ABSTRACT

It is important to identify the causal relationship between occupational exposure and the disease in the area of compensation because most cancers have long latent period. This review presents the principles that should be considered when evaluating the work-relatedness. We reviewed reports on occupational cancers published by the International Agency for Research on Cancer, American Conference of Governmental Industrial Hygienists, National Toxicology Program, Environmental Protection Agency, European Union, which are the world’s most prestigious organizations. In addition, we reviewed relevant papers and books published in Korea. The process is conducted in the order of cancer diagnosis, exposure assessment for carcinogens, and work-relatedness assessment. The probability of causation is determined stochastically rather than deterministically. There is no absolute standard for accreditation criteria and results may vary according to expert opinions and in each country or organization. Revealing the causal relationship of occupational cancers is a difficult process owing to inconsistency in relevant epidemiological studies, lack of well-established biological mechanisms, loss of objective occupational historical data, and other complexity of individual cases. Causation is unclear in many cases. Nevertheless, the data should be reviewed in detail for each case suspected of work-related cancers, and an assessment should be made through valid and plausible logic and literature evidences.

Keywords: Occupational exposure; Carcinogens; Causation; Work-relatedness assessment

INTRODUCTION

Most cancers are caused by a combination of various factors, including age, heredity, lifestyle, nutrition and environmental conditions including occupational carcinogen exposure; hence, the identification of a distinct cause is often difficult. In contrast, occupational cancers are preventable in principle because their causes are often known and the risks can be ameliorated by eliminating or reducing worker exposure to carcinogenic factors [1,2]. Occupational cancer was first reported in the 18th century by Percivall Pott, who discovered it in chimney sweeps exposed to charcoal [3]. It was not until the 1970s that chemicals such as arsenic, asbestos, benzene, chromium, nickel, radon, and vinyl chloride, which were mostly found in occupational settings, were found to be carcinogenic in humans [4].
Additionally, certain occupations (e.g., painting) or industries (e.g., rubber manufacturing industry), pesticides, drugs, biological factors, and lifestyle habits were considered to be causes of cancer. An estimated 4%–5% of cancer cases in developed countries result from occupational exposure [5,6]. Steenland et al. [7] reported that 10%–20% of lung cancer cases and Silverman et al. [8,9] reported that 21%–27% of bladder cancer cases were related to occupational exposure. Purdue et al. [10] reported that an estimated 2%–8% of cancers resulted from occupational exposure to carcinogens (3%–14% in men and 1%–2% in women). Kim [11] reported an estimated 5,846 cases of occupational cancers in 2005; however, only 30 patients received compensation.

Article 141 of the Occupational Safety and Health Act (2020) states that if the cause of occupational diseases (including occupational cancer) is found, the epidemiological inspection of such diseases can be conducted [12]. In the case of occupational cancer, the Korea Occupational Safety Health Agency (KOSHA) presents a general order of identifying carcinogen exposure, investigating the latency period, investigating exposure dosage and intensity, and assessing work-relatedness [13]. Although there are some differences in content compared to those in KOSHA, the European Commission (EC) and the Australasian Faculty of Occupational Medicine (AFOM) also perform work-relatedness assessment [14,15]. It is essential to consider occupational causes for cancers. This paper introduces the relevant principles that should be considered in work-relatedness assessments according to the epidemiological case investigation guidelines published by KOSHA [13,16].

METHODS

We reviewed reports published by the International Agency for Research on Cancer (IARC), American Conference of Governmental Industrial Hygienists (ACGIH), National Toxicology Program (NTP), Environmental Protection Agency (EPA), which are the world’s most prestigious organizations. We also reviewed relevant reports and books published in Korea. Additionally, this paper and subsequent case study also have some similarities with the assessment of medical relatedness in clinical practice, but we intend to summarize the general process and subsequent issues by taking into account the epidemiological case investigation guidelines of KOSHA.

RESULTS AND DISCUSSION

Cancer diagnosis

Diagnosis is the first step in evaluating work-relatedness. Although the processes vary for each type of cancer, clinical diagnosis is generally performed in the order of history taking, physical examination, blood test, imaging (computed tomography [CT], magnetic resonance imaging [MRI], and ultrasound [US]) and biopsy. However, worker’s medical records should be carefully considered to identify the diagnostic methods and types of cancer in the epidemiological case investigation. Histological subtypes should be considered for most cancers, especially hematologic cancers such as leukemia and lymphoma. If it is impossible to confirm the cancer histologically due to death or other reasons, the disease could be diagnosed presumptively with clinical symptoms based on existing medical referrals. In the case of metastatic cancer, the cancer origin should be identified and the investigation should be performed only for the primary cancer.
Exposure assessment

Upon confirmation of the primary cancer, the investigation should be start from identifying known carcinogens of the cancer. After the exposure is confirmed, its level is then estimated.

