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REVIEWS AND COMMENTARY

Alcohol-containing Mouthwashes and Oropharyngeal Cancer: A Spurious Association due to Underascertainment of Confounders?

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Recently it has been suggested that the use of alcohol-containing mouthwashes may increase the risk of oropharyngeal cancer. Heavy alcohol intake and tobacco use are established causes of oropharyngeal cancer. Their use is associated with mouthwash use. In addition, alcohol and tobacco use both tend to be underreported. Here the authors show that, under the hypothesis that mouthwash does not increase the risk of oropharyngeal cancer, confounding due to underascertained exposure to alcohol and tobacco would result in a spuriously elevated odds ratio for mouthwash use. As a general principle, a null association becomes apparently positive if a confounding variable is incompletely ascertained: a spurious association may be produced even in the absence of a difference in the extent of the underascertainment of the confounder among the comparison groups. *Am J Epidemiol* 1996;144:1091–5.

confounding factors (epidemiology); oropharyngeal neoplasms

In etiologic research, it is well recognized that the usual effect of measurement error in a putative cause is to weaken any given association. It is also recognized that imprecise measurement of a confounding variable results in incomplete control of the confounder and, more particularly, that underascertainment of the confounder usually results in overestimation of the magnitude of any given association (1). What does not appear to be as well appreciated, however, is that, when the null holds true, underascertainment of a confounder can result in a spurious association. Such an association can occur without having to assume differences in the extent of the underascertainment among the comparison groups. Below, some recent work on the epidemiology of oropharyngeal cancer (2) is considered in order to reemphasize that point by means of a hypothetic numeric example. A mathematic proof is given in the Appendix.

In a large population-based case-control study of oropharyngeal cancer, Winn et al. (2) reported confounder-adjusted odds ratio estimates for alcohol-containing mouthwash use of 1.6 (95 percent confidence interval 1.1–2.3) in females and 1.4 (95 percent confidence interval 1.0–1.8) in males. The elevated risks were largely confined to drinkers and smokers. In a further study by the same group (3), it was estimated that smoking ≥40 cigarettes per day increased the risk some 2.8-fold in males and 6.2-fold in females; the corresponding estimates for the intake of ≥30 drinks per week of alcohol were 8.8-fold and 9.1-fold. For the combination of heavy smoking and drinking, the odds ratios were 37.7 and 107.9. The cumulative population-attributable risks for all levels of smoking and alcohol intake were estimated at 80 percent for males, 61 percent for females, and 74 percent overall.

Progressively increasing risks with rising levels of tobacco and alcohol exposure, as well as an apparent interaction between the two factors, have also been

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reported in many other studies (4, 5), so much so that the separate and combined effects of tobacco and alcohol on the risk of oropharyngeal cancer are commonly cited as an example of documented effect modification in epidemiologic research. It is generally accepted that tobacco and alcohol are powerful causes of oropharyngeal cancer (4, 5).

Some mouthwashes contain alcohol in concentrations of up to 25 percent (6). Winn et al. (2) argued that it is therefore biologically plausible that they may increase the risk of oropharyngeal cancer. However, the ingestion of alcohol has many effects, other than topical ones, that appear to play a role in alcohol-associated carcinogenesis (7). The quantity of alcohol ingested by using mouthwash is exceedingly low (6). In addition, there are major differences in other ingredients between alcohol-containing mouthwashes and alcoholic beverages (5, 8).

In discussing the association of mouthwash use with oropharyngeal cancer, Winn et al. felt that they "could rule out sizable confounding due to smoking and drinking, the major determinants of [oropharyngeal cancer]" (2, p. 3046) because they adjusted for these factors. They also considered the possibility that mouthwash users may have underreported their exposures, but they judged that "the misclassification would have to be considerably greater for the cases than for the controls to account for the observed excess risks" (2, p. 3046).

Certain other points are relevant. There have been seven studies that evaluated the relation of mouthwash use to the risk of oropharyngeal cancer (2, 9–14), with inconsistent results. The findings in some studies were null (10, 12) and, among those that reported positive associations (2, 9–11, 13), some were inconsistent. Thus, in some studies the association was evident only among females (10, 11); in the study of Winn et al. (2), it was evident in both sexes. In some studies the association was confined to nonsmokers and nondrinkers (or very light drinkers) (10, 11); in the study of Winn et al. (2), it was confined to drinkers and smokers even though, in an earlier study by the same group (11), the association was confined to nonsmokers and nondrinkers. In two studies there was no evidence of association (10, 12).

Wynder et al. (10) and Kabat et al. (14) also reported inconsistent findings in successive studies. Following the publication of a hypothesis-generating study by Weaver et al. (9), they examined data in another study (10) conducted primarily to elucidate the etiologic role of tobacco and alcohol. For mouthwash use, they observed an odds ratio of 3.6 (95 percent confidence interval 1.5–8.9) among nonsmoking, nondrinking females; among males, however, regardless of smoking and drinking status, there was no evidence of an association.

