

# Is milk responsible for male reproductive disorders?

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**Summary** The role of environmental compounds with estrogenic activity in the development of male reproductive disorders has been a source of great concern. Among the routes of human exposure to estrogens, we are particularly concerned about cows' milk, which contains considerable amounts of estrogens. The major sources of animal-derived estrogens in the human diet are milk and dairy products, which account for 60–70% of the estrogens consumed. Humans consume milk obtained from heifers in the latter half of pregnancy, when the estrogen levels in cows are markedly elevated. The milk that we now consume may be quite unlike that consumed 100 years ago. Modern genetically-improved dairy cows, such as the Holstein, are usually fed a combination of grass and concentrates (grain/protein mixes and various by-products), allowing them to lactate during the latter half of pregnancy, even at 220 days of gestation. We hypothesize that milk is responsible, at least in part, for some male reproductive disorders. © 2001 Harcourt Publishers Ltd

## INTRODUCTION

In the past 50 years, the incidence of testicular cancer has increased while semen quality has decreased (1–8). Since this decline in male reproductive health is both recent and appears to have occurred in many countries, Sharpe and Skakkebaek (9) presumed that the disorders reflect adverse effects on men of environmental and lifestyle factors. They listed several routes of human exposure to estrogens that have changed in the past half-century.

Of these, we are particularly concerned about cows' milk, which contains considerable amounts of estrogens (10–16). Estrogens are also contained in animal meat and eggs, but the major sources of animal-derived estrogens in the human diet are milk and dairy products, according to Hartmann et al. (14), which account for 60–70% of the estrogens. The high estrogen content is because humans

consume milk obtained from heifers in the latter half of pregnancy, when estrogen levels are markedly elevated (11,12,15). We hypothesize that milk is responsible, at least in part, for the decreased sperm count and increased incidence of male reproductive abnormalities.

## TRADITIONAL AND MODERN MILK

Man is the only mammal that consumes milk after weaning. When we name cows' milk as one of the important routes of human exposure to estrogens, the general response of Western people is that 'man has been drinking cows' milk for around 2000 years without apparent harm' (17). However, the milk that we consume today may be quite unlike that consumed 100 years ago. Hurt (18) described how poor the milk production was in the mid-eighteenth century, stating that 'cows that produced a gallon per day were considered good milkers, but a quart per day was most common'. Nowadays, however, production levels as high as 24 kg per day are typical in modern dairy farming (19).

In 1908, Fritz Haber combined nitrogen (N) from the air with hydrogen to synthesize ammonia (NH<sub>4</sub>-N), and in 1914, Karl Bosch completed the first large ammonia

Received 20 September 2000

Accepted 5 February 2001

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manufacturing plant (20). As new technology lowered the price of N fertilizer, farmers began applying it to raise yields, enabling dairy farmers to use surplus crops as feed grains for cows. Furthermore, during the 1960s and 1970s, when the Green Revolution spread throughout the world (21), the possibility of year-round milk production was realized worldwide.

A survey in Inner Mongolia by AS and PYW found that cows fed only on pasture do not lactate during the latter half of pregnancy. Mongolian cows become pregnant as a result of natural mating in July or August, and give birth to calves in April or May. The Mongolian nomads milk their cows for only 5 months from June to October, obtaining, at best, 5 L milk per day from a cow. One of these nomads told us, 'Cows produce milk for the calves of the next generation, not for humans. If we steal too much milk from pregnant cows, they cannot give us good calves.'

However, modern genetically-improved dairy cows, such as the Holstein, which are artificially inseminated three months after calving, are usually kept on a combination of grass and concentrates (grain/protein mixes and various by-products). They continue to lactate for almost the whole of pregnancy, extending the milk-producing period to 305 days per year (19).

