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The possible role of female sex hormones in milk from pregnant cows in the development of breast, ovarian and corpus uteri cancers

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Summary The continued increase in incidence of some hormone-related cancers worldwide is of great concern. Although estrogen-like substances in the environment were blamed for this increase, the possible role of endogenous estrogens from food has not been widely discussed. We are particularly concerned about cows' milk, which contains a considerable quantity of estrogens. 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.'' However, the milk that we are now consuming is quite different from that consumed 100 years ago. Unlike their pasture-fed counterparts of 100 years ago, modern dairy cows are usually pregnant and continue to lactate during the latter half of pregnancy, when the concentration of estrogens in blood, and hence in milk, increases.

The correlation of incidence and mortality rates with environmental variables in worldwide countries provides useful clues to the etiology of cancer. In this study, we correlated incidence rates for breast, ovarian, and corpus uteri cancers (1993–97 from Cancer Incidence in Five Continents) with food intake (1961–97 from FAOSTAT) in 40 countries. Meat was most closely correlated with the breast cancer incidence ($r = 0.827$), followed by milk (0.817) and cheese (0.751). Stepwise multiple-regression analysis (SMRA) identified meat as the factor contributing most greatly to the incidence of breast cancer ($[R] = 0.862$). Milk was most closely correlated with the incidence of ovarian cancer ($r = 0.779$), followed by animal fats (0.717) and cheese (0.697). SMRA revealed that milk plus cheese make the greatest contribution to the incidence of ovarian cancer ($[R] = 0.767$). Milk was most closely correlated with corpus uteri cancer ($r = 0.814$), followed by cheese (0.787). SMRA revealed that milk plus cheese make the most significant contribution to the incidence of corpus uteri cancer ($[R] = 0.861$). In conclusion, increased consumption of animal-derived food may have adverse effects on the development of hormone-dependent cancers. Among dietary risk factors, we are most concerned with milk and dairy products, because the milk we drink today is produced from pregnant cows, in which estrogen and progesterone levels are markedly elevated.

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Introduction

Breast cancer is one of the most frequent cancers among women [1]. The incidence of breast cancer has been increasing in both developed and developing countries [2]. The fact that people from low-risk countries increase their risk on immigrating to higher-risk countries suggest that some modifiable lifestyle and/or environmental factors are responsible for the development of breast cancer [3]. It has been postulated that most cancer-afflicted women develop subclinical breast cancer at an early age and that diet plays an important role in the progression from such lesions to clinical disease [4]. In addition, the variation in the breast cancer incidence rate worldwide suggests that lifestyle factors, especially diet, influence breast cancer risk.

Epithelial ovarian cancer kills more women each year than all other gynecological cancers combined [5]. The incidence of ovarian cancer also varies widely among countries. In general, incidence rates are higher in developed than in less developed countries. Rates are higher among younger Chinese and Japanese women born in the United States than among their Asian-born counterparts [6]. Such immigration studies suggest that lifestyle and environmental factors play a major role in the etiology of this malignancy.

Endometrial cancer is the sixth most common cancer worldwide, accounting for ~2% of all cancers in women [7]. As with breast and ovarian cancers, there is a wide difference in the incidence rate of corpus uteri cancer across countries. The rate amongst US Japanese is several-fold higher than that for Japanese living in their native country [3]. This finding suggests that lifestyle and environmental factors, rather than hereditary influence, affect the incidence of this cancer.

The common feature of breast, ovarian, and corpus uteri cancers is that they are comparatively rare in women under 40 years of age. The risk increases sharply after around age 40 and peaks between the ages of 65 and 79 [8]. The three malignancies share common risk factors, including obesity, menarche at young age, late menopause, and nulliparity, in addition to an increased risk inherent to and dependent upon family history [5]. In addition, the risk of these three cancers changes within a few years of shifts in exposure to sex hormones, and some of the changes in risk persist for many years, indicating that hormones can affect both early and late stages of carcinogenesis. Sex hormones may play a major role in their etiology, likely by controlling the rate of cell division, cell differentiation, and number of susceptible cells [9].

According to Armstrong and Doll [10], 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. In this study, we used incidence and mortality data for the three most prevalent female cancers — breast, ovarian, and corpus uteri cancers from 40 countries — and correlated the rates with dietary variables.

Materials and methods

Cancer incidence

Cancer Incidence in Five Continents edited by Parkin et al. [11] provided us with comparable data on the incidence of cancer between 1993 and 1997 in different geographical locations (200 populations in 50 countries). In this study, we used data from 40 of these countries, for which both cancer incidence rates and food consumption data from FAOSTAT Database Collections [12] were available. The age-specific incidence rates were standardized to the world population and the mean value of the age-adjusted incidence rates were calculated.