Wynder and his colleagues were concerned about the inconsistencies in the subgroup analyses and, hence, about the possibility that the association may have been a chance one arising in the course of multiple stratification; alternatively, they were concerned that there may have been uncontrolled confounding. They therefore conducted a more focused repeat study confined to females (14). Overall, there was no evidence of an association but, when mouthwash was used to conceal odor on the breath of users of cigarettes or alcohol, the odds ratios were 3.3 (95 percent confidence interval 1.2–8.8) and 3.3 (95 percent confidence interval 1.0–10.3), respectively. By contrast, the corresponding estimates for the use of mouthwash to conceal the odor of onions or garlic on the breath, and mouth infections or dental caries, were each 0.7. The authors suggested that, in those studies that reported positive associations, there may have been a tendency for mouthwash use to be reported as a surrogate for underreported tobacco and alcohol exposure.

The suggestion made by Wynder's group is plausible, since it is well known that drinkers tend to understate the amount of alcohol consumed (5, 15–17). It is also clear that smoking is now underreported (18, 19). Presumably these tendencies reflect social pressures. There is no corresponding motivation to underreport mouthwash use.

We can now proceed to examine the effects of full reporting of mouthwash use, together with underreporting of alcohol intake and tobacco use, in a context in which it is known that the latter two factors are powerful determinants of the risk of oropharyngeal cancer.

A HYPOTHETIC NUMERIC EXAMPLE

Consider a hypothetic set of 100 cases of oropharyngeal cancer and 100 controls. Ignore tobacco for the moment. For simplicity, consider alcohol intake and mouthwash use to be categorical variables (yes, no), and make the following assumptions (table 1):

1. Alcohol causes oropharyngeal cancer; mouthwash does not.
2. First, assume that alcohol and mouthwash use are both fully reported. The odds ratio for alcohol use is 6.0 and, for mouthwash use, it is 1.0 (table 1, columns 1–3).
3. Next, assume that alcohol use is 50 percent underreported by both the cases and the controls; mouthwash use remains fully reported (table 1, columns 4–6). Then, in this example, 15 of the

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TABLE 1. Hypothetic distributions of alcohol and mouthwash use among 100 cases and 100 controls

Factor	100% of alcohol use reported and 100% of mouthwash use reported			50% of alcohol use reported and 100% of mouthwash use reported		
	Cases	Controls	OR*	Cases	Controls	OR
Alcohol only	30	10	6.0	15	5	4.3
Alcohol and mouthwash	30	10	6.0	15	5	4.3
Mouthwash only	10	20	1.0	25	25	1.4
Neither	30	60	1.0†	45	65	1.0†
Total	100	100		100	100	

* OR, odds ratio.
† Reference category.

30 cases who in fact take alcohol alone (column 1) report that they do not and are added to the 30 cases who report the use of neither alcohol nor mouthwash (column 1), giving a total of 45 (column 4). Similarly, 15 of the 30 cases who in fact take alcohol plus mouthwash (column 1) report that they use mouthwash only and are added to the 10 who in fact use mouthwash only (column 1), giving a total of 25 (column 4). The controls are reclassified in the same way.

The odds ratio estimates for alcohol use only and for alcohol plus mouthwash use are now each reduced from a "true" value of 6.0 to 4.3. That is, the risk for alcohol use is underestimated because of underreporting, but it is still clearly identifiable. What is important in the present context, however, is that a "true" odds ratio of 1.0 for mouthwash use becomes spuriously elevated to a value of 1.4.

It should also be noted that the distorting effect of the odds ratio for mouthwash use is hardly changed if the underreporting of alcohol use is considerably less than 50 percent. Given 25 percent underascertainment, for example, with analogous arithmetic, the odds ratio for mouthwash use only changes from 1.4 to 1.3. Moreover, the distortion occurs even though the rate of underreporting is identical in the cases and the controls; there is no need to invoke differential underreporting of alcohol intake in the two comparison groups.

Winn et al. (2) reported elevated risks for mouthwash use that were largely confined to drinkers. Assume that the analysis described above is confined to drinkers and that the factors in table 1 are redefined as heavy and light alcohol intake, with or without concomitant mouthwash use. If it is assumed that 50 percent of heavy drinkers report that they are light drinkers, the odds ratio estimates are once again as shown in table 1.

Now consider smoking. If smoking is also underreported, the confounding effects would be analogous to those illustrated for alcohol. In addition, if there is underascertainment of both alcohol intake and cigarette smoking, the distortion of the odds ratio would be all the greater. Still further, if there is underascertainment of the combination of drinking and smoking, the distortion would be greater still, because it is the combined exposure that is the most powerful determinant of risk.

