Carcinoma of the Pharynx and Tonsils in an Occupational Cohort of Asphalt Workers

Francesca Zanardi,[a] *Renata Salvarani,*[b] *Robin M.T. Cooke,*[a] *Roberta Pirastu,*[c] *Michela Baccini,*[d] *David Christiani,*[e] *Stefania Curti,*[a] *Alessandro Risi,*[f] *Anna Barbieri,*[a] *Giuseppe Barbieri,*[b] *Stefano Mattioli,*[a] *and Francesco Saverio Violante*[a]

Background: We investigated a possible association between pharyngeal/tonsillar carcinoma and mixed carcinogen exposures in an asphalt roll company in Italy that used asbestos until 1979, when a new factory was built using a different production process.

Methods: We evaluated all workers involved in the entire production history of the company, divided into two subcohorts based on exposure status (workers in the original factory, 1964–1979, and those who worked only in the new factory, 1980–1997). We ascertained the vital status of the study population in February 2001.

Results: Among the subset of workers in the earlier subcohort, there were five deaths from pharyngeal/tonsillar carcinoma for a standardized mortality ratio of 21 (95% confidence interval = 8.8–51). No cases were recorded among workers hired after 1979.

Conclusion: The increased standardized mortality ratio for this relatively rare cancer among workers exposed before 1979 may have been due to carcinogenic exposures at the plant.

(*Epidemiology* 2013;24: 100–103)

Submitted 10 June 2011; accepted 28 September 2012.

From the [a]Section of Occupational Medicine, Department of Internal Medicine, Geriatrics and Nephrology, Alma Mater Studiorum-University of Bologna, Bologna, Italy; [b]Occupational Health Unit, Bologna Local Health Authority, San Giorgio di Piano, Bologna, Italy; [c]Department of Biology and Biotechnology "Charles Darwin," La Sapienza University of Rome, Rome, Italy; [d]Department of Statistic, University of Florence, Florence, Italy; [e]Harvard University, Environmental Health and Epidemiology Departments, Boston, MA; and [f]Occupational Medicine Service, Alma Mater Studiorum-University of Bologna, Bologna, Italy.

Supported by INAIL (Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro) Direzione Regionale Emilia-Romagna, Bologna, Italy; Regione Emilia-Romagna (Emilia-Romagna Regional Administration), Bologna, Italy; and the University of Bologna. The work of F.Z. was partially supported by the Epidemiology Master's course at the University of Turin.

The authors report no conflict of interests.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com). This content is not peer-reviewed or copy-edited; it is the sole responsibility of the author.

Correspondence: Stefano Mattioli, Unità Operativa di Medicina del Lavoro, Policlinico S. Orsola-Malpighi, via Pelagio Palagi 9, I-40138 Bologna, Italy. E-mail: s.mattioli@unibo.it.

ISSN: 1044-3983/13/2401-0100
DOI: 10.1097/EDE.0b013e318276cc95

Pharyngeal carcinoma is relatively uncommon, most often present in men in the 6th or 7th decade of life.[1] Recently, its incidence has increased in developing countries.[2] Tobacco and alcohol are important risk factors, along with environmental, genetic, and viral factors.[3–7] Occupational associations between exposure to well-defined carcinogens, such as asbestos or polycyclic aromatic hydrocarbons (PAHs), and cancer of the pharynx have been suggested by several studies.[8–11] We investigated a possible association of pharyngeal/tonsillar carcinoma and mixed carcinogen exposures in a factory that produced asphalt rolls containing asbestos.

METHODS

Study Design

We conducted an occupational cohort study in which we evaluated all the workers—including subcontracted warehouse workers—involved in the 33-year production history of the company (based in the Emilia-Romagna region of Italy) from its first day of production on 7 January 1964 until the closure of the plant on 7 February 1997. We ascertained the vital status of the study population on 7 February 2001. Information on the workplace and available exposure and health monitoring data is summarized in the eAppendix, http://links.lww.com/EDE/A627 (part 1). In 1979, the original factory was closed because of a fire, and the management agreed to eliminate asbestos from all production processes. Production of asphalt roofing rolls resumed in 1980 in a new factory constructed nearby and broadly in line with modern occupational health and safety standards. These changes allowed us to evaluate two subcohorts of workers based on exposure status: (1) those who started work between January 1964 and June 1979, who were exposed to the old factory in which asbestos was used; (2) those who worked only in the new factory (ie, after June 1979). We assessed cause-specific mortality experienced by these two subcohorts, calculating standardized mortality ratios (SMRs) for carcinoma of the lip, oral cavity, and pharynx (international classification of disease ICD-9, 140–149).

