Carcinogenicity of Dark Liquor

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Abstract: To investigate whether the non-alcohol content of distilled alcoholic beverages affects the carcinogenicity of the beverage, we conducted an epidemiologic study of laryngeal and hypopharyngeal cancer. We interviewed 384 cases (or spouses, for deceased cases), and compared their responses with those of 876 controls. We classed distilled liquors as dark or light, a rough division according to content of potentially carcinogenic compounds in the beverages. The relative effect on hypopharyngeal cancer risk was much stronger for those who reported high consumption of dark liquor (relative risk = 4.4, 90% confidence interval = 2.9, 6.8) than for those reporting comparable consumption of light liquor (relative risk = 1.3, 90% CI = 0.8, 2.1). For laryngeal cancer, consumption of dark liquor had a smaller effect, and there was little distinction between the effects of dark and light liquor. The data appear consistent with the theory that the non-alcoholic content of distilled alcoholic beverages is a determinant of cancer risk, and that alcoholic beverages act topically rather than systemically in their carcinogenic action. (*Am J Public Health* 1989; 79:1516–1520.)

Introduction

Alcohol consumption is carcinogenic to most of the tissues in the upper aerodigestive tract, including the larynx, pharynx, and mouth.[1–6] Little is known, however, about the mechanism for alcohol carcinogenicity. The effect of alcohol on cancer risk appears greater for tobacco smokers than for non-smokers,[7] and some have questioned whether alcohol consumption is carcinogenic among nonsmokers.[8] Theories about the mechanism of alcohol carcinogenesis include the possibility that alcohol has a topical action, acting as a solvent for carcinogenic compounds, possibly enhancing their penetration through mucosa[8,9]; that alcohol consumption alters the nutritional balance and consequently leads to reduced consumption of dietary preventives that act through a central mechanism on epithelial cells[8,10,11]; and that alcohol directly affects metabolism in a way that increases the susceptibility of certain mucosal cells to cancer.[8] If alcohol acts as a solvent, its carcinogenic effect should be greater among smokers than among non-smokers. In addition, alcoholic beverages that come with already dissolved carcinogens should be more carcinogenic than alcoholic beverages free of such ingredients. This latter effect should be more easily measured among non-smokers, since smokers may inhale enough carcinogens in smoke to overwhelm the possibly smaller effect of carcinogenic substances in the beverages themselves.

Various carcinogens or potential carcinogens have been detected in alcoholic beverages. Beer, for example, has been reported to contain nitrosodimethylamine.[12] Scotch whisky is made by exposing sprouted barley to the smoke of burning peat,[13,14] and many spirits, including bourbon, dark rum, and rye are aged in charred oak barrels.[14] Cognac is aged in limousin oak barrels from which the beverage acquires a high tannin content.[14] Tannin is reportedly carcinogenic in both rats and mice following subcutaneous injection.[15] Despite the presence of these carcinogens in alcoholic beverages, it is uncertain whether the type of alcoholic beverage is an important determinant of cancer risk. For this investigation, we restricted our attention to distilled alcoholic beverages, which have the highest concentrations of alcohol, and evaluated the comparative carcinogenic effects of dark liquor versus light liquor. We classed all whiskeys, dark rum, and cognac as dark liquors, and vodka, gin, and light rum as light liquors. Dark liquors as a group contain much higher concentrations of organic compounds that include higher alcohols, esters, and aldehydes and other congeners.[16] Light liquors are highly distilled alcoholic beverages that are comparatively free of additional chemicals. Many vodkas, for example, are nearly pure ethanol solutions.[16]

Methods

The study population comprised all residents of the Boston Standard Metropolitan Statistical Area during the period January 1, 1982 through December 31, 1984. We prospectively identified cases of laryngeal and hypopharyngeal cancer that were diagnosed in the study population during the study period with the cooperation of 119 otolaryngologists in the area. We would have liked to include cases of mouth cancer in the study, but the otolaryngologists who were our major source for case ascertainment did not see in their practices a high enough proportion of the mouth cancer cases occurring in Greater Boston, whereas they saw the great majority of cases of laryngeal and hypopharyngeal cancer. Before the study, we wrote to all otolaryngologists and head and neck surgeons in Greater Boston and surrounding communities (as far as Worcester); during the study period we continued to approach new practitioners for their cooperation. In all we asked 214 otolaryngologists and head and neck surgeons to cooperate, of whom 119 agreed. Most of the physicians who did not cooperate, some of whom were retired or semi-retired, saw few cancer patients, so that the proportion of potentially eligible cases who were ascertained through physicians' practices is far greater than the proportion of cooperating physicians. We contacted all cooperating physicians monthly to learn of any newly diagnosed eligible cases. All cases had to have a histologically confirmed diagnosis of cancer of the larynx or hypopharynx. We sought written permission from the responsible physician to contact each eligible case.

