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REVIEW

Risk of bladder, kidney and prostate cancer from occupational exposure to welding fumes: a systematic review and meta-analysis

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Abstract

Background Our aimed to conduct a meta-analysis of cohort studies on risk of genitourinary (GU) cancers in workers exposed to welding fumes (WF).

Methods We performed a systematic review of studies published on Pubmed, Scopus and Embase following PRISMA criteria. Two researchers selected cohort studies on WF exposure. From 2582 articles, 7 non-overlapping studies were included. Quality of studies was scored according to CASP. We run a random effects meta-analysis to calculate the relative risk (RR) and 95% confidence intervals (CI) of GU cancer, overall and stratified by cancer, country, and quality score.

Results We included seven studies reporting results on GU cancers, including prostate, bladder and kidney cancer (PC, BC, and KC). The RR was 1.19 (95% CI = 1.07–1.32, 16 risk estimates) for GU cancer; 1.13 (95% CI = 0.90–1.42, 4 risk estimates) for PC; 1.26 (95% CI = 0.98–1.60, 7 risk estimates) for BC and 1.28 (95% CI = 1.12–1.47, 5 risk estimates) for KC. Heterogeneity was present in all meta-analyses ($p < 0.001$). The increased risk was more pronounced in North American than in European studies (respectively, OR = 1.35, 95% CI = 1.18–1.55; OR = 1.13, 95% CI = 1.01–1.27 p heterogeneity = 0.03). There was no heterogeneity according to quality score ($p = 0.4$). Data were insufficient to investigate associations by industry or welding type. Publication bias for each cancer was excluded.

Conclusion This meta-analysis suggests increased risk of KC and BC, but not of PC, in workers exposed to WF. Confounding by other occupational and non-occupational risk factors could not be excluded. Data were not adequate to address the risk of specific exposure circumstances.

Keywords Welding fumes · Welder · Kidney cancer · Bladder cancer · Prostate cancer · Occupational carcinogens

Introduction

Exposure to welding fumes (WF) concerns about 110 million workers worldwide (Honaryar et al. 2019).

Welding entails contact with gaseous and aerosol combinations of metals (e.g., chromium, iron, nickel, etc.), metal oxides, and other chemicals. The characteristics of WF, and hence their carcinogenicity, depend on the welding method (e.g., gas or arc) and the metal which is welded (i.e., mild or stainless steel) (Honaryar et al. 2019).

Welders have an increased risk of several health conditions, including cancer (Wang et al. 2022). Monitoring of the level of welding emissions is important, and much effort is dedicated to the quantitative assessment of WF exposure (Wang et al. 2022) and its control (Lehnert et al. 2022). IARC classified WF as 'possibly carcinogenic to humans' (Group 2B) in 1990 (International Agency for Research on Cancer (IARC) 1990), and upgraded its evaluation to Group 1 (established human carcinogen) in 2017 based on results on lung cancer (International Agency for Research on Cancer (IARC) 2018; Guha et al. 2017). Also, the occupational setting in which welding occurs impacts on the overall occupational hazard of the workers. Agents whose exposure might occur with WF include asbestos and second-hand

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smoke (Danielsen et al. 2000; Ambroise et al. 2006). Honaryar and coauthors recently conducted a meta-analysis on the association between WF and lung cancer, supporting the causal relationship existing independently from asbestos exposure and tobacco smoking (Honaryar et al. 2019). However, no such meta-analyses have been conducted for other than respiratory-tract cancers.

The inhalation of occupational carcinogens makes the respiratory tract particularly vulnerable to their effect. In addition, an increased risk of cancer of the urinary tract has been shown for several agents which are excreted via the urine (https://monographs.iarc.who.int/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf). IARC lists WF among the agents with limited evidence of carcinogenicity in relation with kidney cancer (KC) (https://monographs.iarc.who.int/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf). While several occupational carcinogens have been identified for bladder cancer (BC) (https://monographs.iarc.who.int/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf), an association with WF exposure is not established. No occupational carcinogens are associated to prostate cancer (PC) according to IARC (https://monographs.iarc.who.int/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf). Indeed, the etiology of PC remains poorly understood except from non-modifiable risk factors such as family history and race (Gandaglia et al. 2021).

