Original Article

Retrospective study of preventive effect of maize on mortality from Parkinson's disease in Japan

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The findings of a negative association between past maize (*Zea mays*) production and current Parkinson's disease mortality by each prefecture in Japan tends to support the hypothesis that the nutritional condition that causes niacin deficiency might protect people from Parkinson's disease. Specifically, the negative association between both the area planted for dried corn in 1960, 1970 or 1977 and the area planted for sweet corn in 1960 and age-adjusted death rates for Parkinson's disease is ecological evidence supporting the hypothesis. Extending the analysis to other cultivated crops, even stronger negative associations of age-adjusted death rates for Parkinson's disease and cultivation of rice and soybeans were found, but associations were not significant for a large variety of vegetables. The findings for soybean and rice are attributed to the correspondence (co-linearity) of cultivation of these other two seed-crops with maize. Hence, further testing of the theory of niacin deprivation and prevention of Parkinson's disease finds some circumstantial support in the cultivation patterns of a grain of poor niacin and tryptophan availability.

Introduction

Some chemical compounds in the environment have been suspected to cause Parkinson's disease since 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine was discovered to cause this disease artificially.[1] The prevalence rate of Parkinson's disease in countries with high proportion of aged population is so high that it is considered to be one of the diseases of the aged. Previous epidemiological reports indicate the importance of niacin in relation to the pathogenesis of Parkinson's disease. Parkinson's disease is very low in Africa and China where people tend to suffer from pellagra and niacin deficiency.[2] Isoniazid, an anti-tubercular agent, relieves the symptom of Parkinson's disease,[3] but it causes pellagra as a side effect. Parkinson's disease patients drink less alcohol,[4] but heavy drinkers often suffer from pellagra. Consequently, the people who tend to suffer from niacin deficiency might tend not to suffer from Parkinson's disease.

Niacin is used for the synthesis of nicotinamide adenine dinucleotide (NAD) in the body, and in the metabolism process, NAD releases nicotinamide by ADP-ribosylation, and the nicotinamide is methylated to 1-methylnicotinamide (MNA). Nicotinamide N-methyl-transferase (EC2.1.1.1) activities of rat brain and liver were assayed with gas chromatographic-mass spectrometric analysis, and it was suggested that MNA could be formed enzymatically in mammal brain.[5] The MNA significantly decreased dopamine content in the striatum. MNA destroyed several subunits of cerebral NADH: ubiquinone oxidoreductase.[6] These findings indicate that MNA might be involved in the pathogenesis of Parkinson's disease.

Because maize (*Zea mays*) contains niacytin which humans cannot use as niacin, and because maize contains low tryptophan, niacin deficiency is observed in populations where maize is a staple food.[7] When various countries in the world are hierarchically sorted by the main source of energy consumption, South Africa, Zimbabwe and Japan are classified as having a high intake of maize.[8] The prevalence or mortality rates of Parkinson's disease in South Africa,[9] Zimbabwe[10] and Japan,[11] is relatively lower than other countries. In China, the maize consumption districts coincide with the production districts. Keshan disease is common in the maize producing districts, where selenium intake is very low.[12] Correlation coefficients among the prevalence

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rates of Parkinson's disease, maize yield, niacin intake and selenium intake by each province in China were analyzed.[13] Positive correlation was seen between selenium intake and niacin intake. Niacin deficiency was also seen in the Keshan disease prevalent area. Negative association was seen between maize production and niacin intake and between maize production and prevalence rate of Parkinson's disease. From these results maize appears to be an important food to prevent Parkinson's disease.

There are several sets of diagnostic criteria for Parkinson's disease. In addition, especially in developing countries, there is possibility that many Parkinson's disease patients do not consult a doctor, and these cases are not diagnosed as Parkinson's disease. These problems often make it difficult to estimate the prevalence rate exactly. Even if the diagnostic criteria are almost unified in Japan, the death rate of Parkinson's disease is more reliable than the prevalence rate in a nationwide survey. In Japan, adequate amounts of niacin are commonly taken from many sources. However, for a while after World War II, most people had relatively low niacin intakes and maize was mainly consumed in the production districts. In this study, the relationship between past maize production and current Parkinson's disease death rates by each prefecture in Japan was analysed to support the hypothesis that the nutritional condition that causes niacin deficiency might protect people from Parkinson's disease.

