Cigarette Smoking, N-Acetyltransferase 2 Acetylation Status, and Bladder Cancer Risk: A Case-Series Meta-analysis of a Gene-Environment Interaction

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Abstract
Tobacco use is an established cause of bladder cancer. The ability to detoxify aromatic amines, which are present in tobacco and are potent bladder carcinogens, is compromised in persons with the N-acetyltransferase 2 slow acetylation polymorphism. The relationship of cigarette smoking with bladder cancer risk therefore has been hypothesized to be stronger among slow acetylators. The few studies to formally explore such a possibility have produced inconsistent results, however. To assess this potential gene-environment interaction in as many bladder cancer studies as possible and to summarize results, we conducted a meta-analysis using data from 16 bladder cancer studies conducted in the general population (n = 1999 cases). Most had been conducted in European countries. Because control subjects were unavailable for a number of these studies, we used a case-series design, which can be used to assess multiplicative gene-environment interaction without inclusion of control subjects. A case-series interaction odds ratio (OR) > 1.0 indicates that the relationship of cigarette smoking and bladder cancer risk is stronger among slow acetylators as compared with rapid acetylators. We observed an interaction between smoking and N-acetyltransferase 2 slow acetylation (OR, 1.3; 95% confidence interval, 1.0–1.6) that was somewhat stronger when analyses were restricted to studies conducted in Europe (OR, 1.5; confidence interval, 1.1–1.9), a pooling that included nearly 80% of the collected data. Using the predominantly male European study population and assuming a 2.5-fold elevation in bladder cancer risk from smoking, we estimated that the population attributable risk percent was 35% for slow acetylators who had ever smoked and 13% for rapid acetylators who had ever smoked. These results suggest that the relationship of smoking and bladder cancer is stronger among slow acetylators than among rapid acetylators.

Introduction
Tobacco use is an established cause of bladder cancer, resulting in a 2- to 3-fold increased risk among individuals who have ever smoked. Although certain occupational exposures (e.g., benzidine) confer a much greater elevation in risk, cigarette smoking is nevertheless responsible for more cases of bladder cancer than any other risk factor because of its higher prevalence (1). It is estimated that in some populations, 50% of bladder cancer in males and 25% of bladder cancer in females could be prevented with elimination of cigarette smoking (2).

Aromatic amines are suspected to be the primary causative agent for bladder cancer in tobacco smoke (3). N-acetylation, which occurs mainly in the liver and is chiefly regulated by the enzyme NAT2, can detoxify monoarylamines (e.g., 4-amino-biphenyl), rendering them less susceptible to metabolic activation by P-450 enzymes (3). The lack of two functional NAT2 alleles confers the slow acetylation phenotype, which is thought to compromise detoxification ability (3). For that reason, Lower et al. (4) hypothesized in 1979 that slow acetylators would be at an elevated bladder cancer risk.

Since then, at least 22 case-control studies have examined the relationship of NAT2 acetylation status and bladder cancer in the general population (4–24). A recent meta-analysis of those studies (25) reported a positive association between slow acetylation status and bladder cancer, although there was a suggestion that the relationship varied somewhat by geographic region; a positive association was observed for studies conducted in Europe and Asia, but not for studies conducted in the United States. Few of the 22 studies formally explored whether the relationship of cigarette smoking and bladder cancer differed by acetylation status; results were inconsistent among the studies that performed such analyses (5–7, 17, 19, 22).

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2The abbreviations used are: NAT2, N-acetyltransferase 2; OR, odds ratio; CI, confidence interval.
Because cigarette smoking is a relatively common habit, and the slow acetylation phenotype is a relatively common metabolic polymorphism [about 55% in populations of European descent, 35% in populations of African descent, and 15% in populations of Asian descent (26)], a potential modifying effect of acetylation status on the relationship between cigarette smoking and bladder cancer risk is of considerable interest. To explore such a possibility, as well as to summarize results of separate studies, we undertook a meta-analysis of bladder cancer studies that had been conducted in the general population and had collected data on cigarette smoking and acetylation status.

