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Environmental and Occupational Determinants of Cancer:
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AN OVERVIEW OF THE EVIDENCE ON ENVIRONMENTAL AND OCCUPATIONAL DETERMINANTS OF CANCER

I.-BACKGROUND AND RATIONALE

Cancer is a generic term for a large group of diseases that can affect any part of the body. Other terms used are malignant tumours and neoplasms. One defining feature of cancer is the creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs. This process is referred to as metastasis [1].

Cancer is the second most common cause of death worldwide after cardiovascular diseases [2, 3]. Globally, there were reported 12.7 million new cases of cancer in 2008 (6,639,000 in men and 6,038,000 in women) and 7.6 million deaths due to cancer (4,225,000 in men and 3,345,000 in women) [4, 5]. Cancer is not a modern disease, but as cancer risk increases steeply with age, it is more common nowadays due to increasing life expectancy. It has been estimated that the incidence of cancer will double between 2000 and 2020 and nearly triple by 2030 [6]. Until recently, cancer was considered a disease of westernized, industrialized countries, however, in 2008, 56% of new cases (7.1 millions) and 63% of all cancer deaths (4.8 millions) were reported by low- and middle-income countries [4]; this figure is predicted to increase due to a rise in life expectancy of the populations in low- and middle-income countries and due to their large overall population size.

Cancer can impose a substantial burden through long-term human suffering for individuals and families, economic impact on active members of society and high costs for health-care systems. A recent report showed that cancer causes the highest economic loss of all the 15 leading causes of death worldwide. The total economic impact of premature death and disability from cancer was $895 billion in 2008 not including direct costs of treatment. The top three cancers that had the highest economic impact globally are lung cancer ($188 billion), colon/rectal cancer ($99 billion) and breast cancer ($88 billion) [7]. Only 5% of the global resources for cancer are spent in developing countries [8]. In those countries, cancers are usually detected at advanced stages, when many are more difficult to treat, therefore treatment interventions are more costly and less successful. The estimated rise in cancer incidence will have a greater impact on countries that have a low health budget and fragile or absent health systems.

Cancer is a multifactorial disease due to a combined effect of genetic and external factors acting concurrently and sequentially. Overwhelming evidence indicates that the predominant contributor to many types of cancer is the environment [9]. This finds support from multi-generation migrants studies showing adoption to the cancer risk of the host country [10, 11]. In addition, other studies with identical twins have shown the role of the environment in the development of cancer and that genes are not the main explanation [12]. For instance, the concordance for breast cancer in twins was found to be only 20% [13]. The combination of environmental exposures with some gene polymorphisms may be synergistic and contribute to a substantial proportion of the cancer burden in the general population.

The proportion of cancer cases attributable to modifiable risk factors varies greatly across countries, but is estimated to always exceed at least one third of cases. Those cancers would be preventable, therefore the first step in cancer prevention planning is to perform a systematic assessment of cancer risk factors at the country level to obtain good quality and comparable country-level data [14, 15]. Annually, roughly 19% (confidence interval 12-29%) of all cancers are estimated to be attributable to the environment, including in work settings, resulting in 1.3 million deaths [16]. "*Environment*" is defined by the World Health Organization (WHO) for the purpose of environmental attribution as "*all the physical, chemical and biological factors external to the human host, and all related behaviours, but excluding those natural environments that cannot reasonably be modified*". This definition is in fact limited to those parts of the environment that can in principle be modified, so as to reduce the health impact of the environment, such as pollution, electromagnetic fields, occupational risks, built environments or agricultural methods; and excludes behaviour and life style not related to the environment, such as alcohol and tobacco consumption, as well as behaviour related to the social and cultural environment, genetics, and parts of the "unmodifiable" natural environment [16]. Therefore environmental interventions are key for reducing the incidence and mortality of cancer, by eliminating or decreasing the exposure to environmental carcinogens, including in work settings, mainly by means of primary prevention measures including individual measures of protection.

