

A STUDY OF THE GEOGRAPHICAL PATTERN OF CANCER MORTALITY FOR SELECTED SITES BY MEANS OF FACTOR ANALYSIS

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Abstract—The spatial distribution of cancer mortality and morbidity has been studied by many authors, and its characteristic pattern as to the various cancer sites was the object of the research of many epidemiologists.

It has been generally recognized that any of the specific factors do not contribute independently but interdependently to the etiology in chronic diseases. With this in mind, it is natural to assume that there exist multiple factors which collaborate with each other in the pathogenesis of cancer of various sites.

To test interdependence of variables, we set out to analyse the pattern of the geographical distributions of the cancer deaths in Japan, using the method of factor analysis which has been characterized as a useful method for analyzing the correlated variables.

Five independent factors are extracted from the mutual correlations among the site-specific mortality rates on various cancers and that these factors were commonly found in both sexes, although slight discordance was noticed in some factors. Among the factors extracted, the first one attracted us the most, since the fact that bone, bladder, skin and buccal cancers clustered in one group suggest a possible relationship of these cancers to atmospheric temperature. An alternative fact that interests us is the conspicuous variability in the geographical distribution of lung cancer. Finally, we add that consistently high correlations were obtained for the mortality rates between any two of the different three time periods.

INTRODUCTION

The study of the geographical distribution of mortality rates or morbidity rates is thought of as one of the most important fields in cancer epidemiology. Many authors have published a number of researches on mortality or morbidity of various cancer sites in Japan as well as in foreign countries [1–3]. It is clear that one of the reasons epidemiologists consider the geographical patterns of cancer mortality or morbidity distributions is the elucidation of the etiological factors of cancer in each site. It has been generally recognized that any of the specific factors do not contribute independently but interdependently to the etiology in chronic diseases including cancer. Even though several researchers have attempted to calculate correlation coefficients between the rates for more than two cancer sites, only a few of them have tried to analyse the mutual relationship among cancer sites synthetically [4–6].

In this paper we try to analyse the mutual relationship of geographical distributions among each cancer site based upon the assumption that there may exist some common factors which collaborate with each other in the pathogenesis of various cancer sites. Recently, factor analysis, characterized as a method to analyse the interrelationship among many variables, has been proved very valuable in psychology, economics as well as in medicine. Therefore we applied this method to the research on the geographical distribution of cancer mortality rates.

METHODS

The data from *Mortality Statistics of Malignant*

Neoplasms in Japan [7] were utilized for our analysis. In this book, the records of the cancer mortality were classified with respect to 46 prefectures all over Japan excluding Okinawa, calendar years (from 1958 to 1971), age (by five years classification), sex and cancer sites. We selected 18 sites for male and 19 sites for female as shown in Table 1.

The mortality rates were calculated by indirect standardizing method for the following three periods: (1) from 1958 to 1962, (2) from 1963 to 1967 and (3) from 1968 to 1971. The standard populations used for calculating the corrected mortality rates were Japanese national figures for each census year: (1) 1960, (2) 1965 and (3) 1970. The correlation coefficients were calculated for each prefecture, cancer site and period. As the correlation coefficients between any two of the three periods were relatively high in many cancer sites, factor analysis by the varimax method was carried out, using the mean values of mortalities of the three periods. Furthermore, we calculated factor scores of the factors obtained for each of the 46 prefectures, and then calculated the correlation coefficients between factor scores and some environmental variables.

RESULTS

Factor loadings of cancer mortality

As a result of factor analysis, four common factors were extracted for males and females respectively. We changed the order of extracted factors so that the factors for males might correspond to those for females in terms of the clusters of cancer sites which each factor revealed. Figures 1 and 3 show the configurations of the first factor (vertical line) and of the

Table 1. Selected cancer sites with I.C.D. code

Cancer sites	I.C.D. Code 7th revision (1958-1967)	I.C.D. Code 8th revision (1968-1971)	Abbreviation in this report
1. Oral cavity and pharynx	140-148	140-149	Oral
2. Esophagus	150	150	Esophagus
3. Stomach	151	151	Stomach
4. Intestine (duodenum, small intestine and colon)	152, 153	152, 153	Intestine
5. Rectum and rectosigmoid	154	154	Rectum
6. Liver (including unspecified as primary or secondary)	155.0, 155.8	155, 197.7 197.8	Liver
7. Bile duct and gall bladder	155.1, 156	156	Bile duct
8. Pancreas	157	157	Pancreas
9. Larynx	161	161	Larynx
10. Trachea, bronchus and lung	162, 163	162	Lung
11. Bone	196	170	Bone
12. Skin (including melanoma)	190, 191	172, 173	Skin
13. Breast	170	174	Breast
14. Uterus (female only)	171-174	180-182	Uterus
15. Ovary (female only)	175.a	183.0	Ovary
16. Prostate (male only)	177	185	Prostate
17. Bladder	181.a	188	Bladder
18. Kidney (including pelvis)	180	198.0, 189.1	Kidney
19. Lymphatic tissue (excluding leukemia)	200-203, 205	200, 203, 208, 209	Lymphatic
20. Leukemia	204	204-207	

second factor (horizontal line) for males and females respectively, while Figs 2 and 4 show those of the third factor (vertical line) and fourth factor (horizontal line) for males and females respectively.

