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BILIARY TRACT CANCERS IN JAPAN: A STUDY FROM THE POINT OF VIEW OF ENVIRONMENTAL EPIDEMIOLOGY

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ABSTRACT

The findings that the standardized mortality ratio (SMR) for biliary tract cancers in Japan was associated with the rice production per area prompted us to test the role of agricultural chemicals on the occurrence of cancer. For the examination of agricultural chemicals, an environmental pollution index (EPI) was introduced. The index refers to the quotient obtained by dividing a total amount of agricultural chemicals annually distributed to each prefecture by the area of the prefecture. Then, Pearson's correlation analysis was made between EPIs from 1962 to 1975 and SMR in 1975. The number of chemical products subjected to analysis was about 300 every year. Among these chemicals, EPIs of phenoxy herbicides, MCPA and MCPB were frequently associated with the SMR for biliary tract cancer.

INTRODUCTION

Cancers of the biliary tract (the gallbladder and the extrahepatic biliary passages, ICD 156) have not been extensively investigated from the point of view of epidemiology. They have received less attention in epidemiological analysis, probably because of the low death rate for biliary tract cancers as compared with those of other cancers. Tominaga et al.[1] reported on the characteristics of biliary tract cancers in Japan.

According to their description, the age-adjusted death rates in Japan were 3.3/100,000 in males and 3.5/100,000 in females in 1972 (World population in the same year was used as a standard population for a direct adjustment of the rate). Notwithstanding the low death rate of biliary tract cancers, we should pay attention to the fact that the rates in males and females in Japan rank first and ninth among 31 countries, respectively. Even within Japan, the death rates varied considerably when the regional standardized mortality ratios (SMRs) were compared among 46 prefectures.

In the course of our analysis of the space clustering of SMRs for biliary tract cancers in Japan, we began to notice that the distribution of high SMRs often corresponded to prefectures where rice production per area was high. In fact, this correlation was statistically confirmed.[2] The SMRs in 1975 were correlated to the rice production per area in the same year ($r=0.544$ in males, $P<0.001$; $r=0.377$ in females, $P<0.01$). The correlation was also observed when the SMRs in 1975 were related to the rice production per area in 1970 ($r=0.567$ in males, $P<0.001$; $r=0.440$ in females, $P<0.001$).

In order to find a missing link between rice production and deaths from biliary tract cancers, if such a relation should actually exist, we generated a working hypothesis concerning how they are related to each other. Some environmental factors, such as agricultural chemicals, dietary pattern which may be specific to each area, geographic characteristics of soils or drinking water etc., may be considered as a link between the two. Among these, the role of agricultural chemicals is investigated from the point of view of environmental epidemiology in the present study.

MATERIALS AND METHODS

Calculation of SMRs for cancer map. The mortality data on biliary tract cancers were obtained from the Vital Statistics of the Ministry of Health and Welfare of Japan.[3,4] Total deaths from biliary tract cancers in 1975 were extracted from reported cases under ICD 156. In the present study, however, deaths from cancers of the gallbladder (ICD 156.0) and the extrahepatic bile ducts (ICD 156.1 and 156.2) were not treated separately. Total population of Japan was obtained from the official Census.

To make a cancer map, the total number of deaths from 1969 to 1978 was taken from Vital Statistics. Then, the age-adjusted mortality rate of each prefecture was calculated by using the total population in 1973 as a standard population. Throughout the present examination, the data in 46 prefectures except for Okinawa were subjected for analysis.

Relationship between environmental pollution index (EPI) from agricultural chemical products and SMR for biliary tract cancers. The amount of agricultural chemical products annually distributed to each prefecture has been recorded in "Noyaku Yoran",[5] A Handbook of Agricultural Chemicals, since 1963. For example, the year of 1962 in this Handbook refers to the year that starts from October 1, 1962 and ends on September 30, 1963.

Since the amount of chemicals actually used for plants is difficult to obtain from local agencies in all prefectures, we substituted the records in the Handbook for an estimate of the amounts used. Total amounts of each agricultural chemical product distributed to each prefecture were divided by the prefecture's total area and the quotient was designated as the environmental pollution index (EPI) of the chemical product. It was expressed as kg/km^2 or l/km^2 in the case of powder or emulsion type, respectively.

