The experience of Japan as a clue to the etiology of testis and prostate cancers: milk and dairy products are causatively related to these malignancies

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Summary

In Japan dramatic lifestyle changes occurred after World War 2. To examine the experience of Japan as a clue to the etiology, trends in the mortality rates of testicular and prostate cancers from 1947 to 1998 were related to changes in dietary practices. The male population born before 1945 had a peak in death from testicular cancer in their thirties or forties, whereas those born after 1946 had a peak in their twenties. The death rate of prostate cancer increased 25-fold almost linearly after the war. The intake of milk, meat, and eggs increased 20-, 9-, and 7-fold, respectively, after the war. In connection with the development and growth of testicular and prostate cancers in Japan, particular attention should be paid to milk, because the increase in its consumption in this country is a recent occurrence and because milk contains considerable amounts of estrogens plus saturated fats.

Introduction

The incidence of testicular cancer has steadily risen in the past 40 or 50 years in Western countries (1-5). Prostate cancer is one the most common cancer among men in most western countries (6). The incidence of both cancers is much higher in Western countries than in Asian countries, including Japan (7).

In our previous work (8), we correlated the incidence and mortality rates of testicular and prostate cancers in 42 countries with the dietary variables in these countries using the cancer rates provided by the International Agency for Research on Cancer (IARC) (7) and the food supply data provided by the Food and Agriculture Organization (FAO) (9). Among the food items examined, cheese was most closely correlated with the incidence of testis cancer at ages 20-39. The food that was most closely correlated with the incidence of prostate cancer was milk. The results of the study suggested a role for milk and dairy products in the development and growth of both malignancies.

The common feature of testis and prostate cancers in Japan is that the incidence of both malignancies has increased markedly after the end of World War 2. Japan is one of the countries where dramatic lifestyle changes have occurred after the war. For example, as shown in **Fig. 1**, the consumption of milk and dairy products, meat, and eggs increased 20-, 9-, and 7-fold, respectively, over the 48 years from 1950 to 1998.

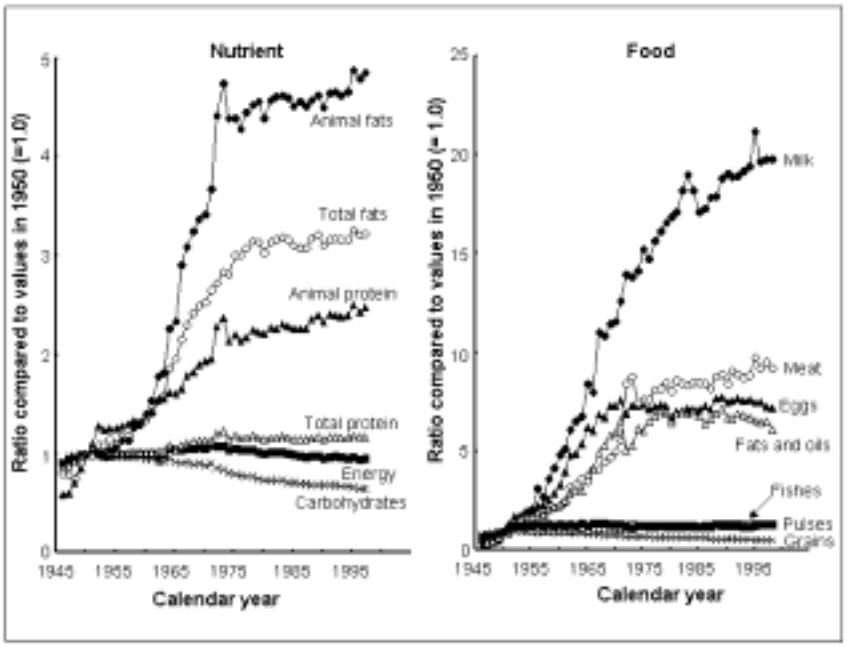


Fig. 1. Intake of macronutrients and foods in Japan after World War 2. Values on the ordinate are relative to the value in 1950 (= 1.0).

