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Update on Occupational Cancer in 2024

REVIEW

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Update on Occupational Cancer for Better Cancer Prevention and Control

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Abstract

Occupational cancer remains an ongoing and emerging issue in cancer prevention and control and is more easily preventable in practice than other causes. As of 2024, changes in various aspects, such as methods for estimating the burden of cancer, evidence on novel carcinogens and classification systems, modernization of working conditions, job characteristics, occupational exposure, and societal changes have played a significant role. Furthermore, advances in technology, including wearable devices, exposome, and biomedical technology, offer more precise methods for identifying the associations between occupational carcinogens and cancer. Diagnosing occupational cancer and investigating clusters are crucial for understanding its etiology. Prevention at every level- from primary to quarterly prevention- and promotional activities are crucial for exposed workers, often outweighing the importance of treatment, which can be costly. This updated information, as reviewed in this article, and cooperative work with occupational medicine physicians, could contribute to improving clinical practices for better cancer prevention and control.

Keywords: Cancer- occupational carcinogen- prevention and control- occupational medicine

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Introduction

Cancer is the leading cause of morbidity and mortality on the global, regional, and national scales, particularly among working-age demographics, creating economic and social challenges for both patients and their communities. Over the past decade, rapid advancements in science and technology have significantly enhanced our understanding of occupational cancers. Various risk factors contribute to cancer, including genetics, lifestyle, environmental, and occupational factors. Although occupational causes constitute a relatively small proportion compared with other factors and are still underestimated and underreported worldwide, nearly half of all recognized carcinogens are occupational, making cancer prevention and control key areas of focus.

Since the first industrial revolution, which introduced novel medical investigative methods and technologies, unique risks have been introduced to workers. Currently, the challenges of the Fourth and Fifth Industrial Revolutions have marked a significant shift in both perspectives and possibilities. Occupational cancer is an emerging challenge in various fields owing to its individual effects, burden on society, difficulties in risk assessment, and the continued ineffectiveness of control measures [1]. Future work will involve a mixture of traditional carcinogens, such as chemicals, physical and biological hazards, and emerging carcinogens, such as shift work, engine exhaustion, and electromagnetic fields (EMF). Additionally, globalization will introduce new technologies and risk factors in both developed and developing countries, along with heightened social awareness of occupational cancer. These chronological changes introduce both risks and the potential for more effective control [2]. Therefore, cancer prevention and control providers should update their knowledge on the following issues to stimulate and fill the identified gaps and further develop findings, manage properly, and prepare for the prevention and control of future occupational cancer epidemics.

Burden of occupational cancer

Global cancer burden data from GLOBOCAN estimates 20.0 million new cancer cases, and an estimated 35.3 million expected cases by 2050 in their 2022 report. The most common cancer in males is lung cancer, followed by prostate, colorectal, and stomach cancers. Breast cancer is the most common cancer in females, followed by the lung, colorectal, and cervical cancers. There were 9.7 million new cancer-related deaths reported [3]. Epidemiological transitions from changing demographics to shifts in carcinogenic exposure, particularly in low- and middle-income countries, are increasing the global

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cancer burden. Therefore, these numbers are important for estimating the cancer burden caused by occupational exposure. Understanding this magnitude is crucial for identifying high-risk groups; monitoring occupational exposure trends over time; conducting occupational cancer surveillance; setting priorities for preventive measures; and developing or implementing effective prevention and mitigation strategies, legislation, and policies [4].

The recognition of occupational cancer is increasing through various methods for calculating the cancer burden, including estimation of the attributable fraction, direct utilization from the literature, expert panel estimations, tracking of new incident cases over time, and linkage analysis with national databases such as census data, cancer registries, or death certifications [5]. Additionally, advancements in information technology, such as spatial analysis, can reveal the burden and trends of occupational cancer [6]. Currently, the estimation of attributable numbers and fractions is popular and makes an important contribution to the knowledge base for prioritizing strategic health and safety planning or research to fill information gaps. More than 40 years ago, Doll and Peto estimated this occupation-related cancer burden with a large degree of uncertainty, approximating that 4% (range 2–8%) of all cancer death cases were attributable to occupational exposures based on the concept of population attributable risk or PAF [7]. However, Doll and Peto did not estimate the genetic contributions to cancer risk, highlighting that inherited susceptibility factors, such as age, cannot be avoided. This attributable fraction method also differs by cancer type, with lung cancer accounting for over two-thirds of deaths attributed to occupation, and asbestos being the single agent linked to the highest number of cancer deaths [8]. Another important issue is the use of exposure data to calculate the burden of occupational cancer. It is essential to determine where the carcinogen intensity of exposure occurs and the number of workers affected. This information can be found in various databases such as the CARcinogen Exposure(CAREX) system. The CAREX was first developed in the European Union and has since been adapted for use in other regions including Canada, Australia, and Asia [9]. CAREX estimates the prevalence of occupational carcinogen exposure across various settings, including industry sectors, occupations, prioritized carcinogens, and sex [10].

