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Title: Oral and pharyngeal cancer risk associated with occupational carcinogenic substances – a systematic review

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ABSTRACT

Background: Oral and pharyngeal cancers (OPC) represent the seventh most common type of cancer and the seventh leading cause of deaths by cancer worldwide. Few studies have assessed the occupational exposure risks associated with OPC and in many cases the results are conflicting. The aim of this study was to determine, through a systematic review, association of OPC and exposure to different occupational carcinogenic substances.

Methods: The addressed focused question was “Is there an association of occupational carcinogenic substances with OPC?” PubMed, Medline, EMBASE and ISI Web of Science databases were searched between January 1995 up to and including July 2016 using the keywords “oral cancer”, “pharyngeal cancer”, “pharyngeal neoplasms”, “oral neoplasms”, “occupational disease”, “occupational exposure”, “occupational risk factor” in various combinations. Letters to the Editor, review articles, case-reports and unpublished articles were excluded.

Findings: Fourteen original articles were included. Majority of the studies were conducted in European countries and used a case-control design. The results showed a significant association between formaldehyde, wood dust, coal dust, asbestos, welding fumes and risk of developing OPC, while marginal association was observed with metal and leather dust. No associated risk was observed for textile fibers.

Conclusion: There is some evidence to suggest associations of occupational substances with OPC, particularly in the pharynx. Future well-designed studies are required to confirm or rule out with confidence the associated exposure risk of these substances.

Key words: *Cancer; carcinogen; occupation; risk; systematic review*

INTRODUCTION

Oral and oropharyngeal cancers (OPCs) represent the seventh most common type of cancer reported worldwide and are among the leading causes of death caused by cancer.¹ OPC includes cancers of the lip and oral cavity (codes ICD-10: C00, C02-06), oropharynx (OP) (C 01, 09-10), nasopharynx (C11), hypopharynx (C13), oral cavity and pharynx not otherwise specified or overlapping (C14).

According to Globocan in 2012 there were an estimated 300,373 lip and oral cancers (ASR 4.0), 86691 nasopharyngeal cancers (ASR 1.2) and 142387 oro and hypopharyngeal cancers taken together (ASR 1.9). Although the incidence is higher among men and in developing nations, studies have reported an increased risk for OPC attributed to an aging population, ethnic diversity and culturally specific dietary habits, and behavioral and environmental factors. Several advances have been made in the surgical and non-surgical management of oral and oropharyngeal cancers; however, little improvement has been observed in the 5-year survival rate.²

OPCs are a biologically diverse group of tumors occurring in response to varying etiological factors. The majority of cases are attributed to the separate and combined use of tobacco (smoked and smokeless), excessive alcohol consumption, betel quid and betel quid substitutes, and human papillomavirus (HPV-16) infection.²⁻⁷ While these risk factors have received the most attention in etiologic research for OPC, and justifiably so, as they are attributed to the vast majority of these tumors, there is evidence to suggest that exposure to occupational substances may also contribute to this disease.^{8,9} It is also possible that tobacco and alcohol might interact with occupational carcinogens on the risk of oral and pharyngeal cancers. As manufacturing becomes progressively more globalized, the elucidation of occupational risk factors is increasingly critical for the formulation and implementation of adequate safety policies and procedures.

It is plausible that occupation may contribute to the risk of OPC; however, there is a dearth of literature on this topic, and of those that do exist, the results are sometimes contradictory. Therefore, the aim of this study was to determine, through a systematic review, the association between OPC and exposure to different occupational carcinogenic substances.

SEARCH STRATEGY

Key question

A key question was constructed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines according to the Prevention, Intervention, Control, Outcomes (PICO) protocol.¹⁰ The question was “*Is there an association between occupational carcinogenic substances and OPC?*”.

Study selection and data extraction

An automated detailed literature search of PubMed, Medline (National Library of Medicine, Bethesda, MD), EMBASE and ISI Web of Science was carried out using various combinations of corresponding descriptors (MeSH) and free text terms such as *oral cancer, pharyngeal cancer, pharyngeal neoplasms, oral neoplasms, occupational disease, occupational exposure and occupational risk factor*. To restrict the results, the search was limited to studies published in English from January 1995 up to and including July 2016.

