

Incidence and Mortality of Testis and Prostate Cancers in Relation to World Dietary Practices - Dairies are Causatively Related to these Malignancies

Adapted from:

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Abstract

The incidence and mortality rates of testis and prostate cancers in 42 countries were correlated with the dietary practices in these countries using the cancer rates (1988-92) provided by the International Agency for Research on Cancer (IARC) and the food supply data (1961-90) provided by the Food and Agriculture Organization (FAO). Among the food items we examined, cheese was most closely correlated with the incidence of testis cancer at ages 20-39, followed by animal fats and milk. The correlation coefficient (r) was highest ($r = 0.804$) when calculated for cheese consumed during the period 1961-65 (maternal or prepubertal consumption). Stepwise-multiple-regression analysis revealed that milk + cheese (1961-65) made a significant contribution to the incidence of testis cancer (standardized regression coefficient $[R] = 0.654$). Concerning prostate cancer, milk (1961-90) was most closely correlated ($r = 0.711$) with its incidence, followed by meat and coffee.

Stepwise-multiple-regression analysis identified milk + cheese as a factor contributing to the incidence of prostate cancer ($R = 0.525$). The food that was most closely correlated with the mortality rate of prostate cancer was milk ($r = 0.766$), followed by coffee, cheese and animal fats. Stepwise-multiple-regression analysis revealed that milk + cheese was a factor contributing most to the mortality of prostate cancer ($R = 0.580$). The results of our study suggest an important role of milk and dairy products in the development and growth of testis and prostate cancers. The close correlation between cheese and testis cancer and between milk and prostate cancer suggests that further mechanistic studies should be undertaken concerning the development of male genital organ cancers.

Introduction

Japanese lifestyle underwent drastic changes after the end of the Pacific War (1945). Most conspicuous was the change in dietary practices. The intake of milk and dairy products, meat

and eggs increased 20-, 9- and 7-fold, respectively, during the 48 years between 1950 and 1998. It has been observed that in Japanese males born before 1945, death from testis cancer peaked in their thirties or forties, whereas in those born after 1946, the peak was in their twenties (a birth cohort effect). From these observations, Ganmaa *et al.* (1) presumed that the development of testis cancer in Japanese men is related to the dietary practices of Japanese boys at the time of puberty or earlier.

The age-adjusted death rate of prostate cancer has risen 25-fold almost linearly during the last 48 years from 1947-95, with no birth cohort effect on the death rate. From this, Ganmaa *et al.* (1) also presumed that the increased death from this cancer relates to an accumulation of the effects of dietary factors throughout life.

The incidence of testis cancer in Western countries has steadily risen in the past 40 or 50 years (2-4). Prostate cancer is the most common cancer among men in most Western countries (5). The incidence and mortality of both malignancies vary greatly from country to country (6,7).

The correlation of incidence and mortality rate with the prevalence of environmental agents in various geographical areas provides useful clues to the etiology of cancer (8,9). In particular, correlation of cancer rates with dietary practices in different countries is a worthwhile exercise.

With the availability of international cancer incidence and mortality data (6,7,10,11), a further correlation analysis is justified. In our study, we used incidence and mortality data for testis and prostate cancers from each of 42 countries and correlated the rates with dietary variables.

Materials and Methods

Incidence of testis and prostate cancers

Cancer Incidence in Five Continents edited by Parkin *et al.* (6) provided us with comparable data on the incidence of cancer between 1988-92 in different geographical locations (183 populations in 50 countries). In our study, we used data from 42 of these countries, for which both cancer incidence rates and food consumption data (FAOSTAT Database Collections) (12) were available.

