RBSO Revista Brasileira de Saúde Ocupacional
ISSN: 2317-6369 (online)
https://doi.org/10.1590/2317-6369/37620en2022v47e14

Review Article

Occupational exposure and cancer: an umbrella review

Exposição ocupacional e câncer: uma revisão guarda-chuva

Raphael Mendonça Guimarães[a]
https://orcid.org/0000-0003-1225-6719

Viviane Gomes Parreira Dutra[a]
https://orcid.org/0000-0001-6939-742X

Andréia Rodrigues Gonçalves Ayres[b]
https://orcid.org/0000-0001-8331-0343

Helena Beatriz da Rocha Garbin[a]
https://orcid.org/0000-0002-9606-9349

Thalyta Cássia de Freitas Martins[a]
https://orcid.org/0000-0002-6225-7245

Karina Cardoso Meira[c]
https://orcid.org/0000-0002-1722-5703

[a] Fundação Oswaldo Cruz (Fiocruz), Escola Nacional de Saúde Pública. Rio de Janeiro, RJ, Brazil.

[b] Universidade Federal do Estado do Rio de Janeiro (UNIRIO), Hospital Universitário Gaffrée e Guinle. Rio de Janeiro, RJ, Brazil.

[c] Universidade Federal do Rio Grande do Norte (UFRN), Escola de Saúde. Natal, RN, Brazil.

Correspondence:
Raphael Mendonça Guimarães
Email:
raphael.guimaraes@fiocruz.br

The authors report that this study was not presented at any scientific events.

The authors declare that the work has not been subsidized, and there are no conflicts of interest.

Abstract

Objective: *to provide an overview of the associations between occupational exposure and risk of occurrence or death from cancer.* Methods: *this umbrella review used the Medline and Web of Science databases. Based on the search protocol, meta-analysis was included for several occupational circumstances and selected cancers that had some level of evidence associated with the occupation.* Results: *37 meta-analysis were included, covering 18 cancer locations. By assessing the heterogeneity of studies, quality of evidence, and strength of association, results highly indicated associations between solvent exposure and multiple myeloma, asbestos and lung cancer, hydrocarbons and upper aerodigestive tract cancer, occupational stress and colorectal cancer.* Conclusion: *robust evidence shows an association between occupational exposures and types of cancer not initially foreseen in the guidelines for work-related cancer surveillance in Brazil. Gaps in relevant exposures require further research and more consistent meta-analysis, including: exposure to inorganic dust and lung cancer and mesothelioma; solvents and hematological tumors. Evidence of cancer in other anatomical regions was less robust, showing signs of uncertainty or bias.*

Keywords: *occupational exposure; cancer; occupational cancer, occupational health.*

Resumo

Objetivo: *fornecer uma visão geral das associações entre exposição ocupacional e risco da ocorrência ou morte por câncer.* Métodos: *esta revisão guarda-chuva da literatura utilizou as bases Medline e Web of Science. A partir de protocolo de busca, foram incluídas metanálises para diversas circunstâncias ocupacionais e cânceres selecionados que possuíssem algum nível de evidência para associação com ocupação.* Resultados: *foram incluídas 37 metanálises, abrangendo 18 localizações de câncer. Considerando a avaliação da heterogeneidade dos estudos, da qualidade da evidência e da força de associação, obteve-se evidências altamente sugestivas de associações entre exposição a solvente e mieloma múltiplo; amianto e câncer de pulmão; hidrocarbonetos e câncer de trato aerodigestivo superior; e estresse ocupacional e câncer colorretal.* Conclusão: *há evidências robustas para associar exposições ocupacionais e tipos de câncer não previstos, inicialmente, nas orientações de vigilância do câncer relacionado ao trabalho no Brasil. Permanecem lacunas sobre exposições de grande relevância, que carecem de metanálises mais consistentes, por exemplo, exposição a poeiras inorgânicas e câncer de pulmão e mesotelioma; exposição a solventes e tumores hematológicos. Evidências de câncer em outras regiões anatômicas foram menos robustas, apresentando indícios de incerteza ou viés.*

Palavras-Chave: *exposição ocupacional; câncer; câncer ocupacional, saúde do trabalhador.*

Received: 11/05/2020
Reviewed: 02/20/2021
Approved: 03/02/2021

Introduction

Cancer is the first or second leading cause of premature death (deaths between 30 and 69 years old) in 73% of countries worldwide. In 2016, 29.8% of deaths from non-communicable diseases were caused by cancer[1]. In Brazil, the estimated incidence of this disease for the 2020-2022 triennium indicates more than 625,000 new cases per year[2].

Current scientific evidence supports the association between work and some types of cancer[3,4,5]. In fact, the World Health Organization estimates that about 19% of all cancers are attributed to the environment, including work environments[6]. Occupational exposure is the main route of human exposure to about half of the chemicals and mixtures classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans[7,8].

In Brazil, work-related cancers have been poorly estimated. National evidence and registration are insufficient because of the under-registration of cases and the invisibility of the location of cancers recognized by the Brazilian surveillance system[9]. Initially, according to the definition of work-related cancer from the Information System for Notifiable Diseases (SINAN), sentinel events would be cases of leukemia caused by benzene exposure, asbestos mesothelioma, and liver angiosarcoma by exposure to vinyl chloride, among others[10]. More recently, the Ministry of Health began considering these events as "all cases of cancer caused by exposure to factors, agents, and risk situations in the work environment and process, even after the exposure has ceased" (p.2)[11].

Several new epidemiological studies are conducted and published annually to examine if occupational exposure increases the risk of developing other types of cancer. The global burden of disease for work-related kidney, breast, nasopharynx, larynx, lung, mesothelioma, ovary, and leukemia cancers was recently estimated[12]. However, prospective cohort studies and meta-analysis show that occupational exposures are also associated with cancers in other locations, such as the central nervous system, prostate, nasal cavity, esophagus, bladder, liver, and bile ducts[13]. Assuming these associations are causative, a significant burden of cancer could be avoided since occupational exposures are largely preventable[14].

For more than half a century, IARC has classified agents, combinations of agents, and exposure circumstances according to carcinogenicity/threat to humans in their monographs. Among the assessed items, classified as "definitely", "probably", or "possibly" carcinogenic, many are related to work[15].

Seeking to contribute to evidence-based decision-making, this study aims to overview the associations between occupational exposure and cancer development or death risk. Studies that show positive results and statistically significant associations are more likely to be published than those with negative findings with no statistical significance, thus misguiding clinical and public health decisions[16]. Moreover, biases in the literature explain the effect indicated by state of the art.

