Original Article

Time-lag estimate between dietary intake and breast cancer mortality in Japan

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This study examines the relationship between the nutrient intake, including total dietary fiber (TDF) and fat, and the age-adjusted mortality from breast cancer (MBC) in Japanese females during the period from 1948 to 2000. The information for MBC in females was based on the data in Vital Statistics of Japan. Nutritional data were collected from the National Nutrition Survey reports. The data were analyzed by Pearson's correlation and a partial correlation, adjusting for the effect of reproductive factors. The time lag was estimated by measuring the strength of the linear relationship set up for a 0-35-year delay in mortality and statistically evaluated by comparing the correlation coefficients. The partial correlation analysis indicated that the individual intakes of total fat (r=0.688), animal protein (r=0.657), carbohydrate (r=-0.886), and plant protein (r=-0.770) were significantly (p<0.01) correlated with MBC. Each of these coefficients of correlation changed and reached a maximum value with increasing time lag. The estimated time lag values for the influence of fat, animal protein and TDF were 20-32 years, 19-31 years and 9-35 years, respectively. It is deduced from the results that the increased MBC in Japanese women is related to the long-term effect from the intake of a high-fat, high-animal protein and low-fiber diet typical in the western world.

Key Words: Japanese breast cancer mortality; partial correlation coefficient; time lag; dietary fiber; dietary fat

Introduction

The age-adjusted mortality from breast cancer (MBC) for females in Japan has been increasing in recent decades, although it remains lower than that in Europe and America. An analysis of international data has shown a strong positive correlation between the *per capita* fat intake and age-adjusted mortality from breast cancer.[1] However, recent international comparisons of epidemiological data do not strongly support a link between breast cancer and fat intake.[2, 3] Some factors that affect the risk of breast cancer probably act early in life.[4] If the dietary intake over the preceding 20-30 years represents any influence of dietary factors on the mortality from breast cancer, this may explain the inconsistent findings of epidemiological studies, in which only the adult diet has been measured. The westernization of the Japanese diet has been proposed as a causative factor by epidemiological studies of breast cancer.[5, 6]

On the other hand, reproductive factors such as non-delivery, late age at the first birth, and early age at menarche have been consistently associated with an increase in breast cancer risk.[2, 3] There was a gradual decline in the total fertility rate in Japan from 1948 to 1960, and this tends to continue.[7] The average age at the first birth of Japanese women is late, and one in four mothers now has her first child after the age of 30. This social phenomenon might have played a part in the changing risk factor, increasing the incidence of breast cancer in Japanese women.

To our knowledge, there is no other ecological study of the relationship between the nutritional intake and mortality of Japanese women that has taken the reproductive factor into consideration. The aim of our study was to examine the association between the long-term consequences of nutritional intake and MBC. We evaluated the time lag by using a partial statistical correlation, set up for a 0—35-year delay, adjusted for the effects of reproductive risk factors.

Materials and Methods

The annual age-adjusted mortality for breast cancer (MBC) in females and the total fertility rate from 1948 to 2000 are based on data from the Vital Statistics of Japan.[7] Nutrient intakes during this period are based on data from the

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Manuscript received 22 February 2006. Revision accepted 29 June 2006.

National Nutrition Survey (NNS) reports.[8] As no data for total dietary fiber (TDF) intake is available in the NNS reports, we calculated the TDF value as a product of the value of the nutrient intake by food group per capita per day reported in the NNS reports and the TDF content of each food item or food group. The TDF contents of food items and food groups are based on values measured by the enzyme-gravimetric method of Prosky *et al.*.[9, 10]

The relationship between the nutrient intake and MBC was analyzed by Pearson's correlation (a simple correlation coefficient) and scattergrams. The relationship between the nutrient intake and MBC, with the effects of reproductive factors being controlled, was obtained by a partial correlation coefficient. The total fertility rate, showing a tendency toward a falling birthrate, was used as an indicator of reproductive factors. The lag years, namely the duration in years before the influence of nutrient intake was reflected by MBC, was estimated by determining the simple and partial correlation coefficients between the nutrient intake for a given period and MBC for a given period, or the given period with each additional year up to 35 years. For example, one lag year is the correlation coefficient between the nutrient intake from 1948 to 1999 and MBC from 1949 to 2000. The highest value for the correlation coefficient was determined as the maximum correlation coefficient. The difference between the maximum correlation coefficient and the correlation coefficient for every other lag year was evaluated by comparing the two correlation coefficients. Lag years in which the correlation coefficient showed no significant difference were determined to be equivalent to the year of the maximum correlation coefficient; thus, these lag years were also included in the lag year period. Statistical significance is defined as $p<0.05$. Calculations for the simple and partial correlation coefficients were performed with the SPSS statistical software package (SPSS Inc.).