A systematic assessment of the risk of development of cancer of different organs in welders, who are specifically exposed to WF, may help in understanding WF carcinogenic properties and in better defining the cancer risk of the exposed workers.

Our aim was to perform a meta-analysis of cohort studies on the risk of GU cancers in welders, including KC, BC, and PC.

Methods

The STROBE guidelines were followed to conduct this systematic review and meta-analysis (Elm et al. 2008).

A study protocol was built and registered in the PROSPERO database (Registration No. CRD42021252458).

The systematic review was based on the PECOS criteria with population being workers exposed to substantial levels of WF in multiple industries, exposure being WF, comparison being populations unexposed to WF, either the relevant general population or an unexposed cohort, outcome being incidence or mortality from cancer other than the lungs, and study design being prospective cohort, including nested case–control studies.

We conducted a search of PubMed, Scopus, and Embase databases with the aim to include all studies reporting results on welders and risk of any type of cancer other than lung cancer, for which a causal association with WF exposure has already been established (International Agency for Research on Cancer (IARC) 2018). The search was performed independently by two authors (GC and PB) and aimed at identifying industry-based studies of cancer among welders. We generated strings by using the keywords *(welding or (welding fumes) or welder) and (cancer or neoplasm or leukemia or lymphoma or cohort).* The search included studies published before May 2021. If multiple reports were published on the same population, we included only the most informative report, typically the one including the largest number of cases or deaths. Studies with modest overlap (i.e., less than 10%) were considered independent. We excluded studies with no reference to WF, those with exposure other than occupational, those without data on cancer other than lung cancer, and those with a design other than cohort or case–control nested in a cohort.

We abstracted data using a standardized form on (i) sociodemographic factors, (ii) occupation and industry type, (iii) person-years of observation, (iv) type of cancer, (v) measure of association (odds ratio (OR), risk ratio, rate ratio, standardized mortality ratio [SMR], or standardized incidence ratio [SIR], henceforth referred to as relative risk [RR]) and 95% confidence intervals (CI), (vi) factors adjusted for in the analysis and (vii) characteristics of the study population (eg., number of subjects included, number of cancer cases). The dataset was organized by follow-up period and country. When available, we abstracted results on dose–response analysis for different indicators of WF exposure.

Next, assessed the quality of the study included in the meta-analysis based on the CASP scale (https, casp-uk.b-cdn.net, wp-content, uploads 2018, 03, CASP-Qualitative-Checklist-2018_fillable_form.pdf. 2018). The CASP assessment was based on 11 items for a total score of 14 points. We used the average of the scores assessed separately by two authors (GC and MH). Studies which scored 10 or less were considered of low quality, while those which scored more than 10 were considered of high quality.

The present study focus on GU cancers, including KC, BC and PC. We conducted a series of meta-analyses of non-overlapping studies based on random effects model (DerSimonian and Laird 1986). First, we performed the analysis by cancer type. Next, we stratified the meta-analyses by geographic region (North America vs Europe) and quality score (low vs high). Data were insufficient to perform further stratified analyses, e.g., by occupation or welding type. We tested for heterogeneity among studies using the Q statistics and the I-square test (Higgins and Thompson 2002). Finally, we assessed publication bias by the visual inspection of funnel plot and the Egger test (Egger et al. 1997).

All the statistical analyses were performed on STATA, version 16.1 (Stata Corp., College Station, TX, US) (StataCorp. 2019).

We reported the meta-analysis according to the PRISMA guidelines (Page et al. 2021). The checklist is available in Fig. 1.