For the present analysis, the SMR of each prefecture in 1975 was obtained by making use of the total population in the same year as a standard population. EPIs of each chemical product from 1962 to 1966 were then related to the SMR in 1975 by using Pearson's correlation analysis. Prior to the actual calculation of correlation coefficients, the logarithmic transformation of EPIs and SMRs was made in order to obtain the normality of the distribution.

Relationship between EPI of agricultural chemical components and SMR for biliary tract cancers. Agricultural chemical products which frequently correlated with the SMR during 5 years from 1962 to 1966 were rendered for further analysis. The total cumulative amounts of chemical components common in such products were found by checking the contents of the components in all commercially distributed agricultural chemical products. Amounts in emulsion type chemicals, however, were excluded from the calculation, because the amount used was negligible as compared with that of the powder type. EPIs of the components in the years from 1962 to 1975 were then related to the SMRs in 1975 by using Pearson's correlation analysis after logarithmic transformation of EPIs and SMRs.

Lag correlation analysis. In order to investigate the strength of the relationship between the EPIs of MCPA and MCPB and biliary tract cancers, lag correlation analysis was used. The average EPIs in each year from 1962 to 1975 were calculated from the data already mentioned in the previous section. The mortality data were the death rates from the biliary tract cancers which were age-adjusted by the direct method. The standard population was the total population of Japan in 1935, which is commonly used for an adjustment of the rates in an epidemiological study in Japan. For the present analysis, the time lag was taken to be from 0 to 10 years. Then, 3-year smoothing averages of each factor were successively compared.

Relationship between EPIs of special components and the SMR for other cancers. For evaluation of specificity of the relationship of some particular components, such as Blasticidin S, MCPA and MCPB to biliary tract cancer SMR, an analysis was made to examine the EPIs to SMRs for other cancers, such as those of the oesophagus, liver, lung, pancreas, stomach, colon and rectum. For this analysis, EPIs for ten years (1962-1971) were calculated, since the SMRs were expressed as 10 year averages; these were simply adopted from the previous reports by Shigematsu et al.[6]

RESULTS

Geographic distribution of SMRs for biliary tract cancers. Figure 1 shows cancer maps

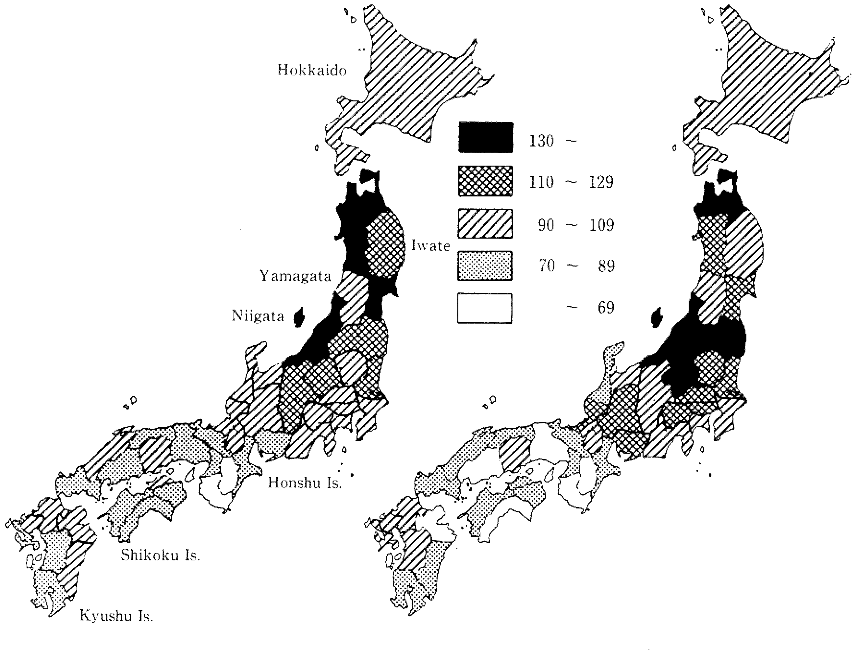

Fig. 1. Standardized Mortality Ratios[1] (SMRs) for Biliary Tract Cancers (ICD 156) by Prefecture in Japan (1969-1978).

