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INCIDENCE AND MORTALITY OF TESTICULAR AND PROSTATIC CANCERS IN RELATION TO WORLD DIETARY PRACTICES

Davaasambuu GANMAA, Xiang-Ming LI, Jing WANG, Li-Qiang QIN, Pei-Yu WANG, Akio SATO*

Department of Environmental Health, Medical University of Yamanashi, Tamaho, Yamanashi, Japan

The incidence and mortality rates of testicular and prostatic 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 testicular 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 testicular cancer (standardized regression coefficient [*R*] = 0.654). Concerning prostatic 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 prostatic cancer (*R* = 0.525). The food that was most closely correlated with the mortality rate of prostatic 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 to mortality from prostatic cancer (*R* = 0.580). The results of our study suggest a role of milk and dairy products in the development and growth of testicular and prostatic cancers. The close correlation between cheese and testicular cancer and between milk and prostatic cancer suggests that further mechanistic studies should be undertaken concerning the development of male genital organ cancers.

Key words: *testicular cancer; prostatic cancer; dietary practices; milk; cheese*

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 testicular 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 testicular 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 prostatic 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 testicular cancer in western countries has steadily risen in the past 40 or 50 years.[2–4] Prostatic 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 testicular and prostatic cancers from each of 42 countries and correlated the rates with dietary variables.

MATERIAL AND METHODS

Incidence of testicular and prostatic 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 1 cancer registry is operating. If more than 1 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, 6 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 5 cancer registries were averaged after age-standardization to the world population.

In several countries, only 1 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.

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*Correspondence to: Department of Environmental Health, Medical University of Yamanashi, Tamaho, Yamanashi 409-3898, Japan. Fax: +81-55-273-6754. E-mail: asato@res.yamanashi-med.ac.jp.

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In most of the countries examined, the incidence of testicular 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 testicular cancer and food intake. The incidence of prostatic cancer increased with age.[6] Therefore, for this cancer, the age-adjusted incidence rates for all ages were used for the evaluation.

Mortality of testicular and prostatic 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 prostatic 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 testicular 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 prostatic cancer, the average food intake from 1961–90 was used. The reason for this is that testicular cancer development may relate to the prenatal environment or the environment of boys at or before puberty, whereas prostatic 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 testicular and prostatic 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 testicular cancer and food intake

The truncated age-adjusted incidence rates for testicular 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).

The simple correlation coefficients for the correlation between the incidence rate of testicular cancer and food intake in 42 countries are shown in Table I. 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 testicular cancer.

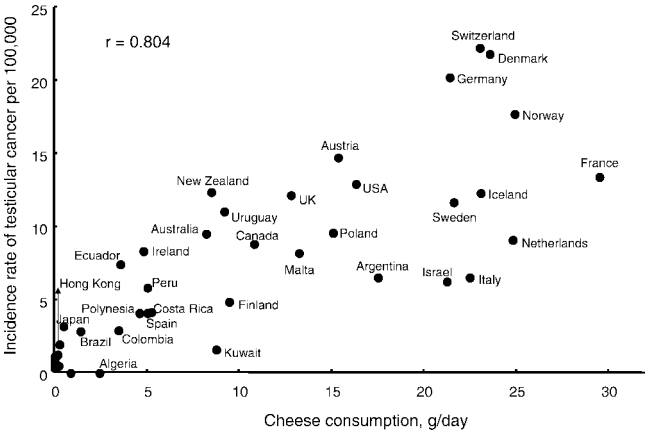

FIGURE 1 – Correlation between testicular cancer incidence rates at ages 20–39 years and *per capita* cheese consumption (1961–65) in 42 countries. Polynesia, French Polynesia.