Materials and Methods

Data Collection. We conducted our first search for studies in 1991. MEDLINE was used to conduct literature searches; citations in identified articles and review articles (27) also were examined (28, 29). Any case-control study of bladder cancer that was conducted in the general population and that collected data on cigarette smoking and NAT2 acetylation status (either as a phenotype or an NAT2 genotype) was eligible for inclusion; studies conducted in or derived in part from cohorts of workers with documented exposure to carcinogenic aromatic amines were excluded. Investigators associated with eligible studies were invited to contribute data to our effort. In addition to smoking history and acetylation status, we also requested data on age, sex, history of potential occupational exposure to aromatic amines, tumor stage, tumor grade, date of diagnosis, and date of study enrollment.

After several years of data collection efforts, information had been received for only about half the identified studies, primarily because data sets were no longer available. Ultimately, we decided to employ a case-series design because this method would allow for inclusion of unavailable studies if case cross-classification of cigarette smoking (ever/never) and acetylation status (slow/rapid) had been published. Although control cross-classifications were available for some studies, it was unclear how representative the control series were of the individual base populations, especially with regard to tobacco use. Therefore, we did not use these data to address our primary research questions.

Another MEDLINE search was conducted to identify studies that had been published after our initial search and before the end of 1998. The results of this search brought the number of eligible published studies to 20 (4–13, 15–23), 15 (4–6, 8–13, 15–17, 19, 20, 22) of which (1908 of 2179 cases; 88%) could be included in the meta-analysis. For the newly included studies, acetylation and smoking were abstracted directly from published manuscripts, although in one instance it was necessary to contact authors for clarification (17). We also included data from one study that had been supplied to us as unpublished data during the early stages of our project but is presently submitted (91 cases). The final data set for the meta-analysis included 16 studies and 1999 cases. Of those, response rates were available for only one study (17).

Data on acetylation status (phenotype or NAT2 genotype) and cigarette smoking (never/ever smoked) were available for all cases. Some investigator-supplied data sets also provided information on age (9, 12, 13, 16, 20) and potential occupational exposure to aromatic amines (13).3 Participants’ sex was known for all studies except two (4),3 although sex-specific cross-tabulations of acetylation status and cigarette smoking were available for only seven (6, 9, 11–13, 16, 20). Race was not available for most studies, but it is reasonable to assume that studies conducted in Europe were comprised primarily of Caucasians. Of the two studies conducted in the United States, one was known to be comprised solely of Caucasians (15); in the other, 93% of cases were known to be Caucasian (22).

In two studies, individuals who used tobacco products other than cigarettes could be identified (16);3 they were excluded to minimize tobacco exposure among never-smokers. Two studies were known to have included prevalent cases (5, 17), although it is likely that many other studies included such cases also. Ten studies had data on smoking and acetylation status for control subjects (5, 6, 10–12, 16, 19, 20, 22).3 Most of these series (5, 6, 11, 16, 19, 20, 22)3 consisted of either clinic attendees or hospital in-patients.

Statistical Analyses. In a case-series study of gene-environment interaction, an OR (referred to as a “case-series interaction OR” in the remainder of this paper) is calculated from cross-classification of exposure and genetic information among cases only (30–33). A case-series interaction OR >1 in the present study indicates that the relationship of cigarette smoking and bladder cancer is stronger among slow acetylators than among rapid acetylators. Independence of exposure and the genetic factor in the base population is necessary for valid interpretation of a case-series interaction OR. In the present study, the validity of that assumption was assessed by calculating $\chi^2$ statistics for the available controls series as well as for a pooled analysis of those series (34, 35). Logistic regression was used to estimate ORs and 95% CIs in the individual case series (36, 37). Meta-analysis techniques that weighted the estimated $\beta$ coefficient for each individual study by a function of its variance were used to calculate a summary estimate (38, 39). Because results for fixed and random effects models were nearly identical and because the hypothesis of homogeneity was not rejected in any instance [using the Q-statistic (38) at a significance level of 0.05], results from only fixed effect models are presented.

We also addressed the association between ever having smoked cigarettes (versus never smoking) and slow acetylation status (versus rapid acetylation status) among bladder cancer cases. Because a number of studies have shown excellent correlation between NAT2 phenotype determined pharmacologically and that predicted by NAT2 genotyping (40–44) and because the relationship of NAT2 acetylation status and bladder cancer risk did not vary by method used to assess NAT2 in a recent meta-analysis (25), only in one instance do we present separate results from studies using genotyping. The result of that analysis further supports pooling of studies.

