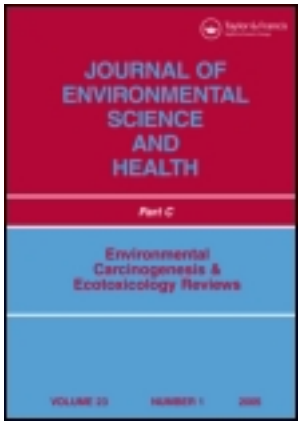

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A Current Global View of Environmental and Occupational Cancers

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A Current Global View of Environmental and Occupational Cancers

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This review is focused on current information of avoidable environmental pollution and occupational exposure as causes of cancer. Approximately 2% to 8% of all cancers are thought to be due to occupation. In addition, occupational and environmental cancers have their own characteristics, e.g., specific chemicals and cancers, multiple factors, multiple causation and interaction, or latency period. Concerning carcinogens, asbestos/silica/wood dust, soot/polycyclic aromatic hydrocarbons [benzo(a) pyrene], heavy metals (arsenic, chromium, nickel), aromatic amines (4-aminobiphenyl, benzidine), organic solvents (benzene or vinyl chloride), radiation/radon, or indoor pollutants (formaldehyde, tobacco smoking) are mentioned with their specific cancers, e.g., lung, skin, and bladder cancers, mesothelioma or leukemia, and exposure routes, rubber or pigment manufacturing, textile, painting, insulation, mining, and so on. In addition, nanoparticles, electromagnetic waves, and climate changes are suspected as future carcinogenic sources. Moreover, the aspects of environmental and occupational cancers are quite different between developing and developed countries. The recent follow-up of occupational cancers in Nordic countries shows a good example for developed countries. On the other hand, newly industrializing countries face an increased burden of occupational and environmental cancers. Developing countries are particularly suffering from preventable cancers in mining, agriculture, or industries without proper implication of safety regulations. Therefore, industrialized countries are expected to educate and provide support for developing countries. In addition, citizens can encounter new environmental and occupational carcinogen nominators such as nanomaterials, electromagnetic wave, and climate exchanges. As their carcinogenicity or involvement in carcinogenesis is not clearly unknown, proper consideration for them should be taken into account. For these purposes, new technologies with a balance of environment and gene are required. Currently, various approaches with advanced technologies—genomics, exposomics, etc.—have accelerated development of new biomarkers for biological monitoring of occupational and environmental carcinogens. These advanced approaches are promising to improve quality of life and to prevent occupational and environmental cancers.

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1. INTRODUCTION

Cancer is one of the leading causes of death worldwide. There was an estimated 12.4 million cases of cancer in 2008 and 7.6 million deaths from cancer [1]. Globally, lung cancer was the most common cancer. In the United States, 1 in 4 deaths are due to cancer [2]. Since Richard Nixon's National Cancer Act in 1971, the United States has spent a huge amount of funds for cancer research as a global leader. In 2004/2005, the global spending on cancer research was estimated as 14,030 million Euros, with the United States leading, dominated by the National Cancer Institute accounting for the largest absolute spending [3]. However, the cancer incidence during past 30 years (1975–2005) has steadily increased even though cancer modality has decreased in United States. Concerning lung cancer, smoking, including environmental tobacco smoking (ETS), which is the leading cause of lung cancer, has declined in men and women; however, women's decline in smoking is slower than men [4], and cancer deaths from lung cancer have been consistent for the past decades in the United States [2]. Thus, the most important issue in cancer research should be how to lower incidences of cancers with effective use of funding. For this purpose, cancer prevention, which has occupied a relatively low portion in total spending of cancer research (e.g., 4% and 9% in Europe and United States, respectively [3]), should be emphasized because most cancers can be avoided [5].

Based on strong etiological associations between cancers and their risks, such as tobacco, diet, etc. [6], more than 40% of cancers are estimated to be avoidable [5, 7]. The avoidable cancers are broadly raveled as environment-related or acquired cancers (approximately 70% of all cancers), compared to inheritable cancers (∼10% of all cancers) [1]. When a narrow spectrum is used for categorizing environmental cancers by causes, occupational and environmental cancers are approximately 10% of all cancers [8, 9].

Occupational cancers are concentrated among specific groups of the working population for whom the risk of developing a particular form of cancer may be much higher than for the general population [7]. In addition, environmental cancers are also strongly related to high and frequent exposure to their specific carcinogens, which are condensed in geographically specific regions, such as mesothelioma in Cappadocia, Turkey [10], and arsenic-related cancers in Bangladesh [11]. Thus, etiologies of occupational and environmental cancers are relatively clear, and their prevention can be effective compared to other cancers, even though environmental or occupational causes of cancers can explain approximately 5%∼10% of cancer death [6, 9]. However, the number of deaths due to occupational cancers may be more than 152,000 per year [7].

Recently, "European Agency for Safety & Health at Work" reported that worldwide occupational cancers reached approximately 9.6% of all cancer

deaths [8]. In addition, there was big disparity in occupational-related cancers between sexes and between developed countries (mostly located in the northern hemisphere) and developing countries (mostly located in the southern hemisphere) [12]. The sex issue may reflect that males are exposed to more dangerous substances than females. In addition, the developing countries had approximately 3 times higher incidences of occupational cancers than developed countries. Thus, we should consider socio-economic effects on incidence or prevention of occupational cancer. When the global burden attributable to occupational risk factors are considered, the following 7 conditions should be mentioned: low back pain, hearing loss, chronic obstructive pulmonary disease (COPD), asthma, "trachea, bronchus, or lung cancers," unintentional injuries, and leukemia [13]. Cancers, i.e., trachea, bronchus, or lung cancer and leukemia, reached 11% of global burden to occupational risk factors. Lung cancer accounted for almost 70% of occupational cancers and at least 1%–2% of all cancer deaths were ascribed to asbestos [14]. Approximately 20%–30% of the male and 5%–20% of the female working-age population (people aged 15–64 years) may have been exposed to lung carcinogens during their working lives, accounting for approximately 10% of lung cancers worldwide [15]. Mesothelioma, which is the cancer of the outer lining of the lung or chest cavity, is to a large extent caused by work-related exposure to asbestos. More than half of the occupational burden of lung cancer was attributed to asbestos [14]. For example, the recent Nordic Occupational Cancer Study (NOCCA), which covered the 15 million people aged 30–64 years in the 1960, 1970, 1980/1981, and/or 1990 censuses in Denmark, Finland, Iceland, Norway, and Sweden, showed that plumbers showed the highest standardized incidence ratio (SIR) for mesothelioma [16].

