ARTYKUŁ REDAKCYJNY

EDITORIAL

Cancer risk in relation to exposure to trace elements

Ryzyko choroby nowotworowej w związku z ekspozycją na metale śladowe

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Abstract

Cancer is a major public health concern in many parts of the world. The genesis of cancer is multi-causal with some well known causal factors for some sites of cancer. However, some cancer causes are not clear up to nowadays. There are substantial geographic variations in mortality of some sites of cancer in different regions of the world that could be in relation with some environmental factors and trace elements such as arsenic, chromium and cadmium. The review summarizes the recent studies on that matter.

Keywords: cancer, trace elements, arsenic, chromium, cadmium

Streszczenie

W wielu częściach świata nowotwory są głównym zagadnieniem zdrowia publicznego. Powstawanie nowotworu jest zależne od wielu przyczyn , niektóre z nich są znane, jednak przyczyny innych nie są dotąd wyjaśnione. Istotne zróżnicowanie geograficzne odnośnie śmiertelności nowotworów narządowych w różnych regionach świata może być związane z czynnikami środowiskowymi i ze śladowymi metalami jak arsen, chrom i kadm. Niniejszy przegląd przedstawia aktualne badania na ten temat.

Słowa kluczowe: cancer, trace elements, arsenic, chromium, cadmium

Introduction

Cancer is a major public health concern in many parts of the world accounting more than 10 million new cancer cases each year and being the cause of approximately 12% of all death. The lung, breast, colorectum, and stomach are the most common cancers worldwide [1]. Prostate cancer is the fifth most common cancer overall and the second most common among men, bladder cancer, ranks ninth in terms of incidence, and is more common in developed countries [1].

The genesis of cancer is multi-causal with some well known causal factors for some sites of cancer although some cancer causes are not clear up to nowadays. A substantial geographic variations in cancer mortality in some regions of the world make us think about environmental factors of the disease. Among many environmental factors trace elements are of particular interest. Trace elements refer to chemical elements present or required in small quantities. Trace elements are found naturally in the environment and human exposure derives from a variety of sources, including air, drinking water, and food (Table I) [3].

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Table I. Average exposure to trace elements from environmental sources

Trace element	Exposure by source		
	Air	Water[a]	Diet
Arsenic	1–2000 ng [4, 5]	< 1 ng–7200 μg, depending on geographic location [4, 7, 8]	50–200 μg (3.5 μg of inorganic arsenic) [2, 4]
Chromium	0.07–157 ng (200 ng in industrial areas) [9]	0.8–16 μg [9]	50–200 μg [9]
Cadmium	1–40 ng [6, 7]	0.01–0.2 μg (50 μg in heavily polluted areas) [6, 7]	3–160 μg, approximately 1–3 μg is absorbed [6, 7]

Sources [2, 4, 5, 6, 7, 8, 9]
[a] Assuming an intake of 2 l water/day

Arsenic

Arsenic (As) is ubiquitous in the environment due to both anthropogenic and natural processes [10, 11]. The major sources of human exposure to As may be through food, water, air and soil in that dietary intake is the major exposure route [12]. As species from drinking water are mainly found in the form of inorganic arsenicals, whereas organoarsenic compounds (e.g., arsenobetaine and arsenosugars) predominate in seafood [13, 14]. A high level of As in groundwater (up to 2–5000 μg/l) is found in areas of Argentina, Bangladesh, Bolivia, Chile, China (Xinjiang, Shanxi), India (West Bengal), Mexico, Mongolia, Taiwan, Thailand, the USA (Arizona, California, Nevada) and Vietnam. The most significant exposures, in terms of levels and populations, occur around the Gulf of Bengal, in South America and in Taiwan. In Europe, intermediate levels (not higher than 200 μg/l) are found in areas of Hungary and Romania in the Danube basin, as well as in Spain, Greece and Germany [15]. World Health Organization lowered the Maximum Contamination Level for As in drinking water from 0.05 to 0.01 mg/l [16], although dietary exposure to organic arsenicals was formerly neglected due to their relatively nontoxic nature. However, more and more studies have focused on As exposure through seafood rather than drinking water because some seafood contains high As concentrations [17, 18].

The toxicity of As in humans varies in its chemical form. It has been recognized that inorganic As is more toxic than its organic forms [13]. Inorganic trivalent arsenical, which reacts directly with protein-bound sulfhydryls, is considered more toxic than the inorganic pentavalent form [17]. Inorganic As is proposed to be metabolized to monomethylarsonic acid and dimethylarsinic acid of lower toxicity [18, 19].