Data on age were available for 32% of the pooled data set, and data on potential occupational exposure to aromatic amines were available for 19%. By limiting analyses to subsets where these variables were available, we assessed potential confounding effects. Age was categorized as <55 years, 55–64 years, 65–74 years, and ≥75 years. Potential occupational exposure to aromatic amines was coded as history or no history of exposure. If the OR of interest changed by >10% with inclusion of the variable, confounding was said to exist. Potential effect modification by sex could not be assessed owing to the small cell

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Table 1 Data sources used in the meta-analysis

<table>
<thead>
<tr>
<th>First author, Date</th>
<th>No. of cases</th>
<th>Data source</th>
<th>Country (city or state)</th>
<th>Phenotyping or genotyping (drug used for phenotyping or mutant allele)¹²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brockmoller, 1996⁵</td>
<td>374</td>
<td>Publication</td>
<td>Germany (Berlin)</td>
<td>Genotyping (NAT2*5, 6, 7)</td>
</tr>
<tr>
<td>Oikkels, 1997⁴</td>
<td>253</td>
<td>Publication</td>
<td>Denmark (Aarhus)</td>
<td>Genotyping (NAT2*5, 6, 7)</td>
</tr>
<tr>
<td>Taylor, 1998</td>
<td>230</td>
<td>Publication</td>
<td>United States (North Carolina)</td>
<td>Genotyping (NAT2*5, 6, 7, 14)</td>
</tr>
<tr>
<td>Risch, 1995⁶</td>
<td>178</td>
<td>Publication</td>
<td>England (Birmingham)</td>
<td>Genotyping (NAT2*5, 6, 7)</td>
</tr>
<tr>
<td>Mommsen, 1986¹⁶</td>
<td>149</td>
<td>Investigator</td>
<td>Denmark (Aarhus)</td>
<td>Phenotyping (sulfamethazine)</td>
</tr>
<tr>
<td>Ladero, 1985¹³</td>
<td>130</td>
<td>Investigator</td>
<td>Spain (Madrid)</td>
<td>Phenotyping (sulfamethazine)</td>
</tr>
<tr>
<td>Hanssen, 1985⁸</td>
<td>105</td>
<td>Publication</td>
<td>Germany (Hamburg)</td>
<td>Phenotyping (sulfamethazine)</td>
</tr>
<tr>
<td>Roots, 1989</td>
<td>101</td>
<td>Investigator</td>
<td>Germany (Berlin)</td>
<td>Phenotyping (caffeine)</td>
</tr>
<tr>
<td>Kaisary, 1987¹¹</td>
<td>98</td>
<td>Investigator</td>
<td>England (Bristol)</td>
<td>Phenotyping (dapsone)</td>
</tr>
<tr>
<td>Romkes, 2000¹³</td>
<td>91</td>
<td>Investigator</td>
<td>England (Bristol)</td>
<td>Phenotyping (dapsone)</td>
</tr>
<tr>
<td>Dewan, 1995</td>
<td>77</td>
<td>Publication</td>
<td>India (Ahmedabad)</td>
<td>Phenotyping (isomiazid)</td>
</tr>
<tr>
<td>Lower, 1979</td>
<td>67</td>
<td>Publication</td>
<td>Denmark (Copenhagen)</td>
<td>Phenotyping (sulfamethazine)</td>
</tr>
<tr>
<td>Horai, 1989</td>
<td>50</td>
<td>Investigator</td>
<td>Japan (Tokyo)</td>
<td>Phenotyping (dapsone)</td>
</tr>
<tr>
<td>Ishizu, 1995¹⁰</td>
<td>47</td>
<td>Publication</td>
<td>Japan (Tokyo)</td>
<td>Phenotyping (isomiazid)</td>
</tr>
<tr>
<td>Miller, 1983¹⁵</td>
<td>26</td>
<td>Publication</td>
<td>United States (Western NY state)</td>
<td>Phenotyping (sulfamethazine)</td>
</tr>
<tr>
<td>Karakaya, 1986¹²</td>
<td>23</td>
<td>Investigator</td>
<td>Turkey (Ankara)</td>
<td>Phenotyping (sulfamethazine)</td>
</tr>
</tbody>
</table>

¹ Authors were contacted to verify joint-frequencies derived from published data.