In addition, approximately 2% of worldwide leukemia cases are attributable to occupational exposures to benzene, 1,3-butadiene, and non-arsenical insecticides [1, 15].

On the other hand, environmental pollution is assumed to account for 1%–4% of all cancers through drinking water, indoor and ambient air, or food [1]. One of the most profound statistics shows that arsenic exposure was attributable to 5%–10% of all cancer deaths in an arsenic-contaminated region [11]. In addition, indoor air pollution from domestic coal fires is responsible for approximately 1.5% of worldwide lung cancer deaths [17]. As coal use in households is particularly widespread in Asia, coal-related indoor pollution, e.g., cooking or heating, can be thought of as an etiology for nonsmokers' lung cancers in Asia [17, 18].

In addition, there have been huge advances of biomarkers, particularly susceptibility biomarkers with genomic approaches [19], for biological monitoring of occupational and environmental cancers for the past 30 years. To lower the incidences of cancers [2], continuous improvement of the biomarkers is needed with balance between "environment and gene."

Therefore, the present study will describe current issues of occupational and environmental cancers. To establish effective strategies for the prevention from these cancers, future desirable biomarkers and their application (biological monitoring) will be addressed.

2. CHARACTERISTICS OF ENVIRONMENTAL AND OCCUPATIONAL CANCERS

Historically, Ramazzini (1633–1714), the father of occupational medicine, described various workers' diseases in 52 occupations and was the first scientist who described occupational cancers, such as breast cancer in Catholic nuns, which is now known to be due to the unabated presence of estrogen [20–22]. In addition, Pott (1714–1788) described the earliest observations of scrotal cancers among chimney sweeps [21, 22]. Thus, occupational and environmental cancers can be thought to have their own characteristics, such as specific carcinogens, and common features with other cancers, such as multiple factors, multiple causation and interaction, or long latency period. However, sometimes patients can encounter difficulty in compensation due to ambiguous occupational or environmental causes.

Recently, World Cancer Report (WCR) showed specific occupational carcinogens, agents, industrial process, or occupations, for target organs [1]. For the agents, there are asbestos/silica/wood dust, soot/polycyclic aromatic hydrocarbons [benzo(a) pyrene], heavy metals (arsenic, chromium, nickel), aromatic amines (4-aminobiphenyl, benzidine), organic solvents (benzene or vinyl chloride), radiation/radon or indoor pollutants (formaldehyde, tobacco smoking), etc. Occupational cancers included lung, skin, and bladder cancers; mesothelioma; leukemia; and so on. Finally, specific industrial processes or occupations for occupational cancers included rubber or pigment manufacturing, textile, painting, insulation, welding, mining, and so on.

For environment cancers (narrow spectrum, related to environmental pollution), WCR described 14 categories of IARC group 1—the agent (mixture) is carcinogenic to humans, e.g., aflatoxins, arsenic, asbestos, benzene, ETS, radon, TCDD, etc., and 7 categories of group 2A—the agent (mixture) is probably carcinogenic to humans, e.g., diesel engine exhaust; UV A, B, and C; PCBs; etc. [1]. However, many risk factors can act in combination with others to accelerate occurrences of environmental or occupational cancers.

In addition, burden of occupational and environmental cancers may change with simultaneous variations of multiple risk factors in populations. Considering individual differences in susceptibility to occupational and environmental cancers, setting new standards or regulation criteria are carefully suggested [23]. For example, Hansson has asked whether every exposed person, including the most sensitive people, should be protected rather than basing protections

on the population average. He suggested two approaches to protecting a group: (1) special standards for the group (differentiated protection) and (2) general standards strict enough to protect all members (unified protection). He also identified 6 major factors that are relevant for choice between these two strategies: difference in the risk, costs of abatement, identifiably of sensitive individuals, privacy, social exclusion, and previous discrimination [24]. Thus, not only multiple exposure but also gene and environmental interaction, or susceptibility factors have been emphasized to explain characteristics of environmental or occupational cancers. For example, many researchers studied susceptibility to occupational leukemia, which is related to benzene exposure, focusing on genetic polymorphisms in its metabolic enzymes, NAD(P)H:quinone oxidoreductase (NQO1), cytochrome P450 2E1 (CYP2E1), myeloperoxidase (MPO), glutathione-S-transferase M1 and T1 (GSTM1, GSTT1), and microsomal epoxide hydrolase (EPHX1) [25, 26]. It seems clear that a lowered or absent NQO1 activity, which detoxifies carcinogenic or reactive benzoquinones into catechol or hydroquinone, can increase benzene toxicity. In addition, NQO1 genetic variations have been emphasized as an antioxidant enzyme for chemoprevention [27] and a future susceptibility biomarker to cancers [28].

3. ENVIRONMENTAL AND OCCUPATIONAL CARCINOGENS

Environmental carcinogens can be separated into 5 categories due to exposure routes. First, air-borne carcinogens are ETS, formaldehyde, radon, etc., via mainly indoor and polycyclic aromatic hydrocarbons (PAHs), chlorofluorocarbons (CFCs), etc., via mainly outdoor. Second, polychlorinated biphenyls (PCBs) are mainly contaminated in soil. Third, people can be exposed to arsenic, trihalomethanes, nitrite, radium, and radon mainly via water [29]. Fourth, aflatoxins come from food [30]. Unfortunately, approximately 4.5 billion persons living in developing countries are estimated to be chronically exposed to largely uncontrolled amounts of the toxins. Fifth, asbestos or erionite are naturally localized carcinogens [31].