Note: 1) A standard population is the total population in 1973, Japan. Prefectures mentioned in the text are shown in this map.

which were drawn based on 10 year averages for SMRs of biliary tract cancers in both sexes. The SMRs in 46 prefectures were classified into 5 levels; under 70, 70-89, 90-109, 110-129, and 130 and over. Figure 1 shows distinct geographic patterns of high SMRs for the cancers in the north-eastern part of Japan except for Hokkaido, and lower SMRs in the south-western part of Honshu, Shikoku and Kyushu. Generally, the SMRs in males and females showed similar patterns of geographic distribution, with a few exceptions.

In the north-eastern part of Japan, where the SMRs for biliary tract cancers were high for the most part, SMRs in Niigata prefecture were the highest in both sexes (158. 43 in males and 172. 35 in females). In contrast, SMRs in Yamagata (107. 35 in males and 104. 91 in females) and SMRs of females in Iwate (103. 55) were almost average, although those districts were located within the high mortality area. In prefectures located at the transitional area of north-eastern and south-western Honshu, there were some discrepancies of SMRs between males and females. Other than these areas, SMRs distributed in south-western Honshu, Shikoku and Kyushu were consistently lower than the average in both sexes.

Relationship between all agricultural chemical products and SMRs. Numbers of agricultural chemical products subjected for analysis were 300 in 1962, 257 in 1963, 301 in 1964, 307 in 1965 and 281 in 1966. Out of these chemical products, 13, 15, 19, 21 and 21 products in each corresponding year showed significant correlations with SMR for biliary tract cancers of males in 1975. In females, correlations of 17, 19, 21, 24 and 19 products were found to be significant, respectively. In most instances, those products contained copper, arsenic, mercury, PCP, DDT, Blasticidin S, MCPA and MCPB.

Relationship between each component of agricultural chemicals and SMR.

(1) Copper. As shown in Table 1, there was no statistically significant correlation between the EPI of copper and SMR in both sexes.

(2) Arsenic. No significant correlation was observed except for the relationship between EPI in 1964 and SMR of females in 1975.

(3) Mercury. Mercuric compounds, such as phenyl mercury acetate, had been used as fungicide until 1971 in Japan. In the present study, the amount of mercuric compound was converted to the dose of inorganic mercury (Hg). Then, the EPI of Hg was calculated. No significant correlation was found in both sexes.

(4) PCP. It had been extensively used as a typical herbicide throughout the country until quite recently. There was no statistically significant correlation between them.

Analysis of copper, arsenic, mercury and PCP was not extended further, since statistically significant associations were rarely observed, as shown in Table 1.

(5) DDT. Significant correlations were frequently demonstrated between EPIs and male SMRs only (Table 2). However, these correlations disappeared after 1969, and finally the use of DDT itself was banned in 1971.

(6) Blasticidin S. This antibiotic fungicide was discovered in Japan and used to be a good substitute for mercuric fungicide. Changes in EPIs of Blasticidin S are shown in Figure 2. During the six years from 1962 to 1967, the correlation coefficients between the

Table 1. Correlation Coefficients[1] between Environmental Pollution Index (EPI)[2] by Copper, Arsenic, Mercury, or PCP (1962-1966) and SMR[3] for Biliary Tract Cancers (1975)

Year	Copper		Arsenic		Mercury		PCP	
	Male	Female	Male	Female	Male	Female	Male	Female
1962	-0.003	-0.032	-0.233	-0.103	0.159	0.153	0.015	-0.028
1963	0.092	-0.086	-0.260	-0.164	0.092	0.003	0.119	0.113
1964	0.021	-0.166	0.219	0.321*	0.111	0.102	0.144	0.151
1965	0.115	-0.024	-0.142	-0.157	0.253	0.208	0.146	0.100
1966	0.200	-0.060	-0.143	-0.127	0.222	0.093	0.289	0.260

Notes: 1) Pearson's correlation coefficients after the logarithmic transformation of EPIs and SMRs. Significant levels: $^*p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$

2) EPI was calculated by dividing the total amount of component annually distributed to each prefecture by its area, and expressed as kg/km^2.

3) A standard population is the total population in Japan, 1975.