This great change in the Japanese lifestyle before and after the dividing line of 1945 appears to have affected the incidence of testis and prostate cancers. Since the lifestyle changes in Japan are relatively recent and sudden, it is important to examine the experience of Japan as a clue to the etiology of both malignancies.

Materials and methods

Mortality rates of testis and prostate cancers

In Japan, there is a working cancer registration system in several regions. However, reliable national data on the incidence of testis and prostate cancers are unavailable. In contrast, the death certification system is well established in Japan. Mortality data for testis and prostate cancers were gathered from published tabulations of the Vital Statistics of Japan for 1947-1998 (10), in which the data have been organized into 5-year age (age-specific death rate).

The first census of the population in Japan after World War 2 was taken in 1947. Since then, the census has been taken every 5 years in the calendar years ending in 0 or 5. The population confirmed by the census was used as representative of the grouped data; for example, the population in 1955 represented the population for the 5 years between 1953 and 1957 or the 10 years between 1951 and 1960. When necessary, age adjustments were made to

the standard European population.

Nutrition and food intake

The National Nutritional Survey in Japan has been conducted by the Ministry of Health and Welfare annually since 1946 and an annual report is published. Nutrition and food intake data (g/day) were collected from the tabulation summarized by the Health and Welfare Statistics Association (11) and other published tabulations (12). The intake of protein, fats and carbohydrates and the consumption of each selected food item (milk and dairy products, eggs, meat, fish, and fishery products, cereals, fats, and oils, and pulses) were expressed as a ratio compared to the value in 1950 (=1.0).

Results

Testis cancer

The age-standardized death rate (per million) of testis cancer in Japan was 0.98 in 1947, increasing rapidly thereafter to reach a maximum rate of 3.49 around 1975, and then decreasing gradually to a low of 1.61 in 1995 (**Fig. 2**).

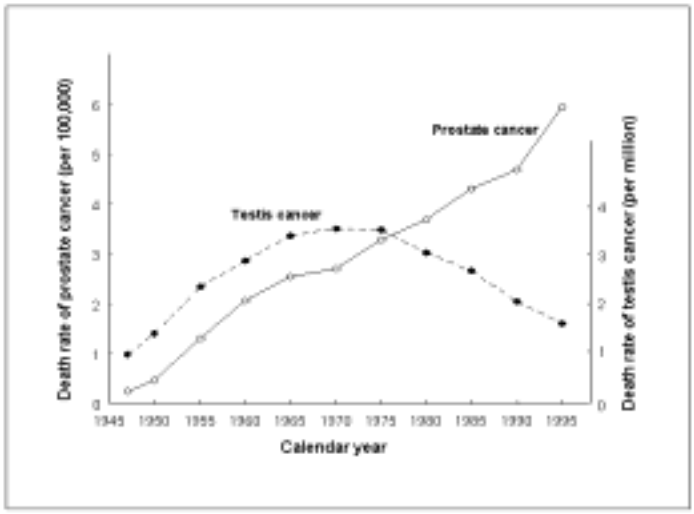


Fig.2. Age-standardized death rates for testis and prostate cancers in Japan after World War 2. Note that the death rate for testis cancer is expressed per million, while that for prostate cancer is per 100,000.

The age-specific death rate of testis cancer in 1961-70 or later had a characteristic age distribution with peak rates in early childhood (ages 0-4), young adults (ages 20-34), and the elderly (older than 65 years old) (**Fig. 3**). The peak at ages 0-4, however, virtually disappeared in 1981-1990 and later. The change that occurred in the 10 years between 1978 and 1987 was dramatic; 33 boys were killed by the cancer in 1978-1982, whereas only 3 were killed in 1983-1987. In addition, before 1981, 70-90% of the fatal testis cancer in Japanese boys under 15-years-old occurred in the age range 0-4. This figure decreased to 30-50% after 1982.