In the case of occupational cancers, approximately 60 agents, mixtures, and 20 exposure circumstances in the working environment can be thought of as carcinogens [1]. Some occupational carcinogens also belong to environmental carcinogens, e.g., arsenic, asbestos, benzene, and formaldehyde (Table 1). In the case of formaldehyde, Occupational Safety and Health Administration in United States regulates that the permissible exposure limit for formaldehyde in the workplace is 0.75 ppm measured as an 8-hour time-weighted average (TWA) [32]. In addition, the public may be exposed to formaldehyde in outdoor ambient air of 3 ppb and in housing of 17 ppb [33, 34]. While public exposure level of formaldehyde may be lower than that of occupational exposure, the indoor exposure to formaldehyde is quite high and becomes a concern for highly

Table 1: List of Occupational and Environmental Carcinogens[a]

Carcinogens	Cancer Site/Cancer
Occupational carcinogens	
4-aminobiphenyl	Bladder
Arsenic and arsenic compounds[b]	Lung, skin
Asbestos[b]	Pleura, lung
Benzene[b]	Leukemia
Benzidine	Bladder
Beryllium and beryllium comp.	Lung
Bis(chloromethyl)ether*	Lung
1,3-Butadiene[b]	Leukemia
Chloromethyl methyl ether*	Lung
Cadmium and cadmium comp.	Lung
Chromium(VI) compounds [b]	Nasal cavity, lung
Coal-tar pitches	Skin, lung, bladder
Coal-tars	Skin, lung
Ethylene oxide[b]	NA[c]
Formaldehyde[b]	Nasopharynx
Gallium arsenide	NA[c]
Mineral oils, untreated and mildly treated	Skin
Mustard gas (sulphur mustard)	Pharynx, lung
2-Naththylamine*	Bladder
Nickel compounds Nasal	Cavity, lung
Radon-222 and its decay products[b]	Lung
Shale-oils	Skin
Silica, crystalline[b]	Lung
Soots	Skin, lung
Strong-inorganic-acid mists containing sulphuric acid	Larynx, lung
Talc containing asbestiform fibers	Lung
2,3,7,8-Tetrachlorodibenzo-p-dioxin[b]	NA**
Vinyl chloride	Liver
Wood dust	Nasal cavity
Occupational probable carcinogens	
Acrylamide	—
Benzidine-based dyes	Bladder
Captafol	—
α-Chlorinated toluenes (benzalchloride, benzotrichloride, benzyl chloride, benzoyl chloride)	—
4-Chloro-o-toluidine	Bladder
Cobalt metal with tungsten carbide	Lung
Creosotes	Skin
Diesel engine exhaust	Lung
Diethyl sulfate	—
Dimethylcarbamoyl chloride	—
1,2-Dimethylhydrazine	—
Dimethyl sulfate	—
Epichlorohydrin	—
Ethylene dibromide	—
Indium phosphide	—
Lead compounds, inorganic	Lung, stomach
Methyl methanesulfonate	—
4-4′-Methylene-bis-2-chloroaniline (MOCA)	Bladder

Table 1: List of Occupational and Environmental Carcinogens[a] *(Continued)*

Carcinogens	Cancer Site/Cancer
Non-arsenical insecticides	Leukemia
Polychlorinated biphenyls	Liver, lymphoma
Styrene-7,8-oxide	—
Tetrachloroethylene[b]	Esophagus, lymphoma
o-Toluidine	Bladder
Trichloroethylene	Liver, lymphoma
1,2,3-Trichloropropane	—
Tris(2,3-dibromopropyl)phosphate	—
Vinyl bromide	—
Vinyl fluoride	—
Industrial processes and occupations	
Aluminum production	Lung, bladder
Auramine, manufacture of	Bladder
Boot and shoe manufacture and repair	Nasal cavity, leukemia
Chimney sweeping	Skin, lung
Coal gasification	Skin, lung, bladder
Coal-tar distillation	Skin
Coke production	Skin, lung, kidney
Furniture and cabinet making	Nasal cavity
Hematite mining (underground) with exposure to radon	Lung
Iron and steel founding	Lung
Isopropanol manufacture (strong-acid process)	Nasal cavity
Magenta, manufacture of	Bladder
Painter	Lung, bladder
Paving and roofing with coal-tar pitch	Lung
Rubber industry	Bladder, leukemia
Art glass, glass containers and pressed ware, manufacture	(Lung, stomach)
Carbon electrode manufacture	(Lung)
Hairdresser or barber	(Bladder, lung)
Petroleum refining	(Leukemia, skin)
Environmental carcinogens	
Aflatoxins	Liver
Erionite	Lung, pleura
Environmental tobacco smoke	Lung
Solar radiation	Skin
Diesel engine exhaust	Lung, bladder
Ultraviolet radiation A	Skin
Ultraviolet radiation B	Skin
Ultraviolet radiation C	Skin
Polychlorinated biphenyls	Liver, bile ducts, leukemia, lymphoma

[a]In alphabetical order (1).
[b]Both occupational and environmental carcinogens or probable carcinogens.
[c]Not applicable.

susceptible populations, e.g., children, elderly, and pregnant women. Therefore, an air quality guideline of 0.1 mg/m^3 (0.08 ppm) is considered protective against both acute and chronic sensory irritation in the airways in the general population, assuming a log normal distribution of nasal sensory irritation [35].

