Prognostic Factors and Survival of Laryngeal Cancer Patients from Turin, Italy

A Population-based Study

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Little information is available on the role of risk factors for cancer of the larynx in survival. This study analyzed survival through the end of 1994 for 355 cases of laryngeal cancer diagnosed among residents of Turin, Italy, during 1979–1982. Relative survival at 5 years was 75% in women and 67% in men. The role of clinical and etiologic factors was analyzed in detail among 222 male cases. The role of nodal involvement as a strong predictor of poor survival was confirmed. Patients of low socioeconomic status experienced poorer survival than other patients, as did heavy smokers. Alcohol drinking and diet did not seem to strongly influence survival. Survival in this series of laryngeal cancer cases closely parallels that observed in other case series from Europe. While the results regarding socioeconomic status, tobacco smoking, and alcohol drinking parallel those of the few previous studies available, this investigation did not confirm a role for diet in the survival of laryngeal cancer patients, a finding that was recently seen in another study from northern Italy. Am J Epidemiol 1997; 145:1100–5.

alcohol drinking; diet; laryngeal neoplasms; smoking; survival

In the early 1980s, the International Agency for Research on Cancer coordinated a collaborative multicenter population-based case-control study on the association between cancer of the larynx and some aspects of lifestyle and occupational exposures. The six populations included in the study were all located in southern Europe and were characterized by a high incidence of and mortality from cancer of the larynx (1). One of these areas was the city of Turin, Italy. The current report focuses on survival among laryngeal cancer cases compiled in Turin and its relation with the risk factors investigated in the etiologic study. Data on the survival of patients enrolled in the other Italian area of the study, the province of Varese, were recently published elsewhere (2).

MATERIALS AND METHODS

The study included a consecutively assembled, population-based series of 355 incident cases of cancer of the larynx diagnosed between January 1979 and December 1982 among residents of Turin (a city of 1,117,154 residents in 1981) (3). Cases were histologically verified invasive epidermoid carcinomas. A total of 327 cases occurred among men and 28 among women.

Information on clinical characteristics was collected for 272 cases (252 men and 20 women), including TNM (tumor–node–metastasis) classification, subsite within the larynx, and lifelong exposure to risk factors for laryngeal cancer. For the purpose of this analysis, we classified tumors according to whether they arose from the endolarynx, particularly the supraglottic region (the remaining being mostly glottic tumors), or the epilarynx (closer to the hypopharynx). The distribution of data on sex, age, marital status, education, and place of birth did not differ between these cases and those without clinical information. A questionnaire was used to collect information on smoking, alcohol drinking, occupational exposures, and diet (1).
Active follow-up was carried out by checking the city population files. Information on the vital status of subjects who had migrated was obtained by writing to the new municipality of residence. For deceased subjects, a copy of the death certificate was obtained. Underlying cause of death was coded according to the International Classification of Diseases, Ninth Revision (4). The end of follow-up was December 31, 1994, for the cases with clinical and anamnestic information; for the remaining cases, it was December 31, 1990. Vital status was ascertained for all 355 cases; information on cause of death was obtained for 218 of the 227 deceased cases (96 percent).

Survival rates were calculated using the Kaplan-Meier method (5). Differences between groups were tested using the log-rank test. Relative survival (6) was estimated using national mortality rates. Standardized mortality ratios were calculated with the indirect method (7); expected numbers of deaths were derived by applying the national mortality rates; and 95 percent confidence intervals were calculated on the basis of a Poisson distribution of deaths.

Determinants of survival in 222 male cases (contributing 147 deaths) with complete information on both clinical aspects and risk factors were evaluated by multivariate analysis carried out according to Cox’s regression model (8), estimating hazard ratios and 95 percent confidence intervals. The hazard ratio is a measure of the risk of dying during follow-up in a given category relative to a referent category.

RESULTS

Observed survival for men at 1, 3, 5, and 10 years postdiagnosis was 84 percent, 66 percent, 58 percent, and 41 percent, respectively; corresponding relative survival figures were 89 percent, 71 percent, 67 percent, and 56 percent. Among women, observed survival was 93 percent at 1 year, 71 percent at 3 years, 68 percent at 5 years, and 60 percent at 10 years; figures for relative survival were 94 percent at 1 year and 75 percent at 3, 5, and 10 years. The difference in survival between men and women was statistically significant. Table 1 shows observed survival according to selected characteristics of the patients; similar results were obtained for relative survival. Patients in older age groups experienced significantly worse survival than younger patients, the difference being particularly relevant between patients aged <70 years at diagnosis and those aged ≥70 years at diagnosis. As expected, patients with T3 or T4 tumors had worse survival than patients with T1 or T2 tumors; however, no difference was seen between T1 and T2 cases. Similar results were obtained when patients were categorized according to stage rather than tumor from the TNM classification. Patients with lymph node involvement had worse survival than patients without it.

