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REVIEW

Occupation as a risk factor for oral and pharyngeal cancer

Jeannette Puñal-Riobóo,[a] Leonor Varela-Lema,[a] Juan Miguel Barros-Dios,[b,c,d] María Adoración Juiz-Crespo,[e] and Alberto Ruano-Raviña[a,c,d,*]

[a]*Agencia de Evaluación de Tecnologías Sanitarias de Galicia, Consellería de Sanidade, Santiago de Compostela, A Coruña, Spain*
[b]*Servicio de Medicina Preventiva, Hospital Clínico Universitario, Santiago de Compostela, A Coruña, Spain*
[c]*Área de Medicina Preventiva y Salud Pública, Universidad de Santiago de Compostela, Santiago de Compostela, A Coruña, Spain*
[d]*CIBER de Epidemiología y Salud Pública, CIBERESP, Spain*
[e]*Centro de Salud de Porto do Son, Servicio Gallego de Salud, Spain*

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Abstract
Introduction and objectives: Oral and pharyngeal cancers represent the fifth most common cancer type and the seventh cause of deaths by cancer worldwide. Few studies have assessed the risks associated with occupational exposure and in many cases the results are contradictory. The objective of this study is to determine the association between occupational exposure to carcinogenic substances and risk of oral and pharyngeal cancer (including nasopharynx and hypopharynx) through a systematic review.
Material and methods: A literature search was carried out in MEDLINE (PubMed) and EMBASE. The articles were selected by two independent investigators on the basis of inclusion and exclusion criteria (sample size, publication type, etc.).
Results: Ten original articles were included, all with a case-control design. The results showed that a prolonged exposure to formaldehyde may increase the risk of nasopharyngeal and hypopharyngeal cancer, whilst other chemical products were not associated with these tumours. The exposure to different types of particles (such as wood dust in nasopharyngeal cancer) and smoke of various origins has also been associated with several oral and pharyngeal tumours.
Conclusions: The literature reviewed shows that occupational exposure to formaldehyde may be associated with an increased risk of nasopharyngeal and hypopharyngeal cancer. The results regarding other occupational exposures are not consistent, therefore additional studies with more statistical power and better design are needed to ascertain if occupation is really a relevant risk factor for these types of cancer.

*Corresponding author.
E-mail address: alberto.ruano@usc.es (A. Ruano-Raviña).

PALABRAS CLAVE
Neoplasmas bucales;
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Neoplasmas hipofaríngeos;
Neoplasmas orofaríngeos

La ocupación como factor de riesgo del cáncer oral y de faringe

Resumen
Introducción y objetivos: Los cánceres de la cavidad oral y la faringe constituyen el quinto tumor en orden de incidencia y la séptima causa de muerte por cáncer en todo el mundo. Pocos estudios han evaluado la exposición ocupacional como factor de riesgo de estos tumores y en ocasiones han presentado resultados contradictorios. El objetivo de este estudio es conocer el riesgo de cáncer de la cavidad oral y la faringe (incluidas la nasofaringe y la hipofaringe) asociado a la exposición ocupacional a sustancias potencialmente carcinógenas mediante una revisión sistemática.
Material y métodos: Se realizó una búsqueda bibliográfica en MEDLINE (PubMed) y EMBASE. Los artículos fueron seleccionados por dos investigadores independientes según una serie de criterios de inclusión y exclusión (tamaño de muestra, tipo de publicación, etc.).
Resultados: Se incluyeron 10 artículos originales, todos con diseño de casos y controles. La exposición prolongada a formaldehído mostró un mayor riesgo de cáncer de nasofaringe e hipofaringe, mientras que otros productos químicos no se asociaron con estos tumores. La exposición a distintos tipos de partículas (como el polvo de madera en el cáncer de nasofaringe) y humos de diversas procedencias también se ha relacionado con diversos tumores de la cavidad oral y la faringe.
Conclusiones: La literatura revisada muestra que la exposición ocupacional al formaldehído puede tener relación con un aumento en el riesgo de cáncer de nasofaringe e hipofaringe. Los resultados para otras exposiciones ocupacionales no son concordantes, por lo que son necesarios estudios más potentes y mejor diseñados para conocer si realmente la ocupación es un factor de riesgo relevante en la aparición de estos tumores.