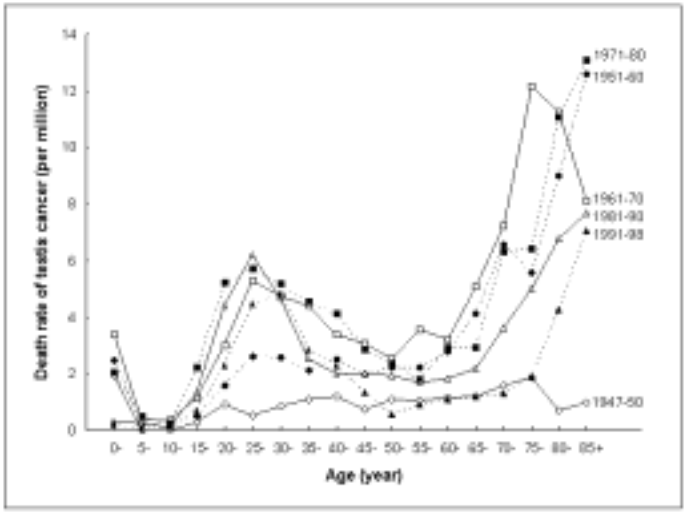
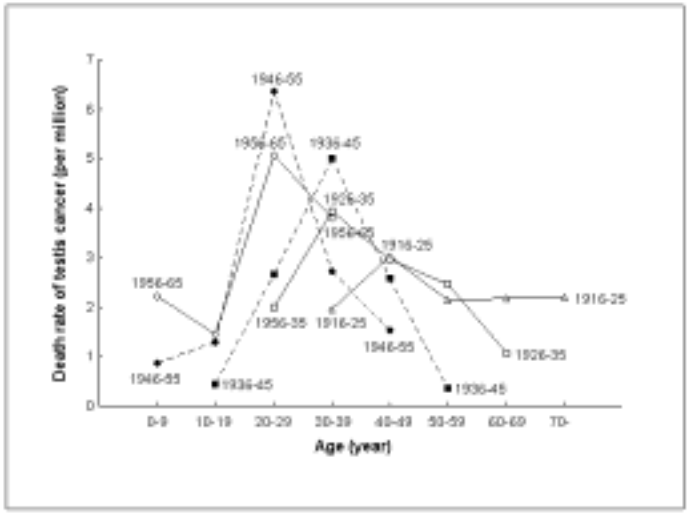


Fig. 3. Age specific death rates for testis cancer. Mean values for each period are shown.



The age-specific death rates were arranged to show the experience of the same people (grouped by year of birth) for 1947-1998 (**Fig. 4**). Only the death rates for the birth cohorts having a peak rate between their teens and forties are shown in the figure.

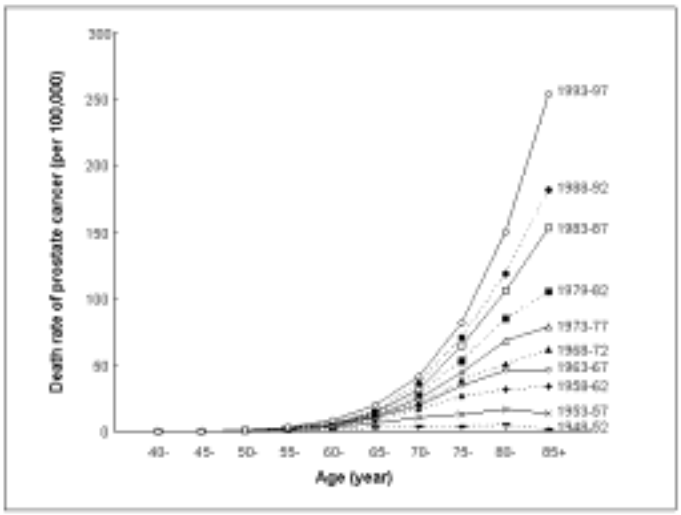
Fig.4. Age-specific death rates for testis cancer by birth cohort.

The population born in 1916-1925 had a peak death rate of testis cancer in their forties, those born in 1926-1945 had a peak in their thirties, and those born in 1946-1964 had a peak in their twenties. Thus, the pattern of death rate of testis cancer in men born after World War 2 (birth cohorts 1946-1955 and 1956-1964) was clearly different from that of men born during and before the war (birth cohorts 1936-1945 and earlier).