Results

The annual changes in the nutrient intake and mortality from breast cancer for the Japanese population are shown in Fig. 1. The TDF intake *per capita* decreased rapidly

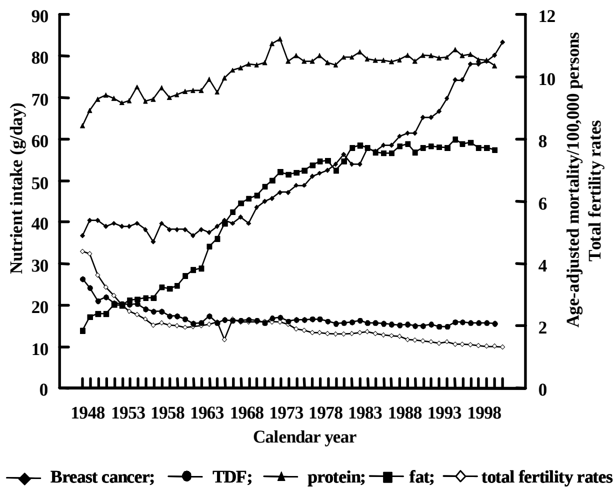

Figure 1. Changes in dietary fiber, fat intake and mortality from breast cancer in Japan.
*TDF, total dietary fiber.

from 26.4 g in 1948 to 15.8 g in 1963, and subsequently stabilized at around 16.0 g. The total decrease in TDF has been about 40% during the last 53 years. The fat intake increased rapidly from 18.0 g in 1950 to 59.9 g in 1996 and subsequently showed signs of a slight decrease. The total increase in fat has been about four times during the last 53 years. The fat intake adjusted for total energy and the fat/TDF intake also respectively increased from 6.2% to 26.5% and from 0.53 to 3.67 during the same period. The total protein intake has shown a gradual increase from 1948 to 1970 and has stabilized at around 80 g since 1973. While the intake of animal protein has increased by about 3 times during the past 53 years, the intake of plant protein has decreased by 32%.

The inter-relationship between MBC and the fat energy ratio is shown in Fig. 2. The fat energy ratio rapidly increased from 6.2% to 20.7%, and MBC slowly increased during the same period (from 1948 to 1973). Since 1973, the fat energy ratio has slowly increased, while MBC has rapidly increased. The turning point for the value of fat energy ratio was about 20%.

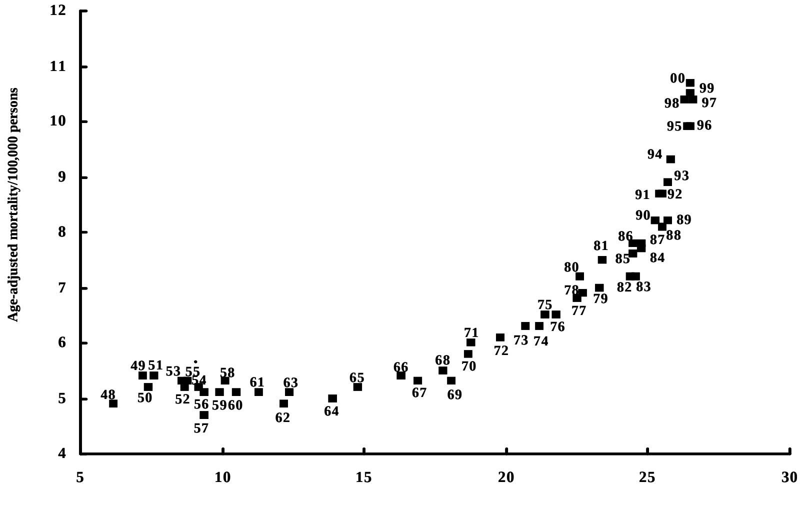

Figure 2. Relationships between age-adjusted mortality from breast cancer and fat energy ratio
* Numbers show the years.

Table 1. Maximum simple correlation coefficient and estimated time lag between nutrient intake and age-adjusted breast cancer mortality in Japan (1948-2000)†

Nutrient	Simple coefficient of correlation‡	Maximum simple coefficient of correlation		Time lag
	r [n=53]	r [n]	Time lag (year)	(year)
Energy	-0.683**	0.838** [26]	27	23−33
Total protein	0.674**	0.933** [27]	26	14−31
Animal protein	0.809**	0.970** [28]	25	13−35
Plant protein	-0.858**	-0.973** [34]	19	10−23
Fat	0.793**	0.991** [24]	29	24−31
Fat/energy ratio	0.853**	0.992** [24]	29	23−32
Carbohydrate	-0.930**	-0.971** [41]	12	1−25
TDF§	-0.536**	-0.904** [18]	35	12−35
Fat/TDF	0.801**	0.993** [23]	30	26−32

†The time lag was estimated by measuring the strength of the linear relationship set up for a 0─35-year delay in mortality and statistically evaluated by comparing the correlation coefficients. ‡0-year lag; ** p<0.01; §total dietary fiber