First factor (contribution rate: 33.1% for males and 35.2% for females)

Since contribution rate for both sexes occupies more than one third of the total variance, this factor might prove the most important pattern of geographical distribution. High loadings were found in skin, leukemia and liver for both sexes. Besides those cancer sites, high loadings were also found in prostate, bladder and lymphatic tissue for males, and kidney, ovary and uterus for females (Figs 1 and 3).

Second factor (contribution rate: 25.4% for males and 35.1% for females)

The contribution rate of this factor for males is smaller than that of the first factor, while for females it is almost the same as that of the first factor. High loadings were found in oral and lung cancer for both sexes. Relatively high factor loadings were found in intestine for both sexes. In addition to these sites, relatively high factor loadings were found in rectum, larynx and bone for males and lymphatic, bladder and pancreas for females.

Third factor (contribution rate: 31.0% for males and 18.5% for females)

The contribution rate of this factor was different between males and females. The pancreas and bile duct produce high values on this factor for both sexes. Lymphatic tissue is high for females. Relatively high factor loadings were found in the opposite axis in liver for both sexes, in skin for males and in larynx for females (Figs 2 and 4).

Fourth factor (contribution rate: 10.5% for males and 11.2% for females)

It is only esophageal cancer that was plotted highly on this factor for both sexes. It can be surmised that the distribution of esophageal cancer might be almost independent of the other cancer sites.

Factor scores and their correlation with some environmental factors

Factor scores of the four factors thus obtained are demonstrated in eight maps of Japan as shown in

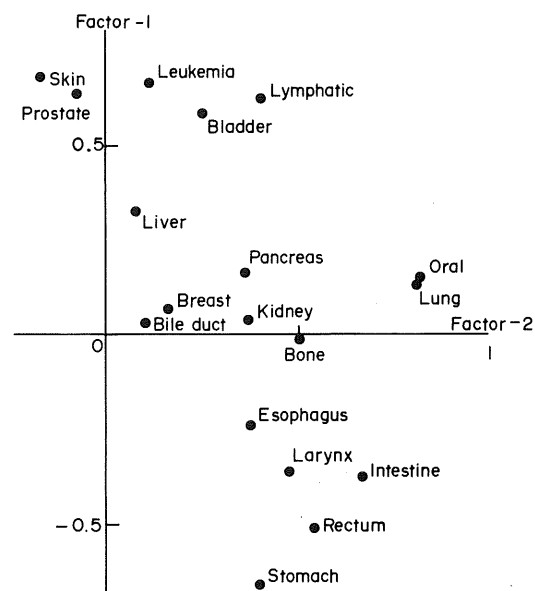


Fig. 1. Configuration of 18 cancer sites by factor loadings for 46 prefectures in Japan: male (Factor 1 and Factor 2).

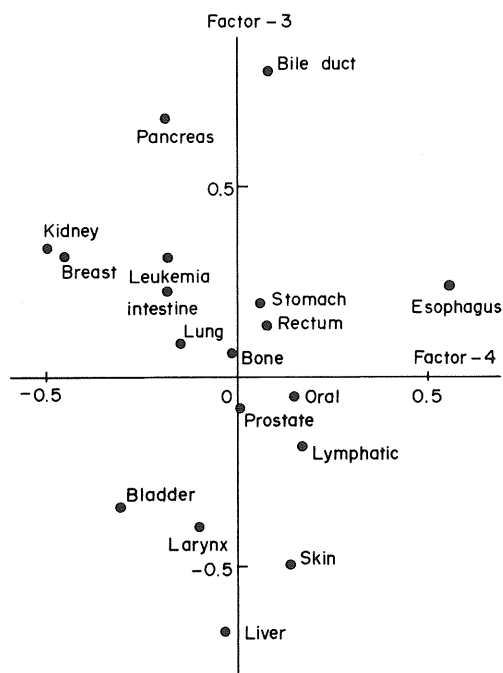


Fig. 2. Configuration of 18 cancer sites by factor loadings for 46 prefectures in Japan: male (Factor 3 and Factor 4).

Figs 6–13, in each of which factor scores of 46 prefectures are depicted in terms of five grades determined according to the values; i.e. (a) more than 1.5 (very high), (b) 0.5–1.5 (high), (c) –0.5 to 0.5 (intermediate), (d) –0.5 to –1.5 (low) and (e) less than –1.5 (very low). (Names and locations of 46 prefectures are shown in Fig. 5.) The factor score of the first factor, on which skin, leukemia and liver cancers have high

loadings for both sexes, is seen in Fig. 6 (males) and Fig. 10 (females).

It is to be noted that the mortality of these cancer sites occurs more frequently in the southern parts of Japan, especially in the south Kyushu area for both sexes. However, the factor loadings of the first score indicate high values in prostate, bladder and lymphatic tissue for males, and in kidney, ovary and uterus for females. These differences are demonstrated in the maps of factor scores, in which the very high values found in such prefectures as Tottori and Miyagi are only for males. The scores of the second factor which show high loadings in oral cancer, lung and intestine for both sexes, indicate high values in Tokyo and Osaka for both sexes (Figs 7 and 11). The factor scores are very high for males in Yamaguchi, and for females in Hokkaido, Miyagi and Kanagawa prefectures. These results may imply high factor loadings in rectum, larynx and bone for males and lymphatic tissue, bladder and pancreas for females.

The scores of the third factor, of which high factor loadings are found in pancreas and bile duct for both sexes, are clearly high in the north-eastern Japan for both sexes (Figs 8 and 12).