Prospero databases were searched for any registered protocols on similar topics. In addition, the systematic review was registered as a protocol with Prospero (PROSPERO 2017:CRD42017064484).

Two reviewers (KHA, SP), using a standardized guide, initially screened titles and abstracts of studies based on inclusion and exclusion criteria defined specifically for this study (Table 1). Full texts of studies found relevant were retrieved and independently reviewed using a standardized and pilot tested form. The studies were only included in the review after the agreement of both authors (Kappa score = 0.85).

We included original clinical studies including cohort, case control and cross sectional studies if the total study number for each anatomical site was at least 100 cases. In case of various anatomical locations, studies with at least 50 cases of each site were included. We limited the review to studies that analysed humans exclusively evaluating head and neck sites including lip and oral cavity, oropharynx, nasopharynx and hypopharynx. Only studies that were adjusted for consumption of tobacco and alcohol through multivariate analysis were considered and finally we limited the review to articles published in English language only.

Case reports, experimental studies, review articles, letters to the editor, unpublished data and articles not published in English were excluded.

The data presented in these studies were carefully extracted and included in evidence tables. The abstracted data included year of publication, study type, sample characteristics (age, gender, and location), type of occupational exposure, anatomical site of the evaluated cancer and risk associated with exposure. Table 2 summarizes the characteristics of each of the studies included in this review. A qualitative synthesis of the literature was performed.

FINDINGS

A total of 14 studies¹¹⁻²⁴ that met eligibility criteria were included in the review (Figure 1). The majority of studies were conducted in European countries (n=6), including Sweden,^{11,12} France,^{13,14} Serbia,¹⁹ and the Netherlands.²² Four studies were conducted in the United States,^{16,20,21,24} two in Taiwan,^{17,23} and one study each in Malaysia¹⁵ and Puerto Rico.¹⁸ Most studies included in the systematic review used the case-control design,^{11-21,24} except two studies, one of which used a prospective longitudinal study design²² and the other a retrospective matched-cohort study design.²³ The sample size was greater than 500 subjects in most of the studies.^{11-18,20,21,23,24} Three studies^{20,21,24} evaluated occupational exposure on the same group of patients and were treated as independent studies.

Chemical products

Overall, the literature did not show a significant association between OPC and occupational exposure to formaldehyde.^{11,17} For specific locations, two studies reported an associated risk between hypopharyngeal [OR=3.78 (1.50-9.49)] and nasopharyngeal [OR=2.7 (1.2-6.0)] cancer and formaldehyde that increased with duration and cumulative level of exposure. One study also reported a strong association between formaldehyde and nasopharyngeal cancer among individuals who were EBV seropositive [RR=2.7 (1.2-5.9)].¹⁷

Studies that assessed other chemicals, such as dyes, solvents, pesticides, polycyclic aromatic hydrocarbons (PAHs), chlorine, etc., did not report any increased associated risk for OPC.^{11,12,15,17,18}

Asbestos and man-made vitreous fibers

Asbestos was associated with increased risk for OPC, including neoplasms in the oral cavity,²³ pharynx,²¹ and hypopharynx.¹⁴ Additionally, mineral wool was found to be associated with

increased risk for hypopharyngeal cancer [OR=1.55 (0.99-2.41)].¹⁴ No associated risk was found for occupational exposure to other man-made vitreous fibers (MMVF).