Data Collection and Statistical Analysis

We used company records to extract job history information of all workers. For each cohort member, we sent survey cards to local government offices to ascertain vital status and current residence or, for those who had died, date, place, and

cause of death. We requested copies of death certificates for the deceased and embarkation details for workers who had left the country. In each subcohort, subgroups of workers were categorized by occupational exposure characteristics, based on job descriptions contained in factory inspection reports: blue-collar production sector workers (including subcontracted warehouse workers); other blue-collar workers; white-collar workers. This assessment was made without knowledge of case status.

We used Student's *t* test to compare the mean age at initial employment and the mean duration of employment between the two subcohorts. We tabulated observed cause-specific deaths alongside expected numbers specific for sex, age, and calendar period (5-year classification); we then calculated the SMR in the entire cohort, based on mortality rates in the resident population of the Emilia-Romagna region.[11] For cause-specific categories of interest (death from all causes; all cancers; cancer of the lip, oral cavity, and pharynx; gastric carcinoma; lung cancer; cardiovascular diseases), we also calculated SMR by subcohort (before or after 1979), occupational exposure (production-line, other blue-collar, white-collar), and latency. For all estimates, we used the Poisson distribution to calculate 95% confidence intervals (CIs).[12] All analyses were conducted using Stata 11.0 (Stata Corporation, Texas, TX).

RESULTS

Study Cohort

The study cohort comprised 415 workers, including 52 subcontracted warehouse workers who were occupationally exposed to the production sector. The majority of workers (71%, $n = 295$) were in the subcohort who worked in the old factory.

Table 1 shows the occupational characteristics of the subcohorts. Mean age at initial employment was 29.3 years in both subcohorts. Mean number of working years was greater in the earlier subcohort (overall, 10.6 vs. 3.6 years; among production-line workers, 11.6 vs. 4.5 years).

Outcome

Vital status at the end of follow-up is reported in Table 2; loss to follow-up was 1.2% (5/415). Forty deaths were recorded during a total of 9948 person-years of follow-up. Cancer was the most common underlying cause of death (63%, 25/40). Carcinoma of the pharynx/tonsils caused 5 (25%) of the cancer-related deaths (eTable 1, http://links.lww.com/EDE/A627); although health officials were aware of three cases, an additional two cases were uncovered during survival data collection. Cause-specific SMRs for the entire cohort are presented in eTable 2 (http://links.lww.com/EDE/A627). Among the group of workers exposed to the production sector where asbestos was used, the SMR for carcinoma of the lip, oral cavity, and pharynx was 21 (95% CI = 8.8–51; Table 3).

We also recorded an approximately threefold excess mortality rate for gastric cancer, but no evidence of increased mortality from lung cancer or cardiovascular diseases. Mantel-Haenszel estimates of rate ratios adjusted for latency and cause-specific SMRs according to latency are presented in eTables 3 and 4 (http://links.lww.com/EDE/A627).

TABLE 1. Occupational Characteristics of the Entire Cohort and the Two Main Subcohorts

	Entered Employment Before June 1979			Employed Only After June 1979		
	Men No.	Women No.	Total No.	Men No.	Women No.	Total No.
Blue-collar workers exposed to the production line	104	0	104	41	0	41
Production-line workers	67	0	67	26	0	26
Smelters	17	0	17	5	0	5
Pasters	11	0	11	0	0	0
Rollers	37	0	37	21	0	21
Shredding machine operators	2	0	2	0	0	0
Subcontracted warehouse workers (handling raw materials)	37	0	37	15	0	15
Nonproduction-line blue-collar workers	60	3	63	17	1	18
End-product warehouse workers (not handling raw materials)	9	0	9	6	0	6
Machinery operators	11	0	11	0	0	0
Factory maintenance staff	21	0	21	1	0	1
Other[a]	19	3	22	10	1	11
White-collar workers	75	53	128	46	15	61
Office clerks	21	35	56	13	3	16
Representatives	54	18	72	33	12	45
Total	239	56	295	104	16	120

[a]Supervisors, technicians, maintenance workers, canteen workers, office cleaning staff, resident porter/night watchman.