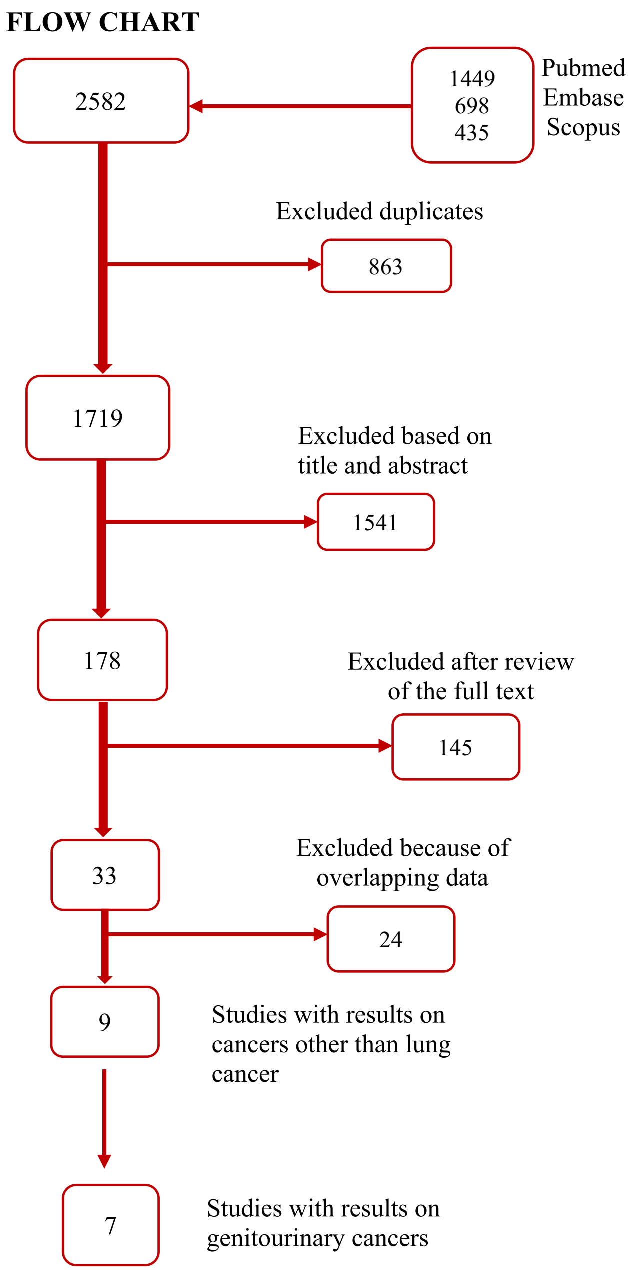

Fig. 1 Flow chart of the process of systematic review of the literature

Results

The meta-analyses we performed were based on the selection of cohorts of welders, as there were no studies of workers with substantial exposure to WF who were not identified as welders. We identified 2,582 articles published on Pubmed, Embase and Scopus before May 2021 and retained 1,719 of those, after excluding 863 duplicates. An additional 1,541 articles were excluded based on the screening of title and abstract, leaving 178 articles, of which 145 were excluded after reviewing the full text. We therefore identified 33 articles, which however were reduced to 9 independent studies because of overlapping data among multiple studies, in particular studies from the Nordic countries which were included in a large analysis by Pukkala and coauthors based on the Nordic Occupational Cancer (NOCCA) study (Pukkala et al. 2009). Two of the nine studies did not report results for GU cancer Figs. 1, 2, 3.

The meta-analysis was therefore performed on 7 studies (16 risk estimates), including 5 for BC (7 risk estimates), 3 for KC (5 risk estimates), and 4 for PC (4 risk estimates). The characteristics of the studies included in the meta-analyses are summarized in Table 1 (Pukkala et al. 2009; Beaumont and Weiss 1980; Becker 1999; Zeegers et al. 2004; Moulin et al. 1993; Puntoni et al. 2001; MacLeod et al. 2017).

Table 2 reports the main results of the meta-analyses.

Overall, we found a RR of 1.20 (95% CI = 1.08–1.33, p heterogeneity < 0.001) when considering all GU cancers combined. In this combined analysis the p value of Egger test for publication bias was 0.018.

The summary RR of PC was 1.13 (95% CI = 0.90–1.42, p of heterogeneity = 0.12, based on four risk estimates); that of BC was 1.26 (95% CI = 0.98–1.60, p of heterogeneity = to 0.05, based on seven risk estimates); that of KC was 1.28 (95% CI = 1.12–1.47, p of heterogeneity = 0.34, based on five risk estimates). Results by cancer type were not statistically different ($p = 0.324$). There was no evidence of publication bias (p values = 0.397, 0.343, and 0.161 for PC, BC, and KC, respectively).