The International Agency for Research on Cancer recognized arsenic and arsenic compounds as carcinogenic to humans (Group I) [4]. There is strong evidence of an increased risk of bladder, skin and lung cancers following consumption of water with high As contamination [20, 21, 22, 23]. Very limited data are available on the risk of other neoplasms at low or intermediate exposure levels. [15]. Although some authors support the possibility of an increased risk of specific lung cancer histological types at lower levels of As exposure and recommend large-scale population-based studies [24]. The evidence for an increased risk of other cancers, such as those of the liver, colon and kidney, are weaker but suggestive of a systemic effect [15]. Most of the available studies have been conducted in areas with elevated As content (above 200 μg/l). It has been determined median cumulative cancer incidence ratios 2.67×10^{-6} and 3.83×10^{-6} for children and adults, indicating a low cancer risk for local residents exposed to As after ingestion of seafood [25].

Epidemiologic data from regions of the world with very high levels of As in drinking water (> 150 μg/l) show a strong association between As exposure and risk of several internal cancers. A causal interpretation of the data is mainly based on the strength and consistency of study findings. At lower levels of exposure (< 100 μg/l), in the absence of unambiguous human data, extrapolation from the high exposure studies has been used to estimate risk. Misclassification of exposure usually results in depressing observed levels of risk, and studies conducted in populations with exposures below 100 μg/l have been limited by the challenge of estimating past exposures, a critically important aspect of studying relative small increases in risk [26].

Chromium

Chromium (Cr) is the 21st most abundant element in the Earth's crust [27]. While several valence states of Cr are possible, only the trivalent (Cr^{3+}) and hexavalent (Cr^{6+}) forms have significant environmental stability. Most of the naturally occurring Cr is in the Cr^{3+} form as chromite ore [28], while Cr^{6+} tends to occur as a result of anthropogenic uses. These include pigments, metal finishing (including Cr plating) and wood preservatives [29]. Although the highest levels of exposure occur in industrial settings, lesser levels of exposure are also common in the general population. Cr is also constituent of tobacco smoke and has been suspected to play a role in tobacco-induced carcinogenesis [30].

Cr is a human carcinogen primarily absorbed by inhalation exposure in occupational settings. The International Agency for Research on Cancer declared in 1980 that Cr and some of its compounds are carcinogenic and, in 1987, concluded that Cr^{6+} is a human carcinogen but that Cr^{3+} was not yet classifiable [31]. Adverse health effects of Cr have long been known and include skin ulceration, perforated nasal septum, nasal bleeding, and conjunctivitis. Recent studies updating chromium worker cohorts demonstrated an excess lung cancer risk from exposure to Cr^{6+} [32, 33].

Some epidemiological studies found elevated standardized mortality ratios (SMR) for prostate, lymphoma, Hodgkin's, leukemia, stomach, renal, bladder, and genital cancer. This index for cancers of the brain varied from 2.5 to 8.44 in a number of studies [34]. According to the reported elevation of brain cancers, and knowledge that Cr gets into the central nervous system, there should also be concern about the possibility that Cr^{6+} may be neurotoxic [35]. Although Cr^{6+} is not generally considered to be a neurotoxin, perhaps this should be reconsidered since Cr gains entry into the central nervous system and may be a carcinogenic at this site [36].

The meta-analyses of 49 epidemiologic studies mostly relating exposure to Cr^{6+} compounds declared no excess mortality from all causes combined among chrome-exposed persons. A minimal excess of cancer overall, was due primarily to an excess of lung cancer but SMR was 112 among the better-quality, smoking-controlled studies. The overall SMR for stomach cancer was 113 but it was 82 among the studies that were controlled for economic status. Findings were unremarkable for the six other cancers evaluated: prostate, kidney, and central nervous system cancer and leukemia, Hodgkin's disease and other lymphatohematopoietic cancer. Finally, the authors concluded that Cr^{6+} is a weak cause of lung cancer and is not a cause of any of the other seven forms of cancer evaluated [37]. It has been stated that the relationship between Cr^{6+} and lung cancer is weak because of the great capacity of the lung to reduce Cr^{6+} to the non-carcinogenic Cr^{3+}. Only very heavy exposure to Cr^{6+} could overwhelm the lung's reducing capacity and produce cancer [38]. Crump et al. [39] also inferred that Cr^{6+} was only weakly carcinogenic for the lung. However, most of the evidence regarding lung cancer risks related to these agents comes from cohort studies in a narrow range of industries in which exposures have been relatively high. In the majority of these studies, it has been difficult to rule out confounding by smoking or other occupational co-exposures as a possible explanation for the associations [40].