As an independent source of case ascertainment, we included all cases of laryngeal and hypopharyngeal cancer recorded by the Massachusetts Cancer Registry. The Massachusetts Cancer Registry is a population-based registry to which all hospitals and clinics are required to report all cancer cases, excluding certain skin carcinomas. (At the time that we began this study, the Registry was new and was not an

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adequate source by itself for case ascertainment.) For each case identified by the Registry, we approached the responsible physician and obtained written permission to contact the patient, if the patient had not been identified previously.

For each case identified, we randomly selected as control subjects up to three people from the listing of residents of the same town as the case. These listings are published by each town under state law; with them we were able to ascertain conveniently a geographically representative series of controls that had roughly the same age and sex distribution as the cases. The process called for randomly identifying a place in the town book, and from that place identifying the next resident of the same sex born in either the same calendar year as the case subject or one year earlier or later. This step was repeated for each control subject. The matching criterion for year of birth was relaxed slightly for cases 70 years of age or over. To be eligible, controls had to be alive and still residing in the same town as the case at the time that we attempted to contact them. Many of the potential control subjects that we identified, upon investigation, were not alive; in these instances we continued to pick names from the town listing until we reached a maximum of three controls per case. (Toward the end of data collection, to avoid prolonging the study, we did not seek a full set of three controls for each case.)

All cases and controls received an introductory letter that stated in general terms that we were conducting a health study and desired to arrange an interview. The subjects were then contacted, usually by telephone, to arrange a personal interview conducted by trained study personnel. Those subjects who agreed were interviewed at home using a completely structured interview form. The interviewers were not told that the specific focus of the study concerned alcoholic beverages. The interview covered demographic data, medical history, occupational history, tobacco intake, certain dietary factors, drugs, mouthwashes and gargles, and other items. We obtained detailed data about timing, intensity, and type of exposure to alcoholic beverages and tobacco products. Nearly all interviews were conducted in English; three were in Spanish. For cases who had died or were unable to communicate owing to recent laryngeal surgery, interviews were conducted with the help of a spouse or with the spouse directly. One interview was conducted with the mother of a case, with whom the subject lived all his life except during military service.

For the stratified analyses, the estimation of relative risk (RR) across several strata was performed using maximum likelihood techniques to estimate the common odds ratio.[17]

Results

We identified 679 eligible cases, of whom 425 were ascertained directly from the cooperating physicians, and 254 were ascertained later through the Massachusetts Cancer Registry. We attempted to contact 625 of these cases, and could locate 604. No contact was attempted for 29 because the responsible physician was not cooperating with the study; for 20 because the physician's office requested that we not include the patient in the study; and for five cases, ascertained through the Veterans Administration, because there was no response to several requests from the responsible physician for consent by the patient to include him or her in the study. Of the 604 cases located, 42 were too ill for us to interview. An additional 128 patients had died before we contacted them. Of these 128, we obtained an interview with the spouses of 27, but 71 left no surviving spouse, 12 spouses were not available or did not respond, 10 spouses refused to be interviewed, and eight cases were identified through the Veterans Administration, which did not permit us to contact the surviving spouse. An additional 77 cases refused to participate, eight because of language problems. The total number of cases or spouses who were interviewed was 384; 18 of these interviews were with spouses of living cases who could not communicate readily, and one was with the mother of a case. The "response rate" among cases may be calculated in various ways. Of the 679 originally identified cases, only 57 percent are included among those interviewed, but this group represents 82 percent of those for whom an interview was possible (604 located cases minus 42 who were too ill, 83 who died with no spouse to contact, eight for whom we were not allowed to contact the spouse, and eight with language difficulties).

We identified 2,312 potential control subjects. We received no response to our initial letter addressed to 721 of these people. Many of these, however, no longer lived at the listed address when we attempted contact, or had died. The total, therefore, includes the names of an uncertain number of subjects who were not actually eligible for inclusion as a control. We were able to locate 1,591 of the potential controls; of these, 27 did not participate because of language problems, and 588 did not participate for various other reasons. We interviewed 883 controls, of whom seven gave interviews that we considered unreliable and did not use. The proportion of located controls whom we interviewed (55 percent) is lower than we would have liked, and reflects the increasing difficulty of obtaining cooperation for general population studies.[18]

The most important risk factors to consider as potential confounding factors in a study of laryngeal and hypopharyngeal cancer are age, sex, alcohol consumption, and tobacco use. Total alcohol consumption may be regarded as a possible confounder of the non-alcoholic component of dark or light distilled liquor consumption. Tobacco use may not only confound, but also modify an alcohol effect. Occupational risk factors for these cancers have also been reported, but these risk factors affect only small proportions of the population, and should not be strongly related to type of alcoholic beverage consumed, so that confounding from occupational risk factors was not a concern in this analysis. Socioeconomic status is not a strong risk factor conditional on total alcohol consumption and tobacco use.