Results for the three GU cancers combined stratified by country showed a more markedly increased risk in North American studies (OR = 1.35, 95% CI = 1.16–1.58, based on 3 risk estimates) than in European studies (OR = 1.13, 95% CI = 1.01–1.27, based on 13 risk estimates), which resulted in significant heterogeneity across these strata ($p = 0.03$). When stratifying for quality score (Supplementary Fig. 1), both lower quality studies (based on 7 risk estimates) and higher quality studies (based on 9 risk estimates) resulted in a significant increased risk (OR = 1.65, 95% CI = 1.10–2.46 and OR = 1.16, 95% CI = 1.04–1.28 respectively, p for heterogeneity = 0.06).

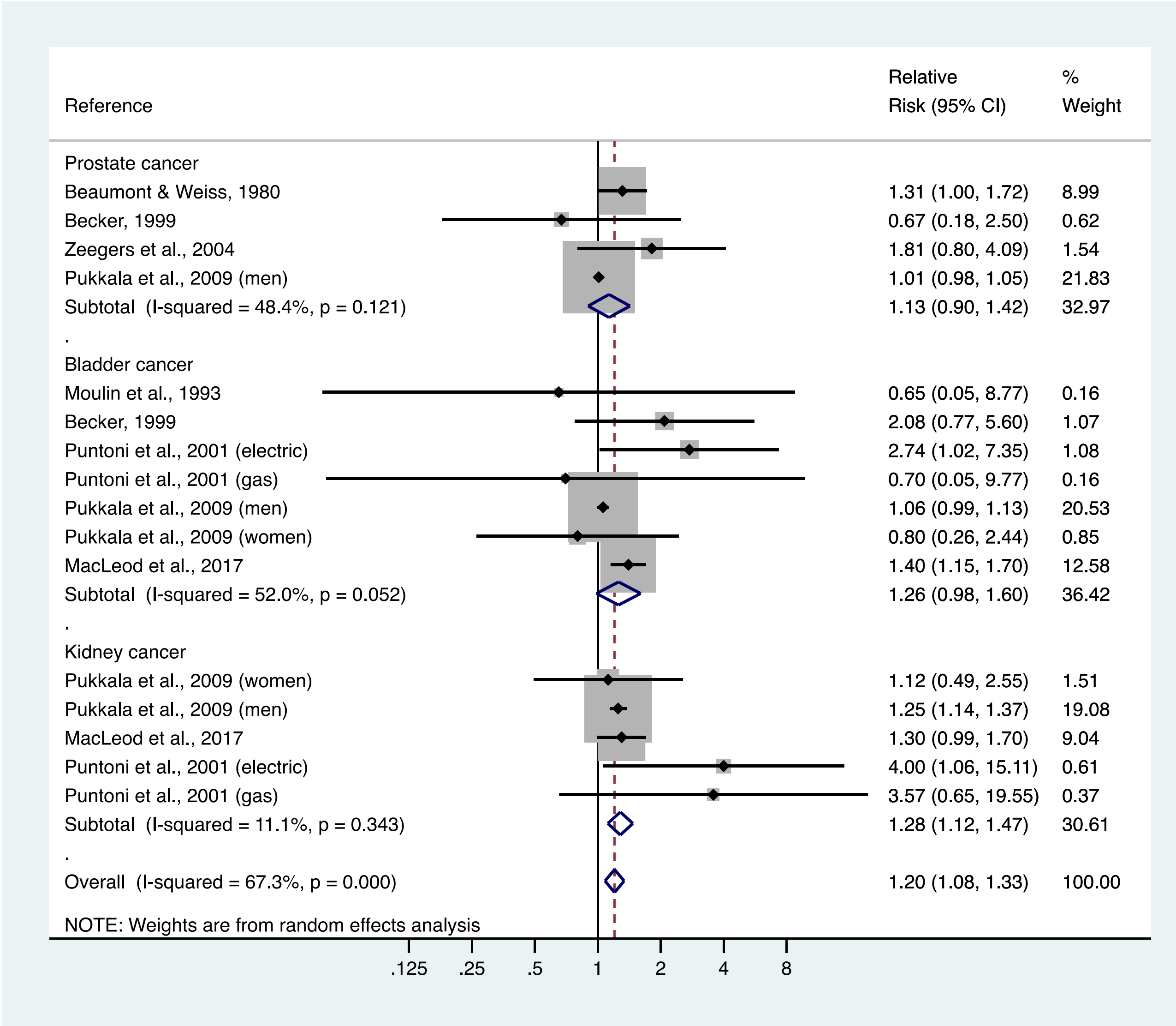

Fig. 2 Results of the metanalyses on genitourinary cancer, including prostate, bladder and kidney cancer, and occupational exposure to welding fumes

Information was too sparse to investigate the association by sex, outcome, type of industry and welding method.