TABLE 2. Vital Status on 7 February 2001 and Person-Years of Follow-Up

	Men (n = 343)	Women (n = 72)	Overall (n = 415)
Alive	298	72	370
Dead	40	—	40
From known causes	39	—	39
From unknown cause	1	—	1
Lost to follow-up	5	—	5
Person-years	8,156	1,792	9,948
Up to 40 years of age	4,612	1,543	6,155
After 40 years of age	3,544	249	3,793

DISCUSSION

Cohort analysis of a small cluster of cases of a rare cancer in a single factory can be hypothesis-generating. The SMR was so likely increased (a 21-fold excess) that we have grounds to believe that the associations observed are unlikely to be due to chance, even if it is not clear which of the various occupational exposures could be implicated.

The study had been initiated after specific concerns about widespread chronic inflammatory diseases of the upper airways among the production-line workers and a cluster of cases of cancer of the pharynx/tonsils. All five subjects affected by cancer of the pharynx/tonsils were among the well-defined production-line workers who experienced, in the old factory, heavy industrial coexposure to a mixture of chrysotile asbestos fibers, bitumen fumes, solvents, PAH, and other dusts, all of which can be carcinogenic.[13–18]

Multiple chemical factors found in bitumen fumes could combine to influence the onset of neoplastic disease.[19–21] As in most historical cohort studies, we were unable to distinguish the work-related etiologic contribution from individual factors[1,8,22] such as smoking and low socioeconomic status. All five workers shared a relatively young age of onset, within 10

TABLE 3. Cause-Specific SMR in the Two Subcohorts Stratified by Occupational Category (Reference Population, Regione Emilia-Romagna)

	Entered Employment Before June 1979			Employed Only After June 1979		
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
All causes						
Overall	34	40.8	0.8 (0.6–1.2)	6	5.5	1.1 (0.5–2.4)
Blue-collar workers on the production line	26	22.5	1.2 (0.8–1.7)	3	2.0	1.5 (0.5–4.6)
Nonproduction-line blue-collar workers	6	11.5	0.5 (0.2–1.2)	1	0.6	1.7 (0.2–11.9)
White-collar workers	2	6.8	0.3 (0.1–1.2)	2	2.9	0.7 (0.2–2.8)
All cancers						
Overall	23	15.7	1.5 (1.0–2.2)	2	1.9	1.1 (0.3–4.2)
Blue-collar workers on the production line	22	8.6	2.6 (1.7–3.9)	1	0.7	1.4 (0.2–9.9)
Nonproduction-line blue-collar workers	1	4.5	0.2 (0.03–1.57)	0	0.2	—
White-collar workers	0	2.6	—	1	1.0	1.0 (0.1–7.2)
Lip, oral cavity, and pharynx cancer						
Overall	5	0.4	11.4 (4.8–27.4)	0	0.06	—
Blue-collar workers on the production line	5	0.2	21.1 (8.8–50.7)	0	0.02	—
Nonproduction-line blue-collar workers	0	0.1	—	0	0.01	—
White-collar workers	0	0.1	—	0	0.03	—
Stomach cancer						
Overall	5	1.6	3.0 (1.3–7.3)	0	0.2	—
Blue-collar workers on the production line	5	0.9	5.3 (2.2–12.8)	0	0.06	—
Nonproduction-line blue-collar workers	0	0.5	—	0	0.01	—
White-collar workers	0	0.2	—	0	0.09	—
Trachea, bronchus, and lung cancer						
Overall	5	5.0	1.0 (0.4–2.4)	0	0.6	—
Blue-collar workers on the production line	4	2.9	1.4 (0.5–3.7)	0	0.2	—
Nonproduction-line blue-collar workers	1	1.5	0.7 (0.1–4.8)	0	0.1	—
White-collar workers	0	0.7	—	0	0.3	—
Circulatory system diseases						
Overall	7	13.0	0.5 (0.3–1.1)	0	1.3	—
Blue-collar workers on the production line	3	7.8	0.4 (0.1–1.2)	0	0.5	—
Nonproduction-line blue-collar workers	4	3.7	1.1 (0.4–2.9)	0	0.1	—
White-collar workers	0	1.5	—	0	0.7	—

