Effect of Smoking and Alcohol Consumption on Laryngeal Cancer Risk in Coastal Texas


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ABSTRACT

Data from case-control studies of respiratory cancer conducted in the Texas Gulf Coast region between 1975 and 1980 were used to examine the effects of smoking and alcohol on laryngeal cancer risk. Analyses were limited to living white males, ages 30–79, which included 151 histologically confirmed incident laryngeal cancer cases and 235 population-based controls. A dose-dependent effect for cigarette smoking was observed, with odds ratios ranging from 4.4 for ever smoking up to one-half pack daily, to 10.4 for smoking more than two packs per day. Risks were strongest for current smokers and declined markedly following smoking cessation. Higher risks were associated with smoking nonfiltered than filtered cigarettes. No significantly elevated risks were associated with the use of other tobacco products. Odds ratios for alcoholic beverages did not increase linearly with increasing use; instead risks were twofold for consumption of four or more drinks weekly. Patterns of risk associated with beer and hard liquor were not consistent and few participants drank wine. Although the data were sparse, a dose-response effect for alcohol intake was suggested for tumors of the supraglottis (n = 23), while for nonsupraglottic cases, alcohol risks were elevated but did not increase beyond those observed for four drinks per week. Predicted risks for the combined effects of cigarette and alcohol use were intermediate between an additive and multiplicative form of interaction.

INTRODUCTION

Cigarette smoking and alcohol consumption are established risk factors for laryngeal cancer (1–24). Some studies have suggested that the risk for combined exposure is greater than that predicted from each agent acting alone (6, 8–10, 19, 23, 25), yet with alcohol use and smoking being highly correlated practices, the synergistic effect reported for heavy smoking and drinking may reflect strong residual confounding for which no satisfactory adjustment can be made. This report examines the effects of smoking and alcohol use individually and explores their interaction in a case-control study of laryngeal cancer in Texas.

METHODS

Parallel case-control studies of lung and laryngeal cancer were conducted in the Texas Gulf Coast region during 1980–1982. For the latter, incident laryngeal cancer cases (ICD-9 codes 169.0, 169.1, 169.2, 169.3, 169.4, 169.6) between the ages of 30 and 79, and diagnosed from January 1, 1978, through December 31, 1980, were eligible for study. Details of the study design have been published elsewhere (26). Briefly, cases were ascertained from 56 hospitals in a six-county region (Brazoria, Chambers, Galveston, Harris, Jefferson, and Orange) and from a review of state health department records. Although both living and decedent cases were initially identified, we included only white males who were alive at interview for this analysis of smoking and alcohol effects. Controls for living respondents were identified from either the Texas Department of Public Safety drivers’ license files (for those younger than 65 years) or the HCFA roster of medicare recipients (for those over 65), and were frequency matched to cases by residence (Harris county [i.e., the Houston metropolitan area] versus other study counties), 5-year age category, and ethnicity (Anglo or Hispanic as determined by the GUESS algorithm). The study was conducted between 1980 and 1982, during which case medical records were abstracted and interviewer-administered questionnaires were completed in each subject’s home, probing for smoking and alcohol consumption patterns, occupational and residential history, cancer in a family member, medical history, demographic characteristics, and dietary practices. Results of the analyses of occupational exposures and dietary factors have been presented elsewhere (27, 28).

Information on the usual amount and frequency of consumption of each type of alcoholic beverage (beer, wine, and hard liquor) was obtained for every decade of life between ages 20 and 69. Weekly ethanol intake for each decade was determined assuming 12 oz. of beer, 4 oz. of wine, and 1.0 oz. of hard liquor are standard serving sizes per drink and each ounce of beer, wine and hard liquor provides 1.1, 2.9, and 9.4 g of ethanol, respectively (29). Usual alcohol intake was calculated as the lifetime average weekly intake; the term “drink” hereafter refers to the number of drink equivalents (i.e., 13.2 g of ethanol) consumed per week. Smoking history data were less specific. Questions covered the form of tobacco used (cigarette, pipe, cigar, snuff, chewing tobacco), starting and stopping ages, and usual amount consumed. The type of cigarette usually smoked was also obtained, e.g., filtered, non-filtered, and hand or commercially rolled.