Table 2 Independence of NAT2 acetylation status and cigarette smoking among available control subjects

<table>
<thead>
<tr>
<th>First author</th>
<th>Never-smokers</th>
<th>Slow acetylators</th>
<th>Rapid acetylators</th>
<th>Ever-smokers</th>
<th>Slow acetylators</th>
<th>Rapid acetylators</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brockmoller (5)</td>
<td>373</td>
<td>51 (61)</td>
<td>33 (39)</td>
<td>165 (57)</td>
<td>124 (43)</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Taylor (22)</td>
<td>203</td>
<td>44 (60)</td>
<td>30 (40)</td>
<td>65 (50)</td>
<td>64 (50)</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Risch (19)</td>
<td>39</td>
<td>6 (55)</td>
<td>5 (45)</td>
<td>11 (40)</td>
<td>17 (60)</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Mommsen (16)</td>
<td>69</td>
<td>11 (50)</td>
<td>11 (50)</td>
<td>25 (53)</td>
<td>22 (47)</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Roots (20)</td>
<td>101</td>
<td>6 (33)</td>
<td>12 (67)</td>
<td>39 (47)</td>
<td>44 (53)</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Kaisary (11)</td>
<td>116</td>
<td>29 (40)</td>
<td>44 (60)</td>
<td>20 (47)</td>
<td>23 (53)</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>Romkes⁶</td>
<td>70</td>
<td>10 (48)</td>
<td>11 (52)</td>
<td>24 (49)</td>
<td>25 (51)</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Dewan (6)</td>
<td>80</td>
<td>11 (35)</td>
<td>20 (63)</td>
<td>17 (35)</td>
<td>32 (65)</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Ishizu (10)</td>
<td>91</td>
<td>7 (16)</td>
<td>38 (84)</td>
<td>6 (13)</td>
<td>40 (87)</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Karakaya (12)</td>
<td>109</td>
<td>39 (65)</td>
<td>21 (35)</td>
<td>28 (57)</td>
<td>21 (43)</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>1251</td>
<td>214 (49)</td>
<td>225 (51)</td>
<td>400 (49)</td>
<td>412 (51)</td>
<td>0.40</td>
<td></td>
</tr>
</tbody>
</table>

⁶ Weighted by study site; P for Q-statistic (test for homogeneity): 0.88.

Results

Selected characteristics of the 16 data sets are shown in Table 1. Most were obtained from publications reporting provided NAT2 phenotype rather than genotype information. The majority of cases were European (77%) and male (73%, based on the 14 studies with that information). Individual data sets ranged in size from 23 to 374 cases. The pooled data set contained 1999 cases.

Smoking history and acetylation status were independent among available control subjects (Table 2). Overall, 49% of non-smokers were slow acetylators, as were 49% of ever-smokers (P = 0.40). In many of the control series, the percentages of slow acetylators among smokers and nonsmokers were quite similar.

A case-series interaction OR of 1.3 (95% CI, 1.0–1.6) was observed when data were pooled (Table 3), suggesting that the relationship of cigarette smoking and bladder cancer is stronger among slow acetylators compared with rapid acetylators. Neither age nor potential occupational exposure to aromatic amines confounded that relationship (data not shown). Restriction to studies that used genotyping produced results similar to the overall finding. Individual study results varied (Table 3; Fig. 1).

sizes produced by cross-tabulations of acetylation status and cigarette smoking, even in analyses restricted to males.

To provide a more accustomed interpretation, we converted our case-series interaction OR to the corresponding measures that would be generated using data from a case-control study (that is, the ORs for non-smoking slow acetylators, smoking rapid acetylators, and smoking slow acetylators, all relative to non-smoking rapid acetylators). Four additional parameters were necessary: prevalence of smoking and NAT2 slow acetylation in the base population, and the bladder cancer ORs for smoking and NAT2 slow acetylation. Details of this method are presented in the “Appendix.” Calculations were restricted to European studies because several of the necessary parameters (e.g., prevalence of NAT2 slow acetylation and the association of NAT2 slow acetylation with bladder cancer) vary by geographic region (25) and substantial amounts of data were available for the European region only (77% of the total data set). Population attributable risk percents (45) were calculated using the European smoking and slow acetylation prevalences and the derived case-control ORs.
although the summary ORs generated by the five studies consisting of about 150 subjects (OR, 1.5; CI, 1.1–2.0) and by the 10 studies conducted in European countries (OR, 1.5; CI, 1.1–1.9) suggested stronger interaction. An OR of 1.7 (CI, 1.2–2.3) was generated from the four European studies that had about 150 subjects (48% of all data).

