Scand J Work Environ Health 2002;28(4):278–284

Occupational dust exposure and the risk of laryngeal cancer in Turkey

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Elci OC, Akpinar-Elci M, Blair A, Dosemeci M. Occupational dust exposure and the risk of laryngeal cancer in Turkey. *Scand J Work Environ Health* 2002;28(4):278–284.

Objectives A hospital-based case-referent study was conducted to identify occupational risk factors for laryngeal cancer. In a previous report an association was found between laryngeal cancer and occupations with potential dust exposure; a job-exposure matrix was developed to aid further evaluation of laryngeal cancer risks from five occupational dust exposures.

Methods Among 7631 cancer cases from the Okmeydani Hospital, Istanbul, between 1979 and 1984, 958 larynx cancer cases were identified among men. After exclusions, 940 laryngeal cancer cases and 1519 referents were available. A standardized questionnaire was used to obtain basic information on the patients. Seven-digit standard occupational and industrial codes were created to classify the job and industrial titles. A job-exposure matrix was developed for occupational dusts, including silica, asbestos, wood, cotton, and grain, and age-, smoking-, and alcohol-adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to evaluate risks of laryngeal cancer.

Results An excess of laryngeal cancer occurred for workers potentially exposed to silica and cotton dust, particularly for supraglottic cancer (OR 1.8, 95% CI 1.3–2.3, for silica and OR 1.6, 95% CI 1.1–2.5, for cotton dust), and there was a significant dose-response relationship with silica exposure. No relationship was found between laryngeal cancer and asbestos, grain, or wood dust exposures.

Conclusion Laryngeal cancer, especially supraglottic tumors, is associated with silica and cotton dust exposures in Turkey.

Key terms case-referent study, case-control study, cotton, epidemiology, larynx, work, silica.

Laryngeal cancer is an important cancer in Turkey, with an age-standardized incidence rate of 11.5 per 100 000 for men, which is almost twice that of the world rate (5.7 per 100 000) (1). As the second leading cancer, it has been responsible for about 7.0% of the deaths among men in Turkey (2, 3). Although alcohol and tobacco consumption is the most important factor in the etiology of laryngeal cancer, occupational and environmental factors also play a role (4–6). Increased risk of laryngeal cancer among those exposed to various dusts has been reported (7–9).

We conducted a hospital-based case-referent study of several cancers in Istanbul, Turkey. In a previous report, we found that the risk of laryngeal cancer was associated with several occupations and that supraglottic laryngeal cancer appeared to be linked to occupations with possible occupational exposure to dust (10). To evaluate further this observation, we developed a job-exposure matrix to assess the potential risks from five occupational dust exposures.

Subjects and methods

Both the cases and referents were selected from patients admitted to the Oncology Treatment Center of the Social Security Agency Okmeydani Hospital, Istanbul,

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Turkey, between 1979 and 1984. The center provides cancer treatment for workers in the Marmara region, which is the northwest part of Turkey, and also to some workers from other regions. The nationwide target population of the hospitals of the Social Security Agency is limited to workers who have similar population characteristics. Each hospital serves a defined geographic area. This oncology treatment center was part of the largest hospital in the area. As a regular procedure upon admission to the hospital, regardless of their diagnosis, all patients give their informed consents and respond to a standardized questionnaire administered by trained interviewers seeking information on demography, occupational history, and tobacco and alcohol use. All the patients with a primary tumor were selected as our study population. None of these patients refused to participate in the study. Details of the data collection have been explained elsewhere (11). Among the 7631 primary cancer cases admitted to this hospital between 1979 and 1984, there were 958 laryngeal cancers.

An oncologist from the hospital reviewed the records of patients for diagnostic verification and coded them according to the classification system of the International Classification of Diseases for Oncology (ICD-O) (12). We used four-digit ICD-O codes of laryngeal cancers (ICD-O 161.0, 161.1, 161.2, 161.9) to classify tumor location. Cases with subglottic (ICD-O 161.2, N = 12) and unclassified (ICD-O 161.9, N = 263) cancers were combined for this analysis (N = 275, 29.3%). Glottic (ICD-O 161.0, N = 227, 24.1%) and supraglottic (ICD-O 161.1, N = 438, 46.6%) tumors were considered separately. More than 95% of the laryngeal cancer cases had a histopathologic diagnosis of squamous cell carcinoma; because of the small variability, we did not include histological subgroups in our analyses.

