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REVIEW

Occupational exposures to asbestos, polycyclic aromatic hydrocarbons and solvents, and cancers of the oral cavity and pharynx: a quantitative literature review

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Abstract
Purpose The role of occupational risk factors in oral and pharyngeal cancer is not well known and is possibly underestimated. This quantitative review summarizes epidemiological findings on exposure to asbestos, polycyclic aromatic hydrocarbons and solvents, and cancers of the oral cavity and pharynx.
Methods A systematic literature search was performed. We analyzed 63 publications: 8 from case–control studies and 55 from cohort studies. For agents with at least five available studies with homogenous exposure, a series of meta-analyses was conducted to provide quantitative pooled estimates of risks, using random effect models.
Results Exposure to asbestos (meta-RR 1.25; 95% CI 1.10–1.42) and to polycyclic aromatic hydrocarbons (meta-RR 1.14; 95% CI 1.02–1.28) was found to be associated with oral and pharyngeal cancer risk. On the other hand, no association was found with exposure to solvents in general (meta-RR 0.98; 95% CI 0.77–1.23) but the strong heterogeneity between studies suggested differences in exposures. The small number of studies with homogeneous exposure did not allow meta-analyses for specific solvents.
Conclusions Future investigations should overcome common weaknesses of past studies, in terms of sample size, characterization of exposure, and classification of cancer sites.

Keywords Pharyngeal cancer · Oral cancer · Occupational exposure · Review · Meta-analysis

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Introduction

Cancers of the oral cavity (OC) and pharynx are the eighth most frequent cancers worldwide, with 482,000 new cases in 2008 (Ferlay et al. 2010). The two major recognized risk factors for head and neck cancers are alcohol and tobacco consumption and their joint effect seems to be multiplicative or even greater than multiplicative (Hashibe et al. 2009). In spite of these established risk factors, part of the etiology of oral and pharyngeal cancer remains unexplained. Recent estimates of population attributable risks indicate that tobacco and alcohol accounted for 64% of oral cancer cases and 72% of pharyngeal cancer cases (Hashibe et al. 2009). This points to the need to clarify the role of other known or suspected risk factors. Consumption of fruits and vegetables and diet diversity has been inversely associated with oral and pharyngeal cancers (Levi et al. 1998). The role of infection by human papilloma virus (HPV) has been highlighted, especially for oropharyngeal cancers (D'Souza et al. 2007). The role of occupational factors in oral and pharyngeal cancer is not considered as important but may have been underestimated. Indeed, several studies have reported associations between occupation or occupational exposures and these cancers. In addition, occupational exposures could explain, at least partly, the large social inequalities observed for these

cancers (Conway et al. 2010), as it has been suggested for laryngeal cancer (Menvielle et al. 2004). The aim of this paper was to review epidemiologic data on occupational exposures to asbestos, polycyclic aromatic hydrocarbons and solvents, and cancers of the OC, oropharynx (OP), and hypopharynx (HP), in order to update the current state of knowledge and to identify leads for future research.

Methods

A systematic literature search was performed in the PubMed database using the following keywords: "cancer, oral, pharyngeal, pharynx, hypopharyngeal, hypopharynx, oropharyngeal, oropharynx, occupation, occupational exposure." Additional searches were performed using "asbestos, rubber industry, formaldehyde, wood dust, textile dust, man-made vitreous fibers (MMVF), cement dust, polycyclic aromatic hydrocarbons (PAHs), engine exhaust, diesel, solvent, inorganic solvent, silica," which are the agents that have been linked to these cancers in the first literature search. This additional search allowed to retrieve occupational cohort studies that reported results on cancer of the oral cavity (OC) and pharynx but did not mention these sites in the abstract. For the present paper, we focused on exposures to asbestos, PAHs and solvents, for which the most data were available. Concerning cancer of the pharynx, we considered data on oropharynx (OP) and hypopharynx (HP) when it was available. In the absence of data on these two specific cancer sites, we considered pharyngeal cancer as a whole. We searched for relevant epidemiologic papers published between 1980 and 2010, in French and in English. We also checked the lists of references to identify additional candidate studies.