We first examined the relation between cancer occurrence and the maximum amount of either dark or light liquor consumed weekly at any time. For analysis, we categorized subjects into three levels of maximum consumption (one drink per week or less, two-six drinks per week, and seven or more drinks per week), and compared those in the highest category with those in the lowest. The crude RR for drinking seven or more drinks per week of light liquor, relative to one or less, was estimated to be 1.7, with a 90 percent confidence interval (CI) of 1.3, 2.3. Controlling sex and age by stratification and calculating the maximum likelihood estimate of a common odds ratio indicated that despite the matching (which can introduce confounding) there was no confounding by these factors. We defined tobacco use in terms of pack-years of cigarette smoking (one pack-year equals 7,305 cigarettes smoked), or pack-year equivalents, based on comparable amounts of tobacco consumed, for cigar, pipe and cigarillo smokers and users of smokeless tobacco. We considered one cigar the equivalent of five cigarettes; one

pipeful, one plug, or one cigarillo the equivalent of two cigarettes. For these analyses we divided total tobacco use into two categories, those who reported less than 25 pack-years ("light" smokers) and those who had reported at least 25 pack-years ("heavy" smokers). Finer stratification of smoking produced intolerably small numbers within strata, and the consistently heavy smoking of laryngeal cancer cases precluded using a category boundary less than 25 pack-years. This stratification diminished the point estimate for light liquor consumption slightly, to 1.5. We then controlled simultaneously for tobacco and for the total amount of alcohol consumed; we estimated the total lifetime consumption of ethanol, including beer, wine, and other sources, and we then categorized the total into three levels: fewer than 1,000 drinks, 1,000–14,999 drinks and 15,000 or more drinks. One drink was equivalent to one shot (1½ ounces) of distilled liquor, 12 ounces of beer, and five ounces of wine. Control of tobacco and total alcohol consumption reduced the effect of light liquor consumption, comparing the highest level with the lowest, to an estimated RR of 1.1 with a 90% CI 0.8, 1.5.

The crude RR of consuming seven or more drinks per week of dark liquor, relative to one drink per week or less, was estimated to be 2.6, 90% CI 2.0, 3.2. This value was essentially unchanged after controlling for age and sex by stratification. Controlling for pack-years of tobacco use, however, reduced the point estimate to 1.9, 90% CI 1.5, 2.4. Controlling additionally for total lifetime alcohol consumption reduced the effect estimate to a RR of 1.3, 90% CI 1.0, 1.7.

The difference in effect estimates for the maximum rate of consumption of dark versus light liquor is relatively modest; nevertheless, even after control of confounding by tobacco and total alcohol consumption, there was some indication of a possible carcinogenic effect for dark liquor that did not exist for light liquor.

Cases were classified according to site of tumor into three major categories, hypopharyngeal (84 cases), supraglottic (125) and glottic (175), and the above analyses were repeated for each anatomic site separately. There were no cases of subglottic cancer among the 384 cases interviewed. These results are summarized in Table 1. The effects of dark liquor and light liquor appear similar for the supraglottis and glottis, but dark liquor appears to increase the risk of hypopharyngeal cancer whereas light liquor does not.

To determine whether the effect of dark liquor varied according to level of tobacco use, we examined the effects of drinking various quantities of light and dark liquor separately for light and heavy tobacco users. The distribution of cases for each type of cancer, and controls, is given by the maximum weekly intake of dark liquor and by category of tobacco use in Table 2. There is an increasing pattern of risk for greater maximum weekly consumption of dark liquor for both tobacco-use categories. The trend is again concentrated among hypopharyngeal cases (although it is unstable owing to the small number of cases among those with fewer than 25 pack-years of tobacco use). The joint effect of tobacco use and heavy consumption of dark liquor appears substantially greater than additive for the hypopharyngeal cases. This observation is based on a comparison of the highest versus lowest category of liquor consumption for each of the tobacco categories: the difference is 16.7 in the high-use category and 5.0 in the low-use category. The small number of cases in the latter category affects this comparison also, making the evidence for interaction in these data tentative.