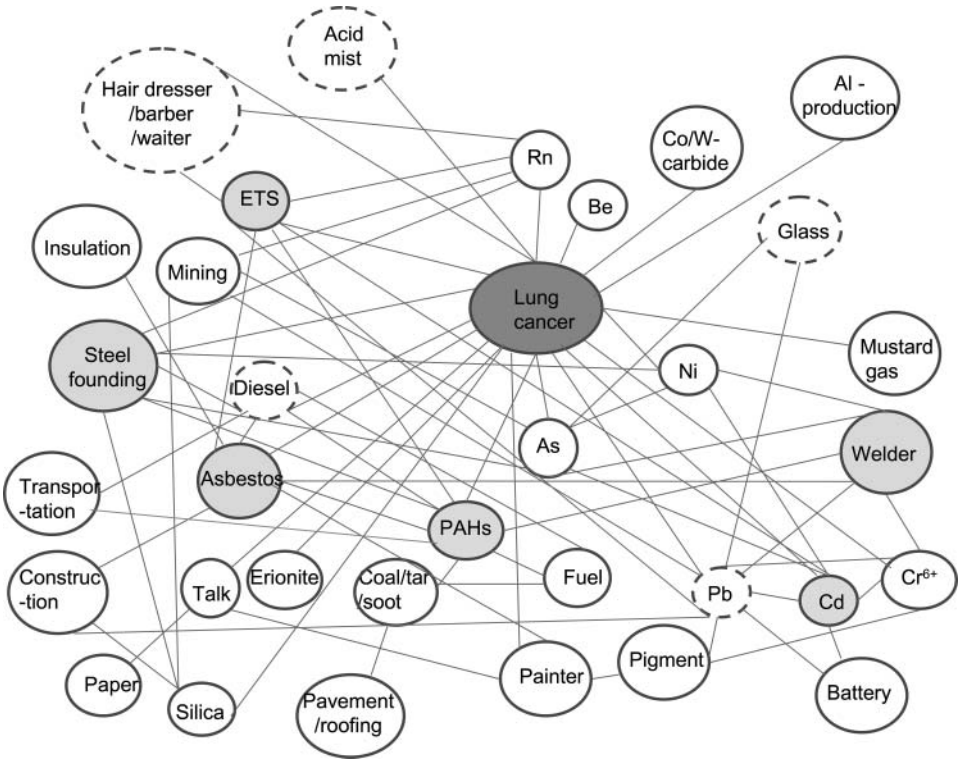

Figure 1: Exposure network of occupation- and environment- induced lung cancer (8, 114). Solid circles (exposure sources) indicate human carcinogens (1); Dotted circles indicate human probable carcinogens (1, 16). Hubs, ETS (environmental tobacco smoking), steel founding, asbestos, PAHs (polycyclic aromatic hydrocarbons), cadmium, and welder were identified as having more than 5 connections within the network.

As mentioned in the characteristics, various causes of occupational and environmental cancers can simultaneously work to induce final cancers. For example, Figure 1 shows causes of occupation- and environment-related lung cancer with a systemic review. More than 30 chemicals, processes, and mixtures induce cancer via dependent ways rather than independent ways. In a case of asbestos of the system, workers are exposed to asbestos via various routes, e.g., insulation, construction, welding, or painting. In addition, people are non-occupationally exposed to asbestos via geographical reason [36, 37], diesel exhaust [38], or polycyclic aromatic hydrocarbons (PAHs) [8]. Moreover, ETS exacerbates the carcinogenic effects of asbestos [16, 38, 39]. In addition, steel founding and welding process can be considered as major routes to expose people to asbestos, PAHs, and various metals [8]. People are exposed to PAHs via various combustion pathways, working in a coke oven, living near

incinerators, using transportation, and son on [8]. Thus, occupational and environmental cancers are the end point or biological response of a specific or multiple exposures.

4. CURRENT ISSUES OF ENVIRONMENTAL AND OCCUPATIONAL CANCERS

When considering the global aspects of environmental and occupational cancers, first, disparity between the developing countries and developed countries can be mentioned. The recent follow-up of occupational cancers in 15 million people of 5 Nordic countries shows a good example for developed countries' occupational cancer status [16]. The high SIRs of tobacco workers and waiters suggests that ETS is the most popular and powerful carcinogen in these countries. On the other hand, developing or low-resource environment countries still face on increased burden of occupational and environmental cancers because of poor regulation and screening programs or even an absence of systems to record occupation- or environment-related cancer deaths. For example, there is a big difference in the handling of asbestos between developing and developed countries [40]. Although the hazards of asbestos are well known in developed countries, awareness of its adverse health effects is less in other parts of the world. Experience of asbestos use and its adverse health effects in developed countries have resulted in development of expertise in the diagnosis and treatment of asbestos-related diseases as well as in screening. This can be used to help developing countries facing the issue of asbestos exposure [37]. If not, people who live in developing countries can be victims of occupational or environmental cancers via transfer of carcinogens from developed countries. Historically, carbon disulfide poisoning in the rayon manufacturing industry, bladder cancer in the benzidine industry, and mesothelioma in the asbestos industry occurred in developing Korea via transfer of industries from developed Japan [41]. In addition to the need for cooperation between the developed and developing countries, we also consider different strategies in each country for prevention of occupational and environmental cancers. The developed countries encounter issues of low-dose exposure to environmental and occupational carcinogens; thus, the threshold levels of the carcinogens are re-considered for the prevention of cancer. For example, TLV_{TWA} (time-weight average of threshold limit), exposure levels of benzene in work places, are cut into 1 ppm from 100 ppm over half decades [42, 43]. In addition, there was strong regret for the 10-year delay in reduction of the TLV because it might cause more than 200 deaths in the United States [44]. Developing countries are still concerned about balancing high-dose exposure to the carcinogens with their economical purpose. Thus, they are suffering from avoidable cancers in mining, agriculture, and industries. To make matters worse, their governments or related

industries cover up the risks and people even lose their individual protection timing due to poor knowledge of the risks.

Second, further completed understanding of environmental and occupational carcinogens is required. Approximately 30,000 chemicals are being used in workers worldwide. Barely 1% of them have been thoroughly tested for health risks [45]. Thus, toxicologists and coworkers are asked to perform further risk assessment for the unknown carcinogens. In the Comprehensive Environmental Response, Compensation, and Liability Act the priority list of hazardous substances [46], arsenic, lead, mercury, vinyl chloride, PCBs, cadmium, and PAHs including benzo(a)pyrene have ranked among the top 10. In addition, not only chemicals but also carcinogenic materials should be considered. At first, asbestos is a group of minerals that occur in the environment as bundles of fibers and has been steadily emphasized for occupational and environmental carcinogens as a silent killer due to long patent period, approximately 20 to 30 years. Even though it is not currently being used in developed countries, asbestos removal and monitoring for past exposure to asbestos in people have been emphasized. The number of asbestos deaths increased from 77 in 1968 to 1265 in 1999 in United States [47]. Interestingly, some nanomolecules (e.g., nanotubes), which are developed by nanotechnologies and a completely new material to be useful for electronic, optics, body armor, medicine, etc., are very similar in shape to asbestos fibers (long and rigid) and may cause inflammation and progressive lung damage. Bonner and colleagues showed three critical events that nanotubes might lead to long-term harmful effects in the pleura [48–50]. First, carbon nanotubes are deposited in the airspaces near the pleura and mesothelium. Second, carbon nanotubes are found in the tissue close to the pleura both inside and outside macrophages. Third, the nanotubes stimulate scar formation in the lung. Several well-regarded studies published over the past few years have shown that carbon nanotubes deposited in the lungs cause inflammation and scar formation in various model systems. However, the mechanism by which particulates with ultrafine structure cause inflammation and ultimately cancer is largely unknown. Therefore standard evaluation methods for nanomaterials should be established to minimize risks for human health [51].