The score distribution of the fourth factor, which resembles that of the first factor, was high for esophageal cancer. In the southern Kyushu area factor scores are very high for both sexes. Besides this area, Saitama prefecture for males and Gunma, Nara and Wakayama prefectures for females have positively high factor scores (Figs 9 and 13).

In order to scrutinize these factor score distributions, we chose the geographical distributions of the mean temperature and total precipitation as the indices of natural environmental factors, as well as population density and the rate of primary industry engagement as those of social environmental factors, and calculated the correlation coefficients with factor scores for 46 prefectures. The results are shown in Table 2.

The first factor has a significant correlation for males with the rate of primary industry and for

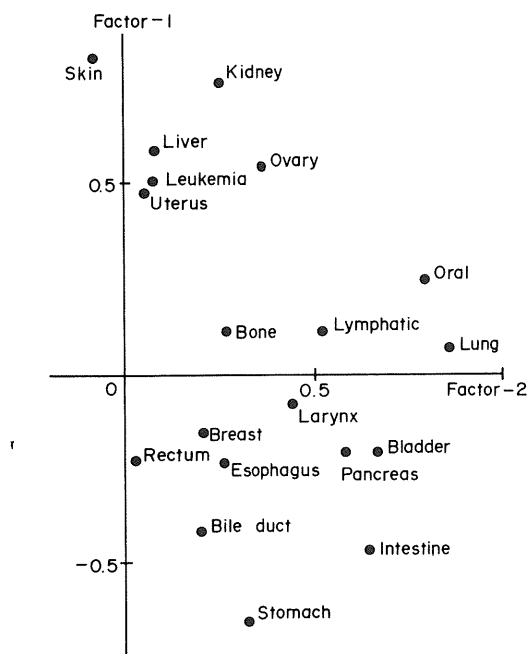


Fig. 3. Configuration of 19 cancer sites by factor loadings for 46 prefectures in Japan: female (Factor 1 and Factor 2).

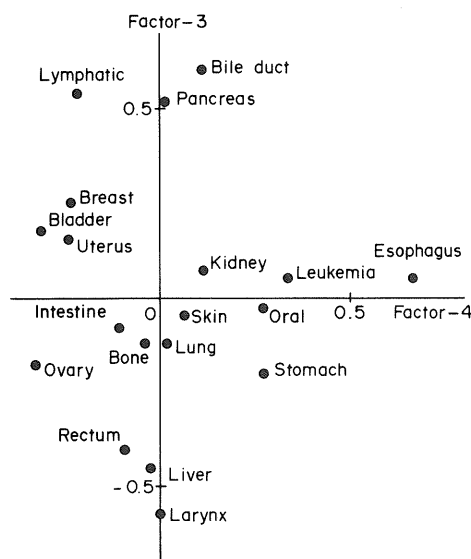


Fig. 4. Configuration of 19 cancer sites by factor loadings for 46 prefectures in Japan: female (Factor 3 and Factor 4).

1 Hokkaido	21 Gifu	41 Saga
2 Aomori	22 Shizuoka	42 Nagasaki
3 Iwate	23 Aichi	43 Kumamoto
4 Miyagi	24 Mie	44 Oita
5 Akita	25 Shiga	45 Miyazaki
6 Yamagata	26 Kyoto	46 Kagoshima
7 Fukushima	27 Osaka	
8 Ibaragi	28 Hyogo	
9 Tochigi	29 Nara	
10 Gunma	30 Wakayama	
11 Saitama	31 Tottori	
12 Chiba	32 Shimane	
13 Tokyo	33 Okayama	
14 Kanagawa	34 Hiroshima	
15 Niigata	35 Yamaguchi	
16 Toyama	36 Tokushima	
17 Ishikawa	37 Kagawa	
18 Fukui	38 Ehime	
19 Yamanashi	39 Kochi	
20 Nagano	40 Fukuoka	