The simple coefficient of correlation indicates that the individual intake of total fat (r=0.793), protein (r=0.674) and animal protein (r=0.809) was positively correlated with MBC, while the individual intake of TDF (r=-0.536), carbohydrate (r=-0.930) and plant protein (r=-0.858) was negatively correlated with MBC (Table 1). A positive correlation was apparent in the fat/TDF ratio (r=0.801). These coefficients of correlation changed and reached a maximum value after a certain time lag. The intake of fat reached its maximum correlation after a 29-year delay (r=0.991), while that of protein showed a maximum correlation after a 26-year delay (r=0.933). A comparison of the correlation coefficients shows the same level of correlation for fat with a 24─31-year delay, while that of protein had a 14─31- year delay. The maximum negative correlation between TDF and MBC was -0.904 after a 35-year lag, and the same level of correlation was found with a 12─35-year delay. The intake of TDF from cereals showed a maximum negative correlation among the TDF sources with a 35-year delay (r=-0.967), and the same level of correlation was found with a 22─35-year delay. The relationship between fat/TDF and MBC had the highest positive correlation after a 30-year delay (r=0.993) among all the items.

The partial correlation coefficients were respectively lower than the simple correlation coefficients (Table 2). A highly significant positive partial correlation for MBC was found with the fat (r=0.688) and animal protein (r=0.657) intake. On the other hand, a significant negative partial correlation was found with the intake of carbohydrate (r=-0.886) and plant protein (r=-0.770). There was a statistically significant correlation for MBC with the intake of TDF from cereals (r=-0.399), but not with TDF generally. Although the correlations incorporating a chronological partial coefficient were at a lower level than those with a chronological simple coefficient, the approximate time lag for the partial maximum correlation was similar to the period for the simple correlation coefficient. Fat and protein both showed a high partial correlation coefficient without being influenced by natality. The estimated time lag for fat was 20─32 years, while that for protein was 19─31 years. The maximum negative partial correlation between TDF and MBC was -0.757 after a 35-year lag, and the same level of correlation was found with a 9─35-year delay. The intake of TDF from cereals showed the maximum negative partial correlation (r=-0.940) among the TDF sources with a 32-year delay. The relationship between fat/TDF and MBC had the highest

Table 2. Maximum partial correlation coefficient and estimated time lag between nutrient intake and age-adjusted breast cancer mortality in Japan (1948-2000) †

Nutrient	Partial coefficient of correlation‡	Maximum partial coefficient of correlation		Maximum
	r [n=53]	r [n]	Time lag (year)	(year)
Energy	-0.682**	0.820** [26]	27	24−33
Total protein	0.402**	0.901** [27]	26	19−31
Animal protein	0.657**	0.958** [27]	26	19−31
Plant protein	-0.770**	-0.947** [34]	19	7−24
Fat	0.688**	0.988** [27]	26	20−32
Fat/energy ratio	0.779**	0.987** [24]	29	20−31
Carbohydrate	-0.886**	-0.967** [35]	18	3−25
TDF§	0.145	-0.757** [18]	35	9−35
Fat/TDF	0.640**	0.989** [23]	30	24−32

†The partial coefficient of correlation was calculated after allowing for the total fertility rate. The time lag was estimated by measuring the strength of the linear relationship set up for a 0─35-year delay in mortality and statistically evaluated by comparing the correlation coefficients. ‡0-year lag; ** p<0.01; §total dietary fiber

positive partial correlation after a 30-year delay (r=0.989).

Discussion

Japanese dietary habits have changed dramatically during the last half century. The NNS in Japan has been undertaken annually since 1946, and this survey has given accurate information on the daily food consumption and nutrition intake per capita. However, the definition of food groups has varied to some extent over the years, and we considered that defining the food intake by food group was inappropriate to use as a marker for eating habits. We therefore used the nutrients as markers for the eating habits because we felt that the nutrients would better reflect the eating changes. The results of our analysis suggest that the increased MBC in Japanese women is related to the long-term intake of a high-fat, high-animal protein and low-fiber diet typical in the western world. The decreased intake of rice and potatoes is one of the main causes for the downward trend of carbohydrate and TDF intake during the period of high economic growth (1960-1975) in Japan.[11, 12] In contrast, the increased intake of fats, oils and animal food is associated with the upward trend in the intake of fat energy and animal protein during the same period.