Methods

To summarize and assess the existing evidence and its quality, a comprehensive umbrella review was conducted with meta-analysis that investigated the association between occupational exposure and risk of cancer occurrence or death[17].

Research question

The PECOS strategy was used, considering: adult workers aged 18 years or older (P = population) assessed for occupational exposure to carcinogens (E = exposure) and compared with non-exposed workers (C = comparison of exposures or control) to verify the association with the development of work-related cancer (O = outcome) in systematic reviews and meta-analysis (S = studies), resulting in the following guide question: "What cancers are most associated with occupational exposure?".

Eligibility criteria

Meta-analysis on the association between occupational exposure and cancer risk was eligible. No restrictions were established regarding the type or year of publication. Eligibility was restricted to English, Spanish, French, and Portuguese

publications. Studies conducted in population groups of non-workers and people with children were excluded.

Information sources and search strategies

Searches were conducted in Medline and Web of Science databases for systematic reviews and meta-analysis published until March 2020 to investigate the association between occupational exposures and cancer risk. Initially, the agreement between the different bases was verified. Since it surpassed 90%, the search was conducted from the most comprehensive basis, Medline, using the following terms: (*occupational* OR *work-related*) AND (*cancer* OR *neoplasm* OR *tumor*) AND (*risk factor* OR *attributable risk*) AND (*exposure*) AND (*systematic review* OR *meta-analysis*).

Review selection and assessment of methodological quality

After excluding duplicates, two researchers (Ayres and Garbin) independently selected eligible systematic reviews and meta-analysis from their titles and abstracts. The articles chosen initially were submitted for duplication check. The eligibility data were stored by double data entry. The disagreements between the evaluators regarding eligibility were resolved by a third researcher (Dutra).

At the end of this stage, the selected articles were read in full to verify if they met the PECOS criteria. In the next step, the quality of the remaining articles was verified. The methodological quality assessment of systematic reviews and meta-analysis included was conducted independently using the AMSTAR-2 (Assessment of Multiple Systematic Reviews) instrument[18].

Different criteria measured agreement between the researchers: i) agreement on article classification, attributed by AMSTAR-2 (critical quality; low quality; moderate quality; and high quality) and measured by weighted kappa; ii) item-to-item agreement, assessed by simple kappa; iii) 16 assessment items of AMSTAR-2. These criteria are weighted differently according to the degree of relevance of the domains evaluated (e.g., quality of statistical measures, information on publication bias, etc.). To obtain a simple agreement measure for the articles, a general score was created from the simple sum of the items. The Altman-Bland plot assessed the agreement of this score.

Data collection

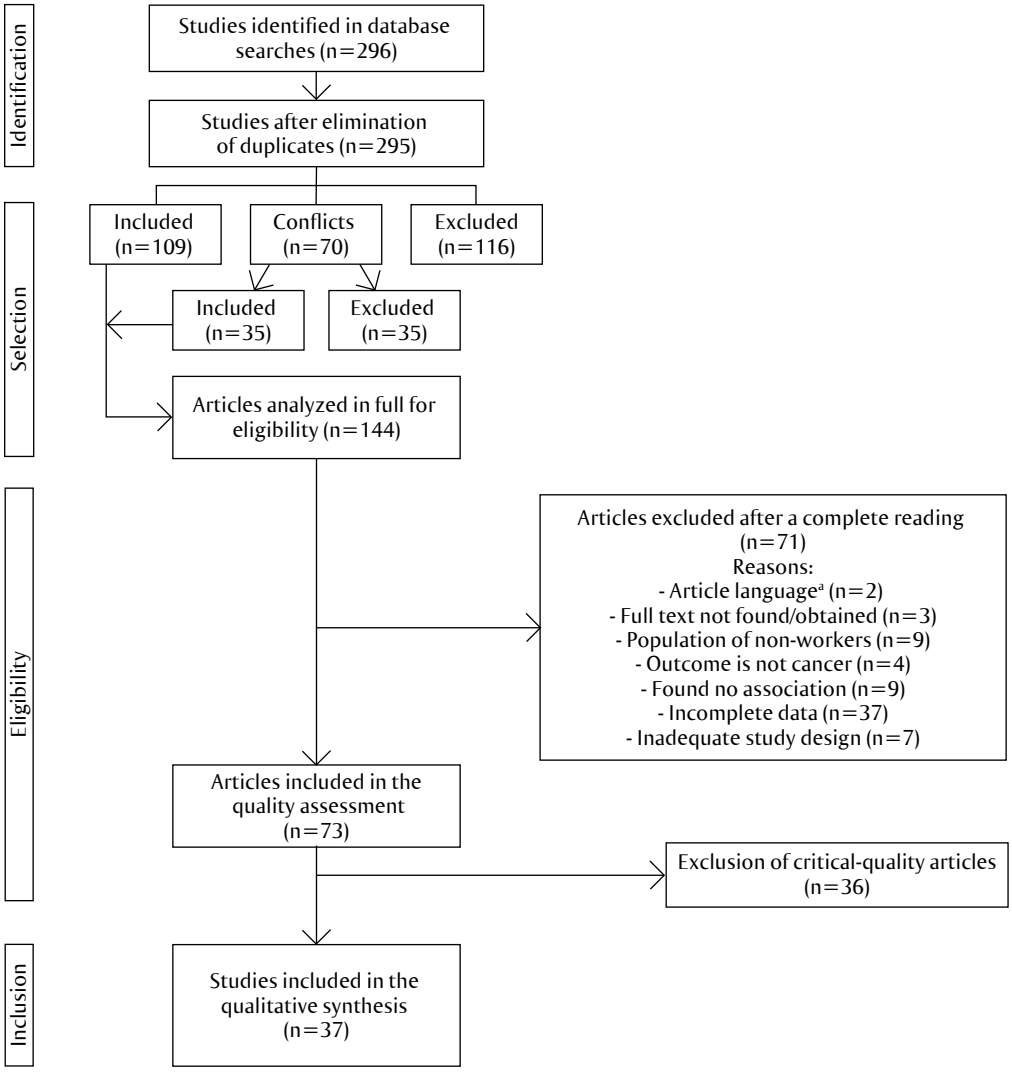
A data collection form was developed. The first stage included data on the type of study, research group, year of publication, journal, type of cancer, type of exposure, epidemiological measure (Mortality, incidence, prevalence), and search strategy (descriptors).

