Role of Tobacco and Alcoholic Beverages in the Etiology of Cancer of the Oral Cavity/Oropharynx in Torino, Italy

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ABSTRACT

A population-based case-control study of cancer of oral cavity-oropharynx was conducted in the city of Torino, Italy, between 1982 and 1984. One hundred twenty-two cases (86 males and 36 females) and 606 controls (385 males and 221 females) were compared with respect to lifetime smoking and drinking habits. A 4- to 6-fold increase in risk among subjects with medium or high tobacco consumption was observed, as well as a trend in increasing risk with duration and with earlier age at the start of smoking. Other findings included a sharp reduction in risk with cessation of smoking, no clear protective effect of usage of filter, no differences risk according to color of tobacco, and a higher risk for cigar versus pipe/cigarette smokers.

An effect of alcoholic beverages was found in subjects with an average daily consumption of 120 or more grams of alcohol, with a higher risk in beer drinkers.

Among heavy consumers of alcohol and tobacco, risks of both oral and oropharyngeal cancer were very high. A positive association between oral cancer and low educational level, after adjustment for alcohol and tobacco, was found. Attributable risks for alcohol and tobacco in the population were 23% and 72% in men and 34% and 54% in women.

INTRODUCTION

It has long been known that tobacco smoke and alcohol abuse play a role in the etiology of cancer of the oral cavity/oropharynx (1, 2) and that the two agents act synergistically. Other risk factors shown or suggested for oral cancer include chewing of tobacco alone or in mixtures (3), poor oral hygiene and use of oral prostheses (4), low intake of fresh vegetables and fruit (5), work in the textile industry (6–8), and mouthwash use (9, 10).

The reasons for undertaking the population-based case-control study on cancer of the oral cavity/oropharynx in the city of Torino (northwestern Italy) were: (a) the consideration that among Italians (as well as in other countries of southwestern Europe) intake of alcoholic beverages is closely associated with meals: thus reliable estimates can be obtained through interviews focusing on diet including food and drink intake (11); (b) in northern Italy, mortality rates for cancer of the oral cavity/oropharynx are higher than rates in the central or southern regions, with a clear trend according to latitude (12); (c) tobacco smoke exerts its effect on the oral mucosa of low alcohol consumers or teetotallers (2); in many countries the assessment of the effect of alcohol per se alone encounters a major limitation due to the low proportion of moderate or heavy drinkers among nonsmokers. In northern Italy drinking is a widely

diffused and socially accepted cultural habit in both sexes and is common in nonsmokers as well as smokers; (d) in Italy there has been a tendency to shift from cigarettes prepared with air-cured black tobacco to cigarettes made with flue-cured blond tobacco. The Italian population includes sizeable proportions that smoked exclusively or predominantly, either blond or black tobacco. Among these, differences in the carcinogenic risk entailed by either type of cigarette can be investigated. A greater risk for smokers of black tobacco has been shown for cancer of the lung (13), larynx/hypopharynx (14), and bladder (15). To the best of our knowledge, this issue has not been investigated in any previous epidemiological study on cancer of the oral cavity/oropharynx, including the only case-control study carried out in Italy of which we are aware (16).

This paper compares lifelong alcohol and tobacco consumption among cases and controls.

MATERIALS AND METHODS

The study included all incident cases who were residents of the city of Torino and diagnosed for oral/oropharyngeal cancers between July 1, 1982, and December 31, 1984. Controls were assembled with the same inclusion criteria, multicentric population-based case-control study on cancer of the larynx/hypopharynx described in detail elsewhere (11). They were a random sample stratified by sex and age from the files of residents of the city of Torino and were interviewed between 1980 and 1984.

Cancers at the following sites were considered (topographical code according to ICD-9): mucosa of lip (140.3, 140.4, 140.5); tongue (141); gum (143); floor of the mouth (144); other and unspecified parts of the mouth (145); and oropharynx (146). All cases were histologically confirmed as squamous invasive carcinomas with the exception of one acinar cell carcinoma.