Cause of death for these patients was analyzed in a standardized mortality analysis (table 2). Overall, this series of patients experienced a threefold increase in mortality which was completely accounted for by deaths from laryngeal cancer and other tobacco-related cancers (oral cavity, esophagus, lung, bladder): After exclusion of these causes of death, there were 60 deaths observed and 69.4 expected. A total of 129 death certificates reported laryngeal cancer (ICD-9 code 161) as the underlying cause of death, while hypopharyngeal cancer (ICD-9 code 148) was reported for an additional two patients. Increased mortality was found for other cancers, while a deficit was seen for most nonneoplastic causes of death, with the exception of external and ill-defined causes (both based, however, on small numbers).

Table 3 presents the results of the multivariate analysis of sociodemographic and clinical characteristics of the male patients. A nonsignificantly better prognosis was suggested for more educated patients and for subjects born in southern Italy, as well as for skilled workers (including professionals).

When clinical variables were considered (table 3), no statistically significant differences were found in

### TABLE 1. Observed survival of laryngeal cancer patients at 1, 3, and 5 years of follow-up, Turin, Italy, 1979-1994

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Observed survival (%)</th>
<th>p-value (log-rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 year</td>
<td>3 years</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>327</td>
<td>84</td>
</tr>
<tr>
<td>Women</td>
<td>28</td>
<td>93</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>51</td>
<td>88</td>
</tr>
<tr>
<td>50–59</td>
<td>122</td>
<td>91</td>
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<tr>
<td>60–69</td>
<td>108</td>
<td>83</td>
</tr>
<tr>
<td>≥70</td>
<td>74</td>
<td>74</td>
</tr>
</tbody>
</table>

* TNM, tumor-node-metastasis.
† Information on T stage was missing for 49 cases.
‡ Information on N stage was missing for 50 cases.
the survival of patients with tumors originating at different subsites within the larynx. No significant difference in survival was found in multivariate analysis by the extension of the tumor once other clinical variables of important prognostic value, particularly the presence of lymphonodal metastasis and the site of origin of the tumor, were included in the regression model. This result suggests a confounding effect of the latter variables and a lack of a strong independent effect of tumor size.

Too few patients had N2 or N3 lesions to allow for a separate analysis; similarly, in only two patients were extranodal metastases present at the time of diagnosis. Most patients (72 percent) had been diagnosed and treated at the only university hospital in Turin; no difference in survival was found between this group and the remaining patients (for patients diagnosed in other hospitals, hazard ratio (HR) = 0.8, 95 percent confidence interval (CI) 0.5–1.1).

Table 4 shows the results of the analysis of survival according to exposure to known or suspected risk factors for laryngeal cancer. Poorer survival was experienced by heavy smokers compared with light smokers (too few patients were nonsmokers to form a stable reference category). After controlling for tobacco consumption, no effect of type of tobacco was found (for tobacco that was more than two thirds black tobacco, HR = 1.2, 95 percent CI 0.8–1.9, compared with tobacco that was more than two thirds blond tobacco), nor was there an effect of cigar or pipe smoking (for ever smokers of pipes or cigars, HR = 1.0, 95 percent CI 0.5–1.9, compared with smokers of cigarettes only).

A small, non-statistically significant effect on survival was also found for heavy alcohol drinking, with no difference being seen according to type of alcoholic beverage (most of the alcohol consumed, however, was wine). An analysis of the combined effect of alcohol drinking and tobacco smoking showed a hazard ratio of 2.3 (95 percent CI 1.1–4.9) among cases heavily exposed to both agents (≥26 cigarettes per day and ≥121 g of alcohol per day); the hazard ratio was 1.8 (95 percent CI 1.0–3.2) in heavy smokers who drank 0–120 g/day and 1.8 (95 percent CI 0.6–5.0) in heavy drinkers who smoked 0–15 cigarettes/day, using as the reference category cases in the lowest category of consumption of both agents.

A nonsignificantly reduced risk was found in the quartiles of the highest intakes of vitamin C, vitamin E, and fiber, as well as total fat, total carbohydrates, and total calories (table 4). A polyunsaturated fat: saturated fat ratio above the cutpoint used for the lowest quartile (0.28) was also associated with reduced mortality, but no trend was detected among the other categories. Analyses of occupational exposure to carcinogens did not reveal a significant difference in survival among cases with definite exposure to asbestos (HR = 1.4, 95 percent CI 0.8–2.5, compared with the unexposed), polycyclic aromatic hydrocarbons (HR = 0.7, 95 percent CI 0.5–1.1), or dust (HR = 1.0, 95 percent CI 0.6–1.5).