Introduction

Oral and pharyngeal cancers combined represent the fifth most common type of cancer and the seventh cause of deaths by cancer worldwide, although oral cancer is more common than pharyngeal. Oral and pharyngeal cancers are three times more common in males than in females.[1]

Alcohol and tobacco are known risk factors for oral, pharyngeal,[2,3] hypopharyngeal[4-6] and nasopharyngeal cancers.[7,8] There is evidence of a dose-response relationship between their consumption and the occurrence of these cancers, as well as a strong interaction between them. It has also been reported that a diet rich in fruits and vegetables is associated with a lower risk of oral and pharyngeal[9], hypopharyngeal[10] and nasopharyngeal[11-13] cancers. These data indicate that external factors are the predominant cause of this disease. Following this reasoning, it is plausible that occupation may also contribute to the risk of oral and pharyngeal cancer. However, there is very little literature published in this respect and the results are sometimes contradictory. Exposure to such substances as formaldehyde and polycyclic aromatic hydrocarbons[14] may cause oral and pharyngeal cancer.

The aim of this study was to determine, through a systematic review, the risk of cancer of the oral cavity and the pharynx (including nasopharynx and hypopharynx) associated with occupational exposure to different carcinogenic substances.

Material and methods

Bibliographic search

A systematic review of scientific literature was conducted. In order to do this, a specific bibliographic search was carried out in PubMed (MEDLINE) by combining corresponding descriptors (MeSH) and adding free terms such as *oral cancer, pharyngeal cancer, pharyngeal neoplasms, oral neoplasms, occupational disease, occupational exposure* and *occupational risk factor*. In order to restrict the results, the search was limited to studies published in English, Spanish and Portuguese between 1995 and 2008.

Study selection and data extraction

Two researchers read the summaries of the studies obtained from the search independently. Potentially relevant articles were retrieved for full-text assessment, and were eventually selected based on inclusion and exclusion criteria defined specifically for this study (Table 1). The data presented in these studies were carefully extracted and included in evidence tables. The characteristics of each of the studies included can be found in Table 2. To minimise the possibility of confusion, only studies whose results were adjusted by alcohol and tobacco consumption were included.

Table 1 Selection criteria for studies included in the review

Aspects considered	Inclusion criteria
Type of publication	We included systematic reviews, cohort studies, and case and control studies
Sample size	We included studies with at least 100 cases. When we studied various anatomical locations we included studies with at least 50 cases of each
Location of evaluated cancer	We included studies evaluating oral and pharynx cancer (oropharynx, nasopharynx and hypopharynx)
Evaluation of results	We included studies that showed the risk of oropharyngeal cancer through odds ratio adjusted at least by consumption of alcohol and tobacco
Language	We included studies in English, Spanish and Portuguese
Study unit	We included studies that analysed humans exclusively

Information collected and analysed

For each of the studies, data was collected regarding the design of the study, year of publication, sample size, characteristics of the population studied, type of occupational exposure, location of the cancer evaluated and risk associated with the exposure.

Results

The search produced 62 references. Following the inclusion and exclusion criteria, 20 articles were selected. After a full-text assessment of the selected studies, the total number was narrowed down to 10 articles.[15-24] Figure illustrates the selection process of these studies, together with the reasons for the exclusion of other studies. The majority of the retrieved studies were conducted in European countries[20-24] such as France,[21,22] Sweden,[20,23] and Serbia.[24] Of the 5 remaining studies, 2 came from Asia and the others were from the United States,[17] Puerto Rico[16] and Brazil.[15] All the articles included used a case-control design. The sample size was >500 subjects in all of the studies except 2.[17,24] All the studies retrieved cases from hospital records or cancer registries and general population screenings. Two of the studies included,[21,22] which evaluated various occupational exposures on the same group of individuals, were treated as independent research. The results have been classified according to the type of substances evaluated and are detailed below.