TABLE I – CORRELATION COEFFICIENTS BETWEEN TESTICULAR CANCER INCIDENCE RATE AT AGES 20–39 (1988–92) AND FOOD CONSUMPTION[1]

	Correlation coefficient		
	1961–65	1961–70	1961–90
Animal fats	0.770[4]	0.764[4]	0.767[4]
Butter	0.558[4]	0.583[4]	0.626[4]
Cheese	0.804[4]	0.792[4]	0.769[4]
Eggs	0.616[4]	0.609[4]	0.604[4]
Meat	0.655[4]	0.660[4]	0.686[4]
Fish	0.093	0.066	0.045
Milk	0.741[4]	0.736[4]	0.745[4]
Cereals	−0.358[2]	−0.395[3]	−0.468[3]
Pulses	−0.442[3]	−0.441[3]	−0.486[3]
Fruits	0.333[2]	0.355[2]	0.334[2]
Vegetables	0.103	0.090	0.079
Vegetable oils	0.478[3]	0.503[4]	0.447[3]
Alcohol	0.495[4]	0.514[4]	0.602[4]
Coffee	0.578[4]	0.574[4]	0.606[4]
Tea	0.058	0.072	0.078

[1]Average values during 1961–65, 1961–70, and 1961–90.–[2]$p < 0.05$.–[3]$p < 0.01$.–[4]$p < 0.001$.

Stepwise-multiple-regression analysis to clarify the food items affecting testicular cancer incidence revealed that milk + cheese (1961–65) made a significant contribution to increasing the incidence of testicular cancer around 1990 (standardized regression coefficient [R] = 0.654), followed by alcohol (0.272) (Table II).

Mortality of testicular 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 testicular 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 testicular cancer in these countries was 0.350.

Animal fats had the highest correlation coefficient ($r = 0.317$) for the age-adjusted mortality rates of testicular 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.

TABLE II – STEPWISE-MULTIPLE-REGRESSION ANALYSIS (FORWARD) ON THE CONSUMPTION OF SELECTED FOOD ITEMS (INDEPENDENT VARIABLES[1]) AFFECTING INCIDENCE/MORTALITY RATES OF TESTICULAR AND PROSTATIC CANCERS (DEPENDENT VARIABLE)

	Coefficient	Std. error	R^2	F-to-remove
Testicular cancer incidence *vs.* 11 independents (1961–65) (Step: 2)				
Milk and cheese	0.013	0.002	0.654	37.981
Alcohol	0.012	0.005	0.272	6.562
Prostatic cancer incidence *vs.* 11 independents (1961–90) (Step: 2)				
Milk and cheese	0.036	0.007	0.525	24.180
Cereals	−0.091	0.023	−0.425	15.807
Prostatic cancer mortality *vs.* 11 independents (1961–90) (Step: 2)				
Milk and cheese	0.014	0.002	0.580	35.045
Cereals	−0.031	0.007	−0.418	18.644

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

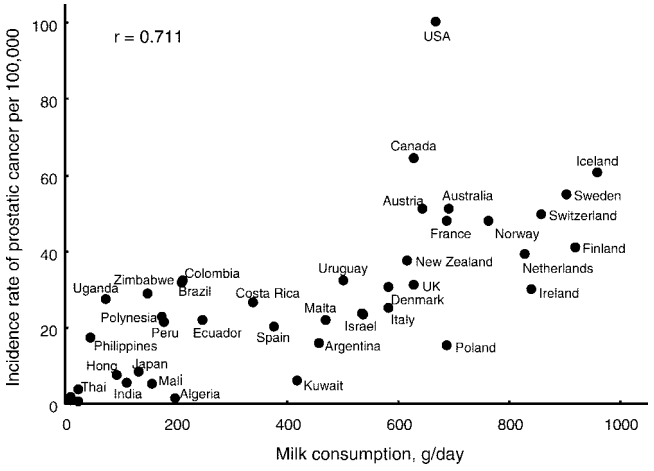

FIGURE 2 – Correlation between the age-adjusted incidence rates of prostatic cancer and *per capita* milk consumption (1961–90) in 42 countries. Hong, Hong Kong; Polynesia, French Polynesia; Thai, Thailand.

Incidence of prostatic cancer and food intake

The age-adjusted incidence rate (*per* 100,000) of prostatic 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.

Among the food items examined, milk (1961–90) was most closely correlated with prostatic cancer incidence ($r = 0.711$), followed by meat (0.642) and coffee (0.606) (Table III). 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.

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

Mortality of prostatic 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).