We performed a series of meta-analyses to provide quantitative pooled estimates of the relative risk, considering agents for which at least five studies with homogeneous exposure were available. We calculated a meta-RR and its 95% confidence interval using the Der Simonian and Laird model (DerSimonian and Laird 1986), which is a random effect model, taking into account the between-study heterogeneity. Forest plots were used to present results graphically. Heterogeneity across studies was quantified by computing the I^2, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance (Higgins et al. 2003). We pooled SMRs, ORs, and RRs, assuming that those different effect estimates represent the relative risk. We checked for overlapping studies and considered the more recently published updates. Meta-analyses were restricted to dichotomic indices of exposure (ever/never), and results were reported as a meta-RR. In three case–control studies (Berrino et al. 2003; Coble et al. 2003; Gustavsson et al. 1998), the "ever exposed" category was not available and impossible to infer from the reported data. For these three studies, we used the extreme categories (low and high, possible, and probable) of the exposure score and combined each in turn with the "ever" category from the other studies. We then calculated two relative risks, a "low exposure meta-RR" and a "high exposure meta-RR." We studied cancers of the OC and pharynx separately as well as grouped together. When we studied cancer of the OC and pharynx grouped together, only data considering both cancer localisations were included in the meta-analysis, i.e., results from case–control studies studying these cancers separately were not included in this analysis. In order to make the studies comparable, and when it was possible, we aggregated the data for men and women when analyzed separately in the original study. We did the same for cancer sites (OC and pharynx) where possible. In a small number of cases (Huebner et al. 1992; Merletti et al. 1991), ORs were given without confidence intervals and those results could not be included in the meta-analysis. We also performed analyses according to study design and to different exposure circumstances. Publication bias was studied using Begg's funnel plots and the Egger's test (Egger et al. 1997a, b). All analyses were performed using the STATA software (Stata Corp. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP. 2007).

Results

We analyzed 63 publications: 8 from case–control studies (see Table 1 of Supplementary material), 55 from cohort studies and record linkage studies (see Tables 2 to 5 of Supplementary material). Table 1 summarizes the results from the different meta-analyses.

Asbestos

Case–control studies

Five case–control studies considered the relationship between exposure to asbestos and malignant neoplasms of the OC and/or pharynx (Berrino et al. 2003; Gustavsson et al. 1998; Huebner et al. 1992; Marchand et al. 2000; Merletti et al. 1991). Results from the Marchand et al. study (2000) suggested an association between asbestos exposure and hypopharyngeal cancer, with significantly increased ORs of 1.8 and 2.1, respectively, for people ever exposed and for people with high cumulative exposure. An international study also found a nonsignificantly increased OR of 1.8 for cancers of the HP in subjects younger than 55 years of age (Berrino et al. 2003). Results for subjects

Table 1 Results from the meta-analyses on exposure to asbestos, polycyclic aromatic hydrocarbons and solvents, and cancers of the oral cavity and pharynx

Agent	Cancer site	Meta-RR (IC 95%)	Number of case–control studies	Number of cohort studies	*p* value for heterogeneity	I^2 (%)	*p* value for Egger's test
Asbestos	Oral cavity and pharynx	1.25 (1.10–1.42)	0	23	0.09	29	0.68
	Oral cavity (high)[a]	1.15 (0.84–1.57)	1	4	0.25	26	0.47
	Oral cavity (low)[a]	1.13 (0.81–1.57)	1	4	0.19	34	0.49
	Pharynx (high)[a]	1.27 (0.98–1.66)	3	5	0.18	31	0.78
	Pharynx (low)[a]	1.26 (0.96–1.66)	3	5	0.16	33	0.78
PAHs	Oral cavity and pharynx	1.14 (1.02–1.28)	0	22	0.71	0	0.73
	Oral cavity (high)[a]	1.25 (0.98–1.60)	1	6	0.64	0	0.86
	Oral cavity (low)[a]	1.15 (0.89–1.49)	1	6	0.63	0	0.97
	Pharynx (high)[a]	1.37 (1.01–1.85)	2	6	0.88	0	0.35
	Pharynx (low)[a]	1.16 (0.85–1.60)	2	6	0.82	0	0.84
Solvents	Oral cavity and pharynx (high)[a]	1.00 (0.73–1.35)	2	3	0.06	56	0.95
	Oral cavity and pharynx (low)[a]	0.98 (0.77–1.23)	2	3	0.17	38	0.42
	Oral cavity[b]	–	0	2	–	–	–
	Pharynx[b]	–	2	2	–	–	–

[a] High exposure meta-RR or low exposure meta-RR (see text)

[b] Meta-analysis was not performed (less than 5 available studies)

older than 55 were not presented in this study; authors only mentioned that exposure to asbestos was not associated with hypopharyngeal cancer at a statistically significant level. The other available studies showed nonsignificant results, with ORs of around one or slightly lower than one.

Cohort studies

Twenty-four cohort studies (Dement et al. 2009a; Dement et al. 2009b; Enterline et al. 1987; Giaroli et al. 1994; Harding et al. 2009; Hein et al. 2007; Hughes et al. 1987; Krstev et al. 2007; Levin et al. 1998; Loomis et al. 2009; Nokso-Koivisto and Pukkala 1994; Parnes 1990; Pira et al. 2007, 2009; Puntoni et al. 2001; Purdue et al. 2006; Raffn et al. 1989; Reid et al. 2004; Sluis-Cremer et al. 1992; Strand et al. 2010; Tsai et al. 2007; Ulvestad et al. 2002, 2004; Ward et al. 1994) and a Finnish record linkage study (Tarvainen et al. 2008) presented results on workers exposed to asbestos and cancers of the OC and/or pharynx. Among them, three referred to miners and millers (Pira et al. 2009; Reid et al. 2004; Sluis-Cremer et al. 1992), six concerned workers of the construction industry (Dement et al. 2009a, b; Krstev et al. 2007; Puntoni et al. 2001; Purdue et al. 2006; Ulvestad et al. 2004), three dealt with asbestos textile workers (Hein et al. 2007; Loomis et al. 2009; Pira et al. 2007), and four concerned cement-asbestos workers (Giaroli et al. 1994; Hughes et al. 1987; Raffn et al. 1989; Ulvestad et al. 2002). Figure 1 presents the results from the 23 cohort studies considering cancers of the OC and pharynx together.