In several countries, more than one cancer registry is operating. If more than one registry was available for a country, those with the editors' comment that 'The editors were unable to verify these data' (6) were excluded from our study. The remaining age-specific incidence rates in the same country were standardized to the world population. The mean value of the age-adjusted incidence rates was employed as a representative rate for the country (Australia, Brazil, China, France, Germany, India, Italy, Japan, Peru, Poland, Spain, Switzerland, Thailand and UK). For example, in Japan, six cancer registries (Hiroshima, Miyagi, Nagasaki, Osaka, Saga and Yamagata) are operating and the results are listed in

Cancer Incidence in Five Continents. The editors remarked on the data from Saga that ‘The editors were unable to verify these data.’ (6) The data from Saga were therefore excluded and the rates of the other five cancer registries were averaged after age-standardization to the world population.

In several countries, only one cancer registry reported data to the IARC. The incidence rate from the registry was then assumed to represent the incidence for the country (Algeria, Argentina, Austria, Columbia, Costa Rica, Ecuador, French Polynesia, Ireland, Korea, Mali, Malta, Philippines, Uganda, Uruguay, and Vietnam).

In some countries, cancer registries provided data for different ethnic groups. In our study, the rates for Africans were used for Zimbabwe; those for all Jews were used for Israel; those for Kuwait were used for Kuwaitis; and those for Non-Maori were used for New Zealand.

Canada, Denmark, Finland, Hong Kong, Iceland, The Netherlands, Norway and Sweden collected data for their cancer registry on a national basis. The incidence rates for these countries were used as provided.

Many cancer registries operate in the U.S. Among them, the registry for white people by the SEER program was used as a representative registry for the U.S.

In most of the countries examined, the incidence of testis cancer peaked in groups of ages 25-29 or 30-34 (6). Therefore, truncated age-adjusted incidence rates for 20-39-year-olds were used to evaluate the relationship between the incidence of testis cancer and food intake. The incidence of prostate cancer increased with age (6). Therefore, for this cancer, the age-adjusted incidence rates for all ages were used for the evaluation.

Mortality of testis and prostate cancers

The age-specific mortality rates of both cancers that are listed in tabulated form in GLOBOCAN 1 (7) were employed in our study. The mortality data for French Polynesia are not given in GLOBOCAN 1; data for the other 41 countries mentioned above in the section on cancer incidence were used in the evaluation.

Food consumption

The consumption data (Mt/1,000 *capita*/year) for various food items from 1961-91 that are available from the FAOSTAT Database Collections (12) were used. The food items used for our study were animal fats, meat (bovine meat, pig meat, poultry meat, and mutton and goat meat), eggs, butter, milk excluding butter, whole milk, cereals excluding wine, pulses, beans, soy beans, peas, fruits excluding wine, vegetables, tomatoes, coffee, tea and alcoholic beverages. Tomatoes were considered separately because they are claimed to be a protective factor against prostate cancer (13-15). The consumption of each food or drink was converted from Mt/1,000 *capita*/year to g/*capita*/day.

To evaluate the relationship between food intake and testis cancer incidence, three food intake values (average intake from 1961-65, from 1961-70 and from 1961-90) were used. To evaluate the relationship between food intake and prostate cancer, the average food intake from 1961-90 was used. The reason for this is that testis cancer development may relate to the prenatal environment or the environment of boys at or before puberty, whereas prostate cancer development may relate to an accumulation of environmental factors throughout life (1).

Statistical analysis

All of the data were analyzed by Stat View (SAS Institute Inc., Cary, NC). The 0.05 level of probability was used as the criterion for significance. Simple correlation coefficients (r) were calculated to examine the association between the incidence or mortality rates of testis and prostate cancers and the consumption of each food item. Consumption of several food items was closely interrelated (collinearity, $r > 0.8$). For example, the r -value calculated for the correlation between the amount of milk and cheese consumed in 1961-90 was 0.812. Hence, consumption of milk and cheese in the same period was grouped as milk + cheese. The contributions of these grouped food items to the incidence or mortality were evaluated by stepwise-multiple-regression analysis. The food items selected for the analysis (independent variables) were the following 11 items: animal fats + butter, milk + cheese, eggs, meat, cereals, pulses, fruits, vegetables, vegetable oils, coffee, and alcohol.

