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Original article

Work-related laryngeal cancer: Trends in France from 2001 to 2016

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ABSTRACT

Objectives: As part of the 2014–2019 cancer plan and in order to improve our knowledge of work-related cancers, we analysed the work-related laryngeal cancer risk situations identified in the French national occupational disease surveillance and prevention network (rnv3p) from 2001 to 2016.
Material and methods: This study focused on cases of work-related laryngeal cancer, which the expert physician considered to be directly related to exposure (intermediate or strong causal relationship). Demographic data, occupational exposure circumstances (hazards, occupation, business sector), non-occupational risk factors and the occupational physician's opinion concerning notification as an occupational disease were analysed.
Results: Two hundred forty-four cases of laryngeal cancer were registered between 2001 and 2016. One hundred and forty seven cases were considered to be work-related, with an intermediate or strong causal relationship in 87 cases. This exclusively male population had a median age of 59 years. Ninety-seven different forms of exposure were identified, including asbestos in 78 cases. The main business sectors concerned were specialized construction (14 cases) and metallurgy (7 cases). Occupational disease notification was recommended in 60 patients, corresponding to asbestos exposure in 80% of cases.
Conclusions: Asbestos is the laryngeal cancer risk factor most commonly reported in the network from 2001 to 2016. This study confirms the role of asbestos in laryngeal carcinogenesis. Laryngeal cancer may therefore need to be compensated as an occupational disease in France, as in other European countries.

1. Introduction

Occupational cancers are currently underestimated in France, as workplace exposure to carcinogens can sometimes be complex to identify in a context of multiple exposures or ignorance concerning certain high-risk situations [1]. The French Sumer 2010 survey (medical surveillance of exposure to occupational risks) identified about 2.2 million workers exposed to at least one chemical carcinogen in 2010 [2]. One of the objectives of the 2014–2019 cancer plan concerns the prevention of work-related cancers, particularly with action 12.4 designed to improve our knowledge concerning these aetiologies and provide support for epidemiological surveillance of work-related cancers (INCa. 2014–2019 cancer plan. Institutional documents collection/Cancer Plan. February 2015). The objective of this plan is especially to improve the knowledge of cancers according to occupation and business sector by reinforcing the notification and data analysis circuit of the national occupational disease surveillance and prevention network (rnv3p). The rnv3p is a French national network comprising 30 Centres de Consultation de

Abbreviations: ANSES:, Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail [French Agency for Food, Environmental and Occupational Health and Safety]; CCPP:, Occupational Disease Centre; CNIL:, Commission nationale de l'informatique et des libertés [French data protection agency]; IARC:, International Agency for Research on Cancer; CRRMP:, Comité régional de reconnaissance des maladies professionnelles [Regional Occupational Disease Compensation Committee]; PAH:, Polycyclic aromatic hydrocarbons; ICARE:, Investigations sur les cancers respiratoires et l'environnement professionnel [Investigations on respiratory cancers and the workplace]; INCa:, Institut national du cancer [French national cancer institute]; IP:, Incapacité permanente [Permanent disability]; Rnv3p:, Réseau national de vigilance et de prévention des pathologies professionnelles [national occupational disease surveillance and prevention network]; SMR:, Standardized Mortality Ratio; Sumer:, Surveillance médicale des expositions aux risques professionnels [Medical surveillance of exposure to occupational risks].

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Pathologie Professionnelle (CCPP) [occupational diseases centres] [3].

In the context of the cancer plan objectives, Santé Publique France and the Institut National du cancer (INCa) [French National Cancer Institute] asked the French National Agency for Food, Environmental and Occupational Health and Safety (Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail, ANSES) to pilot the rnv3p network. Data from the network were analysed in order to describe the occupational exposures identified as being at increased risk for each type of cancer. In this context, the present study focused on laryngeal cancer.