Chemical products

In general, the literature reviewed has not shown a significant association between cancer of the oral cavity and the pharynx and exposure to formaldehyde.[20,24] As for specific locations, 1 study showed an increased risk of nasopharyngeal cancer when the duration and intensity of exposure was high (≥18 years, odds ratio [OR]=2.1 [range, 1-4.5],[17] >10 years (medium-low intensity) or ≤10 years (medium-high intensity), OR=2.1 [1-4.2] and OR=2.6 [1.1-6.3] respectively[18]), a result not confirmed by Armstrong et al.[19] Another study showed that the risk of hypopharyngeal cancer was almost 4 times higher in subjects with a probability of exposure to formaldehyde >50%.[21]

Some studies[16,18-20,23,24] assessed the risk of oral and pharyngeal cancer associated with exposure to various chemicals such as dyes, solvents, pesticides, polycyclic aromatic hydrocarbons, chlorine, etc. Others[18,19] assessed the risk of nasopharyngeal cancer due to exposure to bleaches, varnishes, adhesives and biocides. No increased risk was found in any of the cases.

Particles of mineral fibres (glass fibre), asbestos and cement

Exposure to glass fibres and asbestos is not associated with an increased risk of oropharyngeal cancer,[17] although it has been associated with an increased risk of hypopharyngeal cancer (OR=1.80 [1.08-2.99]).[22] According to the studies reviewed, exposure to cement particles does not increase the risk of cancer of the oropharynx[24] or nasopharynx.[19]

Wood particles

Conflicting results have been found regarding the association between exposure to wood particles and oropharyngeal cancer. Whereas some studies found no significant risk,[15,16] others showed that exposed subjects were at 4[24] and even 5 times[23] greater risk than those not exposed. Two of the selected articles suggested that exposure to wood particles could increase the risk of nasopharyngeal cancer,[18,19] while another indicated no increased risk.[17] The only study that specifically investigated hypopharynx tumours found no association with exposure to wood particles.[21]

Metal particles

According to the selected studies, exposure to different metal particles does not increase the risk of oral and pharyngeal cancer.[16,20,24] Just one study, which evaluated tumours of only the nasopharynx, showed a significant association.[19]

Coal particles

Coal particles have been associated with an increased risk of cancer of the hypopharynx,[21] but not of oropharyngeal cancer.[24]