Results

Incidence of testis cancer and food intake

The truncated age-adjusted incidence rates for testis cancer in the 20-39 age group varied greatly from one country to another; Switzerland had the highest rate at 22.2/100,000, followed by Denmark (21.8) and Germany (20.2) (**Fig. 1**). The lowest rate (0/100,000) was found in Algeria and Zimbabwe, followed by Uganda (0.32), and Mali and China (both 0.49).



Fig. 1. Correlation between testis cancer incidence rates at ages 20-39 years and *per capita* cheese consumption (1961-65) in 42 countries.

Table 1. Correlation coefficients between testis cancer incidence rate at ages 20-39 (1988-92) and food consumption¹

	Correlation coefficient		
	1961-65	1961-70	1961-90
Animal fats	0.770 ²	0.764 ²	0.767 ²
Butter	0.588 ²	0.583 ²	0.626 ²
Cheese	0.804 ²	0.792 ²	0.769 ²
Eggs	0.616 ²	0.609 ²	0.604 ²
Meat	0.655 ²	0.660 ²	0.686 ²
Fish	0.093	0.066	0.045
Milk	0.741 ²	0.736 ²	0.745 ²
Cereals	-0.358 ²	-0.395 ²	-0.465 ²
Pulses	-0.442 ²	-0.441 ²	-0.486 ²
Fruits	0.333 ²	0.385 ²	0.334 ²
Vegetables	0.103	0.090	0.079
Vegetable oils	0.475 ²	0.503 ²	0.447 ²
Alcohol	0.495 ²	0.514 ²	0.602 ²
Coffee	0.578 ²	0.574 ²	0.606 ²
Ten	0.058	0.072	0.078

¹Average values during 1961-65, 1961-70, and 1961-90.
²p<0.05; ³p<0.01; ⁴p<0.001.

Table 2. Stepwise-multiple-regression analysis on the consumption of selected food items (independent variables¹) affecting the incidence of testis cancer (dependent variable)

	Coefficient	Std. Error	R ²	F-to-remove
Cancer incidence vs. 11 independents (1961-65)				
Milk + cheese	0.013	0.002	0.654	37.981
Alcohol	0.012	0.005	0.272	6.562
Cancer incidence vs. 11 independents (1961-70)				
Milk + cheese	0.013	0.002	0.639	35.247
Alcohol	0.012	0.005	0.280	6.776

¹Fats + butter, meat, eggs, milk + cheese, cereals, pulses, fruits, vegetables, vegetable oils, coffee, and alcohol were used as the independent variables.
²R², standardized regression coefficient.

The simple correlation coefficients for the correlation between the incidence rate of testis cancer and food intake in 42 countries are shown in **Table 1**. Among the food items consumed in 1961-65, cheese was the most closely correlated with cancer incidence ($r = 0.804$), followed by animal fats (0.770) and milk (0.741). Concerning the years when cheese was consumed, the correlation coefficient was highest for cheese consumption in the 1961-65 period. On the other hand, cereals (-0.358) and pulses (-0.442) were negatively correlated with the incidence of testis cancer.

Stepwise-multiple-regression analysis to clarify the food items affecting testis cancer incidence revealed that milk + cheese (1961-65) made a significant

contribution to increasing the incidence of testis cancer around 1990 (standardized regression coefficient [R] = 0.654), followed by alcohol (0.272) (**Table 2**).

Mortality of testis cancer and food intake

In Norway, the age-adjusted incidence rate (per 100,000) was 8.0, whereas the mortality rate was 0.36. The fatality rate (ratio of mortality to incidence) of testis cancer in this country was less than 5%. On the other hand, the incidence rate in Algeria was 0.20, with a mortality rate of 0.19 (fatality rate, 95%). The average fatality rate in the 41 countries examined was 24.6%. The correlation coefficient between age-adjusted incidence rate and age-adjusted mortality rate of testis cancer in these countries was 0.350.