To date, the overall burden of occupational cancer has remained relatively high and has not declined. Cancers attributed to occupations depend on the evaluation method [11]. This proportion of data is pivotal for assessing the estimated cancer burden. For example, annual deaths due to occupational cancer have increased from 666,000 in 2011 to 742,000 in 2015 and further to 880,000 in 2021 [12]. These trends suggest that the measures implemented thus far may not have been sufficiently effective. Furthermore, the annual statistics for each country remain lower than this number, which is a concern that cancer prevention and control providers must address [13].

Although cancers resulting from occupations comprise only a small portion of the total cancer burden(almost less than 20%), their importance should not be overlooked. If workers in any country are observed to have increased longevity, the proportion of cancer cases, including those specific to certain occupations, will increase. Moreover, this burden of work provides a unique opportunity to study the causes of cancer, because exposures are often better documented and of higher intensity than those encountered environmentally.

Carcinogen classification

By identifying the agents and processes that cause occupational cancer, valuable insights can be gained. This knowledge can be used to prevent other work- and non-work-related cancers. The incidence of cancer declines if its etiology is known, making the identification of carcinogens an essential first step in cancer prevention. More than 1,000 hazards, including traditional and contemporary carcinogens, were evaluated to determine whether they are agents, mixtures, work circumstances, or occupations [14]. The worldwide carcinogen classification system used in clinical practice refers to the International Agency for Research on Cancer (IARC), which established its first monograph series in 1927 [15]. In 2024, more than 137 monographs have been published.

In January 2019, the IARC updated its monograph preamble procedure to ensure a modern and transparent approach to synthesizing evidence for identifying cancer hazards. This process involves identifying, reviewing, evaluating, and integrating evidence to determine the causes of human cancers. These updates include strengthening the systematic review methodology, placing greater emphasis on mechanistic evidence based on key carcinogenic characteristics, considering the quality and informativeness of epidemiological studies, enhancing the harmonization of evaluation criteria for different evidence streams (including human epidemiological studies, experimental studies on animals, and studies on cancer development in response to the agent), and implementing a single-step process to integrate mechanistic data with cancer findings in humans and experimental animals for comprehensive evaluation [16]. Importantly, this concept remains unchanged. The IARC classification refers to the strength of evidence for a cancer hazard rather than the level of cancer risk.

The IARC updated the carcinogen classification from five groups (Groups 1, 2A, 2B, 3, or 4) into four groups (Groups 1, 2A, 2 B, or 3) by combining the previous Groups 3 and 4 as not classifiable as to its carcinogenicity to humans. Group 1 was based on sufficient evidence in humans or both sufficient evidence in experimental animals and strong mechanistic evidence in exposed humans. For Group 2, Group 2A was based on two streams of evidence: at least one of the exposed humans or human cells, whereas Group 2B was based on one stream of evidence (Table 1). In addition, strong evidence of the key characteristics affected the evaluation of groups 1, 2, and 2B. A summary of the updated IARC carcinogen groups 1 and 2A from monographs 101–136 is shown in Tables 2 and 3 [17].

Table 1. Updated IARC Classification for Cancer Hazard Identification (Adapted from Samet JM , et al , 2020).

Evidence of cancer in Humans	Evidence of cancer in experimental animals	Mechanistic evidence	Classification based on basis of overall evaluation
Sufficient			Carcinogenic to humans (Group 1)
	Sufficient	Strong(key characteristics from exposed human)	
Limited	Sufficient		Probably carcinogenic to humans (Group 2A)
Limited		Strong (key characteristics of carcinogens)	
	Sufficient	Strong(key characteristics from human cells or tissues)	
		Strong (mechanistic class of agents for which one or more member have been classified in Group2A or 1)	
Limited			Possibly carcinogenic to humans (Group 2B)
	Sufficient		
		Strong (key characteristics of carcinogens)	
Limited		Strong (experimental animals, not in human)	
		Strong (experimental animals, not in human)	Not classifiable as to its carcinogenicity to humans (Group 3)
All other situations not listed above			

Current carcinogens characteristics and their exposure

In 2018, Marant Micallef et al. reviewed the characteristics of 193 group 1 and 2A occupational carcinogens and found that inhalation was the primary route of exposure, followed by dermal contact. They noted that oral absorption was less significant and usually resulted from poor personal hygiene such as smoking or eating in the workplace without hand washing. They found that lung cancer had the strongest association with occupational carcinogenic exposure, followed by bladder cancer and non-Hodgkin's lymphoma. Ionizing radiation was linked to the highest number of cancer sites, followed by asbestos exposure, and working in the rubber manufacturing industry. Asbestos, bis(chloromethyl)ether, nickel, and wood dust have the most significant impact on cancer risk, with relative risks exceeding 5.0 [18].