Table 2 Evidence tables

Author/ year	Sample design and size	Characteristics of study population	Type of exposure	Location of cancer	OR	Comments
Vlajinac et al (2006)[24]	Case-control study. 100 cases and 100 controls	Age (average): 59 years in cases and controls. Gender: 89 males en cases and controls	Evaluated exposure to different factors: high and lot temperature, dry air, chromium, aniline dyes, cement dust, wood, coal, metal, etc.	Tongue base cancer; palate cancer; tonsil cancer	Oropharynx cancer was related with occupational exposure to dry air (OR=0.15 [0.06-0.36]) and to wood dust (OR=4.16 [1.45-11.91])	OR were adjusted by education, BMI and family history of oropharynx cancer
Andreotti et al (2006)[15]	Multicentre case-control study. Three hundred and twenty five cases and 468 controls	Age (mean): 55 years in cases and 56.3 in controls. Gender: 84.6% of males in cases and 81.1% in controls	Evaluated exposure of different work positions: agriculture, mining, metalwork, wood items factory, restaurants, public administration, education, etc.	Oral cavity and pharynx cancer	Observed a higher risk in mechanics of vehicles exposed to fuel smoke, (solvents, metals, etc.) when exposure was ≥10 years (OR=26.21 [2.34-294.06]). Also observed risk in employees in the offices of garages (OR=2.45 [1.14-5.27]), which increased with exposures ≥10 years (OR=7.90 [2.03-30.72]). No significant risk was found in the other exposures evaluated	Statistical analysis only included males
Coble et al (2003)[16]	Case-control study. Three hundred twenty-seven cases and 499 controls	Gender: 699 males (286 cases/413 controls) and 127 females (41 cases/86 controls)	Exposure to dust (wood, stone, etc.), exposure to solvents (dyes), exposure to metals (cut/weld, plating, etc.)	Oral and pharynx cancer	Did not find a risk of oral and pharynx cancer in males exposed to the 3 substances evaluated	OR, as well as for tobacco and alcohol, was also adjusted for place of residence
Hildesheim et al (2001)[18]	Case-control study. Three hundred seventy five cases and 325 controls	Age (mean): 45 years in cases and controls. Gender, 69.3%of males in cases and 68.6% in controls. Anti-EBV antibodies : 98.6% of cases and 29.6% of controls	Wood dust, formaldehyde, solvents	Nasopharynx cancer	Individuals exposed to wood dust presented a RR=1.7 [1-3]. The risk increased if exposure was >10 years (RR=2.4 [1.1-5]) or if accumulated exposure was ≥25 years (RR=2.4 [1.2-5.1]). Found an increase of risk in subjects exposed for over 10 years and average intensity (RR=2.1 [1-4.2]) or for 10 or more years and medium-high intensity (RR=2.6 [1.1-6.3]). Found a higher risk of nasopharynx cancer in exposure to solvents ≥10 years (RR=1.5 [0.99-2.3])	Accumulated exposure was calculated: duration exposure × mean intensity of exposure

Armstrong et al (2000)[19]	Case-control study. Two hundred eighty-two cases and 282 controls	Age (years): 19-72 in males and 24-74 in females. Gender: 195 males and 87 females (similar in cases and controls)	Dust: construction, metal, zinc, textile, wood and cement. Smoke: cooking, wood, engines, etc. Chemical products: dyes, formaldehyde, oil/engine fuel, paint	Nasopharynx cancer	Exposure to wood dust and industrial heat could increase risk (OR=2.36 [1.33-4.19] and OR=2.21 [1.12-4.33] respectively). Found a dose-response relation (during exposure 10 times higher) in exposure to wood dust (OR=1.24 [1.07-1.44]) and industrial heating (OR=1.21 [1.01-1.45])	Calculation of OR was adjusted by diet
Marchand et al (2000)[22]	Case-control study. Four hundred ninety seven cases and 295 controls	Not shown	Asbestos and four types of synthetic mineral fibres: mineral wool, ceramic fibres, glass filaments and micro fibres	Larynx cancer (296 cases), hypopharynx cancer (201 cases)	Showed increased risk of hypopharynx cancer associated to exposure to asbestos (OR=1.80 [1.08-2.99]). Found a relationship between exposure to mineral wools and hypopharynx cancer (OR=1.55 [0.99-2.41]). Did not find a higher risk of hypopharynx cancer by exposure to the other substances evaluated. The majority of subjects exposed to mineral wools were also exposed to asbestos. Did not find a significant relationship	Cases of larynx cancer were excluded from the results
Laforest et al (2000)[21]	Case-control study. Four hundred ninety seven cases and 296 controls	Age ≤59 years, 63.2% in hypopharynx, 50% in larynx and 47.6%in controls; ≥60 years, 36.8% in hypopharynx, 50% in larynx and 52.4%in controls. Gender: only males	Leather particles, wood, flour, coal, silica, textile and formaldehyde	Larynx cancer (296 cases) and hypopharyn x (201 cases)	Observed a significant risk of hypopharynx cancer when probability of exposure to formaldehyde was >50% (OR=3.78 [1.50-9.49]). Observed an increased risk in subjects exposed to coal dust (OR=2.31 [1.21-4.40]). Observed a dose-response relationship; if probability was >90%, the risk was OR=3.12 (1.22-8.01) and if the accumulated level was high (>2 mg/ m^3), the risk was OR=3.73 (1.23-11.3). If exposure to coal dust was >20 years, OR=3.31 (1.05-10.3) and if the accumulated level was high, OR=3.44 (1.13-10.4)	Cases of larynx cancer were excluded from the results. OR associated to coal dust was adjusted for formaldehyde
Vaughan et al (2000)[17]	Case-control study. One hundred ninety-six cases and 244 controls	Age (mean): 54.3 years in cases and 55.2 in controls. Gender: 67.9% of males in cases and 67.2% in controls	Formaldehyde, wood dust	Nasopharynx cancer	Observed significant differences when exposure to formaldehyde was ≥18 years (OR=2.1 [1.0-4.5]). Analysis was stratified by histological type. Found a risk of squamous cell cancer with exposures	OR was adjusted for race, region, education and proxy bias.