Discussion

We conducted the first meta-analysis on the risk of GU cancers in workers exposed to WF.

Based on seven cohort studies, we observed an association with KC and BC, but not PC. Stratified analyses conducted on GU cancers corroborated the result of the overall meta-analysis, and showed an association in North American studies rather than in European studies.

The results we found for BC and KC are mainly driven by MacLeod et al.'s (2017) and Pukkala et al.'s (2009) cohort studies. Both are census-based analysis, meaning the exposure was assessed based on the job title recorded at the census, which partially limits the sensitivity of these data.

While the analysis by MacLeod et al. was based on a large population, this study could not account for additional exposures, such as asbestos and smoking (MacLeod et al. 2017). This may have especially influenced the result for BC (Latifovic 2020; Cumberbatch et al. 2018), while those for KC could be considered reliable, as a recent meta-analysis found no association with asbestos exposure (Chow et al. 2010; Zunarelli et al. 2021).

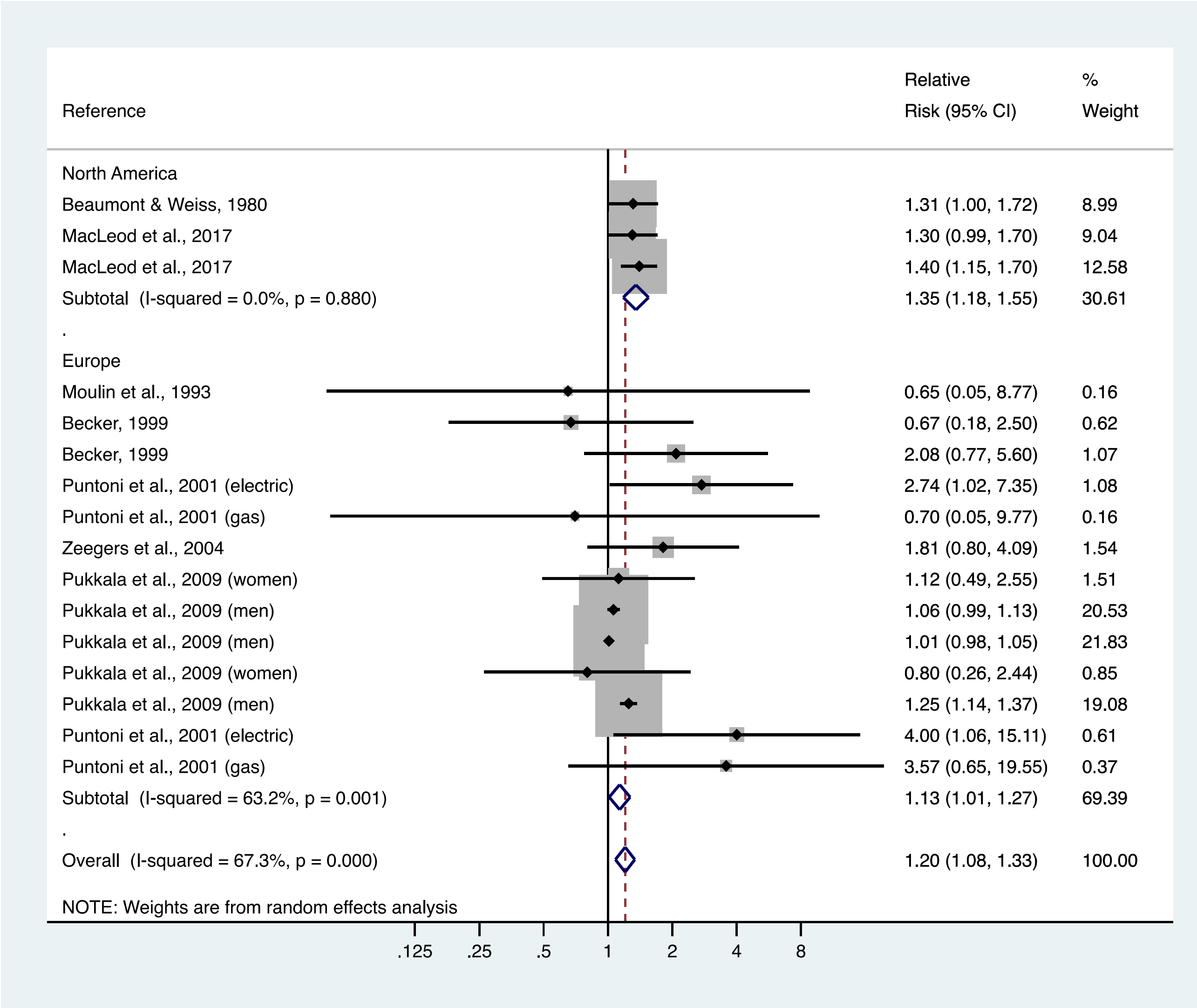

Fig. 3 Results of the metanalysis stratified by country (North America vs Europe) of the risk of genitourinary cancer and occupational exposure to welding fumes

Previous evidence on the risk of BC in welders suggested a positive association, despite not full consistency when accounting for the duration of exposure (MacLeod et al. 2017). Pukkala et al. (Pukkala et al. 2009) reconducted some occupational associations with BC to smoking habits. In particular, the author stated that many of the occupational differences in cancer risk ascribed to the prevalence of smoking habits are in turn related to socio-economic factors such as education (Pukkala et al. 2009). This is consistent with what reported by several studies on welders, which result to be more often smokers than general population (Danielsen et al. 2000; Ambroise et al. 2006).

Both MacLeod et al. (MacLeod et al. 2017) and Pukkala et al. (2009) found similar excess risk of KC in welders. The observed excess risk could result from the exposure to the compounds released in the fumes of welding process, such as cadmium, as reported in different previous studies (Il'yasova and Schwartz 2005; Song et al. 2015).