As of 2024, according to IARC monographs volume 1–136, carcinogens share common traits in the work environment, displaying low potency, yet leading to cancer development in multiple organs. Emerging hazards such as nanoparticles and EMF are used as alternatives to carcinogens; however, their carcinogenic risks remain unclear and require medical surveillance [19]. Nonchemical carcinogenic concerns also exist when evaluating potential cancer risks associated with factors such as shift work, as in IARC Group 2A [20]. The radiofrequency EMF was IARC Group 2B [21-22]. Additionally, various work environments and conditions, such as those faced by firefighters exposed to multiple carcinogens, have been evaluated as human carcinogens or IARC Group 1 [23]. However, exposure to asbestos and silica has remained the most significant contributor to occupational carcinogen-related cancer burden over the past 20 years.

Despite the reduction in the average exposure levels to carcinogens, the overall cancer burden attributed to occupational carcinogens has increased, primarily because of the lingering effects of past exposure hazards [8]. Moreover, modern society has changed its medical anthropology. For example, gender equity has led to more females entering the workforce, exposing them to risks similar to those faced by males. Numerous studies have reported occupational cancer cases in females such as breast cancer [24]. Globalization is the relocation of carcinogens from developed to developing countries with limited resources for occupational cancer control and prevention and a lack of experts in occupational medicine and industrial hygienists. Even with low exposure to certain work conditions, continuous monitoring is essential [25]. In addition, there is increasing public concern and research regarding work-related common cancers in the general population, such as occupational sedentariness and breast cancer [26], occupational physical activity, and lung cancer [27]. Some novel carcinogens have also been re-evaluated, revealing new associations with other organs, such as benzene and lung cancer [28].

Exposure and effect assessment

Revolutionary technological advancements, including the development of new tools, methods, and technologies for assessment, artificial intelligence algorithms, and diagnostic tools, are being utilized to provide reliable and accurate cancer assessments [29] and enhance occupational medicine practice [30]. These advancements include the following.

Wearable devices

In the digital era, there has been rapid growth in digitalization, leading to the development of wearable systems that are crucial in clinical practice for monitoring, detecting, preventing, and managing worker health. These systems include a wide range of devices designed to be worn on the body such as accessories and clothing. Wearable systems include biosensors, smartwatches, fitness trackers, virtual reality sets, and smart jewelry.

Table 2. Updated List of Occupational Carcinogens Group 1 from IARC Monographs 101–137, 2012–2024.

IARC Monograph Volume	Carcinogens	Description	Sufficient evidence in human carcinogenicity and causes	Positive association between occupational exposure and cancers
136	Acrylonitrile	A volatile organic compound used in the polymer production for manufacturing fibers for textiles, plastics.	Lung cancer	Bladder cancer
135	Perfluorooctanoic acid (PFOA)	A fluorochemicals for production of fluoropolymers and stain-, oil-, and water-resistant surface treatments.	-	Renal cell carcinoma Testicular cancer
132	Firefighter	This occupation may encounter exposure to combustion products from fires (such as PAHs and particulate matter), building materials (including asbestos), chemicals found in firefighting foams (such as per- and polyfluorinated substances), flame retardants, diesel exhaust, and other hazards like night shift work and UV or other forms of radiation.	Mesothelioma, Bladder cancer	Colon, Prostate, and testis cancers; Malignant melanoma of the skin, Non-Hodgkin lymphoma
120 (version Sep 2019)	Benzene	A simple aromatic hydrocarbon resulting from human activities such as combustion, primarily used as a chemical intermediate.	Acute myeloid leukemia in adults	Non-Hodgkin lymphoma, Chronic lymphoid leukemia, Multiple myeloma, Chronic myeloid leukemia, Acute myeloid leukemia in children, Lung cancer
118	Welding fume Ultraviolet radiation from welding	Welding involves exposure to fumes, gases, ultraviolet radiation, electromagnetic fields, and often asbestos and solvents.	Lung cancer Ocular melanoma	Kidney cancer
117 (version Oct 2019)	Pentachlorophenol	A chemical previously used as a wood preservative and insecticide, now restricted due to its toxicity.	Non-Hodgkin lymphoma	-
113 (version Mar 2019)	Lindane	An agricultural insecticide largely banned due to its toxicity.	Non-Hodgkin lymphoma	-
111	Fluoro-edenite fibrous amphibole	A new end-member of the calcic amphibole group composed of most fluoro- edenite which are used in the local building industry, paving	Mesothelioma	-
	Acheson process	The manufacturing process for silicon carbide particles, producing silicon carbide fibers as by-products.	Lung cancer	-
110 (version Dec 2016)	1,2-Dichloropropane	A chlorinated solvent used primarily as a production intermediate, also in paint stripping and printing-press cleaning.	Biliary tract cancer (Cholangiocarcinoma)	-
109	Outdoor air pollution Particulate matter in outdoor air pollution	A diverse blend of pollutants originates from both natural and human activities, encompassing transportation, power generation, industrial operations, heating, and cooking. Frequently monitored pollutants include particulate matter (PM2.5, PM10), nitrogen dioxide, and sulfur dioxide.	Lung cancer Lung cancer	Urinary bladder cancer
107 (version Aug 2018)	Polychlorinated Biphenyls (PCBs)	A class of aromatic compounds with numerous congeners, previously used in various industrial applications.	Malignant melanoma	Non-Hodgkin lymphoma, Breast cancer
106	Trichloroethylene	A chlorinated solvent used in multiple industries, including aircraft and automobile manufacturing and repair, as well as screw-cutting.	Kidney cancer	Non-Hodgkin lymphoma, Liver cancer
105	Diesel engine exhaust	Emitted from combustion engines used in transportation, industrial machinery, and electricity generators, containing a complex mixture of gases and particulates.	Lung cancer	Urinary bladder cancer

