THE EFFECT OF JOINT EXPOSURE TO ALCOHOL AND TOBACCO ON RISK OF CANCER OF THE MOUTH AND PHARYNX*

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INTRODUCTION

It is known that alcohol consumption and smoking are risk factors for cancer of the oral cavity [1-3]. It therefore seems useful to determine how the joint action of the two factors is related to oral cancer risk. The basic question addressed in this paper is the following: do these two exposures confer their risks independently or in some 'interactive' fashion?

It is necessary to define precisely the concept of independent action, as a basis for defining interaction. Measures of disease risk can be interpreted as probability measures. Persons not exposed to a certain risk factor have a specific probability for developing a disease, and persons exposed have a higher probability. The risk factor increases the probability by an amount 'x' – the difference between the two probabilities. If another risk factor increases the baseline probability by an amount 'y', then those persons with exposure to both should experience an excess probability of x + y, since the probabilities for rare independent events can be added together to obtain the probability that either event will occur. If one were dealing with a very common disease it might be necessary to modify this expression to take account of the problem of competing risks. For most diseases, however, the simple additive expression is sufficiently accurate. This criterion for independence of risk factors in disease is consistent with the concepts presented by MacMahon and Pugh [4] and by Cole and MacMahon [5]. The key concept is the additivity of the excess risk associated with different exposures. If the excess risk for persons exposed to both factors is greater or less than x + y, an interaction effect, either synergy or antagonism, may be said to be present.

The question of interaction between alcohol and tobacco in the causation of oral cancer was examined by Wynder et al [2]. However, their analysis was based on the

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premise that the effect of multiple independent exposures would be measured by multiplication of the relative risks associated with each exposure, not by addition of the excess risks.

METHODS

The selection and characteristics of the study group that provides the data for this analysis have been described elsewhere [1]. In brief, the study comprised 598 men with squamous cell carcinoma of the mouth or pharynx, and 598 controls matched for age and sex. All were selected from three New York City Veterans Administration Hospitals. Smoking and drinking histories were elicited routinely by the admitting physician, and abstracted from the clinical record. To derive a single measure of smoking exposure, one cigar was considered the equivalent of four cigarettes, and one pipeful of tobacco the equivalent of two cigarettes. Alcohol exposure was evaluated in terms of ounces of alcohol per day. Those subjects whose histories were incomplete for either variable were excluded from this analysis. Of the total 1196 subjects, 483 cases and 447 controls had recorded information adequate for estimation both of smoking and of alcohol consumption.

Subjects were classified by smoking history, alcohol consumption, and age. Although cases and controls were originally matched by age, age was controlled in the analysis because the age match may be reduced when stratifying over other variables. In addition, in excluding those subjects with incomplete histories, the age match likewise was broken.

RESULTS

If smoking and drinking are examined in a simple all-or-none risk table, there is a strong suggestion of synergy (Table 1). The cell entries in this table were obtained by combining the relative risk estimates from each age stratum using the standardization procedure suggested by Miettinen [6], with the age distribution of all controls as the standard. Cole and MacMahon [5] have described how such a table may be used to evaluate interaction. A measure of excess risk, the relative excess risk, may be obtained for each variable by subtracting 1 from the relative risk. In this case, the relative excess risk for smoking is 0.53 and that for alcohol consumption 0.23. The sum of these separate risks is 0.76 rather than the excess of 4.71 observed for persons with both exposures. This table suggests a model of almost complete synergy, since the increase in risk associated with either exposure alone is small.

The preceding analysis involved a degradation of the data, into a dichotomous classification. The detailed data were used to examine the effect of joint exposure more

<table>
<thead>
<tr>
<th></th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Alcohol No</td>
<td>1.00</td>
</tr>
<tr>
<td>Alcohol Yes</td>
<td>1.23</td>
</tr>
</tbody>
</table>

*Risks are expressed relative to a risk of 1.00 for persons who neither smoked nor drank alcohol.
A linear regression model was constructed with disease as the dependent variable, and age, smoking, and alcohol consumption as independent variables. The units used were years of age, number of cigarette-equivalents smoked per day, and number of ounces of alcohol drunk per day. With no interaction term included, alcohol and smoking both are strong predictors of disease with t-ratios of 7.82 and 5.64 respectively. To test the interaction of alcohol and smoking, the alcohol-smoking product term was added to the regression. In this model, the t-ratio for the product term was only 0.46, indicating that the product term contributes little to the model, and does not displace the strong predictive value of the separate alcohol and smoking terms, which had t-ratios of 3.63 and 3.47 respectively.