Reid et al. (2004) investigated incidence of upper aerodigestive tract cancers among crocidolite miners and millers. They found increased SIRs for cancers of the OC and a significantly increased SIR for pharyngeal cancer. The authors did not observe any dose–response relationship with cumulative exposure and concluded that the elevated risks could be due to tobacco consumption. A study on miners in South Africa (Sluis-Cremer et al. 1992) found a significantly increased SMR of around 2.1 for workers exposed to amphibole fibers and cancer of the OC and pharynx, which reached 2.9 when considering the subcohort of crocidolite-exposed workers. A nonsignificantly increased risk was found in the third cohort (Pira et al. 2009). Results from cohort studies of construction workers (Dement et al. 2009a, b; Krstev et al. 2007; Puntoni et al. 2001; Purdue et al. 2006; Ulvestad et al. 2004) are difficult to interpret because of the multiple co-exposures of the workers.

Studies on asbestos textile workers (Hein et al. 2007; Loomis et al. 2009; Pira et al. 2007) showed consistently increased but nonsignificant risks.

Asbestos-cement workers cohort studies (Giaroli et al. 1994; Hughes et al. 1987; Raffn et al. 1989; Ulvestad et al. 2002) showed nonsignificantly decreased risks except for

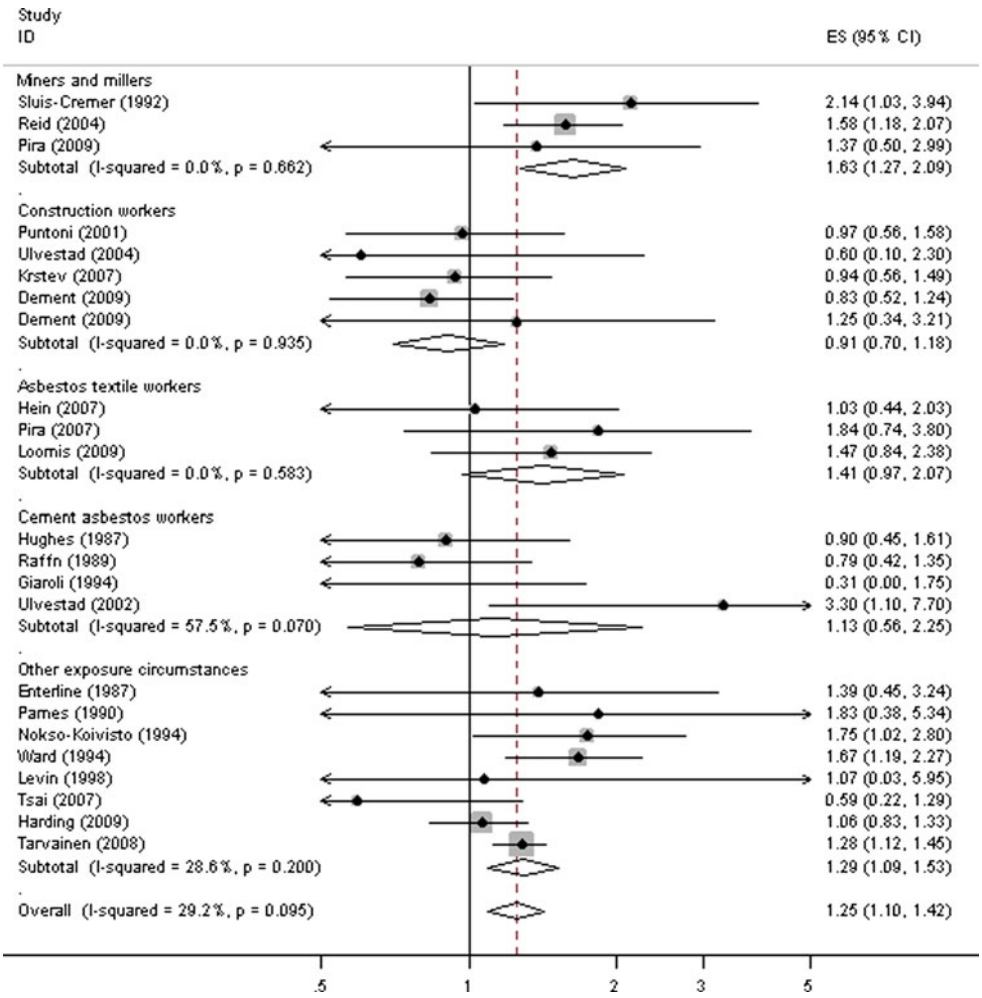

Fig. 1 Relative risks (effect size *ES*) of oral cavity and pharyngeal cancer among workers exposed to asbestos and corresponding 95% confidence interval (*CI*), by study, exposure circumstance and overall (*p* value from Egger's test for publication bias = 0.68)

the Norwegian study (Ulvestad et al. 2002) in which a highly increased SIR of around 3 was observed for cancers of the OC and the pharynx.