Table 2 *(continuation)*

Author/ year	Sample design and size	Characteristics of study population	Type of exposure	Location of cancer	OR	Comments
					≥18 years (OR=2.5 [1.1-5.9]. When probability of exposure was probable or definitive, OR=2.1 (1.1-4.2) and when it was definitive, OR=13.3 (2.5-70). Did not find an increased risk associated to exposure to wood dust	
Schildt et al (1999)[23]	Case-control study. Four hundred ten cases and 410 controls	Age (years), mean: 72.3 in females and 69.6 in males. Gender: 276 males and 134 females	Organic solvents, pesticides (DDT, mercurial) diesel oil, chlorine, gas, sulphur compounds and plastics	Oral cancer	Paper industry workers present an OR=4.0 (1.3-12). Those of wood, an OR=5.5 (1.2-25). Did not find a relationship between exposure to pesticides, impregnation compounds, mercurial, etc., and risk of oral cancer	
Gustavsson et al (1998)[20]	Case-control study. Five hundred forty-five cases and 641 controls	Age: 40-79 years. Gender: males	Polycyclic aromatic hydrocarbons, asbestos, wood dust, metal dust, paper, textile, leather, welding smoke, formaldehyde, etc.	Oral and oropharynx cancer, hypopharynx, oesophagus and larynx	Exposure to welding smoke could increase the risk of pharynx cancer when exposure was >8 years RR=2.26 [1.09-4.68]). The small size (of suspended particles could be linked with oral cancer (RR=1.76 [0.98-3.16], while the high level did not result statistically significant (RR=1.35 [0.70-2.6])	Collected results in oral, oropharynx and hypopharynx cancer. RR was adjusted by region

OR indicates odds ratio adjusted for variables of age, gender, consumption of tobacco and alcohol in all the studies. Other studies also adjusted the OR for other variables.

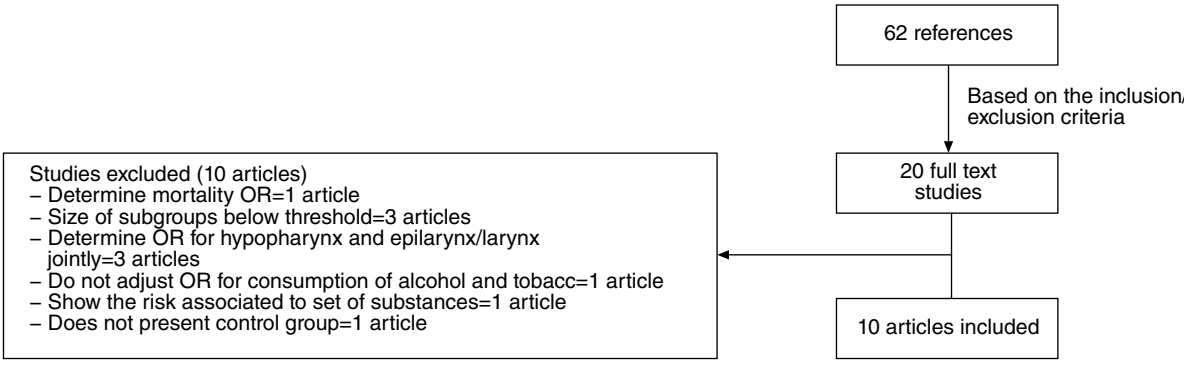

Figure 1 Selection of the articles included in the review. OR indicates odds ratio.