Table 2. Correlation Coefficients[1] between Environmental Pollution Index (EPI)[2] by DDT, Blasticidin S, MCPA, or MCPB (1962-1975) and SMR[3] for Biliary Tract Cancers (1975)

Year	DDT		Blasticidin S		MCPA		MCPB	
	Male	Female	Male	Female	Male	Female	Male	Female
1962	0.395**	0.179	0.408**	0.253	0.376**	0.174	0.509***	0.462**
1963	0.348*	0.225	0.119	0.000	0.292*	0.203	0.328*	0.307*
1964	0.319*	0.163	0.309*	0.204	0.333*	0.181	0.207	0.213
1965	0.239	0.102	0.321*	0.148	0.329*	0.215	0.235	0.291*
1966	0.392**	0.276	0.457**	0.360*	0.299*	0.199	0.344*	0.133
1967	0.361*	0.116	0.345*	0.008	0.344*	0.226	0.332*	0.302*
1968	0.353*	0.161	0.040	0.107	0.368*	0.219	0.360*	0.416**
1969	0.138	0.015	0.145	-0.061	0.258	0.180	0.393*	0.535***
1970	0.253	0.362*	0.165	0.060	0.185	0.123	0.341*	0.480***
1971	-	-	0.064	0.059	0.262	0.211	0.217	0.233
1972	-	-	0.305*	0.303*	0.298*	0.255	0.326*	0.441**
1973	-	-	0.121	0.260	0.302*	0.375*	0.096	0.170
1974	-	-	0.081	0.172	0.368*	0.350*	0.075	0.210
1975	-	-	0.196	0.167	0.260	0.282	0.362*	0.397*

Notes: 1) Pearson's correlation coefficients after the logarithmic transformation of EPIs and SMRs. Significant levels: *$p<0.05$, **$p<0.01$, ***$p<0.001$
2) EPI was calculated by dividing the total amount of component annually distributed to each prefecture by its area, and expressed as kg/km^2.
3) A standard population is the total population in Japan, 1975.

EPIs and male SMRs were frequently significant, as shown in Table 2. But, this significant relationship disappeared after 1968. In females, no significant association was present except for the years of 1966 and 1972.

(7) MCPA and MCPB. These chemicals are derivatives of the chlorinated phenols, and used as herbicides mostly in paddy fields. Ethyl ester type of MCPA and MCPB was commonly used in Japan. Changes of their environmental pollution are shown in Figure 2. Up to the analysis of 1968, associations between EPIs of MCPA and male SMRs were always evident as shown in Table 2. But in females, there was no significant association except for the years of 1973 and 1974. In the case of MCPB, statistically significant correlations were often observed in both sexes throughout the 14 years from 1962 to 1975.

Lag correlation analysis. As shown in Figure 3, the lag correlation coefficients between MCPA-EPIs and the death rates in both sexes increased gradually up to the 5-year time lag. After that, the coefficients reached a plateau. However, they showed a tendency to decrease after nine years. In contrast to the changes of MCPA-EPIs, the correlation coefficients between MCPB-EPIs and death rates for the biliary tract cancers in both sexes stayed between 0.7 and 0.9.

