ECOLOGICAL CORRELATION BETWEEN THE USE OF AGRICULTURAL CHEMICALS AND BILIARY TRACT CANCERS IN JAPAN

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ABSTRACT

The prefectures with higher standardized mortality ratios (SMRs) for biliary tract cancers are areas where rice production is high. Based on this epidemiological finding, we tested the hypothesis of whether or not the use of agricultural chemicals are related to the occurrence of cancers. An ecological correlation analysis between the use of agricultural chemicals (1962–1975) and the SMRs (1985) was made among 46 prefectures. Afterwards, statistically significant associations with SMRs were frequently found in CNP, MCPA and PCNB.

INTRODUCTION

Cancers of the biliary tract (the gallbladder and the extrahepatic biliary passages, ICD 156) have recently been brought into focus from the point of view of epidemiology. One reason for this is that the death rate from biliary tract cancers in Japanese males is the highest among 31 countries studied (Tominaga et al.[1], 1979). Even within Japan, the geographical distribution of its standardized mortality ratios (SMRs) is well characterized; the prefectures with higher SMRs are related to the areas where the rice production is high (Yamamoto et al.[2], 1986). To disclose the determinants of this distribution, we considered such factors as agricultural chemical usage, dietary patterns and geological

characteristics in the areas where rice production is high. First of all, we tested a hypothesis concerning the role of agricultural chemicals. A preliminary finding has already been reported elsewhere (Yamamoto et al.[2], 1986). In our previous analysis, however, chemicals which had been just recently introduced were not taken into account. It is our present purpose to screen all of the agricultural chemicals which have been used in the agricultural land.

MATERIALS AND METHODS

SMRs for biliary tract cancers in 1985 were calculated from the mortality data obtained from the Vital Statistics Bureau of the Ministry of Health and Welfare. The total population in 1985 was used as a standard population.

Environmental pollution index (EPI) of each agricultural chemical was calculated, as described in our previous report (Yamamoto et al.[2], 1986). By using the Pearson's correlation and the Spearman's rank correlation analyses, the correlation coefficients between EPIs in 1975 and SMRs in 1985 were obtained among 46 prefectures excluding Okinawa.

Of more than 500 products used in 1975, products containing CNP, Copper, EDDP, MCPA, MCPB, NIP and PCNB had EPIs showing positive associations with SMRs. Based on these findings the cumulative total amounts of these chemical components in each year from 1962 to 1975 were calculated and an analysis of the correlation with SMRs in 1985 was made.

RESULTS

SMRs for biliary tract cancers in 1985

Of the 46 prefectures studied, male SMRs ranged from 73.7 to 145.7. The significant test obtained by calculating $(O-E)^2/E$ values revealed that the prefectures with significantly higher SMRs were Niigata (139.1, $P<0.001$), Yamagata (145.7, $P<0.01$), Aomori (138.7, $P<0.01$), Fukuoka (123.9, $P<0.01$) and Nagasaki (127.3, $P<0.05$). The prefectures with lower SMRs were Gifu (73.7, $P<0.05$), Kyoto (76.9, $P<0.05$) and Kanagawa (80.1, $P<0.05$).

In the case of females, the ranges of SMRs were from 51.6 to 147.7. Significantly higher SMRs were observed in Aomori (143.4, $P<0.001$), Niigata (141.9, $P<0.001$), Fukui (147.7, $P<0.01$), Nagasaki (134.7, $P<0.01$), Fukushima (127.6, $P<0.01$), Ibaragi (123.9, $P<0.01$), Yamagata (126.0, $P<0.05$) and Gunma (125.3, $P<0.05$). Lower SMRs were in Kochi (51.6, $P<0.001$), Hiroshima (65.8, $P<0.001$), Shimane (64.4, $P<0.01$), Miyagi (65.6, $P<0.01$), Hyogo (81.8, $P<0.01$), Wakayama (69.6, $P<0.05$) and Kanagawa (86.6, $P<0.05$).