Environmental factors that represent risks for the development of cancer typically affect the general population through exposures that cannot be directly controlled by the individual. These factors can be found in the environment as physical (ionizing and non-ionizing radiation such as exposure to radon or ultraviolet (UV) radiation, respectively), chemical (such as asbestos, dioxins and other pollutants found in industrial emissions and second-hand smoke, contaminants or natural constituents found in food and drinking water such as pesticide residues, arsenic or aflatoxins), and biological carcinogens (such as certain viruses). Carcinogenic effects in human beings result from exposure to radiation, air pollutants, food and water components or contaminants, as well as daily consumer exposure from man-made products. These exposures may occur on multiple occasions and in various settings during the course of a life time, from households and schools, to the working environment. Children, including the embryo, fetus, infant and all life stages until the completion of adolescence are often at greater risk from environmental hazards than adults [17]. Additionally, parental occupational exposures may increase the risk of cancer in their offspring. Pesticides, benzene, asbestos and ionizing radiation have been investigated [18].

Exposure may be widespread, as it is the case for air pollution, or could be restricted to an area close to a certain industrial site. These exposures have been associated with a variety of neoplasms, but particularly cancer of the lung, skin or leukaemia. Occupational health risks are also directly related to physical, chemical and biological factors in the environment and frequently related to passive exposures and behaviours. The types of cancer that have most commonly been linked with occupational exposures and for which evidence is strong, are those of the lung, urinary bladder, mesothelioma, larynx, leukaemia, angiosarcoma of the liver, nose and nasal cavity and skin [19].

II.- ENVIRONMENTAL AND OCCUPATIONAL CARCINOGENS

1. CHEMICAL EXPOSURES

Historically, the chemical carcinogen or group of carcinogens which has received the most attention has been tobacco smoke, and deservedly so. However, there is also strong evidence that industrial and manufacturing exposures to chemicals, agricultural exposures to pesticides or aflatoxin, indoor and outdoor air pollution and chemical contamination of water can constitute cancer-causing factors present in our living and working environment. Carcinogenic exposures from consumer products, predominantly man-made, that people are exposed to involuntarily in their daily life, may occur from paints in buildings, pesticides applied in gardens and playgrounds, chemicals used at home for cleaning or in schools, toys, etc..

Air pollution, outdoor and indoor, is a major environmental health problem both in developed and developing countries. Volatile organic compounds, nitrogen-containing and halogenated organic compounds, polycyclic aromatic hydrocarbons (PAHs) [20], toxic metals, and many by-products of incomplete combustion (e.g. dioxins) are all carcinogens that pollute the air [21].

Outdoor air pollution in urban settings

Many of these toxins are released into the air from mining operations and other industrial facilities, from the use of coal and other fossil fuels for power generation which is often the case in developed countries, and from municipal waste sites and inadequate domestic incineration [22].

Motor vehicles can add significantly to air pollution in urban areas. Certain substances in vehicles exhaust are classified as carcinogenic to humans (Group 1) and probably carcinogenic to humans (Group 2A) by the International Agency for Research on Cancer (IARC) [23]. Epidemiologic studies have found a higher lung cancer risk among urban residents and persons living near industrial point sources compared to persons living in rural areas [24]. Large cohort studies on air pollution and mortality have been conducted in several metropolitan areas across the United States, showing a significant increase in mortality from lung cancer [25, 26]. These findings have been subsequently corroborated in an independent re-analysis [27].

Some chemicals such as benzene can also be found in the refuelling emissions near petrol filing stations and inside the vehicles. Benzene has been shown to cause acute myeloid leukaemia and is suggested to be associated with acute and chronic lymphoblastic leukaemia, non-Hodgkin lymphoma and multiple myeloma [28].

