Meta-analysis of Multiple Myeloma and Benzene Exposure

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Epidemiologic studies have suggested that benzene exposure may be a risk factor of multiple myeloma (MM). We performed meta-analyses of case-control studies to assess the association between occupational exposure to benzene and the risk of MM. We divided the occupational sources of benzene exposure into 4 categories, benzene and/or organic solvents, petroleum, petroleum products, and engine exhaust, for conducting the meta-analysis. As a result, a significant positive association was indicated between exposure to engine exhaust and MM (summary odds ratio or summary OR=1.34, 95% confidence interval or 95%CI=1.14-1.57). However, no significant associations were obtained for benzene and/or organic solvents (summary OR=0.74, 95%CI=0.60-0.90), petroleum (summary OR=1.11, 95%CI=0.96-1.28) and petroleum products (summary OR=1.08, 95%CI=0.89-1.33) with risk of MM. These results suggested that benzene exposure itself was not likely to be a risk factor of MM. It is thought that several harmful chemical agents in engine exhaust, other than benzene, could be etiologically related to the risk of MM. Further case-control studies on MM are needed to obtain more information about detailed occupational exposure to toxic substances.

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INTRODUCTION

Multiple myeloma (MM) is a malignant proliferation of plasma cells in the bone marrow, and is characterized by lytic bone lesions, plasma cell accumulation in the bone marrow and the appearance of monoclonal proteins in the serum or urine. MM is more frequent in older people, and recently, its mortality rates have increased with the aging of the population ¹. The survival experience is reported to be poorer for MM than for other cancers ².

Epidemiologic efforts have suggested that several occupational sources are likely to be risk factors for MM. However, none of these sources have been etiologically confirmed as a cause of MM. Although it is well known that the bone marrow is damaged by chronic exposure to benzene ³, the positive association of benzene exposure with the risk of MM has not

been consistently reported. Two hypotheses are considered as the reason for this inconsistency. One of them is the rarity of the disease as well as the small number of workers exposed to benzene. The other is the difficulty in getting information detailed levels and histories of benzene exposure in workers.

Because we plan to start an epidemiological study of MM in Hokkaido, Japan, we performed meta-analyses ⁴ of previously published studies on the association of the occupational benzene exposure with a risk of MM.

MATERIALS AND METHODS

We searched the suitable articles using the Medline database from January 1966 through August 2000 under the following 4 criteria. 1) The article was either population-based or hospital-based case-control study. 2) The study reported the

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association between multiple myeloma and occupational or industrial exposure to benzene, petroleum, petroleum products, or engine exhaust. 3) The control was individually matched to each case at least on age and sex. 4) An Odds ratio (OR) and its confidence interval (CI) of exposure on MM was described. At last, 9 studies that filled all of the above conditions were selected.

Benzene is mainly included in petroleum and is discharged throughout the environment as engine exhaust^{5,6}. So, occupational sources of benzene exposure were divided into the following 4 categories: ① benzene and/or organic solvents, ② petroleum, ③ petroleum products (rubber and/or plastic product), and ④ engine exhaust.

The homogeneity of the data in each exposure category was tested by the Q statistics based on the variance of ORs, and it was considered as statistically significant if p value was than 0.05. As a result, the homogeneity of the ORs in every exposure category was accepted.

There are the fixed effects model and the random effects model in the methods of data synthesis. In general, if the studies are homogenous, fixed and random effects models give similar results. We performed the data synthesis with Greenland's method¹⁶, which was one of the fixed effects model, because this method did not always require the numbers of exposed cases and controls.

The process of the Greenland's method is as follows.

1) Standard error (SE_j) = $\log(OR_j / \text{lower } 95\%CI_j) / 1.96$

2) Weight of the study result (w_j) = $1 / SE_j^2$

3) Summary OR = $\exp[(\sum w_j \times \log OR_j) / \sum w_j]$

4) $95\%CI = \exp[\log(\text{summary } OR_j) \pm (1.96 \times s)]$

(Where, s is the inverse of the square root of $\sum w_j$.)

RESULTS

Table 1 shows exposure substances, job titles, the numbers of cases and controls, and authors of each study, which are included to each exposure categories. Because the heterogeneity of the ORs in every exposure category was denied with the Q statistics, the meta-analyses were performed with Greenland's method. The results are shown from Figure 1 to Figure 4. A logarithmic scale is used in order to exhibit these figures in a limited space.