Information was obtained on types of studies included (cross-sectional, case-control, and cohort), the number of studies, variables of the quality assessment instrument (AMSTAR-2), heterogeneity (yes, no, or not applicable), a summary measure of association (with a respective confidence interval of 95%), summary measure for random effects (with a respective confidence interval of 95%), the p-value for random effects, Egger's p-value or visual inspection by funnel chart, I^2, credibility value, and excess of significance (O/E and p-value)[19].

Results

The search strategy initially found 296 articles. One duplicated article was excluded, leaving 295 articles assessed from their titles and abstract. The kappa agreement index between the two researchers for article inclusion or exclusion was 0.86. At the end of this stage, 144 articles were read in full to verify if they met the PECOS criteria. After the entire reading, 71 articles were excluded. In the following stage, the 73 articles included were verified for quality, out of which 36 were classified as having critical quality and therefore excluded. Finally, 37 articles were selected. (**Figure 1**).

The interobserver agreement on the quality of the selected articles was satisfactory. The item-to-item agreement for AMSTAR questions obtained by simple kappa was 0.83. The classification attributed to each article, in turn, was compared using weighted kappa, which got an excellent classification (k_w=0.92). Moreover, the score obtained for each article, calculated from the simple sum of AMSTAR-2 items, was compared by the Bland-Altman method, showing the absence of classification bias (**Figure 2**).



[a] articles not written in English, Spanish, French, or Portuguese were excluded.

Figure 1 Flowchart of study selection

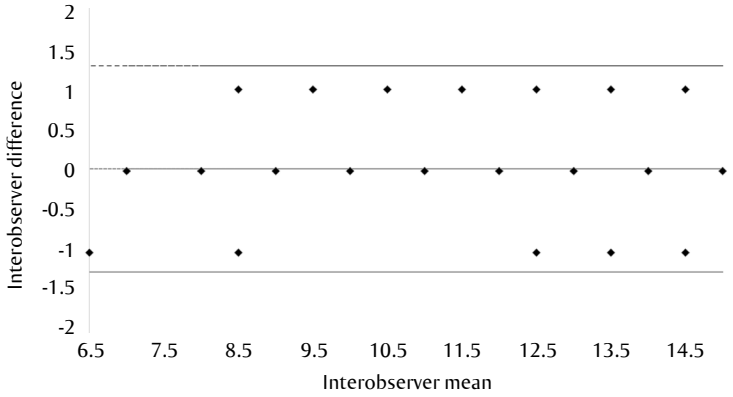


Figure 2 Bland-Altman graph, used to assess the agreement of the quality classification score of articles included in the umbrella review (n=37)

Regarding the evidence found, of 37 included articles, 19 were published in 2012. For the epidemiological measures, six articles used mortality measures, eight used incidence measures only, and 23 used both measures. As for design study, ten studies conducted meta-analysis based on cohort studies, three used case-control studies, and 24 used both designs, estimating summary measures that considered the study design itself for the calculation.

Regarding study quality, studies were classified by AMSTAR-2 as low quality (n=15), medium quality (n=17), or high quality (n=5).

The main measure of random effects used was a relative risk (n=23). Eight studies used the odds ratio, whereas the six others used standardized measures such as the Proportional Mortality Ratio and Proportional Incidence Ratio. Furthermore, 26 articles showed no p-value for random effect measurements. However, to maintain the quality of the summary measure, 20 articles presented sensitivity analysis to obtain the measurement. No study had information about excess significance.

To verify the magnitude of heterogeneity in the studies, 24 articles presented the I^2 value, out of which six had I^2 values between 50% and 75%, indicating intermediate heterogeneity, and three had values above 75%, that is, high heterogeneity. Regarding publication bias analysis, 14 studies did not conduct the research using the Egger test. However, of the nine studies which conducted visual inspection using the funnel chart, only three presented symmetry, suggesting publication bias[20]. Among those who took the Egger test (n=23), only two found evidence of bias ($p<0.05$).

The main exposures identified are exposure to inorganic dust (n=5), civil construction (n=3), exposure to solvents (n=4), services that use paint (n=4), agriculture (n=3), and civil construction (n=3). The most frequent cancers on the list were lung cancer and mesothelioma (n=15), bladder cancer (n=8), kidney cancer (21), and stomach, breast, and colon cancer (n=3 each) (8.10%).

The study assessed the heterogeneity of studies, quality of evidence obtained by AMSTAR, the strength of association, and the type of measure of association (that is if obtained from longitudinal data). The most robust and consistent results indicated associations between solvent exposure and multiple myeloma, asbestos and lung cancer, hydrocarbons and upper aerodigestive tract cancer, and occupational stress and colorectal cancer. **Charts 1** and **2** and **Table 1** summarize the study characteristics, describing the selected studies, the typology of the studies, and the assessment of quality and heterogeneity, respectively.

Chart 1 Overview of selected studies (n=37)

Author	*Year*	*Journal*	*Type of cancer*	*Type of Exposure*
Lenters et al.[21]	2010	Cancer Causes Control	Lung	Endotoxin in cotton farmers
Kwak et al.[22]	2019	Occup Environ Med	Colorectal	Asbestos
Yang et al.[23]	2019	International Journal of Cancer	All cancers	Stress
			Lung	
			Colorectal	
			Esophagus	
			Bladder	
			Stomach	
Kabir et al.[24]	2017	Iran J Public Health	Prostate	Dioxin for pesticide production
Mundt et al.[25]	2018	American College of Occupational and Environmental Medicine	Lung	Bitumen – Paving
				Bitumen – Roofs
			Upper aerodigestive tract	Bitumen – Roofs
			Esophagus	Bitumen – Roofs
Chang et al.[26]	2017	Canadian Respiratory Journal	Lung	Talc

(Continue)

Chart 1 Continuation...