Flowing nanotubes, electromagnetic waves can be mentioned as new candidates of carcinogens. Electromagnetic radiation can be divided into two types: ionizing (high-frequency) and non-ionizing (low-frequency) [52]. Ionizing radiation, such as that produced by x-ray machines, can pose a cancer risk. Cell phones emit radiofrequency (RF) energy, which is radio waves and nonionizing electromagnetic radiation. Use of cellular telephones has grown explosively during the past two decades; thus, the public has become concerned over the health risks of their cellular telephones. The most significant study of long-term use of cellular telephones is the 13-country interphone study, which is a multinational consortium of case-control studies [53]). The researchers

reported that overall, cell phone users have no increased risk for two of the most common types of brain tumor: glioma and meningioma. Most recent studies suggest that the amount of RF energy produced by cell phones is too low to cause significant tissue heating or an increase in body temperature [54]. However, more research and monitoring are needed to determine whether cellular phones pose a cancer risk.

Third, global warming or climate change can also be considered as a new risk for environmental cancers. The effects of climate change on human health are not as well understood but are thought to result from changes in the distribution of various risk factors such as heat waves, floods, droughts, air pollution, aeroallergens, and vector-borne diseases [55]. There are potential impacts on cancer both directly and indirectly from climate change and mitigation strategies [56]. Climate change will result in higher ambient temperatures that may increase the transfer of volatile and semi-volatile compounds from water and wastewater into the atmosphere and alter the distribution of contaminants to places more distant from the sources, changing subsequent human exposures [57]. Climate change is also expected to increase heavy precipitation and flooding events, which may increase the chance of toxic contamination leaks from storage facilities or runoff into water from land containing toxic pollutants. Very little is known about how such transfers will affect people's exposure to these chemicals—some of which are known carcinogens—and its ultimate impact on incidence of cancer [58]. More research is needed to determine the likelihood of this type of contamination, the geographical areas and populations most likely to be impacted, and the health outcomes such as environmental and occupational cancers that could result.

5. FUTURE ASPECTS: DEVELOPMENT OF BIOMARKERS AND BIOLOGICAL MONITORING

To establish effective strategies for prevention of avoidable occupational and environmental cancers, ideal biomarkers (exposure, response, and susceptibility biomarkers) will be further developed for early diagnosis and prevention of cancers. The ideal biomarkers will be used for proper biomonitoring of occupational and environmental carcinogens. First, exposure biomarkers—internal doses of typical metabolites of chemical carcinogens—will be further improved. For example, levels of t,t-muconic acid, S-phenylmercapturic acid, or toluene in urine have been analyzed as a biological exposure index for benzene exposure [59]. However, exposure assessment usually includes uncertainty, given the paucity of exposure data and incomplete knowledge of exposure mechanisms of most chemicals [60].

A number of approaches have been developed to reduce the uncertainty. Particularly, molecular epidemiologic approaches have played a role in

resolving the uncertainty to identify and assess the relationship between biological markers and health outcomes [61]. In addition, toxicokinetic or physiologically based pharmacokinetic models have been applied for risk assessment of carcinogens and finally for their governmental regulation.

Concerning mixed exposure, synergistic toxicity or attenuation of carcinogenicity can be considered. In the case of some of endocrine-disrupting chemicals such as bisphenol A, they were emphasized to accelerate cancers via mixed exposure with carcinogens via epigenetic mechanisms [60]. However, folate or genistein, an isoflavone, showed repair of bisphenol A-induced epigenetic damages in the agouti mouse model [62].

Even though current evidence suggests that non-genetic factors contribute about 90% of the risks of chronic diseases, the vast majority of human exposures that might initiate disease processes have not been explored [63]. Exposomics, which is the study of the exposome and relies on other omics, is appreciated as a powerful approach for evaluating environmental exposures and their influences on future occupational and environmental cancers [64]. The "exposome" can be defined as the measure of all the exposures of an individual in a lifetime and how those exposures relate to disease [65]. As his or her exposure begins before birth and includes insults from environmental and occupational sources, understanding how his or her exposures from occupation, environment, diet, lifestyle, and so on interact with his or her own unique characteristics such as genetics, physiology, and epigenetic makeup resulting in occupational and environmental cancers.

To explore the exposome, it makes sense to employ a top-down approach based on biomonitoring (e.g., blood sampling) rather than a bottom-up approach that samples air, water, food, and so on [63]. Because sources and levels of exposure change over time, exposomes can be constructed by analyzing toxicants in blood specimens obtained during critical stages of life.

However, the limitation of exposoimcs, such as measurement techniques for long-term exposure, should be overcome for their ideal application, i.e. proper biological monitoring.

Second, response biomarkers should be reconsidered. For example, DNA or hemoglobin adducts of heterocyclic aromatic amines (HCAs) or PAHs played roles as specific biomarkers for carcinogenic HCAs and PAHs [66, 67].

Succeeding the exposure biology (adductomics), advanced technologies, e.g., transcriptomics, epigenomics, and proteomics, are applicable for researches of response biomarkers. Table 2 shows currently developed response biomarkers of occupational and environmental cancers with the advanced technologies [68].

In the case of transcriptomic biomarkers, there are some examples for arsenic, asbestos, benzene, cadmium, and ionizing radiation. For arsenic exposure, Andrew and colleagues (69) found that the high-arsenic exposure group exhibited higher levels of several killer cell immunoglobulin-like receptors