Qualitative assessment: identification of carcinogens and exposure

1) Identification of carcinogens for the diagnosed cancer
Carcinogens, carcinogenic processes, and carci-no-jobs known to cause the diagnosed cancer of the workers should be identified. Identification of specific carcinogenic hazards considers several characteristics; among them, epidemiological studies on humans and experimental studies on animals (usually rodents) are considered the most important as direct evidence, with absorption, metabolism, physiology, mutagenicity, cytotoxicity, and similarities in chemical structure-activity considered as additional evidence [17]. Several prestigious institutions such as the IARC, ACGIH, NTP, and EPA use the above criteria to classify the carcinogenicity of many carcinogens through their assessments.

The IARC criteria have been widely used as the primary reference in recognition of the vastness and validity of the literature review of carcinogenicity in occupational and environmental medicine. Cogliano et al. [18] reviewed IARC reports published over 40 years and reclassified the carcinogens as having sufficient or limited evidence in humans for each target organ, allowing easier reference for the epidemiological case investigation on diagnosed cancer. In general, carcinogenicity is accepted for IARC group 1 or 2A carcinogens. When referring to the IARC report, it should be noted that the carcinogenicity in humans (sufficient evidence/limited evidence) and IARC group 1/2A/2B/3/4 are different. Moreover, further investigation is required on literatures released after relevant IARC monograph was published.

2) Exposure identification of the carcinogens
Next, a process is needed to collect data on the workers to decide whether the worker was exposed to carcinogens for the working period. For this purpose, information on jobs and working/production processes can be referenced through occupational history, Material Safety Data Sheets (MSDSs), working environment monitoring reports, relevant legislations, and common hazards in the industry. After reviewing this pre-investigation information, the worker, or his/her proxy, such as co-workers or family members, who knows the working environment is interviewed to confirm the facts of the pre-investigation and supplement the available information. Ladou [19] described the essential questions of the occupational history: questions on overall occupational history, exposure, symptoms, protective equipment, engineering control, fellow workers, and military service. These data are integrated to determine whether the worker was exposed to the carcinogens and to determine whether the exposure level useful to be determined. For instance, benzidine, which was widely used in direct dye manufacturing in the 1970s and 1980s, was banned in Korea except for research purposes under the Industrial Safety and Health Act in 2000. If the substance is not identified in the MSDS and working environment monitoring, further investigation is not necessary.

Quantitative assessment: estimation of the exposure level
Quantitative investigation is the process of numerically evaluating the exposure level and duration of exposure to the identified carcinogen or carcinogens. Past occupational exposure must be assessed because cancers have a latency period of years to decades; however, accurate estimation is difficult due to the shutting down of the past workplace, insufficient past occupational data, loss of contact with colleagues, incorrect memories of the worker or
worker’s family, or the possibility of exaggeration and concealment of facts [20]. Therefore, to identify past exposures to identified carcinogens, working environment monitoring or periodic health examination for workers results including the Biological Exposure Indices (BEIs) of the carcinogens can be used primarily. Domestic employers are required to preserve working environment monitoring for 5 years for general harmful substances and 30 years for confirmed carcinogens [21]. When reviewing the working environment monitoring, the focus should be on the types and presence of carcinogens to which the worker could have been exposed at the time, rather than on numerical interpretation.

It is also necessary to utilize “exposure reconstruction” through the Job Exposure Matrix (JEM), expert opinion of exposure judgments, and structured questionnaires. The JEM is a tool for estimating exposure levels and dose-response relationships by grouping individuals exposed to specific carcinogenic or other hazard substances. The cumulative exposure estimates are based on the assumption that the worker has had exposure similar to that in a particular industry group in the JEM. The JEM for benzene and trichloroethylene are typically used in Korea [22,23].

Workplace investigation might be implemented if necessary. The target workplace can be selected in consideration of whether the workplace exists, the performance of similar processes, the use of carcinogens, and the latent period of the disease. Advices could be obtained from an industrial hygienist or factory managers on identifying working processes and MSDS. When conducting epidemiological case investigation, working environment monitoring is usually performed by an industrial hygienist if necessary. The main limitation is whether extrapolation can be done or not, because the working environment or process has changed from that in the past [16]. The work type and process, use of protective equipment, ventilation system (general ventilation, local exhaust system) and changes in materials, processes and worksite should be identified. Monitoring and sampling of the workplace can be performed if exposure assessment is required.

**Considerations for work-relatedness assessment**

The compensation is paid to worker under the Industrial Accident Compensation Insurance Act if the work-relatedness of worker’s cancer is approved. Thus, work-relatedness assessment is related to social and legal issues beyond medical judgment too. Causal inference between the diagnosed cancer and identified carcinogens is key to assessing the work-relatedness of occupational cancer. Melhorn et al. [24] referred to causation as the relationship between any cause and the effect resulting from that cause. Rothman [25] defined the cause for a particular condition as any prior event, condition, or characteristic that played an essential role in the occurrence of the disease when other conditions were fixed. Causal inference in occupational cancer is the process of deducing whether the risk of cancer increases when workers are exposed to identified carcinogens compared to the risk among those who are not exposed. The following topics should be considered when establishing causation.