One hundred thirteen cases were identified in 14 stomatology, otorhinolaryngology, radio- or chemotherapy units operating in the city of Torino or its outskirts. They were interviewed in the hospital within a few days or weeks after diagnosis. In addition, early in 1983, 1984, and 1985, the files of all public and private pathology services operating in the city of Torino and its outskirts were surveyed. A further 27 histologically confirmed incident cases were thus identified, of which 20 were alive and could be traced. Twelve agreed to be interviewed at home.

Clinical information recorded for each case at the time of diagnosis included, among other items, a detailed topographical description of the lesion and was reviewed by one of us (A. M.) in order to assess the site of origin of the cancer in each case.

Cases and controls were personally interviewed by 8 trained interviewers using the same questionnaire. There were no changes in the interview process, interviewers, or questionnaire over the period of the study. Lifelong smoking and drinking histories and a detailed description of lifelong occupational history, of current diet, and of any major change in the past were collected by a standard questionnaire (11). Brands of cigarettes (including tobacco used for hand-rolled cigarettes), tobacco smoked in pipes, and cigars were classified as black or blond on a priori information from the Italian State Monopoly of Tobacco and, for a few brands, on interviews of tobacconists. Two % of cigarettes could not be classified with regard to tobacco type. Cigarettes of mixed

Received 9/22/88; revised 2/24/89; accepted 5/3/89.

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1 This investigation was supported by the Consiglio Nazionale delle Ricerche, Rome (Progetto Finalizzato Oncologia, Contracts 85.02391.44 and 86.00595.44); Associazione Italiana per la Ricerca sul Cancro; and Ministry of Public Education. Compute: facilities were made available by a grant from Consorzio per il Sistema Informativo, CSI-Piemonte, Torino. The International Agency for Research on Cancer, Lyons (France), contributed to the training of the interviewers. Participation in the study took place within the framework of the United States-Italy Cooperation for Cancer Research.

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3 Dr. G. D. Noia, personal communication.
type (which represented a small proportion of all cigarettes) were classified according to the prevalent color. For the conversion of alcoholic drinks into ethanol dose, 1 liter of wine, beer, aperitif, and liquors was considered to correspond, respectively, to 94, 40, 145, and 317 g of ethanol (17).

Further information on place of birth, civil status, and educational title was collected for all eligible cases and controls from the files of residents in the city of Torino. Educational level was considered as an indicator of socioeconomic status under 3 categories: primary (up to 5 yr of school); secondary (6 to 8 yr); and high-school-university degree.

ORs stratified on age (3 classes) were calculated according to Mantel and Haenszel (18) with test-based confidence intervals (19). Unconditional logistic regression was used to control confounding. Age (6 classes), education (3 classes), and area of birth (2 classes) were present in all models. Lifelong nonsmokers and teetotalers were excluded from models estimating risks for different patterns of tobacco and alcohol exposure, respectively. ORs for smoking and drinking habits were estimated from a basic model including smoking variables (consumption; duration; time since quitting; type of product, cigarettes, pipe, and cigars), average consumption of alcohol, and type of alcoholic beverage. When age at start of smoking was entered in the model, duration of smoking was excluded. Roles of filter and type of tobacco were studied in cigarette smokers only.

The combined effect of both exposures was analyzed through a model including—in addition to age, education, and area of birth—a term for each combination of alcohol and tobacco exposure, the reference category being subjects with lowest consumptions (see Table 5 for details). The average risks for alcohol and tobacco were estimated from a single model and, therefore, they were adjusted for each other.

The ARs in the population, based on marginal ORs of Table 5, were computed according to Miettinen (20); approximate 95% confidence intervals of AR were obtained from a 4-fold table as suggested by Walter (21). SAS programs were used for both stratified and multivariate analyses (22, 23).

Throughout the period covered by the study, eligible cases were 103 men and 40 women, corresponding to annual incidence rates (age standardized on the world population) of 5.76 and 1.72 x 10^-4. Eighty-six and 36, respectively, were interviewed. Table 1 reports the site of the cancer among interviewed cases according to the classification of one of us (A. M.). Among noninterviewed cases of either sex, 9 were male and 36, respectively, were interviewed. Table 1 reports the site of cancer among interviewed cases (Table 1).

