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ORIGINAL ARTICLE / RESEARCH

Benzene Exposure and Its Relation to Multiple Myeloma

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ABSTRACT

The positive epidemiological evidence for benzene as a risk factor for multiple myeloma is supported by biological plausibility. According to the investigators, findings are consistent with previous reports 9of haematological malignancies following occupational exposure to benzene and definitely raise the possibility that multiple myeloma could also be linked to benzene exposure. This does not necessarily mean that any increase in the incidence of multiple myeloma in recent years can necessarily be ascribed to benzene exposure, but it raises the issue that needs to be further investigated for relation between benzene exposure and multiple myeloma.

Key words: Benzene, multiple myeloma, occupational exposure

Introduction

Human exposure to benzene in work environment is a global occupational health problem. Benzene is an established human carcinogen that may cause aplastic anaemia, acute myeloid leukaemia, myelodysplastic syndrome and multiple myeloma, among the workers who are occupationally exposed to benzene. Epidemiologic studies have suggested that benzene exposure may be a risk factor of multiple myeloma [1],[2]. Here we are reviewing the literature for risk of multiple myeloma due to occupational exposure of benzene.

Review of Literature

Benzene, an aromatic hydrocarbon, is used as a solvent for rubber, gum, resins, fats, and alkaloids, and in the manufacturing of drugs, dyes, and explosives. It has been used in many industries, including the manufacturing of artificial leather, natural leather products, enamels, rubber, waterproof fabrics, lacquers, shellac, paint removers, batteries, and bronzing, silvering and gilding liquids, in electroplating, lithography, photography, dry cleaning and feather preparation, and in the aeroplane, linoleum and celluloid industries [3]. Certain petroleum fractions contain significant quantities of benzene and are often used to clean machinery parts or to remove grease from the hands. A benzene derivative is present in the exhaust gases encountered in the sulphite pulp industry [4]. Benzene is volatile and, consequently, is readily absorbed by inhalation in badly ventilated rooms. It is also absorbed through the skin [5]. In 1977, the National Institute for Occupational Safety and Health recommended that exposure to the workers should be less than 1 ppm [6]. In industrialised countries, similar exposure limits have been established, but higher levels are common in the manufacturing sector of developing nations

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[7],[8]. Benzene is found in gasoline, automobile emissions, and cigarette smoke [9], and a concern of possible benzene exposure in the general population has been raised, as the result of surveys, using sensitive assays of urinary metabolites of benzene [10]. Great variations are noted among the workers occupationally exposed to benzene and its related mortality. Even low levels of benzene exposure may be potentially dangerous [11].

Regarding multiple myeloma, it is a tumour of plasma cells [12]. These are antibody-producing cells derived from B lymphocytes, which are located primarily in the bone marrow. For the most part, the tumours are diffusely present within bone marrow, although occasionally individual tumours are found in extramedullary sites also. Despite the diffuse presence of myeloma cells within the marrow, in almost all the cases, multiple myeloma begins with somatic mutation in a single cell. This is evident from a major diagnostic test for this disease, the presence of a monoclonal antibody demonstrable on serum protein electrophoresis. Analysis of this reveals that it is uniform in its chemical composition, an elegant example of the origin of aberrant proliferate cell. Definitive diagnosis of multiple myeloma depends on the presence of an increased number of plasma cell, sometimes with abnormal morphology, in the bone marrow. Occasionally, an individual with an abnormal serum protein electrophoresis is observed who does not have bone marrow or other clinical findings consistent with multiple myeloma. These individuals with "benign monoclonal gammopathy" will occasionally progress to classical multiple myeloma [13].

Benzene Metabolism and Toxicology

After inhalation or absorption, benzene targets organs, viz. liver, kidney, lung, heart, brain, etc. It is metabolised mainly in the liver by cytochrome P450 multifunctional oxygenase system. Benzene causes haematotoxicity through its phenolic metabolites that act in concert to produce DNA strand breaks, chromosomal damage, sister chromatid exchange, inhibition of topoisomerase II and damage to mitotic spindle. The carcinogenic and myelotoxic effects of benzene are associated with free radical formation either as benzene metabolites or as lipid peroxidation products. Benzene oxide and phenol have been considered as proheptons. Liver microsomes play an important role in biotransformation of benzene, whereas, in kidney, it produces degenerative intracellular changes [14].