Animal fats had the highest correlation coefficient ($r = 0.317$) for the age-adjusted mortality rates of testis cancer. Using truncated age-adjusted mortality rates for ages 15-44 changed this correlation slightly; the coefficient for animal fats was increased to 0.390.

Incidence of prostate cancer and food intake

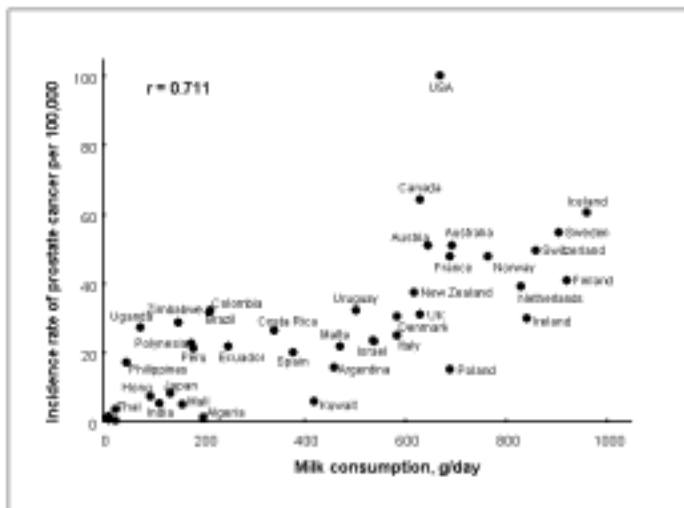


Fig. 2. Correlation between the age-adjusted incidence rates of prostate cancer and *per capita* milk consumption (1961-90) in 42 countries.

The age-adjusted incidence rate (per 100,000) of prostate cancer was highest in the U.S. (100.8), followed by Canada (64.7), Iceland (61.0) and Sweden (55.3). Korea had the lowest incidence rate at 0.90, followed by Vietnam (1.20), Algeria (1.80) and China (1.90) (**Fig. 2**). The difference between the highest and lowest incidence rates was as great as 84-fold.

Table 3. Correlation coefficients between age-adjusted prostate cancer incidence (1988-92) and food consumption¹

	Correlation coefficient		
	1961-65	1961-70	1961-90
Animal fats	0.552 ²	0.572 ²	0.490 ²
Meat	0.457 ²	0.655 ²	0.642 ²
Fish	0.129	0.100	0.093
Eggs	0.551 ²	0.531 ²	0.463 ²
Butter	0.485 ²	0.479 ²	0.450 ²
Cheese	0.569 ²	0.563 ²	0.586 ²
Milk	0.751 ²	0.740 ²	0.711
Cereals	-0.556 ²	-0.587 ²	-0.648 ²
Pulses	-0.313 ²	-0.304	-0.302
Vegetables	-0.001	-0.018	-0.043
Vegetable oils	0.344 ²	0.378 ²	0.436 ²
Tomatoes	0.134	0.142	0.148
Fruits	0.272	0.274	0.316 ²
Coffee	0.641 ²	0.625 ²	0.606 ²
Tea	-0.047	-0.032	-0.045
Alcohol	0.426 ²	0.440 ²	0.491

¹Average values during 1961-65, 1961-70, and 1961-90.
²p<0.05; ³p<0.01; ⁴p<0.001.

Among the food items examined, milk (1961-90) was most closely correlated with prostate cancer incidence ($r = 0.711$), followed by meat (0.642) and coffee (0.606) (**Table 3**). On the other hand, cereals were negatively correlated with its incidence (-0.648). The correlation coefficients for milk and meat consumed in the 1961-65 period were high (0.751 for milk and 0.657 for meat) compared to the values for milk (0.711) and meat (0.606) in the 1961-90 period.