The multivariate analysis presented in tables 3 and 4 was repeated, taking into account mortality from laryngeal cancer only and considering deaths from other causes as censoring events. The results were only slightly different from those presented above. In particular, no effect of age was found below age 60 years, and the weak inverse association of several dietary components was not confirmed.

**DISCUSSION**

This study analyzed the survival of a population-based case series of patients with laryngeal cancer. This approach avoids bias in the selection of patients which may affect any hospital-based series. The survival rate found in this study is comparable to the results of similar studies conducted in Europe for laryngeal cancer (9–12), particularly the results of a systematic analysis of survival from cancer registries (12). In particular, the relative survival among 668 male patients registered in three Italian cancer regis-

tries was 85 percent at 1 year, 73 percent at 3 years, and 65 percent at 5 years.

The patients in this series did not experience an increased risk of death from causes other than cancers at sites that either may be invaded by laryngeal cancer (such as the oral cavity and esophagus) or share the same risk factors (such as the lung and bladder), apart from ill-defined conditions and accidents—two groups of causes that are possibly related to the lower socioeconomic status of these patients in comparison with the national population. The results regarding causes of death should be interpreted with care, however, because of the limitations in the diagnosis of cancer on death certificates. One large study from Trieste, Italy, comparing necropsy and death certificates found a proportion of agreement, in men, of 80 percent for lung cancer and 76 percent for laryngeal cancer (13). Similar results have been obtained in smaller studies from Italy (14). These results are comparable to those of studies conducted in other countries, such as the United States (15), and they confirm the inappropriateness of restricting the survival analysis to deaths due to laryngeal cancer.

While patients with lymph node involvement had lower survival than other patients, a relatively weak effect of tumor size, as expressed by the TNM index, was found. Although T3-T4 patients had worse survival than T1-T2 patients, the difference was small and nonsignificant, and it was further reduced when site of origin of the lesion and nodal involvement were controlled for. This result is not in agreement with those of most of the available studies (16), and it might be due to misclassification of T stage in our study. The small number of T3-T4 patients, however, may also suggest a role for chance: The upper confidence limit shown in table 3 is compatible with the results of several other studies (17, 18). This study, on the other hand, was not informative with respect to the role of extranodal metastases in survival.

To our knowledge, this study's analysis of the influence of laryngeal cancer risk factors on survival is an original contribution to the literature. Although the analysis of risk factors was conducted in only 222 male cases (68 percent of all of the male cases), a bias in the risk estimates would only have been introduced if the association between survival and risk factors had been different in the cases without information compared with the group included in the analysis. Data on the sociodemographic variables were available for the entire series of patients and were analyzed according to inclusion in the analysis of risk factors; no statistically significant differences were found by age and education, while patients born in southern Italy were more likely to be included than patients born elsewhere. An additional argument against the hypothesis of a bias is provided by the survival of the subgroup of cases with complete information, which was similar to that of the entire series of cases in this study and to the survival of other population-based series.

Tobacco smoking seems to have affected, albeit to a limited extent, the survival of the patients in this study, and this effect was independent of an increased mortality due to causes other than laryngeal cancer. No effect of alcohol drinking on survival was found. The analysis of the series of laryngeal cancer cases enrolled in Varese also showed decreased survival of heavy smokers compared with light smokers, and very little effect of alcohol drinking (2).

This study did not suggest a strong association between diet and survival for patients with laryngeal cancer. In particular, this study did not confirm the results of the Varese analysis, which showed a protective effect of high intakes of citrus fruits and vegetables and of nutrients such as vegetable protein, monounsaturated fat, fiber, and vitamin C (2). Since the results of these previous studies were not adjusted for place of birth, which in Italy is linked to dietary habits and which was a predictor of survival in this analysis, the hazard ratios shown in table 4 were computed again without taking this variable into account; however, the results were not substantially modified, suggesting a true discrepancy in the results regarding the effect of diet on survival between the two groups of patients. The distributions of nutrient intakes were similar in the Turin and Varese series.

No association was found between survival and exposure to the occupational respiratory carcinogens asbestos, polycyclic aromatic hydrocarbons, and dust; however, the role of these agents in laryngeal cancer has not been fully established (19).

A nonsignificant association was found between survival and educational level. This association was not explained by confounding by tumor site, nodal involvement, or tobacco smoking. Although few studies on socioeconomic status and cancer survival have specifically examined laryngeal cancer, low socioeconomic status is a strong indicator of poor survival for many epithelial neoplasms of the respiratory and digestive systems (20), particularly for laryngeal cancer in one study (21).

In conclusion, analysis of survival in this series of laryngeal cancer cases confirmed the well-established role of nodal involvement as a strong predictor of poor survival. Extension of the lesion did not seem to act as an independent prognostic factor. Men experienced poorer survival than women, as did patients of low socioeconomic status and smokers. Alcohol drinking
and dietary habits did not seem to strongly influence survival.

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