We converted our European OR of 1.5 to a series of point estimates that would be expected using data from a comparable case-control study (see “Appendix”). Calculations were made using the following values: 54% and 59% prevalence for NAT2 slow acetylation and ever smoking, respectively; bladder cancer ORs of 1.5 and 2.5 for NAT2 slow acetylation and ever smoking, respectively. All parameters were derived from the European studies included in this meta-analysis, with exception of the bladder cancer OR for smoking, which was obtained from a review article (see “Appendix”). Based on these assumptions, nonsmoking slow acetylators are predicted to have no elevation in bladder cancer risk, relative to nonsmoking rapid acetylators (Table 4). Relative to that same group, rapid acetylators who smoke are predicted to have about a 2-fold elevation in risk, and slow acetylators who smoke, about a 3-fold elevation in risk. Using these findings, the estimated population attributable risk percent for smoking was 48%, which partitioned to 13% for rapid acetylators and 35% for slow acetylators.

Discussion
This meta-analysis suggests that the association of cigarette smoking and bladder cancer risk is stronger (30–50%) among NAT2 slow acetylators as compared with rapid acetylators.
These results, coupled with a number of assumptions about smoking and NAT2 slow acetylation prevalence and their relationship with bladder cancer risk among European countries: calculation of case-control ORs from the case-series interaction OR of 1.5

<table>
<thead>
<tr>
<th>Status</th>
<th>Rapid acetylation</th>
<th>Slow acetylation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never-smokers</td>
<td>1.00</td>
<td>1.10</td>
</tr>
<tr>
<td>Ever-smokers</td>
<td>1.95</td>
<td>3.21</td>
</tr>
</tbody>
</table>

*a Calculated assuming: prevalence of ever having smoked cigarettes, 59%; prevalence of NAT2 slow acetylation, 54%: OR of NAT2 slow acetylation and bladder cancer, 1.5: OR of bladder cancer among ever smokers, 2.5 (see “Appendix” for methods and data sources).

*b Reference category.

size, as would be expected given the usual effects of random variation (47) both within and across studies. Although many of the studies producing null or inverse associations were published at a time when the slow acetylator hypothesis was not firmly established (thus minimizing the chance that results would not be published), two studies published in the second half of the 1990s (10, 22), a time when the slow acetylator hypothesis was better known and more widely accepted, produced null associations also. The validity of our results may be affected by confounding, misclassification, or other limitations of our data. Adjustment for age and possible occupational exposure to aromatic amines, the most plausible confounding variables, did not meaningfully change the ORs of interest, but these analyses could only be carried out on a small subset of the data and therefore may not be generalizable to the rest. Limited information on use of tobacco products other than cigarettes, as well as environmental tobacco smoke, prevented us from excluding from our unexposed category all individuals who were exposed to aromatic amines from other tobacco sources. Such misclassification would tend to attenuate our results. Our findings also may be affected by error in assigned acetylation status, as well as misreport of cigarette smoking history. Certain unusual misclassification scenarios could bias results away from the null, but the most probable situation, the one in which smoking and acetylation status misclassification are independent of one another and sensitivity and specificity of the two exposures are not severely compromised (that is, the sum of sensitivity and specificity is ≥1), would result in bias toward the null (48). Given these limitations, it is likely these findings, if anything, are underestimates of the true relationship.

With regard to the assumptions required for valid interpretation of case-series findings, we are confident that in these studies, smoking and acetylation status were independent, but we are less certain about the representativeness of the bladder cancer cases. At least two studies included prevalent cases (5, 17), and it is likely that some of the older studies did as well. It has been suggested that the NAT2 slow polymorphism is more influential in aggressive bladder cancer (49) and as such, it would have been best to analyze data separately for certain tumor characteristics. A large study published in 1996, however, observed similar proportions of NAT2 slow acetylators among incident and prevalent cases, as well as for different tumor grades and histological subtypes (5).

