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Epidemiology of Malignant Neoplasms in Black-Foot Disease Areas: A Long-Term Observation of Death Statistics in Pu-tai Township

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The black-foot disease is a disease of the peripheral blood vessels endemic to the coastal area of the southwestern part of Taiwan. The cause of the disease is known to be related to the drinking water collected from the artesian wells. The incidence of black-foot disease has declined with the use of running water, deaths from malignant neoplasms in this area, however, have significantly increased in the recent years. To explain the relation between black-foot disease, malignant neoplasms, and artesian well water, the study selected one of the four black-foot disease prevalent townships, Pu-tai township, for a close study through the non-concurrent epidemiological follow-up approach. The villages in the Township differ greatly in the morbidity rates of the black-foot disease, the Township, therefore, is divided into four zones by the morbidity rates to study the relation between the rate of malignant neoplasms and the morbidity of black-foot disease, and further, its relation to the drinking of the artesian well water.

There are 23 villages in Pu-tai Township. They are grouped into A, B, C, and D zones by geographical location and the morbidity rates of black-foot disease.

The following data are then collected: from Pu-tai Township Household Registration Office, all death certificates for the 23 villages, and mid-year population by village, sex, and age for the years between 1956 and 1986; cancer deaths by sex and age for 1966-1973 from the Vital Statistics of Taiwan Province, and for 1974-1986, from the Health Statistics; and population data by sex and age for 1966-1973 from the Demographic Fact Book of Taiwan Province, and for 1974-1986, from the Taiwan-Fukien Demographic Data Book. These data are used for a comparative analysis of the standardized mortality ratios (SMR).

Information of the black-foot disease patients in the villages is taken from the survey records of the black-foot disease patients prepared by the Institute of Public Health of the National Taiwan University Medical College. The records contain information up to the end of 1987 of patients born before 1946. The number of patients is then divided by the number of population at the end of 1946 by village to calculate the cumulative incidence rates of black-foot disease by village.

The study results show that the cumulative incidence rates differ significantly between the four zones, decreasing from south to north: 49.74% in A zone, 12.24% in B zone, 5.28% in C zone, and 0.83% in D zone. Between 1956 and 1986, there were 1,778 cancer deaths in Pu-tai Township cancer that frequencies over 10% are urothelial cancer (252 cases, 14.2%), lung cancer (289 cases, 16.3%), liver cancer (341 cases, 19.2%), and stomach cancer (177 cases, 10.0%). The sex ratios are: 1.29 (142/110), 1.49 (173/116), 2.71 (249/92), and 1.42 (104/73) respectively. The average ages at death for both male and female by the four types of cancer do not differ significantly.

When the average ages at death from various types of cancer are compared between the four zones with different morbidity rates of black-foot disease, the findings are: there is a significant difference in the urothelial cancer regardless of sex, with the lowest age at death in A zone; for both lung and stomach cancers, only the males show significant difference in the four zones; no difference is found in the average ages at death for liver cancer for both sexes in the four zones, though A zone still has the lowest average death age

The age compositions of population in the four zones are similar. A comparative analysis of the standardized mortality ratios by zone and by sex for the four types of cancer is made. The results are: for urothelial cancer, except D zone, the deaths in the A, B, and C zones for both sexes are significantly higher than those of the Taiwan Area (95% confidence intervals higher than 1.00), and the SMR's of A zone, regardless of sex, are as high as 4.0 (see Table 1). For lung cancer, except in D zone and the male in C zone, the SMR's are significantly higher than those of the Taiwan Area, 11.61 in A zone (12.24 for male and 10.67 for female), 3.50 in B zone (3.29 for male and 3.87 for female), 1.79 in C zone (1.44 for male and 2.43 for female), and 1.19 in D zone (1.24 for male and 1.19 for female). For liver cancer, except the female in C zone, the SMR's are significantly higher than those of the Taiwan Area, 3.84 in A zone, 2.21 in B zone, 1.79 in D zone, and 1.69 in C zone. For stomach cancer, only the SMR of 2.17 in A zone shows a significant difference. When the four types of cancer are compared with the black-foot disease, the mortality rates of the urothelial cancer and the lung cancer show a linear relation with the black-foot disease; the liver and the stomach cancers do not, however.

Table 1. Standardized Mortality Ratios (SMR) of Urothelial Cancer by Zone and Sex for the 23 Villages of Pu-tai Township and the 95% Confidence Intervals (1956-1986)

Zone	Sex	No. of Deaths		SMR	95% Confidence Intervals**
		Observed	Expected*		
A	M	57	1.33	42.86	32.64-55.98 32.81-60.30 35.88-53.32
	F	45	1.00	45.00	
	Total	102	2.33	43.78	
B	M	43	3.44	12.50	9.04-16.85 9.66-19.74 10.04-16.52
	F	33	2.35	14.04	
	Total	76	5.79	13.13	
C	M	35	4.94	7.09	4.94- 9.86 5.93-12.93 6.04-10.07
	F	28	3.14	8.92	
	Total	63	8.08	7.80	
D	M	7	3.25	2.15	0.86- 4.43 0.48- 4.48 1.00- 3.58
	F	4	2.28	1.75	
	Total	11	5.53	2.00	

*Expected number is calculated from the sex- and age-specific death rates of the Taiwan Area

**Haenszel et al, 1962

A comparative analysis of cohorts for the four types of cancer has also been made. The analyses of O/E ratios have only been made in three birth cohort groups (1901-10, 1911-20, and 1921-30), who are at the age of forty to fifty nine, for the statistics of population is limited, the death cases of cancer under the age of forty are few, and the competition causes of death above the age of sixty are many beside that their diagnosis are relatively inaccurate. It is found that there are significantly more urothelial cancers in the 1911-20 than in the 1901-10 cohorts, and the ratio in the 1921-30 cohort, though, has declined, the difference is not significant (see Table 2)