Methods

The death rates in 1999 and age-adjusted death rates during 1977-1985 for Parkinson's disease were obtained from Vital Statistics of Japan by Health and Welfare Statistics Association[14] and Imaizumi,[15] respectively. Sweet corn, dried corn and other crop production and the area planted in 1960, 1970, 1977, 1985 and 1999 were from the Statistical Yearbook of Ministry of Agriculture Forestry and Fisheries, Japan.[16] There is no data on dried corn production in 1985 and 1999 in the Statistical Yearbook. All data for 46 prefectures, except Okinawa (Okinawa was under the government of USA until 1972), were analysed. The relationships between items examined were analysed statistically by calculating Pearson's correlation coefficients.

Results

Table 1 shows the correlation coefficients between death rates or age-adjusted death rates for Parkinson's disease, and maize production by prefecture in Japan. A negative association was seen between both the area planted for dried corn in 1960, 1970 or 1977 and the area planted for sweet corn in 1960 and the age-adjusted death rates, but it gradually weakened between 1970 and 1999. No correlation was seen between death rates and any maize data. Extending the analysis to other cultivated crops in 1960, even stronger negative associations of age-adjusted death rates for Parkinson's disease and cultivation of rice and soybeans were found, but associations were not significant for a large variety of vegetables (Table 2). The correlation coefficients among maize, rice and dried soybean production in 1960 were calculated (Table 3 and 4). High correlation was seen among them, especially

Table 1. Correlation coefficients between death rates or age-adjusted death rates for Parkinson's disease and maize production, by prefecture in Japan.

Year		Death rate in 1999	Age-adjusted death rate, 1977-1985
1960	Sweet corn production	-0.189	-0.290
	The area planted for sweet corn	-0.184	-0.300 (P<0.05)
	Dried corn production	-0.031	-0.282
	The area planted for dried corn	-0.072	-0.303 (P<0.05)
1970	Sweet corn production	-0.169	-0.271
	The area planted for sweet corn	-0.176	-0.278
	Dried corn production	-0.025	-0.252
	The area planted for dried corn	-0.068	-0.298 (P<0.05)
1977	Sweet corn production	-0.159	-0.236
	The area planted for sweet corn	-0.156	-0.245
	Dried corn production	-0.062	-0.269
	The area planted for dried corn	-0.054	-0.298 (P<0.05)
1985	Sweet corn production	-0.159	-0.207
	The area planted for sweet corn	-0.156	-0.227
	Dried corn production	-	-
	The area planted for dried corn	-0.054	-0.209
1999	Sweet corn production	-0.130	-0.171
	The area planted for sweet corn	-0.128	-0.170
	Dried corn production	-	-
	The area planted for dried corn	-0.008	-0.133

Table 2. Correlation coefficients between age-adjusted death rates for Parkinson's disease and crop production in 1960, by prefecture in Japan.

Rice production	-0.375 (P<0.01)	Tomato production	0.063
The area planted for rice	-0.310 (P<0.05)	The area planted for tomato	-0.003
Wheat production	-0.013	Cabbage production	-0.016
The area planted for wheat	0.000	The area planted for cabbage	-0.022
Sweet potato production	0.182	Chinese cabbage production	-0.191
The area planted for sweet potato	0.182	The area planted for Chinese cabbage	-0.267
Potato production	-0.209	Spinach production	0.012
The area planted for potato	-0.207	The area planted for spinach	-0.005
Soybean production	-0.337 (P<0.05)	Welsh onion production	-0.007
The area planted for soybean	-0.360 (P<0.01)	The area planted for welsh onion	-0.091
Cucumber production	-0.126	Onion production	0.110
The area planted for cucumber	-0.148	The area planted for onion	0.140
Eggplant production	-0.099	Carrot production	-0.127
The area planted for eggplant	-0.206	The area planted for carrot	-0.151

between sweet corn and dried corn, between sweet corn and dried soybean and between dried corn and dried soybean.