Table 3. Updated List of Occupational Carcinogens Group 2A from IARC Monographs 101–137, 2012–2024.

Metals:	**Pesticides:**
* Cobalt metal (without tungsten carbide or other metal alloys) (Volume 131)	* Aldrin and dieldrin (Volume 117)
	* DDT (Volume 113)
* Soluble cobalt(II) salts (Volume 131)	* Malathion (Volume 112)
* Trivalent antimony (Volume 131)	* Glyphosate (Volume 112)
Industrial chemicals:	**Aromatic amines and derivatives:**
* 2-Bromopropane (Volume133)	* ortho-Anisidine, and its salt, ortho-anisidinehydrochloride (Volume 127)
* Acrolein (Volume 128)	*ortho-Nitroanisole (Volume 127)
* Glycidyl methacrylate (Volume 125)	*Aniline, the parent compound of aniline hydrochloride (Volume 127)
* Styrene (Volume 121)	* 3,3′,4,4′-Tetrachloroazobenzene (Volume 117)
* N,N-Dimethylformamide (Volume 115)	*2-Mercaptobenzothiazole (Volume 115)
* fuel hydrazine (Volume 115)	*N- and S-heterocyclic polycyclic aromatic hydro- carbons such as Dibenz [a,j]acridine (Volume 103)
* Tetrabromobisphenol A (Volume 115)	**Others:**
* Tetrafluoroethylene (Volume 110)	* Talc not containing asbestos (Volume 136)
* 1,3-Propane sultone (Volume 110)	* Night shift work (Volume 124)
* Tetrachloroethylene and its metabolite such as chloral hydrate (Volume 106)	* Silicon carbide whiskers (Volume 111)
* 1,1,1-Trichloroethane (Volume 130)	* Bitumens and bitumen emissions (Volume 103)
* Dichloromethane (Volume 110)	

Typically, these devices incorporate Internet connectivity, allowing data to be synchronized with other devices for analysis and tracking [31]. They have been deployed across various occupational sectors to replicate the benefits of physical well-being observed among healthy workers. The use of wearable devices has led to increased awareness and monitoring as well as improvements in worker safety. Various devices have been utilized to assess exposure to carcinogens, such as ultraviolet radiation [32] and EMF [33]. Wearable devices are used to promote a healthy lifestyle for cancer prevention [34]. A systematic review by Ray et al. found that the most common types of cancer detected by wearable systems are breast, skin, prostate, and other types of cancer [35].

Exposome

Exposure assessment in occupational epidemiology is crucial to identify the association between carcinogens and cancer risk. The nature of exposure has changed and no single occupational carcinogen has persisted throughout a worker's life. Surveys on carcinogen exposure have found that workers are typically exposed to 2–10 different carcinogens [36]. Moreover, many sources such as pollution, lifestyle, and dietary or social determinants contribute to the cumulative carcinogenic risks encountered over a lifetime. Therefore, it is difficult to identify an association between carcinogens and cancer risk. In recent decades, a new concept in preventive field call "Exposome" have emerged to address this issue. This was first mentioned by Christopher Paul Wild, former director of the IARC, in 2007 [37]. Exposome is a holistic lifelong exposure from three aspects:

1. External exposures, such as hazards from work (physical, chemical, and biological hazards), diet, lifestyle, and ambient environment;

2. general external exposure such as socioeconomic status and natural build environment; and

3. internal such as metabolism, endogenous circulating hormone, individual anatomy and physiology, gut microbiota, and inflammation.

Understanding exposomes, including occupational factors, involves encompassing all environmental exposures throughout a worker's life, potentially clarifying the epigenetic and genotoxic changes in workers. This understanding of carcinogenesis aids in identifying and mitigating cancer risks in the workplace for prevention and control [38].

