Occupational polycyclic aromatic hydrocarbon exposure and risk of larynx cancer: a systematic review and meta-analysis

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ABSTRACT

Polycyclic aromatic hydrocarbons (PAH) are genotoxic substances formed during combustion. Occupational PAH exposure has been shown to increase the risk of lung cancer and may be associated with other respiratory cancers. We conducted a systematic review and meta-analysis to clarify the relationship between occupational PAH exposures and larynx malignancies. We searched EMBASE and MEDLINE (until July 2014) using a series of search strings developed to seek case–control studies or longitudinal studies of workers (Population) exposed to PAHs (Exposure) and their risk for larynx cancer incidence and/or mortality (Outcome). Two independent reviewers screened the titles and abstracts for eligible articles and a third reviewer negotiated consensus. Further assessments of eligibility and sources of bias were conducted in a similar manner. The study results were pooled with random effects meta-analysis. The search resulted in 3377 records. The data of 92 full-text articles representing 63 studies were included and extracted. The majority of studies (n=47) was judged likely to be biased; only 16 studies were judged as methodologically adequate. The pooled effect size was 1.45 (95% CI 1.30 to 1.62; I^2=30.7%; $\hat{\tau}^2$=0.03) for larynx cancer incidence and 1.34 (95% CI 1.18 to 1.53; I^2=23.8%; $\hat{\tau}^2$=0.03) for larynx cancer mortality. While few studies allowed an investigation of dose–response, these indicate a positive dose–response effect. Although most studies may underestimate the true effect due to inexact approximations of PAH exposure, the meta-analysis suggests a robust positive association between PAH and larynx cancer.

What this paper adds

- Increased risk of lung cancer due to occupational polycyclic aromatic hydrocarbon (PAH) exposure is generally recognised, however the relationship between occupational PAH exposure and larynx cancer has not yet been well established.
- This systematic review specifically examines the causal relationship between occupational PAH exposure and malignancies of the larynx.
- The results of this systematic review and meta-analysis show a robust relationship between occupational PAH exposure and larynx cancer diagnoses, suggesting a need to consider larynx cancer following occupational PAH exposure as a potential occupational disease.

INTRODUCTION

Polycyclic aromatic hydrocarbons (PAH) have been found to be human carcinogens by the International Agency for Research on Cancer (IARC) which classified benzo[a]pyrene (BaP), a well-researched PAH and common indicator for PAH exposure, as a group 1 substance (carcinogenic to humans).[1] Genotoxic effects of PAHs result from cysteine methylation caused by PAH metabolites, which in turn disrupt gene expression.[2] The cumulative DNA damage and subsequent disruption of gene expression increases the risk of cancer in human cells.

PAHs are common air pollutants formed as by-products of incomplete combustion of organic matter, and new evidence of the health hazards related to prenatal PAH exposure[3] and the potential effects of possible PAH-related endocrine disruptions[4] have recently increased public awareness of PAHs. Despite the practically ubiquitous nature of PAHs as man-made pollutants, occupations involving the burning of wood or coal (ie, coke oven workers, foundry workers and chimney sweeps), coal refinement, exposure to coal or oil derivatives, such as industrial carbon black, asphalt or metal working fluids (MWF; ie, rubber production, printers, street pavers, roofers and metalworkers), and the production of aluminium using carbon electrodes involve intensified and prolonged exposures to PAHs.

An increased risk for lung cancer due to occupational PAH exposure was observed by numerous epidemiological studies examining, for example, the coke oven industry, the production of generator gas, the production of aluminium, street pavers, roofers and chimney sweeps.[1 5] Most reviews of existing observational research have also focused mainly on the relationship between occupational PAH exposure and lung cancer.[6 7] Owing to the strength of evidence supporting a link between PAH exposure and the incidence of lung cancer, Germany recognises lung cancers in conjunction with a verified cumulative occupational exposure of 100 BaP-years ((µg/m³)×year) as an occupational disease (German occupational disease #4113). However, the aetiological relationship between occupational PAH exposure and other cancers of the respiratory tract, such as larynx cancer, has not yet been extensively examined.

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Larynx or laryngeal cancer is a malignancy of the voice box and a common head and neck cancer. In 2012, the global age-standardised incidence per 100 000 of larynx cancer was 3.9 (crude 3.9) among men and 0.5 (crude 0.5) among women.[8] Treatment of early stage larynx cancers often result in permanent vocal damage and difficulty swallowing, and despite continuing advancements in treatments, unresponsive or late stage cancers can require a total laryngectomy, greatly diminishing quality of life. Risk factors for larynx cancer include tobacco and alcohol use,[9 10] infection with human papillomavirus[11] and occupational exposures to harmful substances, such as asbestos.[12] A recent review of literature regarding an array of occupational exposures and larynx cancer indicates an increased risk of cancer associated with exposure to PAH.[13] The goal of this systematic review is to clarify the potential aetiological role of PAH on the risk of larynx cancer by applying the principles of evidence-based medicine and examining existing evidence regarding a dose–response relationship.