Various risk factors are involved in the pathogenesis of laryngeal cancer. The non-occupational aetiologies include smoking and drinking, with a synergistic effect of cumulative consumption [4–6]. Papillomavirus type 16 (HPV 16) infection can also predispose to laryngeal cancer, but with only a limited level of evidence [7,8].

Occupational risk factors for laryngeal cancer with a sufficient level of evidence include the following agents:

- asbestos: the International Agency for Research on Cancer (IARC) has classified asbestos as a group 1[1] carcinogen for the larynx since 2009 [9]. The relationship between asbestos and laryngeal cancer has been demonstrated in numerous studies [10–17], including a recent meta-analysis (Peng et al.) that reported a Standardized Mortality Ratio (SMR) of 1.69 (95%CI [1.45–1.97]) [16];
- mists from strong inorganic acids, classified as group 1 carcinogens since 2012 [18].

Other occupational exposures could also predispose to the development of laryngeal cancer, but with lower levels of evidence, including polycyclic aromatic hydrocarbons (PAH) [17,19,20], engine exhaust [17,21], working in the rubber industry (also classified as group 1 carcinogens by the IARC, but with limited evidence for man in relation to laryngeal cancer [18]), textile dusts, as well as mineral wool [17].

There is no occupational disease table allowing workers' compensation for laryngeal cancer in France. Nevertheless, laryngeal cancer can be recognized as an occupational disease, based on a case-by-case assessment by regional structures called Comités régionaux de reconnaissance des maladies professionnelles (CRRMP) [regional occupational disease compensation committees]. In this context, only health states associated with at least 25% permanent disability can be examined by the CRRMP. The degree of disability is evaluated by the social welfare consultant physician when the patient's health state is consolidated. A patient with laryngeal cancer may be attributed a degree of disability higher than, equal to or less than 25% depending on the sequelae of the disease. Consequently, not all cases of laryngeal cancer are systematically considered to be responsible for a sufficient degree of disability to qualify for occupational disease recognition by the CRRMP. In 2015, only 5 cases of laryngeal cancer in the general scheme in France were granted workers' compensation (CNAMTS. Risque Maladie professionnelle: Sinistralité de l'année 2015 par CTN, code NAF, tableau de MP et syndrome. December 2016).

In order to provide new data and to address the cancer plan action concerned, we studied and analysed occupational situations at high risk of laryngeal cancer identified in the rnv3p database between 2001 and 2016.

[1] The IARC classifies agents into 4 categories on the basis of available scientific data:roup 1: Carcinogenic to humansroup 2A: Probably carcinogenic to humansroup 2B: Possibly carcinogenic to humansroup 3: Not classifiable as to its carcinogenicity to humansroup 4: Probably not carcinogenic to humans

2. Material and methods

The rnv3p, the French national occupational disease surveillance and prevention network, was created in 2001. It comprises 30 occupational disease centres, mostly located in university hospitals. These clinics systematically enter data into a national database.

Patients are referred to occupational disease centres by occupational health physicians, general practitioners or specialists for various reasons: request for expert opinion by the occupational health physician concerning the patient's medical fitness for his or her work, assistance with occupational disease recognition, demonstration of a link between the patient's occupation and health state or for post-exposure follow-up.

After each occupational health clinic consultation, the occupational health physician ensures coding in a secure national work-related health problems database. A work-related health problem comprises three types of information:

- the patient's disease (coded according to the International Classification of Diseases, Tenth Revision, ICD-10);
- occupational exposures (substances, agents, products, equipment, etc.) with evaluation of the causal relationship between each exposure and the disease, evaluated as absent, weak, intermediate or strong;
- the occupation in which the patient was exposed, including the business sector (according to the French Insee business sector nomenclature, 2008 revision, NAF-08) and the occupation (according to the International Labour Organization International Standard Classification of Occupations, 2008 revision, CITP-08).