### ESTROGENS IN MILK AND DAIRY PRODUCTS

There is about 30 pg/ml estrone sulfate in the whey fraction of milk from non-pregnant cows (15). During pregnancy, however, this level becomes elevated to 151 pg/ml from day 41 to day 60, and to maximum levels of about 1000 pg/ml from 220 to 240 days of gestation. Peak levels of circulating estrogens in non-pregnant cows during ovulation are several hundred fold lower than those in cows in late pregnancy, according to Gyawu and Pope (12), which suggests that milk from cows in late pregnancy contains much larger amounts of estrogens than does milk from non-pregnant cows.

The oral bioactivity of estradiol and estrone may be relatively low. According to Andersson and Skakkebaek (22), however, estrone sulfate has a high oral activity, and once inside the body it can be converted to estrone and estradiol.

In addition to estrogens, milk contains a large amount of another female hormone, progesterone, at concentrations ranging from 1400 pg/ml in skim milk to 10 000 pg/ml in whole milk and 300 000 pg/g in butter (14).

Batra et al. (10) measured the levels of estradiol-17 $\beta$  in plasma and whole milk of Murrah buffaloes by radioimmunoassay, and found a very close correlation between levels in plasma and milk; the estradiol concentration in milk was approximately twice that in plasma. Thus, hormone concentrations in whole milk can exceed those in plasma, probably because of synthesis in the

mammary gland (11). This phenomenon has been used to diagnose pregnancy in cattle by analyzing the progesterone, estrone, or estradiol-17 $\beta$  content of milk (15,23).

It might be argued that the increased volume of milk per cow per day in modern dairy farming would dilute the estrogens transferred from the circulation of a cow to the milk. However, modern milk contains almost the same amounts of protein, fat, calcium, etc., as traditional milk; it is unlikely that the mammary gland of a high-producing dairy cow secretes nutrients selectively, leaving estrogens alone in the circulation.

### ESTROGENS AND MALE REPRODUCTIVE ORGANS

Endogenous estradiol-17 $\beta$  secreted by the ovaries in the female, exerts negative feedback effects on the secretion of gonadotropins FSH and LH, affecting the hypothalamo-pituitary system (9,24–26). FSH regulates the multiplication of Sertoli cells, which, in turn, are responsible for orchestrating and regulating spermatogenesis. Estrogens can not only impair the development of the male reproductive tract via physiological pathways, but also alter the multiplication of Sertoli cells. In humans, significant qualitative and quantitative changes in the Sertoli cell population take place even after birth, especially during the prepubertal period (27).

Animal studies have shown that alteration of the Sertoli cell number in early life determines testicular size and sperm output in adulthood (28). In rats, the oral dose of exogenous estradiol sufficient to induce sterility was reported to be high (29). However, in the male rat, intraperitoneal doses as low as 10 ng estradiol/rat were reported to induce morphological lesions and spermatogenic arrest, without affecting gonadotropin release, after 21 daily exposures (30). This suggests that estradiol has a direct effect on developing spermatids.

The dose of 10 ng used for rats (30) can be extrapolated to humans by using body surface area, on the assumption that the two species have the same sensitivity to exogenous estrogens. Assuming that body surface area is proportional to body weight (kg) to the power of 0.7 (31), i.e. (body weight)<sup>0.7</sup>, then 10 ng of estradiol in a rat (0.1 kg) corresponds to 410 or 540 ng of estradiol in a child weighing 20 or 30 kg, respectively.

This extrapolation certainly cannot be applied directly to the estrogens in milk, since the bioavailability of estrogens taken orally may differ from that of intraperitoneally administered estrogens (14). However, since no data are available on the species difference in susceptibility to exogenous estrogens, and since susceptibility is expected to differ greatly among children, it is not unreasonable to suggest that several hundred nanograms

of estrogens from foods might be enough to affect spermatogenesis in particularly susceptible boys.

### ADVERSE EFFECTS OF MILK ON MALE REPRODUCTIVE ORGANS

The adverse effects of milk on male reproductive organs 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, powdered milk) are used in a variety of foods, including cakes, candies, ice cream, and chocolates.

Davies et al. (32) 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 the cases were men with testicular 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.