Workers with incomplete information on age, smoking, alcohol, job titles, industry titles, and tumor site and also the small number of women (N = 7) were excluded, leaving 940 laryngeal cancer cases for this study. From the hospital registry, we selected all the male patients with Hodgkin's disease (N = 202), soft tissue sarcoma (N = 130), and cancers of nonmelanoma skin (N = 657), testis (N = 219), bone (N = 66), male breast (N = 34), and a series of noncancer subjects (N = 211) for the reference group (N = 1519). These cancers were selected for the reference group because they are thought not to share similar etiologic factors with laryngeal cancer. Two hundred and eleven patients with benign pathologies were also used as referents. Initially they were misdiagnosed as cancer and admitted to the Okmeydani Hospital for treatment and then re-evaluated and diagnosed with other (benign) pathologies.

We coded occupations and industries using a modification of the Standard Occupational Classification (SOC) and Standard Industrial Classification (SIC) system (13). We created special 7-digit SOC and SIC codes to evaluate occupational exposures in specific groups (10, 14).

With the use of the 7-digit SOC and SIC codes, job-exposure assignments were completed for common occupational dusts in Turkey, including silica, asbestos, wood, cotton, grain, and leather dust, by an industrial hygienist who had extensive experience in occupational settings in Turkey. We had only nine cases exposed to leather dust; therefore we excluded the results on leather dust exposure from this manuscript. For each occupation and industry, we assigned exposure intensity and probability levels independently on a scale of 0–3 (0 = no, 1 = low, 2 = medium, and 3 = high exposure). For the intensity assignments, the exposure intensity of the substance of interest was 1 = lower than threshold limit value (TLV) (15), 2 = between the TLV and two times the TLV (15), 3 = greater than two times the TLV (15). For probability, we assigned the exposure probability of the workers for a substance of interest as 1 = lower than 25%, 2 = between 25 and 75%, 3 = greater than 75% in given occupational and industrial categories.

We then combined occupational and industrial exposure scores, where appropriate, using the following algorithms. For some situations, exposure was dependent on occupation only, and we calculated the final score by an algorithm based on the SOC (intensity = $\text{intensity}_{soc} \times \text{intensity}_{soc}$; and probability = $\text{probability}_{soc} \times \text{probability}_{soc}$). If the exposure depended on occupation and industry, the exposure score was assigned using an algorithm multiplying the SOC-based and SIC-based assignments (intensity = $\text{intensity}_{soc} \times \text{intensity}_{sic}$; and probability = $\text{probability}_{soc} \times \text{probability}_{sic}$). In the application of these algorithms, each person received final intensity and probability scores for each occupation and industry combination. We classified these scores as follows: no (score 0), low (score 1–2), medium (score 3–4), and high (score 6–9) exposure. Examples of the application of the job-exposure matrix are presented in table 1. During the exposure assignment, the case or referent status of the subjects was masked. Details of the exposure assessment procedures have been reported elsewhere (16).

To evaluate possible dose-response relationships within the exposure intensity groups and exposure probability groups, we used a linear trend analysis; to estimate odds ratios (OR) and 95% confidence intervals (95% CI) adjusted for age, smoking, and alcohol, we used the unconditional logistic regression analysis in SPSS® version 10.1. The mean age was 52.9 (SD10.3) years for the laryngeal cancer cases and 47.1 (SD 15.4) years for the referents. Although 73.9% of the cases were smokers and 24.5% regularly consumed alcohol, smoking and alcohol consumption were less common among the referents (58.6 and 13.4%, respectively). The age-adjusted odds

Table 1. Examples of the application of the job-exposure matrix.[a] (SOC=Standard Occupational Classification, SIC=Standard Industrial Classification)

Example [b]	Exposure			
	Intensity	Origin	Score	Group
Case A				
Occupation: stone cutter (6861–029)	3	SOC	$3^2 = 9$	High
Industry: road construction (1611–012)	2			
Case B				
Occupation: drilling operator (7518–012)	2	SOC & SIC	2 x 2 = 4	Medium
Industry: road construction (1611–012)	2			

[a] Based on silica exposure.
[b] Code of the SOC or SIC in parentheses.