Wood particles

Eight studies evaluated the associated risk between wood particles and OPC,^{11-13,15-19} two of which reported a five-fold [OR=5.5 (1.2-25)]¹² and four-fold [OR=4.16 (1.45-11.91)]¹⁸ greater risk for oral cavity and oropharyngeal cancer among subjects exposed to wood particles. Two studies also observed a strong dose-response relationship between wood particles and nasopharyngeal cancer with increasing duration and cumulative exposure.^{15,17}

Metal particles

The majority of studies evaluating occupational exposure risk of metal dust did not show any significant association with OPC.^{15,18-20} Only one study evaluating twenty different kinds of occupational substances, including metal dust, demonstrated an increased associated risk with nasopharyngeal cancer.¹⁹

Coal particles

Two studies evaluated the association of coal dust and OPC.^{13,19} Although one study showed a significant association between hypopharyngeal cancer and occupational exposure to coal dust [OR=2.31 (1.21-4.40)],¹⁹ no association was observed for other anatomical cancer sites.

Textile and leather fibers

None of the studies reviewed reported an association between risk of occupational exposure to textile fibers and OPC.^{11,13,15} Among the three studies that evaluated OPC associated risk of leather dust,^{11,13,20} one study showed a slightly increased risk among head and neck cancer patients [OR=1.5 (1.2-1.9)].²⁰ Of the remaining two studies, one study did not explore the association due to low numbers of exposure,¹³ while the other, despite a low sample number, reported consistently elevated relative risks for head and neck cancer, overall and by site (RR=2.06-2.83).¹¹

Smoke and fumes from different sources

Three studies evaluated the occupational exposure risk between fuel smoke, welding fumes and fumes from chemicals among OPC patients.^{11,15,19} One study showed an increased risk of oral and pharyngeal cancer after > 8 years of occupational exposure to welding fumes [(RR=2.3 (1.1-4.7)].¹¹ Another study reported an increased associated risk between nasopharyngeal cancer and exposure to fumes from different sources (cooking, engines, wood, etc.), proportional to intensity.¹⁹

Building materials (cement dust, asphalt)

Three studies evaluated the association between building materials (cement, asphalt) and OPC.^{15,19,24} None of the studies found a significant associated occupational exposure risk between cement or asphalt among building workers.

INTERPRETATION

The present study updates a previous systematic review published in Spanish language in 2010²⁵ to focus on the association between OPC and occupational exposure to different substances. Although occupation is not traditionally considered a common risk factor for OPC, the literature reviewed clearly demonstrates that occupational exposure to certain substances can contribute to an increased risk for OPC in certain anatomical sites. The IARC Monographs identify environmental factors that can increase the risk of human cancer. These include chemicals, complex mixtures, occupational exposures, physical agents, and biological agents, in addition to lifestyle factors. Although lung, bladder, renal, skin cancers and leukemia and non Hodgkin lymphomas are specifically linked to occupational exposures, very little is known about head and neck cancers except nasal cancers.

It is well recognised that tobacco or alcohol consumption are more frequent in occupations classified as "blue collar" (manual workers) and these environmental exposures might interact with occupational carcinogens increasing the risk of oral and pharyngeal cancers. Though the original data in the publications reviewed were adjusted for these factors, models for interactions are not often examined in papers dealing with risk factors for cancer.

Cumulative exposure to chemicals, especially formaldehyde, was found to be associated with tumors of the hypopharynx.¹³ Few studies have shown a link between formaldehyde and cancer of the oral cavity;^{26,27} however, our literature review did not show evidence of a significant association. The International Agency for Research on Cancer (IARC) classified formaldehyde as carcinogenic to humans (Group 1) and reported a strong association with cancer of the nasopharynx.²⁸ The carcinogenic effect of formaldehyde may be due to its genotoxicity, given that it causes DNA-protein crosslinks and increases cell proliferation.