The dietary component queried about foods eaten during the subject’s adult life and at least 4 years prior to the interview. Usual intake of fruits and vegetables combined was categorized as low, moderate, or high based on lower and upper quartiles of the control distribution. In preliminary analyses, both living and decedent respondents were evaluated. Our decision to exclude decedents was motivated by markedly different patterns of risk between the respondent groups for most alcohol variables, with ORs significantly greater than one for surrogates but not for self respondents. Since separate analyses for each respondent group would thus be required, and since dietary histories were not collected in proxy interviews, we excluded surrogate respondents from our analyses.

Crude ORs were calculated as estimates of the RRs, and CIs were calculated by the method described by Woolf (30). Maximum likelihood estimates of adjusted ORs were obtained from unconditional logistic regression analyses (31, 32), and stratified analyses were performed to confirm these findings (33). Fruit and vegetable intake, ever-employment in potentially high-risk occupations identified in this study (28), years of education, and self-reported history of cancer in a first-degree relative were examined as possible confounders of the observed associations. Persons who quit smoking at least 3 years prior to the midpoint of the case ascertainment period (i.e., January 1, 1978) were considered exsmokers. Several indicators of alcohol use were evaluated including separate measures for beer, wine, and hard liquor intake, as well as...
average and maximum drinks consumed weekly, alcohol use 10 years prior to the study, and the duration of drinking. Unless otherwise indicated, all ORs were adjusted for the usual number of cigarettes smoked, alcohol use, age, residence (Houston vicinity, or not), fruit and vegetable intake, and ever-employment in a high-risk occupation.

A logistic regression model (which assumes agents combine in a multiplicative fashion) has typically been used to describe the simultaneous effect of several risk factors; however, other RR models which allow interactions to vary from subadditive to supramultiplicative have recently been proposed (34–36). To analyze the interaction of smoking and alcohol in this study, we used an extension of a generalized model for OR estimation proposed by Thomas (35); both additive and multiplicative risk functions are simpler forms of this model.

RESULTS

General. In the laryngeal cancer study, a total of 303 cases and 384 controls were initially identified, of which 209 and 250, respectively, were interviewed. Reasons for noninterview were refusal to participate (34 cases and 57 controls) and inability to locate or not reside in the study catchment area during the case ascertainment period (60 cases and 77 controls). Of those who completed a questionnaire, 153 (73%) cases and 179 (72%) controls were alive at interview and considered in this analysis. Two cases and eight controls were excluded from the final data set due to incomplete or interviewer-assessed poor quality data, leaving 151 cases and 171 controls for analysis.

Because a large sample size was required to statistically describe the interaction between smoking and drinking, we added white male controls from the lung cancer study who were alive at interview (n = 64); this increased our control series to 235. While the same study design, questionnaire instrument, and interviewers were also used in the lung cancer study, these additional 64 controls were not matched to our larynx cases. However, the age distribution of these controls was similar to that of the cases, with the median age for the lung controls being 59, and that for the larynx cases, 60.

All cases were diagnosed with squamous cell carcinoma. Tumors originated in the supraglottis in 23 cases (15%), glottis in 92 cases (61%), subglottis in one case, and not otherwise specified in 35 cases (23%). The median age for both cases and controls was 60. Cases were more likely than controls to have had fewer years of education (OR = 0.6, 95% CI = 0.4–1.0 for 9 or more years of schooling), and to eat fewer fruits and vegetables (OR = 0.6, 95% CI = 0.4–1.0; and OR = 0.8, 95% CI = 0.4–1.5 for moderate and high intake, respectively). The occupational data showed a nonsignificant excess risk following exposure to chromates, asbestos, paints, and diesel or gasoline fumes (OR = 1.3, 95% CI = 0.8–2.3). A history of cancer in close family relatives was not related to disease risk (OR = 1.0, 95% CI = 0.6–1.6).

Smoking. Persons who smoked at least 6 months during their adult life were considered ever-smokers. Only eight cases (5%) reported no history of cigarette smoking compared to 63 controls (27%). After adjustment for alcohol use, a strong trend of increasing risk based on the number of cigarettes smoked daily was evident; relative to never-smokers, ORs ranged from 4.4 (95% CI = 1.3–14.6) for light smokers (1–10 cigarettes per day) to 10.4 (95% CI = 3.7–29.1) for smokers of more than two packs daily. Similarly, a dose-response effect was seen for duration-of-smoking categories where ORs ranged from 2.5 (95% CI = 1.0–6.4) for smokers of less than 35 years, to 17.1 (95% CI = 5.7–51.8) for smokers of 45 or more years.