Several studies assessed the risk of cancer of the OC and pharynx in various categories of workers exposed to asbestos, such as brake manufacturing workers (Parnes 1990), cable manufacturing workers (Ward et al. 1994), insulation materials manufacturing workers (Levin et al. 1998), locomotive drivers (Nokso-Koivisto and Pukkala 1994), various asbestos companies workers (Enterline et al. 1987; Harding et al. 2009), workers from various occupational groups exposed to different agents including asbestos (Strand et al. 2010; Tarvainen et al. 2008; Tsai et al. 2007). Nonsignificantly (Enterline et al. 1987; Harding et al. 2009; Levin et al. 1998; Parnes 1990; Strand et al. 2010) or significantly (Nokso-Koivisto and Pukkala 1994; Ward et al. 1994) increased risks were found in most of these studies. In the Tarvainen et al. record linkage study (2008), significantly increased SIRs for cancer of the OC and pharynx (excluding nasopharynx) were associated with exposure to asbestos but no dose–response pattern was observed.

In one cohort study (Giaroli et al. 1994), zero cases were observed for cancer of the OC and pharynx, thus leading to SMR equal to zero. In order to be able to integrate this study in the meta-analysis, we computed new SMR by adding one to both the observed number of cases and the expected number of cases (Jones et al. 2009). The resulting meta-RR for cancer of the oral cavity and pharynx grouped together was 1.25 (95% CI 1.10–1.42) (Fig. 1). When we excluded the study with no observed cases, the meta-RR was almost the same (meta-RR 1.25; 95% CI 1.10–1.43). Analysis by exposure circumstance showed meta-RRs of 1.63 (95% CI 1.27–2.09) for miners and millers, 0.91 (95% CI 0.70–1.18) for construction workers, 1.41 (95% CI 0.97–2.07) for asbestos textile workers, 1.13 (95% CI 0.56–2.25) for asbestos-cement workers. Other exposure circumstances could not be studied separately and were analyzed together, yielding a meta-RR of 1.29 (95% CI 1.09–1.53).

Considering cancer of the OC, the "high exposure meta-RR" was 1.15 (95% CI 0.84–1.57) and the "low exposure meta-RR" was 1.13 (95% CI 0.81–1.57). Both meta-RRs were based on five studies. Heterogeneity across studies

seemed to be moderate, with I^2 of 26% and 34%, respectively, for the "high exposure meta-RR" ($p = 0.25$) and the "low exposure meta-RR" ($p = 0.19$).

For pharyngeal cancer, the "high exposure meta-RR" was 1.27 (95% CI 0.98–1.66) and the "low exposure meta-RR" was almost the same (meta-RR 1.26; 95% CI 0.96–1.66). Both meta-RRs had I^2 of around 30% ($p = 0.18$ for the "high exposure result", $P = 0.16$ for the "low exposure result"), showing moderate heterogeneity across studies. The association between asbestos exposure and cancer of the HP, suggested in case–control studies, could not be confirmed in cohort studies because of the lack of data on anatomic subsites of cancer.

Polycyclic aromatic hydrocarbons (PAHs)

PAHs are a class of chemicals including hundreds of compounds. Occupational exposures to these chemicals involve several industries and occupations such as aluminium production, carbon products manufacturing, paving and roofing, coal tar distillation, coke gasification, iron and steel foundries, chimney sweeps, and wood impregnation.

Case–control studies

Results from case–control studies dealing with exposure to PAHs and cancers of OC, OP, and HP (Berrino et al. 2003; Gustavsson et al. 1998; Merletti et al. 1991) did not show any significant excess risk except in the Gustavsson et al. study (1998) that showed a dose–response pattern with cumulative exposure for OC cancer and cancer of the HP and OP.

Cohort studies

Cohort studies of aluminium industry workers (Gibbs and Sevigny 2007; Moulin et al. 2000a; Sim et al. 2009; Spinelli et al. 2006) presenting results for oral and pharyngeal cancers all showed decreased risks except for a Canadian cohort, in which a slightly increased SIR of around 1.15 was found when considering the whole cohort, while a significantly increased SIR of around 2.7 was found for workers highly exposed to benzo-a-pyrene (Gibbs and Sevigny 2007).