Table 2: Omics- Response Biomarkers of Occupational and Environmental Cancers

Omics Biomarkers	Exposure	Subjects	Ref.[a]
Transcriptomics[b]			
HLA-DQA1, KIR3DL2, etc.; *CXCL1, SFRS5, PTGS2*, etc.; *RBP-Jkappa, Oct-1, E2F*	Arsenic	Arsenic-exposed residents; pregnant mothers and infants; TK6 lymphoblastoid cells	69; 70; 71
ADAM28	Asbestos	Lung cancer patients	72
CXCL16, ZNF331, JUN, PF4 (CXCL4); IL1A, PTGS2, etc.	Benzene	Benzene-exposed workers	72; 74
XIAP; ZF5, Sp1, SREBP-1	Cadmium	Prostate cancer cells; TK6 lymphoblastoid cells	75;71
XPA, ERCC5, LIG3, SEPT6, DUSP22, RHOA	Ionizing Radiation	Radiation workers	78
Epigenomics[c]			
RASSF1A, PRSS3; p53	Arsenic	Bladder cancer patients	79; 81
17 Gene members (*EEF1E1, mir126, MMP15*, etc.)	Arsenic	Ongoing exposed people	82
LINE-1, AluI, p15, MAGE-1	Benzene	Healthy subjects by low-level exposure to benzene	83
p16(INK4A), SFRP	Cigarette smoking	Bladder cancer patients	79
Proteomic biomarkers[d]			
hBD-1	Arsenic exposure	Exposed residents[e]	84
KIF18A, KIF5A	Asbestos	Asbestosis patients	85
CXC-chemokines	Benzene workers	Benzene-exposed workers	87

[a] References: Semicolons (;) were used to match biomarkers and references.
[b] Relation between gene expression and exposure
[c] Relation between gene-specific hypermethylation and exposure
[d] Impact of exposure to carcinogens on the composition of proteome (68)
[e] Individuals ingesting As contaminated water: high $\geq$100 ug total urinary As/L) vs low exposure ($<$100 ug total urinary As/L)

that inhibit natural killer cell activity, e.g., *HLA-DQA1* (major histocompatibility complex, class II, DQ alpha 1), *KIR3DL2* (killer cell immunoglobulin-like receptor, three domains, long cytoplasmic tail, 2). In addition, Fry and colleagues [70] focused on infants born to arsenic-exposed mothers and performed biomonitoring with pregnant mothers' toenail and cord blood in Thailand. Using microarray, they found activation of inflammation/NF-kappaB (Nuclear factor-jB) signal-related 11 potential gene biomarkers, i.e., *CXCL1* [chemokine (C-X-C motif) ligand 1], *DUSP1* (dual specificity phosphatase 1), *EGR-1*(early growth response 1), *IER2* (immediate early response 2), *JUNB* (jun B proto-oncogene), *MIRN21* (microRNA 21), *OSM* (oncostatin M), *PTGS2* (prostaglandin-endoperoxide synthase 2), *RNF149* (ring finger protein 149), *SFRS5* (splicing factor suppressor of cytokine signaling 3), and *SOC3* (suppressor of cytokine signaling 3). The authors' *in vitro* study identified arsenic specific enrichment for the following transcription factors: *E2F* (EF2 transcription factor), *Oct-1* (octamer-1 transcription factor), and *RBP-Jkappa* transcription factor (*RBP-Jkappa*) [71].

Concerning transcriptomic biomarkers for asbestos, Wright and associates reported that *ADAM28*, encoding a disintegrin and metalloproteinase domain protein, which interacts with integrins, was consistently unregulated in asbestos-related lung cancer patients compared to non-asbestos–related lung cancer [72].

For benzene-response biomarkers, Rothman and colleagues reported 2 different sets of biomarkers: *CXCL16, ZNF* (zinc finger protein) *331, JUN* [v-jun sarcoma virus 17 oncogene homolog (avian)], and *PF4* (platelet factor 4, *CXCL4*) were suggested in their report [73]. Recently, they suggested 16 new genes, which were not overlapped the previous reports [73, 74] e.g. *PTX3* (pentraxin-related gene), *CD44* (CD44 antigen), *PTGS2* (prostaglandin-endoperoxide synthase 2, COX2), *IL1A* (interleukin 1, alpha), *SERPINB2* (serpin peptidase inhibitor, clade B, member 2) [74].

For Cd-biomarkers, Golovine and associates reported that cadmium down-regulated expression of the *XLAP* (X-linked inhibitor of apoptosis protein) through an NF-kappa B-independent proteasome-mediated mechanism [75]. Fry and colleagues reported the cadmium-modulated gene set; the enriched transcription factors included *Sp1* (sp1 transcription factor), *SREBP-1* (sterol regulatory element binding transcription factor 1), and *ZF1* (zinc finger protein 161 homolog) [71].

Interestingly, *PTGS2*, which is known to be up-regulated in colorectal cancer and even has been targeted for cancer therapy [76], was suggested as a biomarker for both of arsenic and benzene (Table 2).

In addition, altered expression of metallothioneins, which play a key role in transport of essential heavy metals, detoxification of toxic metals, and protection of cells against oxidation stress in peripheral blood and serum can provide

interesting information about type or clinical stage of cancers or response to therapy [77].

For biomarkers of ionizing radiation, Fachin and associates found transcriptional changes in 78 genes (21 up-regulated and 57 down-regulated) involved in several biological processes such as ubiquitin cycle [*UHRF2* (ubiquitin-like with *PHD* and ring finger domains 2) and *PIAS1* (protein inhibitor of activated STAT, 1)], DNA repair [*LIG3* (ligase III, DNA, ATP-dependent 3), *XPA (*xeroderma pigmentosum, complementation group A), *ERCC5* (excision repair cross-complementing rodent repair deficiency, complementation group 5), *RAD52* (RAD52 homolog), and *DCLRE1C* (DNA cross-link repair 1C)], cell cycle regulation/proliferation [*RHOA* (Ras homolog gene family, member A), *CABLES2* (Cdk5 and Abl enzyme substrate 2), *TGFB2* (transforming growth factor, beta 2), and *IL16* (interleukin 16)], and stress response [*GSTP1* (glutathionine S-transferase P1), *PPP2R5A* (protein phosphatase 2, regulatory subunit B', alpha), and *DUSP22* (dual specificity phosphatase 22)] and confirmed the previously mentioned microarray results with real-time PCR, particularly for *XPA*, *ERCC5*, *LIG3*, *SEPT6*, *DUSP22*, *and RHOA* [78].

In the case of epigenomic biomarkers, arsenic-response biomarkers have been developed. Marsit and associates reported association between promoter methylation at *RASSF1A* [Ras association (RalGDS/AF-6) domain family member 1] and *PRSS3* (protease, serine, 3) and toenail arsenic levels in bladder cancer patients [79]. They also observed that cigarette smoking was associated with a more than two-fold increased risk of promoter methylation of the *p16*(*INK4A*) gene, with greater risk seen in patients with exposures more recent to disease diagnosis; smoking was also significantly associated with any *SFRP* (secreted frizzled-related protein) methylation. However, their recent two populations study suggested other epigenetic biomarkers, *HOXB2* (a member of the homeobox family of transcription factors), *KRT13* (keratin 13), and *FRZB* (frizzled-related protein), instead of confirming the previous biomarkers [80].