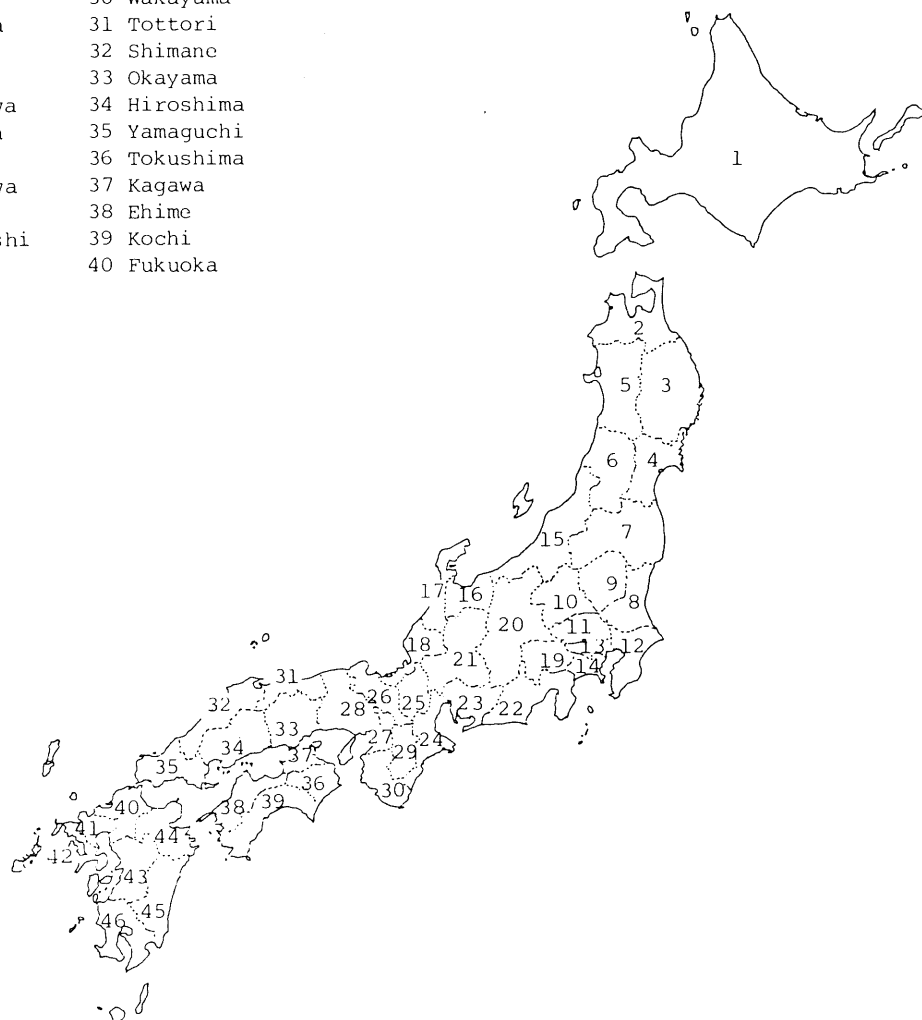


Fig. 5. Japanese map with the names of 46 prefectures excluding Okinawa.

females with the mean temperature and total precipitation. So far other researchers have reported a relationship between the rate of primary industry and several cancer sites [8]; however, our results are slightly different from that. That report indicated that prostate, skin and stomach cancer have significant correlations with the rate of primary industry for males. Our results indicate that the first factor, which correlates significantly with the rate of primary industry for males, implies skin, prostate, leukemia, lymphatic tissue and bladder, but indicates a negatively high value for stomach cancer. The discordance needs further study. On the other hand, the positive

correlation between natural environmental factors and the first factor for females may reflect rapid growth conditions of biological agents for the cancer sites of the first factor, because some of the cancer sites, of which high factor loadings are found in the first factor (i.e. uterus, liver and leukemia) are suspected to be related with viral infections [9-11].

The second factor has a significant positive correlation with population density, but it shows a significant negative correlation with the rate of primary industry for both sexes. These environmental factors are relevant to industrialization or urbanization. It is generally accepted that lung and intestinal cancers are