Conclusions on the role of WF independently from lifestyle habits and other occupational exposures can derive through studies designed to disentangle their effects, as also MacLeod stated (MacLeod et al. 2017).

PC has one of the strongest heritability components among all neoplasms, while its environmental etiology is poorly understood (Gandaglia et al. 2021; Rebbeck 2017). Our meta-analysis revealed no association between PC and exposure to WF. Among the four studies from which the result was derived, the one by Beaumont and Wiss (Beaumont and Weiss 1980) reported a significant increased risk, but the large part of the weight depended on the NOCCA

Table 1 Selected characteristics of the studies included in the metanalyses for the different genitourinary cancer types

Study	Cancer type	Country	Years of FU	N participants	Persons years	Industry	*N* cases	Adjustments (other than age and calendar time)
Beaumont and Weiss (1980)	PC	US	1950–76	8679	43,669	Shipyards, metal fabrication shops, small boat yards and field construction	147	NA
Becker (1999)	PC BC	Germany	1980–95	1221	38,924	Arc welders	3 5	No; the author stated that previous evaluations evidenced that smoking was not a relevant confounder in this cohort
Zeegers et al. (2004)	PC	Netherland	1986–93	58,279	NA	Welders	12	Family history of prostate cancer; consumption of vegetables, fruit, dairy products, meat, and alcohol; cigarette smoking; and level of education
Pukkala et al. (2009)	BC KC PC	Denmark, Finland, Iceland, Norway, Sweden	1961–2005	NA	15 million people	Welders	822 533 2871	NA
Moulin et al. (1993)	BC	France	1975–88	9404	34,131	Factory/shipyard	1	Axelson's indirect adjustment*
Puntoni et al. (2001)	BC, KC	Italy	1960–96	267	5847	Shipyard ever employed in electric welding	5	NA
MacLeod et al. (2017)	BC, KC	Canada	1991–2010		2,051,315	Welders in construction and manufacturing fields	100 60	Province of residence and educational level no high school diploma, high school with/without trade certificate, postsecondary nonuniversity diploma, or university degree