Prostate cancer

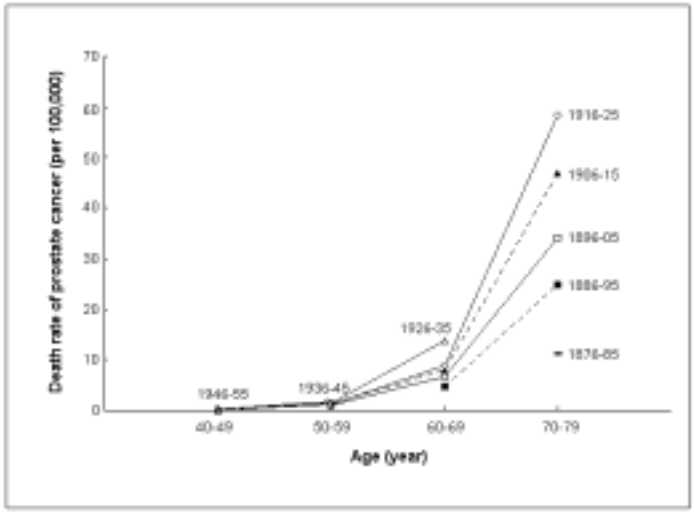
The age-standardized death rate (per 100,000) of prostate cancer in Japan was 0.24 in 1947, increasing rapidly thereafter to a maximum rate of 5.94 in 1995, a 25-fold increase over the past 48 years (**Fig. 2**). The recent increase between 1990 and 1995 was particularly

remarkable.



The pattern of increase in the age-specific death rate of prostate cancer by age was essentially the same in all periods examined (**Fig. 5**). In their fifties or younger, Japanese men were rarely killed by the cancer; the older the men, the higher was the death rate. The death rate in men of 50-year-old or older has risen almost exponentially with age since 1983-1987.

Fig. 5. Age-specific death rates for prostate cancer. Mean values for each period are shown.



The age-specific death rates of prostate cancer by year of birth are shown in **Fig. 6**. The later the year of birth, the higher the death rate in later life. No birth cohort effects were observed in the mortality of prostate cancer.

Fig. 6. Age-specific death rates for prostate cancer by birth cohort.

Dietary practices

Annual intake of nutrients and major food items is shown in **Fig. 1**, as a ratio compared to the value in 1950 (=1.0). Over the last 48 years (1950-1998), total energy intake rather decreased a little; the daily energy intake was 2098 kcal in 1950 and 1979 kcal in 1998. While the increase in total protein intake (animal and plant) during the same period was small (68.1 g/day in 1950 to 79.2 g/day in 1998), the animal protein intake more than doubled from 17.6 g/day in 1950 to 42.8 g/day in 1998. Fat intake, which was 18.3 g/day in 1950, started to rapidly increase around 1964, attaining the highest value of 58-59 g in the 1990s. The increase in animal fat intake was particularly marked; it increased about 5-fold from 6.1 g/day in 1952

(the value in 1950 is unavailable) to 29.2 g/day in 1998.

In terms of food items, animal-derived food consumption increased conspicuously in the last 48 years (1950-1998); the consumption of milk and dairy products, meat, and eggs increased 20- (6.8 to 135.0g/day), 9- (8.4 to 77.5g/day), and 7-fold (5.6 to 40.5g/day), respectively, during this period (**Fig. 1**). On the other hand, the consumption of cereals, which was 476.8 g/day in 1950, decreased to 257.9g/day in 1998. Among cereals, the consumption of rice, the principal food of Japanese, decreased to almost half during the same period from 338.7g/day in 1950 to 164.8g/day in 1998.

Discussion

The time-related trend in the mortality of any cancer involves relative changes in the diagnosis, recording, and fatality rate of the cancer. The changes in the mortality from testis cancer in Japan after World War 2 were substantial (**Fig. 2**). If the changes were due to differences in diagnosis or certification, there must have been a large loss of fatal cases from the recording system in both the 1960s or earlier and the 1980s or later. This is unlikely in Japan, where both health care and death certification systems are well established. Changes in environmental factors after the war are therefore likely to have caused the upward trend in the mortality of testis cancer in the 1950s and 1960s.