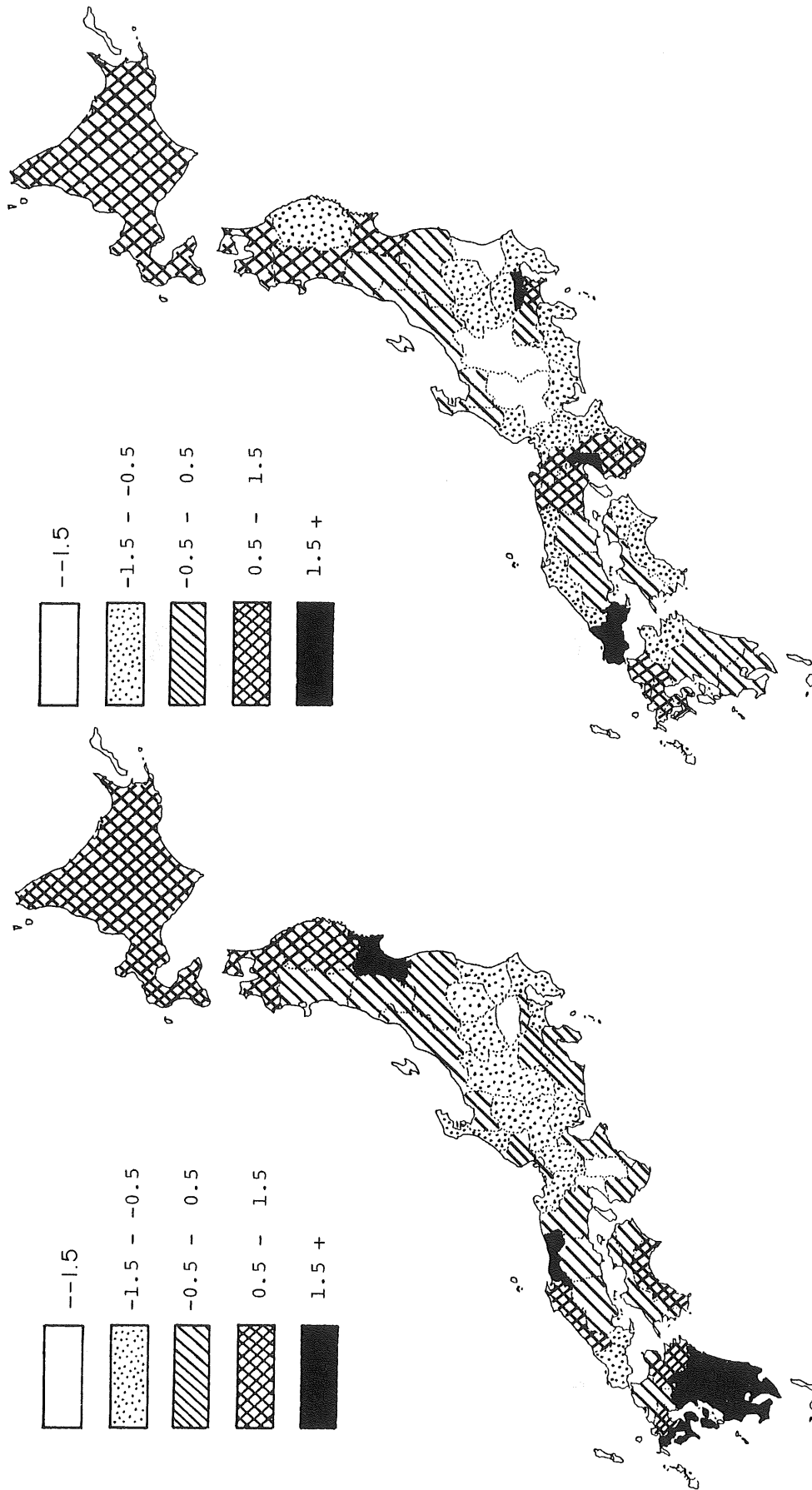


Fig. 6. Geographic distribution of factor scores in males (Factor 1).

Fig. 7. Geographic distribution of factor scores in males (Factor 2).

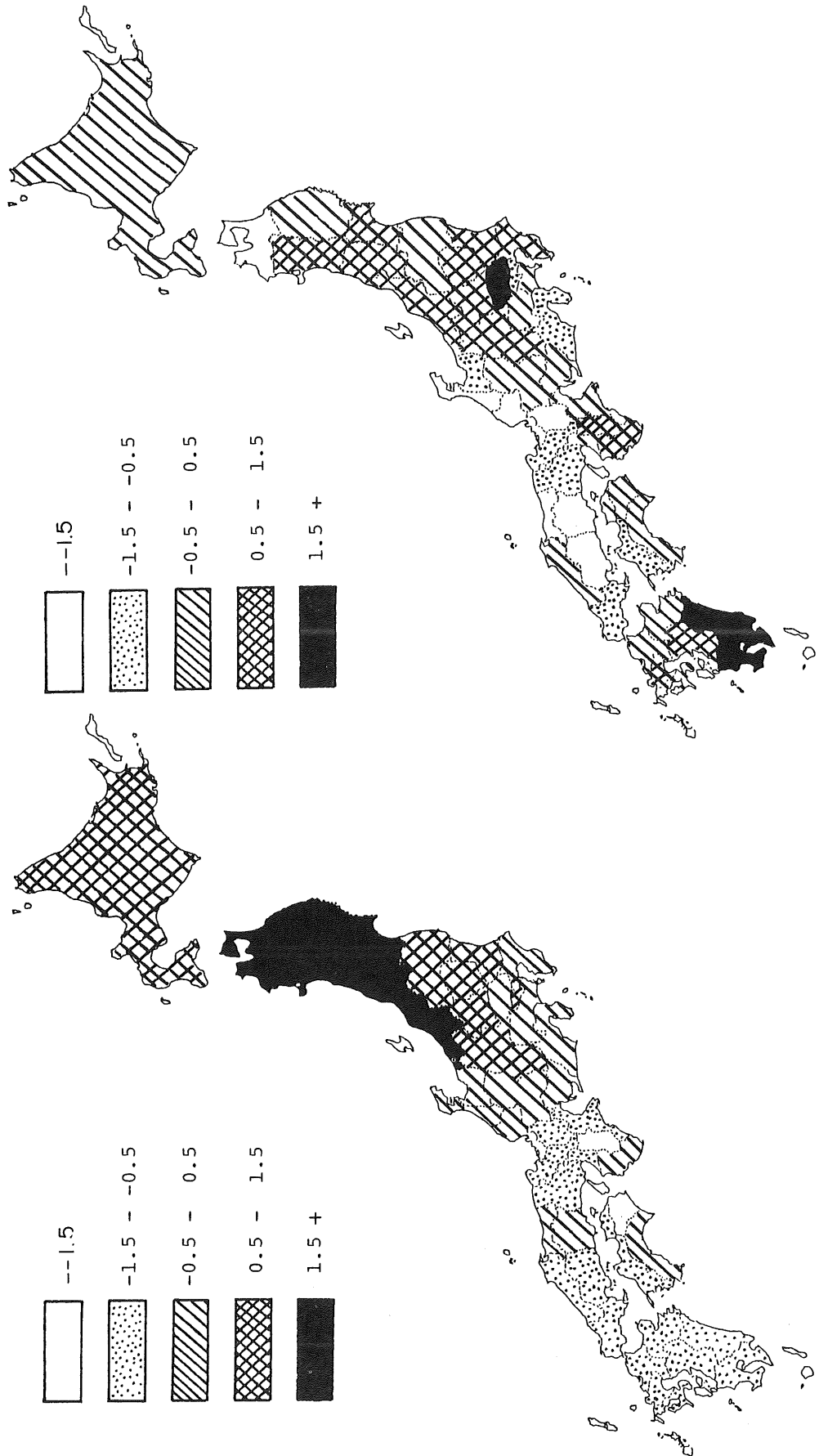


Fig. 8. Geographic distribution of factor scores in males (Factor 3).