An example of a study utilizing this concept was by Faisandier et al., who identified an association with non-Hodgkin lymphomas [39]. Innovation in exposomes presents significant opportunities for clinical practice. This includes establishing causes (hazard and risk) in exposure assessments for epidemiological studies, with the capability to capture low concentrations and co-exposures, and assess confounders. It provides dose–response data for subsequent risk assessments and supports the biological plausibility of exposure-disease associations, bridging experimental and human data. It can also identify alternative or intermediate disease endpoints and assess the risk of different tumor subtypes. Furthermore, exposome innovation allows stratifying the risk for susceptible subgroups and identifying critical windows in time. Surveillance enables biological monitoring of the prevalence and levels of exposure, evaluation of interventions through short-term endpoints, and use of mechanism-based markers [40].

Biomarker

Advances in biomedical technology, particularly

in molecular biology, in recent years have provided biomarkers that serve as indicators of risks, making it feasible to investigate the underlying mechanism behind carcinogens and their associated cancers. This has a widespread impact on the multi-omics approach, integrating data from multiple levels, such as genes, mRNAs, regulatory factors, proteins, and metabolism [40-41].

MicroRNAs are important regulators of gene expression. They have the potential to be used as biomarkers for detecting the genotoxicity and carcinogenicity of chemicals and for indicating exposure to carcinogens such as asbestos [42] and persistent organic pollutants (POP) [43]. In practice, evidence suggests that the expression of specific microRNAs, such as, MiR-126, miR-132-3p, and miR-103a-3p, in blood serum or plasma is the most promising diagnostic biomarker for asbestos-related malignant pleural mesothelioma. MiR-126, alone and in combination with miR-222, has also been associated with lung cancer diagnosis, together with miR-1254 and miR-574-5p.

Moreover, early biomarkers of this effect will enable early detection, prevention, and control. For instance, the frequency of cytogenetic and genetic alterations in peripheral white blood cells, such as t8;21, del(5q), del(7q), and AML1/ETO fused transcript, is a significant biomarker for leukemia. These biomarkers support the hypothesis that the mechanism of action of benzene involves chromosomal damage during carcinogenesis [44].

Furthermore, susceptibility biomarkers, including specific genetic polymorphisms, have gained importance in clinical practice for predicting individual susceptibility to carcinogens. This concept, known as "Gene and environmental interaction" [45], can be highly specific to certain exposures, and non-genetic factors of susceptibility, such as urine pH influenced by diet, can interact with xenobiotic exposures, significantly affecting DNA adduct levels [46]. Understanding these interactions is crucial for assessing cancer risk. However, the integration of susceptibility biomarkers into routine clinical practices remains limited globally, necessitating the consideration of ethical, legal, and social implications [47].

Diagnosis of occupational cancer

Advances in occupational medicine have provided opportunities to determine the incidence of occupational cancer. This is crucial not only for clinical management but also for compensation. Diagnosing cancer with a long latency period due to occupational exposure can be challenging. There are often gaps or inconsistencies in relevant epidemiological studies or biological data, as well as a lack or absence of historical data compounded by individual complexity. Therefore, a diagnosis should strive to establish a logical and reasonable basis, from a neutral perspective. This involves a step-by-step diagnosis based on logical criteria [48], which are more accurate for diagnosis, as follows:

Step 1: Evidence of malignant cancer diagnosis

Recent advancements in cancer diagnostics such as tumor imaging, histopathological or molecular techniques, and identification of the primary site are crucial. To establish a connection between specific carcinogens and cancer in workers, it must be demonstrated that carcinogens significantly increase the risk of cancer development at a specific site. If the primary site cannot be identified, the cancer is poorly defined, or only metastatic sites are detected, it becomes challenging to conclusively determine the occupational cause of the disease, which is essential for diagnosing an occupational illness. Currently, techniques such as immunohistochemistry, which rely on the presence of specific antigens, aid in distinguishing between primary tumors and metastatic lesions. For instance, commonly used markers that differentiate between pleural mesothelioma and lung adenocarcinoma include markers positive for mesothelioma, such as WT1, calretinin, D2-40 (podoplanin), and cytokeratin 5/6, whereas markers positive for lung adenocarcinoma include MOC-31, BG8, CEA, B72.3, Ber-EP4, and TTF1 [49].

Step 2: Evidence of potential carcinogen exposure

This step confirms exposure in the work environment to hazards considered carcinogenic to humans according to the relevant IARC classification of carcinogens. Exposure to agents classified as likely carcinogenic to humans in the work environment supports the assumption of an occupational cause of cancer and enables the diagnosis of an occupational disease. The level and duration of the exposure are also critical. Since there is no safe threshold for carcinogen exposure or many countries lack standards for carcinogenic substances owing to the difficulty of determining safe exposure levels, any contact poses a risk that increases with longer and higher exposure. For example, a study by Kauppinrn et al. recommended minimal exposure should average over year with at least 30 min per week or once per week for 90% of work year [50].