Testis cancer

Mortality from testis cancer in Japan has recently been decreasing almost linearly, a trend that started at 1975 (**Fig. 2**). The reason for this phenomenon remains unknown. The incidence of testis cancer (per 100,000) in one region of eastern Japan (Gunma Prefecture) doubled from 1.6 to 3.2 in the 10 years between 1985 and 1994 (13). Hence, a decrease in the incidence of testis cancer is unlikely to have occurred in Japan nationwide to a degree that would explain the recent decrease in the death rate.

Early diagnosis (biomarkers such as human chorionic gonadotropin [HCG] and α-fetoprotein [AFP], 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, leading to the decreased death rate in the 1970s and later. Indeed, cisplatin-based chemotherapy (a combination of platinum, vinblastine and bleomycin [PVB]), which dramatically improved the clinical outlook of male patients with disseminated germ cell tumors (14), was first introduced in Japan in 1975 (15).

The death rate of testis cancer was lowest in Japanese boys aged 5-14 years (**Fig. 3**). Not only the death rate, but also the incidence rate is low in this age group. According to the cancer registry in Miyagi Prefecture (northeastern district of Japan), during 1988-1992 (7), the age-standardized incidence rate (per 100,000) of testis cancer at ages 5-14 was one-tenth (0.158) that at ages 15-24 (1.624). The low incidence rate together with the low death rate in

the age group of 5-14 years is thought to reflect the fact that testis cancer develops and grows in the presence of sex hormones or gonadotropins, *i.e.*, after the onset of puberty.

The peak death rate of the population born before World War 2 was in their thirties or forties, whereas for those born after the war it was in their twenties (**Fig. 4**). The peak shift in birth cohorts to younger ages indicates the presence of cohort effects in death from testis cancer (16).

The increased incidence of testis cancer in Western countries during the last 4 or 5 decades is also associated with birth cohort effects (1-5). The birth cohort effect in Japan suggests that some environmental factors relating to the development of testis cancer changed after the dividing year of 1945, when Japan was defeated by the Allied Forces. The birth cohort effect also suggests that the causative factors operate early in life, possibly in the fetal, perinatal or prepubertal period (1).

According to Möller (1), the incidence of testis cancer in Denmark was low in men born during World War 2, when the supply of many commodities, including dietary items, was short. He suggested that a dietary factor might be involved in the birth cohort effect, and that a change in maternal consumption is more likely to have affected the offspring before or just after birth.

The daily life of Japanese underwent drastic changes after World War 2, and one of the most conspicuous was the change in dietary practices. Western dishes use more animal products as ingredients. They have only become popular in Japan in the past 50 years, where an essentially no-meat/no-milk culture prevailed until the end of the war (**Fig. 1**). Among food items, the increase in the consumption of milk and dairy products has been striking; milk consumption, which was 6.8 g/day in 1950, increased almost 20-fold to 135.0g/day in 1998. Each Japanese child is given 200 ml of whole milk daily at lunch in school. For this reason, the average daily milk consumption of this age group reaches 322 g, a remarkable quantity in Japan, where the population's average milk consumption is as low as 135g/day. Pregnant women in Japan are also encouraged to consume milk and dairy products, to meet their calcium requirements during pregnancy.

Milk contains, in addition to fats, considerable amounts of estrogens (17). The high estrogen content occurs because present milk cows are mostly pregnant (18). In this respect, the milk that we now consume may be quite unlike that consumed 100 years ago, when pregnant cows did not proficiently produce milk.

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

Davies *et al.* (19) 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 the cases were men with testis cancer, and for each of the 200 cases, there were four controls: two cancer controls and two population controls. All the responding subjects completed a dietary questionnaire that included questions on their current and adolescent consumption of milk, dairy products, fruits, and vegetables. Cases had consumed significantly more milk in adolescence than controls.

Consumption of dairy products is said to be excessive in developed countries, a trend that probably started in the 1940s and 1950s (20). It is not unreasonable to assume that the increased incidence of testis cancer in the past 50 years in Western countries (1-5) is associated with the increased consumption of milk and dairy products.

Prostate cancer

The incidence of prostate cancer in Japan is much lower than that reported in Western countries; the rate in Japan is 50-60 times lower than that in USA (6). Since 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 (21), the mortality rate may be more reliable than the incidence rate for elucidating the true nature of prostate cancer.