Fig. 9. Geographic distribution of factor scores in males (Factor 4).



Fig. 11. Geographic distribution of factor scores in females (Factor 2).

Fig. 10. Geographic distribution of factor scores in females (Factor 1).

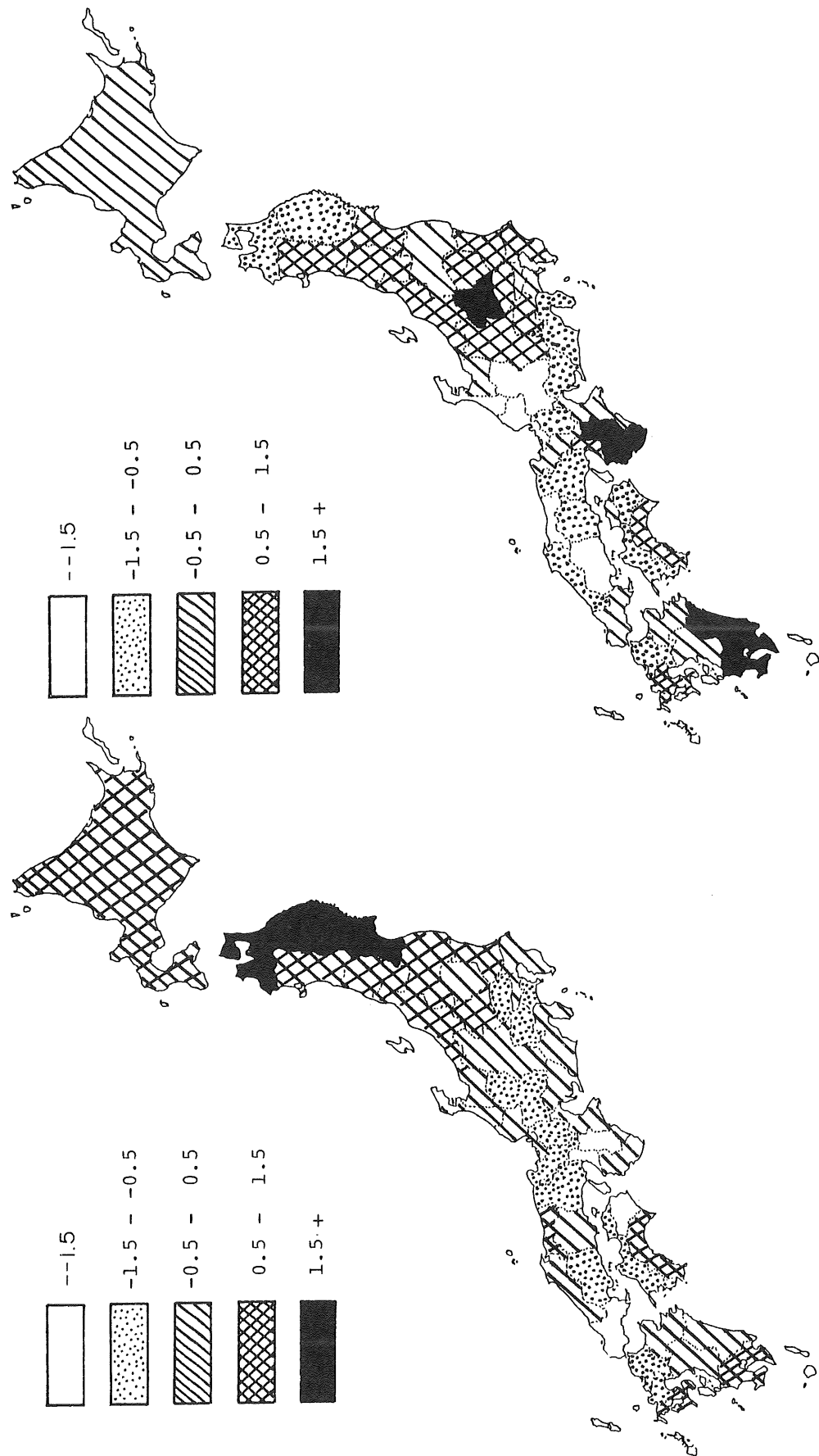


Fig. 12. Geographic distribution of factor scores in females (Factor 3).

Fig. 13. Geographic distribution of factor scores in females (Factor 4).

Table 2. Correlation coefficient between factor scores and some environmental factors

Environmental factors	Male				Female			
	Fac. 1	Fac. 2	Fac. 3	Fac. 4	Fac. 1	Fac. 2	Fac. 3	Fac. 4
Population density	-0.246	0.553*	-0.169	0.027	-0.048	0.506	-0.262	-0.041
Mean temperature	-0.614*	-0.143	0.453*	0.050	-0.804*	0.046	0.037	0.031
Total precipitation	0.037	-0.211	0.400*	-0.169	-0.269	-0.140	0.305	-0.168
Rate of primary industry	0.550*	-0.513*	0.320	0.132	0.273	-0.431*	0.543*	0.256

* $P \leq 0.01$.

related to industrialization. But it is not yet accepted that oral cancer has a strong correlation with urbanization. Further study is necessary from this viewpoint.

For the third factor, a negatively significant correlation is recognized with the mean temperature for both sexes and a positively significant correlation is recognized with the rate of primary industry for females. It is well known that pancreas and bile duct cancers are very hard to diagnose and their etiology is also difficult to investigate. The fact that these cancer sites have a similar distribution of mortality, with correlations to some environmental factors, should provide one of the clues to elucidate the unknown etiology of these cancers.