**Consideration of the minimum induction and maximum latent periods**

The period from exposure to an identified carcinogen and definite diagnosis should be reviewed. The minimum period from exposure to onset is defined as the minimum induction period, while the maximum value is defined as the maximum latent period [15]. Due to study limitations, these two criteria are not absolutely necessary but should be considered. Depending on the type of carcinogen and cancer diagnosed, the minimum induction period
and maximum latent period differ. However, at least 10 years for solid cancer and 1 year for hematologic cancer are generally considered appropriate periods from carcinogen exposure to diagnosis [20].

Biological mechanisms to cause cancers
The possible exposure pathways of the identified carcinogens (e.g., digestion, inhalation, dermal exposure) and the mechanism of cancer development should be identified to establish a basis for biological plausibility with reference to literature related to carcinogen absorption, distribution, metabolism, and excretion in humans and animals. For instance, the positive correlation between asbestos exposure and gastric cancer is well established [26]. However, pathophysiology is not clear, although the hypotheses include that 1) the ingestion of food or beverage contaminated with asbestos and 2) inhalation of asbestos fibers may increase lung permeability due to chronic inflammatory reactions that can spread throughout the body via lymphatics or blood [27,28]. Conversely, exposure pathways and cancer mechanisms may be established but carcinogenicity may be underestimated due to the lack of epidemiological evidence (e.g., urinary tract cancer, except for bladder cancer caused by exposure to aromatic amines). Aromatic amines are metabolized in the liver and excreted in the urine. The N-acetyl hydroxylamine intermediate is highly active and causes cancer by damaging the DNA in the urothelium, which forms the mucous membrane of the urinary system [29]. Aromatic amines are currently listed in IARC group 1 risk factors for bladder cancer [30]. But they are not listed among IARC risk factors for other urinary tract cancers such as renal, pelvis, or urethral cancers because relevant evidences might not be sufficiently supported mainly form few researches of very rare diseases [30].

Review on epidemiological studies
Epidemiological studies on the causal relationship between carcinogens and diagnosed cancer should be reviewed. Databases such as PubMed, IARC monographs, and Google Scholar can be used by applying relevant search words from Medical Subject Headings (MeSH) terms within PubMed. Among the identified epidemiological studies, it is necessary to decide which studies should be considered first, taking into account the study design (e.g., cohort studies, case-control studies, case series), exposure estimation methods, diagnostic methods, bias, and confounding [24]. Studies should be ranked in order of consideration as described in the reference [31]. To draw valid conclusions, it is necessary to select whether the study findings apply appropriately the workers, in terms of the study subjects, exposure assessment, or duration of exposure. No epidemiological studies with results applicable to workers may exist. In such cases, studies conducted in similar industry groups, foreign workers, or adjacent exposure periods may be extrapolated with appropriate assumptions.

Work-relatedness assessment
The KOSHA guide refers to the basis of diagnosis, exposure level, natural history of the disease, and epidemiological evidence as important factors in assessing work-relatedness of occupational cancer [13,16]. Further consideration of the contribution of other causal factors (e.g., non-occupational carcinogens, age, gender, and underlying diseases) is required. Most scientific papers could be published after correcting general confounders (e.g., age, sex, smoking) [32].

The degree of causation is explained to an individual probabilistically rather than deterministically due to the complexity of biological phenomena, limited understanding of the many underlying processes, and individual susceptibility [33]. The degree of causation is
generally assessed according to four categories (definite/probable/possible/suspicious) and only those cases with definite or probable are generally considered to have work-relatedness [34].

When applying causation, experts often refer to results from epidemiological studies (e.g., relative risks in cohort studies, odds ratios in case-control studies, and attributable risk of calculating differences in the incidence of diseases among groups). Some experts judge work-relatedness by substituting causation with relative risk 2.0 or attributable risk 50%, and such cases have been identified in the United States, Britain, and Germany [35]. However, Greenland et al. [36] cautioned that applying such values to causal probabilities may result in scientific errors and increase the risk of underestimating causal probabilities if the contribution or comparative risks are applied to causation. A relative risk of less than 2.0 or attributable risk less than 50% may be admitted with adequate epidemiological and biological evidence. There is no absolute standard in assessments and the scope of accreditation may depend not only on the opinions of experts but also on the standards and consensus of country.

In 2019, the Ministry of Employment and Labor proposed ‘The principle of presumption’ in occupational cancers based on domestic papers to shorten the period of processing epidemiological case investigation [32,37]. This includes guidelines for omitting epidemiological case investigation and allow experts to make quick assessment on issues that have proven to be work-relatedness in the past.

CONCLUSIONS

We introduce the principles to be considered when evaluating work-relatedness in workers suspected of being at risk for occupational cancer. Since the 1960s, manufacturing has been the foundation of national economic development, and as a result, employees suffered various health obstacles as they dealt with various harmful factors in Korea. However, revealing the causal relationship of occupational cancer is a difficult process owing to the lack or inconsistency of relevant epidemiological studies or biological data, lack or absence of historical data, and individual complexity. Causation is unclear in many cases. Nevertheless, in assessing occupational cancer, experts should do their best to establish a logical and reasonable basis from a neutral standpoint. In summary, when conducting epidemiological case investigation, a detailed assessment should be conducted by combining the data collected by individuals. After reviewing the previous epidemiological studies and biological data, a final assessment should be made by applying reasonable logic.

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