Box 1 Highly polycyclic aromatic hydrocarbon-exposed jobs and branches of work[1 5]

- Coke oven plant workers;
- Chimney sweeps;
- Aluminium production using the Söderberg process;
- Roofers handling coal tar pitch;
- Electrographite production;
- City gas production;
- Refining of stone coal and brown coal tar;
- Road construction with coal tar-based binding material;
- Carbon black production;
- Foundry industry, iron and steel production;Printing industry;
- Rubber industry;
- Automobile industry with lubricating grease/oil exposure;
- Metal-machining.

METHODS

In accordance with the Population Intervention Comparison Outcome (PICO) framework for developing systematic review search strategies,[14] we set out to determine if there is an association between occupational (P) exposures to PAH (I, which is mostly understood as E=exposure in observational aetiological studies) and the occurrence of larynx cancer (O). This research question served as a guide for the development of the search string, and also provided a structure for the definition of inclusion and exclusion criteria. A search of MEDLINE (via PubMed) and EMBASE (via Ovid) was conducted in 2008, updated in early 2011 and in July 2014 using the same search strings. Altogether the search time frame comprised literature published from 1 January 1953 through 14 July 2014 for MEDLINE and 1 January 1974 through 14 July 2014 for EMBASE. The extensive search string included terms regarding work and occupations, terms for PAH and components of PAH (eg, polycyclic aromatic hydrocarbon, benzanthracene, benzopyrene, etc) as well as terms for jobs and occupations with elevated PAH exposure, and terms for larynx cancer. Additionally, a term for the study design (cohort or follow-up or longitudinal or case–control or case referent or case–cohort or review or systematic or evaluation) was used in an attempt to limit the search results to studies of a longitudinal nature. Combinations of the search terms categories were used to obtain as many relevant citations as possible. The search strategy also included a search string without the term 'larynx cancer' to find articles addressing numerous cancer sites, where larynx was not mentioned in the title, abstract or key words. Owing to the length of the applied search strategy, the complete search strings are available in the online supplementary file.

An a priori defined set of inclusion and exclusion criteria for the selection of relevant studies was recorded in the study protocol. The initial criteria included studies of (P) persons aged 13 years or older and with a defined occupation, reporting (I) exposure as work-place measurements of PAH or BaP, and (O) outcome as pathological/histological objective diagnosis of a primary manifestation of larynx cancer, tumour or malignancy (including premalignant conditions). However, after examination of the first full-text studies, the initial inclusion criteria, particularly regarding exposure assessment, were found to be too limiting. To resolve this problem, the inclusion criteria were expanded to also include occupational exposure determined by expert assessment, with the aid of a job exposure matrix (JEM) or estimated based on information from task-specific questionnaires. Studies were also included when they contained risk information for workers in highly exposed PAH occupations or branches of industry[1 5] (see box 1), where a cumulative PAH exposure of at least 20 $\mu g/m^3 \times$years could be expected.[15] Exposure measurements providing the most accurate and objective estimates of occupational exposure were considered preferable. The reviewers were able to read studies published in English, German, French (AS, AF/MW, UB-A) and Italian (AF).

Title and abstract screening was done independently by two reviewers (MW/AF and UB-A). In cases of discrepancies, a third reviewer (AS) negotiated a consensus. Full-text articles were also examined independently by two reviewers (MW/AF and UB-A). Data extraction of the full texts was done by one reviewer (MW) and the extracted information was examined and augmented by the second reviewer (UB-A). In addition to the evaluation of the inclusion and exclusion criteria, the internal and external validity or methodological quality of the full-text articles were also evaluated by two independent reviewers (MW and UB-A).

The study quality was assessed with a hybrid evaluation tool that has previously been applied by systematic reviews of occupational health-related issues.[16 17] This evaluation tool comprises items of the SIGN and CASP quality assessment tools[18 19] and has been previously published.[16] In accordance with the SIGN checklist, methodological study quality was classified as

> "++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter;
>
> + Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions;
>
> – Few or no criteria fulfilled."[19]

We considered selection bias and lack of consideration for confounding to be especially serious potential sources of bias. Selection bias was considered sufficiently addressed when a study reported a well-defined study sample, a response rate of at least 50%, and little loss-to-follow-up. Owing to the importance of smoking and alcohol consumption as confounders for larynx cancer, these should have also been addressed for the risk estimates to be considered resistant to bias. A study could be considered resistant to bias (++) when the study was large, representative, with good response, and little loss-to-follow-up.