Author	*Year*	*Journal*	*Type of cancer*	*Type of Exposure*
Boniol et al.[27]	2017	International Journal of Epidemiology	Bladder	Rubber industry
			Leukemia	
			Lymphoid and Hematopoietic System	
			Larynx	
Lu et al.[28]	2017	Oncotarget	Non-Hodgkin lymphoma	Ultraviolet rays
Guo et al.[29]	2017	Medicine	Stomach	Butcher
			Oral cavity, pharynx	
			Lung	
			Liver	
			Glioma	
Poinen–Rughooputh et al.[30]	2016	BMC Public Health	Lung	Silica dust
Lee et al.[31]	2016	Occup Environ Med	Stomach	Crystalline silica (Total)
				Crystalline silica (Civil Construction)
				Crystalline silica (Foundry)
				Crystalline silica (Mining)
				Crystalline silica (Other industries)
Liu et al.[32]	2016	Journal of Travel Medicine	Breast	In-flight service
Ju–Kun et al.[33]	2016	Medicine	Prostate	Cadmium
Ju Kun et al.[34]	2015	Scientific Reports	Kidney	Cadmium
Hancock et al.[35]	2015	Occup Environ Med	Lung	Wood dust
Ngamwong et al.[36]	2015	Plos One	Lung	Asbestos
He et al.[37]	2014	Int Arch Occup Environ Health	Breast	Shift work
Liu et al.[38]	2013	Cancer Causes Control	Multiple Myeloma	Methylene Chloride – Solvent
Karami et al.[39]	2012	Occup Environ Med	Kidney	Trichloroethylene – Solvent
Tsoi et al.[40]	2012	Occup Environ Med	Lung	Driver
Guha et al.[41]	2010	Environmental Health Perspectives	Lung	Painter
Schmitt et al.[42]	2011	British Journal of Dermatology	Cutaneous squamous cell carcinoma	Ultraviolet rays
Guha et al.[43]	2010	Occup Environ Med	Bladder	Painter
Khalade et al.[44]	2010	Environmental Health	Leukemia	Benzene
Harling et al.[45]	2010	Occup Environ Med	Bladder	Hairdresser
Bachand et al.[46]	2010	Critical Reviews in Toxicology	Lung	Painter
Kelsh et al.[47]	2010	Epidemiology	Kidney	Trichloroethylene – Solvent

(Continue)

Chart 1 Continuation...

Author	*Year*	*Journal*	*Type of cancer*	*Type of Exposure*
Takkouche et al.[48]	2009	International Journal of Epidemiology	Lung	Hairdresser
			Larynx	
			Bladder	
			Multiple Myeloma	
			Breast	
			Ovary	
			Hematopoietic system	
			Leukemia	
			Colon	
Manju et al.[49]	2009	Asian Pacific J Cancer Prev	Bladder	Truck driver
				Bus driver
				Train driver
Lacasse et al.[50]	2009	Cancer Causes Control	Lung	Silica
Van Maele–Fabry et al.[51]	2008	Environmental Research	Myeloid leukemia	Herbicide-type pesticide (non-phenoxy)
Stayner et al.[52]	2007	American Journal of Public Health	Lung	Environmental tobacco smoke
Van Maele–Fabry.[53]	2006	Cancer Causes Control	Prostate	Pesticides
Megdal et al.[54]	2005	European Journal of Cancer	Breast	Flight attendant
				Other shift work
				General
Boffetta et al.[55]	2003	Scand J Work Environ Health	Soft tissue sarcoma	Vinyl chloride
Ojajärvi et al.[56]	2000	Occup Environ Med	Pancreas	Nickel
Lipsett et al.[57]	1999	American Journal of Public Health	Lung	Diesel – Truck driver
				Diesel – Train driver
				Diesel – Mechanic
				Professional driver

Chart 2 Description of the selected studies by typology and measure of association (n=37)

Author	*Type of cancer*	*Type of Exposure*	*Types of studies*	*Measure*	*Number of studies*
Lenters et al.[21]	Lung	Endotoxin in cotton farmers	Cohort, Case-cohort, and Case-control	Mortality	Cohort (n=15); Case-control (n=2)
Kwak et al.[22]	Colorectal	Asbestos	Cohort	Mortality	Cohort (n=46)
Yang et al.[23]	All cancers	Stress	Cohort, Case-control	Incidence	Cohort (n=4); Case-control (n=5)
	Lung				
	Colorectal				
	Esophagus				
	Bladder				
	Stomach				

(Continue)

Chart 2 Continuation...

Author	*Type of cancer*	*Type of Exposure*	*Types of studies*	*Measure*	*Number of studies*
Kabir et al.[24]	Prostate	Dioxin for pesticide production	Cohort	Mortality	Cohort (n=5)
Mundt et al.[25]	Lung	Bitumen – Paving	Cohort, Case-control	Global Association	Cohort (n=8); Case-control (n=13)
		Bitumen – Roofs			Cohort (n=11); Case-control (n=8)
	Upper aerodigestive tract	Bitumen – Roofs			Case-control (n=5)
	Esophagus	Bitumen – Roofs			Case-control (n=4)
Chang et al.[26]	Lung	Talc	Cohort	Incidence and Mortality	Cohort (n=13)
Boniol et al.[27]	Bladder	Rubber industry	Cohort, Case-control	Incidence and Mortality	Cohort (n=35); Case-control (n=19)
	Leukemia				Cohort (n=35); Case-control (n=4)
	Lymphoid and Hematopoietic System				Cohort (n=32); Case-control (n=2)
	Larynx				Cohort (n=22); Case-control (n=2)
Lu et al.[28]	Non-Hodgkin lymphoma	Ultraviolet rays	Cohort, Case-control	Incidence	Cohort (n=1); Case-control (n=10)
Guo et al.[29]	Stomach	Butcher	Cohort, Case-control	Incidence	Cohort (n=3)
	Oral cavity, pharynx				Cohort (n=2)
	Lung				Cohort (n=3); Case-control (n=3)
	Liver				Cohort (n=2)
	Glioma				Case-control (n=2)
Poinen–Rughooputh et al.[30]	Lung	Silica dust	Cohort, Case-control, and Proportional Mortality studies	Incidence and Mortality	Cohort=63 studies
					Cohort=19 studies
					Cohort=1 study
					Case-control mortality (n=5)
					Case-control incidence (n=9)
					Case-control (n=3)
Lee et al.[31]	Stomach	Crystalline silica (Total)	Cohort, Case-control	Incidence and Mortality	Cohort (n=20); Case-control (n=9)
		Crystalline silica (Civil Construction)			
		Crystalline silica (Foundry)			
		Crystalline silica (Mining)			
		Crystalline silica (Other industries)			
Liu et al.[32]	Breast	In-flight service	Cohort	Incidence	Cohort (n=10)

(Continue)

Chart 2 Continuation...