Table 4. Stepwise-multiple-regression analysis on the consumption of selected food items (independent variables¹) affecting the incidence of prostate cancer (dependent variable)

	Coefficient	Std. Error	R ²	F-to-remove
Cancer incidence vs. 11 independents (1961-90)				
Milk + cheese	0.036	0.007	0.525	24.190
Cereals	-0.091	0.023	-0.425	15.807
Cancer mortality vs. 11 independents (1961-90)				
Milk + cheese	0.014	0.002	0.580	35.045
Cereals	-0.051	0.007	-0.418	18.644

¹Fats + butter, meat, eggs, milk + cheese, cereals, pulses, fruits, vegetables, vegetable oils, coffee, and alcohol were used as the independent variables.
²R, standardized regression coefficient.

Multiple-regression analysis identified milk + cheese (1961-90) as a factor contributing to an increased incidence of prostate cancer ($R = 0.525$), whereas it identified cereals as a factor contributing to a decreased incidence (-0.425) (**Table 4**).

Mortality of prostate cancer and food intake

The highest rate (per 100,000) of age-adjusted mortality was 26.2 for Switzerland,

followed by 24.8 for Norway and 24.2 for Iceland. China had the lowest rate of 0.65, followed by Vietnam (0.78) and Algeria (2.13) (Fig. 3).

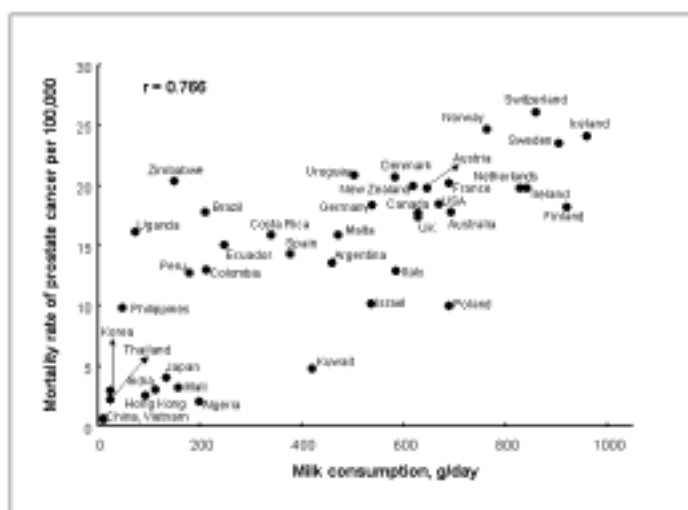


Fig.3. Correlation between the age-adjusted mortality rates of prostate cancer and per capita milk consumption (1961-1990).

Table 5. Correlation coefficients between age-adjusted prostate cancer mortality (1990) and food consumption¹

	Correlation coefficient		
	1961-65	1961-70	1961-90
Animal fats	0.627 [†]	0.610 [†]	0.606 [†]
Meat	0.609 [†]	0.602 [†]	0.594 [†]
Fish	0.064	0.029	0.015
Eggs	0.442 [‡]	0.423 [‡]	0.392 [‡]
Butter	0.569 [†]	0.575 [†]	0.576 [†]
Cheese	0.645 [†]	0.632 [†]	0.618 [†]
Milk	0.778 [†]	0.772 [†]	0.766 [†]
Cereals	-0.530 [†]	-0.575 [†]	-0.661 [†]
Pulses	-0.286	-0.262	-0.283
Vegetables	-0.108	-0.133	-0.162
Vegetable oils	0.358 [†]	0.377 [†]	0.366 [†]
Tomatoes	-0.058	-0.049	-0.015
Fruits	0.327 [†]	0.343 [†]	0.356 [†]
Coffee	0.616 [†]	0.620 [†]	0.633 [†]
Tea	0.086	0.109	0.106
Alcohol	0.530 [†]	0.546 [†]	0.585 [†]

¹Average values during 1961-65, 1961-70, and 1961-90.
[†]p<0.05; [‡]p<0.01; [§]p<0.001.