Mortality rates of prostatic 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 prostatic cancer was milk ($r = 0.766$), followed by coffee (0.633), cheese (0.618) and animal fats (0.606) (Table III). In contrast, cereals was negatively correlated with the mortality (−0.661).

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

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.[6] 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]

Testicular 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 testicular 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 testicular cancer was as low as 0.350. In this regard, incidence is a better index for this malignancy than mortality.

In most populations, testicular cancer has a peak incidence rate in people in their twenties or thirties.[6] The increased incidence of testicular 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 testicular 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 testicular cancer was cheese, followed by animal fats and milk (Table I, 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 the 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 testicular cancer, then that consumed before birth

TABLE III – CORRELATION COEFFICIENTS BETWEEN AGE-ADJUSTED INCIDENCE (1988–92) AND MORTALITY (1990) OF PROSTATIC CANCER AND FOOD CONSUMPTION

	Correlation coefficient (average values)					
	Incidence			Mortality		
	1961–65	1961–70	1961–90	1961–65	1961–70	1961–90
Animal fats	0.552[3]	0.522[3]	0.480[2]	0.627[3]	0.610[3]	0.606[3]
Meat	0.657[3]	0.655[3]	0.642[3]	0.609[3]	0.602[3]	0.594[3]
Fish	0.129	0.100	0.093	0.064	0.029	0.015
Eggs	0.551[2]	0.531[3]	0.463[2]	0.442[2]	0.423[2]	0.392[1]
Butter	0.485[2]	0.479[2]	0.450[2]	0.569[3]	0.575[3]	0.576[3]
Cheese	0.568[3]	0.563[3]	0.586[3]	0.645[3]	0.632[3]	0.618[3]
Milk	0.751[3]	0.740[3]	0.711[3]	0.778[3]	0.772[3]	0.766[3]
Cereals	−0.556[3]	−0.587[3]	−0.648[3]	−0.530[3]	−0.575[3]	−0.661[3]
Pulses	−0.313[1]	−0.304	−0.302	−0.286	−0.262	−0.283
Vegetables	−0.001	−0.018	−0.043	−0.108	−0.133	−0.162
Vegetable oils	0.344[1]	0.378[1]	0.436[2]	0.355[1]	0.377[1]	0.366[1]
Tomatoes	0.134	0.142	0.148	−0.058	−0.049	−0.015
Fruits	0.272	0.274	0.316[1]	0.327[1]	0.343[1]	0.356[1]
Coffee	0.641[3]	0.625[3]	0.606[3]	0.616[3]	0.620[3]	0.633[3]
Tea	−0.047	−0.032	−0.045	0.086	0.109	0.106
Alcohol	0.426[1]	0.440[2]	0.491[2]	0.530[3]	0.546[3]	0.585[3]

[1] $p < 0.05$.–[2] $p < 0.01$.–[3] $p < 0.001$.

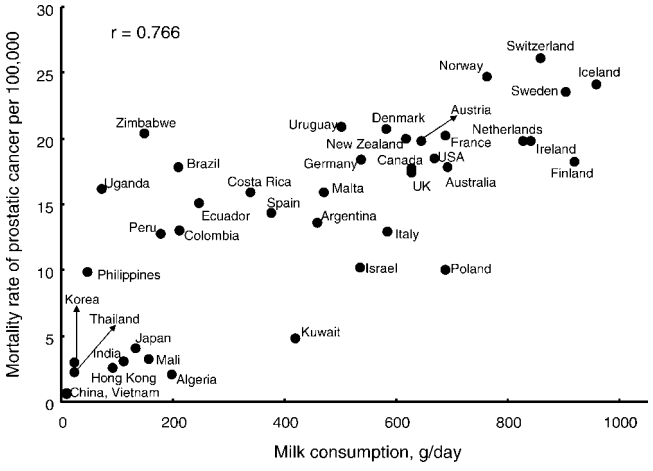

FIGURE 3 – Correlation between the age-adjusted mortality rates of prostatic cancer and *per capita* milk consumption (1961–90) in 41 countries.

(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. These foods are also preferentially consumed by prepubertal boys because of their growth-promoting effect.