Table 2. Risk of laryngeal cancer by exposure and anatomic location. (OR=odds ratio, 95% CI=95% confidence interval)

Exposure (ever-never)	All laryngeal cancers				Supraglottic cancer				Glottic cancer				Other cancers			
	Cases (N)	Referents (N)	OR [a]	95% CI	Cases (N)	Referents (N)	OR [a]	95% CI	Cases (N)	Referents (N)	OR [a]	95% CI	Cases (N)	Referents (N)	OR [a]	95% CI
Silica dust	186	227	1.5	1.2–1.9	100	227	1.8	1.3–2.3	34	227	1.1	0.7–1.7	52	227	1.4	0.9–2.0
Asbestos	150	250	1.0	0.8–1.3	71	250	1.0	0.8–1.4	28	250	0.8	0.5–1.2	51	250	1.2	0.9–1.7
Wood dust	109	173	1.1	0.8–1.4	55	173	1.2	0.9–1.7	21	173	0.9	0.6–1.5	33	173	1.2	0.8–1.7
Cotton dust	54	74	1.3	0.9–1.9	30	74	1.6	1.1–2.5	10	74	1.1	0.5–2.2	14	74	1.2	0.7–2.2
Grain dust	31	37	1.3	0.8–2.1	13	37	1.1	0.6–2.1	5	37	0.9	0.4–2.4	13	37	1.9	0.9–3.8

[a] Adjusted for age, smoking, and alcohol consumption.

ratio was for laryngeal cancer among the smokers and alcohol consumers were 1.7 (95% CI 1.4–2.1) and 2.0 (95% CI 1.6–2.6), respectively. We did not have pack · year and bottle · year information for up to 50% of the subjects who reported smoking or drinking alcohol. For those with pack · year or bottle · year information, the odds ratios for laryngeal cancer did not differ for occupational exposures by the odds ratios for ever-never data. Consequently, we used ever-never data in our analyses.

Results

The evaluation of the job-exposure matrix showed that the most common exposures among the laryngeal cancer cases were silica, asbestos, and wood dust (20%, 16%, and 12%, respectively). Exposure to cotton dust (6%) and grain dust (3%) was lower than the other exposures.

Risks of laryngeal cancer by anatomic distributions from ever-never exposure are presented in table 2. We observed an excess of laryngeal cancer among the subjects exposed to silica dust and cotton dust, particularly for supraglottic cancers (OR 1.8, 95% CI 1.3–2.3, and OR 1.6, 95% CI 1.1–2.5, respectively). The odds ratio for "other" laryngeal cancers was elevated for grain dust, but the heterogeneity of this category made it difficult to interpret.

In table 3, we present the risks of laryngeal cancer by the anatomic location of the tumors according to the exposure intensity levels. Laryngeal cancer risk increased by silica exposure intensity levels of low, medium, and high (OR 1.4, 1.5, and 1.7, respectively) ($\chi^2_{trend} = 11.5$ P = 0.001). This dose-response relationship was the sharpest among the cases with supraglottic tumors (OR 1.4, 1.8, and 2.2, respectively) ($\chi^2_{trend} = 19.3$ P<0.001). Although the dose-response relationship between cotton dust exposure and the risk of laryngeal cancer was not statistically significant ($\chi^2_{trend} = 1.9$ P = 0.169), it was significant for supraglottic cancers, for which there was a 2.4-fold excess risk for high-level exposure ($\chi^2_{trend} = 4.8$ P = 0.028). We did not observe any dose-response relationship with asbestos, grain, or wood dust exposure.

Laryngeal cancer risks from exposure probability are presented in table 4 by anatomic location. The probability of the silica exposure and the risk of laryngeal cancer showed a dose-response relationship (OR 0.8, 1.5, and 1.8 respectively) ($\chi^2_{trend} = 12.5$ P<0.001). The

Table 3. Risk of laryngeal cancer by exposure intensity levels and anatomic location. (OR=odds ratio, 95% CI=95% confidence interval)

