Trace Elements and Cancer

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Abstract: In regard to iron, malignant neoplasms are often seen in various organs in idiopathic hemochromatosis, and complication by lung cancer is especially common. In regard to the carcinogenicity of copper, large amounts of copper and iron have been reported to accumulate in the liver and spleen of patients with cancer of the respiratory tract, urinary tract, and thorax. Increases in skin and pulmonary epithelial cancer, and the precancerous condition cutaneous keratosis (Bowen’s disease) are seen as a result of chronic oral or airway exposure to arsenic. In addition, there is a report that leukemia has been observed in aplastic anemia and a report that arsenic causes cancer of the bladder, kidney, digestive tract, and liver, etc. Lung cancer is cited in associations between chromium and carcinogenesis. Nickel has been reported to be associated with lung cancer and nasal cavity cancer. High mortality from lung cancer in factories handling beryllium and increased tumors of the central nervous system have also been suggested.

Key words: Trace element; Cancer; Metal carcinogenicity

Introduction

Arsenic, chromium, and nickel are said to contribute to the development of cancer based on the epidemiologic evidence, and beryllium, cadmium, chromium, cobalt, lead, nickel, zinc, and iron have been found to be carcinogenic in experimental animals. In this paper, we will describe the carcinogenicity of a variety of metals.

Carcinogenicity of Metals

1. Iron

Sarcomas and skin cancers have been reported to have developed when animals were intramuscularly injected with iron dextran.1) Boyd et al.2) reported an association between iron ore miners and the incidence of lung cancer, but it also appeared that they may have been exposed to radon, which was also present, and
smoking.

Various malignant neoplasms of different organs are often seen in idiopathic hemochromatosis, but liver cancer is an especially common complication. The mechanisms of the hepatocarcinogenesis are thought to be that iron bound to low-molecular protein in the liver generates hydroxyl radicals via the Fenton reaction that damage DNA, and a direct action of iron on the replication process of the DNA. In a study of iron deposits in the surrounding liver parenchyma in a group of HCV-positive liver cirrhosis patients with liver cancer and a group without liver cancer, the iron deposits were reported to be clearly more common in the group with liver cancer.

2. Copper

Accumulation of large amounts of copper and iron has been reported in the liver and spleen of patients with cancer of the respiratory tract, urinary tract, and thorax, and the copper content of benign tumors of the esophagus, bronchi, and intestine is said to be lower than in cancers.

LEC rats (Long-Evans rats with cinnamon-like color) are animal models of Wilson disease, in which copper accumulates in liver tissue. The animals develop hepatitis at 4 months of age and approximately 40% die, and at approximately 1 year of age those that survive develop liver cancer via cirrhotic change. Gel-filtration analyses have shown that the majority of the increased copper exists in the form of Cu-MT (copper-metallothionein), and it is thought that hydroxyl radicals are generated in the presence of hydrogen peroxide as a result of a Fenton-like reaction and cause hepatitis and hepatocarcinogenesis.

Liver tissue copper content increases in human chronic hepatitis C and liver cirrhosis as the liver disease progresses, and the copper content of well differentiated hepatocellular carcinoma becomes significantly greater than that of moderately or poorly differentiated hepatocellular carcinoma. According to the gel-filtration method, the increased copper in hepatocellular carcinoma also appears to exist in the form of Cu-MT and hydroxyl radicals are generated by a Fenton-like reaction, and similarities to LEC rats have been found. Hydroxyl radicals form the DNA damage marker 8-OHdG (hydroxydeoxyguanosine), and tissue 8-OHdG levels have been shown to be high in chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma.

3. Zinc

Zinc deficiency causes dermatitis, alopecia, and taste disorders, and excessive intake can cause acute poisoning. In experimental models, development of teratomas and cancers were observed when zinc chloride was injected into the testes of chicks and rats.

No epidemiologic evidence of any type of increased cancer incidence has yet been obtained in zinc factory workers or ordinary populations. Zinc is a component of SOD (superoxide dismutase), an enzyme that removes free radicals, and since it is also necessary for activation of DNA repair enzymes, zinc has the opposite effect and protects against carcinogenesis.

4. Arsenic

In a study in which carcinogenesis was observed when animals were exposed to arsenic, Yamamoto et al. reported that bladder, kidney, liver, and thyroid tumors were induced when rats were given another initiator at the same time as a dimethylarsinic acid solution, and the development of skin, lung, and bladder tumors was later reported in mice and rats. Increases in skin and pulmonary epithelial cancer, and the development of precancerous cutaneous keratosis (Bowen’s disease) are seen when chronically exposed orally or via the airway.