It is interesting to compare Table 1 with a risk table using more detailed data (Table 2). Here, the effect of increasing each exposure is apparent at every level of the other, illustrating the individual effect of the exposures. In addition, by applying the technique used to generate expected excess risk in Table 1, we see that the observed risks in the lower right portion of the table are greater than expected; for example, we observe a relative excess risk of 14.5 for those in the highest-smoking, highest-drinking category, compared with an expected relative excess risk of \(1.33 + 1.43 = 2.76\). This table also suggests a synergistic model, but unlike Table 1, the synergy appears to supplement definite individual effects.

<table>
<thead>
<tr>
<th>Table 2. Relative risk* of Oral Cancer According to Level of Exposure to Smoking and Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking (cigarette equivalents/day)</td>
</tr>
<tr>
<td>0 &lt; 20 20-39 40+</td>
</tr>
<tr>
<td>Alcohol (oz/day)</td>
</tr>
<tr>
<td>0        1.00 1.52 1.43 2.43</td>
</tr>
<tr>
<td>&lt; 0.4    1.40 1.67 3.18 3.25</td>
</tr>
<tr>
<td>0.4-1.5  1.60 4.36 4.46 8.21</td>
</tr>
<tr>
<td>1.6+     2.33 4.13 9.59 15.5</td>
</tr>
</tbody>
</table>

*Risks are expressed relative to a risk of 1.00 for persons who neither smoked nor drank.

**Discussion**

Clearly the categories in Table 1 are too crude to evaluate interaction in this situation. By using more refined data in the regression analysis and in the cross-tabulation of Table 2, strong individual effects of smoking and alcohol consumption are observed, while in Table 1 neither exposure appeared to confer much risk in the absence of the other. The apparent discrepancy arises from the correlation between smoking habits and alcohol consumption (in this study \(r = +0.33\)). Part of the apparent synergy seen in Table 1 is due to confounding of the two exposures: smokers who abstain from alcohol do not smoke as heavily as those who drink alcohol, and similarly for drinkers who do not smoke.

Table 2 also must be interpreted cautiously. Those cells which most strongly indicate synergy fall along the bottom row and right hand column of the table. These cells represent open-ended exposure categories, where a great excess of one exposure (or both in the lower right corner cell) might account for the 'excess' risk observed, without
invoking any explanation of synergy. For example, it is incorrect to assume that
non-smokers who are drinkers of 1.6+ oz per day consume the same amount of
alcohol as those smoking 20–39 cigarettes a day and drinking 1.6+ oz of alcohol daily,
because the two exposures are correlated, and the categories are open-ended with
respect to alcohol consumption. The observed risks also exceed their expected values
in the cells contiguous to the lower right hand borders. These categories are not
open-ended, and offer better evidence for a synergistic effect of the two exposures.
Nevertheless, it is possible that the data suggest synergy because the categories
remain too broad. Furthermore, a randomly low value in one or two of the cells used
to generate the expected values for the other cells can falsely suggest synergy. For
example, the risk of 1.43 for non-drinkers smoking 20–39 cigarette equivalents daily
might be an underestimate of a true risk closer to 2. Thus, Table 2 is suggestive of a
combined effect equal to the sum of two strong individual effects plus a synergistic
component. Nevertheless, the evidence is not convincing enough to discard com-
pletely the simpler model of independent effects.

| Table 3. Relative risk* of oral cancer according to level of exposure to smoking and alcohol, data of Wynder et al† |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Alcohol (units/day)‡             | Smoking (cigarettes/day) |
|                                 | ≤ 15 | 16–20 | 21–34 | > 34 |
| < 1                            | 1.00 | 2.86  | 1.79  | 8.40  |
| 1–2                           | 1.70 | 2.05  | 1.94  | 3.88  |
| 3–6                           | 6.20 | 7.02  | 8.91  | 5.33  |
| > 6                           | 9.69 | 11.6  | 17.0  | 19.4  |

*Risks are expressed relative to a risk of 1.00 for persons who smoked
less than 16 cigarettes a day and drank less than 1 unit of alcohol a day.
†Unadjusted for age.
‡One unit of alcohol equals 1 oz whiskey or 8 oz beer.