Also, exposures should have been measured objectively and accurately (preferably cumulative exposures from workplace monitoring), and bias due to tobacco and alcohol consumption and other workplace exposures adequately adjusted. Studies meeting some of the above requirements, where bias seemed unlikely but could not be ruled out were categorised as (+). Studies not directly addressing smoking but reporting a low risk (risk estimate ≤1) of non-malignant respiratory diseases were considered less likely to be biased by smoking and could also be categorised as (+). Finally, studies with insufficient consideration of confounding due to smoking and alcohol, and lacking PAH-specific risk estimates were considered susceptible to bias (−). Once again, a third reviewer (AS) was consulted in cases where consensus was not initially attained.

Meta-analysis was used to pool the results from the published studies. When a study was described in several publications or with multiple follow-ups, only the data from the publications with the best quality and—in the case of several studies with the same quality—the most recent publication (ie, longest follow-up) were pooled, respectively. Owing to the heterogeneity of the populations examined by the studies, a DerSimonian and Laird random-effects[20] meta-analysis of adjusted estimates was conducted using the metan package of STATA[21 22] to obtain a pooled effect size (ES) for the risk of a malignancy of the larynx associated with occupational PAH exposure. Owing to the low prevalence of larynx cancer, we considered ORs to be an adequate approximation of the RR for the purposes of pooling. Likewise, standardised incidence and mortality ratios (SIR, SMR) and proportional mortality ratios were considered acceptable approximations of RR.[23] When studies reported no observed cases of larynx cancer among the sampled population during the observation period, 0.5 was added to the observed and expected values of the SIR/SMR.[14] Owing to the general unavailability of reported SD estimates, the natural logarithms of the reported 95% confidence limits were entered into metan to account for the variance of the individual study estimates. Subgroup analyses were performed to explore the influence of study characteristics, such as study outcome (ie, incidence vs mortality), study design and the nature of the occupational exposure on the pooled ESs and the heterogeneity measured. Sensitivity analyses were conducted to determine the influence of individual studies on the pooled estimate by removing all risk estimates of each study from the meta-analysis and reporting the resulting range of pooled estimates. Finally, potential publication bias was examined with a funnel plot created with the metafunnel command.

RESULTS

In 2008, the search of the MEDLINE (via PubMed) and EMBASE databases resulted in 2752 retrieved titles and abstracts (MEDLINE n=1786; EMBASE n=966). The search updates in 2011 and 2014 resulted in 427 (MEDLINE via OVID, n=226 and EMBASE, n=201) and 734 further records (MEDLINE via OVID, n=297 and EMBASE, n=437), respectively. After the removal of duplicate records, 3266 (2008 n=2368; 2011 n=309; 2014 n=589) articles remained in the title and abstract assessment. Of these articles, only 123 were considered acceptable for the full-text assessment. During the full-text assessment, 53 of these articles did not meet the inclusion criteria so that the remaining 70 articles were included in the systematic review.

In addition to the database search, the full-text articles' references lists and reference lists of related reviews[1 24] were searched for additional relevant studies. Altogether, this manual search resulted in 179 references. After exclusion of duplicate articles and 77 non-eligible titles and abstracts, 34 full texts were assessed for eligibility. Ultimately, 22 hand search studies were included in the final quality assessment and data extraction. Altogether, a total of 92 articles describing 63 studies were found to meet the inclusion criteria. A list of the excluded full-text articles and reasons for exclusion is available on request. A flow chart depicting the complete article obtainment process is found in figure 1.