Author	*Type of cancer*	*Type of Exposure*	*Types of studies*	*Measure*	*Number of studies*
Ju–Kun et al.[33]	Prostate	Cadmium	Cohort, Case-control	Incidence and Mortality	Coorte (n=14); Caso–controle (n=8)
Ju Kun et al.[34]	Kidney	Cadmium	Case-control	Mortality	Case-control (n=9)
Hancock et al.[35]	Lung	Wood dust	Cohort, Case-control	Incidence	Cohort (n=9); Case-control (n=29)
Ngamwong et al.[36]	Lung	Asbestos	Cohort, Case-control	Incidence and Mortality	Cohort (n=7); Case-control (n=10)
He et al.[37]	Breast	Shift work	Cohort, Case-control	Incidence and Mortality	Cohort (n=10); Case-control (n=18)
Liu et al.[38]	Multiple Myeloma	Methylene Chloride – Solvent	Cohort, Case-control	Incidence and Mortality	Cohort (n=2); Case-control (n=1)
Karami et al.[39]	Kidney	Trichloroethylene – Solvent	Cohort, Case-control	Incidence and Mortality	Cohort (n=15); Case-control (n=13)
Tsoi et al.[40]	Lung	Driver	Cohort, Case-control	Incidence and Mortality	Cohort (n=8); Case-control (n=11)
Guha et al.[41]	Lung	Painter	Cohort, Case-control	Incidence and Mortality	Cohort (n=18); Case-control (n=29)
Schmitt et al.[42]	Squamous cell carcinoma	Ultraviolet rays	Cohort, Case-control	Incidence and Mortality	Cohort (n=6); Case-control (n=12)
Guha et al.[43]	Bladder	Painter	Cohort, Case-control	Incidence and Mortality	Cohort (n=11); Case-control (n=30)
Khalade et al.[44]	Leukemia	Benzene	Cohort, Case-control	Incidence and Mortality	Cohort (n=12); Case-control (n=3)
Harling et al.[45]	Bladder	Hairdresser	Cohort, Case-control	Incidence and Mortality	Cohort (n=14); Case-control (n=28)
Bachand et al.[46]	Lung	Painter	Cohort, Case-control	Incidence and Mortality	Cohort (n=16); Case-control (n=24)
Kelsh et al.[47]	Kidney	Trichloroethylene – Solvent	Cohort, Case-control	Incidence and Mortality	Cohort (n=23); Case-control (n=7)
Takkouche et al.[48]	Lung	Hairdresser	Cohort, Case-control	Incidence and Mortality	Cohort (n=8); Case-control (n=10)
	Larynx				Cohort (n=7); Case-control (n=5)
	Bladder				Cohort (n=8); Case-control (n=26)
	Multiple Myeloma				Cohort (n=8); Case-control (n=1)
	Breast				Cohort (n=7); Case-control (n=9)
	Ovary				Cohort (n=6); Case-control (n=4)
	Hematopoietic system				Cohort (n=24); Case-control (n=35)
	Leukemia				Cohort (n=6); Case-control (n=10)
	Colon				Cohort (n=6); Case-control (n=5)

(Continue)

Chart 2 Continuation...

Author	*Type of cancer*	*Type of Exposure*	*Types of studies*	*Measure*	*Number of studies*
Manju et al.[49]	Bladder	Truck driver	Case-control	Incidence and Mortality	Case-control (n=22)
		Bus driver			Case-control (n=12)
		Train driver			Case-control (n=16)
Lacasse et al.[50]	Lung	Silica	Cohort, Case-control	Incidence and Mortality	Cohort (n=4); Case-control (n=5)
Van Maele–Fabry et al.[51]	Myeloid leukemia	Herbicide-type pesticide (non-phenoxy)	Cohort	Mortality	Cohort (n=3)
Stayner et al.[52]	Lung	Environmental tobacco smoke	Cohort	Incidence	Cohort (n=21)
Van Maele–Fabry.[53]	Prostate	Pesticide	Cohort	Incidence	Cohort (n=16)
Megdal et al.[54]	Breast	Flight attendant	Cohort, Case-control	Incidence	Cohort (n=7)
		Other shift work			Cohort (n=4); Case-control (n=2)
		General			Cohort (n=11); Case-control (n=2)
Boffetta et al.[55]	Soft tissue sarcoma	Vinyl chloride	Cohort	Mortality	Cohort (n=4)
Ojajärvi et al.[56]	Pancreas	Nickel	Cohort, Case-control	Incidence and Mortality	Case-control (n=4)
Lipsett et al.[57]	Lung	Diesel – Truck driver	Cohort, Case-control	Incidence and Mortality	Cohort (n=9)
		Diesel – Train driver			Cohort (n=6)
		Diesel – Mechanic			Cohort (n=6)
		Professional driver			Cohort (n=6)

Table 1 Description of the selected studies by assessment of heterogeneity and quality of evidence (n=37)

Author	*Type of cancer*	*Type of Exposure*	*Association of the largest study*		*Measure for random effects*			I^2	*Egger's test p-value*	*Credibility value*	*AMSTAR 2*
			Measure	*95% CI*	*Measure*	*95% CI*	*p-value*				
Lenters et al.[21]	Lung	Endotoxin in cotton farmers	RR=0.36	0.34 – 0.38	RR=0.62	0.52 – 0.75	< 0.001	97.9	0.20	No	MQ
Kwak et al.[22]	Colorectal	Asbestos	SMR=1.36	1.24 – 1.49	RR=1.16	1.05 – 1.29	< 0.001	62	0.645	Yes	HQ
Yang et al.[23]	All cancers	Stress	#	#	RR=1.17	1.09 – 1.25	NR	7.3	#	Yes	HQ
	Lung		NR	NR	RR=1.24	1.02 – 1.49	NR	0	0.976		
	Colorectal		NR	NR	RR=1.36	1.16 – 1.59	NR	0	0.008		
	Esophagus		NR	NR	RR=2.12	1.30 – 3.47	NR	30	0.139		
	Bladder		#	#	RR=1.37	1.03 – 1.81	NR	#	NR		
	Stomach		#	#	RR=1.53	1.08 – 2.15	NR	#	NR		
Kabir et al.[24]	Prostate	Dioxin for pesticide production	RR=1.10	0.85 – 1.39	SMR=1.20	1.02 – 1.42	0.027	0	NR	No	MQ

(Continue)

Table 1 Continuation...