Indoor air pollution

In most low-income, and many middle-income countries, the use of coal, wood and other biomass in the home for cooking and heating is very common, leading to high levels of indoor air pollution and contributing also to outdoor air pollution. Burning fossil fuels and wood in households produce PAHs, increasing the risk of lung cancer and other types of cancers. The use of coal in homes, and to some extent in schools, is especially extensive in China where the association between lung cancer in men and women and cooking with open coal stoves has been shown consistently in multiple studies [29, 30]. The most frequent solid fuel used in Asian countries other than China is biomass. Although the causal link between biomass fuel use and lung cancer is still considered inconclusive due to the relatively small number and inconsistent methods and findings of available studies, indoor emissions from household combustion of biomass fuel (primarily wood) have been classified as Group 2A (probably carcinogenic to humans) by IARC because of to the presence of PAHs and other carcinogenic compounds in wood smoke, and the mechanistic evidence of mutagenicity and cytogenetic damage caused by wood smoke. There is also epidemiologic and experimental evidence that cooking-oil emissions from high-temperature frying may pose a cancer hazard [31]. A number of studies have also reported associations between solid fuel use and upper aero-digestive tract cancers (in the larynx, the pharynx, the nasopharynx, the nasal cavity and paranasal sinuses) [32, 33] , and with cervical cancer [34].

Second-hand smoke contains most of the constituents of tobacco smoke (arsenic, benzene, 1,3-butadiene, cadmium, PAHs, etc.), including 69 known carcinogens, and its causal association with lung cancer has been shown. There is also some limited evidence of an association with other types of cancers in the larynx and the pharynx, the nasopharynx, the nasal cavity and paranasal sinuses, cervix, breast and gastrointestinal tract [35, 36]. Second-hand smoke contributes to both outdoor and indoor air pollution.

Asbestos

Asbestos is the generic name for a group of naturally-occurring inorganic fibrous silicates. All forms of asbestos are carcinogenic to humans. Inhalation of asbestos contributes substantially to the burden of lung cancer and is causing mesothelioma, cancer of the larynx and the ovaries [21, 37]. There is some evidence suggesting an association between exposure to asbestos with causation of cancer of the pharynx, the stomach and colorectal cancer [21].

Asbestos exposures account for the largest proportion of occupational cancer. The construction industry and extractive mining of asbestos are sources of workers' exposure. Although the use of asbestos has been greatly restricted in many countries (over 50 countries have banned the use of all forms of asbestos), workers employed in construction trades, electricians and carpenters can still experience high levels of asbestos exposures through renovations, repairs and demolition; as well as workers exposed to asbestos-containing products, such as in brake maintenance and repair. Some countries still continue to mine and use chrysotile [38].

Asbestos is one of the best characterized occupational causes of human cancer, however the general population is also exposed because asbestos is released into the environment from the use and deterioration of many asbestos products [39].

Other occupational exposures related to chemicals

A long list of agents found in the workplace are known or probable causes of cancer. IARC has classified as human carcinogens 29 chemicals or physical agents, groups of agents or mixtures, to which exposure is mainly occupational and 15 industrial processes or occupations [6]. Solvents such as benzene used in shoe production or the pharmaceutical and chemical industries are associated with acute non-lymphocytic leukaemia, aromatic amines used in the rubber industry were found to cause cancer of the urinary bladder [40], cadmium and chromium (VI) found in dye and pigments production cause lung cancer [21], and formaldehyde used in textile and plastic industries is related to nasopharyngeal cancer [40]. Mineral oils, used as a lubricant by metal workers, in pharmaceutical and cosmetic preparations, and in the printing industry (ink formulation) are associated with skin cancer [19]. Nickel refining and smelting and welding is associated with cancer of the lung, nasal cavity and paranasal sinuses [21]. Exposure to arsenic in smelting nonferrous metals and metallurgical industries are also associated with lung, skin and urinary bladder cancer [21]. Various PAH-related industries and -containing mixtures are also described as carcinogenic to humans by IARC: aluminium production, coal gasification, coke production, etc. [40].

