adenocarcinoma. We as-sessed the sensitivity of the restricted cubic spline functions for continuous ICS and TSC to alternative knot locations (10th, 50th, and 90th percentiles and 5th, 50th, and 95th per-centiles) in an analysis of all lung cancer subtypes combined among men and women. We observed a marginal impact on both model fit (Akaike information criterion) and model pre-diction. Therefore, all analyses were conducted with the a pri-ori specified knot locations (20th, 50th, and 80th percentiles). Bootstrapped 95% confidence intervals of the functions for ICS and TSC were estimated via 1,000 bootstrap replications of the original data, and we used the 2.5th and 97.5th percent-iles of the resulting distribution. To avoid overinterpretation of patterns for regions in which the data were extremely sparse, we excluded predictions for intensities less than the 1st percentile and higher than the 99th percentile of the dis-tribution of the exposed persons from all plots. The same ap-proach was used for TSC. A likelihood ratio test (18) was used to compare differences in fit with the data between nested models. Because (conditional on attained age) age at smoking initiation 1) is multicollinear with duration of smok-ing and TSC, 2) typically shows relatively little variation, and 3) is not very strongly associated with cancer occurrence, we did not assess the effect of age at smoking initiation in our analysis (2).

RESULTS

The pooled data set consisted of 17,975 cases (14,255 men and 3,720 women) and 22,353 controls (17,267 men and 5,086 women). Further details of the study population are provided in Web Table 1.

We first applied models A and C to a data set that was re-stricted to current and never smokers who were 50–75 years of age. Figure 1A shows the effect of ICS on the lung cancer EOR per PCS, estimated using models A (point estimates for deciles of ICS) and C (continuous line) among current and never smokers (i.e., excluding former smokers). EORs per PCS estimated with model A increased with increasing ICS below 20 cigarettes (1 pack) per day and slightly decreased with increasing ICS at intensities higher than 20 cigarettes per day. The continuous prediction of model C followed the pattern of the point estimates predicted with model A. Importantly, because of model specification, model C would predict EOR = 0 for zero ICS. Parameter estimates for Φ_1 and Φ_2 were 0.0258 (standard error, 0.0062) and −0.0216 (standard error, 0.0052), respectively.

Next, we compared the effect of ICS predicted by model C (Figure 1B, gray line) with the effect of ICS predicted by a model that included a flexible spline function for ICS (model D; Figure 1B, dashed line). Knots of the restricted cubic spline were located at 10, 19, and 26 cigarettes per day. A comparison based on the Akaike information criterion (19) suggested that model D (Akaike information criterion = 22,677) had a better fit to the data than did model C (Akaike information criterion = 22,687). For intensities higher than 20 cigarettes per day, model D predicted a slightly stronger decrease in EOR per PCS with increasing ICS than did model C. Furthermore, model D was not restricted to start at EOR/PCS = 0 for zero ICS, which resulted in a less pronounced increase in EOR per PCS with increasing ICS below 20 cigarettes per day.

The continuous black line in Figure 1B is the effect of ICS predicted by a model that was fitted on current, former, and never smokers of all ages and included flexible spline func-tions for both ICS and TSC (model E). The effect of ICS pre-dicted by model E closely resembled the prediction of model D. The effect of TSC predicted by model E is presented in Figure 1C. Knots of the restricted cubic spline were located at 6, 15, and 28 years since smoking cessation. Model E pre-dicted a strong reduction (83%) in the EOR for lung cancer per PCS with increasing TSC.

In Table 1, we report the fit of model E to the study data. In model E_0, the functions for ICS and TSC were set to 0; thus, the effect of PCS on the odds ratio for lung cancer was not modified. On the basis of a likelihood ratio test, both model E_1 (in which the effect of TSC on the EOR for lung cancer per PCS was set to 0) and model E_2 (in which the effect of ICS was set to 0) provided a significantly better fit to the data than did model E_0. Furthermore, model E_3, in which functions for both ICS and TSC were estimated, provided a significantly better fit to the study data than did models E_1 and E_2. Model E_3 (hereafter referred to as model E) was therefore se-lected for further analyses of the data set.