Step 3: Work-related assessment using epidemiological support[51-55]

Based on the Bradford Hill criteria, important criteria must have at least the following information:

Temporal relationship

The timing between exposure to a carcinogen and cancer development must be appropriate, considering the type of tumor and the latency period. It is crucial to determine whether the cancer latency period is sufficient to establish a causal link between disease and exposure. The latency period primarily depends on the carcinogen type as well as on factors such as the patient's age at exposure and the dose. This period can range from several years to several decades, often exceeding 10 years for occupational cancers in solid organ and 1–5 years for hematologic systems. When exposure involves multiple carcinogens affecting the same organ, the risk increases and the latency period may be shorter. Some guidelines for diagnosing occupational diseases specify minimum latency periods

and exposure levels for certain cancers [51].

Consistency

Exact evidence-based knowledge is required. It is necessary to verify whether the cancer location and carcinogen type are aligned with current medical knowledge. The location of cancer primarily depends on the carcinogen type, absorption and excretion routes, and its affinity for various organs. Information on the carcinogenic effects of various substances can be found in the IARC monographs (for example, Tables 2 and 3) and databases such as MEDLINE and Toxline.

Strength of association

The magnitude used to establish causation often relies on findings from epidemiological studies, such as relative risks in cohort studies, odds ratios in case-control studies, and attributable risks calculated from differences in disease incidence among groups. Some experts determine work-relatedness by equating causation with a relative risk of 2.0 or an attributable risk of 50%. However, caution is warranted when interpreting such data because applying these thresholds to causal probabilities can lead to scientific errors and potentially underestimate the likelihood of causation if contributions or comparative risks are misapplied. Currently, there is no universal standard for assessments, and the criteria for causation may vary not only among occupational medicine professionals but also based on national standards and consensus within each country [52].

Biological plausibility

This plausibility involves understanding the mechanisms by which cancer develops. Typically, IARC reviews carcinogens and categorizes them according to their ability to cause cancer in specific organs. However, the link between carcinogens and cancer in specific organs has not yet been clearly established. In such cases, it is essential to identify the potential exposure pathways of known carcinogens and understand the mechanisms by which cancer develops. This involves referencing the literature on how carcinogens are absorbed, distributed, metabolized, and excreted by humans and animals to establish a basis for biological plausibility [53].

Step 4:Other nonoccupational risks and relevant factors were excluded

Work-related cancers can be categorized into two groups. The first group is cancers with a clearly identified cause linked to employment and a strong relative risk, for example, mesothelioma from asbestos and liver angiosarcoma from vinyl chloride monomers. Although nonoccupational causes are likely to account for a small proportion of cancers, cases with confirmed exposure to known carcinogens are recognized as occupational cancers. However, this group represents a small proportion of the global cancer burden. The second group, which is more common, encompasses cancers with both occupational and nonoccupational causes, such as lung and bladder cancer. The establishment of occupational origins of these cancers is complex. Therefore, the impact of known nonoccupational cancer risk factors should be considered. Cancers caused by occupational carcinogens do not have specific features and do not differ in course or clinical and histological characteristics from cancers in populations that are not occupationally exposed to these factors. This process considers the existence of non-occupational risk factors for cancer development, with smoking being the most important factor in various organs, particularly the respiratory system. Other common non-occupational causes include infectious agents such as the Epstein-Barr virus for nasopharyngeal carcinoma and hepatitis B and C for liver cancer. The contribution of other causal factors, such as non-occupational carcinogens, age, sex, and underlying diseases, should be considered. Other relevant information, such as clusters of cancer cases or debated information such as environmental data, should also be considered. Finally, the validity of the testimony and the reliability and credibility of the opinions and sources should be evaluated before summarization.

Step 5: Summarize work relatedness based on all available information [52, 54, 55]

Key factors such as the basis of diagnosis, exposure levels, disease progression, and epidemiological evidence play crucial roles in assessing the connection between occupational factors and cancer. Therefore, it is important to consider the contributions of other potential causal factors. Determining the degree of causation is often approached probabilistically rather than deterministically because of the complex nature of biological processes, limited understanding of the underlying mechanisms, and variations in individual susceptibility. Causation is typically categorized into four levels: definite or certain (100%), very likely (>80 %), probable or likely (60–80%), and possible or more likely than not (50–60%). Generally, only cases falling into the definite through probable categories (>60%) were considered to have a clear work-relatedness.