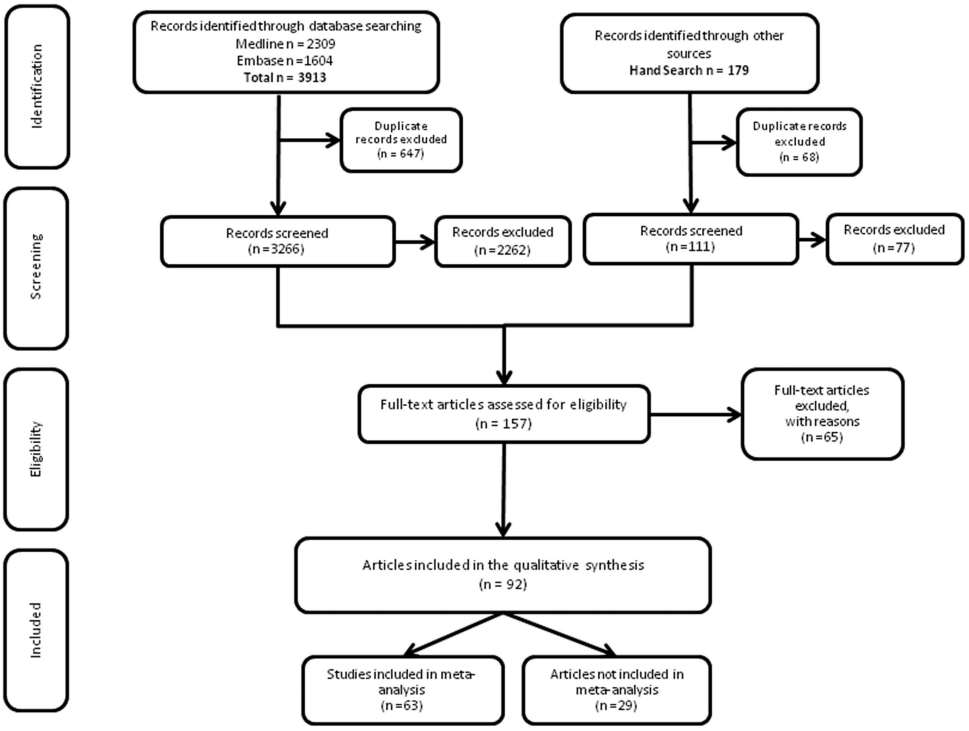

Figure 1 Flow chart depicting the literature search and the evaluation process for finding relevant studies.

None of the full-text articles assessed addressed all or most of the study quality criteria necessary to achieve the best quality rating (++). Sixteen (25.4%) of the 63 studies were of adequate methodological quality (+), meaning the results of these studies can be considered to be somewhat resistant to bias and relatively sound. Of these studies nine were cohort (includes 1 record-linkage study),[25–33] four were population-based case–control[34–36 37] and three were hospital-based case–control studies.[38–40]

A majority (n=47, 74.6%) of the full-text articles assessed were found to be lacking essential quality criteria and were given a low (–) rating. Owing to the potential effects of bias, the reported risk estimates of these studies could differ from the true risk and should be considered with caution. Of the studies in this category eight utilised case–control designs; more specifically, two were population-based case–control studies,[41 42] one was a case–control study nested within a cohort[43] and five were hospital-based case–control studies.[44–48] However, a majority (n=39) of the studies in this category could be considered cohort studies. Historical cohorts of factories or groups of workers were described in 32 studies,[49–80] while 7 articles reported the cancer risks of numerous occupations using cancer or death registry information and record-linkage methods.[81–87]

With regard to the exposure metrics applied by the studies, a majority of the studies (n=40) examined the risks of exposed occupations or industries.[28 29 31 38 40 49–59 61–64 66–71 73–86] Only the studies by Gibbs *et al*[26] and Gustavsson *et al*[27] measured exposure to PAH as BaP-years determined through the monitoring of workplace air samples. However, only Gibbs *et al* used these measurements for reporting the risks of larynx cancer. Eight studies used expert assessment to determine exposure, but only Gustavsson *et al*[36] specifically considered exposure to PAHs while others examined PAH-related exposures (ie, MWF, coke combustion, carbon black).[25 33 41 47 48 65 87] Five studies applied a JEM[30 32 35 39 60] to assess past (excessive) PAH exposures, but two studies only report larynx cancer risk estimates for the entire group.[30 32] Only the Becher *et al*[34] study used a questionnaire to quantify hours of PAH exposure. Finally, four studies used a JEM[37 43 44 72] and three studies used questionnaires[42 45 46] to assess PAH-related exposures. Study characteristics of all of the studies assessed are shown in the data extraction tables (see online supplementary file).

Owing to the fact that some of the 63 studies were described in several publications, sometimes due to the reporting of follow-ups, only the article with the longest follow-up and best quality was included in the meta-analysis (figure 1). In the case of publications reporting the ES for several (exclusive) population samples representing different occupational or exposure groups, several ESs were obtained from a single publication. If a portion of the sample population was included in more than one of the reported ESs due to an affiliation with several occupational categories, only the occupational group with the potentially highest PAH exposure was extracted and included in the meta-analysis. The 89 effect estimates from all 63 studies ranged from 0.16 to 28.27 and resulted in an overall pooled ES of 1.40 (95% CI 1.29 to 1.52; I^2=27.0%, $\hat{\tau}^2$=0.03).