There is convincing evidence of increased risk of different types of cancer in relation to occupational exposures to chemicals, however, a complete evaluation of specific carcinogenic exposures in different occupations or industrial processes is usually difficult, particularly in low-income countries where the available data on occupational cancer risks are limited. Although several of the agents to which workers are exposed in industry are also present in the general environment, the exposure levels at the workplace are usually higher. The expected impact of occupationally-related cancers in low- and middle-income countries is higher due to lack of or less stringent monitoring of worker protection, less occupational hygiene and safety, and child labour.

2. PHYSICAL EXPOSURES TO IONIZING AND NON-IONIZING RADIATIONS

Radiation is omnipresent throughout the environment and has natural and man-made sources. Ionizing radiation is one of the most intensely studied carcinogens, classified in Group 1 by IARC [41, 42], and results from mining, military and industrial applications, or medical uses. Non-ionizing radiation includes electric and magnetic fields, from static fields to radio waves, microwaves, infrared, ultraviolet and visible radiation.

Radon in households

Radon is a inert radioactive gas occurring naturally in the ground as a result of decay of uranium. Radon gas atoms can in turn disintegrate, producing polonium, bismuth and lead, which are also radioactive, attach themselves to airborne particles and tend to accumulate upwards in enclosed spaces, such as underground mines and the basements of residences. Radon may be found anywhere worldwide, depending on the geological features of the area. The more permeable the ground, the more readily radon gas can rise to the surface. Infiltration of radon from the soil into buildings is mainly due to warm air rising upwards through cracks and joints in walls and floors. Radon can also dissolve in groundwater and dissipates when the water comes in contact with the air. Radon volatilizing from drinking water may also raise indoor air concentrations.

In many countries, radon is the second most important cause of lung cancer after smoking. Radon is much more likely to cause lung cancer in people who smoke, and is the primary cause of lung cancer among non-smokers [43, 44]. The risk of lung cancer increases with the concentration of radon in the air and the duration of exposure. If radon gas is inhaled, its radioactive particles are deposited in the respiratory tract and irradiate lung, but years or even decades may elapse between the exposure and the onset of lung cancer [43].

Medical exposure to ionizing radiation

The medical applications of ionizing radiation have greatly expanded worldwide due to an increasing use of X-rays in diagnostic imaging and interventional radiology, the development of new technologies using radiopharmaceuticals for diagnosis and treatment in nuclear medicine, and the multiple applications of X-rays, gamma-rays, and charged particles in radiotherapy. The clinical value of radiation for the diagnosis and treatment of human diseases is unquestioned. When a radiological procedure is appropriately prescribed (justification) and properly performed (optimization) the individual benefits exceed the radiation risks. However, this balance is lost if the procedures do not have a clear clinical indication or when patients receive a higher dose than necessary. Although new applications and medical equipment continue to become safer, inappropriate or incorrect handling can lead to unnecessary or unintended radiation doses, and cause potential health hazards for patients and staff. Radiation-induced cancer risk increases with dose, with higher risks for children and young people, as they are significantly more sensitive to radiation exposure than adults. [45]. Even the low radiation dose used in diagnostic imaging may have a risk of inducing cancer that increases with the patient's lifetime cumulative radiation dose [46]. Epidemiological studies in humans demonstrate that ionizing radiation can give rise to cancer in multiple anatomical sites: leukaemia (short latency) and tumours in solid organs (long latency: bone, lung, liver, thyroid, breast, etc.) [47]. Internally-deposited radionuclides such as radiopharmaceuticals used in nuclear medicine (e.g. iodine-131, phosphorous-32) are also classified by IARC as carcinogens to humans [48].

The greatest contribution to ionizing radiation exposure of health-care workers comes from the use of X-rays in image-guided interventional procedures, and the use of radiopharmaceuticals in nuclear medicine (e.g. positron emission tomography (PET)). Studies carried out among radiologists exposed in the 1950s to high doses provided substantial evidence that radiation can cause leukaemia and solid cancers in those workers [49]. There is a need to empower health-care workers with the required knowledge and skills to ensure safe and effective use of radiation in health care.