The ARs in the population, based on marginal ORs of Table 5, were computed according to Miettinen (20); approximate 95% confidence intervals of AR were obtained from a 4-fold table as suggested by Walter (21). SAS programs were used for both stratified and multivariate analyses (22, 23).

Among men, an effect of alcoholic beverages is obvious only in men a higher risk is also suggested for subjects who smoked both sexes; exsmokers show a reduction of risk when compared with current smokers. Cigarette and pipe smokers have similar risks (OR = 3.8), while cigar smokers, with or without the combination of other tobacco products, seem to be at very high risk (OR = 14.6, lower 95% confidence limit = 4.7). Women smoked only cigarettes.

In men a higher risk is also suggested for subjects who smoked black cigarettes. No clear difference in risk is observed according to the proportion of filter cigarettes smoked.

Among men, an effect of alcoholic beverages is obvious only in subjects with an average daily consumption of 120 or more g of alcohol. Among women, a dose-effect relationship is suggested. An elevated risk in both sexes is found for subjects who drank beer with or without other beverages.

Temporal aspects of drinking habits, such as age at start, duration, and time since quitting, did not show any trend.

When both age and education were considered in this stratified analysis, ORs showed no major changes, ruling out an important confounding effect of education. The multivariate analysis confirmed the results of the stratified analysis (Table 4). However, in men, no difference in risk related to tobacco color of cigarettes was identified at this stage.

An increased risk was confirmed for cigar smokers in men and beer drinkers in both sexes.

Table 5 shows the distribution of cases and controls for each combination of alcohol and tobacco consumption with the
### Table 3
Number of cases and controls, ORs adjusted for age, and 95% confidence intervals for smoking and drinking habits, by sex

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 86)</th>
<th>Women (n = 221)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases Controls</td>
<td>ORs 95% CI</td>
</tr>
<tr>
<td><strong>Tobacco (g/day)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>5</td>
<td>85</td>
</tr>
<tr>
<td>1–7</td>
<td>3</td>
<td>58</td>
</tr>
<tr>
<td>8–15</td>
<td>27</td>
<td>91</td>
</tr>
<tr>
<td>16–25</td>
<td>37</td>
<td>106</td>
</tr>
<tr>
<td>&gt;25</td>
<td>14</td>
<td>45</td>
</tr>
<tr>
<td><strong>Duration of smoking (yr)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–20</td>
<td>4</td>
<td>54</td>
</tr>
<tr>
<td>21–30</td>
<td>5</td>
<td>52</td>
</tr>
<tr>
<td>31–40</td>
<td>29</td>
<td>79</td>
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<tr>
<td>41–50</td>
<td>26</td>
<td>77</td>
</tr>
<tr>
<td>&gt;50</td>
<td>17</td>
<td>38</td>
</tr>
<tr>
<td><strong>Age at beginning (yr)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>21</td>
<td>48</td>
</tr>
<tr>
<td>15–17</td>
<td>27</td>
<td>91</td>
</tr>
<tr>
<td>18–20</td>
<td>24</td>
<td>119</td>
</tr>
<tr>
<td>&gt;20</td>
<td>9</td>
<td>42</td>
</tr>
<tr>
<td><strong>Yr since quitting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>68</td>
<td>195</td>
</tr>
<tr>
<td>2–5</td>
<td>11</td>
<td>42</td>
</tr>
<tr>
<td>&gt;5</td>
<td>2</td>
<td>63</td>
</tr>
<tr>
<td><strong>Type of smoker</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only cigarettes</td>
<td>68</td>
<td>263</td>
</tr>
<tr>
<td>Pipe只有</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>Cigar only</td>
<td>11</td>
<td>12</td>
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<tr>
<td><strong>Color of tobacco</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;66% Blond</td>
<td>13</td>
<td>84</td>
</tr>
<tr>
<td>Mixed (both colors &lt;66%)</td>
<td>7</td>
<td>37</td>
</tr>
<tr>
<td>&gt;66% black</td>
<td>48</td>
<td>142</td>
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<tr>
<td><strong>Usage of filter</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;66% with filter</td>
<td>20</td>
<td>97</td>
</tr>
<tr>
<td>Mixed (both types &lt;66%)</td>
<td>13</td>
<td>42</td>
</tr>
<tr>
<td>&gt;66% without filter</td>
<td>35</td>
<td>124</td>
</tr>
<tr>
<td><strong>Alcohol (g/day)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrinkers</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>1–20</td>
<td>8</td>
<td>45</td>
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<td>21–40</td>
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<td>49</td>
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<td>41–60</td>
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<td>142</td>
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<td>81–120</td>
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<td>62</td>
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<tr>
<td>&gt;120</td>
<td>22</td>
<td>32</td>
</tr>
<tr>
<td><strong>Alcoholic beverages</strong></td>
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</tr>
<tr>
<td>Wine only</td>
<td>21</td>
<td>132</td>
</tr>
<tr>
<td>Beer</td>
<td>31</td>
<td>86</td>
</tr>
<tr>
<td>Aperitifs</td>
<td>30</td>
<td>95</td>
</tr>
<tr>
<td>Liquor</td>
<td></td>
<td>45</td>
</tr>
</tbody>
</table>