We were unable to examine whether the presence of a gene-environment interaction differs by level of smoking intensity (amount smoked per day) or duration (years smoked and pack-years smoked). Although such data were available for a small subset of the studies (around 20% of all subjects), we were concerned that such limited information would not produce generalizable results. Furthermore, a dearth of light smokers made point estimates for such categories very imprecise. The findings of a cross-sectional study that addressed the influence of NAT2 acetylation on the development of 4-aminobiphenyl hemoglobin adducts support the notion that the magnitude of the gene-environment interaction differs by smoking level, but suggests that the interaction may be most pronounced at lower levels of use (50).

The study of gene-environment interactions may help enhance our understanding of how some exposures impact bladder cancer risk. Our meta-analysis of cigarette smoking, NAT2 acetylation status, and bladder cancer risk has addressed a number of pertinent issues, but our summary result, which was based in part on a number of small, older studies, must be
replicated in larger studies. Future studies should address the impact of varied smoking habits, as well as the joint impact of other susceptibility factors for tobacco-induced bladder cancer.

Acknowledgments

We thank Jay Lubin for his assistance with statistical computing and methodology.

Appendix

Calculations used to determine case-control ORs from case-series interaction ORs and other information. The ORs for the effect of smoking among NAT2 rapid acetylators (OR_{RGc,1|E=0}) and the effect of NAT2 slow acetylation among nonsmokers (OR_{RGc,1|E=0}) were calculated using these five estimates:

- Interaction effect (OR_{E=0}) of 1.5. Obtained using the 10 European studies included in this meta-analysis.
- Prevalence of NAT2 slow acetylation (P_{G=1}) of 54%. Obtained using the 10 European studies included in this meta-analysis.
- Crude OR for the main effect of NAT2 slow acetylation and bladder cancer risk (OR_{RGc,1}) of 1.5. Obtained using the 10 European studies included in this meta-analysis.
- Crude OR for the main effect of smoking and bladder cancer risk (OR_{RGc,1|E=0}) of 2.5. Midpoint of the 2-to-3-fold increase in risk reported by Silverman et al. (1). The crude OR for the main effect of ever smoking was not calculated from European studies included in this meta-analysis because of concerns that smokers were overrepresented in the hospital/clinic based control series.
- Prevalence of smoking (P_{E=1}) of 59%. Derived using the OR for smoking (2.5) and the prevalence of ever smoking among cases (78%) in the 10 European studies included in this meta-analysis.

The following equations* were used to solve for OR_{RGc,1|E=0} and OR_{RGc,1|E=0}:

\[
OR_{RGc,1} = \frac{P_{G=0} \times OR_{E=0|G=0} + P_{G=1} \times OR_{E=0|G=0} \times OR_{RGc,1|E=0}}{P_{E=0} \times OR_{G=0|E=0} + P_{E=1} \times OR_{G=0|E=0} \times OR_{RGc,1|G=0}}
\]

The joint effect for NAT2 slow acetylation and smoking (OR_{RGc,1|G=0}) was then calculated by multiplying OR_{RGc,1|E=0} \times OR_{RGc,1|G=0} \times OR_{RGc,1|E=0}.

*These equations are derived as follows: The crude OR for the main effect of exposure on disease risk (OR_{E=0}) can be expressed in terms of the cell counts of two \times two tables—\(E\) by \(B\) for \(G = 1\) and \(E\) by \(D\) for \(G = 0\). The crude OR for the main effect of the genetic factor on disease risk (OR_{RGc,1}) can be expressed in terms of the cell counts of two \times two tables—\(E\) by \(D\) for \(E = 1\) and \(E\) by \(D\) for \(E = 0\). Algebraic manipulation of OR_{RGc,1} and OR_{E=0} expressed in terms of the cell counts results in the formulas we present in the “Appendix” because all of the terms on the right-hand side of the equation can also be expressed in terms of the cell counts of the two \times two tables. These formulas assume that \(E\) and \(G\) are independent among the controls. In the instance of no interaction (OR_{RGc,1} = 1), the formulas for the crude ORs will be the same as the Mantel-Haenszel OR. These formulas were presented in Ref. 55.

References


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Cigarette Smoking, N-Acetyltransferase 2 Acetylation Status, and Bladder Cancer Risk: A Case-Series Meta-analysis of a Gene-Environment Interaction