The results of the subgroup analyses examining the influence of various factors on the pooled ESs and heterogeneity measured are shown in table 1. Notably, an initial examination of the 48 risk estimates reported for incidence of larynx cancer resulted in a pooled ES of 1.45 (95% CI 1.30 to 1.62; I^2=30.7%, $\hat{\tau}^2$=0.03) compared with 1.34 (95% CI 1.18 to 1.53; I^2=23.8%, $\hat{\tau}^2$=0.03) from the 41 larynx cancer mortality risk estimates. The assessed study quality had little influence on the pooled estimates (+and–studies had pooled ES of 1.36 and 1.41, respectively), but although the estimates of between-study variance were the same ($\hat{\tau}^2$=0.03) for both subgroups, the amount of variation due to heterogeneity (I^2) indicated that the pooled effect estimates from better rated studies (+) were less heterogeneous (I^2=16.0%) compared with the studies fulfilling few or none of the quality criteria (–) (I^2=30.9%).

To examine what influence the source and nature of occupational PAH exposure might have on the risk of larynx cancer, risk estimates corresponding to similar occupational groups, industrial branches or exposure source materials were pooled. These subgroups included tar-exposed workers (eg, roofers, street pavers), workers in the aluminium industry, workers exposed to MWF, foundry workers, electrographite production workers, chimney sweeps, print industry workers, rubber industry workers and coke oven workers (table 1). The two highest pooled ES were observed for rubber industry workers and coke oven workers at 2.41 (95% CI 1.54 to 3.79; $n_{\text{risk estimates}}$=8; I^2=39.1%, $\hat{\tau}^2$=0.15) and 2.21 (95% CI 1.60 to 3.05; $n_{\text{risk estimates}}$=2; I^2=0%, $\hat{\tau}^2$=0.00), respectively. In contrast, the lowest pooled ES was observed for the printing industry (ES=1.24 (95% CI 1.10 to 1.39); n=8; I^2=4.2%, $\hat{\tau}^2$=0.00).

Four studies assessed PAH exposure by grouping persons that were deemed to have had an increased occupational PAH exposure due to the nature of their employment or job tasks, and therefore could not be included in the subgroup analysis of occupations, industrial branches and exposures. Likewise, five additional effect estimates included in the overall pooling were not pooled with the occupational subgroups due to the distinct nature of the exposures represented by these estimates.

The sensitivity analysis resulted in pooled ES ranging between 1.38 and 1.42. The lowest pooled ES was obtained without the risk estimates of the Imbernon study,[43] and the greatest ES resulted without the risk estimates of the Pukkala *et al*[86] study. During the evaluation of the studies, it was discovered that the Waldron study[87] did not technically meet the inclusion criteria, since it examined secondary malignancies in a cohort of patients with scrotal cancer. To determine how much influence this might have had on the pooled ES, a post hoc sensitivity analysis was conducted without the Waldron study. The minimal change to the pooled ES resulting from the removal of this study is shown in table 1.

The funnel plot of the risk estimates seen in figure 2 appears to depict some publication bias. The highest risk estimate with greatest SE without a low-risk counterpart (figure 2) stems from the Hoshuyama *et al*[60] study of steel workers in China, which published separate risk estimates for PAH-exposed workers with differing dust exposures. This RR of 28.27 depicts a risk for PAH–exposed workers additionally exposed to two or more dusts and was published together with two more moderate estimates.

DISCUSSION

Overall, the epidemiological evidence implies that risk of larynx cancer is associated with occupational exposures to PAH. The pooled results found both incidence and mortality of larynx cancer elevated among persons exposed to PAHs through their work, although the quality of the literature examined was considered to be mediocre at best. Few studies made attempts to measure actual PAH exposure at the workplace and fewer estimated cumulative exposure levels. Important confounders, such as alcohol and tobacco consumption or other occupational exposures, were often disregarded or poorly addressed.

Table 1 Pooled ESs resulting from the meta-analysis, subgroup analyses and sensitivity analyses with number of risk estimates included in the pooling and the amount of variation due to heterogeneity (I^2), and the estimate of between-study variance () in each subgroup