The fourth factor does not correlate with these four environmental factors.

Comparison between the study on 46 prefectures in Japan and that on 24 countries in the world

We summarized in Table 3 the results of the factor analysis study on 46 prefectures in Japan. In the meantime, we also applied the same procedure to the cancer mortality data of 24 countries in the world [12]. In the latter study, 13 cancer sites for males and 14 cancer sites for females were selected and besides four environmental factors which were used in the former study, 20 kinds of food consumption data were selected for calculation of correlation coefficients with factor score of 24 countries.

Table 3. Cancer sites and prefectures related to the extracted factors in Japanese data

Sites			Prefectures	
MALES				
1st factor	(+)	Skin, leukemia, lymphatic, prostate, bladder	(+)	Miyagi, Tottori, Nagasaki, Kumamoto, Kagoshima, Miyazaki
	(-)	Stomach, rectum	(-)	Saitama, Ohsaka, Nara
2nd factor	(+)	Oral, lung, intestine, rectum	(+)	Tokyo, Ohsaka, Yamaguchi
			(-)	Ibaragi, Nagano, Gifu
3rd factor	(+)	Bile duct, pancreas	(+)	Aomori, Akita, Iwate, Yamagata, Miyagi, Niigata
	(-)	Liver, skin, larynx	(-)	Nara, Tokushima
4th factor	(+)	Esophagus	(+)	Saitama, Kagoshima, Miyazaki
	(-)	Kidney, breast	(-)	Aomori, Ishikawa, Fukui, Shiga, Tottori, Okayama, Hiroshima
FEMALES				
1st factor	(+)	Skin, kidney, liver, ovary, leukemia, uterus	(+)	Nagasaki, Kumamoto, Miyazaki, Kagoshima
	(-)	Stomach, intestine, bile duct	(-)	Saitama
2nd factor	(+)	Oral, lung, bladder, intestine, pancreas, lymphatic	(+)	Hokkaido, Miyagi, Tokyo, Kanagawa, Ohsaka
			(-)	Ibaragi, Nagano
3rd factor	(+)	Bile duct, lymphatic, pancreas	(+)	Aomori, Iwate, Miyagi
	(-)	Larynx, liver, rectum	(-)	Nara, Ohsaka, Tokushima, Yamaguchi
4th factor	(+)	Esophagus	(+)	Gunma, Nara, Wakayama, Kagoshima, Miyagi
			(-)	Ishikawa, Fukui, Gifu, Tottori, Hiroshima

(+) indicates the sites and prefectures which have positively high factor loadings and factor scores respectively.

(-) indicates the sites and prefectures which have negatively high factor loadings and factor scores respectively.

Table 4. Cancer sites, countries, and the indices related to the extracted factors in 24 countries' data

		Sites		Countries		Indices
MALES						
1st factor	(+)	Prostate, pancreas, skin, leukemia	(+)	U.S.A., Australia	(+)	Sugar, animal protein
	(-)	Stomach, liver	(-)	Japan, Italy, Chile	(-)	Cereals, population density
2nd factor	(+)	Intestine, rectum, lung	(+)	Denmark, England	(+)	Animal fat, energy, meat
3rd factor	(+)	Larynx, oral, esophagus	(+)	France, Italy	(+)	Alcohol beverages, vegetables
4th factor	(+)	Stomach, esophagus, thyroid	(+)	Finland, Chile	(-)	Fruit
FEMALES						
1st factor	(+)	Leukemia, skin	(+)	U.S.A.(White), Norway, New Zealand	(+)	Milk, animal products, sugar
	(-)	Stomach, uterus, liver	(-)	Chile, Japan	(-)	Population density
2nd factor	(+)	Intestine, rectum, lung	(+)	Canada, Belgium, England	(+)	Oil fats, energy, meat
3rd factor	(+)	Larynx, oral, esophagus	(+)	Ireland, Scotland	(-)	Vegetable oil
4th factor	(+)	Thyroid, pancreas, lung	(+)	Israel, Australia	(-)	Vegetables, rainfall

(+) indicates the sites, countries, and indices which are related to the factor with positively high values, respectively.

(-) indicates the sites, countries, and indices which are related to the factor with negatively high values, respectively.

The summary of the latter study is shown in Table 4. The comparison between Tables 3 and 4 reveals that:

(1) In spite of different data sources, similar clustering of cancer sites is noted, i.e. for males, prostate, leukemia and skin (the first factor), intestine and lung (the second factor), for females, skin and leukemia (the first factor), intestine and lung (the second factor);

(2) The correlations with some environmental factors, especially population density, behave similarly concerning the first factor.

From these results it may be suggested that some clusterings exist with respect to the geographical distribution of various sites of cancer mortality and that some common etiological factors correspond to those cancer sites.

DISCUSSION

On the correlational study with regard to geographic distribution

The assumption in a series of our studies is that the variation in the geographical pattern of a disease may reflect its causal factors, and that the analysis of the interrelationship of the geographical distribution of different diseases may reveal some common etiological factors which collaborate with each other in the pathogenesis of the diseases.