years of first being hired at the plant. By contrast, no further case of cancer of the pharynx or oral cavity emerged among the subcohort of workers exposed only to the new factory, in which there was little or no use of asbestos and presumably much lower levels to bitumen fumes, solvents, PAH, and dusts.

Absence of excess rates of lung cancer, especially in the "exposed" subcohort in which the follow-up was longer, is in line with a large International Agency for Research on Cancer study, which showed no evidence of bitumen causing lung cancer.[23] Similarly, the apparent excess in gastric cancer among the production-line workers in the exposed subcohort could either reflect the increased risks reported for asphalt workers in general[24–26] or be related to a particular coexposure. A healthy worker effect was observable in both subcohorts. However, the hypothesis that the particular conditions found in the original factory constituted a risk factor for pharyngeal/oral cancer (and probably also gastric cancer) is reinforced by the observation that within the highly exposed production-line workers of the earlier subcohort, cause-specific SMRs were remarkably increased for these particular cancers, but not for other causes of death such as cardiovascular disease.

Study Limitations

The limited exposure information did not allow dose-response analysis and hampered formulation of more detailed etiologic hypotheses. The small number of person-years and the relatively short follow-up impeded assessment of tumors with a long latency, such as mesothelioma.

In summary, we observed a cluster of pharyngeal/tonsillar carcinoma among workers exposed to the production sector of a factory producing asphalt rolls when asbestos was being used as a binding agent. The magnitude of the SMR for this rare type of cancer suggests that the events may not have been due to chance. Although it is unclear which mixed carcinogen exposures were implicated, these observations may be relevant to the etiology of pharyngeal/tonsillar carcinoma. Industrial cohort studies in settings in which asbestos was used in asphalt production could provide further information regarding the cancer-related risks associated with similar industrial mixed carcinogen exposures.

ACKNOWLEDGMENTS

We thank Chiara Scardoni for translation work.