Occupational cancer cluster and investigation

In clinical practice, the unusual number of cancer cases warrants further investigation. These cases may result from chance or differences in access to healthcare or cancer screening. Other contributing factors may include genetic susceptibility, occupational exposure, environmental factors, and behavioral risk. Some unusual cancer patterns are considered cancer clusters. A cancer cluster is defined as a greater-than-expected number of the same or etiologically related cancer cases occurring within a group of people in a geographic area over a defined period [56]. Although these events are not often but not rare, a recent review of cancer cluster concerns from 2001–2020 in the USA indicated that only approximately 4% were considered clusters that could pinpoint occupational carcinogen causation [57]. Most etiologies are single agent and rare histologic types of cancer. The first occupational cancer cluster was reported by Pott et al.. He identified occupational cancer in the scrotum of chimney sweepers in 1775 AD, due to exposure to soot, later found to contain polycyclic aromatic hydrocarbons. Since then, numerous

cancer cluster investigations in various workplaces or occupations have been conducted, revealing occupational carcinogens such as radium, asbestos, and vinyl chloride monomers [58]. Common criteria for deciding whether to pursue a more thorough investigation of a cluster typically include identifying a single type of cancer, establishing biological plausibility and a sufficient latency period for the reported cancer, political or public pressure, identifying a common cancer occurring in an unusual age group, discovering a rare type of cancer, identifying exposure to a carcinogenic substance, and observing an elevated ratio of confirmed cancer cases compared to expected cases [59].

Addressing concerns about workplace cancer clusters involves refining investigation approaches through several procedures, including using cancer registries; reviewing medical and environmental records; conducting worker interviews or administering questionnaires; performing industrial hygiene sampling; and calculating rates such as the proportional mortality ratio, standardized incidence ratio, or standardized mortality ratio. These methods helped identify occupational carcinogen causation in the epidemic of cancer cluster blasting in 2013, such as the notable cholangiocarcinoma cluster in the printing industry, where investigations linked it to dinitrocholomethane (DCM) and dichloropropane (DCP), classified as Group 1 and 2B carcinogens by the IARC [60].

Prevention and control

Finally, the best activities for occupational cancer in clinical practice are prevention rather than treatment, which is more complex, expensive, and less efficient [61]. Regarding the prevention and control of occupational cancer, various prevention levels, activities, and measures can be employed in the workplace to ensure the health protection of workers through different levels of prevention.

Primary prevention

In addition to understanding the burden of occupational cancer, reviewing well-established occupational carcinogens, and assessing exposure levels in different occupational settings, identifying carcinogenic risks through epidemiological studies is an early step toward cancer prevention. Primary prevention lowers cancer risk in healthy and susceptible workers. It is important for various aspects of primary prevention, such as calling for ban policies for asbestos to improve the working environment [62]. Although elimination remains the most effective way to prevent exposure, practical challenges arise for various reasons, particularly with successful carcinogens such as asbestos and residual DDT. The ILO Convention C-139 states that carcinogenic substances or agents must be replaced by non-carcinogenic substances or agents or by less harmful substances or agents.

Although carcinogens are still widely used today, in practice, it is not possible to eliminate them completely from work systems. No exposure is the optimal approach for primary prevention; however, in practice, it is unattainable for most carcinogens. Minimization of exposure should be pursued through various preventive and control measures. Technological innovation through continuous scientific progress or identification of the innovative working process could substitute for these harms [63]. Substitution measures have emerged as the second-best strategy. However, some substitute agents have unknown long-term effects and require surveillance. Robotics plays a crucial role in the work system and provides an opportunity to decrease the exposure of workers.

Legislation and regulations also serve as effective tools for primary prevention, yet their effectiveness hinges on the specifics of the regulations and the rigor of enforcement. Implementing measures across a hierarchy of controls can mitigate disease risk and reduce exposure. Monitoring, surveillance, and screening are effective in preventing and assessing the impact of legislative and policy change [64]. However, multifaceted interventions are typically more effective than single-focus activities.

In contrast, non-occupational risks in workers are also important according to the total worker health concept [65]. The IARC has developed 12 recommendations, including avoiding smoking and alcohol; maintaining a healthy body weight, diet, and physical activity; avoiding carcinogen exposure from natural sources such as radiation or from work; participating in vaccination and screening programs; and decreasing risk factors that can reduce cancer risk by up to 40%. These risks should be addressed in worker health promotions for cancer control, both at work and throughout their personal lives. Removing the influence of one factor may, in turn, reduce the impact of the other factor [66]. In addition to prevention, lifestyle changes for workers must be promoted to decrease the synergistic risk of occupational cancer.

Secondary prevention

Secondary prevention involves early detection through screening and early diagnosis. Faster diagnosis and regular screening could improve the survival rate of patients with cancer and increase the rate of return to work [67]. Surveillance through screening programs may target workers at the highest risk based on their genetic makeup, co-exposure, or comorbidities. After detecting and diagnosing occupational cancer, reports on relevant parities are important to determine the burden of the disease. Additionally, actions should be taken to protect workers who have been previously exposed to occupational carcinogens. Following up with exposed workers is crucial, considering the long latency period that may occur after the initial exposure.

Nevertheless, the fundamental practice of obtaining occupational histories remains crucial for identifying the past or current exposure necessary to diagnose work-related cancer. Integrating a structured questionnaire into clinical routines in hospitals has significantly enhanced the detection of suspected cases [68]. Modern technologies such as online tools that facilitate hospital workflows play a role in generating data for the mandatory reporting of work-related cancer and initiating investigations and surveillance [69]. However, based on the latest systematic review, there is currently no evidence supporting the use

of telemedicine for occupational examinations instead of in-person evaluations [70].