Mortality rates of prostate cancer were highly correlated with its incidence rates (r = 0.790). In some countries, however, a great difference was found between mortality and incidence. For example, the ratio of mortality to incidence (%) in the U.S. was 18.4 and that in Canada was 27.6.

The food (1961-90) most closely correlated with mortality of prostate cancer was milk (r = 0.766),

followed by coffee (0.633), cheese (0.618) and animal fats (0.606) (Table 5). In contrast, cereals was negatively correlated with the mortality (-0.661).

Consistent with the analysis of prostate cancer incidence, stepwise-multiple regression analysis revealed that milk + cheese (1961-90) made a most significant contribution to the mortality of prostate cancer (R = 0.580), whereas cereals contributed negatively to the mortality (-0.418) (Table 4).

Discussion

The ecological studies that correlate cancer incidence/mortality rates with the dietary practices in various geographical areas have certain shortcomings. The rates of incidence and mortality of any cancer are affected by regional differences in the diagnosis, registration/certification and the fatality rate of the cancer. It is certain that the cancer incidence and mortality data sets from developing countries are less complete than those from developed countries because of problems with under-diagnosis and under-certification of death due to the local medical and economic background and problems enumerating the population. Also, the consumption data for each food item in a country are not based on actual nutrition surveys, but are a rough estimate from the following equation: food supply *per capita* = (production + import + stock changes - export - feed - seed - processing - waste - other use)/population. Hence, it is difficult to determine the extent to which the available food data translates into daily *per capita* consumption. Nevertheless, the overall relationships are convincing, plausible and at least serve as guides for further epidemiological and experimental studies (8,9).

Testis cancer

Early diagnosis (biomarkers such as human chorionic gonadotropin and α -fetoprotein, CT scan, biopsy, *etc.*) and treatment (radiotherapy, chemotherapy including cisplatin [*cis*-diamminedichloro-platinum], *etc.*) of testis cancer may have improved the survival of patients with the disease. Indeed, cisplatin-based chemotherapy (a combination of platinum, vinblastine and bleomycin [PVB]) markedly improved the clinical outlook of male patients with disseminated germ cell tumors (16). This may explain why the correlation coefficient between the incidence and mortality of testis cancer was as low as 0.350. In this regard, incidence is a better index for this malignancy than mortality.

In most populations, testis cancer has a peak incidence rate in people in their twenties or thirties (6). The increased incidence of testis cancer in Western countries during the last 4 or 5 decades is associated with birth cohort effects (2-4). In Japan, where dramatic lifestyle changes occurred after the Pacific War, the peak death rate in the population born before the war was in their thirties or forties, whereas for those born after the war it was in their twenties (1). This birth cohort effect on the incidence/mortality of testis cancer suggests that the causative factors relating to this malignancy operate early in life, possibly in the fetal (*i.e.*, maternal), perinatal (also, maternal), or prepubertal period.

The food that was most closely correlated with the incidence of testis cancer was cheese, followed by animal fats and milk (**Table 1, Fig. 1**). Cheese consumption in the period from 1961-65 was highly correlated ($r = 0.804$) with the incidence around 1990. Stepwise-multiple-regression analysis also revealed that milk + cheese consumed in 1961-65 contributed most to the incidence. Patients who were diagnosed with the malignancy at age 29 (the middle age of 20-39) in 1990 were born in 1961. If cheese or milk is a cause of testis cancer, then that consumed before birth (maternal consumption) or in the prepubertal period

may be associated with the development of the cancer. Pregnant women are encouraged to consume milk and dairy products to meet their calcium requirements during pregnancy. Prepubertal boys are also preferentially encouraged to consume milk and dairy products because of their growth-promoting effect.

In most countries, the incidence rate of testis cancer, which is lowest in boys 5-14 years old, increases sharply in boys aged 15-19 years. This is thought to reflect the fact that testis cancers develop and grow in the presence of sex hormones or gonadotropins, *i.e.*, after the onset of puberty (2).