Figure 1 illustrates the geographic differences in SMRs by prefecture. The levels of classification are under 70, 70-89, 90-109, 110-129 and 130 and over. As shown in Figure 1, the prefectures with higher SMRs in both sexes were located in the north-eastern part of Honshu, while those with lower SMRs were in the south-western part of Honshu,
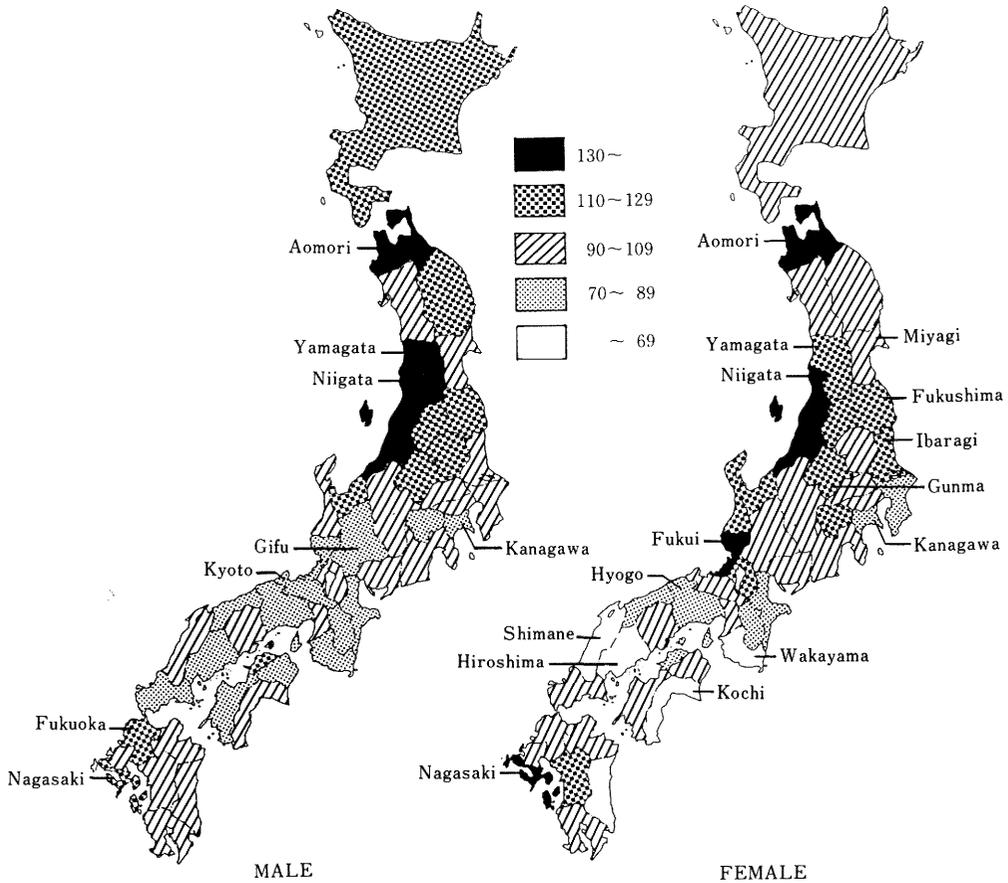
Fig. 1. Standardized Mortality Ratios[1] for Biliary Tract Cancers (ICD 156) by Prefectures in Japan (1985).
Note : 1) Standard population is the total population in 1985, Japan.
Prefectures mentioned in the text are shown in this map.

Shikoku and Kyushu with a few exceptions.

Relationship between EPIs and SMRs

The results of Pearson's correlation coefficients are summarized in Table 1. Significant associations between EPIs of MCPA and SMRs for both sexes were evident. The present result was consistent with that of our previous report (Yamamoto et al.[2], 1986). The association between EPIs of CNP and SMRs for both sexes, however, was a new finding. EPIs of MCPB, NIP and PCNB were also occasionally associated with SMRs, as shown in Table 1. In the case of copper and EDDP, a statistically significant

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Table 1. Correlation Coefficients[1] between Environmental Pollution Index (EPI)[2] of CNP, MCPA, MCPB, NIP, PCNB (1962-1975) and SMR[3] for Biliary Tract Cancers (1985)

Year	CNP		MCPA		MCPB		NIP		PCNB	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
1962	–	–	0.130	0.285	-0.310*	-0.311*	–	–	-0.090	-0.304*
1963	–	–	0.203	0.375*	0.392**	0.442**	0.058	0.066	0.251	-0.092
1964	–	–	0.361*	0.177	0.334*	0.482***	0.077	0.174	0.099	0.198
1965	–	–	0.363*	0.281	0.250	0.450**	0.091	0.253	-0.156	0.018
1966	–	–	0.327*	0.333*	0.237	0.133	0.172	0.285	0.237	0.073
1967	0.180	0.157	0.321*	0.278	0.116	0.076	0.214	0.393*	0.163	0.266
1968	0.146	0.067	0.386**	0.300*	0.160	0.062	0.246	0.389**	0.210	0.367*
1969	0.202	0.246	0.385**	0.192	-0.223	-0.136	0.296*	0.471***	0.264	0.214
1970	0.300*	0.368*	0.315*	0.395**	-0.110	-0.145	0.270	0.345*	0.279	0.353*
1971	0.450**	0.401**	0.502***	0.328*	0.168	-0.090	0.216	0.302*	0.290	0.258
1972	0.495***	0.427**	0.492***	0.323*	0.034	-0.086	0.267	0.325*	0.466**	0.532***
1973	0.528***	0.456**	0.520***	0.346*	0.384**	0.225	0.233	0.222	0.437**	0.431**
1974	0.529***	0.444**	0.553***	0.366*	0.359*	0.304*	0.162	0.350*	0.399**	0.457**
1975	0.559***	0.492***	0.593***	0.315*	0.393**	0.148	0.043	0.290	0.362*	0.367*