	Pooled ES	Risk estimates (n)	I^2 (%)	$\hat{\tau}^2$
All studies	1.40 (1.29 to 1.52)	89	27.0	0.03
Incidence	1.45 (1.30 to 1.62)	48	30.7	0.03
Mortality	1.34 (1.18 to 1.53)	41	23.8	0.03
Quality+	1.36 (1.17 to 1.58)	22	16.0	0.02
Quality–	1.42 (1.28 to 1.57)	67	30.9	0.03
Case–control	1.55 (1.20 to 2.00)	15	55.1	0.12
Cohort/register	1.37 (1.26 to 1.49)	74	18.0	0.02
Occupational exposure groups				
Asphalt exposed	1.30 (0.95 to 1.78)	12	51.0	0.13
Aluminium production	1.32 (1.04 to 1.67)	10	0.0	0.0
Metal-working fluids	1.55 (1.10 to 2.20)	12	58.4	0.18
Foundry	1.27 (1.17 to 1.39)	19	0.0	0.0
Electrographite	1.33 (0.52 to 3.38)	3	31.4	0.22
Chimney sweeps	1.47 (1.08 to 1.99)	6	0.0	0.0
Printing industry	1.24 (1.10 to 1.39)	8	4.2	0.0
Rubber industry	2.41 (1.54 to 3.79)	8	39.1	0.15
Coke oven workers	2.21 (1.60 to 3.04)	2	0.0	0.0
Sensitivity analyses				
Minimum pooled ES*	1.38 (1.28 to 1.50)	87	25.3	0.03
Maximum pooled ES†	1.42 (1.29 to 1.57)	82	28.4	0.04
Post hoc analysis excluding Waldron[87]	1.39 (1.28 to 1.50)	88	23.5	0.02

*Imbernon *et al* 1995[43] removed.
†Pukkala *et al* 2009[86] removed.
ES, effect size.

Nevertheless, we found a robust association between occupational PAH exposure and larynx cancer.

The findings of this systematic review corroborate the findings of the recently published review by Paget-Bailly *et al*[13] that examined various occupational exposures and larynx malignancies. Paget-Bailly *et al* also found an increased risk of larynx cancer, reporting a statistically significant pooled ES of 1.29 (95% CI 1.10 to 1.52) for occupational PAH exposures, but included only 22 studies in their meta-analysis.

Unlike the review by Paget-Bailley *et al*, the research question and search string applied here focused only on occupational exposures to PAH and larynx cancer. Correspondingly, inclusion and exclusion criteria were formulated and described in an unpublished study protocol from June 2008 to assure the research question was properly addressed. However, modifications were made to the a priori inclusion and exclusion criteria during the early stages of the full-text assessment due to the evident lack of studies reporting exposure as actual work-site measurements of PAH. The new inclusion criteria permitted the consideration of qualitatively acceptable studies estimating exposure to PAH with the help of expert assessments or job-exposure matrices and numerous studies reporting larynx cancer rates for occupational groups known to be exposed to PAHs. While the expansion of the inclusion criteria at an intermediate research stage could be considered a shortcoming of this study, the extensiveness of the search strings which also included a comprehensive list of potentially PAH-exposed occupation and job titles made the expansion feasible.

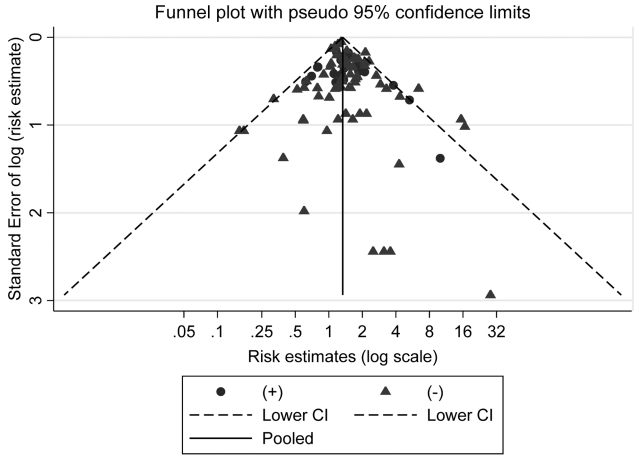

Figure 2 Funnel plot of the risk estimates labelled according to methodological quality classification.

One potential asset of this systematic review is the assessment of bias, which provides insight concerning the reliability of the body of published study results. It is notable that none of the studies was judged to be without some potential influence of bias and a majority of the studies were found to be highly likely to be biased, perhaps in part due to the fact that the record-linkage/cohort studies were predominantly exploratory and only indirectly examined the relationship between PAH and larynx cancer. However, although an established SIGN/CASP hybrid checklist[18 19] provided guidance for the assessment of internal and external validity, the quality score remained a somewhat subjective rating with the reviewers presuming an amount of bias that could be attributed to certain study design and analyses aspects with respect to the study question. However, to enhance objectivity and reproducibility of the quality assessment, for some important sources of potential bias (eg, selection bias, confounding), concrete a priori criteria had been formulated.