① Benzene and/or organic solvents (Figure 1): Of 8 studies evaluating these substances with regard to the risk of MM, 7 studies reported benzene or benzene-containing solvents as the exposure substances. Although one study¹⁴ reported only job titles, other than the exposure substances, we selected painter as an occupation possibly involving exposure to organic solvents while working. As shown in Figure 1, the ORs were significantly decreased in 2 studies^{13,14}. As a result of the meta-analysis, the summary OR of 8 studies was 0.74 (95%CI 0.60-0.90), and it was significantly decreased.

② Petroleum (Figure 2): Of 6 studies evaluating petroleum

with regard to the risk of MM, 3 studies reported petroleum as the exposure substance. The other 3 studies reported workplaces exposed to petroleum such as those dealing with coal and oil products, refineries, and places of petroleum and coal manufacturing. As shown in Figure 2, the ORs were significantly increased in 2 studies^{8,11}. However, the summary OR of 6 studies was 1.11 (95%CI 0.96-1.28), and it was not significant.

③ Petroleum products (rubber and/or plastic products) (Figure 3): All 7 studies evaluated workplaces producing rubber and/or plastic, other than exposure to petroleum products, with regard to the risk of MM. As shown in Figure 3, the OR was significantly increased in one study¹⁴, especially, among black males. However, the summary OR of 7 studies was 1.08 (95%CI 0.89-1.33), and it was not significant.

④ Engine exhaust (Figure 4): Six studies evaluated engine exhaust as the exposure substances. One study¹⁵ reported 2 workplaces, garage and service station, and motor-vehicle operating room, where workers are probably exposed to engine exhaust. As shown in Figure 4, the ORs were significantly increased in 3 studies^{7,9,11}. The summary OR of 7 studies was 1.34(95%CI 1.14-1.57), and it was statistically significantly elevated.

DISCUSSION

Previous epidemiological research has suggested that occupational exposure to chemicals, radiation exposure, chronic allergic stimulation, and viral infection are the possible risk factors for MM. A number of studies have pointed out the relation of occupational exposure to pesticides, wood dust, organic solvents, petroleum, asbestos, metal, radiation, rubber, and plastic, to the risk of MM.

In addition, several studies reported the positive association of farming or agriculture with the risk of MM^{6,9,10,15,18-25}. Khunder²⁶ showed a significant positive association of farming with the risk of MM [relative risk (RR) =1.23, 95%CI 1.14-1.32] in his meta-analysis. He suggested that farmers are exposed to several agents, including solvents, viruses and other microbes, dust and agricultural chemicals, that might be associated with risk of MM. Except for farming, however, most occupational exposures have not been shown consistently to be risk factor for MM.

Benzene is included in petroleum and is discharged throughout the environment as engine exhaust. The result of our meta-analysis of exposure to engine exhaust indicated a significantly increased risk of MM (OR=1.34, 95%CI=1.14-1.57). Two hypotheses could be proposed for this significant result. The first is that the air concentrations of benzene are high in the workplaces of drivers or service-station workers, who are frequently exposed to engine exhaust. The air concentrations of benzene are estimated to be $0.2\mu\text{g}/\text{m}^3$ in the country areas and $349\mu\text{g}/\text{m}^3$ in industrial areas with much traffic²⁷. The median

Table 1. Exposure substances, job titles and the numbers of cases and controls according to exposure categories.

Exposure category	Substance or job title	No. of Cases	No. of Controls	Author
① Benzene and/or organic solvents	Aromatic hydrocarbons	698	1,683	Morris (1986) ⁷⁾
	Solvents	131	431	Flodin (1987) ⁹⁾
	Benzene	100	100	Linnet (1987) ⁸⁾
	Chemicals, Acids, Solvents	154	616	Boffetta (1989) ¹⁰⁾
	Benzene	1,098	4,169	Heineman (1992) ¹¹⁾
	Organic solvents	1,010	4,040	Pottern (1992) ¹²⁾
	Organic solvents	275	275	Eriksson (1992) ¹³⁾
	Painter	12,148	60,740	Figgs (1994) ¹⁴⁾
② Petroleum	Gasoline	698	1,683	Morris (1986) ⁷⁾
	Petroleum	100	100	Linnet (1987) ⁸⁾
	Gasoline	1,098	4,169	Heineman (1992) ¹¹⁾
	Coal and oil product	1,010	4,040	Pottern (1992) ¹²⁾
	Refinery worker	275	275	Eriksson (1992) ¹³⁾
	Petroleum and coal refining and manufacturing	692	1,983	Dermers (1993) ¹⁵⁾
③ Petroleum products	Plastic and rubber compounds	698	1,683	Morris (1986) ⁷⁾
	Plastic-rubber chemicals	131	431	Flodin (1987) ⁹⁾
	Chemical/rubber/plastic	1,098	4,169	Heineman (1992) ¹¹⁾
	Chemical/rubber/plastic	1,010	4,040	Pottern (1992) ¹²⁾
	Rubber and plastic product manufacturing	692	1,683	Dermers (1993) ¹⁵⁾
	Rubber and miscellaneous plastic products (black male)	12,148	60,740	Figgs (1994) ¹⁴⁾
	Rubber and miscellaneous plastic products (white female)	12,148	60,740	Figgs (1994) ¹⁴⁾
④ Engine exhaust	Automobile exhaust	698	1,683	Morris (1986) ⁷⁾
	Engine exhaust	131	431	Flodin (1987) ⁹⁾
	Gasoline exhaust	154	616	Boffetta (1989) ¹⁰⁾
	Engine exhausts	1,098	4,169	Heineman (1992) ¹¹⁾
	Exhaust gases	1,010	4,040	Pottern (1992) ¹²⁾
	Engine exhausts	275	275	Eriksson (1992) ¹³⁾
	Garage and service station	692	1,683	Dermers (1993) ¹⁵⁾
	Motor vehicle operators	692	1,683	Dermers (1993) ¹⁵⁾