In most countries, the incidence rate of testicular cancer, which is lowest in boys 5–14 years old, increases sharply in boys aged 15–19 years.[6] This is thought to reflect the fact that testicular 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 testicular cancer.

Consumption of dairy products is said to be excessive in developed countries, a trend that probably started in the 1940s and 1950s.[19] The increased incidence of testicular 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 testicular 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 testicular cancer had consumed significantly more milk during adolescence than had controls.

Prostatic cancer

The age-adjusted incidence and mortality rates of prostatic cancer have risen almost linearly all over the world during the 20-year 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 prostatic cancer may relate to the accumulation throughout life of environmental factors affecting the development and growth of prostatic cancer.

The age-adjusted incidence rate (*per* 100,000) of prostatic 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 prostatic cancer screening,[22] the mortality rate may be more reliable than the incidence rate for elucidating the true nature of prostatic cancer in some countries. The correlation coefficient between testicular and prostate cancer incidence was 0.614, whereas the coefficient between testicular cancer incidence and prostatic 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 prostatic 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 prostatic 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 prostatic cancer. The simple correlation coefficients between the incidence and mortality of prostatic cancer and the consumption of pulses were −0.302 and −0.283, respectively (Table III). 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 1961–98, from 7.7 to 9.0 kg/*capita*/year. Thus, the remarkable increase in the death of Japanese men from prostatic cancer in the last 48 years is contradictory to the claimed protective effect of soybeans against prostatic cancer.

Tomatoes, which contain a carotenoid, lycopene, have been claimed to be a negative risk factor for prostatic 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 prostatic cancer (Table III).

Consumption of milk and dairy products has been listed as a risk factor for prostatic cancer in several reports,[9,23,26,37–43] most without precise biological interpretations.

Dairy products are hypothesized to be a risk factor of prostatic 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] 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, however, between vitamin D metabolites and prostatic 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 prostatic cancer has long been associated with androgens, because orchidectomy androgen ablation with GnRH analogues and antiandrogen administration appear to be useful remedies for prostatic cancer.[48,49]

Prostatic 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 prostatic cancer.

A prospective, nested case-control study conducted in the U.S suggests that increased levels of plasma testosterone increase the risk of prostatic 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 prostatic 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 prostatic cancer) with those of young adult white and black Americans (a population at high risk for prostatic cancer) also found no significant differences.[54]

The growth of human prostatic 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 prostatic epithelial cells.[56] In addition, testosterone and dihydrotestosterone is not the only ligands for androgen receptor (AR). Estradiol-17β 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 prostatic 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 prostatic cancer (Table III). As discussed in the section on testicular 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. Men 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 testicular and prostatic cancers. It is clear, however, that the high correlation between cheese and testicular cancer and between milk and prostatic cancer should be taken as a suggestion for further epidemiological and mechanistic studies.

REFERENCES

1. Ganmaa D, Qin LQ, Wang PY, et al. Descriptive epidemiology of testicular and prostatic cancers in Japan in relation to dietary practices. J Epidemiol, in press.
2. Möller H. Clues to the etiology of testicular germ cell tumors from descriptive epidemiology. Eur Urol 1993;23:8–13.
3. Bergström R, Adami HO, Möhner M, et al. Increase in testicular cancer incidence in six European countries: a birth cohort phenomenon. J Natl Cancer Inst 1996;88:727–33.
4. McKiernan JM, Goluboff ET, Liberson GL, et al. Rising risk of testicular cancer by birth cohort in the United States from 1973–95. J Urol 1999;162:361–3.
5. Hsing AW, Tsao L, Devesa SS. International trends and patterns of prostate cancer incidence and mortality. Int J Cancer 2000;85:60–7.
6. Parkin DM, Whelan SK, Ferlay J, et al. Cancer incidence in five continents, Vol. VII. IARC Scientific Publications 143, Lyon: IARC, 1997.
7. Ferlay J, Parkin DM, Pisani P. GLOBOCAN 1: cancer incidence and mortality worldwide. Lyon: IARC, 1998.
8. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int J Cancer 1975;15:617–31.
9. Rose DP, Boyar AP, Wynder EL. International comparisons of mortality rates for cancer of the breast, ovary, prostate and colon and per capita food consumption. Cancer 1986;58:2363–71.
10. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. Int J Cancer 1999;80:827–41.
11. Pisani P, Parkin DM, Bray F, et al. Estimates of the worldwide mortality from 25 cancers in 1990. Int J Cancer 1999;83:18–29.
12. FAOSTAT Database Collections. http://apps.fao.org/cgi-bin/nph-db.pl?subset=nutrition/
13. Giovannucci E, Ascherio A, Rimm EB, et al. Intake of carotenoids and retinol in relation to risk of prostate cancer. J Natl Cancer Inst 1995;87:1767–76.
14. Gann PH, Ma J, Giovannucci E, et al. Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. Cancer Res 1999;59:1225–30.
15. Giovannucci E. Tomatoes, tomato-based products, lycopene and cancer: review of the epidemiologic literature. J Natl Cancer Inst 1999; 91:317–31.