The data presented by Wynder et al [2] were transformed to produce a table like
Table 2 (Table 3). To produce more stable estimates of relative risk, a different
classification scheme of the two exposures was necessary; as a result, the individual
relative risk estimates are not comparable with those of Table 2. Nevertheless, the
evaluation of synergy does not depend on the classification employed. From Table 3,
the effect of the two exposures appears to be additive, and thus independent.

The regression analysis tests a specific alternative to independent effects, that of
multiplicative effects. Although there seems to be a small multiplicative component,
the primary effects remain additive. There seemed little reason to test more complic-
ated models.

ATTRIBUTABLE RISKS

To evaluate the practical import of the risk conferred by these exposures, it is
worthwhile to calculate the attributable risks. MacMahon and Pugh [4] show how to
calculate attributable risk as a percentage of the total risk in a group exposed to a
presumed etiologic factor. When two or more exposures are involved, a modification
of their formulation is needed. They derive the incidence rate in those unexposed \( I_0 \) as a function of the overall incidence rate: \[ I_0 = \frac{I}{P_o + R P_e} \] where \( I \) is the total incidence rate, \( R \) is the relative risk for the exposure at issue, and \( P_e \) and \( P_o \) are the proportions of the population exposed and unexposed, respectively. In a case-control study, \( R \) can be estimated, and \( P_e \) and \( P_o \) are estimated from the control series. The analogous formula for several exposures is

\[ I_0 = \frac{I}{P_o + R_1 P_1 + R_2 P_2 + \ldots + R_n P_n} \]

where the exposure categories are mutually exclusive and collectively exhaustive. Applying this to the present data, we have \( R_1 = 1.23 \) (relative risk for those who drink only), \( R_2 = 1.53 \) (relative risk for those who smoke only), \( R_s = 5.71 \) (relative risk for those who smoke and drink), and \( I_0 = \frac{0.09 + (1.23)(0.10) + (1.53)(0.15) + (5.71)(0.66)}{I} = 0.24 I \). The attributable risk in the exposed is \( I_e - I_0 \), where \( I_e \) is the incidence rate in the exposed. MacMahon and Pugh show how to get a percent estimate for this without knowing the actual incidence rate. By extending this method, we can derive the population attributable risk percent, defined as

\[ \frac{I - I_0}{I} \]

In this example, the population attributable risk percent is \( \frac{I - 0.24 I}{I} = 1 - 0.24 = 76 \) per cent. This is interpreted to mean that if each exposure is accepted as a cause of the disease, together they account for about 76 per cent of the disease in a male population comparable to that under study. In other words, about 76 per cent of the disease in males might be eliminated by removing both these exposures. Assuming that the exposures have independent effects, it can be estimated from the regression model that 43 per cent of the disease is attributable to alcohol consumption, and 33 per cent to smoking.

Interestingly, Wynder et al [2], using a different approach, estimated that 14 out of every 19, or 74 per cent of all cases in males could be prevented by eliminating these exposures.

The practical importance of interaction models lies in their relevance to planning preventive measures. If a complete or strongly synergistic model aptly describes the etiology of oral cancer, then about 76 per cent of the disease in men could be eliminated by eliminating either exposure alone, assuming, of course, that the exposures are causes of the disease, and that the proportion of the population exposed has been accurately estimated. On the other hand, if, as seems likely in the present case, a large component of the effect of the exposures is independent, then both exposures must be removed to prevent about 76 per cent of oral cancer in males.

**SUMMARY**

The effect of joint exposure to smoking and alcohol on risk of development of oral cancer was evaluated from a case-control study. Although a simple \( 2 \times 2 \) relative risk table suggests almost complete synergy of the two exposures, regression analysis and a more detailed relative risk table which reduces confounding demonstrate the definite individual effects of the two exposures in addition to the synergistic effect. If smoking and drinking both are causes of oral cancer—as the data suggest—then the removal of both will be necessary to prevent a large proportion of the disease in males.
REFERENCES