The potential publication bias and the missing assessment of conflicts of interest among the authors of the individual articles can also be considered as a weakness of this systematic review. The funnel plot shown in figure 2 does seem to be asymmetrical. However, since many of the studies included were more exploratory or focused on a different key question (ie, risk of lung cancer or cancer in general), publication bias with respect to larynx malignancies seems unlikely. We also did not take conflicts of interest into consideration while assessing the articles, but many of the studies examined were published before it was customary to disclose this information, making it difficult to adequately consider the potential influence this might have had on the results.

One goal of this study was to examine if the evidence of a *causal* relationship between occupational PAH exposure and larynx cancer exists. To examine the evidence of causality, we considered the fulfilment of some of the ancillary criteria for causality described by Sir Austin Bradford Hill in 1965 below.[88]

This systematic review resulted in a pooled effect risk of circa 1.4—representing an increased risk of about 40% for PAH-exposed workers. Although we attempted to include only exposure categories including persons with a cumulative PAH exposure of at least 20 $\mu g/m^3 \times$years, many studies did not permit an approximation of cumulative PAH exposure, so individuals with low cumulative exposures were also included in the exposed category. Considering that this misclassification bias might result in an underestimation of the risk and the fact that the pooled estimate is clearly significant, the strength of this association can be considered acceptable.

Sensitivity analyses were conducted to examine the effects of different study aspects, such as methodological quality, on the pooled results. These sensitivity analyses repeatedly resulted in significantly increased pooled risks, suggesting the fulfilment of the consistency of the association criterion. Additionally, Paget-Bailly *et al*[13] also reported a statistically significant increased pooled risk for occupational PAH exposure and larynx cancer. However, at 1.29 (95% CI 1.10 to 1.52), the pooled risk was somewhat lower. This may be in part due to differences in the original articles examined. Paget-Bailly *et al* included only 22 studies in their meta-analysis. Additionally, while we included multiple risk estimates originating from a single publication if the risk estimates described different exposure levels or populations and we were convinced individuals would not be included in the pooling twice, Paget-Bailly *et al* pooled one risk estimate per study. Despite the methodical differences of the reviews, overall, the results of both studies are in agreement, supporting the consistency of the association.

Essentially, the results of our study are also consistent with the IARC Monograph 92 results,[1] which describe several cohort studies examining PAH-exposed occupations and reporting an association with larynx cancer diagnoses. Additionally, the IARC Monograph describes three case–control studies of larynx cancers[34 36 89] that "consistently showed statistically significant associations with exposure to PAHs."[1] However, the IARC Monograph does not go so far as make a formal statement regarding an association between PAH exposure and larynx cancers in humans.

Cross-sectional studies were excluded from this review to ensure some consideration of temporality. However, a subclinical tumour may exist for many years prior to the manifestation of clinical symptoms, and exposure to a potential risk factor of interest (PAH) during this time may not necessarily have any additional aetiological influence on the course of the disease. One possibility to examine bias due to such interim exposures is to conduct a latent-time analysis as described by Straif *et al*.[33] Overall, a slight underestimation of the relationship between the PAH exposure and larynx cancer seems possible due to the fact that most of the studies considered did not account for a symptom-free latency period (and the corresponding exclusion of PAH exposures during this time).

Few studies permitted an examination of the dose–response relationship between the amount and duration of PAH exposure and the incidence of larynx cancer. Becher *et al*[34] was the only study to examine the relationship between categories of PAH exposure duration (self-reported) and the risk of larynx cancer. The linear trend between the cumulative exposure categories and the corresponding OR estimates (0 h: OR=1.0 (reference); >0–1300 h OR=1.06 (95% CI 0.28 to 4.0); >1300 h OR=3.8 (95% CI 1.3 to 11.1)) was statistically significant ($p<0.01$).

The death certificate-based case–control study by Russi *et al*[41] categorised the occupational exposure with cutting oils, a surrogate for PAH exposure, into low, high and missing categories. The resulting analysis with population control persons found no association between PAH exposure level and OR. An analysis using patients with oral cancer as controls did result in a statistically significant OR for the high exposure category 1.48 (95% CI 1.01 to 2.16), and the linear trend test approached statistical significance ($p=0.08$).

Hogstedt *et al*[59] found an overall SIR of 1.65 (95% CI 0.79 to 3.04), but observed no dose–response relationship when risk was stratified for four categories of exposure duration (employment). However, few cases of larynx cancer were observed in the study ($n_{obs}=10$), and the alcohol consumption of cohort members 50 years of age and older was reported to be about twice that of the general population, suggesting the reported risk estimates may be biased.