A work-related health problem can therefore be linked to one or more occupational exposures. When a case is considered by the expert physician to be an occupational disease, it is no longer defined as a work-related problem, but a work-related disease. The physician also expresses his/her opinion concerning a possible occupational disease notification. When the case does not justify occupational disease notification, the reason for this decision is indicated as follows:

- disease not classified in the occupational disease tables with a predictable permanent disability of less than 25%;
- absence of risk management: the patient is not covered by a social welfare scheme allowing access to occupational disease recognition;
- insufficient clinical data: either due to insufficiently precise data concerning the diagnosis, but for which the link with occupational exposure cannot be excluded, or due to insufficient occupational exposure in terms of intensity or duration, but nevertheless suspected to be responsible for the disease, or the presence of cofactors not justifying presentation to the CRRMP according to the doctor;
- insufficient scientific data: data of the literature at the time of the consultation do not show a sufficient link to support occupational disease recognition by the CRRMP.

The practitioner must also complete a free text comment, especially in order to specify any occupational or non-occupational risk factors. Extraction of data from rnv3p was performed on the database locked on 10/05/2017 and concerned all cases reported between 2001 and 2016 for which the principal diagnosis was coded by the following ICD-10 codes: D02.0 (carcinoma in situ of larynx), C32 (malignant neoplasm of larynx) with C32.0 (glottis), C32.1 (supraglottis), C32.2 (subglottis), C32.3 (laryngeal cartilage), C32.8 (overlapping lesion of larynx), C32.9 (malignant neoplasm of larynx, unspecified).

Cases of work-related laryngeal cancer with at least one exposure considered by the occupational physician to be directly related to the disease, coded as strong (direct and essential causal relationship) or intermediate (direct but not essential causal relationship).

The variables recorded for the patients concerned were therefore sociodemographic data (age, sex), occupational exposures, occupation, business sector, and the physician's opinion concerning possible occupational disease notification. The comments recorded by the physician were analysed one by one to identify any non-occupational risk factors, such as smoking and drinking, when this information was available.

Data extraction was performed with R software (version 3.4.x) on the rnv3p Oracle database (version 11.x). The quality of the data coded was optimized by the use of a computerized coding tool, centralized controls and regular organization of a coding school in order to ensure a certain degree of homogeneity between centres. The rnv3p obtained Commission nationale de l'informatique et des libertés (CNIL) (French data protection authority) permission in 2011 for the follow-up and management of the patients' medical files (according to Article 8-IV of French law of 6 January 1978) and for health research (chapter IX).

3. Results

Two hundred forty-four cases of work-related laryngeal cancer were identified in the rnv3p database between 2001 and 2016; 60.2% (147) of these cases were considered to be occupational diseases with at least a weak causal relationship and 35.6% (87) of these cases were considered to have a direct causal relationship, eg., coded as intermediate or strong. Only these 87 cases are described in the present analysis. The study population was exclusively male, with a median age of 59 years and a mean age of 59.7 years. The standard deviation was 8.38 years and the age range for this sample was 33 years (43–76 years).

A total of 97 cases of occupational exposures with an intermediate or strong causal relationship were detected (Table 1). Asbestos was the predominant hazard, reported for 80.4% of the sample. The 87 cases of work-related laryngeal cancer were observed in 30 different business sectors (Fig. 1) and concerned 44 different occupations (Table 2).

Analysis of the free text comments showed that the presence or absence of an alcohol-related disorder was reported for only 11 cases of work-related laryngeal cancer. Ongoing or past chronic alcoholism was reported for 3 cases. Information concerning smoking was not available for 39 patients (44.8%), 38 patients (43.7%) had a personal history of ongoing or past smoking, and 10 patients (11.5%) had never smoked.

Table 1
Occupational hazards.