Tertiary prevention

Tertiary measures can prevent disability and mortality. With advancements in medical treatment and the improved longevity of cancer survivors, returning to the workforce has become vital for reducing morbidity and mortality. Cancer survivors commonly face challenges such as decreased work capacity, functional limitations, and disabilities owing to persistent physical symptoms. However, many patients can successfully re-enter the workforce after treatment, bringing benefits not only to the individual by enhancing the overall quality of life but also to employers and impacting the economic burden for society at large [1]. As individuals undergo treatment and emerge as cancer survivors, the intricate process of returning to work becomes crucial. This dynamic transition from battling life-threatening illnesses to resuming occupational activities necessitates careful consideration and proactive measures in occupational medicine.

After cancer treatment, many individuals face the challenge of returning to work even after overcoming a serious health crisis. A recent meta-analysis revealed that individuals undergoing chemotherapy and/or radiation treatment and those with brain and colorectal cancers are at risk of unemployment or changes in employment status [71]. This potential impact on economic stability and overall well-being underscores the importance of developing robust tertiary prevention strategies in clinical practice.

Returning to and being fit for work are pivotal aspects of the tertiary prevention paradigm. Clinical practice must encompass a comprehensive assessment of an individual's post-treatment physical and mental well-being. Tailored rehabilitation programs, vocational counseling, and workplace accommodation are essential components that facilitate a successful return to the professional domain. Employers also play a crucial role in fostering supportive work environments that accommodate cancer survivors' unique needs. Promoting flexibility, understanding, and awareness can contribute significantly to the successful reintegration of individuals into the workforce [72].

Cancer survivorship care concerning cancer and its treatment should focus on preventing and monitoring recurrences and new cancers. It should also include the surveillance and management of both physical and psychosocial effects. In terms of general health care, emphasis should be placed on monitoring and managing chronic medical conditions, promoting health, and preventing disease [73].

Quarterly prevention

With the rapid advancement of medical technology and emergence of new medical practices, practitioners are advised to prioritize the concept of quaternary prevention and employ suitable medical technologies. Quaternary prevention, as defined by the WONCA International Dictionary for General/Family Practice, involves actions aimed at identifying patients vulnerable to over-medicalization, shielding them from unnecessary medical interventions, and proposing ethically sound treatments [74]. This new concept of prevention should be of concern in clinical practice, particularly when resources are limited. For example, workers working in the same environment face different risks. For instance, screening all workers without differentiating risk in the workplace using tumor markers may result in false positives from other causes, causing panic and conflict between workers and employers. Therefore, the utilization of high medical technology or advanced interventions must consider the cost-effectiveness of these interventions. Prevention activities should be conducted based on risk levels to protect workers from harm.

Occupational medicine physician role [75-77]

Occupational medicine physicians responsible for worker health through various activities are key individuals in occupational cancer prevention and control in clinical practice. Conducting workplace assessments, including walk-through surveys, health risk assessments, and monitoring and recording workers' exposure to carcinogens is a key responsibility. Medical surveillance and follow-up involve health assessments before assignment to tasks involving carcinogens for baseline data, periodic health assessments during employment, health assessments upon resumption of work after a prolonged absence due to cancer or other health issues, and health assessments at and after termination of assignments involving carcinogen exposure.

The efficient diagnosis of occupational cancers while avoiding over investigation and overtreatment is crucial. Collaboration and communication with other medical specialists involved in cancer treatment, rehabilitation, and returning to work are essential. Determining the work relatedness of a cancer diagnosis benefits workers financially by covering past and future treatment expenses, vocational rehabilitation, permanent or partial disability benefits, and compensation for reduced earning capacity. In addition, when cancer clusters occur, investigating the possible occupational causes is necessary for prevention and control.

In administrative management, promoting health and prevention to minimize all risks, both work- and non-work-related, is vital. Educating and training workers and other occupational health providers on risk exposure and protective measures is important. Effective communication and interactions with employers, industrial hygienists, other occupational health professionals, and trade unions are crucial aspects of this role.

Conclusion

Various workplace hazards and occupations can be human carcinogens and cancer sites, significantly contributing to the occupational cancer burden. Updating preventive science knowledge in epidemiology, toxicology, information technology, biomedical technology, and occupational medicine is essential to improve clinical practices and effectively address occupational cancer

prevention and control. A comprehensive approach that integrates and applies updated information from this review and involves cooperative work with occupational medicine physicians would be beneficial for workers. Although addressing these complexities requires transdisciplinary approaches and interprofessional collaboration, the fundamental concept of occupational cancer prevention and control remains unchanged. Identifying and managing carcinogens by minimizing exposure is crucial for protecting workers' health and well-being.

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