Author	Type of cancer	Type of Exposure	Association of the largest study		Measure for random effects			I^2	Egger's test p-value	Credibility value	AMSTAR 2
			Measure	95% CI	Measure	95% CI	p-value				
Mundt et al.[25]	Lung	Bitumen – Paving	SMR=1.26	1.20 – 1.31	RR=1.12	1.04 – 1.21	NR	50.2	0.267	Yes	MQ
		Bitumen – Roofs	SMR=1.37	1.28 – 1.47	RR=1.79	1.46 – 2.19	NR	83.7			
	Upper aerodigestive tract	Bitumen – Roofs	SMR=1.27	1.10 – 1.46	RR=1.32	1.17 – 1.49	NR	0	0.013		
	Esophagus	Bitumen – Roofs	SMR=1.34	1.07 – 1.66	RR=1.34	1.07 – 1.67	NR	25.2	0.021		
Chang et al.[26]	Lung	Talc	RR=1.39	1.32 – 1.47	SMR=1.45	1.22 – 1.72	< 0.001	72.9	0.65	Yes	HQ
Boniol et al.[27]	Bladder	Rubber industry	RR=1.00	0.82 – 1.22	SRR=1.36	1.18 – 1.57	NR	43	1.69	No	LQ
	Leukemia		RR=1.16	0.91 – 1.47	SRR=1.29	1.11 – 1.52	NR	32	0.98		
	Lymphoid and Hematopoietic System		RR=1.13	1.02 – 1.26	SRR=1.16	1.02 – 1.31	NR	NR	NR		
	Larynx		RR=1.31	1.24 – 1.37	SRR=1.46	1.10 – 1.94	NR	39	NR		
Lu et al.[28]	Non-Hodgkin lymphoma	UVR	OR=1.1	1.00 – 1.20	OR[a]=1.14	1.05 – 1.23	NR	25.4	0.37	Yes	HQ
Guo et al.[29]	Stomach	Butcher	OR=1.33	1.00 – 1.77	OR=1.42	1.14 – 1.76	0.002	0	0.979	Yes	MQ
	Oral cavity, pharynx		OR=1.60	1.00 – 2.70	OR=1.6	1.07 – 2.40	0.022	0			
	Lung		SMR=1.03	0.97 – 1.08	OR=1.47	1.23 – 1.74	0	9.4			
	Liver		OR=2.77	1.38 – 4.99	OR=2.56	1.52 – 4.32	0	0			
	Glioma		OR=1.78	0.99 – 3.18	OR=1.95	1.19 – 3.97	0.008	0			
Poinen–Rughooputh et al.[30]	Lung	Silica dust	SMR=1.10	1.03 – 1.18	SMR=1.55	1.38 – 1.75	< 0.0001	96.18	0.02	No	MQ
			SIR=1.30	1.12 – 1.51	SIR=1.30	1.45 – 1.96	< 0.0001	74.51	0.24		
			#	#	RR=1.65	1.13 – 2.40	1	#	#		
			NR	NR	OR=1.82	1.25 – 2.66	0.0017	51.17	0.51		
			OR=1.41	1.22 – 1.62	OR=1.34	1.24 – 1.46	< 0.0001	0	0.46		
			NR	NR	MOR=1.69	1.26 – 2.26	< 0.0001	86.70	1.00		
Lee et al.[31]	Stomach	Crystalline silica (Total)	RR=1.28	1.13 – 1.44	RR=1.25	1.18 – 1.34	NR	74.3	< 0.10	Yes	LQ
		Crystalline silica (Civil Construction)	#	#	RR=1.18	1.04 – 1.35	NR	80.5	0.5		
		Crystalline silica (Foundry)	#	#	RR=1.31	1.21 – 1.43	NR	11.5	0.9		
		Crystalline silica (Mining)	#	#	RR=1.36	1.23 – 1.50	NR	49.8	0.3		
		Crystalline silica (other industries)	#	#	RR=1.31	1.06 – 1.61	NR	62.1	0.1		
Liu et al.[32]	Breast	In-flight service	SIR=1.37	1.23 – 1.52	SIR=1.40	1.30 – 1.50	0.744	0	0.25	Yes	MQ
Ju–Kun et al.[33]	Prostate	Cadmium	SMR=0.90	0.61 – 1.29	SMR=1.66	1.10 – 2.50	NR	69.9	0.881	Yes	LQ
Ju Kun et al.[34]	Kidney	Cadmium	OR=1.48	1.17 – 1.87	OR=1.47	1.27 – 1.71	0.000	0	<0.10	Yes	MQ
Hancock et al.[35]	Lung	Wood dust	RR=1.17	1.04 – 1.31	RR=1.25	1.11 – 1.41	NR	82.1	0.456	No	MQ
Ngamwong et al.[36]	Lung	Asbestos	OR=1.75	0.96 – 3.18	OR=1.7	1.31 – 2.21	NR	0	0.079	Yes	MQ
He et al.[37]	Breast	Shift work	RR=0.97	0.67 – 1.40	RR=1.14	1.08 – 1.21	NR	77.5	0.548	Yes	MQ

(Continue)

Table 1 Continuation...