UV and tanning beds

UV radiation is part of the electromagnetic spectrum. UV exposure is a recognized cause of different types of skin and ocular cancer. Solar radiation has been classified as a Group 1 carcinogenic agent by IARC [50] but there are currently no recommendations for “safe doses” to human skin [6]. Depletion of the ozone layer caused by chemicals released in the atmosphere is believed to be responsible for global increases in UVB radiation. Populations with fair skin from Australia, the Nordic countries and Canada are at higher risk of melanoma [51]. Epidemiological studies show that cutaneous melanoma is associated with short-term exposure to unusually intense sunlight, often in the pursuit of tanned skin [52, 53].

Artificial sources of UV radiation have become very common in many countries, especially among young women, mainly in the form of tanning beds for tanning purposes. Exposure to powerful indoor tanning devices is associated with an increased risk of cutaneous melanoma and the risk increases when tanning bed use starts before 30 years of age [54]. Moreover, several case-control studies provide a consistent positive association with the occurrence of ocular melanoma [55, 58]. IARC has recently raised the classification of the use of tanning beds to Group 1, carcinogenic to humans [48].

Outdoor workers, such as farmers and construction outdoor workers, are exposed to solar radiation, frequently at the midday hours when the sun is strongest. In the 1980s, epidemiological studies suggested that lifetime accumulation of exposure to sunlight in some occupational groups increased the risk of squamous skin cancer [6].

III.-BURDEN OF CANCER DUE TO THE ENVIRONMENT

To identify cancer prevention opportunities, the causes and risk factors for the most common cancers need to be determined. The relationship between exposure to carcinogens and the development of cancer is determined by an estimate of the magnitude of risk resulting from a specified level of exposure. The exposure levels to the general public are typically lower than in occupational or other settings in which cancer risks have been shown. Nevertheless, despite difficulties of measurement, low-level exposures to carcinogenic pollutants are a major concern because of the multiplicity of substances, the involuntary exposure and the large numbers of people that may be exposed. Therefore, quantitative risk assessment is a critically important step for decision making.

Estimates of the burden of disease identify major risk factors and high-risk populations, evaluate the extent of a public health problem, and support decisions on priority actions for risk reduction. The disease burden in any given population depends on the distribution of exposure, its level and duration, genetic factors, as well as exposures to other factors.

Priority setting for cancer prevention needs to take into account the burden of cancer in different regions of the world, therefore primary prevention strategies should be adapted to national conditions. The major contributors to cancer incidence in the world are lung cancer (1.61 million of cases), followed by breast (1.38 million of cases) and colon cancer (1.23 million cases). Lung cancer is also the most common cause of cancer deaths worldwide (1.38 million deaths); and stomach (740,000 deaths) and liver cancer (700,000 deaths) are the second and third respectively [4]. Most cases of stomach and liver cancer occur in developing countries.

Although the evidence linking specific environmental and occupational exposures to various cancers is still incomplete and more research is warranted, WHO has recently published two documents providing quantitative estimates of the environmental burden of disease due to major preventable risk factors [16, 57]. The first method [16] is based on a combination of comparative risk assessment methods [57] and evidence synthesis, completed by expert consultation. This resulted in the rough estimate of 19% of all cancer burden to be attributable to the environment, including in work settings. The comparative risk assessment methods [57] estimated the attribution of cancers for each individual risk, and combined with an estimate for radon result in more than 7% of all cancer deaths being attributable to the environment and work settings. These methods, however, have limitations. For example, from the 107 agents, mixture and exposures classified by IARC into Group 1 (including professional activities), from which 60 agents, mixture and exposures are directly related to environmental and occupational settings, only less than the half have been partly assessed for burden of disease (such as asbestos, benzene, beryllium, cadmium, chromium, ethylene oxide, nickel and arsenic in occupational settings; benzo[a]pyrene, indoor emissions of coal; and ionizing radiation, including neutrons or fission products), while the burden of disease of the remainder of the agents, mixtures and exposures, as well as the 58 substances from Group 2A, the 249 from Group 2B and the 512 from Group 3 has mostly not been assessed. This means that most of the environmental and occupational cancer risks are still unknown or underestimated [58].