In addition, there have been reports of leukemia in aplastic anemia and of arsenic causing cancer of the bladder, kidney, digestive tract, liver, etc. The carcinogenetic mechanism is unknown, but there have been reports that arsenic compounds inhibit methyl thymidine
uptake by human skin cells *in vitro* and inhibit DNA synthesis. Chromosome abnormalities have been observed when human leukocytes or cutaneous fibroblasts were exposed, and there is a report that it is due to DNA binding becoming weaker as a result of substitution for phosphorus in DNA.

5. Chromium
   An association between chromium and carcinogenesis has been pointed out in regard to lung cancer. A high incidence of lung cancer has been demonstrated as an occupational disease among workers engaged in the chromate production process in Germany and the United States. The risk of lung cancer among chromium workers compared to an ordinary population is very high, with a lung cancer prevalence rate 100,000 versus 578, and the relative risk from the standpoint of lung cancer deaths has reached from 3.6 to 29.1. Histopathologically, the most common chromium-related lung cancers are squamous cell carcinomas and small cell cancers.

6. Nickel
   In experiments on rats, induction of rhabdomyosarcoma was reported as a result of intramuscular injection of nickel subsulfate, and development of sarcoma in various organs has been reported as a result of intravenous injection of nickel carbon. Lung cancer developed when cats were allowed to inhale nickel dust, and high rates of lung cancer and cancer of the nasal cavity have been found in nickel refinery workers. The principal carcinogens are thought to be inhaled nickel particles and nickel oxide.

7. Vanadium
   Vanadium has been negative in many bacterial tests for mutagenicity. It is not recognized as possessing carcinogenic activity, and no association has been found with cancer in humans or animals. Nevertheless, vanadium promotes cell mutation in some cells, causes tyrosine kinase phosphorylation, and is said to possibly exert an effect on oncogenes. Since it also interferes with proper chromosome arrangement during cell division, the risk of carcinogenicity cannot be ruled out. An association is also said to exist between the vanadium concentration in air and lung cancer, but no clear causality has been established.

8. Beryllium
   Lung tumors have been observed in carcinogenesis experiments in response to intratracheal administration, inhalation exposure, and intraperitoneal administration, and development of osteosarcoma has been reported after intravenous administration. Carcinogenicity in humans has been suggested by high mortality from lung cancer in factories handling beryllium and by increases in tumors of the central nervous system.

   The carcinogenic mechanism is thought to be inhibition of the enzymes required for DNA synthesis, such as thymidine kinase, thymidine synthase, and DNA polymerase.

9. Lead
   Renal cancer has been reported in rats and mice subcutaneously injected with lead phosphate. There are also reports of lung cancer in hamsters after simultaneous intratracheal administration of lead oxide and benzpyrene, and of development of brain tumors when lead acetate was orally administered to rats. A slight association with the development of lung cancer, stomach cancer, and brain tumors has been reported in workers in a lead smelter, and in lead poisoning, but lead has not been definitely concluded to be carcinogenic in humans.

   The carcinogenic mechanism is assumed to be interference with the DNA repair process, but the details are currently unknown.

10. Cadmium
    DNA fragmentation and chromosome mutations have been reported in cultured human cells, sarcoma and testicular interstitial cell
tumors have been reported as a result of injections in rats, and an association with prostate cancer has been reported in humans, but questions about the carcinogenicity of cadmium have arisen based on recent epidemiologic research.\textsuperscript{19}

11. Cobalt
The mechanism of gene mutations by cobalt is known to be DNA breaks and inhibition of DNA repair by cobalt, and gene mutations and carcinogenicity have been reported in cells and in experimental animals. However, no evidence is yet available in humans.\textsuperscript{20}

Conclusion
Metal carcinogenesis has recently been attracting attention not only in terms of occupational diseases but in ordinary environments. In humans, iron is said to cause liver cancer in hemochromatosis, copper to cause liver cancer, respiratory tract cancer, urinary tract cancer, and thoracic cancer, arsenic to cause skin cancer, liver cancer, respiratory tract cancer, and uranium tract cancer, chromium to cause lung cancer, nickel to cause lung cancer and central nervous system tumors, lead to cause lung cancer, stomach cancer, and central nervous system tumors, and cadmium to cause prostate cancer, but many aspects of their carcinogenic mechanisms are unknown.

REFERENCES
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