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* Averaged over the period of consumption.
* Reference category for all tobacco ORs.
* Only or with other tobacco products.
* Analysis restricted to subjects who smoked cigarettes only.
* Reference category for alcohol consumption.
* Reference category, nondrinkers.
* Only or with other beverages.

Corresponding ORs. The small number of cases makes it difficult to analyze the combined effect of alcohol and tobacco, but two features are coherent between men and women: (a) lack of an effect of alcohol in light smoker males and in females who never smoked; (b) sharp increase of the risk for subjects heavily exposed to both alcohol and tobacco. In men, 72.4% of cases is estimated to be attributable to a consumption of more than 7 g of tobacco/day; a corresponding percentage of 23.5 is attributable to the habit of drinking more than 40 g of alcohol/day. In women the AR to smoking is 53.9; a proportion of 34.4% is attributable to drinking more than 20 g/day of alcohol. The AR to the interaction between tobacco and alcohol cannot be clearly estimated from our data due to the absence of effect of alcohol in nonsmokers of both sexes.

Other characteristics of the subjects, considered in the logistic analysis as confounding variables, were found to be of interest. In men, place of birth other than northern Italy (15 cases and 134 controls) was negatively associated with oral cancer (OR = 0.4; 95% CI = 0.2 to 0.7). Moreover, in men a strong interaction between birth in northern Italy and alcohol consumption was observed. Restricting the analysis to men born in northern Italy, the risk for alcohol increased on average by a factor of 2.0; for a daily consumption of 120+ g, the OR was 4.3 (95% CI = 1.1 to 17.0, based on 21 cases and 22 controls) versus an OR of 2.1 in the whole series. Finally, people with less than 5 yr of education showed increased risks compared to more educated subjects (9 or more yr of education), with ORs of 2.1 (1.0 to 4.4) in men and 1.8 (0.7 to 4.7) in women. All these risks were
consistently with previous knowledge.

Several other epidemiological studies, both cohort and case-control, confirmed such a relationship, and most of the results of the present study are consistent with previous knowledge.

The proportion of nonsmoker cases was negligible in men, whereas it was around one-third in women. A similar pattern was previously described (24, 25). In men, the risk for smokers was related to both average consumption and duration of smoking, the OR for light smokers being close to unity. The association with alcohol was limited to an average lifelong consumption of 120 or more g per day. On the contrary, no dose-response for tobacco was found in women (perhaps due to small absolute numbers), and the OR for light smokers was around 5. Similarly, an OR around 3 was found in both light and heavy drinkers in women. The absence of an effect of alcohol in nonsmokers has been previously reported (5). A comparison of doses of alcohol with those reported in other studies is impaired by differences in both data collection and detail of adjustment for confounders. Nevertheless, for similar daily intakes, ORs in the present series were lower than in most studies carried out by differences in both data collection and detail of adjustment for confounders. Although there was no correlation of alcohol and drinking habits in exposed subjects by sex estimated from a logistic model including age, educational level, area of birth, and the average daily tobacco and alcohol consumption.