Exposure	All laryngeal cancers				Supraglottic cancer				Glottic cancer				Other cancers			
	Cases (N)	Referents (N)	OR [a]	95% CI	Cases (N)	Referents (N)	OR [a]	95% CI	Cases (N)	Referents (N)	OR [a]	95% CI	Cases (N)	Referents (N)	OR [a]	95% CI
Silica dust																
Low intensity	48	69	1.4	1.0–2.1	22	69	1.4	0.9–2.4	13	69	1.5	0.8–2.9	13	69	1.3	0.7–2.4
Medium intensity	94	114	1.5	1.1–2.0	51	114	1.8	1.2–2.6	13	114	0.8	0.5–1.5	30	114	1.6	1.1–2.5
High intensity	44	44	1.7	1.1–2.6	27	44	2.2	1.3–3.6	8	44	1.2	0.5–2.6	9	44	1.2	0.5–2.4
Asbestos																
Low intensity	45	84	0.9	0.6–1.3	18	84	0.8	0.5–1.3	10	84	0.8	0.4–1.6	17	84	1.2	0.7–2.1
Medium intensity	93	129	1.2	0.9–1.6	47	129	1.3	0.9–1.9	16	129	0.9	0.5–1.5	30	129	1.4	0.9–2.2
High intensity	12	37	0.6	0.3–1.1	6	37	0.6	0.3–1.5	2	37	0.4	0.1–1.6	4	37	0.7	0.2–1.9
Wood dust																
Low intensity	22	46	0.8	0.5–1.4	9	46	0.8	0.4–1.6	4	46	0.6	0.2–1.7	9	46	1.1	0.5–2.4
Medium intensity	71	89	1.4	1.0–1.9	38	89	1.6	1.1–2.4	12	89	1.0	0.5–2.0	21	89	1.5	0.9–2.5
High intensity	16	38	0.8	0.4–1.4	8	38	0.8	0.4–1.8	5	38	1.0	0.4–2.6	3	38	0.5	0.1–1.6
Cotton dust																
Low intensity	12	23	0.8	0.4–1.6	6	23	0.9	0.3–2.2	4	23	1.2	0.4–3.6	2	23	0.5	0.1–2.2
Medium intensity	11	17	1.2	0.6–2.7	4	17	1.1	0.4–3.3	3	17	1.4	0.4–4.9	4	17	1.6	0.5–4.9
High intensity	31	34	1.7	1.1–2.9	20	34	2.4	1.3–4.2	3	34	0.8	0.3–2.8	8	34	1.6	0.7–3.6
Grain dust [b]																
Low intensity	19	24	1.2	0.6–2.3	9	24	1.2	0.6–2.8	4	24	1.2	0.4–3.7	6	24	1.5	0.6–3.6
Medium + high intensity	12	13	1.4	0.6–3.1	4	13	0.9	0.3–2.8	1	13	0.4	0.1–3.4	7	13	2.8	1.0–7.3

[a] Adjusted for age, smoking, and alcohol consumption.
[b] The medium- and high-intensity groups were merged due to the small number of cases.

Table 4. Risk of laryngeal cancer by exposure probability levels and anatomic location. (OR=odds ratio, 95% CI=95% confidence interval)

Exposure	All laryngeal cancers				Supraglottic cancer				Glottic cancer				Other cancers			
	Cases (N)	Referents (N)	OR [a]	95% CI	Cases (N)	Referents (N)	OR [a]	95% CI	Cases (N)	Referents (N)	OR [a]	95% CI	Cases (N)	Referents (N)	OR [a]	95% CI
Silica dust																
Low probability	19	37	0.8	0.5–1.5	8	37	0.8	0.4–1.7	6	37	1.0	0.4–2.5	5	37	0.7	0.3–1.8
Medium probability	83	101	1.5	1.1–2.0	45	101	1.7	1.2–2.6	14	101	1.0	0.6–1.8	24	101	1.5	0.9–2.4
High probability	84	89	1.8	1.3–2.5	47	89	2.3	1.5–3.3	14	89	1.3	0.7–2.3	23	89	1.7	1.1–2.8
Asbestos																
Low probability	121	176	1.2	0.9–1.5	58	176	1.2	0.9–1.7	23	176	0.9	0.6–1.5	40	176	1.4	1.0–2.1
Medium probability	20	51	0.6	0.4–1.1	8	51	0.5	0.3–1.1	3	51	0.4	0.1–1.2	9	51	1.0	0.5–2.1
High probability	9	23	0.7	0.3–1.5	5	23	0.8	0.3–2.1	2	23	0.6	0.1–2.4	2	23	0.5	0.1–2.1
Wood dust																
Low probability	81	108	1.3	1.0–1.7	41	108	1.4	1.0–2.1	14	108	0.9	0.5–1.6	26	108	1.4	0.9–2.3
Medium probability	19	29	1.4	0.7–2.5	9	29	1.4	0.7–3.1	4	29	1.3	0.4–3.8	6	29	1.4	0.6–3.5
High probability	9	36	0.4	0.2–0.9	5	36	0.5	0.2–1.3	3	36	0.6	0.2–2.1	1	36	0.2	0.0–1.2
Cotton dust [b]																
Low probability	53	74	1.3	0.9–1.9	29	74	1.5	1.0–2.4	10	74	1.1	0.5–2.2	14	74	1.2	0.7–2.2
Medium + high probability	–				–				–				–			
Grain dust [b]																
Low probability	17	24	1.2	0.6–2.2	7	24	1.1	0.4–2.5	4	24	1.4	0.5–4.1	6	24	1.6	0.6–4.0
Medium + high probability	14	13	1.4	0.7–3.2	6	13	1.2	0.4–3.3	1	13	0.4	0.1–2.9	7	13	2.5	1.0–6.6