Table 2. The O/E Ratio of the Urothelial Cancer Death Cases in Three Cohorts (Age 40-59)

	Birth Cohort		
	1901-10	1911-20	1921-30
Observed	12	38	37
Expected*	0.14	0.17	0.2
O/E ratio	85.71	223.53	185
95% Confidence Interval	44.31-150	158.48-305.34	130.06-254.93

*Calculated from the age-specific death rates of Taiwan Area

For the rest three types of cancer, the later cohorts tend to show higher O/E ratios (for lung cancer, the ratios are 15.38, 31.18, and 44.53 respectively; for liver cancer, they are 11.17, 15.14, and 24.52; and for stomach cancer, 8.39, 14.71, and 15.54)

The above findings that the SMR's of both the urothelial cancer and the lung cancer increase with the increase of the morbidity rates of black-foot diseases in the four zones, and that though both the liver and the stomach cancers do not have a significant linear relation with the morbidity rates of black-foot disease, deaths from liver cancer in the four zones in Pu-tai Township are higher than those of the Taiwan Area, and the SMR of stomach cancer in A zone of the highest black-foot morbidity is 2.17 times higher than that of the Taiwan Area, seem to indicate that cancers of the urinary organs, lung, liver, and stomach may be related at varied degrees with the causes of the black-foot disease. For the lack of sex and age-specific death statistics for cancers of all types for the Taiwan Area for the years between 1956 and 1965, the expected values for these years are estimated by using the death statistics of 1966, the SMR's, thus, are relatively under estimated. Even under this under estimation, a close correlation is still found between the four types of cancer and the black-foot disease. It is, therefore, likely that Pu-tai Township exists some local risk factors which may induce black-foot disease and at the same time cause the increase in the four types of cancer.

Pu-tai Township is not an industrial area, it is rather a fish-farming, salt-industry, and agricultural area. The chances of the population being exposed to chemical dyes are rare. Differences of smoking rate among the four zones do not appear so substantial to interpret the different death rates of urothelial cancer and lung cancer. The hepatitis B carrier rate of 15.7% (Chen et al, 1962) is not higher than that of the Taiwan Area, and excess drinking is not customary either. The reason that the rate of liver cancer in the four zones of Pu-tai Township is 1.51-3.85 times higher than that of the Taiwan Area remains unexplained. The epidemiological studies show that the intake of the artesian well water is the major cause of the black-foot disease (Chen et al, 1962), and that the morbidity of black-foot disease has a dose-response relation with the amount of the artesian well water intake, we, therefore, suspect that the local risk factor that induces black-foot disease and causes the increase in cancer is the artesian well water. Further, the significant linear relation between the morbidity of black-foot disease urothelial cancer as well as lung cancer leads us to speculate that the difference in the intake of the artesian well water may be the main reason which causes the differences of these two types of cancer in these four zones. The relation between the liver cancer and the artesian well water may not be as significant, its SMR, therefore, does not increase with the increase of the morbidity of black-foot disease. The intake of artesian well water, perhaps then is a partial reason for the higher rate of liver cancer in this township.

Stomach cancer is significantly higher than that of the Taiwan Area only in A zone with the highest morbidity of black-foot disease. This finding is different from that of Chen et al. They used township as units for analysis, and found that the death rate of stomach cancer was not significantly higher than that of the Taiwan Area. The increase in stomach cancer may require a large amount of exposure to the artesian well water. When a larger area is used as a unit for analysis, the effect of a smaller area may be diluted.

What component of the artesian well water is carcinogenic? Is it the arsenic that is accepted by most as the pathogenic factor of the black-foot disease? Are there other carcinogens, such as the fluorescent substances suggested by Lu (Lu et al, 1988)?

In animal studies, arsenic has not yet been successful in establishing a carcinogenic model. It, however, induces the morphological changes of cells and the mutation of chromosomes, and promotes the chromosomal aberration and the clastogenicity induced by other carcinogenic substances. However, when the animal is exposed to arsenic before the carcinogenic substances, no chromosomal abnormalities such as the ones resulted from the arsenic exposure at a later stage are noted (Lee et al, 1986). Therefore, arsenic perhaps is a promoting or cogenotoxic effect factor. The black-foot disease area has been lower in the social-economic status and poorer in nutrition, the population may have a poorer methylation ability of the liver which may improve the speed and strength of other carcinogenic factors. We, thus, find that the four types of cancer are significantly higher than those of the Taiwan Area in the three villages, Hao-mei, Hsin-min, and Fu-hsing, which are nearest to the sea and are of the lowest economic status that they have to rely on the artesian well as their source of water supply. Their average ages at death are also lower than those of the three zones.

As to the suggestion of Lu that fluorescent substances may be the major carcinogenic factor, although study has indicated that the intensity of fluorescent substances are positively correlated with the bladder cancer (Lu et al, 1986), their experiments also show that the intensity of fluorescent substances and the ability to cause gangrene and fester of the tails and feet of mice are negatively related, but is related positively to the ability of cellular mutation (Lu et al, 1988). These findings do not agree with our finding that there exists a linear correlation between the morbidity of the black-foot disease and the urothelial cancer as well as the lung cancer. The carcinogenicity of the fluorescent substances requires further analysis of the correlation between well water and the death rates of cancer in various areas, and more animal experiments for confirmation. We do not,