Hazard	Causal relationship		Total (*n* (%))
	Intermediate	Strong	
Asbestos	41	37	78 (80.41%)
Polycyclic aromatic hydrocarbons	4	1	5 (5.16%)
Transition metal (chromium, nickel)	2	1	3 (3.09%)
Welding smoke and fumes	2	0	2 (2.06%)
Mineral wool (rock wool, fibreglass)	2	0	2 (2.06%)
Other hazards (sample sizes less than 2)	5	2	7 (7.22%)

Occupational hazards identified for 87 cases of laryngeal cancer reported between 2001 and 2016 in the national occupational disease surveillance and prevention network database.

Table 2
Workstations.

Workstations	Sample size	Proportion (%)
Motor vehicle mechanics and repairers	7	8.05
Welders and flamecutters	6	6.90
Sheet-metal workers - Boilermakers	6	6.90
Plumbers and pipe fitters	5	5.75
Floor layers and tile setters	4	4.60
Metal working machine tool setters and operators	4	4.60
Bricklayers and related workers	3	3.45
Insulation workers	3	3.45
Building and related electricians	3	3.45
Other (sample sizes less than 3)	35	52.85

Workstations identified for 87 cases of laryngeal cancer reported between 2001 and 2016 in the national occupational disease surveillance and prevention network database.

The causal relationship of the following occupational hazards among the 10 non-smoking patients was considered to be intermediate or strong:

- asbestos ($n = 8$). Jobs exposed to asbestos were plumbers-heating engineers, ship machine room cleaners-greasers, motor vehicle mechanics, industrial brake maintenance workers, rotogravure paper drying oven maintenance workers, boilermakers, assemblers-welders and refinery operators;
- PAH ($n = 2$). Jobs exposed to PAH were refinery operators and assemblers-welders;
- diesel motor exhaust ($n = 1$) in a truck driver;
- welding fumes ($n = 1$) in an assembler-welder;
- sulphuric acid ($n = 1$) in an industrial chemistry technician.

Occupational disease notification was performed or recommended to the patient in 60 cases (69.0%) of work-related laryngeal

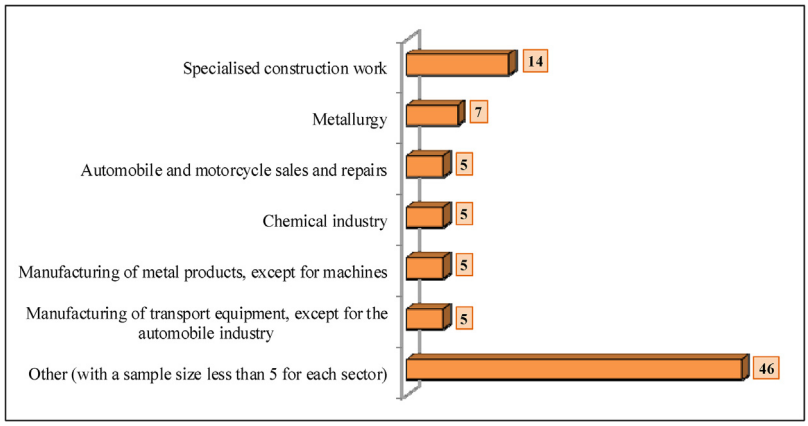

Fig. 1. Business sectors. Business sectors identified for 87 cases of laryngeal cancer between 2001 and 2016 in the national vigilance network and occupational disease prevention database.

cancer, including 13 different occupational hazards, with asbestos exposure in 48 cases (80%). The other hazards, each concerning 1 case of work-related laryngeal cancer, were sulphuric acid, PAH, welding smoke and fumes, organophosphorus pesticides, chlorinated biphenyls, trichloroethylene, chromium, fibreglass, rockwool, cotton dust, diesel exhaust, and compounds released during the manufacture of plastics in the rubber industry.

The reasons for not recommending occupational disease notification in the other 27 cases (31%) were insufficient clinical data (17 cases, 63%), insufficient scientific data (5 cases, 18.5%), a predictable degree of permanent disability less than 25% (4 cases, 14.8%) and this information was not available in one case (3.7%).