Author	*Type of cancer*	*Type of Exposure*	*Association of the largest study*		*Measure for random effects*			I^2	*Egger's test p-value*	*Credibility value*	*AMSTAR 2*
			Measure	*95% CI*	*Measure*	*95% CI*	*p-value*				
Liu et al.[38]	Multiple Myeloma	Methylene chloride	OR=2.0	1.22 – 3.27	OR=2.04	1.31 – 3.17	NR	0	NR	No	MQ
Karami et al.[39]	Kidney	Trichloroethylene	SMR=0.83	0.36 – 1.64	RR=1.32	1.17 – 1.50	NR	0.63	0.81	No	LQ
Tsoi et al.[40]	Lung	Driver	RR=1.00	0.92 – 1.09	RR[b]=1.18	1.05 – 1.33	0.004	48	NR	Yes	HQ
Guha et al.[41]	Lung	Painter	RR=1.32	1.30 – 1.35	RR=1.35	1.29 – 1.41	NR	63.6	NR	Yes	LQ
Schmitt et al.[42]	Squamous cell carcinoma	UVR	OR=1.3	1.10 – 1.60	OR=1.77	1.40 – 2.22	0.0001	NR	0.84	Yes	LQ
Guha et al.[43]	Bladder	Painter	OR=1.08	1.30 – 1.44	RR[b]=1.28	1.15 – 1.43	NR	40.1	NR	Yes	LQ
Khalade et al.[44]	Leukemia	Benzene	RR=1.07	0.88 – 1.31	RR=1.40	1.23 – 1.57	NR	56.5	0.57	No	LQ
Harling et al.[45]	Bladder	Hairdresser	RR=1.42	SI	SRR=1.34	1.34 – 1.48	NR	39.8	0.37	Yes	MQ
Bachand et al.[46]	Lung	Painter	RR=1.49	1.39 – 1.59	RR[c]=1.29	1.10 – 1.51	NR	NR	NR	Yes	MQ
			RR=1.23	1.11 – 1.35	RR[d]=1.36	1.34 – 1.41	NR	NR	NR		
			RE=1.3	1.22 – 1.38	RR[e]=1.22	1.16 – 1.29	NR	NR	NR		
Kelsh et al.[47]	Kidney	Trichloroethylene	SMR=0.99	0.40 – 2.00	SMR=1.42	1.17 – 1.77	0.0001	NR	NR	Yes	MQ
Takkouche et al.[48]	Lung	Hairdresser	RR=1.13	1.08 – 1.18	RR=1.27	1.15 – 1.41	NR	NR	NR	Yes	MQ
	Larynx		RR=0.94	0.71 – 1.25	RR=1.52	1.11 – 2.08					
	Bladder		RR=1.3	0.80 – 2.30	RR=1.30	1.20 – 1.42					
	Multiple Myeloma		RR=1.7	1.10 – 2.60	RR=1.62	1.22 – 2.14					
	Breast		RR=1.05	0.46 – 2.41	RR=1.06	1.02 – 1.10					
	Ovary		RR=1.02	0.92 – 1.14	RR=1.20	1.05 – 1.38					
	Hematopoietic System		RR=2.10	0.70 – 6.50	RR=1.26	1.14 – 1.38					
	Leukemia		RR=1.0	0.30 – 3.20	RR=1.11	1.03 – 1.19					
	Colon		RR=1.05	0.99 – 1.12	RR=1.08	1.02 – 1.13					
Manju et al.[49]	Bladder	Truck driver	OR=1.23	0.88 – 1.75	OR=1.20	1.11 – 1.30	NR	NR	NR	No	LQ
		Bus driver	OR=0.50	0.25 – 1.00	OR=1.19	1.02 – 1.38					
		Train driver	OR=1.41	0.87 – 2.28	OR=1.25	1.07 – 1.47					
Lacasse et al.[50]	Lung	Silica	NR	NR	RR[f]=1.22	1.01 – 1.47	NR	NR	NR	Yes	LQ
					RR[g]=1.84	1.48 – 2.28					
Van Maele–Fabry et al.[51]	Myeloid leukemia	Herbicide-type pesticide (non-phenoxy)	SMR=1.75	0.96 – 2.94	SMR=1.60	1.02 – 2.52	NR	0	0.1	Yes	LQ
Stayner et al.[52]	Lung	Environmental tobacco smoke	RR=1.20	0.90 – 1.50	RR=1.24	1.18 – 1.29	NR	NR	NR	Yes	MQ
Van Maele–Fabry.[53]	Prostate	Pesticide	RR=1.17	0.78 – 1.69	RR=1.28	1.05 – 1.58	NR	NR	0.612	Yes	LQ
Megdal et al.[54]	Breast	Flight attendant	SIR=1.42	1.09 – 1.83	SIR=1.44	1.26 – 1.65	NR	NR	0.7	No	LQ
		Other shift work	RR=1.79	1.06 – 3.01	RR=1.51	1.36 – 1.68	NR	NR			
		General	RR=1.36	1.04 – 1.78	RR=1.48	1.36 – 1.61	NR	NR			

(Continue)

Table 1 Continuation...

Author	Type of cancer	Type of Exposure	Association of the largest study		Measure for random effects			I^2	Egger's test p-value	Credibility value	AMSTAR 2
			Measure	95% CI	Measure	95% CI	p-value				
Boffetta et al.[55]	Soft tissue sarcoma	Vinyl chloride	SMR=2.70	1.39 – 4.72	SMR=2.52	1.56 – 4.07	NR	NR	NR	No	LQ
Ojajärvi et al.[56]	Pancreas	Nickel	SMR=1.6	0.40 – 6.90	MOR=1.9	1.20 – 3.20	NR	NR	NR	No	MQ
Lipsett et al.[57]	Lung	Diesel – Truck driver	RR=1.59	1.00 – 2.53	RR=1.47	1.33 – 1.63	NR	NR	NR	Yes	LQ
		Diesel – Train driver	RR=0.90	0.79 – 1.04	RR=1.45	1.08 – 1.93		NR			
		Diesel – Mechanic	RR=1.06	0.73 – 1.54	RR=1.35	1.03 – 1.78		NR			
		Professional driver	RR=1.48	1.30 – 1.68	RR=1.45	1.31 – 1.60		NR			

Legend: HQ: High Quality; MQ: Medium Quality; LQ: Low Quality; RR: Relative Risk; OR: Odds Ratio; SMR: Standardized Mortality Ratio; SIR: Standardized Incidence Ratio; NR: Not Reported; SRR: Standardized Rate Ratio; MOR: Mortality Odds Ratio; UVR: Ultraviolet Rays; #: Only one study;
[a]: (adjusted by race, refers to White people); [b]: (adjusted for smoking, refers to nonsmokers); [c]: (case-control studies); [d]: (cohort – mortality);
[e]: (cohort – morbidity); [f]: (exposure = 1.0 mg/m3 per year); [g]: (exposure = 6.0 mg/m3 per year).

Discussion

Cancer is a complex and multicausal disease. The component cause of several preventable cancers is occupational exposure. Unlike other risk factors, occupational risks are not caused by individual choice but by activities and institutions that do not protect workers from the harmful effects in work environments and production processes[58].

Corroborating the evidence from previous studies, this study indicates that lung, bladder, stomach, and colon cancers are consistently associated with occupational exposure to carcinogens. Service activities or activities composed of occupational groups with low schoolings, such as construction workers and drivers, are especially harmful.

Certain exposures well established in the literature[9] were not described among the selected articles, including inorganic dust and pleura mesothelioma, vinyl polychloride and liver angiosarcoma, and solvents and leukemia. These exposures have been addressed from new theoretical models, as described in this study.

Mesothelioma, a rare tumor, is highly correlated with asbestos exposure[59]. Since this association has robust evidence, asbestos production and use have been banned for decades in European countries and the United States[60]. Studies on this type of exposure are expected to be conducted in other countries, where these substances have yet to be banned[61].

Recent studies have sought to estimate the association of liver angiosarcoma with some occupational carcinogen exposure by minimizing the occurrence of bias from the possible interaction effect with alcohol and viral infections. Moreover, to further research this interaction, other studies have recently investigated the association between exposure and other forms of liver cancer, such as hepatocellular carcinoma[62]. Their latest method has been the in vitro study of the genotoxicity assessment of vinyl chloride[63,64].