The age-standardized death rate of prostate cancer in Japan has risen about 25-fold almost linearly over the last 48 years (**Fig. 2**). The exponential increase of the rate with age (**Fig. 5**) is coincident with the general features of solid malignant tumors. No birth cohort effect is observed in the age-specific death rate of prostate cancer (**Fig. 6**). Overall, the increase in the number of deaths from prostate cancer in Japan over the last 48 years may relate to the accumulation throughout life of environmental factors that affect the development and growth of the cancer.

Fat intake, especially animal fats, has long been listed as the major risk factor of prostate cancer (22-28). According to the recent review article of Kolonel *et al.* (29), however, while 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 (30-35). Soya, a dietary staple in Japan, is a major source of the isoflavonoids daidzein and genistein (32).

According to Griffiths *et al.* (33), with a traditional diet, a Japanese male consumes approximately 20 mg of isoflavones per day, whereas for Western men, the daily consumption is less than 1 mg/day. They claimed 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 <10 ng/ml for

Western males. This may be one reason why the incidence of prostate cancer in Japan is much lower than that in Western countries.

However, consumption of pulses, including soybeans, in Japan almost doubled between 1947 (43.8 g/day) and 1998 (72.5g/day) (**Fig. 1**). According to the FAOSTAT Database Collections (9), the supply of soybeans as food in Japan also increased between 1961 and 1998 from 7.7 to 9.0 kg/caput/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 the cancer.

Androgens are crucial for the normal development of the prostate gland and in maintaining its functional state in the adult (36). The development of prostate cancer has long been associated with androgens, because orchidectomy, androgen ablation with GnRH analogues, and anti-androgen administration appear to be useful remedies for prostate cancer (37,38).

On the other hand, prostate cancer usually develops in men in their sixties or older, when the testosterone/estradiol ratio is declining (39). The decrease in androgens in elderly men is amplified by an age-related increase in plasma sex hormone-binding globulin (SHBG) that results in a relatively greater decrease in free androgens compared to total androgens (40).

A longitudinal, population-based, nested case-control study conducted by Heikkila *et al.* (41) in Finland found no association between serum testosterone concentration (determined between 1968 and 1972) and the subsequent occurrence of prostate cancer (a follow-up period of 24 years). Ross *et al.* (42) compared 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 the cancer), also finding no significant differences.

It has recently been shown that α and β estrogen receptors are expressed in both normal and malignant prostate epithelial cells (43). The growth of human prostate cancer cells (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 (44).

According to Yeh *et al.* (45), testosterone/dihydrotestosterone is not the only ligand for androgen receptor (AR); estradiol-17β is another important natural ligand for AR, and may play an essential role in AR function and the development of the male reproductive system. Altogether, estrogens play a role in the development and growth of prostate cancer, although the exact nature of their role has not been clearly defined.

Milk consumption has been listed as a risk factor for prostate cancer in several reports (22,25,46-48). A case-control study conducted by Mettlin *et al.* (22) on 371 prostate cancer patients and comparable control subjects in Buffalo, New York showed that a greater frequency of whole milk intake was associated with an increased risk for the cancer. Men who

reported drinking three or more glasses of whole milk daily had a relative risk (RR) of 2.49 (95% confidence interval [CI], 1.27-4.87), compared with men who reported never drinking whole milk. In another case-control study conducted by La Vecchia *et al.* (47) in Northern Italy on 96 histologically confirmed cases and 292 controls with acute, non-neoplastic genital tract disease, milk was also identified as a risk factor for prostate cancer. There was a significant increase in risk with frequency of milk consumption; compared with non-drinkers or occasional milk drinkers, the RR was 5.0 (95% CI, 1.5-16.6) for 2 or more glasses per day.

The increased consumption of meat, eggs, and milk and dairy products in Japan after World War 2 (**Fig. 1**) may be one cause of the remarkable increase in the number of deaths from prostate cancer during the same period. As discussed in the section on testis cancer, among animal-derived food items, milk and dairy products might have played a major role, since they contain considerable amounts of estrogens (17), in addition to saturated fats.

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