4. Discussion

The main agent responsible for work-related laryngeal cancer with an intermediate or strong causal relationship identified in the rnv3p database was asbestos. The business sector most commonly concerned was specialized construction work and the jobs most commonly cited usually involved exposure to asbestos (motor vehicle mechanics and repairers, welders, boilermakers, plumbers, etc.). Much smaller number of cases were identified in the rnv3p database for the other risk factors, suspected or formally demonstrated in the literature, especially PAH or sulphuric acid mists).

This study population was exclusively composed of males, consistent with the sex distribution in the trades and business sectors exposed, especially to asbestos, over recent years. The median age of workers attending occupational health clinics with work-related laryngeal cancer with an intermediate or strong causal relationship was 59 years versus a median age of 63 years at the time of diagnosis of laryngeal cancer, regardless of the cause, in France, according to the most recent epidemiological indicators (INCA. Rapport scientifique: Les cancers en France en 2014, January 2015). These results suggest that the median age of work-related laryngeal cancer is lower than the median age of laryngeal cancer in the general population, but these findings must be interpreted cautiously. It is difficult to compare these two median ages, as the first age corresponds to the age at the time of the visit, i.e. at all possible stages of the disease (diagnosis, treatment, remission, cure, etc.) and the second age corresponds exclusively to the age at the time of diagnosis. This difference in terms of median age can also be explained by the specific recruitment of patients attending an occupational health clinic, predominantly corresponding to people of working age. No inclusion or exclusion criteria were defined and recruitment of cases essentially depended on the network of doctors referring patients to occupational health clinics. The rnv3p network can therefore be used to determine the number of specialist consultations and the number of diseases considered to be work-related, but does not constitute a health surveillance system providing an overview of the real prevalence of diseases in a given business sector. It nevertheless constitutes a complementary database to other epidemiological surveillance systems. The advantage of the rnv3p database is that it includes diseases suspected of being work-related (independently of any medicolegal compensation considerations), with cases examined, documented and assessed by occupational health physicians.

Occupational disease notification was recommended for the majority of cases of laryngeal cancer of this series, while 23 patients were advised not to claim occupational disease status despite an intermediate or strong causal relationship with exposure to asbestos. However, it must be noted that some of these cases were diagnosed in 2002, and scientific knowledge has subsequently been improved, especially with the recognition by IARC in 2009 of the carcinogenicity of asbestos for the larynx. Exposure is described in the rnv3p database at a specific point in time, with no data concerning the duration and intensity of exposure. Exposures are therefore reported regardless of their chronology. The causal relationship and therefore the occupational health physician's conclusion concerning the cases entered in the database cannot be retrospectively revised in the light of new evidence in the scientific literature. Occupational health physicians must now refer their patients to the social welfare consultant physician when the patient's health state has consolidated in order to assess the degree of permanent disability and consider submission to the CRRMP for patients with permanent disability greater than 25%.

Furthermore, the strength of the causal relationship, the opinion concerning occupational disease notification and therefore the conclusion are left to the occupational health physician's discretion, which can result in heterogeneous coding between occupational health physicians working in the various French occupational disease centres. The organization of national coding schools for occupational health physicians and data quality controls is designed to improve and harmonize the quality of data entered into the rnv3p database. It should also be noted that, in some cases, occupational disease notification was not recommended on the basis of the patient's job status, as craftsmen or self-employed workers are not eligible for workers' compensation for work-related disease and do not have access to occupational health physicians, the main physicians referring patients to occupational health clinics.