PC prostate cancer, *BC* bladder cancer, *KC* kidney cancer

*Reference: Axelson O. Aspects on confounding in occupational health epidemiology (Axelson 1978)

Table 2 Results of the metanalyses on the different cancer types separately and overall, and of overall genitourinary cancers by country and CASP level

Outcomes	*N* risk estimates	RR, 95% CI	Test heterogeneity across strata, *p* value	Egger test, *p* value
Overall analysis				
Prostate cancer	4	1.13, 0.90–1.42	0.324	0.397
Bladder cancer	7	1.26 (0.98–1.60)		0.343
Kidney cancer	5	1.28 (1.12–1.47)		0.161
All genitourinary cancers	16	1.20 (1.08–1.33)	NA	0.018
Geographic region				
North America	3	1.35 (1.18–1.55)	0.03	NA
Europe	13	1.13 (1.01–1.27)		NA
Quality score				
Low quality score	7	1.65 (1.10–2.46)	0.06	NA
High quality score	9	1.16 (1.04–1.28)		NA

cohort study, which found no association (Pukkala et al. 2009). Among case–control studies, some have found an increased risk of PC among welders (Siemiatycki 1991; Gulden et al. 1995), while others reported no association, consistent with our study (Keller and Howe 1993; Sauvé et al. 2016), with lack of duration–response association and no differences by welding type.

Additional cohorts investigated the risk of cancer in workers potentially exposed to WF, without presenting specific results for welders (McElvenny et al. 2017; Welch et al. 2015). For example, Welch and coauthors (Welch et al. 2015) studied sheet metal workers in US and Canada, and found no association with urinary tract cancer, and an inverse relationship when considering PC. Next, some historical prospective cohort studies were excluded because their results were overlapping and earlier than the comprehensive analysis conducted by Pukkala et al. (Pukkala et al. 2009), like the works by Danielsen and others (Danielsen et al. 2000, 1993). According to their last study update, Norwegian welders were not at risk of any GU cancer considered in our meta-analysis. Conversely, Tola et al. (Tola et al. 1988) found that Finnish welders employed as machine operators, but not those working as shipyard workers, had an increased risk of PC (OR = 2.8, 95% CI = 1.12–5.57) and BC (OR = 1.54, 95% CI = 0.19–5.56). The authors reported a slightly less prevalent smoking habit in shipyards than in machine shops (Tola et al. 1988). Also, the possible exposure to asbestos was discussed, pointing out how welding activities were performed in separate halls with no asbestos exposure or in working phases which did not imply its exposure. No explanation was given for the excess risk of PC in welders which was found (Tola et al. 1988).

Mechanism of WF effect on the kidney may be hypothesized observing its clearance functions (Vyskocil et al. 1992). Beta-2-microglobulin, a protein of nucleated cells surface which is a marker of kidney damage (Argyropoulos et al. 2017), was not found to differ in urine samples of arc welders and controls in a study from Iran (Aminian et al. 2011). Another study found a non-significantly higher concentration of the protein in the urine of welders rather than controls, and excluded changes in renal functions in the exposed group (Chuang et al. 2015). Evidence of a possible nephrotoxic effect of WF derives from a study conducted in Taiwan, where 66 welding workers and 12 office workers were recruited from a shipyard to provide urine samples at baseline and after 1 working week (Holzscheiter et al. 2014). In this study, the authors reported higher level of neutrophil gelatinase-associated lipocalin (NGAL), a biomarker of kidney injury (Kővágó et al. 2022), as well as higher urinary Al, Cr, Mn, Fe, Co, and Ni levels, in welders compared to controls (Holzscheiter et al. 2014). Animal studies are also inconsistent. A recent publication based on the monitoring of the distribution of different metals in mice organs after inhalation of fumes from different welding methods did not report differences in the kinetics of the metals in mice kidneys at 24 h and 96 h from the exposure (https.www.athensjournals.gr. 2020). Conversely, other researchers found that mice exposed to WF showed impaired kidney functions in comparison to unexposed ones (Sani et al. 2021), and kidney of mice exposed to WF showed pathological alterations such as glomerular necrosis and lymphocyte hyperplasia (Alegre-Martínez et al. 2022). Interestingly, a recent publication reported a correlation between the concentration of nickel in blood from PC patients (not occupationally exposed) and their glomerular filtration rate and blood urea levels, despite being not significantly higher in cases than controls, suggesting a toxic effect on the urinary tract (Sjögren et al. 2022).