In addition, Chanda and colleagues observed significant DNA hypermethylation of the promoter region of the p53 gene among arsenic-exposed subjects compared to control subjects [81]. Recently, Fry and associates reported an arsenic-induced tumor suppressorome—a complex of 17 tumor suppressors known to be silenced in human cancer [82]. It comprised the following hypermethylated genes: *C11orf70* (chromosome 11 open reading frame 70), *CENPE* (centromere protein E, 312 kDa), *EEF1E1* (eukaryotic translation elongation factor 1 epsilon 1, also known as p18), *ENDOG* (endonuclease G), *FOXF1* (forkhead box F1), *HOXB5* (homeobox B5), *HOXB9* (homeobox B9), hsamir-126 (human microRNA 126), *MMP15* (matrix metallopeptidase15 (membrane inserted), *MSX1* (msh homeobox 1, also known as HOX7), *POLD4* (polymerase

(DNA-directed), *delta-4* (also known as p12), *PRDM2* (PR domain containing 2, with *ZNF* domain, also known as RIZ), *RNF20* (ring finger protein 20), *SMARCD2* (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 2), *SUFU* [suppressor of fused homologue (Drosophila)], *TBR1*(T-box, brain, 1), and *TSC22D3* (TSC22 domain family member 3). However, there were no common arsenic epigenetic biomarkers among these 3 articles.

For benzene-epigenomic biomarkers, Bollat and associates reported significant reduction in *LINE-1* (long interspersed nuclear element-1) and *AluI* methylation and hypermethylation in *p15* and hypomethylation in *MAGE-1* (melanoma antigen family A, 1) with analysis of airborne benzene levels [83].

In a case of proteomic studies, Hegedus and colleagues observed a decrease in urinary beta-defensin-1 (*BD-1*) expression due to arsenic exposure among arsenic exposed residents in Nevada, USA, and confirmed their finding in Chilean subjects. Some studies supported the role of *BD-1* as a tumor suppressor gene for urological cancers [84].

For asbestos exposure, Tooker and colleagues found that 3 polypeptide peaks could predict development of cancer in asbestos exposure with 87% sensitivity and 70% specificity with "surface-enhanced laser desorption/ionization time-of-flight mass spectrometry" and "classification and regression trees." They identified them as kinesin family member 5A and 18A [85]. They also tried to find proteomic biomarkers for chronic beryllium disease in serum, but failed to differentiate between patients with beryllium sensitization and patients with chronic beryllium disease [86]. Therefore, future refinements in sample collection or proteomic technology may be needed to improve biomarker discovery.

For benzene proteomic biomarkers, Rothman and associates reported decreased levels of CXC-chemokines in serum of benzene-exposed workers with array-based proteomics [87]. Their results were partially confirmed by their own GeneChip set [73, 74].

Third, susceptibility biomarkers will be reconsidered. For past 30 years, development of genomics has impacted the susceptibility biomarkers. Various genomic polymorphisms showed effects on occupational and environmental cancers (Table 3).

For bladder cancers, which are associated with exposure to smoking, PAHs, and aromatic amines, a recent multi-stage, genome-wide association study reported that *GSTM1* deletion and a tag SNP for *NAT2* (N-acetyltransferase 2) acetylation status affected bladder cancer risks [88]. In addition, Hung and colleagues suggested that individual susceptibility of bladder cancer might be modulated by *MPO* and *MnSOD* (manganese superoxide dismutase) polymorphisms, and that the combination of genetic factors involved in oxidative stress response with environmental carcinogens might play an important role in bladder carcinogenesis [89]. For benzidine exposure,

Table 3: Genomic Susceptibility- Biomarkers of Occupational and Environmental Cancers[a]

Biomarkers	Exposure	Subjects	Ref.
NAT2, GSTM1; MPO, MnSOD	Smoking (PAHs)	Cases (bladder cancer) and controls	88; 89
XRCC1, GSTT1, AS3MT, XPD	Arsenic	Cases (skin cancer) and controls	93–96
GST1, GSTM1, XRCC1, XRCC3, XPD, OGG1	Asbestos	Asbestos-exposed workers; cases (malignant mesothelioma)- controls	97; 98
NQO1, MPO, XRCC1; WRN, p53, BRCA2; ALOXE3, VCAM1, ALOX5	Benzene	Benzene-exposed workers	26; 99; 101
GSTM1, GSTP1, GSTT1, NAT1, NAT2, UGT2B17	Benzidine	Benzidine-exposed workers (bladder cancer)	90–92
HLA–DPB1	Beryllium	Beryllium-exposed workers	102
SP–B	Chromium	Chromium-exposed workers	104
CYP1A1, GSTP1, MPO	ETS[b]	Cases (lung cancer)-controls	105
Cyclin D1, ERCC2/XPD, Ki-ras, p16	Ionizing radiation	Cases (meningioma) and controls	106
ALAD	Lead	Exposed workers	107

[a]Relation between genetic polymorphisms and exposure.
[b]Environmental tobacco smoking.

genetic polymorphisms of phase II metabolic enzymes, GSTs, NATs, and UGT (UDP-glucuronosyltransferase) 2B17 were suggested as susceptibility biomarkers for bladder cancer [90–92].

In a case of arsenic exposure, genetic polymorphisms in *XRCC1* (X-ray repair complementing defective repair in Chinese hamster cells), *GSTT1*, *AS3MT* (arsenic (+III) methyltransferase), and *XPD* (xeroderma pigmentosum group D) were reported to affect susceptibility to arsenic exposure [93–96].

For asbestos exposure, Kukkonen and colleagues reported that *GSTT*1 deletion polymorphism were associated with fibrotic changes and the *GSTM1* deletion polymorphism was associated with the greatest thickness of pleural plaques in 1,008 Finnish asbestos-exposed workers [97]. In addition, Dianzani and colleagues found that genetic polymorphisms in *XRCC1*, *XRCC3*, *XPD*, and *OGG1* (8-oxoguanine DNA glycosylase) 1 affected incidence of malignant mesothelioma in Italian subjects who were geographically highly exposed to asbestos pollution [98].