In a case-control study conducted in Northern Italy on 96 histologically confirmed cases and 292 controls with acute, non-neoplastic or genital tract disease, milk was identified as a risk factor for prostatic cancer (33). There was a significant increase in risk with frequency of milk consumption; compared with nondrinkers or occasional milk drinkers, the relative risk was 5.0 (95% confidence interval 1.5–16.6) for two or more glasses per day.

### ESTROGENS IN MILK AND PREPUBERTAL CHILDREN

Exposure to exogenous sex steroids is a greater risk for prepubertal children, since their endogenous levels are extremely low (22). Hartmann et al. (14) estimated the average daily intake of animal-derived estrogens (estradiol-17 $\beta$  and estrone) for prepubertal boys to be 80 ng, with milk and dairy products accounting for 60–70% of this. Nonetheless, Hartmann et al. concluded that no hormonal effects could be expected from naturally occurring sex steroids in food, because this value is far exceeded by steroid production in prepubertal boys. However, the value 6500 ng/day given by JEFCA-WHO (34) for the daily production rate (PR) of estradiol in prepubertal boys is a significant overestimate, according to Andersson and Skakkebaek (22). JEFCA-WHO used the metabolic clearance rate for adult women and serum estradiol levels higher than realistic when calculating the PR in prepubertal boys. Therefore, prepubertal boys'

average intake of 80 ng/day of food-derived estrogens (14) may not be negligible.

### MILK CONSUMPTION IN JAPAN

Sharpe and Skakkebaek (9) stated that consumption of dairy products is excessive in developed countries, a trend that probably started in the 1940s and 1950s.

This holds true in Japan, where a no-meat/no-milk culture essentially prevailed until the end of World War Two. In the past 50 years, Western dishes using more animal products as ingredients have become popular in Japan (Fig. 1) (35).

Each Japanese child is given 200 ml of milk daily at lunch in school. For this reason, the average daily milk consumption of this age group reaches 322 g (36), a remarkable quantity in Japan, where the population's average milk consumption is as low as 135 g/day (Fig. 2). Pregnant women in Japan are also encouraged to consume milk and dairy products, to meet their calcium requirements during pregnancy.

Commercial milk in Japan contained estrone 21.8–26.0 pg/ml, estradiol-17 $\beta$  25.1–33.6 pg/ml, and estriol 31.4–98.6 pg/ml (authors' unpublished data). **By drinking 300 ml of milk per day, a child's intake of estradiol-17 $\beta$  alone, the most potent estrogenic hormone, is approximately 10 ng per day. This is 4000 times the intake of environmental hormones or xenoestrogens, in terms of hormone activity (37).**

Between 1950 and 1997, milk consumption per person per day increased almost 20-fold, from less than 7 g to 135 g (Fig. 1). This sudden increase in consumption of estrogenic milk might have affected the reproductive organs of Japanese males. For example, the incidence rate of prostatic cancer in Japan is increasing at the fastest rate in the world (38), and the associated age-adjusted death rate has risen almost 13-fold during the last 45 years, from 0.45/100 000 in 1950 to 5.93/100 000 in 1995 (Fig. 3). Reproductive health should be monitored carefully in Japan, where milk consumption started to increase only 40 years ago, and where prepubertal children are the major consumers. Epidemiological studies into reproductive outcomes in Japan will certainly shed light on the relationship between milk and male reproductive health.

### CONCLUSION

The increased incidence of male reproductive disorders over the last 50 years has attracted much attention. Although great concern has been raised over the role of environmental compounds with estrogenic activity in the development of hormone-related diseases, exposure to exogenous sex steroids from food has not been widely