16. Einhorn LH. Treatment of testicular cancer: a new and improved model. J Clin Oncol 1990;8:1777–81.
17. Hartmann S, Lacorn M, Steinhart H. Natural occurrence of steroid hormones in food. Food Chem 1998;62:7–20.
18. Ganmaa D, Wang PY, Qin LQ, et al. Is milk responsible for male reproductive disorders? Med Hypoth 2001;57:510–4.
19. Sharpe RM, Skakkebaek NE. Are estrogens involved in falling sperm counts and disorders of the male reproductive tract? Lancet 1993;341: 1392–5.
20. Ekbom A, Akre O. Increasing incidence of testicular cancer–birth cohort effects. APMIS 1998;106:225–9.
21. Davies TW, Palmer CR, Ruja E, et al. Adolescent milk, dairy product and fruit consumption and testicular cancer. Br J Cancer 1996;74: 657–60.
22. Potosky AL, Miller BA, Albertsen PC, et al. The role of increasing detection in the rising incidence of prostate cancer. JAMA 1995;273: 548–52.
23. Mettlin C, Selenskas S, Natarajan N, et al. Beta-carotene and animal fats and their relationship to prostate cancer risk. A case-control study. Cancer 1989;64:605–12.
24. Nomura AM, Kolonel LN. Prostate cancer: a current perspective. Epidemiol Rev 1991;13:200–27.
25. Giovannucci E, Rimm EB, Colditz GA, et al. A prospective study of dietary fat and risk of prostate cancer. J Natl Cancer Inst 1993;85: 1571–9.
26. Le Marchand L, Kolonel LN, Wilkens LR, et al. Animal fat consumption and prostate cancer: a prospective study in Hawaii. Epidemiology 1994;5:276–82.
27. Whittemore AS, Kolonel LN, Wu AH, et al. Prostate cancer in relation to diet, physical activity and body size in blacks, whites and Asians in the United States and Canada. J Natl Cancer Inst 1995;87: 652–61.
28. Lee MM, Wang RT, Hsing AW, et al. Case-control study of diet and prostate cancer in China. Cancer Causes Control 1998;9:545–52.
29. Hayes RB, Ziegler RG, Gridley G, et al. Dietary factors and risks for prostate cancer among blacks and whites in the United States. Cancer Epidemiol Biomark Prev 1999;8:25–34.
30. Kolonel LN, Nomura AM, Cooney RV. Dietary fat and prostate cancer: current status. J Natl Cancer Inst 1999;91:414–28.
31. Clinton SK, Giovannucci E. Diet, nutrition and prostate cancer. Annu Rev Nutr 1998;18:413–40.
32. Jacobsen BK, Knutsen SF, Fraser GE. Does high soy milk intake reduce prostate cancer incidence? The Adventist Health Study (United States). Cancer Causes Control 1998;9:553–7.
33. Denis L, Morton MS, Griffiths K. Diet and its preventive role in prostatic disease. Eur Urol 1999;35:377–87.
34. Griffiths K, Morton MS, Denis L, et al. Certain aspects of molecular endocrinology that relate to the influence of dietary factors on the pathogenesis of prostate cancer. Eur Urol 1999;35:443–55.
35. Moyad MA. Soy, disease prevention and prostate cancer. Semin Urol Oncol 1999;17:97–102.
36. Strom SS, Yamamura Y, Duphorne CM, et al. Phytoestrogen intake and prostate cancer: a case-control study using a new database. Nutr Cancer 1999;33:20–5.
37. Snowdon DA, Phillips RL, Choi W. Diet, obesity and risk of fatal prostate cancer. Am J Epidemiol 1984;120:244–50.
38. La Vecchia C, Negri E, D'Avanzo B, et al. Dairy products and the risk of prostatic cancer. Oncology 1991;48:406–10.