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) Standard population is the total population in Japan, 1985.

relationship did not exist, and they are thus not included in Table 1.

The results of Spearman's rank correlation analysis are not tabulated here, since the patterns of associations between EPIs and SMRs were similar to those found by Pearson's analysis. In the case of PCNB, however, statistically significant associations became more evident when Spearman's analysis was used, as compared with the Pearson's correlation data in Table 1. Among the EPIs of PCNB for the 14 years from 1962 to 1975, 12 and 11 EPIs of them were significantly correlated with the 1985 SMRs of males and females, respectively.

DISCUSSION

There are some differences in SMRs between the data of 1985 and that of 1969-1978. According to the 10 years' data (1969-1978), SMRs of Niigata prefecture were the highest in both sexes, but in 1985 the top spot was taken over by Yamagata males and Fukui females; however, a careful evaluation of these change is necessary. The present analysis is based on the Vital Statistics records for only one year, and thus there may have been SMR fluctuations. Moreover, it seems rather important to note that the

distribution pattern of prefectures with higher SMRs remains unchanged when the cancer maps of 1985 and 1969-1978 are mutually compared. As a matter of fact, the correlation coefficients between SMRs in 1985 and those over a 10 years' average (1969-1978) are 0.563 (P<0.001) in males and 0.742 (P<0.001) in females.

In order to detect possible factors that determine the characteristic distribution of SMRs for biliary tract cancers, we have been working on a hypothesis concerning the role of agricultural chemicals on the occurrence of cancers. For testing the hypothesis, we introduced an index, that is, the environmental pollution index (EPI). This refers to the quotient obtained by dividing the total amount of chemical components distributed to each prefecture by the area of the prefecture. Next, an ecological correlation analysis between EPIs and SMRs by prefectures was made. It should be explained here about whether or not these statistical procedures are accurate in testing the hypothesis. At present, there is no experimental evidence to support the idea that EPI reflects the degree of actual environmetal contamination by agricultural chemicals. In addition to the use of EPIs, there is also another problem, that is, the risk of committing an ecological fallacy by using an ecological correlation analysis (Robinson[3], 1980).

In spite of the presence of these obstacles in interpreting the results, we dare to make a few comments on our findings. It should be pointed out that only the EPIs of MCPA, CNP and PCNB (using only Spearman's rank correlation analysis in this case) were frequently associated with SMRs among more than 500 agricultural chemicals analyzed. Even if we have to reject our hypothesis in the future, it may be worthwhile, at the present time, to consider the possibility of a causal relationship existing between these chemicals and the occurrence of cancers.

In order to analyse the possibility of this causal relationship, we may first have to investigate what happens to these chemicals after entering the environment and the route of human exposure. Two experimetal works may be suggested; one is to examine the presence of these chemicals as contaminates in drinking water and the other is to examine the residual levels of these chemicals in the rice. Regarding the possible contamination of drinking water, Kato et al.[4] (1986) reported an interesting finding in their case-control study. They revealed that previous use of home wells or the local water supply system was a risk factor in biliary tract cancers. Their findings strongly compel us to conduct a water quality analysis of drinking water collected from the patients' wells. In addition to measuring the agricultural chemicals in suh samples as drinking water and rice, it is also necessary to study the pathological effects of these chemicals by making use of experimetal animals.

ABBREVIATIONS OF CHEMICALS APPEARED IN THE TEXT

1) CNP : 2,4,6-trichlorophenyl-4'-nitrophenylether
2) EDDP: 0-ethyl S,S-diphenyl phosphorodithioate
3) MCPA: 4-chloro-2-methyl-phenoxyacetic acid ethyl ester

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

5) NIP : 2,4-dichlorophenyl-4-nitrophenyl ether

6) PCNB: Pentachloronitrobenzene

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