Table 1 ORs for laryngeal cancer associated with the number of cigarettes smoked per day

<table>
<thead>
<tr>
<th>Cigarettes/day</th>
<th>Case OR</th>
<th>Control OR</th>
<th>P value for trend*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–10</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>11–20</td>
<td>1</td>
<td>1</td>
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<tr>
<td>21–30</td>
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<tr>
<td>31–40</td>
<td>1</td>
<td>1</td>
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</tr>
<tr>
<td>&gt;40</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
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<td>1</td>
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<tr>
<td>Current smokers</td>
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<td>1</td>
<td></td>
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<tr>
<td>1–10</td>
<td>1</td>
<td>1</td>
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<tr>
<td>11–20</td>
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<td>1</td>
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<td>21–30</td>
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<td>31–40</td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Former smokers</td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>3–9-Year smoking cessation, cigarettes/day</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1–10</td>
<td>1</td>
<td>1</td>
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<td>11–20</td>
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<td>21–30</td>
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<td>31–40</td>
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<tr>
<td>&gt;40</td>
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<td>1</td>
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<tr>
<td>10+ Years smoking cessation, cigarettes/day</td>
<td>1</td>
<td>1</td>
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<tr>
<td>1–10</td>
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<td>11–20</td>
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<td>31–40</td>
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<tr>
<td>&gt;40</td>
<td>1</td>
<td>1</td>
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* Adjusted for age, residence, fruit and vegetable consumption, ever-employment in high-risk occupations, and usual alcohol intake.

Test of trend from logistic model.

Table 2 ORs for laryngeal cancer associated with the duration and amount of cigarettes smoked daily; current smokers only

<table>
<thead>
<tr>
<th>Cigarettes/day</th>
<th>Case OR</th>
<th>Control OR</th>
<th>P value for trend*</th>
</tr>
</thead>
<tbody>
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<td>20 cigarettes/day</td>
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<td>1</td>
<td></td>
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<tr>
<td>Years &lt;35</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>35–44</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt;20 cigarettes/day</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Years &lt;35</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>35–44</td>
<td>1</td>
<td>1</td>
<td></td>
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<tr>
<td>45</td>
<td>1</td>
<td>1</td>
<td></td>
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</tbody>
</table>

* Adjusted for age, residence, fruit and vegetable consumption, ever-employment in high-risk occupations, and usual alcohol intake.

Test of trend from logistic model.
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As expected, alcohol consumption differed by age as well as between cases and controls. For cases, alcohol intake tended to increase and then taper off, with peak consumption occurring during their 30s; among controls, intake varied little until declining, beginning in their 50s. For both groups, the proportion of persons drinking dropped noticeably by age 50. Because of this variability, other indicators of its use, such as maximum intake and the amount consumed 10 years prior to the study were also considered. For both measures, the pattern of risk was similar to that observed for usual intake; therefore only ORs associated with usual drinking behavior are shown in this report.

Only a small proportion of cases had a tumor arising in the supraglottis \((n = 23, 15\%)\). Table 4 compares the distributions and risks associated with alcohol and cigarette use for supraglottic and nonsupraglottic cases. The data, although sparse, suggest greater risks associated with drinking and smoking for the supraglottis than the other sites combined. The finding of twofold risks for all but the lightest drinkers was limited to the nonsupraglottic case group, while a dose-response effect for alcohol was suggested in the supraglottic group (Table 4, \(P\) value for trend = 0.087).

Smoking and Alcohol Interaction. Since only eight cases did not smoke it was difficult to assess the role of alcohol in the absence of tobacco use. Conversely, the effect of cigarette smoking independent of alcohol could only be evaluated among the 13 cases who reported little or no use of alcohol. However, among nonsmokers and light smokers (up to one-half pack daily), ORs for alcohol were similar to that seen in the entire study group. No excess risk was associated with consuming less than four drinks weekly (OR = 0.9, 95% CI = 0.1–5.8), while risks for all higher levels of drinking were threefold. Likewise, among nondrinkers and light drinkers (less than four drinks weekly), risks for cigarette smoking showed a strong dose gradient [crude ORs ranged from 4.6 (95% CI = 0.7–31.0) to 22.2 (95% CI = 3.5–141.6) for light to heavy smoking].