Furthermore, several studies suggest that leukemia risk may be associated with occupational or industrial exposures. However, the risk may vary according to the histological type of the disease[65]. Latest risk assessments have sought to establish genetic damage involving parental and intrauterine occupational exposures[66,] while explanatory models seek to create bolder methods to isolate occupational exposure from environment exposure[67].

Studying impact measures is therefore crucial for an adequate interpretation. In this sense, the population attributable fraction (PAF) instrument estimates the fraction of cancer caused by occupational exposures[68].

PAFs are increasingly used to define cancer prevention priorities. However, though most authors recognize that occupational exposure focuses on lower socioeconomic status groups and more vulnerable workers, the instrument is mainly unknown regarding this type of exposure[69]. Since this knowledge gap is related to the lack of data on the occupational pattern of exposures and the occurrence of cancer, establishing the circumstances and cancers related to occupation is essential to solve the problem.

Determining the attributable fraction thus highly depends on good data sources with full information.

This aspect is one of the biggest obstacles in the study of occupational cancer, considering the lack of reliable information regarding occupational exposure to carcinogens. Besides the attributable fraction, the estimates of exposure proportion must also be determined by literature search and national data sources, using methodologies such as CARcinogen EXposure (CAREX)[70].

Though epidemiologists already face several obstacles to conducting studies on work-related cancer, those from middle- and low-income countries such as Brazil are even more challenged because of the lack of public policies and data sources and the likely greater occupational exposure[71]. However, antagonistically, these locations are the ones that most need these studies.

While Brazil has extensive literature on carcinogenic factors such as diet and smoking, the country's studies on work-related cancer are still embryonic. Moreover, national literature is restricted to a few occupational exposures that do not reflect current exposure but are used to estimate the prevalence of exposure to carcinogenic factors caused by work. This restriction limits the estimation of the fraction of work-related cancer. Some estimation attempts[72] are criticized – especially because of the highly specific criteria for agent selection since only those classified as group 1 by IARC[15] were considered. The classification of exposure intensity, which considers only occupational categories and economic activities definitively exposed[73].

Furthermore, discussing cancer is part of one of the strategies of the Strategic Action Plan for Tackling Chronic Non-communicable Diseases in Brazil, which foresees research on the incidence, prevalence, morbidity and Mortality, and risk and protective factors for this disease[74]. Another measure to discuss occupational cancer would be the articulated action with the General Coordination of Occupational Health of the Ministry of Health (CGST/MS), whose priority agenda includes occupational cancer surveillance[10]. Defining clear measures in the agenda is essential to prevent and identify solutions for the main health risks related to work[75]. The history of the asbestos ban shows that slow and unaggressive measures cannot effectively reduce risk[76,77], requiring more ambitious goals for the future. Models that address occupational and personal risk factors and their interactions could thus improve the understanding of health risks and guide research and interventions.

Finally, understanding the mechanisms of biological plausibility for the main findings is essential. A mechanism by which solvents can induce cancer by damaging or altering DNA by mutation can also affect the immune system. Suppressed immunity will thus increase susceptibility to the virus, causing critical cytogenetic transformations and leading to multiple myeloma[78]. In turn, aerodigestive tract cancers develop by the progression of dysplastic lesions within the squamous epithelium and by mutation of the p53 gene, mechanisms induced by hydrocarbons[79]. Moreover, psychological stress can directly affect the risk of colorectal cancer by suppressing immune function or indirectly by changing physical activity and diet levels, which are recognized mechanisms for this type of neoplasm[80].

These observations are relevant since they show the complexity of carcinogenesis mechanisms for these locations, to which occupational exposure is not a sufficient cause but a component cause. Understanding the cellular and molecular events caused by exposures to chemical carcinogens is therefore essential, reinforcing the role of epigenetics. At the same time, analysis of the factors leading to occupational exposure must consider the interaction effect of other behavioral factors.

This review has limitations. Studies classified as having critical quality were excluded from the selection. Study classification was conducted by weighting the classification criteria. However, since some of these criteria are suited for clinical trials, the absence of specific characteristics of AMSTAR-2 compromises classification regardless of real study quality. For example, the criterion "bias risk" makes any clinical trial critical since randomization presupposes a lack of bias. Observational studies – such as the selected articles – presuppose bias and analysis by statistical techniques. Another example is the absence of information on sources of finance, possibly indicating conflict of interest – a characteristic of drug intervention studies that does not apply to the selected studies.

Whenever possible, controlled vocabulary must be used. They are the subject descriptors on which articles are indexed in the database. Unfortunately, since the inclusion of descriptors is "operator-dependent," a study on associations well established in the literature – such as the one between leukemia and benzene – does not have the descriptors "*occupational cancer*" or "*work-related cancer*," it may be considered as biased. Moreover, the search would be biased if cancers of specific locations were included. Therefore, some studies of associations well established in the literature could have been lost in the search refinement.

Furthermore, this review addressed all cancer that presented evidence of association with occupational exposure without selecting any location a priori.

Conclusion

Evidence shows associations between occupational exposures and types of cancer not initially foreseen in the guidelines for work-related cancer surveillance in Brazil. Though several systematic reviews and meta-analysis support the association between work and cancer, they are significantly heterogeneous. The causative associations reported could be imprecise since this study's biases, such as residual confusion and selective reports of positive results, have been undersized or not even evaluated.

Therefore, Brazil requires further research and more consistent meta-analysis on relevant exposures and types of cancer, including exposure to inorganic dust and lung cancer and mesothelioma and exposure to solvents and hematological tumors. Evidence of cancer in other anatomical regions was less robust, showing signs of uncertainty or bias.

Investment in occupational epidemiology is thus essential to identify new associations of exposure and disease, surveil workers' health, and emphasize the use of epidemiological findings of occupation in policy regulation and elaboration. For this, further specific meta-analysis should better reflect the demand for evidence in Brazil, including the association between exposure to asbestos and mesothelioma, exposure to particular solvents and hematological tumors (such as lymphocytic leukemia, non-Hodgkin lymphomas, and multiple myeloma). Finally, the Guidelines for Work-Related Cancer Surveillance[9] should be revisited to cover increased surveillance actions.

Authors' contributions

Guimarães RM and Dutra VGP contributed substantially to study conception and data collection, analysis, and interpretation. Guimarães RM, Dutra VGP, Ayres ARG, Garbin HBR, Martins TCF, and Meira KC contributed to the preparation of the manuscript, critical reviews, and approval of the final version of the manuscript. They assumed full public responsibility for the study and its content.

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