For benzene, relatively many genetic polymorphisms were suggested as susceptibility biomarkers. Kim and associates observed effects of *NQO1, MPO*, and *XRCC1* polymorphisms on chromosome damage among workers at a petroleum refinery [26] Shen and colleagues reported polymorphisms in *WRN* (Werner syndrome)*, TP53*, and *BRCA* (breast cancer gene) *2* impacted maintaining genomic stability for benzene-induced hematotoxicity in Chinese benzene workers [99]. Their results, particularly *WRN*, were confirmed by Lan and colleagues [100]. They also reported polymorphisms in innate immunity-related genes, *MBP* (myelin basic protein), *VCAM1* (vascular cell adhesion molecule 1), *ALOX5* (arachidonate 5-lipoxygenase), *MPO, RAC2* (ras-related C3 botulinum toxin substrate 2), and *CRP*(C-reactive protein, pentraxin-related) were associated with white blood cell counts [101].

For Beryllium, polymorphisms of *HLA–DPB1* (major histocompatibility complex, class II, DP beta 1) were suggested as susceptibility biomarkers [102], which has been cited by others [23, 103]. For a chromium biomarker, *SP-B* (surfactant protein B) was suggested by Ewis and associates [104].

Concerning tobacco smoking, *GSTP1, MPO*, and *CYP1A1* variations affected susceptibility to lung cancer in a study of combined effects of genetic polymorphisms [61]. In addition, *OGG1* among DNA repair genes was also suggested as a susceptibility biomarker for lung cancer [105].

For Ionizing radiation, Sadetzki and colleagues suggested that SNPs in *Kiras* and *ERCC*2 (excision repair cross-complementing rodent repair deficiency complementation group 2) */XPD* SNPs were possible markers for meningioma formation, whereas *cyclin D1* and *p16* SNPs might be markers of genes that have an inverse effect on the risk to develop meningioma in irradiated and non-irradiated populations [106].

For lead, which is probably carcinogenic for that lung or stomach, Shaik and Jamil studied effects of genetic polymorphisms in

ALAD (delta-aminolevulinic acid dehydratase) [107] and MGP (Matrix gamma-carboxy glutamic acid protein) [108] on hematological lead toxicity. As a result, they suggested polymorphisms (G177C) in ALAD, which plays an important role in lead poisoning on blood lead levels among battery manufacturing unit workers in India [107].

Focusing on several highlighted carcinogens [41], the current status of new omics biomarkers was reviewed in the present study. Some biomarkers are confirmed by independent studies (Table 2, Table 3). Other biomarkers need sufficient evidences for their proper application. In addition, to support genetic biomarkers in routine occupational safety and health practice or regulation at this time, the original purpose of the biomarker development should be conserved. That is, ethics and human (workers') rights should be placed in the first priority for application of biomarkers. In the near future, more sensitive and selective biomarkers are expected for the prevention of various occupational and environmental cancers. In addition, their biomarkers should be developed for convenience and economical purposes.

6. STRATEGIES FOR PREVENTION OF ENVIRONMENTAL/ OCCUPATIONAL CANCERS

At least one-third of cancer cases that occur annually throughout the world could be prevented [5, 109]. However, the risk of progressing cancer depends on many factors, including the mode of exposure to a known carcinogen and the length and intensity of the exposure. Avoiding or reducing exposure to risk determinants will result in a decrease in cancer risk [109]. Therefore, we need to establish a coordinated network of institutions for primary prevention of environment-related cancer involving scientific experts, professional societies, non-governmental organizations, academic and governmental institutions, media, and others.

Avoiding exposure to occupational and environmental carcinogens as well as antidotes or detoxification strategies can be applicable, particularly for individualized prevention of the cancers. For example, reactive oxygen/nitrogen species-mediated oxidative damage is a common denominator in the pathogenesis of most of the environmental and occupational carcinogens [89, 110]. Therefore, consideration has been given to the role of antioxidative health supplements, e.g., vitamin C (ascorbic acid), vitamin E (α-tocopherol), curcumin, glutathione, and antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase in their protective roles against carcinogen-induced oxidative stress [110].

However, large trials testing supplementation with multivitamins, folate, selenium, ß-carotene, and vitamins E, C, D, B6, and B12 have found no benefits [111]. Even clinical trials designed to test agents that were found to reduce

cancer risk in secondary analyses of previous trials, such as vitamin E and selenium for prevention of cancers, have failed to find benefit from supplementation [111, 112]. Therefore, to obtain evidences of nutritional prevention of cancer from researches, new directions are needed. For example, new cohorts using improved dietary assessment methods or the modification of existing cohorts to add better methods is certainly one important direction for further research. Second, we need a concerted effort to develop human models for cancer prevention that do not require many thousands of study participants and many years of follow-up.

In addition, we need useful clues for preventing cancers to identify exposure routes of occupational and environmental carcinogenesis. For example, the amount of mutagens, e.g., HCAs, in a cooked hamburger from a restaurant varies considerably from one vendor to another [113]. The variation has much to do with the details of food preparation, such as cooking temperature and cooking time. Both cooking temperature and time can be manipulated to minimize the formation of mutagens. Increasing the frying temperature of ground beef from 200 to 250°C induces mutagenic activity about six- to seven-fold. Reducing cooking temperature and time can significantly lower the amounts of mutagens generated and subsequently consumed in the diet.

Therefore, we need macro-approaches, e.g., governmental cooperation with networking and continuous biological monitoring of occupational and environmental carcinogens with proper biomarkers and micro-approaches, e.g., improvement of individual lifestyle, to avoid and attenuate risks of occupational and environmental cancers.

7. CONCLUSION

Occupational and environmental cancers are avoidable with proper prevention of exposure to their specific or multiple carcinogens. Considering current characteristics of the global or local carcinogens t, I suggest the close cooperation of developed and developing countries for the ideal prevention from occupational and environmental cancers.

In addition, advanced "omics" technologies with a balance of environment and gene will provide effective biomarkers. Proper biological monitoring with the biomarkers is expected to improve quality of life as well as to prevent occupational and environmental cancers.

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