**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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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 modification 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 smoking 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 exposure 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 target 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 straigh-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 example, 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 + β1d × exp(β2 (n)), where β1 represents the EOR per unit of total
exposure (d ) (i.e., the EOR of disease changes in an additive fashion with total exposure) and β2 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 on PCS 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 participating hospitals. The ethics committees of the individual studies approved the conduct of the study, as did the institutional review board at the International Agency for Research on Cancer. 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 calculated 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 included, without restriction on age or smoking status.

Statistical analysis

The model we used in this article provides a balance between 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 framework (Web Appendix, Web Table 2, and Web Figure 1).

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

The model is as follows:

$$\text{OR}_d \text{d} = \beta_d \times \exp(\sum \theta_i n_{i,d}, g); \quad (A)$$

where $\beta$ represents the EOR for each PCS, d. The model specifies a different slope for each intensity category. With $\theta_1$ set to 0 for identifiability, $\theta_2, \ldots, \theta_I$ 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:

$$\text{OR}_d \text{d} \text{P} = \beta_d \times \exp(\sum \theta_i d_{i,d} \times \exp(\Sigma \theta_i n_{i,d} g); \quad (B)$$

where $g_{t}(t)$ is a 3-knot restricted cubic spline function for TSC (knots located at the 20th, 50th, and 80th percentiles of the distribution 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:

$$\text{OR}_d \text{d} = \beta_d \times h_d n_{d}; \quad (C)$$

where $h(n)$ has the functional form $h(n) = \exp(\Phi_1 \ln(n) + \Phi_2 \ln(n)^2)$. $\Phi_1$ and $\Phi_2$ 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:

$$\text{OR}_d \text{d} = \beta_d \times \exp(g_{t} \ln(n); \quad (D)$$

$g_{t}$ 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 analysis, as follows:

\[
\text{OR} = \frac{1 + \beta d \times \exp\left(g_1 \delta n + g_2 \delta t\right)}{1 + \exp\left(g_1 \delta n + g_2 \delta t\right)};
\]

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 continuous 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. Analyses 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 carcinoma, small cell carcinoma, and adenocarcinoma. We assessed 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 percentiles) 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 priori 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 percentile 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 distribution of the exposed persons from all plots. The same approach was used for TSC. A likelihood ratio test (18) was used to compare differences in intensities less than the 1st percentile and higher than the 99th percentile of the distribution of all former smokers. g1 is a function of continuous ICS (n) and g2 is a function of continuous TSC (t).

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 restricted 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 \(\Phi_1\) and \(\Phi_2\) 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 functions for both ICS and TSC (model E). The effect of ICS predicted 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 predicted 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 E0, 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 E1 (in which the effect of TSC on the EOR for lung cancer per PCS was set to 0) and model E2 (in which the effect of ICS was set to 0) provided a significantly better fit to the data than did model E0. Furthermore, model E3, in which functions for both ICS and TSC were estimated, provided a significantly better fit to the study data than did models E1 and E2. Model E3 (hereafter referred to as model E) was therefore selected 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 the men and women combined (Web Figure 2).

In Figure 3, we show study-specific patterns of the modification of EOR per PCS by ICS. These analyses were conducted 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 studies, 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 Lung Cancer i Stockholm (LUCAS) Study, and the Polish arm of the International Agency for Research on Cancer Multicenter Case-Control Study of Occupational, Environment 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 uncertainty 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 modification 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 increasing 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 itself 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 questionnaires 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 intensity (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 variable in magnitude and direction across study locations. This is likely explained by the limited range of PCS at lower exposure 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 example, Peto et al. (15) demonstrated that the ratio of lung cancer in former smokers compared with current smokers fell sharply 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 accommodate various patterns of effect modification and is therefore a suitable tool to explore effect modification by intensity 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 cancers (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), although these may come at the cost of reduced interpretability.

Our model and possible further extensions of it provide insight into whether the use of cumulative exposure in an epidemiologic analysis is justified or whether reducing complex exposure history to a metric such as cumulative
exposure is overly restrictive. Combining information on observed patterns 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, 1985–2009a

<table>
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<th>Model</th>
<th>Excess OR Modification</th>
<th>df</th>
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<th>Squamous Cell Carcinoma</th>
<th>Small Cell Carcinoma</th>
<th>Adenocarcinoma</th>
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<td>22,901</td>
<td></td>
</tr>
<tr>
<td>E2</td>
<td>TSC</td>
<td>44,895</td>
<td>24,506</td>
<td>13,698</td>
<td>22,786</td>
<td></td>
</tr>
<tr>
<td>E3</td>
<td>ICS and TSC</td>
<td>44,843</td>
<td>24,487</td>
<td>13,686</td>
<td>22,714</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>985 &lt;0.0001</td>
<td>612 &lt;0.0001</td>
<td>526 &lt;0.0001</td>
<td>534 &lt;0.0001</td>
</tr>
<tr>
<td>E3</td>
<td></td>
<td>2</td>
<td>884 &lt;0.0001</td>
<td>562 &lt;0.0001</td>
<td>495 &lt;0.0001</td>
<td>499 &lt;0.0001</td>
</tr>
<tr>
<td>E3</td>
<td></td>
<td>2</td>
<td>52 &lt;0.0001</td>
<td>19 0.0001</td>
<td>8  0.0025</td>
<td>12 &lt;0.0001</td>
</tr>
</tbody>
</table>

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 (E1), a function for the time since smoking cessation (E2), or both (E3).

b P values from likelihood ratio tests.