DISCUSSION

In this exercise, we have demonstrated that a null association can become spuriously elevated if confounders are underascertained. Elevated odds ratios of the order of 1.4 and 1.6 can readily be accounted for by such underascertainment when there is quantitative evidence that the confounders at issue (in the present example, tobacco and alcohol exposure (5, 15–17)) are present (2). There also appears to be some confusion about differential and nondifferential underreporting of confounders in producing spurious associations (2); it is not necessary to assume differential underreporting.

In this commentary, we have not addressed other potential sources of bias and confounding. We also doubt whether nonexperimental methods can ever be used to distinguish among bias, confounding, and causality for associations of low magnitude. Setting those matters aside, however, when there is clear evidence of uncontrolled confounding due to the underascertainment of the factors at issue, we argue that a causal inference for associations of low magnitude is not justified.

In the present example, the confounders (tobacco and alcohol) were strongly associated with the outcome (oropharyngeal cancer) and less strongly associated with the exposure (mouthwash use) (2). A more general question raised by this example concerns the degree to which null effects may be distorted away from the null by the underascertainment of confound-

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ers in any given study. A formal consideration of that topic is beyond the scope of this paper, but it would clearly involve the strength of the association for the confounder itself, as well as the extent of the overlap with both the exposure and the outcome. The point being made here, however, is that there are many studies in which it is claimed that, simply because a confounder has been measured and adjusted for, it has been adequately controlled. That claim may not be tenable if there is material underascertainment of the confounder at issue. As illustrated here, such underascertainment may produce artifactual associations.

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APPENDIX

This appendix contains a theorem characterizing the amount of underreporting of alcohol use in a case-control study on alcohol and mouthwash use that is necessary for the observed odds ratio for mouthwash use to be biased upward.

Consider appendix table 1 that summarizes the results from a hypothetic case-control study on alcohol and mouthwash use. Note that it is assumed that the amount of underreporting of alcohol use, p, is equal for both cases and controls. Alcohol is the generic confounder, and mouthwash is the generic putative cause.

Let p denote the proportion of underreporting by users of alcohol only and of alcohol and mouthwash. Appendix table 1 becomes appendix table 2.

The true odds ratio for mouthwash use only, corresponding to appendix table 1, is

$$n_M m / m_M n.$$

When there is underreporting for alcohol use according to the model in appendix table 2, the odds ratio for mouthwash use only becomes

$$[p^2 n_{AM} m_A + p n_{AM} m + n_M p m_A + n_M m] / [p^2 n_A m_{AM} + p n_A m_M + n p m_{AM} + n m_M].$$

Let

$$D = n m_M n_{AM} m_A - n_M n m_A m_{AM}$$

and

$$E = n_M m(n m_{AM} + n_A m_M) - n m_M (n_{AM} m + n_M m_A).$$

Theorem

In the presence of underreporting of alcohol use, the odds ratio for mouthwash use only is biased upward if the proportion underreporting alcohol, p, satisfies one of the following inequalities:

1. If $D > 0$, then $E/D < p < 1$;
2. If $D = 0$ and $E < 0$, then $0 < p \leq 1$; and
3. If $D < 0$, then $0 < p < E/D$.

APPENDIX TABLE 1. Distribution of alcohol and mouthwash use in a hypothetic case-control study

Factor	Cases	Controls
Alcohol only	n_A	m_A
Alcohol and mouthwash	n_{AM}	m_{AM}
Mouthwash only	n_M	m_M
Neither	n	m

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APPENDIX TABLE 2. Distribution of alcohol and mouthwash use in a hypothetic case-control study with alcohol use underreported by the proportion of p

Factor	Cases	Controls
Alcohol only	$(1-p)n_A$	$1-p)m_A$
Alcohol and mouthwash	$(1-p)n_{AM}$	$(1-p)m_{AM}$
Mouthwash only	$pn_{AM}+n_M$	$pm_{AM}+m_M$
Neither	pn_A+n	pm_A+m

Proof

Let

$$a = p^2n_{AM}m_A + pn_{AM}m + n_Mpm_A$$

$$b = n_Mm$$

$$c = p^2n_Am_{AM} + pn_Am_M + npm_{AM}$$

$$d = nm_M.$$

Then the odds ratio for mouthwash only in the presence of underreporting of alcohol can be written as

$$\frac{a+b}{c+d}.$$

Thus, we are trying to determine what values of p will yield the following inequality:

$$(a+b)/(c+d) > b/d$$

which holds if and only if

$$ad - bc > 0$$

which, in the original notation, translates into

$$pD > E$$

from which the result follows.

Demonstration

For the example in table 1, condition 2 of the theorem is satisfied and, thus, any positive amount of underreporting for alcohol use will cause the odds ratio for mouthwash use with underreporting to exceed the odds ratio without underreporting.

Note that the three conditions in the theorem encompass all possible situations for D. However, if $D = 0$ and $E \geq 0$, then no amount of underreporting of alcohol use will result in the observed odds ratio for mouthwash use being biased upward.

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