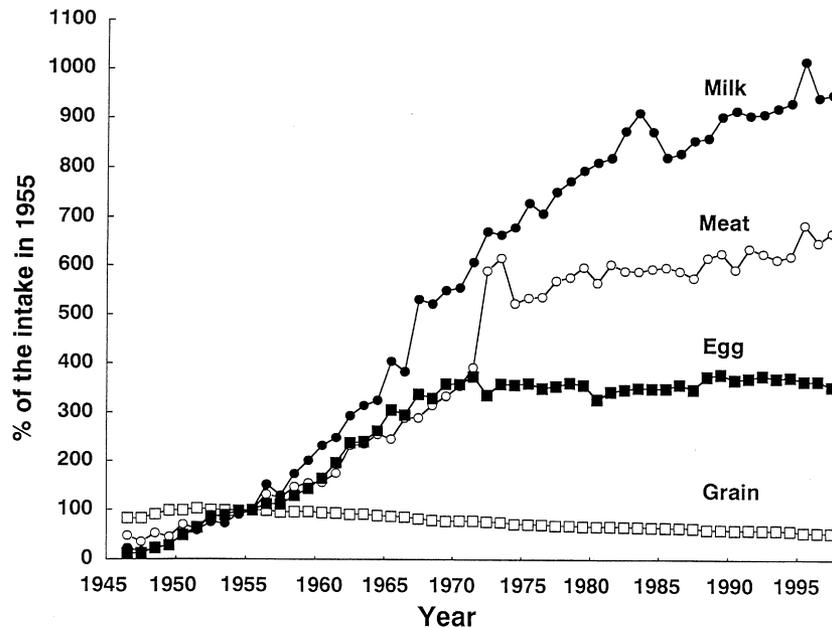


Fig. 1 Consumption of animal products in Japan.

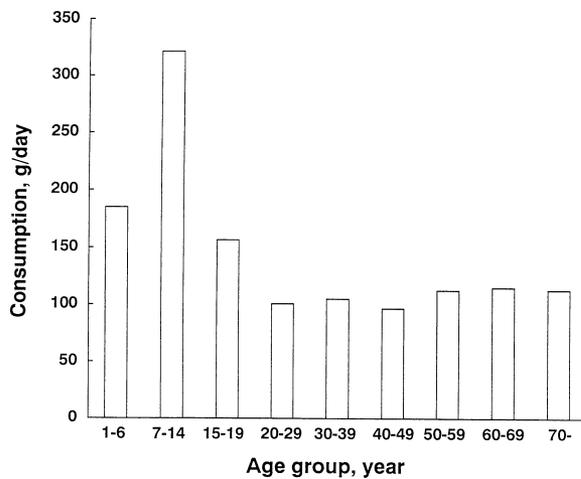


Fig. 2 Milk consumption in Japan.

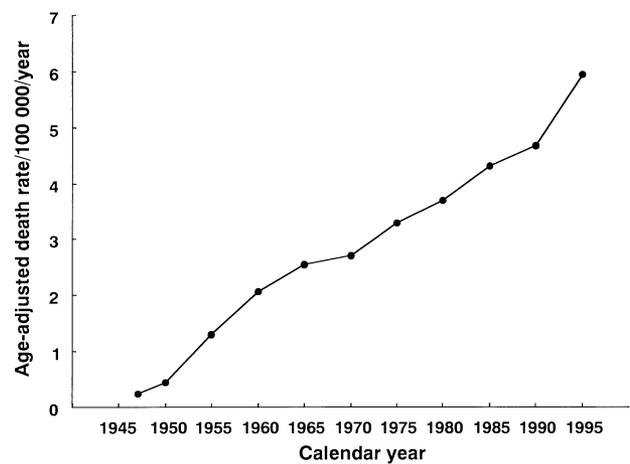


Fig. 3 Deaths from prostate cancer in Japan.

discussed. Humans consume milk from heifers in the latter half of pregnancy, when estrogen levels are markedly elevated. Estradiol-17 $\beta$  is about 10 000-fold more biopotent than most identified environmental xenoestrogens (22). While estrogens in modern milk may be useful for preventing osteoporosis in the elderly, for prepubertal boys in the critical period of sexual development excess consumption of milk and dairy products might interfere with the physiological development of the reproductive system and result in decreased semen quality in adulthood. Epidemiological or experimental studies should be

undertaken to test our hypothesis that milk is responsible, at least in part, for male reproductive disorders.

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