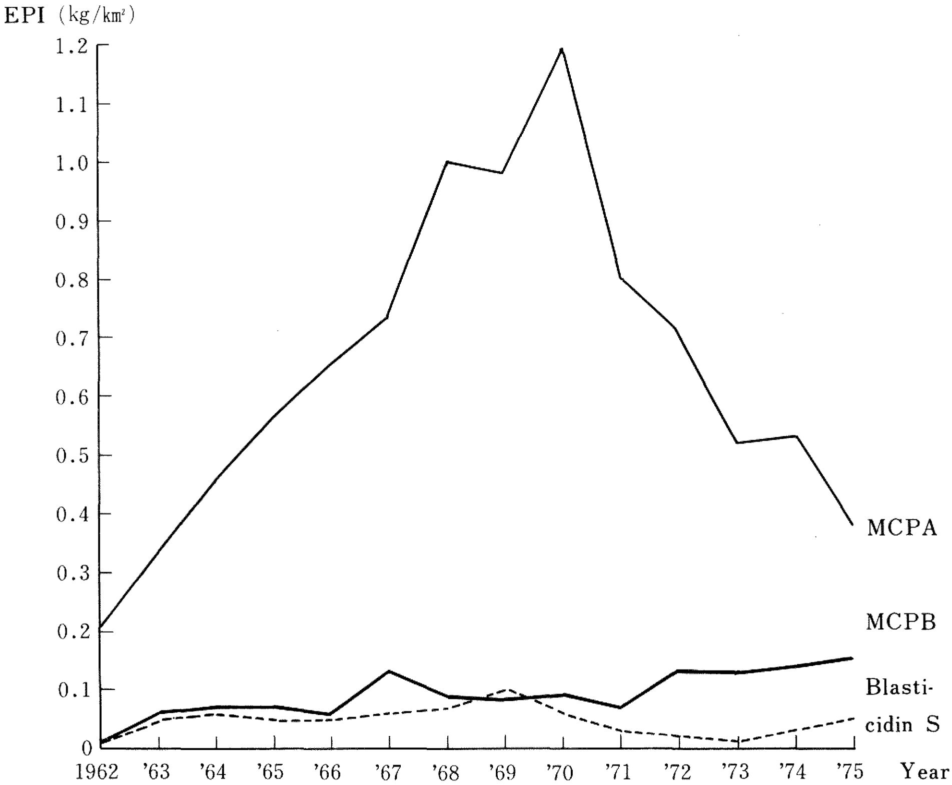

Fig. 2. Changes in Average Environmental Pollution Indices (EPIs) [1] by Blasticidin S, MCPA and MCPB (1962~1975).

Note: 1) EPI is obtained by dividing the total amount of each component of agricultural chemical products by the area of each prefecture.

Relationship between EPIs of special components and SMRs for other cancers. Table 3 shows that the EPI of Blasticidin S was clearly correlated positively with SMRs for cancers of the stomach in both sexes. No association existed between EPIs of Blasticidin S and SMRs for biliary tract cancers. There were positive associations between MCPA and cancers of the stomach and the pancreas as well as the biliary tract. EPIs of MCPB were associated not only with biliary tract cancers, but also those of the stomach in both sexes. Negative association was observed between the EPI of MCPA or MCPB and cancers of the liver. These findings clearly demonstrated that the EPI -SMR association of MCPA or MCPB was not specific only to the biliary tract cancers.

Discussion

The present study was characterized by the analysis of ecological correlation, in which the statistical objects are a group of persons or matters in each prefecture. This