The three cohorts of carbon electrode workers (Donato et al. 2000; Merlo et al. 2004; Teta et al. 1987) showed inconsistent results, with no observed deaths in one study (Teta et al. 1987) and nonsignificantly increased risks in the two other studies (Donato et al. 2000; Merlo et al. 2004).

No excess mortality from oral or pharyngeal cancer was found in the two cohorts of carbon black production workers (Sorahan et al. 2001; Wellmann et al. 2006).

Several studies on coal tar and related products were available, concerning asphalt workers, roofers, coal tar distillation, and creosote. Asphalt workers and roofers cohort studies (Behrens et al. 2009; Boffetta et al. 2003; Hansen 1989; Purdue et al. 2006; Swaen and Slangen 1997) showed SMRs above one. In the study from Behrens et al. (2009), SMRs were significantly increased for oral and pharyngeal cancers. Moreover, workers exposed to bitumen fumes, and workers exposed to bitumen and tar, had a significantly increased SMR of 2.1 and 2.9, respectively. However, the Boffetta et al. study (Boffetta et al. 2003), which is a multicentric study including the data from Behrens et al., did not confirm such an excess of mortality since the SMR for bitumen workers was slightly increased but not statistically significant.

The two studies in the coal tar distillation industry (Moulin et al. 1988; Swaen et al. 1991) found increased SMRs.

Considering workers exposed to creosote, Karlehagen et al. (1992) found an elevated SIR of 2.5 for lip cancer, whereas Wong and Harris (2005) did not observe any case of oral or pharyngeal cancer. We chose not to use the result from the Karlehagen et al. study (1992) in the meta-analysis since it concerned cancer of the lip only, and thus was too restrictive to be compared with results on oral cavity and pharynx cancer.

A nonsignificantly increased risk of oral and pharyngeal cancer was found in the two studies of coke workers (Hurley et al. 1983; Swaen et al. 1991), but studies of foundry workers (Hoshuyama et al. 2006; Moulin et al. 2000b; Sherson et al. 1991; Sorahan et al. 1994) did not show results consistent enough for a definitive conclusion.

Evanoff et al. (1993) studied a cohort of chimney sweeps and found an increased incidence of cancer of OC and pharynx.

Tarvainen et al. (2008) observed nonsignificantly increased SIRs for subjects in the low and middle cumulative exposure categories, with SIRs of around 1.2 and 1.4, respectively. The SIR for the highest cumulative exposure to PAHs was 0.4 but was based on only three observed cases.

A meta-analysis was performed considering data on cancers of OC and pharynx grouped together. In three studies (Sorahan et al. 2001; Teta et al. 1987; Wong and Harris 2005), zero cases were observed for cancer of the OC and pharynx. Like in the asbestos meta-analysis, we computed new SMRs by adding one to both the observed number of cases and the expected number of cases. The resulting meta-RR was 1.14 (95% CI 1.02–1.28) (Fig. 2). When we excluded the three studies with no observed cases, the meta-RR was almost the same (meta-RR 1.15; 95% CI 1.03–1.28). Analysis by exposure circumstance showed meta-RRs of 1.05 (95% CI 0.87–1.26) for