Few respondents indicated no history of alcohol consumption and no cigarette smoking (two cases and 17 controls) precluding their use as a nonexposed referent group; studies examining this interaction have usually assigned nonexposed and lightly exposed persons to the referent category. In our study no excess risk was found for light drinking (smoking-adjusted OR for fewer than four drinks weekly was 0.6, 95% CI = 0.2–1.7); thus we defined our referent group as nonsmokers and nondrinkers or light drinkers (two cases and 37 controls).

The results of the modeling of this interaction suggest that the risks for combined exposure to alcohol and cigarette smoke are best described as intermediate between additive and multiplicative, yet neither the simple additive or multiplicative model could be rejected. All three models fit the data reasonably well [the goodness-of-fit \(x^2\) for the mixture, additive, and multiplicative model were 3.16 \((P = 0.92)\), 4.44 \((P = 0.73)\), and 4.09 \((P = 0.77)\), respectively], but the fit for heavy smokers was improved by the more complex mixture model. The predicted ORs for the interaction of cigarette smoking and alcohol use as estimated by the mixture model are shown in Table 5; comparisons are to nonsmokers who consumed fewer than four drinks weekly. For each smoking level, the risk for having four or more drinks weekly is approximately 1.5 times that for less frequent drinking, while the ORs for smoking show trends of increasing risk for both light and heavy drinkers.

**DISCUSSION**

This study was motivated by high respiratory cancer mortality rates among males in counties of the Gulf Coast region of Texas.
Cigarette smoking is generally regarded as the major risk factor for laryngeal cancer, based on consistent findings from case-control and cohort studies (1). In our study, persons who ever smoked two or more packs of cigarettes daily had a 10-fold risk of laryngeal cancer as compared to never-smokers. A dose-dependent effect of daily cigarette use was seen, with ORs significantly elevated, with a threefold risk persisting for heavy smokers who had quit at least 10 years prior to the study. Declining risks for exsmokers have been reported in previous studies of laryngeal cancer to use population-based controls and include only living respondents for analysis. Since we required cases to be alive at interview, however, our results may describe factors related to long-term survival. Analyses of other components of the questionnaire data identified a protective effect for carotene consumption (28), while metal fabricating and construction work, and exposure to paint, diesel or gasoline fumes, and asbestos appeared to be risk factors (27).

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Most epidemiological studies of laryngeal cancer have shown dose-dependent risks for alcohol use that are lower than those for smoking (4, 7–11, 13, 16, 17, 21). In our study, alcohol was a much weaker risk factor than cigarette smoking. In fact, no excess risk was associated with consuming fewer than four drinks weekly and only a twofold risk was observed for drinking more than that amount. This pattern was not clarified by analyzing each type of beverage consumed or other indicators of alcohol use, such as the maximum amount or the amount consumed 10 years prior to the study.

The lack of a dose-dependent association between alcohol use and laryngeal cancer may possibly be explained by the distribution of tumor sites among our cases. Only 15% of the cases in this analysis (living respondents only) had supraglottic tumors, compared to more than 30% in previous studies which have examined site-specific risks (10, 16, 17) and 27% in the population-based SEER registries for 1975–1980 (39). The effect of alcohol has been shown to be greater in the supraglottis than in other portions of the larynx such as the glottis and subglottis (16, 17, 22). In our data, alcohol risks did not increase with increasing consumption among the nonsupraglottic case group, whereas a dose effect was suggested for the supraglottic group. Unfortunately, the small number of supraglottic cases precluded detailed site-specific analyses. Similar results have been reported in one study (16), where a dose-dependent alcohol effect was limited to tumors of the supraglottis; for other sites, no excess risk was seen for drinking less than 10 oz. of ethanol weekly versus twofold risks for consumption of 10–19 and 20 or more oz. per week. It is noteworthy that supraglottic tumors were diagnosed in 25% of the decedent cases in our survey, consistent with the poorer prognosis for this site compared to the more common glottic tumors (1). Surrogate interviews were not included in our analyses in part owing to a notable difference in alcohol effect (i.e., significant excess risks) as compared to living respondents. If decedent cases had not been excluded, tumors of the supraglottis would have comprised 18% of the case group.