Several studies considered the cumulative dose of exposure to PAH or a surrogate marker and the risk of larynx cancer. Gibbs *et al*[26] examined the larynx cancer incidence in several cohorts of workers employed at one of five aluminium production plants in Quebec, Canada. Cumulative exposure dose and SIR were reported for the combined cohort of 16 301 men. Altogether, the SIRs for the categories representing 0–40 $\mu g/m^3 \times$years of BaP exposure ranged between 94.4 (for 0 $\mu g/m^3 \times$years) and 122.7 (for >0 to <20 $\mu g/m^3 \times$years). In general, the SIR estimates increased with increasing cumulative exposure, peaking for the exposure category corresponding to cumulative exposures between >80 and <160 $\mu g/m^3 \times$years at 204.8 ($p<0.05$) only to sink again to 181.5 for exposures above 160 $\mu g/m^3 \times$years. However, due to the low number of incident cases, only the SIR of the >80 to <160 $\mu g/m^3 \times$years exposure range was statistically significant. At $p=0.084$, the test for trend approached statistical significance.

Eisen *et al* report slight indications of a dose–response relationship between cumulative exposure levels to straight MWF (a surrogate for PAH exposure) among automobile industry workers and larynx cancer mortality. The corresponding linear trend test approached statistical significance ($p=0.075$).[25] In a 2004 follow-up of the same cohort, Friesen *et al*[90] find laryngeal and bladder cancer incidence to be most strongly associated with PAH. However, we did not include the results of this follow-up in our meta-analysis, as the publication only gives HRs for MWF exposure as a continuous variable. Moreover, as the authors point out, the aim of this publication was to elucidate the potential aetiological role of the single MWF components, not to examine the shape of dose–response curves and time windows of exposure in detail. Therefore, the dose–response relationship might not be adequately described by a linear function. Nevertheless, as a considerable methodological

advantage, the 2004 follow-up is based on cancer incidence, not mortality.

Wortley *et al*[37] developed an exposure score which considered the intensity as well as the duration of the exposure. Using this imprecise cumulative exposure approximation, an OR of 1.3 (95% CI 0.5 to 2.6) for incident larynx cancer was reported for the highest cutting fluid exposure category. However, a reliable statement regarding a dose–response relationship cannot be made based on this research. The case–control study by Gustavsson *et al* also assessed cumulative PAH exposure indirectly, with an expert categorising exposure as low, high or none/missing.[36] Compared with a lack of exposure, the ORs for low and high cumulative exposure was 0.77 (95% CI 0.46 to 1.28) and 1.47 (95% CI 0.96 to 2.24), respectively.

Within the framework of this systematic review, we attempted to assign four categories of cumulative PAH exposure for occupations and industrial branches where the original research included no estimates of exposure. Using this rough categorisation, two studies reporting the risks of highly exposed coke oven workers[74 84] achieved the highest exposure level (very high) with Swaen *et al* reporting an SMR of 3.29 (95% CI 0.85 to 8.51). In the subgroup analysis, the pooled risk estimate for these very high exposed workers was 2.21 (95% CI 1.60 to 3.05). The pooled effect estimates for the low, moderate and high exposure categories, on the other hand, were relatively similar ranging from 1.25 to 1.46. Altogether, no clear dose–response relationship could be observed from this expert categorisation of occupations. However, the high combined risk estimate of 2.21 (95% CI 1.60 to 3.05) for the highly PAH-exposed coke oven workers observed by Swaen *et al*[74] and Kennaway and Kennaway risks may increase with exposure.[84]

In industrial workplaces, PAHs are predominantly absorbed through the respiratory system or the skin. In Germany, "lung cancer caused by polycyclic aromatic hydrocarbons if there is evidence of exposure to a cumulative dose of at least 100 benzo [a]pyrene years [($\mu g/m^3$)×years]" is recognised as occupational disease #4113. During inhalation, PAHs pass through the larynx, making it biologically plausible for the known carcinogenicity of PAHs to not only manifest in the lungs but also in the larynx. PAHs have been shown to be genotoxic in cell experiments and to cause cancers in animal models. PAH metabolites can bind with DNA to cause sister chromatid exchanges, chromosome aberrations and point mutations.[1 5] Therefore, a cancerous impact of PAHs on the larynx can be considered biologically plausible.

In conclusion, the literature reviewed suggests occupational PAH exposure is associated with an increased risk of larynx cancer. Although few studies permit an examination of dose–response relationship, those that do, indicate increasing risks at higher exposure levels. In general, the ancillary evidence suggests that occupational PAH exposure has an aetiological influence on the formation of larynx malignancies.

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Occupational polycyclic aromatic hydrocarbon exposure and risk of larynx cancer: a systematic review and meta-analysis

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Notes