Textile fibres

None of the articles reviewed found any association between exposure to textile fibres and the risk of oral and pharyngeal cancer. This was true both when tumours were jointly evaluated[20] and when the nasopharynx[19] and hypopharynx[21] were studied independently.

Smoke from different sources

One study found no association between exposure to diesel fuel smoke, other fumes and particles from chemicals and an increased risk of cancer of the oral cavity and pharynx,[24] whereas another did observe an increased risk.[15] One study found that exposure to welding fumes over a period >8 years increased the risk of oral and pharyngeal cancer.[20] Another study evaluated the association between exposure to fumes from various sources (cooking, burning wood, engines, etc) and nasopharyngeal cancer, and found an increased risk, proportional to the intensity.[19]

Discussion

Although cancer of the oral cavity and pharynx is not traditionally regarded as a common occupational cancer, the literature reviewed agrees that occupational exposure to certain substances can contribute to an increased risk of these tumours in certain locations. Cumulative exposures to formaldehyde have been associated with tumours of the nasopharynx and hypopharynx. Prolonged exposure to fumes from various sources and wood particles has also been associated with nasopharyngeal cancer. An increased risk of hypopharyngeal cancer has been observed in subjects exposed to mineral fibres (fibreglass), asbestos and carbon particles. With regard to the oropharynx, significant risks have been found only in association with exposure to wood particles; the results, nevertheless, are contradictory. Exposure to a large number of chemicals (such as dyes, solvents, pesticides) and particles of cement, metal or textile fibres showed no significant risk in any of the locations (including nasopharynx and hypopharynx). The present study is the first systematic review to date on the risk of cancer of the oral cavity and pharynx (including nasopharynx and hypopharynx) associated with occupational exposure to different compounds. However, due to the high heterogeneity of the studies, it was not possible to conduct a meta-analysis.

With regard to exposure to formaldehyde, while some previous studies linked exposure to this substance with the risk of oral cancer,[14,25,26] the studies included in this review agree, after evaluating various sources of exposure to formaldehyde,[16,18-20,23,24] that it does not increase the risk of cancer of the oral cavity. However, the literature reviewed points in the same direction as other authors regarding the association between formaldehyde and cancer of the nasopharynx and hypopharynx.[17,18] In 2005, the International Agency for Research on Cancer (IARC) classified formaldehyde as carcinogenic to humans (Group 1), and concluded in their review that it increases the risk of nasopharyngeal cancer. The carcinogenic effect of formaldehyde may be due to its genotoxicity, given that it causes DNA-protein crosslinks and also increases cell proliferation.[27]

Subjects exposed to mineral fibres and asbestos while working in industries that produce construction materials (cement, tiles, etc.) or car parts (brakes, transmissions, etc.) seem to be at a greater risk of developing cancer of the hypopharynx. A large case-control study conducted by Marchand et al[28] showed significant association between exposure to mineral fibres and asbestos and cancer of the hypopharynx (OR=1.8 [1.1-2.7]),[22] a result which largely coincides with that observed by other authors (OR=2.1 [1.2.-3.8]). The carcinogenic effect of asbestos and mineral fibres could be caused by the fact that they trigger the release of inflammatory mediators, cytokines and growth factors, which in turn alter the differentiation and proliferation of epithelial and mesothelial cells.[29] The effect of these fibres appears to occur primarily in areas of increased absorption, as a result of the size of the fibre particles. The results obtained in the study conducted by Gustavsson et al[20] agree with previous studies that there is no association between exposure to mineral fibres and asbestos and cancer of the oropharynx, as in other studies.[30,31]