[a] Adjusted for age, smoking, and alcohol consumption.
[b] Medium- and high-probability groups were merged due to small number of cases.

dose-response relationship between silica exposure and supraglottic laryngeal cancer also remained significant (OR 0.8, 1.7, and 2.3, respectively) ($\chi^2_{trend} = 19.1$ P<0.001).

To eliminate possible intensity misclassification from a low-level exposure probability group, we analyzed the risk of laryngeal cancer from silica exposure intensity levels by separating the low probability

Table 5. Risk of supraglottic laryngeal cancer by silica intensity and probability levels.[a] (OR=odds ratio, 95% CI=95% confidence interval)

	Probability															
	All laryngeal cancers								Supraglottic							
	Low exposure				Medium + high exposure				Low exposure				Medium + high exposure			
Intensity	Cases (N)	Referents (N)	OR	95% CI	Cases (N)	Referents (N)	OR	95% CI	Cases (N)	Referents (N)	OR	95% CI	Cases (N)	Referents (N)	OR	95% CI
Low	17	26	1.1	0.6–2.1	31	43	1.7	1.0–2.7	6	26	0.9	0.4–2.2	16	43	1.9	1.0–3.4
Medium	2	11	0.3	0.1–1.3	92	103	1.6	1.2–2.2	2	11	0.6	0.1–2.7	49	103	2.0	1.3–2.8
High	–				44	44	1.7	1.1–2.6	–				27	44	2.2	1.3–3.6

group from the medium + high probability groups. An excess risk of supraglottic cancer remained for the medium + high probability groups regardless of the intensity level (table 5). There were insufficient numbers of exposed cases to perform a similar analysis for cotton dust.

Discussion

In an earlier paper we identified several occupations with possible dust exposure that appeared to increase the risk of laryngeal cancer, especially supraglottic tumors (10). In this report we evaluated the risk of laryngeal cancer for selected occupational dust exposures (ie, asbestos, silica, cotton, grain, and wood) using a job-exposure matrix specifically developed for this investigation. Supraglottic laryngeal cancer was associated with possible exposure to silica and cotton dust.

Although it is categorized as a lung carcinogen, few studies have mentioned silica exposure as a risk factor for laryngeal cancer (17). A high rate of laryngeal cancer was noted in a Mediterranean area where silica exposure is also one of the most common occupational exposures (18). Laforest et al (19) found no significant association between laryngeal cancer and silica exposure, but three other studies suggested a possible relationship between silica exposure and laryngeal cancer without examining the occupational risk in relation to the anatomic location of the tumors (7, 20, 21). In our previous study, we found an increased risk of laryngeal cancer among extractive workers, street cleaners, and, especially, construction workers who had an excess risk of supraglottic tumors (10). They are likely to have had silica exposure. A recent study of the construction industry in the United States reported silica levels for 8- to 10-hour workday estimations up to 280 times higher than the recommended exposure limit (REL) of 0.05 mg/m^3 of the National Institute for Occupational Safety and Health (22). Various other occupational factors, such as diesel exhaust exposure and radioactivity, have also been reported as etiologic factors of laryngeal cancer among workers prone to silica exposure, and they can be considered as possible confounders for our results (23, 24).