Although lung cancer has been established as a consequence of Cr^{6+} exposure in smokers and nonsmokers, some cancers of other tissues of the gastrointestinal and central nervous systems have also been noted [36]. It has been shown that Cr^{6+} exposure, by either inhalation or ingestion, can have systemic effects that are distant from the site of exposure. Since Cr^{6+} is isostructural with sulfate and phosphate at physiological pH, it can be carried throughout the body and even into the brain. Thus, if exposure is in sufficient amounts, the levels of Cr maybe elevated in many different organs. Depending on the genetic susceptibility of an individual, this could pose significant risk to cancer induction in any organ. All cells and organs possess the ability to take up hexavalent chromate, and any cell has the capacity to reduce the Cr^{6+} intracellularly to Cr^{3+}, which reacts with protein to produce toxicity and with DNA to potentially cause cancer. The ability of the stomach to reduce Cr^{6+} is limited, and even at relatively low doses, chromate escapes reduction and enters the body, as illustrated by hairless mouse study [41]. Experimental study showed that the induction of malignant skin cancers in hairless mice exposed to 0.5–5.0 ppm Cr^{6+} in drinking water was dose dependent and highly statistically significant [41]. In spite of Cr being a human carcinogen primarily by inhalation exposure, the experimental system representing an important new animal model developed for chromate-induced cancers by ingestion of drinking water developed, suggested that chromate could likely be considered a human carcinogen by ingestion as well [36].

Cadmium

Cadmium (Cd) is a toxic, nonessential, and bioaccumulating heavy metal widely used in industry. Cd affects human health both through occupational and environmental exposures. In general

population the primary sources of Cd are cigarette smoke, food, water, and ambient air particularly in urban areas and in the vicinity of industrial settings [42]. About 10% of inhaled Cd is deposited in lung tissues and 30–40% is absorbed into blood. Generally, Cd uptake in the gastrointestinal tract is 5–20% and depends on speciation of Cd, interactions between components in the diet affecting the bioavailability of Cd and the person's nutritional status. Approximately, 75% of the total dietary Cd intake is from vegetable food with the highest contribution from cereals [43]. Owing to long half-life of Cd in the human body, it accumulates in the kidneys. The urinary excretion of Cd is proportional to the body burden and used as a dose of lifetime exposure to Cd, whereas concentration in blood represents recent exposure [44].

Cd exerts multiple toxic effects, and has been classified as a human carcinogen by the International Agency for Research on Cancer [45]. Cd carcinogenesis can be explained by several mechanisms: (1) aberrant gene expression, (2) inhibition of DNA damage repair, (3) induction of oxidative stress, and (4) inhibition of apoptosis. The most important among them is oxidative stress because of its involvement in Cd-induced aberrant gene expression, inhibition of DNA damage repair, and apoptosis [46].

Although Cd is known as a human lung carcinogen [45], there is evidence that it may be related to other cancers such as human prostate cancer [47, 48], renal cell carcinoma [49, 50], and breast cancer [51, 52]. The human mammary gland is a controversial target site for Cd. Epidemiological study revealed twice the higher risk of breast cancer in women with creatinine-adjusted urine Cd more than 0.58 μg/g compare to those with Cd less than 0.26 μg/g [52]. Experimental studies suggest several pathways to explain association of Cd with human breast cancer. There is evidence that Cd may have estrogenicity [51]. According to some authors, the bivalent metal cations Cd belongs to a new class of potent environmental estrogens, referred to as metalloestrogens. The studies in vivo and in vitro show that Cd acts like an estradiol activating estrogen receptor (ER) a through a high-affinity interaction with the hormone binding domain of the receptor [53]. There is evidence that the effects of cadmium are mediated by the ER independent of estradiol [51]. Antila et al. [54] defined high content of Cd (3.2–86.9 μg/g) in breast samples from breast cancer patients, but the mean cadmium level did not differ from that of healthy controls. However, three other studies found significant difference between Cd in breast cancer and healthy breast tissue [55, 56, 57].

Multiple studies have linked occupational exposure to cadmium with pulmonary cancer, as well as prostate, renal, liver, hematopoietic system, urinary bladder, pancreatic, and stomach cancers [58, 59, 60, 61, 62]. Some authors concluded that pancreatic cancer in the East Nile Delta region is significantly associated with high levels of serum Cd and farming [63]. However, the data are nor consistent. In contrast to laboratory studies, epidemiological studies do not convincingly implicate Cd as a cause of prostate cancer [64].

In conclusion, arsenic and its compounds, chromium (VI) compounds, cadmium and cadmium compounds are recognized human carcinogens. However, in spite of an association between chronic arsenic ingestion and internal cancers, epidemiologic studies have not produced convincing evidence of risks related to drinking-water concentrations of less than 100 μg As /liter. Compounds of chromium (VI) and cadmium are human carcinogens primarily by inhalation inducing lung cancer. However, due to inconsistency of the data the relationships with the other sites of cancer are not proved finally. Relatively small study size and misclassification of exposure usually results in depressing observed levels of risk and contributes to the variability of findings in most studies and makes interpretation of results challenging.

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