We then conducted multivariate logistic analyses to examine the effects of dark and light liquor consumption in the same analysis. Conditional logistic models, which control for the matching variables of town, age and sex, gave results similar to the corresponding unconditional logistic models,[17] and are not reported. These analyses provided the efficiency to evaluate three levels of consumption of dark and light liquor simultaneously. We categorized subjects according to total number of drinks of dark or light liquor consumed during the subject's lifetime, which we calculated from the detailed histories that we obtained. We used categories of fewer than 200, 200–4,999, and 5,000 or more drinks; those who consumed fewer than 200 drinks formed the referent category. Although the total number of drinks is a function of age, age was found not be confounding, nor was sex, and these variables were therefore omitted from the regression models presented here. The model in Table 3, with terms for two levels of dark and light liquor consumption (in addition to the implied referent category), indicates an association with cancer risk of heavy consumption of dark liquor, and a smaller association for heavy consumption of light liquor. The comparable model restricted to hypopharyngeal cases (Table 4) shows a much stronger effect of heavy consumption of dark liquor and no material association for light liquor consumption. When terms for total alcohol consumption are added to the models in Tables 3 and 4, the effect of heavy consumption of dark liquor is smaller, but some effect

TABLE 1—Relative Risk Estimates for Consuming Seven or More Drinks per Week of Light and Dark Liquor, Relative to Consuming One Drink or Less, with 90% CI, for Three Anatomic Sites, Controlling for Tobacco Use and Total Alcohol Consumption

	Light Liquor		Dark Liquor	
Anatomic Site	RR	90% CI	RR	90% CI
Hypopharynx	1.0	0.6, 1.7	1.6	1.0, 2.5
Supraglottis	1.2	0.7, 1.8	1.2	0.8, 1.8
Glottis	1.0	0.7, 1.6	1.2	0.8, 1.8
All Sites Combined	1.1	0.8, 1.5	1.3	1.0, 1.7

TABLE 2—Distribution of Subjects by Maximum Weekly Consumption of Dark Liquor and by Lifetime Tobacco Use

	Tobacco Consumption					
	Fewer than 25 pack-yrs			25 or more pack-yrs		
	Dark Liquor (drinks/week)			Dark Liquor (drinks/week)		
Subjects	<1	2–6	7+	<1	2–6	7+
Controls	253	53	28	298	88	156
Hypopharynx Cases	3	0	2	25	10	44
Supraglottis Cases	1	2	1	61	16	44
Glottis Cases	20	4	1	68	22	60
RR (all cases combined)	1.0	1.2[a]	1.5[a]	5.4[a]	5.8[a]	10.0[a]
				1.0	1.1[b]	1.8[b]
RR (hypopharynx cases)	1.0	0.0[a]	6.0[a]	7.1[a]	9.6[a]	23.8[a]
				1.0	1.4[b]	3.4[b]
RR (larynx cases)	1.0	1.4[a]	0.9[a]	5.2[a]	5.2[a]	8.0[a]
				1.0	1.0[b]	1.5[b]

[a]Risk ratio with the low-tobacco, low-alcohol category as the referent.
[b]Risk ratio with the high-tobacco, low alcohol category as the referent.

TABLE 3—Relative Risk Estimates and 90% CI for Dark and Light Liquor Consumption in a Multiple Logistic Regression Analysis

Variables	Coefficient	Standard Error	RR Estimate	90% CI
Dark Liquor (200–4,999 drinks)	0.343	0.193	1.41	1.03, 1.94
Dark Liquor (5,000+ drinks)	0.854	0.141	2.35	1.86, 2.96
Light Liquor (200–4,999 drinks)	−0.680	0.234	0.51	0.34, 0.74
Light Liquor (5,000+ drinks)	0.462	0.174	1.59	1.19, 2.11

remains, whereas there is no effect of heavy consumption of light liquor conditional on total ethanol consumption. Table 5 gives the model with total alcohol consumption for hypopharyngeal cases.

We examined the influence of dark liquor consumption for various time periods before the cancer was diagnosed on hypopharyngeal cancer risk. These analyses indicated that consumption of dark liquor within the 10 years preceding diagnosis was much less strongly related to occurrence than was consumption in earlier decades.

Discussion

Methodologically the greatest concern in this study is the response rate, especially that of controls. Only 55 percent of the located controls were interviewed, and an unknown number of eligible controls were not located, in part because many of our subjects came from neighborhoods with high population turnover. The concern is that the subjects actually interviewed could have had exposure histories that differ from those not interviewed, possibly because the exposure is directly or indirectly related to the sequence of steps leading to inclusion in the study. Were the study focusing on total alcohol consumption, this concern would be intensified, since it is easy to image that the amount of alcohol consumed could affect the likelihood of participation. For the exposure of interest, however, which is the type of distilled alcoholic beverage consumed, we conjecture that selection bias from non-participation is a less serious problem. An important bias would have to involve marked selective participation among controls for consumers of dark liquor relative to light liquor or vice versa, independently of the total amount of alcohol consumed. Although there may be social class differences among liquor types that might introduce an association between beverage preference and the decision to participate in the study, the magnitude of these associations would have to be very strong to introduce a worrisome degree of bias into the comparisons reported here.