Discussion

Several researchers have reported on the relationship between niacin intake and Parkinson's disease. Some of them indicated that niacin might be neuroprotective,[17,18] whereas another did not support this hypothesis.[19,20] There are no case-control studies that show the pathogenic effect of niacin intake on Parkinson's disease. Usually in these studies, patients are asked to recall their dietary habits just before the diagnosis, and the controls are asked to recall their dietary habits one or two years prior to the interview. It seems to be difficult to recall them exactly, and the observing time is too short to study the effect on Parkinson's disease. It may be difficult to study the effect of individual dietary habits on diseases. For example, Parkinson's disease is diagnosed in old age and its progress is difficult to follow before diagnosis. For these reasons, we studied the relationship between past maize production and the current Parkinson's disease death rate by each prefecture in Japan.

A negative association was seen between the area planted for maize and age-adjusted death rates for Parkinson's disease. However, a statistically significant correlation was not seen between maize production and the age-adjusted death rates in 1960. In this year maize production was affected by climatic conditions. Statistically significant correlations were seen between sweet corn production and the age-adjusted death rates in 1958, and between dried corn production and the age-adjusted death rates in 1962 (data not shown). These findings suggest that the area planted for each crop might be more reliable than the production data when studying the link between corn and Parkinson's disease.

The association between age-adjusted death rates for Parkinson's disease and cultivation of maize was weaker between 1970 and 1999. This may be because imported maize has increased over this period in response to rising demands for maize in processed products. Most of the maize is now cultivated in limited prefectures such as Hokkaido in Japan. This shift in maize production could affect the statistics, but the main dietary habits of elderly people should be relatively maintained.

Negative association was seen between rice production (also the area planted for rice) and the age-adjusted death rates for Parkinson's disease. Because rice is the most important farm product in Japan, it has been purchased and distributed by the Japanese government. As a result, rice is consumed equally throughout Japan. This negative association might simply reflect that the age-adjusted death rates for Parkinson's disease were lower in rural areas than in urban areas of Japan.[15]

A negative association was also seen between dried soybean production (also the area planted for dried soybean) and the age-adjusted death rates for Parkinson's disease. A high correlation was seen between sweet corn and dried corn, between sweet corn and dried soybean and between dried corn and dried soybean. In contrast to maize (which is cooked/processed straight away), uncooked soybean is distributed throughout Japan as the raw material for processed products such as "miso", "soy", "tofu" and other soy derivatives. The findings for soybean and rice are attributed to the correspondence (co-linearity) of cultivation of these other two seed-crops with maize.

As with sorghum, maize contains abundant leucine which inhibits quinolinate phosphoribosyl transferase, the key enzyme for converting tryptophan to NAD, which in turn leads to pellagra.[7,21] In Japan, adequate amounts of niacin or tryptophan are commonly consumed from many sources. This inhibition by leucine might be critical to the prevention of Parkinson's disease.

From these results niacin is expected to be one of the promoting factors for Parkinson's disease, and maize could be an important food for its prevention. Vitamins are excessively ingested now in Japan.[22] But the previous reports provided weak evidence for the safety of their long-term excessive intake. It may be necessary to revisit the recommended amount of niacin for daily consumption. This is a preliminary inquiry to explore the possibility of further ecological associations between niacin and Parkinson's disease. Further testing of the theory of niacin deprivation and prevention of Parkinson's disease finds some circumstantial support in the cultivation patterns of a grain of poor niacin and tryptophan availability.

Table 3. Correlation coefficients among maize, rice and soybean production in 1960, by prefecture in Japan

	Sweet corn	Dried corn	Rice
Dried corn	0.811		
Rice	0.545	0.455	
Soybean	0.888	0.804	0.625

Table 4. Correlation coefficient among maize, rice and soybean planted area in 1960 by prefecture in Japan

	Sweet corn	Dried corn	Rice
Dried corn	0.922		
Rice	0.598	0.496	
Soybean	0.892	0.872	0.637

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