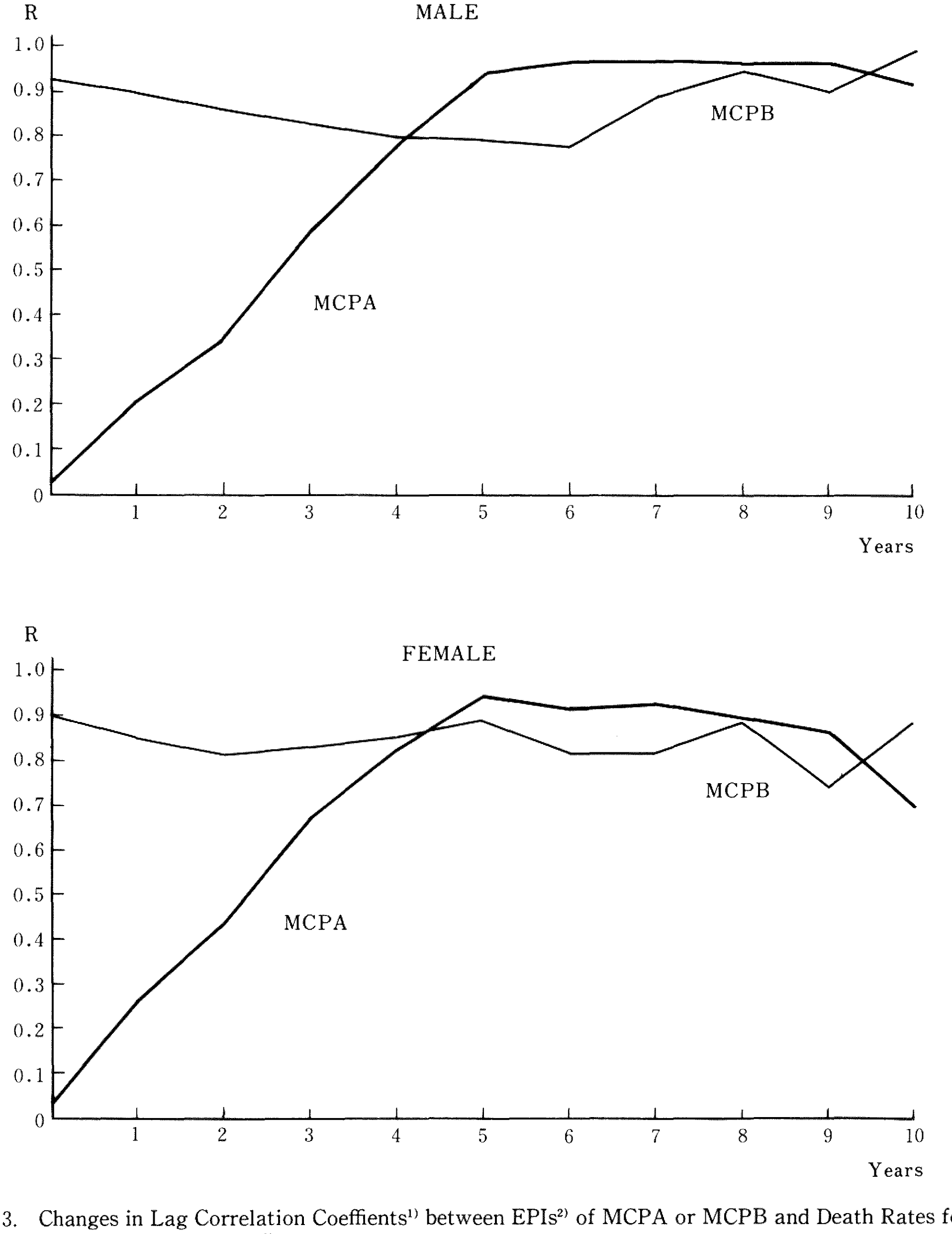

Fig. 3. Changes in Lag Correlation Coeffients[1] between EPIs[2] of MCPA or MCPB and Death Rates for Biliary Tract Cancers.[3]

Notes: 1) Time lag was taken to be from 0 to 10 years, and 3-year moving averages of both factors were then compared.
2) EPIs were the average values of Japan in each year from 1962 to 1975.
3) Death rates were age-adjusted by the direct method. The standard population was the total population of Japan, 1935.

Table 3. Correlation Coefficients[1] between Environmental Pollution Index (EPI)[2] by Blasticidin S, MCPA or MCPB and SMR[3] for Various Types of Cancers

Type of cancers	Blasticidin S		MCPA		MCPB	
	Male	Female	Male	Female	Male	Female
Biliary	0.170	0.118	0.444**	0.363*	0.465**	0.422**
Oesophagus	-0.269	-0.358*	0.242	0.233	0.090	0.050
Liver	-0.040	-0.073	-0.502***	-0.527***	-0.596***	-0.621***
Lung	-0.077	-0.059	0.041	0.088	0.008	-0.030
Pancreas	0.272	0.151	0.306*	0.352*	0.283	0.334*
Stomach	0.379**	0.453**	0.562***	0.530***	0.390**	0.375*
Colon	0.225	0.278	0.274	0.491***	0.198	0.457**
Rectum	-0.087	0.156	0.155	0.378**	0.080	0.230

Notes: 1) Pearson's correlation coefficients after the logarithmic transformation of EPIs and SMRs. Significant levels: *$p<0.05$, **$p<0.01$, ***$p<0.001$
2) EPI was calculated by dividing the total amount of each component distributed to each prefecture for ten years (1962-1971) by the area of each prefecture.
3) SMR calculation was based on the total number of deaths occurring in ten years (1969-1978). A standard population is the total population in Japan, 1973.

is in contrast to individual correlation, which is based on the descriptive characteristics of individuals. In such an analysis as ecological correlation, information is limited, as compared with individual correlation analysis. It is said that there is always the risk of committing an ecological fallacy; that is, an ecological correlation does not always indicate the truth.[7] Without regard to the risk which is inherently present in such an analysis, an ecological correlation is often used as a substitute for an individual correlation, especially at the introductory stage, to find an epidemiological clue for etiological reasoning.

In the present analysis, the preliminary finding that the SMR for cancers of the biliary tract was associated with the rice production per area prompted us to generate a working hypothesis to explain such an association. Among several factors which may possibly lie between the rice production and the death from biliary tract cancers, we first tested the role of agricultural chemicals by studying an ecological correlation.

To our interest, of 250 to 300 chemicals used over the period, the chemicals in which EPIs were significantly associated with SMRs for biliary tract cancers were almost the same every year. As a general rule, prefectures which were polluted with either MCPA, or MCPB had higher death rates from biliary tract cancers. In the case of MCPA, the male SMRs in 1975 were significantly associated with the EPIs from 1962 to 1968. But in females, there was no correlation except for the years of 1973 and 1974. In the case of MCPB, the association was frequently demonstrated in both sexes. However, the pollution of MCPA or MCPB is unlikely to be specific to death from biliary tract cancers, since their EPIs were also associated with cancers of the pancreas in males and of the stomach in both sexes.