The offspring of immigrants from Japan to the United States, but not the immigrants themselves, have breast cancer incidence rates that are similar to those of the general American population. This is in contrast to the colon cancer incidence rates that are seen as early as in the first generation.[13, 14] We have formerly reported that the increase in fat intake was positively associated with the mortality from colon cancer in the Japanese population after a 10–16-year lag.[15] In this present study, the increase in fat intake was maximally correlated with the increase in MBC approximately 24-31 years later. The finding in this study of a time-lag connection between breast and colon cancer is consistent with the results of the study on immigrants. Several extensive reviews of diet and cancer research in human populations in recent years have described that some factors that can affect the risk of breast cancer probably act early in life.[2, 3] Janssens[16] has pointed out that the relationship of fat and other lifestyle factors with breast cancer may result from influence during childhood and adolescence, exactly the period during which the breast is in full development.

Tominaga *et al.*[17] have studied the chronological correlation between the age-adjusted mortality from specific sites of cancer and the fat intake during the period from 1949 to 1987. In their report, the maximum correlation coefficient for colon cancer mortality and fat intake was given as 8 years, while that for MBC and fat intake was given as 9 years, indicating only a one-year difference. The present data were collected over a longer period to make a more realistic comparison for the time lag. We consider that the difference in time lag might have resulted from the population base and the investigation period.

In addition to the high correlation with fat, we noticed the importance of the fat-energy ratio. MBC has increased rapidly since the fat-energy ratio increased by over 20%. This indicates that MBC might be associated at a low level with dietary fat. There is some support for a reduction in the dietary fat composition, even to 20% of energy, during adulthood leading to a substantial reduction in breast cancer in western cultures.[18]

Protein was found to be another significant factor. There are differences between animal and plant proteins and their dietary sources. The increase in animal protein intake and the decrease in plant protein intake, namely westernization of the diet, was accompanied by a 19-31 year delay in relation to MBC. There are several possible biological mechanisms related to the effects of protein on endogenous hormone metabolism. However, based on available epidemiological evidence[19,20] and potential biological plausibility, the association is thought to be indirect, with influence from its effect on hormones.

TDF may also influence the breast cancer risk, although this relationship has received relatively little attention, aggregate data having been equivocal in terms of the protective effect against breast cancer.[21, 22] However, no reliable reports have been presented that were based on the annual change of TDF intake and MBC in Japan during the prolonged period used in this study. We found that TDF intake, especially from cereals, was inversely related to MBC. The results of this study indicate that TDF required a considerable time to exert an effect on MBC, the estimated time lag being prolonged a 9-35 year delay. When the daily intake of TDF was less than 17.0g, MBC rapidly increased, so the present intake (15-16g/day) may not be enough. Kaneda *et al.*[23] have suggested that both the fat and fiber intake should affect the hormone status in premenopausal Japanese women. Vegetarian women, who consume a higher amount of fiber and lower amount of fat than non-vegetarians, have a lower blood level and reduced urinary excretion of estrogens, apparently due to their increased fecal excretion.[24]

A considerable negative correlation was indicated between carbohydrate and MBC, although no clear explanation for this phenomenon is apparent at present; the Japanese food tables estimate the carbohydrate intake by difference and no direct measurement of sugar and starch has been undertaken. One of explanations for the negative correlation resulting from the Japanese food tables is that carbohydrate includes many components such as TDF, starch and resistant starch that are related to MBC. The World Cancer Research Fund[3] has published an extensive review of diets and cancer research in human populations. The panel notes that non-starch polysaccharides (fiber) can possibly decrease the risk of breast cancer, and that diets high in total fat and in animal/saturated fat can possibly increase the risk.

In consequence, the present data indicate that MBC has not only the most striking correlation with fat/TDF among all the nutritional parameters, but also with dietary fat and/or dietary fiber. Although further research is needed to clarify the role of dietary fat and/or dietary fiber in the risk of breast cancer, the results of this study indicate the significance of the long-term effect of nutrient intake on breast cancer.

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日本飲食攝取與乳癌死亡率之間的時間落差

此研究評估營養素攝取，包含總膳食纖維(TDF)及總脂肪攝取與 1948 至 2000 年期間日本女性年齡校正乳癌死亡率(MBC)之相關性。女性 MBC 資訊是根據日本生命統計資料而得。營養素資料則為全國營養調查報告。資料的分析採用皮爾森積差相關及部分相關，並校正其他生育因子的影響。時間落差的估計是測量建立死亡率延遲 0-35 年的直線相關強度，統計評估則比較相關係數。部份相關分析顯示個體總脂肪(r=0.688)、動物蛋白質(r=0.657)、碳水化合物(r=-0.886)及植物性蛋白質(r=-0.770)與 MBC 的相關均達顯著(p<0.01)。隨著時間的落差的增加，每個相關係數改變並到達最大值。評估脂肪、動物性蛋白質及 TDF 三者對於時間落差的影響分別為 20-32 年、19-31 年及 9-35 年。依據結果推論日本女性 MBC 的提高與長期攝取高脂肪、高動物性蛋白質及低纖維的西方飲食具有相關性。

關鍵字:日本人乳癌死亡率、部分相關係數、時間落差、膳食纖維、膳食脂肪。