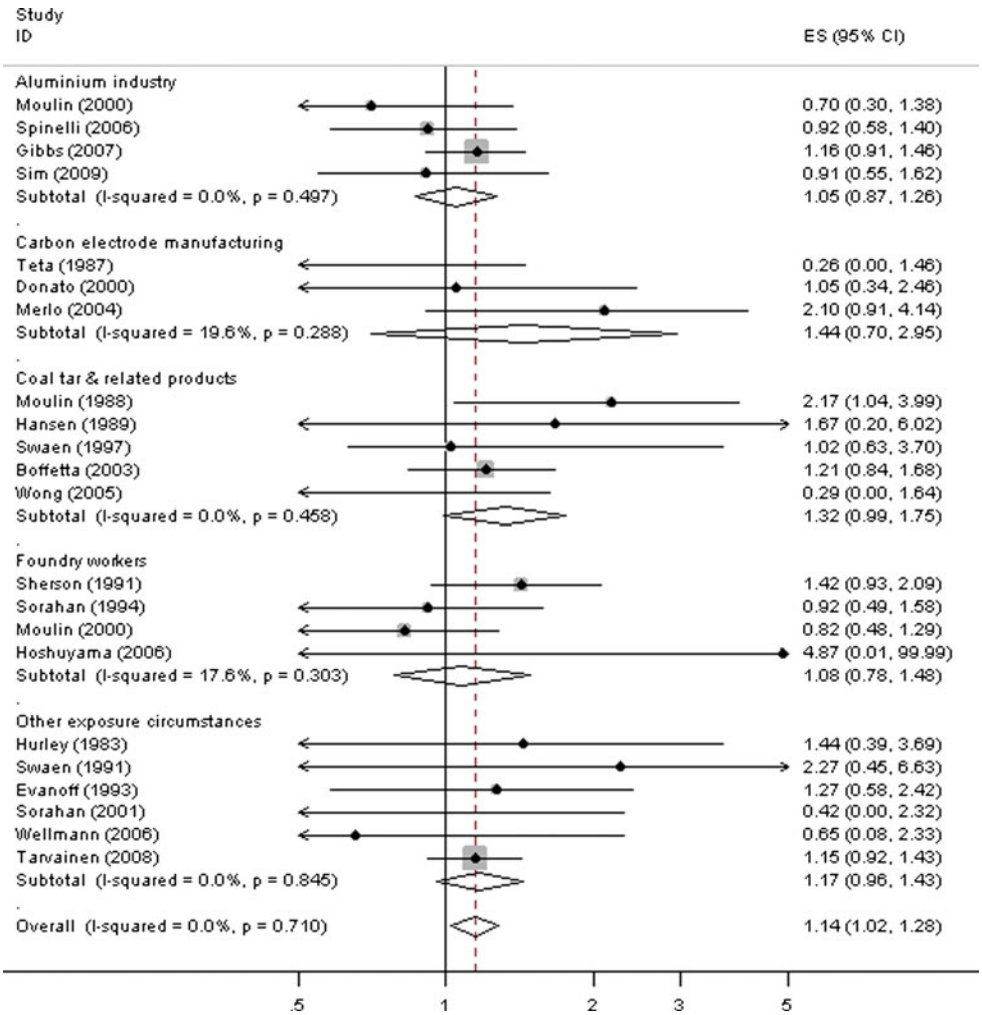

Fig. 2 Relative risks (effect size *ES*) of oral cavity and pharyngeal cancer among workers exposed to polycyclic aromatic hydrocarbons and corresponding 95% confidence interval (*CI*), by study, exposure circumstance and overall (*p* value from Egger's test for publication bias = 0.73)

aluminium industry workers, 1.44 (95% CI 0.70–2.95) for people working in carbon electrode manufactures, 1.32 (95% CI 0.99–1.75) for coal tar and related products workers, and 1.08 (95% CI 0.78–1.48) for foundry workers. Other exposure circumstances could not be studied separately because too few studies were available for meta-analysis. They were analyzed together, yielding a meta-RR of 1.17 (95% CI 0.96–1.43).

The meta-analysis of data on cancer of the OC showed an increased meta-RR of 1.25 (95% CI 0.97–1.60) when the high cumulative exposure RR from the Gustavsson et al. case–control study (1998) was used and 1.15 (95% CI 0.89–1.49) when the low cumulative exposure RR was used.

For pharyngeal cancer, the meta-RR was 1.37 (95% CI 1.01–1.85) when the high exposure estimates from the case–control studies of Gustavsson et al. (1998) and Berrino et al. (2003) were used, whereas the meta-RR decreased slightly to 1.16 (95% CI 0.85-1.60) when the low exposure estimates were used instead.

Solvents

Organic solvents are a chemical category also including a wide variety of compounds: halogenated hydrocarbons, among them chlorinated solvents, aliphatic and alicyclic hydrocarbons, and aromatic monocyclic hydrocarbons. They are widely used in industry, and their characterization varies according to the different studies.

Several studies considered exposure to "solvent as a whole". In a Puerto Rican case–control study on oral and pharyngeal cancers (Coble et al. 2003), the authors underlined a significant dose–response relationship with cumulative exposure to solvents, with ORs reaching 1.6 and 3.2 for the medium and high exposure categories, respectively. In a Finnish record linkage study (Tarvainen et al. 2008), slight increases in the number of cancer cases of OC, HP, OP were observed when exposure to organic solvents was considered. In two cohorts of aircraft maintenance and manufacturing workers where exposures to mixed solvents occurred (Blair et al. 1998; Boice et al.

1999), the SMR for oral and pharyngeal cancers was close to the null value in the Blair et al. study (1998), whereas it was significantly decreased and around 0.4 in the Boice et al. study (1999). Purdue et al. (2006) found a slightly increased risk in a cohort of construction workers exposed to organic solvents for cancer of the OC, but a decreased risk for pharyngeal cancer. Two studies dealt with cancer of the OC and OP grouped together and exposure to solvents (Merletti et al. 1991; Schildt et al. 1999). A decreased OR was observed in the Italian study (Merletti et al. 1991), while the Swedish study (Schildt et al. 1999) showed an increased OR of around 1.2. Berrino et al. (2003) and Shangina et al. (2006) both found increased ORs of around 1.7 for cancer of the HP among people exposed to solvents. The meta-RR for exposure to solvents as a whole and cancer of the OC and pharynx was 1.00 (95% CI 0.73–1.35) when including in the analysis the high cumulative exposure result from Coble et al. study (Coble et al. 2003). The Egger's test did not suggest the presence of publication bias ($p = 0.95$), but the risk estimates showed a strong heterogeneity between studies ($I^2 = 56\%$; $p = 0.06$), which probably reflected heterogeneous exposure circumstances. When including the low cumulative exposure result, the meta-RR was 0.98 (95% CI 0.77–1.23), the I^2 was 38% ($p = 0.17$), and the p value for Egger's test was 0.42.