Similar patterns with ICS were observed in analyses for 3 major subtypes of cancer: squamous cell carcinoma, small cell carcinoma, and adenocarcinoma (Figure 2). Analyses of men and women separately resulted in patterns of the EOR per PCS that were comparable to the analyses of men and women combined (Web Figure 2).

In Figure 3, we show study-specific patterns of the modi-fication of EOR per PCS by ICS. These analyses were con-ducted on all subtypes combined. Predictions were generated by applying model E to each individual study.

Wide confidence intervals in some of the panels of Figure 3 demonstrate that some studies had limited statistical power to explore patterns in the EOR per PCS. Furthermore, model E did not converge when applied a lung cancer study in France, a lung cancer study in Paris, and the Monitoring van Risicofactoren en Gezondheid in Nederland (MORGEN) study, which were 3 studies of modest sample size (Web Table 1). In most stud-ies for which we were able to observe a pattern, a downward trend in EOR per PCS with increasing ICS was observed after reaching a maximum EOR per PCS for approximately 20–30 cigarettes per day. Exceptions

were the Liverpool Lung Project (LLP), the Lungcancer i Stockholm (LUCAS) Study, and the Polish arm of the International Agency for Research on Cancer Multicenter Case-Control Study of Occupational, Environ-ment and Lung Cancer in Central and Eastern Europe (INCO-COPERNICUS), which showed a flat or increasing in EOR per PCS. Confidence intervals for the predicted patterns for these studies did not exclude a downward trend. Higher un-certainty within studies and less consistency across studies was observed for patterns in effect modification by ICS for smoking intensities below 20 cigarettes per day. Among studies for which predictions were relatively precise, upward patterns were generally observed. Absolute levels of the EOR per PCS varied considerably across study locations.

DISCUSSION

Application of our approach in the SYNERGY data set provided insight into the consistency of patterns of modifica-tion of the effect of PCS on the EOR for lung cancer by ICS across a large number of independently designed case-control studies from Central and Eastern Europe, Canada, and New Zealand. We observed negative effect modification of the association of PCS and lung cancer by ICS for persons who smoked more than 20–30 cigarettes per day. Patterns of effect modification were similar across the major cancer sub-types of squamous cell carcinoma, small cell carcinoma, and adenocarcinoma. These findings corroborate the results from analyses conducted on other data sets of smoking and lung cancer (4, 7, 8). Our analysis furthers existing knowledge by showing similar patterns of effect modification across a large number of independently designed studies by allowing for and demonstrating strong effect modification by TSC and by including semiparametric spline functions that allow for flexible assessment of patterns of effect modification.

Intensity of cigarette smoking

The observed variation in the EOR per PCS with increas-ing ICS might be the result of biological processes, such as saturation of metabolism or increasing DNA repair capacity with increasing ICS (4, 20). Increasing misclassification of ICS with increasing ICS could also have contributed to the observed patterns. Studies of cigarette smoking and nicotine dependency have shown that an increase in the number of cigarettes smoked per day might be associated with reduced inhalation per cigarette, and increasing misclassification in the reporting of the number of cigarettes smoked per day it-self with increasing ICS is also conceivable (4, 21). Studies using serum or urine cotinine levels as a marker of tobacco smoking intensity have found that lung cancer risks do not plateau at high exposure levels, which suggests that such patterns observed in studies using smoking behavior ques-tionnaires were likely due to exposure misclassification (22, 23). However, cotinine levels only reflect smoking intensity over the past few days and should therefore not be considered as an “ideal” marker to estimate lifelong average smoking in-tensity (24). Our results suggest that the ICS patterns pre-dicted for the low exposure range by our model E (which is not constrained to start at $\beta = 0$ at no exposure) are highly var-iable in magnitude and direction across study locations. This is likely explained by the limited range of PCS at lower expo-sure intensities (4).