Benzene metabolites cause destruction of the bone marrow, leading to aplastic anaemia, in a dose-responsive fashion [15],[16]. Benzene is also a known human leukaemogen, causing acute myelogenous leukaemia, acute promyelocytic leukaemia and erythroleukaemia [16]. Based on epidemiological studies, benzene has also been casually related to the variety of other haematological neoplasm, including chronic myeloid leukaemia and non Hodgkin's lymphoma and multiple myeloma.[17] An earliest effect of benzene in occupationally exposed groups appears to affect both B and T lymphocytes. The most common mean of detecting genetic damage is conventional cytogenetics. Since chromosome aberrations in peripheral blood have been shown to be associated with increased risk for overall cancer incidence [18], especially for increased mortality from haematological malignancies, it is possible that specific chromosome aberrations may provide even better markers of future risk for haematological malignancies [19]. Recent animal studies have demonstrated that benzene is a carcinogen, producing lympho-haematopoietic malignancies among the workers exposed to benzene [20].

Relationship of Benzene with Multiple Myeloma

There is a high level of biomedical evidences supporting relationship between benzene exposure and multiple myeloma. Biomedical reactive intermediates of benzene are carcinogenic within the bone marrow, and plasma cells are located within the bone marrow. The basic cell type of plasma cells, the B lymphocyte, is affected by benzene and is probably the circulating lymphocyte found to have benzene-induced cytogenetic abnormalities [21]. Thus, we have a carcinogen that is specific to the organ at risk and affect the basic cell type, including producing cytogenetic abnormalities. Case reports by Aksoy et al. [22] and Yin, in China, have noted cases of multiple myeloma in their large cohort of benzene-exposed worker [23]. There are a number of studies that have some suggestion of an increased risk of multiple myeloma among benzene-exposed workers. Cohort studies include that of Decoufle et al. of 259 male employees of a chemical plant [24]. Of

58 deaths, four were due to lymphoreticular tumours with 1.1 expected (95% confidence limits 1.09–10.24). The most thoroughly studied report of benzene-exposed individuals is that of Pliofilm workers in Akron, Ohio, who have been extensively evaluated by National Institute of Occupational Safety and Health Scientists [25]. Although another analysis carried out by Praxton et al. [27] and Wong [28] found lack of epidemiological evidence linking benzene with multiple myeloma, but it was definitely suggestive of benzene exposure as a risk factor. In addition, four cases of multiple myeloma have been noted with 1.0 expected (SMR 409; 95% confidence interval 110–1047). These four cases were not from the most heavily exposed group, leading to speculation that even a relatively low cumulative exposure may produce a relatively well-differentiated tumour such as multiple myeloma. There are hints of higher than expected multiple myeloma incidence in other cohorts of benzene-exposed workers [29].

A follow-up case–control study done on leukaemia deaths has observed a statistically significant association with benzene exposure. Delzell and Monson in a study of 6533 men, employed in the industrial products division of a rubber company, found a statistically increase in multiple myeloma (10 observed, 4.4 expected) as well as lymphoma (10 observed, 4.3 expected) [30]. A variety of case–control studies have attempted to find clues for the aetiology of multiple myeloma. Morris et al. [31] have reported an increased relative risk of multiple myeloma among individuals exposed to a variety of chemicals, including solvents. Painters and carpenters also seemed to have a relatively high risk, in a study done by Friedman, which also tended to confirm the previously reported causal role of radiation in myeloma [32]. Case reports and epidemiological studies of workers exposed to benzene have demonstrated associations with a number of lymphohaematopoietic diseases. Data from all of the 'benzene cohort studies' conducted to date have been selected and evaluated for inclusion in a meta-analysis. In the analysis of cohort data, an understanding of the cohort follow-up period in relation to benzene exposure and risk of multiple myeloma is important [1]. The positive epidemiological evidence for benzene as a cause of multiple myeloma is supported by biological plausibility for such an effect from benzene exposure. Despite the many arguments, the extent of benzene exposure to which workers can develop the multiple myeloma is uncertain. The dose–response relationship between daily environmental benzene exposure in the range of parts per million (ppm) and myeloma has a much larger degree of uncertainty. Studies of refinery workers are difficult to interpret, in relation to benzene exposure and risk of multiple myeloma. Nonetheless, they provide some support for an association between occupational exposure to benzene and risk of multiple myeloma.

Conclusion

The positive epidemiological evidence for benzene as a cause of multiple myeloma is supported by biological plausibility for such an effect from benzene exposure. Studies done so far are difficult to interpret in relation to benzene exposure and risk of multiple myeloma. Nonetheless, they provide some support for an association between refinery work and multiple myeloma. According to the investigators, findings are consistent with previous reports of haematological malignancies following occupational exposure to benzene, and it definitely raises the possibility that multiple myeloma could also be linked to benzene exposure. This does not necessarily mean that any increase in the incidence of multiple myeloma in recent years can necessarily be ascribed to benzene exposure, but it raises the issue that needs to be further investigated for relation between benzene exposure and multiple myeloma.

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