In addition to fats, protein and calcium, milk and dairy products contain considerable amounts of female sex hormones such as estrogens and progesterone (17). The high hormone content in milk is because present-day milk is produced from pregnant cows (18). It is not unreasonable to hypothesize that estrogens or progesterone in milk and dairy products are associated with the development of testis cancer.

Consumption of dairy products is said to be excessive in Western countries, a trend that probably started in the 1940s and 1950s (19). The increased incidence of testis cancer in the past 50 years in Western countries (2-4,20) may be associated with the increased consumption of milk and dairy products.

The adverse effects of milk on the male testis are only sparsely discussed in the literature. One reason for this may be that precise evaluation of individual milk intake is difficult because milk and its products (cheese, cream, butter, fermented milk, powdered milk) are used in a variety of foods, including cakes, candies, ice cream and chocolates, making retrospective evaluation of milk intake at young ages far more difficult.

Davies *et al.* (21) tested the hypothesis that milk and dairy products are risk factors for testis cancer in a case-control study undertaken in East Anglia, UK. All of the responding subjects completed a dietary questionnaire that included questions on their current and adolescent consumption of milk, dairy products, fruits and vegetables. Those with testis cancer had consumed significantly more milk during adolescence than had controls.

Prostate cancer

The age-adjusted incidence and mortality rates of prostate cancer have risen almost linearly all over the world during the 20-year in the period from 1973-77 to 1988-92 (5). The exponential increase of these rates with age is coincident with the general feature of solid malignant tumors. In Japan, where the age-adjusted mortality rate of the cancer has risen almost linearly about 25-fold over the last 48 years (1950-98), no birth cohort effect is observed in the mortality rate (1). This finding suggests that the recent increase in the incidence and mortality of prostate cancer may relate to the accumulation throughout life of environmental factors affecting the development and growth of prostate cancer.

The age-adjusted incidence rate (*per* 100,000) of prostate cancer in the U.S. was

100.8, while the mortality rate in this country was 18.6 (**Figs. 2 and 3**). Because the recent increase in the reported incidence may be associated with the introduction in the mid-1980s of prostate-specific antigen (PSA) for prostate cancer screening (22), the mortality rate may be more reliable than the incidence rate for elucidating the true nature of prostate cancer in some countries. The correlation coefficient between testis and prostate cancer incidence was 0.614, whereas the coefficient between testis cancer incidence and prostate cancer mortality was as high as 0.743.

Fat intake, especially that of animal origin, has long been listed as the major risk factor of prostate cancer (23-29). According to a recent review article by Kolonel *et al.* (30), however, although early epidemiologic studies implicated dietary fat as a likely causal factor for this cancer, scientific support for such an association has diminished in recent years as more epidemiologic evidence has accrued.

Attention has recently been focused on phytoestrogens, such as isoflavonoids, flavonoids and lignans, as a possible explanation for the contrasting rates of prostate cancer between Western and Asian countries (31-36). Soya is a major source of the isoflavonoids, daidzein and genistein (33). According to Griffiths *et al.* (34), a Japanese male consumes approximately 20 mg of isoflavones per day, whereas Western men consume less than 1 mg/day. They say that this is reflected in a high mean plasma concentration of genistein (180 ng/ml, n = 72) in Japanese men, compared to a level of less than 10 ng/ml for Western men.

Soybeans may possibly have a protective effect against the development and growth of prostate cancer. The simple correlation coefficients between the incidence and mortality of prostate cancer and the consumption of pulses were -0.302 and -0.283, respectively (**Tables 3 and 5**). According to Ganmaa *et al.* (1), however, the consumption of pulses, including soybeans, in Japan almost doubled between 1947 (43.8 g/day) and 1998 (72.5 g/day). In addition, the supply of soybeans as food in Japan also increased between 1961 and 1998, from 7.7 to 9.0 kg/capita/year. Thus, the remarkable increase in the death of Japanese men from prostate cancer in the last 48 years is contradictory to the claimed protective effect of soybeans against prostate cancer.