Figure 1. Result of meta-analysis of case-control studies on association between benzene and/or organic solvents and the risk of multiple myeloma.

Figure 2. Result of meta-analysis of case-control studies on association between petroleum and risk of multiple myeloma.

Figure 3. Result of meta-analysis of case-control studies on association between petroleum products and risk of multiple myeloma.

value of the concentrations of benzene in the car is estimated to be $14.0\mu\text{g}/\text{m}^3$ and the concentrations of benzene outside the car are estimated to be under $1.8\mu\text{g}/\text{m}^3$ ²⁷. The air concentration of benzene while filling gas tanks is estimated to be on the order of 1ppm ($3000\mu\text{g}/\text{m}^3$)⁵. The second hypothesis is that engine exhaust includes several other harmful chemical agents such as benzopyrene, ethylene, toluene, xylene, formaldehyde, suspended particulate matter (SPM), and so on. Some of these agents, other than benzene, may be associated with the risk of MM, although the carcinogenic effect of these agents on

hematopoietic cells is not well established.

The most common sources of personal exposures to benzene are cigarette smoking and riding in automobiles. Active and passive smoking are the most important sources of exposure in the general environment. Smokers typically have a breath concentration of benzene around $14\mu\text{g}/\text{m}^3$, while in nonsmokers it is around $2\mu\text{g}/\text{m}^3$ ⁵. However, the association between smoking and risk of MM has not been indicated, as the relative risks of smoking for MM were not significant in most of studies^{8-10,28-31}.

The results of our meta-analyses did not show an increased

Figure 4. Result of meta-analysis of case-control studies on association between engine exhaust and risk of multiple myeloma.

association of benzene or benzene-containing organic solvents, petroleum and petroleum products (rubber and/or plastic products) with the risk of MM. Wong³² reported that risk of MM was not associated with benzene exposure in a cohort of Pliofilm workers, and that there was no exposure-response relationship. Similar results have been reported in the studies of other countries^{33,34}. Wong and Raabe³⁵ reported the pooled-analysis of 22 cohort mortality studies of more than 250,000 petroleum workers and they suggested that there was no causal relation between MM and petroleum workers as well as no exposure-response relationship. Other studies^{3,6,36,37} also did not consistently report the positive association of benzene exposure with the risk of MM.

The results of our meta-analyses suggested that benzene exposure itself is not likely to be a risk factor of MM. Instead, several harmful chemical agents in engine exhaust, rather than benzene, may be etiologically related to the risk of MM. However, further case-control studies on MM are needed to focus on information about detailed exposure to occupational toxic substances.

The assessment of exposure substances in the studies used in our meta-analysis was as follows. Some researchers^{8,10,13} used the questionnaires contained the questions regarding exposure substances. Other researchers^{11,12} used the industry/occupational codes, which were distributed among Danish industrial hygienists who assessed exposure to 20 substance categories and 27 specific substances. The rest of the researchers^{14,15} did not describe exposure substances. However, we could select the jobs with probable exposure to benzene or related exposure substances, from their papers.

We obtained the unexpected result that benzene and/or

organic solvents significantly decreased the risk of MM (ORs=0.74, CI=0.60-0.90). But, we can not interpret this result at this moment, as Eriksson et al¹³ or Figgs et al¹⁴ also could not. We started a case-control study on the association between occupational exposure and MM in Hokkaido, Japan, in July 2001 and would provide the another assessment for this inverse relationship of benzene and/or organic solvents to the risk of MM in the future.

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