39. Talamini R, La Vecchia C, Decarli A, et al. Nutrition, social factors and prostatic cancer in a Northern Italian population. Br J Cancer 1986;53:817–21.
40. Talamini R, Franceschi S, La Vecchia C, et al. Diet and prostatic cancer: a case-control study in northern Italy. Nutr Cancer 1992;18: 277–86.
41. Veierod MB, Laake P, Thelle DS. Dietary fat intake and risk of prostate cancer: a prospective study of 25,708 Norwegian men. Int J Cancer 1997;73:634–8.
42. Chan JM, Giovannucci E, Andersson SO, et al. Dairy products, calcium, phosphorous, vitamin D and risk of prostate cancer (Sweden). Cancer Causes Control 1998;9:559–66.
43. Tzonou A, Signorello LB, Lagiou P, et al. Diet and cancer of the prostate: a case-control study in Greece. Int J Cancer 1999;80:704–8.
44. Giovannucci E, Rimm EB, Wolk A, et al. Calcium and fructose intake in relation to risk of prostate cancer. Cancer Res 1998;58:442–7.
45. Giovannucci E. Dietary influences of $1,25(OH)_2$ vitamin D in relation to prostate cancer: a hypothesis. Cancer Causes Control 1998;9:567–82.
46. Nomura AM, Stemmermann GN, Lee J, et al. Serum vitamin D metabolite levels and the subsequent development of prostate cancer (Hawaii, United States). Cancer Causes Control 1998;9:425–32.
47. vom Saal FS, Finch CE, Nelson HF. Natural history of reproductive aging in humans, laboratory rodents and other selected vertebrates. In: Knobil E, Neill JD, eds. The physiology of reproduction. 2nd ed., Vol. 2. New York: Raven Press, 1995;1213–314.
48. Wilding G. Endocrine control of prostate cancer. Cancer Surveys 1995;23:43–62.
49. Iversen P. Orchidectomy and estrogen therapy revisited. Eur Urol 1998;34(Suppl):7–11.
50. Ghanadian R, Puah CM. Relationships between oestradiol-17β, testosterone, dihydrotestosterone and 5α-androstane-3, 17β-diol in human benign hypertrophy and carcinoma of the prostate. J Endocrinol 1981;88:255–62.
51. Nakhla AM, Khan MS, Romas NP, et al. Estradiol causes the rapid accumulation of cAMP in human prostate. Proc Natl Acad Sci USA 1994;91:5402–5.
52. Gann PH, Hennekens CH, Ma J, et al. Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst 1996; 88:1118–26.
53. Heikkila R, Aho K, Heliovaara M, et al. Serum testosterone and sex hormone-binding globulin concentrations and the risk of prostate carcinoma: a longitudinal study. Cancer 1999;86:312–5.
54. Ross RK, Bernstein L, Lobo RA, et al. 5-Alpha-reductase activity and risk of prostate cancer among Japanese and U.S. white and black males. Lancet 1992;339:887–9.
55. Castagnetta LA, Miceli MD, Sorci CM, et al. Growth of LNCaP human prostate cancer cells is stimulated by estradiol via its own receptor. Endocrinology 1995;136:2309–19.
56. Lau KM, La Spina M, Long J, et al. Expression of estrogen receptor (ER)-alpha and ER-beta in normal and malignant prostatic epithelial cells: regulation by methylation and involvement in growth regulation. Cancer Res 2000;60:3175–82.
57. Yeh S, Miyamoto H, Shima H, et al. From estrogen to androgen receptor: a new pathway for sex hormones in prostate. Proc Natl Acad Sci USA 1998;95:5527–32.