We observed considerable variation across studies in the range of predicted EORs per PCS. The large heterogeneity of results might be associated with factors inherent to the studies, like design, response rates, and statistical power (25). Differential distribution of the relative occurrence of lung cancer subtypes, characteristics of smoking habits, and confounders and effect modifiers such as occupational exposures, indoor radon exposure and dietary components across study populations likely also played a role (14, 25).

Time since smoking cessation

Our finding of a continuous decrease in the EOR per PCS with TSC corroborates findings from other studies. For exam-ple, Peto et al. (15) demonstrated that the ratio of lung cancer in former smokers compared with current smokers fell sharp-ly with increasing TSC. Our analysis demonstrates that this effect remains after adjustment for PCS. Similar patterns with time since exposure cessation have been observed for exposure to benzene and leukemia (26) and for exposure to radon and lung cancer (27).

Extension to other (time-varying) exposures

Through its flexible parameterization, our model can ac-commodate various patterns of effect modification and is therefore a suitable tool to explore effect modification by in-tensity of exposure for a wide range of different exposures. Similar models have successfully been applied in studies of arsenic, as well as alcohol and smoking and a range of can-cers (6, 9, 10). A limitation of these models (including ours) is that they ignore the possible variation in the EOR due to variation in exposure intensity over time. Using the general framework described in the Web Appendix as starting point, our model can be extended to accommodate information on time-varying exposure. Richardson et al. recently provided an example of such a model in a study of radon exposure and lung cancer (28). A further extension is to allow for more complicated patterns of effect modification by including tensor product splines as done by Berhane et al. (29), al-though these may come at the cost of reduced interpretability.

Our model and possible further extensions of it provide in-sight into whether the use of cumulative exposure in an epi-demiologic analysis is justified or whether reducing complex exposure history to a metric such as cumulative

exposure is overly restrictive. Combining information on observed pat-terns of effect modification with mechanistic insights might contribute to the incorporation of biological hypotheses in the development of more biologically relevant exposure metrics (30).

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Table 1. Linear Odds Ratio Models for Total Cigarette Exposure and 3 Lung Cancer Subtypes Fitted on the SYNERGY Data, 1985–2009[a]

Model	Excess OR Modification	df	Type of Cancer									
			Combined			Squamous Cell Carcinoma			Small Cell Carcinoma			Adenocarcinoma		
			LL	LL	P Value[b]	LL	LL	P Value[b]	LL	LL	P Value[b]	LL	LL	P Value[b]
E_0	Not modified		45,828			25,099			14,220			23,001		
E_1	ICS		45,727			25,049			14,185			22,901		
E_1 vs. E_0		2		101	<0.0001		50	<0.0001		31	<0.0001		35	<0.0001
E_2	TSC		44,895			24,506			13,698			22,786		
E_2 vs. E_0		2		933	<0.0001		593	<0.0001		518	<0.0001		522	<0.0001
E_3	ICS and TSC		44,843			24,487			13,686			22,714		
E_3 vs. E_0		4		985	<0.0001		612	<0.0001		526	<0.0001		534	<0.0001
E_3 vs. E_1		2		884	<0.0001		562	<0.0001		495	<0.0001		499	<0.0001
E_3 vs. E_2		2		52	<0.0001		19	0.0001		8	0.0025		12	<0.0001

Abbreviations: df, degrees of freedom for likelihood ratio test; ICS, intensity of cigarette smoke; LL, log likelihood estimate of the fitted model; OR, odds ratio; TSC, time since smoking cessation.

[a] Excess OR was modified by either a function for the intensity of exposure (E_1), a function for the time since smoking cessation (E_2), or both (E_3).

[b] P values from likelihood ratio tests.