TABLE 4—Relative Risk Estimates and 90% CI for Dark and Light Liquor Consumption in a Multiple Logistic Regression Analysis (Hypopharyngeal Cases Only)

Variables	Coefficient	Standard Error	RR Estimate	90% CI
Dark Liquor (200–4,999 drinks)	0.396	0.407	1.49	0.76, 2.90
Dark Liquor (5,000+ drinks)	1.483	0.2631	4.40	2.85, 6.78
Light Liquor (200–4,999 drinks)	−0.385	0.405	0.68	0.35, 1.32
Light Liquor (5,000+ drinks)	0.237	0.311	1.27	0.76, 2.12

TABLE 5—Relative Risk Estimates and 90% CI for Dark and Light Liquor Consumption in a Multiple Logistic Regression Analysis Controlling Alcohol Consumption from All Sources (Hypopharyngeal Cases Only)

Variables	Coefficient	Standard Error	RR Estimate	90% CI
Dark Liquor (200–4,999 drinks)	0.019	0.422	1.02	0.51, 2.04
Dark Liquor (5,000+ drinks)	0.559	0.284	1.75	1.10, 2.79
Light Liquor (200–4,999 drinks)	−0.559	0.405	0.57	0.29, 1.11
Light Liquor (5,000+ drinks)	−0.136	0.308	0.87	0.53, 1.45
Total Alcohol (1,000–14,999 drinks)	1.522	0.671	4.58	1.52, 13.8
Total Alcohol (15,000+ drinks)	2.635	0.632	13.9	4.93, 39.4

Another potential concern is the use of surrogate interviews for 12 percent of cases. Cases who were deceased were included if a spouse could be interviewed. We also interviewed the spouses of 18 cases who had difficulty communicating. Spouse interviews presumably vary in accuracy depending on the information sought. The recent history of tobacco use, alcohol use, and other factors of interest is likely to be more accurate than early use. Alcohol consumption, which sometimes occurs without complete spousal awareness, may be particularly susceptible to error in spousal interviews. Here again our focus on type of beverage more than on amount mitigates the potential bias.

We used no surrogates for controls, since controls had to be alive to be eligible. Technically, since controls were matched individually to cases, controls who were alive at the time that the case was diagnosed should be eligible, regardless of whether they died before we attempted to contact them. Our decision not to include such individuals was motivated by convenience; it presents little problem if we can assume that there is no important departure from a dynamic equilibrium in the prevalence of type of distilled alcoholic beverage consumed.

Because all the exposure information in this study was reported by the subjects, there is presumably a substantial amount of misclassification. Some of the misclassification stems from faulty recall, and some from simplifying assumptions that we could not avoid in constructing summary measures of exposure. To the extent that such misclassification is comparable for cases and controls, the effect estimates in this analysis are underestimates of the actual effects.

The carcinogenic effect of alcoholic beverages is already well established.[19–21] When controlling for total alcohol consumption, which permits the evaluation of the effect of the non-alcohol component of alcoholic beverages, the additional cancer risk estimated for heavy consumption of dark liquor is modest.

What is important to note in these findings, however, is the divergent pattern of risks for upper airway cancer experienced by heavy consumers of dark liquor and heavy consumers of light liquor among hypopharyngeal cases. The site localization and the differences in effects between light and dark liquor are predicted by the theory that the carci-

nogenic action of alcohol is mainly topical, rather than systemic, and that the role of alcohol is to act as a solvent for other carcinogens, increasing the penetration of these carcinogens into epithelial tissue. The interactive effect with tobacco use that was observed is also consistent with this theory. These findings, on the other hand, are difficult to reconcile with alternative theories of alcohol carcinogenesis that suggest that ethanol increases carcinogenic risk through central rather than topical mechanisms.[8]

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'Children and Hospitals Week' Designated for March 25–31, 1990

A public awareness campaign focusing on the special needs of children and families in health care settings will be held March 25–31, 1990 throughout the United States. Designated "Children and Hospitals Week," the nationwide activity will feature health fairs, hospital open houses, preparation programs, "Teddy Bear" Clinics, library and school exhibits, educational conferences, and hundreds of other events. The theme for the week is "Commitment to Caring."

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