The concept of interaction between risk factors has been the focus of much discussion in the epidemiological literature (40–43). Although the combined effect of agents that individually act as tumor initiators, promoters and/or cocarcinogens may not be fully understood, statistically it is assumed each factor independently contributes to disease risk. In our study, a dose effect for cigarette smoking was apparent among the group of...
light drinkers and abstainers, and alcohol was a risk factor among the light smokers and nonsmokers. Our model-based analysis allowed us to test the form of interaction between smoking and alcohol use, and showed that risks for their combined exposure are intermediate between additive and multiplicative. This confirms previous results based on stratified methods (6, 8–11, 23), which is surprising in light of the methodological differences between studies. Our case series, however, is unusual in that few had tumors arising in the supraglottis; therefore, our finding of an elevated but nonincreasing risk for moderate to heavy alcohol use suggests that the form of the smoking and alcohol interaction may differ by site.

The use of a population-based control group avoids some biases encountered with hospitalized controls, since the latter tend to be heavier smokers and drinkers. In our study, in fact, the proportions of smokers and drinkers among controls were similar to national percentages estimated by the Alcohol and Health Practices Survey [a component of the NHIS conducted in 1983 (44)]. This showed 34% of U.S. males currently smoked and nearly 35% never smoked; in our control group these figures were 36% and 27%, respectively. Furthermore, an estimated 18.5% of U.S. males were lifetime abstainers from alcohol; this compares to 18.3% nondrinking controls in our study.

Of primary concern in any epidemiological study is the potential misclassification of exposures, particularly those that occurred in the distant past. Because no secondary sources of information exist for factors associated with an individual’s lifestyle, we must rely on the information provided by the respondent. Kolonel et al. (45), in a study of 300 spouse pairs of respondents in Hawaii, found that agreement on current level and duration of alcohol and tobacco use was poorer than for consumption of most food items. A more recent study (46) noted that the responses of study subjects themselves showed some variability when a dietary interview was repeated months later, although agreement was similar for cases and controls. In this study, next-of-kin respondents showed less agreement over time, particularly for alcoholic beverage consumption. While we recognized that a bias toward long-surviving cases occurred in the distant past. Because no secondary sources of information exist for factors associated with an individual’s lifestyle, we must rely on the information provided by the respondent. Kolonel et al. (45), in a study of 300 spouse pairs of respondents in Hawaii, found that agreement on current level and duration of alcohol and tobacco use was poorer than for consumption of most food items. A more recent study (46) noted that the responses of study subjects themselves showed some variability when a dietary interview was repeated months later, although agreement was similar for cases and controls. In this study, next-of-kin respondents showed less agreement over time, particularly for alcoholic beverage consumption. While we recognized that a bias toward long-surviving cases occurred in the distant past. Because no secondary sources of information exist for factors associated with an individual’s lifestyle, we must rely on the information provided by the respondent. Kolonel et al. (45), in a study of 300 spouse pairs of respondents in Hawaii, found that agreement on current level and duration of alcohol and tobacco use was poorer than for consumption of most food items. A more recent study (46) noted that the responses of study subjects themselves showed some variability when a dietary interview was repeated months later, although agreement was similar for cases and controls. In this study, next-of-kin respondents showed less agreement over time, particularly for alcoholic beverage consumption.

Despite the inherent pitfalls in the analysis of lifestyle patterns, there is no reason to believe that reporting bias would be different for cases versus controls (46), and therefore, the effect of any bias would be to minimize risks (47). Our risk estimates for cigarette use, however, are consistent with, if not greater than, those from most studies of this cancer (8, 10, 11, 13, 16, 18, 19). Although the proportion of drinkers among our controls was similar to national levels, we cannot rule out an underreporting of alcohol use which may have contributed to the absence of a dose-response effect in this study.

In summary, our study confirms earlier investigations, showing cigarette smoking and alcohol are independent risk factors for laryngeal cancer. Our results suggest that alcohol is a weaker carcinogen for the larynx whose potency and biological action depends on site of origin. It may be that the supraglottic area is exposed to the direct effects of alcohol in a manner resembling that for tumors of the oral cavity and pharynx, so that smoking-alcohol interactions may be more evident in this segment of the larynx. Future case-control studies of laryngeal cancer should identify sufficiently large numbers of subjects to allow site-specific examination of the effects of alcohol alone and its interaction with smoking.

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REFERENCES

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