## DISCUSSION

More than 30 yr have elapsed since a formal case-control study first related tobacco and alcohol consumption in a clear way to oral cancer in humans (24). Several other epidemiological studies, both cohort and case-control, confirmed such a relationship, and most of the results of the present study are consistent with previous knowledge.

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subjects (9 or more yr of education). Among respondents only, the corresponding ORs, after controlling for alcohol and tobacco consumptions and area of birth, were remarkably similar, namely, 2.1 and 1.8. These findings suggest an independent effect: of educational level on oral cancer risk.

Issues raised by the present study relate to type of tobacco and alcoholic beverages and to temporal variables related to tobacco consumption. Among tobacco products, cigar consumption exhibited the highest risk. This is consistent with previous findings (24, 29, 32). On the contrary, no previous study on oral cancer attempted to discriminate between the effects of cigarettes made with tobacco of different colors. In the present series, an excess risk associated with black (air-cured) tobacco, suggested during the first stage of the analyses, when age was the only confounder accounted for, was not confirmed after adjustment for drinking, other relevant aspects of smoking, and educational level. This result contrasts with the finding that the smoke from black is more carcinogenic than the smoke from blond (flue-cured) tobacco for the lung (13), larynx/hypopharynx (14), and bladder (15). This discrepancy, which requires confirmation, suggests that different carcinogens of tobacco smoke are involved in the carcinogenic process in different organs.

The reduction of risk after quitting confirms previous results (25, 30, 32). To the best of our knowledge, the effect of age when first starting to smoke has only been considered in one other study (30): both the cited and the present study suggest a trend in reduction of risk as age at beginning increases. This phenomenon has been reported for other tobacco-related diseases, including cancer of the lung (1, 33), larynx/hypopharynx (14), and bladder (15).

As for alcoholic beverages, beer drinking was found to be related to a statistically significant higher risk than wine drinking. This finding is of interest in view of its occurrence in the two sexes and its consistency with some previous observations (26, 30). Information on time of drinking during the day was available for current consumption only. The overwhelming majority of wine was drunk during meals, while over one-half of beer was drunk between meals, the difference being stronger among controls. Time of alcohol consumption might explain the different carcinogenic effect of beer and wine, but more detailed information on lifetime consumption is required to investigate this problem. However, alternative explanations, such as the different concentration of nitrosamines among beverages (34), are also plausible.

In men, risks attributable to alcohol and tobacco in the population of the city of Torino were, respectively, 23% and 72%. The corresponding figures in women were 34% and 54%. For public health purposes, these estimates further focus the importance of the two habits in the etiology of oral/oropharyngeal cancer. Nevertheless, other agents should not be disregarded. In the first place, the present study did not consider other known risk factors, such as dentition status. In addition, the effect of place of birth and educational level, which persisted after adjustment for alcohol and tobacco, indicates the need for investigating other risk factors, such as diet and occupation.

The present finding of a higher proportion of nonsmokers among patients with cancer of the oral tongue is consistent with the recently reported observation of a weaker effect of smoking on tongue cancer compared to other oropharyngeal sites (30).

The major limitations of the present study were its small size, the lack of consideration of some known risk factors such as dentition status, and the potential biases brought about by the different response rate between cases and controls. The latter has been adjusted for, at least partly, by the inclusion of age and education (both related with success of interview) into the logistic regression models. Identification of eligible cases was satisfactory; incidence rates based on the present study are quite similar to those estimated in residents in the city of Torino after the inauguration of the local cancer registry in 1985.3

ACKNOWLEDGMENTS

The authors acknowledge the Group for the Study of Laryngeal Cancer in Latin Countries for the preparation of the questionnaire, Dr. A. Tuyns, Dr. J. Estève (IARC, Lyons), Dr. L. Garfinkel, and Dr. S. Stellman (ACS, New York) for helpful discussions, and Dr. Clara Latino and Dr. Rita Giacometti for technical help.

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