TCE and PCE are two chlorinated solvents that are widely used, especially in the dry cleaning industry. Data on exposure to TCE and cancer were reviewed in 2000 by Wartenberg et al. (2000). They divided the cohort studies into three groups based on the specificity of the exposure information and computed average relative risks for each group. In the first group, studies in which TCE exposure was best characterized, the corresponding average relative risk for oral and pharyngeal cancers was equal to 0.9. In the second group, studies in which there was a putative exposure to TCE but exposure to other solvent or agents could have occurred, the corresponding average relative risk was also equal to 0.9. In the third group, cohorts of dry cleaners and laundry workers, the average relative risk was 1.2. We identified three studies published since this review. In a Danish cohort study (Raaschou-Nielsen et al. 2003) including more than 340 companies with documented use of TCE, Raaschou-Nielsen et al. found SMRs of 1.1 and 1.8 for, respectively, men and women exposed to TCE. In a cohort of rocket engine testing facility workers (Boice et al. 2006), the SMR for men with potential exposure to TCE was 1.25. Chang et al. (2005) studied cancer incidence among workers potentially exposed to TCE, PCE, and other chlorinated solvents in an electronic factory. For cancers of the OC and pharynx, they found a decreased SMR for men while the SMR for women was close to the null value.

The risk of cancer linked to PCE exposure has been reviewed in 2003 by Mundt et al. (2003), and they concluded that the possibility of an association between oral and pharyngeal cancer and PCE appears unlikely. More recently, Pukkala et al. (2009) found a significant excess risk of around 1.2 for OC cancer among female launderers, whereas the risk was decreased among men and close to the null value for cancer of the pharynx for both men and women.

Other specific solvents were also examined in some studies. Ruder et al. (2004) considered mortality among workers exposed to styrene in the boatbuilding industry, but results were inconclusive because of the small number of observed cases. The study by Lehman and Hein (2006) considered exposure to toluene in a cohort of shoe manufacturing workers, and the results showed slightly increased mortality among men. A Finnish record linkage (Tarvainen et al. 2008) studied exposure to different kinds of solvents in relation to cancers of the OC and pharynx. The authors found a significantly increased RR of around 1.7 for people highly exposed (in terms of cumulative exposure) to aliphatic and alicyclic hydrocarbons. Slight increases were also observed for chlorinated solvents and aromatic hydrocarbons.

We chose not to perform meta-analysis for specific types of solvents due to the heterogeneity of exposures in the different studies.

Discussion

Our results provide suggestive evidence of an association between asbestos and PAHs and cancer of the OC or pharynx. The meta-analysis of cohort studies of asbestos-exposed workers resulted in a meta-RR of 1.25 (95% CI 1.10–1.42) for cancer of the OC and pharynx considered together. The highest meta-RR, 1.63 (95% CI 1.27–2.09), was observed in cohorts of miners and millers, who had the highest exposures. Findings from cohort studies were corroborated by the association between asbestos exposure and cancer of the pharynx found in case–control studies. Asbestos is a known lung carcinogen in humans and, in a recent evaluation, was also highlighted as a cause of laryngeal cancer, whereas evidence in humans was considered limited for cancer of the pharynx (Straif et al. 2009). Our results provide some supporting evidence for such an association. The pharynx, like the lung and the larynx, is anatomically in the direct path of inhaled asbestos fibers, and squamous cell carcinomas of the pharynx, larynx, and lung have some histological and clinical similarities. Asbestos fibers, together with smoking and drinking, could produce chronic irritation or inflammation resulting in malignant transformation. Since MMVF have the same

physical properties as asbestos, exposure to these agents is also possibly associated with an increased risk of oral and pharyngeal cancer. A recent meta-analysis on occupational exposure to rock wool and glass wool found a significantly increased meta-RR of 1.32 (95% CI 1.09–1.59) for exposure to "all MMVF" and cancer of the OC and pharynx (Lipworth et al. 2009).

Overall, a significant but moderate association between PAHs exposure and cancer of the OC and pharynx was found (meta-RR 1.14; 95% CI 1.02–1.28), but the strength of the association differed according to the activity. Meta-RRs around one were found for aluminium industry workers (meta-RR 1.05; 95% CI 0.87–1.26) and foundry workers (meta-RR 1.08; 95% CI 0.78–1.48). Nonsignificantly increased meta-RRs were observed for carbon electrode manufacturing workers (meta-RR 1.44; 95% CI 0.70–2.95) and workers exposed to coal tar and related products (meta-RR 1.32; 95% CI 0.99–1.75). As exposure to PAHs could be very different between the various exposure circumstances, in terms of composition and concentration of PAHs, the global meta-RR should be interpreted cautiously. Meta-RRs specific to exposure circumstances should also be interpreted with caution since they are based on few numbers of studies. Despite these limits, carcinogenicity of PAHs regarding oral and pharyngeal cancers remains possible. Thus, several PAHs, as well as occupational activities involving exposure to PAHs, are definite or probable lung carcinogens (Straif et al. 2005) and could be associated with cancers in other sites of the respiratory tract. Moreover, the well known strong association between exposure to tobacco smoke, which contains PAHs, and cancers of the upper aero-digestive tract, suggests that the carcinogenicity role of PAHs in OC and pharynx cancers has some biological plausibility.