With regard to exposure to wood particles, it has been observed that subjects exposed to these particles, both in

the wood industry and in furniture manufacturing, may be at an increased risk of oral and pharyngeal cancer.[23,24] By analysing specific locations, it was found that exposure to wood particles may be associated with an increased risk of nasopharyngeal cancer.[18,19] With regard to the hypopharynx, one study showed a non-significant risk. However, these results may be biased, because some studies[32,33] have found that subjects exposed to wood particles are also exposed to other substances such as solvents, paints, asbestos, dyes and formaldehyde, which can act as confounding factors. An IARC report found that wood particles may have a carcinogenic effect, given that they can cause cell changes in the epithelium and increase the frequency of dysplasia and cuboidal metaplasia.[34]

Other studies reviewed have analysed the risk of oral and pharyngeal cancer associated with exposure to other particles such as metal and coal. Although subjects exposed to metal particles appear to be at a greater risk of nasopharyngeal cancer,[19] there seems to be no association with cancer of the oropharynx.[16,20,24] Some authors postulate that this difference may be due to the fact that medium-sized particles (5-10 µm) tend to deposit in the nasopharynx and are, therefore, potential carcinogens.[35] On the other hand, whereas it seems that exposure to coal dust may increase the number of cases of hypopharyngeal cancer,[21] it is not associated with oropharyngeal cancer.[24] These results are consistent with those found by other authors.[36,37]

The literature reviewed has shown that exposure to textile fibres could increase the risk of nasopharyngeal cancer[19] but not that of cancer of the hypopharynx[21] and oral cavity and pharynx.[20] As with exposure to wood particles, the results may be biased, as textile industry workers are often exposed to potentially carcinogenic chemicals such as dyes, solvents, etc.[38] In the same way as with exposure to particles of metal, due to their small size, textile fibres have easier access to the nasopharynx; the risk of cancer of that location is consequently greater than that of others.[35]

Another possible carcinogen evaluated in the studies reviewed were fumes resulting from fuel combustion, welding, cookers, etc. According to an IARC monograph, fumes from engine or oil combustion or from welding have been classified as potentially carcinogenic.[39] However, the articles viewed found a possible association of exposure to welding and fuel fumes (garage workers) only with cancer of the oral cavity and pharynx,[15,20] but not with nasopharyngeal cancer.[19]

One limitation of this review is that all the studies present a case-control design, in which information is obtained retrospectively, which possibly reduces the quality of the information. Personal interviews with the patients were conducted in 8 of the 10 articles included.[15,16,18-22,24] In addition, the studies reviewed may be biased because the number of subjects exposed to each of the tested substances is very low, thus limiting the statistical power of the results observed. Another possible limitation of this review is that the studies selected were all published after 1995. However, both the working conditions and safety measures currently used are different from those that existed years ago, so it would not make sense to include studies published before 1995.

This review has two important advantages. All of the articles except for 2[19,23] included incident cases, so Neyman bias was avoided; that is, survival would not be influenced by high risk occupations, which could have been the case if prevalent cases had been used. Furthermore, all included studies took relevant variables such as age, gender and alcohol and tobacco consumption into account; given that these are known risk factors for oral and pharyngeal cancer, the validity of the results was consequently increased.

In conclusion, the literature reviewed indicates that prolonged exposure to formaldehyde may be associated with cancers of the nasopharynx and hypopharynx. Other occupational exposures have also been associated with cancer of the oral cavity and pharynx, but the evidence comes from just one or two studies in many cases, and the effect of other concomitant exposures has not been taken into account. More robust epidemiological studies (of cohorts and with a greater sample size) are needed to confirm or rule out the association of various exposures with cancer of the oral cavity and pharynx and its anatomical regions.

Conflict of interest

The authors declare no conflict of interests.

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