REFERENCES

1. Parkin DM, Whelan S, Ferlay J, Teppo L, Thomas DB. *Cancer Incidence in Five Continents. Vol. VIII*. Lyon, France: International Agency for Research on Cancer. Sci Publ. No l55. 2002:364–365.
2. Franceschi S, Bidoli E, Herrero R, Muñoz N. Comparison of cancers of the oral cavity and pharynx worldwide: etiological clues. *Oral Oncol*. 2000;36:106–115.
3. IARC. *Tobacco Smoking. Monographs on the Evaluation of Carcinogenic Risks to Human*. Vol. 38. Lyon, France: International Agency for Research on Cancer; 1986.
4. IARC. *Alcohol Drinking. Monographs on the Evaluation of Carcinogenic Risks to Humans*. Vol. 44. Lyon, France: International Agency for Research on Cancer; 1988.
5. IARC. *Tobacco Smoking and Involuntary Smoking. Monographs on the Evaluation of Carcinogenic Risks to Human*. Vol. 83. Lyon, France: International Agency for Research on Cancer; 2003.
6. IARC. *Formaldehyde, 2-Butoxyethanol and 1-tert-Butoxy-2-propanol. Monographs on the Evaluation of Carcinogenic Risks to Humans*. Vol. 88. Lyon, France: International Agency for Research on Cancer; 2004.
7. Mucci L, Adami HO. Oral and pharyngeal cancer. In: Trichopoulos D, Adami HO, Hunter D, eds. *Textbook of Cancer Epidemiology*. New York, NY: Oxford University Press; 2002:115–128.
8. Berrino F, Richiardi L, Boffetta P, et al. Milan JEM Working Group. Occupation and larynx and hypopharynx cancer: a job-exposure matrix approach in an international case-control study in France, Italy, Spain and Switzerland. *Cancer Causes Control*. 2003;14:213–223.
9. Gustavsson P, Jakobsson R, Johansson H, Lewin F, Norell S, Rutkvist LE. Occupational exposures and squamous cell carcinoma of the oral cavity, pharynx, larynx, and oesophagus: a case-control study in Sweden. *Occup Environ Med*. 1998;55:393–400.
10. Marchand JL, Luce D, Leclerc A, et al. Laryngeal and hypopharyngeal cancer and occupational exposure to asbestos and man-made vitreous fibers: results of a case-control study. *Am J Ind Med*. 2000;37:581–589.
11. Straif K, Benbrahim-Tallaa L, Baan R, et al. WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens–part C: metals, arsenic, dusts, and fibres. *Lancet Oncol*. 2009;10:453–454.
12. Checkoway H, Pearce N, Kriebel D. *Research Methods in Occupational Epidemiology*. 2nd ed. Oxford, UK: Oxford University Press; 2004.
13. Binet S, Pfohl-Leszkowicz A, Brandt H, Lafontaine M, Castegnaro M. Bitumen fumes: review of work on the potential risk to workers and the present knowledge on its origin. *Sci Total Environ*. 2002;300:37–49.
14. Boffetta P, Burstyn I. Studies of carcinogenicity of bitumen fume in humans. *Am J Ind Med*. 2003;43:1–2.
15. Boffetta P, Burstyn I, Partanen T, et al. Cancer mortality among European asphalt workers: an international epidemiological study. I. Results of the analysis based on job titles. *Am J Ind Med*. 2003;43:18–27.
16. Burstyn I, Randem B, Lien JE, Langård S, Kromhout H. Bitumen, polycyclic aromatic hydrocarbons and vehicle exhaust: exposure levels and controls among Norwegian asphalt workers. *Ann Occup Hyg*. 2002;46:79–87.
17. Herrick RF, McClean MD, Meeker JD, Zwack L, Hanley K. Physical and chemical characterization of asphalt (bitumen) paving exposures. *J Occup Environ Hyg*. 2007;4(suppl 1):209–216.
18. Wang J, Lewis DM, Castranova V, et al. Characterization of asphalt fume composition under simulated road paving conditions by GC/MS and microflow LC/quadrupole time-of-flight MS. *Anal Chem*. 2001;73:3691–3700.
19. Finkelstein MM. Asbestos-associated cancers in the Ontario refinery and petrochemical sector. *Am J Ind Med*. 1996;30:610–615.
20. Melius J. Asphalt–a continuing challenge. *Am J Ind Med*. 2003;43:235–236.
21. Schulte PA. Gaps in scientific knowledge about the carcinogenic potential of asphalt/bitumen fumes. *J Occup Environ Hyg*. 2007;4(suppl 1):3–5.
22. Friborg JT, Yuan JM, Wang R, Koh WP, Lee HP, Yu MC. A prospective study of tobacco and alcohol use as risk factors for pharyngeal carcinomas in Singapore Chinese. *Cancer*. 2007;109:1183–1191.
23. Agostini M, Ferro G, Olsson A, et al. Exposure assessment for a nested case-control study of lung cancer among European asphalt workers. *Ann Occup Hyg*. 2010;54:813–823.
24. Hansen ES. Cancer incidence in an occupational cohort exposed to bitumen fumes. *Scand J Work Environ Health*. 1989;15:101–105.
25. Stücker I, Meguellati D, Boffetta P, Cénée S, Margelin D, Hémon D. Cohort mortality study among French asphalt workers. *Am J Ind Med*. 2003;43:58–68.
26. Cocco P, Ward MH, Dosemeci M. Risk of stomach cancer associated with 12 workplace hazards: analysis of death certificates from 24 states of the United States with the aid of job exposure matrices. *Occup Environ Med*. 1999;56:781–787.