Data concerning alcohol and tobacco use are not available in every case, which can constitute a source of bias in the analysis. As indicated by Ferster, many studies in the literature have reported a link between occupational exposure to asbestos and laryngeal cancer, failed to take into account non-occupational risk factors such as tobacco and/or alcohol [22]. However, the population of the French ICARE study (Investigations sur les Cancers Respiratoires et l'Environnement professionnel) presented a relative risk of laryngeal cancer among workers exposed to asbestos of 2.1 (95%CI [1.6–2.8]) after adjustment of the results for tobacco and alcohol use [23]. The present study also showed that 8 of the 10 cases of work-related laryngeal cancer with no documented history of smoking were exposed to asbestos. A personal history of smoking does not exclude the possibility of another, work-related aetiology. Several aetiologies can have a synergistic and cumulative carcinogenic effect, such as asbestos and tobacco for lung cancer [24]. This hypothesis also appears to be valid for laryngeal cancer, in which cumulative exposure to tobacco, alcohol and asbestos in the workers of the ICARE study [25] was associated with an increased relative risk of laryngeal cancer of 26.57 (95%CI [11.52–67.88]). Exposure to multiple carcinogens can also be responsible for a cocktail effect and induce a cumulative risk related to exposure to several substances.

The rnv3p is therefore considering ways to improve the coding of a history of alcohol and tobacco use, non-occupational risk factors than can be involved in many diseases. It is therefore planned to create a tobacco and alcohol item for each case, allowing the occupational physician to describe these risk factors (with, for tobacco, the current smoking status and the estimated consumption and, for alcohol, the cumulative consumption as well as the AUDIT-C, Alcohol Use Disorders Identification Test-Consumption questionnaire), which will allow the results of future studies to be adjusted to these variables. Tobacco use is often used as an argument to minimize the role of occupational exposure in the aetiology of cancer, which does not facilitate compensation of the cancer as an occupational disease. For example, a smoking worker exposed to asbestos, who develops lung cancer is eligible for recognition of occupational disease status on the basis of Table 30b (lung cancer induced by inhalation of asbestos dust) of the general scheme in France when certain conditions are met, regardless of smoking status. In contrast,

for a smoker exposed to asbestos at work, who develops laryngeal cancer, an essential and direct link between occupational exposure and the disease must be established. The worker's smoking status therefore complicates establishment of the essential nature of the causal relationship between the occupational carcinogen and laryngeal cancer.

It would also be interesting to refine the coding by indicating the histological type of cancer in order to determine whether certain histological types are more frequently related to work-related aetiologies, as our analysis of free text zones demonstrated that these data were insufficiently reported.

Another question raised by this study concerns the value of screening and prevention of laryngeal cancer, for which the aetiology is often considered to be tobacco and alcohol without systematically asking the patient about possible occupational exposure. Consequently, after establishing the diagnosis, the patient could be referred to an occupational disease centre for a consultation to identify occupational risk factors and to assist in occupational disease notification.

Establishment of a list of occupational diseases in France including compensation for laryngeal cancer related to asbestos exposure may therefore be justified, which would allow a greater number of patients assessed by the CRRMP to be eligible for workers' compensation and would also allow patients with a consolidated permanent disability less than 25% to have access to compensation. This approach is all the more reasonable in that laryngeal cancer related to inhalation of asbestos dust is registered in the lists of occupational diseases in Germany, Austria, Belgium, Denmark, Luxembourg and Portugal (Eurogip. Cancers d'origine professionnelle: quelle reconnaissance en Europe? Rapport d'enquête 49/F, 52 pages, 2010).

5. Conclusion

Exposure to asbestos is the work-related risk most commonly described in cases of laryngeal cancer present in the rnv3p database from 2001 to 2016. The present study highlights the carcinogenic property of asbestos for the larynx. The creation of an occupational disease table in France therefore appears to be legitimate, in line with other European countries. The present study also highlights the existence of occupational risk factors for laryngeal cancer, which is usually attributed to tobacco and/or alcohol use. Prevention and reinforced protection of workers in relation to occupational carcinogens must remain at the heart of our approach, as defined in the 2014–2019 cancer plan, with better traceability of substances and improved access to recognition of work-related cancers as occupational diseases.

Disclosure of interest

The authors declare that they have no competing interest.

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