We found no excess risk among asbestos-exposed workers. Laryngeal cancer and asbestos exposure has been evaluated in some studies. Several studies including a cohort of Quebec chrysotile workers found no association between laryngeal carcinoma and asbestos exposure (25–32). In a review it was concluded that neither the longitudinal or cross-sectional data could support asbestos as an etiologic factor for laryngeal cancer (33). Other studies, however, suggested asbestos exposure as a possible risk factor (4, 34–35). The difficulty of identifying and estimating asbestos exposure may have prevented us from observing a relationship between asbestos exposure and laryngeal cancer; further investigations would be helpful to clarify the role of asbestos exposure in the etiology of laryngeal cancer.

We saw some evidence of an excess risk of laryngeal cancer, particularly for supraglottic tumor, among the subjects with high-level exposure to cotton dust. In our previous report, we found an excess risk of supraglottic tumors among blue-collar textile workers exposed to cotton dust among their occupational exposures (10). The bacterial endotoxins found in cotton dust induce the release of the tumor necrosis factor (TNF-α) interferon and stimulate mitogenic and macrophage activity, which play an important protective role against lung cancer among cotton workers (37, 38). This protective activity of endotoxins may not apply to laryngeal cancer. There was a significant increase in the number of deaths from laryngeal cancer among cotton-exposed workers in a recent cohort study (39).

We did not observe any risk of laryngeal cancer with exposure to grain and wood dusts. Few studies have evaluated the risk of laryngeal cancer for these exposures and some reported an increased or slightly elevated risk of laryngeal cancer with wood dust exposure (40, 41), but most of the studies did not (4,

19, 35, 42). The International Agency for Research on Cancer (IARC) concluded that wood dust exposure increases the risk of paranasal and hypopharyngeal cancer, but not laryngeal carcinoma (43).

This study offered the opportunity to evaluate the role of some occupational dusts in the etiology of laryngeal cancer, but the study limitations should be considered. We had no actual monitoring data for occupational exposures and duration of exposure. Consequently the misclassification of exposure was a concern. In addition, the SOC and SIC classifications may have been biased due to age differences between the cases and referents, such that older cases were likely to have worked longer years than the referents, which may have increased the probability of occupational exposure. But further evaluation showed that there was a negligible difference between the average number of job titles among the cases and referents. A strength, however, is that the development of the job-exposure matrix was carried out by an experienced industrial hygienist familiar with the industrial settings in Turkey. Previous assessments indicate that intensity misclassification mostly occurred in the low probability of exposure groups (14). In an effort to eliminate any possible risk of intensity misclassification, we analyzed the risk of laryngeal cancer from exposure intensity by separating the low probability and medium + high probability groups (table 5). Excess remained for supraglottic tumors, as well as all for laryngeal cancers, in the medium + high probability silica-exposed groups; this finding supports a possible relationship between silica exposure and laryngeal cancer. The lack of a full-set of population-based referents could also have been a limitation. However, cancer referents have been effectively used in other studies (44). Our analyses using the noncancer patients for referents did not show any significant differences from the odds ratios based on cancer referents. Although we had some information on alcohol and tobacco use, the level of consumption was not available for about 50% of the subjects. We controlled logistic models by ever-never use of tobacco and alcohol and observed a slight decease in the odds ratios. Comparing the smoking ever-never and alcohol ever-never groups independently showed that the odds ratio for silica exposure was slightly higher among the smokers than among the nonsmokers and among the alcohol users than among the nonalcohol users. According to these further evaluations, our results should be interpreted cautiously, given the possibility of residual confounding. However, previous reports have found few examples of confounding by tobacco use and occupational risk of cancer (45, 46).

The major strength of our study was the large number of larynx cancer cases from a developing country; this large number provided the opportunity to evaluate occupational risks by the anatomic location of tumor. Occupational exposures in Turkey may be greater than in developed countries, where most previous studies on occupation and laryngeal cancer have been conducted. Modified 7-digit SOC and SIC codes gave us a chance to examine occupations and industries intensely.

In summary, we found an excess risk of laryngeal cancer among workers exposed to silica and cotton dust in a large study in Turkey. Our analyses by the anatomic location of the cancers showed a particularly strong association with supraglottic larynx cancer. We observed a significant dose-response relationship for supraglottic cancer with silica exposure intensity and probability. Future studies should evaluate the biomechanism of occupational exposures and their relationship to cancer in different anatomic regions of the larynx.

Acknowledgments

The authors wish to thank Dr Michael D Attfield for his review and comments on the statistical analyses and Molly Picket-Harner for her effort in editing the language of this report.

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Received for publication: 5 October 2001