The results on GU cancer overall showed a stronger association in studies from North America compared to studies from Europe. This may be due to the different welding types or industry involved in the studies. It is unlikely that this difference could be reconducted to the prevalence of confounders as asbestos or smoking habits, because given the higher prevalence of these factors in Europe rather than US and Canada even at the time when these cohorts were built we would have expected, on the contrary, stronger association in the European studies.

Further confirmation on the robustness of our findings derives from the meta-analysis stratified by quality score, where higher quality studies (including the two major cohorts by Pukkala et al. (2009) and MacLeod et al. (2017) showed a milder but significantly increased risk of GU cancers in workers exposed to WF.

Despite information on industry and welding type was collected in some studies, it was too sparse to perform analyses and provide any specific evidence with respect to GU cancers. Welders employed in different sectors may have a different risk of cancer, as suggested by Puntoni et al. (Puntoni et al. 2001), who reported a significant increased risk of BC in electric welders, as well as a stronger association with KC in electric welders. More data from independent studies, however, are needed before any conclusion can be drawn.

As stated by Sjogren et al. (Sjögren et al. 2022), occupational exposure limit (OEL) for WF should be based on a critical appraisal of all health effects of welding and take the various welding methods into account. To date, OEL for WF is set at 5 mg/m3 (Sjögren et al. 2022). However, health effects have been reported at lower levels. Indeed, some countries have already introduced lower OEL, eg,, Denmark (0.5–1.7 mg/m3 depending on welding process and material) and The Netherlands (1 mg/m3) (Institut für arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA). GESTIS International Limit Values 2021).

This study has several strengths. First, we summarized data on different types of cancer, namely KC, BC, and PC in association to occupational exposure to WF.

We focused on cohort studies and specifically investigated the work-related exposure to WF. Moreover, our meta-analyses are based on several risk estimates, despite the fact that they derive from a small number of studies. We performed a strict search of publications focused on welders and excluded a large number of studies based on overlapping populations. However, it is a fact that cancers other than lung remain poorly investigated in welders.

Also, we developed a research protocol conducted and reported the research according to established guidelines, and we performed the quality assessment of the included studies. Last, we could exclude publication bias within same-cancer studies.

This study also has some limitations. First, we could not account for important confounders such as tobacco smoking, occupational second-hand smoke, and asbestos, because these data were missing in the included studies. The two largest cohorts (Zeegers et al. 2004; MacLeod et al. 2017) were census-based, therefore no information was available on smoking habits and exposure assessment was based on self-reported job position, possibly suffering from misclassification, which, anyway, would likely be non-differential.

WF exposure was not assessed based on intensity or dose, and information on duration was too heterogeneous to estimate any summary risk.

Another limit which should be considered is the small number of cases reported in most studies, especially for BC and KC, which impairs the precision of the results.

Further, we could not describe results by industry type and welding methods because of the paucity of available data.

In conclusion, workers exposed to WF resulted to have an increased risk of GU cancers, in particular KC and BC, while PC did not result to be associated to WF. Despite being suggestive of a role of WF in the development of GU cancers among exposed workers, the results may be confounded by tobacco smoking and additional occupational exposures (eg., asbestos). Welding methods, such as arc and gas welding, and steel and stainless steel welding, may result in different health effect, but the available literature does not allow to disentangle the carcinogenic potential of the different techniques. Further studies should be designed to investigate the incidence of GU cancer in workers exposed to WF, following a well-established exposure assessment including the identification of welding method, type of industry and intensity/duration of exposure. Also, those studies should include data on potential confounders.

This meta-analysis provides new relevant data on the risk of GU cancers in welders, highlighting the importance of health surveillance of the workers exposed to WF.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00420-023-02040-0.

Data availability The present research was conducted on publicly available data. Details on the literature search, selection of studies and abstraction of data are available from the authors upon request.

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