According to the results of lag correlation analysis, a time lag of 5 to 9 years showed a strong correlation between EPIs of MCPA and deaths from biliary tract cancers. Biological interpretation of this phenomenon should be withheld until the etiological role of MCPA is revealed. In the case of MCPB, however, it is difficult to interpret the results of lag correlation analysis, since the correlation coefficients remained at levels from 0.7 to 0.9.

It should be emphasized that MCPA and MCPB are derivatives of chlorinated phenols and the common chemical structure between them is similar to 2, 4-D and 2, 4, 5-T. There is a case report that a farmer suffered from acute myelocytic leukemia after exposure to MCPA.[8] Exposure to 2, 4-D or 2, 4, 5-T in particular was reportedly connected with the occurrence of malignant neoplasms.[9-19] Though the causal association has not been established yet, the contamination of dioxins in such chemicals has been thought to account for the causation. Under these circumstances, it is worth investigating the relationship between the presence of dioxins and the occurrence of cancer.

First of all, it may be a priority to examine the presence of dioxins as the impurities in MCPA or MCPB. Although there is a report that suggested the possible contamination of dioxins in MCPA, no experimental evidence was provided[20]. Secondly, thermal changes of MCPA and MCPB in the environment should be examined. The reason why such consideration is needed is that it has become a common practice for farmers to burn down the dried straws on the ground of paddy field a few months after the use of such chemicals. There is a possibility that dioxins are newly formed in the ash as the pyrolysates of phenoxy herbicides. Such a speculation is supported by experiments by others,[21,22] who demonstrated the formation of dioxins by pyrolyzing phenoxy herbicides.

Apart from these problems, there is experimental evidence that the flyash of the dried straws induces base-change mutations after treatment with S 9 mix in the Ames' test[23]. Although there is no reason to believe that the mutagenicity of flyash results from the pyrolysate of agricultural chemicals, it is worth investigating as a missing link whether or not such relationship exists.

It is also a matter of concern to know the direct effects of MCPA and MCPB when they are internalized by humans. Recently, Vainio et al.[24] reported that the phenoxy acid herbicides, 2, 4-D and MCPA induce hypolipidemia and peroxisome proliferation in the liver of rats. They pointed out that not only the chemical structure of 2, 4-D and MCPA, but also their biological mechanism is quite similar to the hypolipidemic drug, clofibrate. It has been reported that clofibrate induces the pathological changes in the liver, gallbladder and intestines.[25] It is worthwhile to conjecture on the same kind of side effects existing also in the case of both MCPA and MCPB.

Likely explanations are described above. But, the present analysis does not allow us to realize how the use of such agricultural chemicals are actually related to the occurrence of biliary tract cancers. In order to elucidate the causal association, the fate of these chemicals both in the environment and in the human body should be investigated by employing laboratory methods.

In addition to the role of MCPA and MCPB, the agricultural chemicals introduced after 1975 should be examined concurrently by laboratory analysis. This is because one of the herbicides, CNP, was already found to be related to the SMR for biliary tract cancers in our recent preliminary studies.

ABBREVIATIONS OF CHEMICALS APPEARED IN THE TEXT

1) Blasticidin S: (S)-4-[[3-amino-5-(aminoiminomethyl) methylamino] -1-oxopentyl] amino] -1-[4-amino-2-oxo-(2H)-pyrimidinyl] -1, 2, 3, 4-tetradeoxy-β-D-erythrohex-2 -enopyranuronic acid

2) Clofibrate: ethyl-α-p-chlorophenoxyisobutyrate

3) CNP: 2, 4, 6-trichlorophenyl-4'-nitrophenylether

4) 2, 4-D: 2, 4-dichlorophenoxyacetic acid

5) DDT: 1, 1, 1-trichloro-2, 2-bis (p-chlorophenyl) ethane

6) MCPA: 4-chloro-2-methyl-phenoxyacetic acid

7) MCPB: 4-(4-chloro-2-methyl-phenoxy) butyric acid

8) PCP: Pentachlorophenol

9) 2, 4, 5-T:2, 4, 5-trichlorophenoxyacetic acid

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