Globally, no increased risk of cancer of the OC and pharynx was found to be associated with exposure to solvents in general, but the strong heterogeneity between studies suggested differences in exposures. Elevated risks associated with some specific solvents such as PCE and TCE were also observed in a number of studies, but the small number of studies with homogeneous exposure did not allow to perform meta-analyses.

Overall, the evidence regarding occupational factors for cancers of the OC and pharynx remains inconclusive and this for several reasons. The lack of consistency in the definition or grouping of cancer sites hampered the comparison between studies. Especially in cohort studies, but also in some case–control studies, cancers of the OC and pharynx were grouped in the analysis, sometimes with other head and neck cancers. Cancers of the OP and of the HP are almost never studied separately. Although these cancer sites are in anatomically close areas, they may have different etiologic risk factors. This grouping of cancer sites is often due to another shortcoming of most of the studies, small sample size, and thus limited statistical power to detect moderate increases in risk. This is particularly true for occupational cohorts, which provided much of the information, and were mainly conducted in low-incidence areas, yielding a small number of observed cases. Another limitation is that an important proportion of cohort studies do not present findings on cancers of the OC and pharynx, mainly because these cancers were not the cancers of interest in most of them. We compared the number of available cohort studies presenting results for oral and pharyngeal cancers with the number of cohort studies listed in two meta-analyses on cancer risk and exposure to asbestos (Goodman et al. 1999) and PAHs (Bosetti et al. 2007). The ratio (number of cohort studies presenting findings on oral and pharyngeal cancers divided by the number of cohort studies listed in the two meta-analyses) approximated 50% for exposure to PAHs while it barely reached 17% for exposure to asbestos. Cohort studies also typically lack data on potential confounding factors, such as smoking and alcohol drinking, the major risk factors for oral and pharyngeal cancers. In case–control studies, risk estimates were adjusted for alcohol and tobacco consumption. Conversely, information on occupational exposure was sometimes crude in case–control studies.

The limited number of case–control studies did not allow us to compute separate meta-RRs for case–control study design and cohort study design. However, the comparison of individual results from case–control studies to meta-RRs from cohort studies did not reveal important differences.

In two case–control studies (Huebner et al. 1992; Merletti et al. 1991), the confidence intervals of the ORs were not available and it was not possible for us to compute them. Thus, we were not able to integrate these results in the meta-analysis. Since ORs from these two studies were globally equal to one or lower than one depending on the considered agent (see Table 1 from supplementary material), the fact that we did not include them in the meta-analyses may have led to a slight overestimation of the meta-RRs. We assessed publication bias by formal testing using Egger's test and through visual inspection of the corresponding Begg's funnel plots. No evidence of publication bias was observed, with p values exceeding 0.30 in all analyses (Table 1), and no obvious asymmetry in funnel plots (not shown). We analyzed 62 English language publications and one French publication. Egger et al. (1997a) studied English language bias. They assessed whether German authors were more likely to publish trials with statistically significant results in English rather than in German. They found that authors were more likely to publish trials in an English journal if the results were statistically significant. This may be due to the difficulty to

publish non-statistically significant results in international journals. Their study concerned randomised controlled trials but the same observation may be applied to occupational cohort and case–control studies. Thus, including papers published in languages other than English could help to minimize publication bias. For practical reasons, we restricted ourselves mainly to international journals.

In almost all reviewed studies, exposures were not sufficiently well characterized, either qualitatively or quantitatively, making interpretation difficult. In particular, summary risk estimates were not calculated by exposure level or duration, since no such data were available in most of the studies. The impossibility to assess dose–response relationships rules out any firm conclusion regarding causality. We chose to select studies published from 1980 onward, and this may have led to a loss of information. Oral and pharyngeal cancers are diseases requiring a long latency period between exposure and occurrence of the carcinoma (from ten to more than 30 years). Papers published before 1980 would thus reflect exposures having occurred in the first 60 years of the twentieth century. Because industrial processes are in constant evolution, however, the exposures considered in those papers would probably not reflect current exposure circumstances.

In conclusion, the possible role of asbestos, PAHs and solvents in the risk of oral and pharyngeal cancer needs to be further investigated. To be informative, future studies should overcome past limitations in terms of sample size, characterization of exposure, and classification of cancer sites.

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