Occupational exposure to asbestos and MMVF among subjects working in construction (cement, tiles, etc.) and auto industries (brakes, transmissions, etc.) was found to be associated with an increased risk for developing OPC.¹⁴ Asbestos is considered carcinogenic to humans in all forms;²⁹ however, despite its known toxicity, there is no universal ban in place for its use, particularly in developing countries. Asbestos and MMVF exposure causes the release of inflammatory mediators, cytokines and growth factors, which in turn alter the differentiation and proliferation of epithelial and mesothelial cells; a plausible explanation for their carcinogenicity.³⁰

Occupational wood dust exposure has long been associated with adverse health outcomes, including sinonasal cancer³¹ and adenocarcinoma of ethmoids,³² especially among workers employed in the wood and furniture industries. In our review, while most studies did not show a significant association, a few reported a 2- to 5-fold increased risk for developing OPC among individuals exposed to different types of wood dust.^{12,17} However, these results should be considered with caution as studies have reported that subjects exposed to wood particles are also exposed to other substances such as solvents, paints, asbestos, dyes and formaldehyde, which are potentially confounding factors.^{33,34} 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.³⁵

Metal and coal particles and their associated risk for OPC was analyzed by a few studies.^{13,15,18-20} Although the observed association between coal particles and oral cancer was marginal, the risk of developing hypopharyngeal cancer among subjects exposed to coal particles was significant [OR=2.31 (1.21-4.40)].¹³ Metal particles showed a strong association only with nasopharyngeal cancer,¹⁵ possibly explained by the fact that medium-sized particles (5-10 μm) tend to deposit in the nasopharynx. Several metals and metalloids are considered toxic and carcinogenic by the IARC, including lead, nickel,

chromium, cobalt, arsenic, vanadium and beryllium.³⁶⁻³⁸ While the exact carcinogenic mechanism of most metals is not well understood, many believe that they exert their carcinogenicity through means including (but not limited to) epigenetic alterations, deregulation of cellular proliferation and metabolism, aberrant activation of signal transduction pathways, generation of reactive oxygen species, induction of hypoxia pathways,³⁹ or by competitive binding with enzyme-associated metals.⁴⁰

Leather fibers were another substance found to be associated with increased risk for OPC, particularly cancer of the pharynx.^{11,20} Leather dust can vary greatly in properties, depending on the region and chemicals used during the manufacturing process. Chromium, which is considered a carcinogen by the IARC (Group 1),⁴¹ is often used in the leather manufacturing process and may constitute 0.1%-4.5% of total leather dust weight.⁴²

Smoke and fumes from various sources were also evaluated in the included studies.^{11,15,19} Although there was no dose-response relationship reported, the risk was associated with intensity and number of exposure years. Welding fumes contain many chemicals, including metal dust, irritant gases and polycyclic aromatic hydrocarbons(PAHs), the majority of which are classified as carcinogens by the IARC.

Although exposure to building materials was not found to be associated with OPC, studies have reported occupational exposure risk of cement dust with other cancers of the head and neck region, particularly laryngeal cancers.⁴³ Cement consists of calcium oxide (62– 66%), silicon oxide (19 –22%), aluminum trioxide (4 – 8%) iron oxide (2–5%), magnesium oxide (1–2%), sulfur oxide and alkali oxides. Small doses of microelements such as chromium are also present, and chromium-related compounds have been categorized as human carcinogens by the IARC.⁴⁴

We wish to highlight few limitations of this review so that the conclusions could be viewed in the light of these factors. Our primary search was limited to publications in English and therefore excludes articles published in other languages. For example a publication in Spanish⁴⁵ among Brazilian oral and oropharyngeal cancer patients reported that males working in vehicle maintenance shops had increased risk. We have not included papers with case numbers lower than 100 for each anatomical site unless multiple sites were studied.

CONCLUSION

The reviewed literature revealed an association between the risk for developing OPC and a number of occupational substances, including formaldehyde, wood dust, coal particles and asbestos. However, in most cases, the evidence comes from one or two studies that fail to account for confounding factors, such as exposure to other concomitant substances. Therefore, more robust epidemiological studies of additional cohorts and studies with larger sample sizes are required to conclusively confirm or rule out the occupational exposure risk of these substances to developing cancer of the oral and pharyngeal sites.

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Legends for Tables:

Table 1. Inclusion and exclusion criteria of the studies

Table 2. Characteristics of included studies

Table 3. Occupational substances that may cause other cancers

Legend for Figure:

Figure 1. A PRISMA flow diagram showing the retrieval process of studies included in the systematic review

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