Tomatoes, which contain a carotenoid, lycopene, have been claimed to be a negative risk factor for prostate cancer (13-15). In our study, however, no significant association was observed between the consumption of tomatoes and the incidence ($r = 0.148$) or mortality rate (-0.015) of prostate cancer (**Tables 3 and 5**).

Consumption of milk and dairy products has been listed as a risk factor for prostate cancer in several reports (9,23,26,37-43), most without precise biological interpretations.

Dairy products are hypothesized to be a risk factor of prostate cancer because of their high content of calcium (42.44). The basis of this hypothesis is that calcium suppresses the formation of 1,25-dihydroxyvitamin D (1,25(OH)₂D) from 25-hydroxyvitamin D. This decreases the level of circulating 1,25(OH)₂D, the biologically active form of vitamin D,

which reduces cellular proliferation and enhances cellular differentiation (45). However, a nested case-control study of serum vitamin D metabolite levels and prostate cancer in a cohort of 3,737 Japanese-American men in Hawaii failed to find a significant correlation between vitamin D metabolites and prostate cancer (46). According to this study, the odds ratio for the highest quartiles relative to the lowest was 1.0 (CI = 0.5-2.1) for 1,25(OH)₂D.

Androgens are crucial for the normal development of the prostate gland and for maintaining its functional state in the adult (47). The development of prostate cancer has long been associated with androgens, because orchidectomy androgen ablation with GnRH analogues and antiandrogen administration appear to be useful remedies for prostate cancer (48,49).

Prostate cancer, however, usually develops in men in their sixties or older (6), when the testosterone/estradiol ratio is declining (50). The decrease in androgens in elderly men is amplified by an age-related increase in plasma sex hormone-binding globulin (SHBG), which results in a relatively greater decrease in free androgens compared to total androgens (51). These findings suggest that androgens are not necessarily the only determining factor affecting the development and growth of prostate cancer.

A prospective, nested case-control study conducted in the US suggests that increased levels of plasma testosterone increase the risk of prostate cancer (52). A longitudinal, population-based, nested case-control study in Finland, however, found no association between serum testosterone concentration (determined between 1968-72) and the subsequent occurrence of prostate cancer (a follow-up period of 24 years) (53). A comparison of serum testosterone concentrations in young adult Japanese men (a population at low risk for prostate cancer) with those of young adult white and black Americans (a population at high risk for prostate cancer) also found no significant differences (54).

The growth of human prostate cancer cells (the LNCaP cell line) is significantly stimulated by physiological concentrations of estradiol and the growth increase is comparable to that induced by either testosterone or dihydrotestosterone (55). In fact, alpha and beta estrogen receptors are expressed in both normal and malignant prostate epithelial cells (56). In addition, testosterone and dihydrotestosterone is not the only ligands for androgen receptor (AR). Estradiol-17 β represents another important natural ligand for AR and may play an essential role in AR function and the development of the male reproductive system (57). These suggest that estrogens play a role in the development and growth of prostate cancer, although the exact nature of their role has not been clearly defined.

In our study, the consumption of milk was most closely correlated with the incidence and mortality of prostate cancer (**Table 3, 4 and 5**). As discussed in the section on testis cancer, milk contains considerable amounts of estrogens (16). We hypothesize that the association between milk and the incidence and mortality rates may be due to the high content of estrogens in milk. The man is the only mammal that consumes milk after weaning. Regular

milk intake throughout life may affect the incidence and mortality of this malignancy.

In conclusion, we propose a hypothesis that female sex hormones in milk and dairy products may have an effect on the development of testis and prostate cancers. It is clear, however, that the high correlation between cheese and testis cancer and between milk and prostate cancer should be taken as a suggestion for further epidemiological and mechanistic studies.

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