As for the interpretation of the results by means of correlational studies, we should recognize that the magnitudes of correlation coefficients are easily

biased by the mode of sampling. Figure 14 shows some types of biased correlation coefficients: (a) truncated data will decrease the correlation coefficients; (b) the population data have a positive correlation, but even so the sampling data indicate a negative correlation; and (c) while the population data have a positive correlation, subgroup data all indicate negative correlations.

For example, Table 5 shows that correlation coefficients between two cancer sites obtained from 24 countries in the world differ in value from the samples of 46 prefectures in Japan. The correlation coefficient, especially between stomach and intestine for 24 countries in the world, is drastically different from that for 46 prefectures in Japan (the former -0.729, the latter 0.548).

In view of these disagreements we should take some care about the nature of the samples used for calculating the correlation coefficients when we interpret the magnitude of correlation coefficients and the factor loadings for each variable.

On the methodology of the study

Factor analysis is said to be a method which brings to light the latent factors which may be hidden behind the data, and so far fruitful results have been obtained by applying it to the psychological data such as personality tests or ability tests. Unfortunately, however, we can only very rarely find the case where the latent factors are really obtained from the empirical data. Hence it is considered that the utility of factor analy-

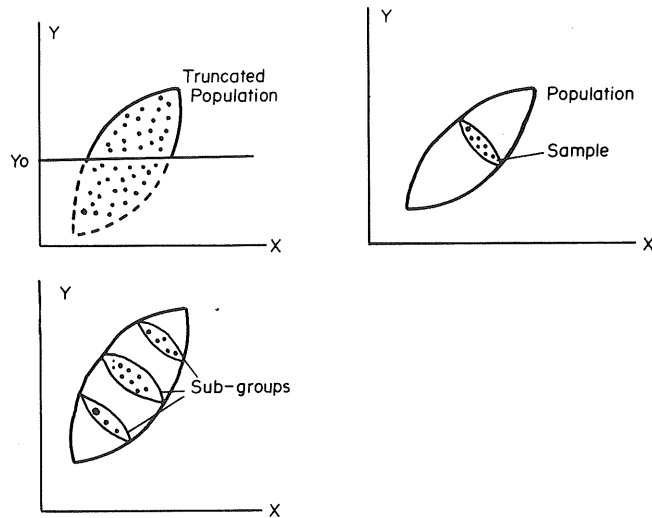


Fig. 14. Some types of correlation diagrams.

sis in epidemiological study lies in reducing complicated information to simpler terms and obtaining the hypothetical factors which serve as clues to bring the unknown factors to light. Recently it has become widely accepted that many confounding factors, which are correlated with each other, are likely to be related to the etiology of various diseases. Thus the application of factor analysis should be useful in providing information on the hypothetical factors that may be closely connected with the onset of some diseases.

Since the results of factor analysis indicate that various cancer sites form clusters with respect to their geographical distributions, we may postulate the existence of some common causes of cancer develop-

ing in particular sites. It should be noted, however, that similarities in the geographical distribution between two diseases may sometimes reflect only statistical bias in sampling. So, it is better to develop an etiological hypothesis about alternative diseases within a cluster only when we have some generally accepted hypothesis about the etiology of a certain disease within a cluster. On this viewpoint, the stepwise regression method may sometimes be useful. So far, we applied this method to the study on cancer mortalities for 24 countries in the world, in which some successful results were obtained [11]. Recently, in order to elucidate causal relationship from the correlational study, analysis has been noticed as a powerful method for uncovering the unknown etiology of

Table 5. Correlation coefficients for selected cancer sites in 46 prefectures in Japan and 24 countries in the world

Cancer sites						
(1) Esophagus	1.000 (1.000)					
(2) Stomach	0.344 (0.385)					
(3) Intestine	-0.221 (0.278)	-0.779 (0.548)				
(4) Rectum	-0.175 (0.405)	-0.339 (0.589)	0.754 (0.574)			
(5) Lung	-0.001 (0.203)	-0.107 (0.244)	0.516 (0.540)	0.589 (0.377)		
(6) Skin	-0.188 (-0.266)	-0.429 (-0.607)	0.462 (-0.513)	0.097 (-0.502)	0.114 (-0.118)	
(7) Leukemia	-0.387 (-0.155)	-0.603 (-0.347)	0.423 (-0.073)	0.329 (-0.255)	0.138 (0.229)	0.392 (0.254)
	(1) Esophagus	(2) Stomach	(3) Intest.	(4) Rectum	(5) Lung	(6) Skin

diseases, since its method would provide information concerning the magnitude of association between cause and effect.

We think it would be worth applying this method to our analysis [13, 14].

As an alternative method of finding some clusters of various sites of cancers, Burbank [15] recommends cluster analysis for the reason that its application would produce a successive hierarchical structure of many cancer sites. But it does not necessarily follow that such hierarchical structure corresponds to the pathogenesis of cancers. In addition, we should mention that cluster analysis is usually interdependent, and the result of cluster analysis can hardly produce information connected with the mutual relationship among the extracted clusters. Hence, we might say that factor analysis prevails over cluster analysis in the utility of the extracted clusters, but we do not intend to deny the usefulness of cluster analysis at all.

To sum up, the results obtained by means of factor analysis of the geographical distributions provide a kind of synthesized information contained in the raw data, but they are nothing but clues to develop hypotheses on the unknown etiology of some cancer sites. We should admit that various other methods of biostatistics and epidemiology might well provide important clues to elucidate the unknown etiology of cancer.

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