In 2004 lung cancer represented 18% of all types of cancers, of which 938,000 deaths or 71% were attributed to smoking (*Data based on* [57]). The most important exposures associated with lung cancer include the following:

- outdoor air pollution caused 108,000 lung cancer deaths [57];
- solid fuels, used by more than half the population in developing countries for cooking and heating, caused 36,000 lung cancer deaths [31, 57];
- second-hand smoke was estimated to cause 21,000 lung cancer deaths [59]. It was the second most prevalent carcinogen in the workplace in the EU, as reported by the International Information System on Occupational Exposure to Carcinogens (CAREX) in 1999;
- selected occupational lung carcinogens (such as arsenic, asbestos, beryllium, cadmium, chromium, etc.) were estimated to cause 111,000 lung cancer deaths [57],
- indoor radon exposure was estimated to cause between 3-14 % (70,000-220,000 deaths) of all lung cancers, depending on the average radon level in a given country and on the method of calculation [43]. Radon is the second most important cause of lung cancer in many countries.

Environmental factors contributing to cancers other than lung cancer include the following:

- UV radiation was estimated to cause 60,000 deaths in 2000, 48,000 of those were melanomas and 12,000 basal and squamous skin carcinomas [50, 60];
- asbestos was estimated to cause 59,000 deaths from mesothelioma in 2004 [57];
- occupational exposure to selected leukaemogens, including benzene and ethylene oxide, and ionizing radiation, was estimated to cause 7,400 leukaemia deaths in 2004 [57];
- arsenic in drinking-water was estimated to cause 3,700 deaths from lung, bladder and skin cancers in Bangladesh alone, which is probably the most impacted country [61];
- part of the 256,000 breast, colon and rectal cancer deaths from lack of physical activities could be prevented by built environment or transport policies encouraging cycling and walking [16, 57];
- certain infectious agents causing cancer, such as *Helicobacter pylori* (stomach cancer), can be transmitted through contaminated water or food;
- chronic hepatitis B and C virus infection can progress to severe long-term liver damage, including cirrhosis and hepatocarcinoma. In 2000, 65,600 hepatitis B virus (HBV) infections in health-care workers were estimated to be caused by injuries with contaminated sharps; and about 16,400 hepatitis C virus (HCV) infections, representing 40% of all HCV infections in health-care workers [62];
- HIV can be transmitted occupationally and has been estimated to result in 1,000 HIV infections in health-care workers in the year 2000. Opportunistic infections of HIV include cancers such as Kaposi's sarcoma and lymphoma [62].

However, the global health impact of the vast majority of environmental and occupational carcinogens and probable carcinogens is not yet quantified. Important additional carcinogens include chemicals such as pesticides, lead, aflatoxins, dioxins, metals and solvents, and their impact on population health has not yet been well estimated.

IV.-NEXT STEPS

Finding ways to prevent the development of cancer in the first instance is an obvious measure for reducing deaths from cancer which would be highly cost-effective in terms of reduction of health-care costs. This calls for intensified primary prevention efforts to eliminate or minimize physical, chemical and biological exposures to known carcinogens and for the implementation of environmental interventions, including in work settings, to reduce the incidence of cancer, and the clinical, personal, economic and social burdens resulting from the disease. These efforts will necessarily need to cover the many carcinogens found in the environment over which the individual has little control, and which require broad, public health driven action by public authorities at the national, regional and even international levels, engaging all stakeholders in a multi-sectoral, collaborative approach. Some possible priorities for action for consideration by participants in the first WHO International Conference on "Environmental and occupational determinants of cancer: Interventions for Primary Prevention" are listed in the second background paper entitled "Primary prevention of cancer through mitigation of environmental and occupational determinants". Those possible priorities are based on interventions that are available and proven effective.

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