Several countries have more than one cancer registry. If more than one registry was available for a country, those that stated ''The editors were unable to verify these data'' were excluded from this study. The remaining age-specific incidence rates in the same country were standardized to the world population. The mean age-adjusted incidence rate was used as a representative rate for Australia, Brazil, China, France, Germany, India, Italy, Japan, Poland, Spain, Switzerland, Thailand, and the United Kingdom.

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

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 whole country (Algeria, Argentina, Austria, Columbia, Costa Rica, Ecuador, Ireland, Korea, Mali, Malta, Philippines, Uganda, Uruguay, and Viet Nam).

Canada, Denmark, Finland, Hong Kong, Iceland, The Netherlands, Norway, and Sweden collected data for their cancer registries on a national basis.

The incidence rates for these countries were used as provided.

Many cancer registries operate in the United States. Of these, the registry for Caucasians produced by the surveillance, epidemiology, and end results (SEER) program was used as representative for the United States.

The age-specific mortality rates of cancers that are listed in GLOBOCAN 2000 [13] were used in this study. The countries selected were the same as those used for the incidence.

Food consumption

The consumption data (Mt/1000 capita/year) for various food items from 1961 to 1997 available from the FAOSTAT Database Collections [12] were used. The food items used for this study were animal fats, meat (beef, pork, poultry, mutton, and goat meat), eggs, butter, milk (excluding butter), whole milk, cereals (excluding wine), pulses, beans, soy beans, peas, fruits (excluding wine), vegetables, coffee, tea, and alcoholic beverages. The consumption of each food or drink was converted from Mt/1000 capita/year to g/capita/day.

Statistical analysis

All of the data were analyzed by Stat View (SAS Institute, 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 breast, ovarian, and corpus uteri 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 1961–97 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 incidence or mortality were evaluated by stepwise multiple-regression analyses. The following eleven food items were selected for the analysis (independent variables): ''animal fats + butter,'' ''milk + cheese,'' eggs, meat, cereals, pulses, fruits, vegetables, vegetable oils, coffee, and alcohol.

Results

Incidence of breast cancer and food intake

The age-adjusted incidence rates per 100,000 for breast cancer differed markedly from one country to another. For example, Uruguay had the highest rate at 114.9, followed by the United States (92.1) and Israel (87.1) (Figs. 1 and 2). The lowest rate was for Korea (12.7), followed by Thailand (16.1) and Mali (20.0).

The simple correlation coefficients between the incidence rate of breast cancer and food intake in

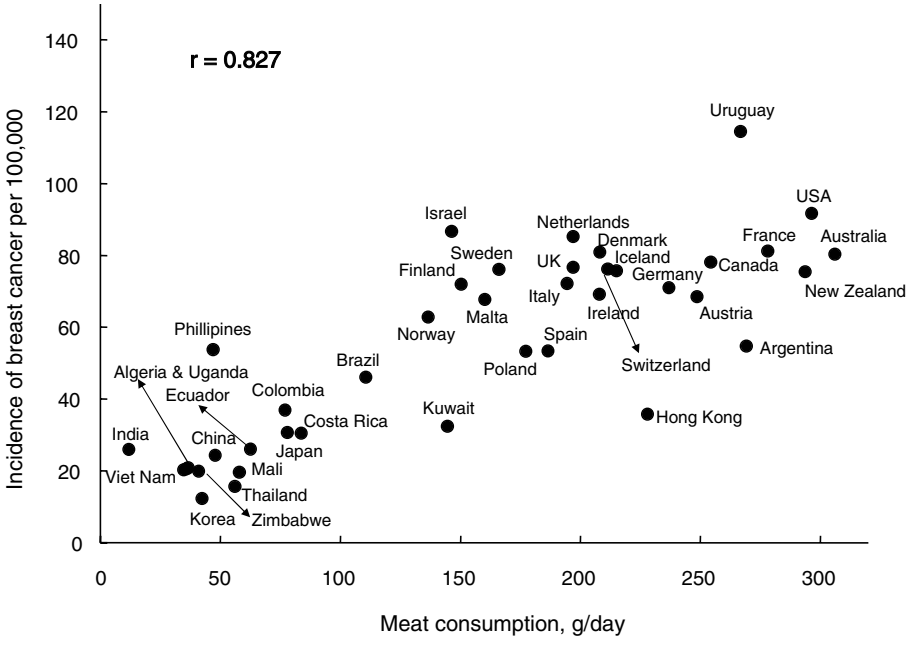

Figure 1 Correlation between the age-adjusted incidence rates of breast cancer (1993–97) and *per capita* meat consumption (1961–97) in 40 countries.

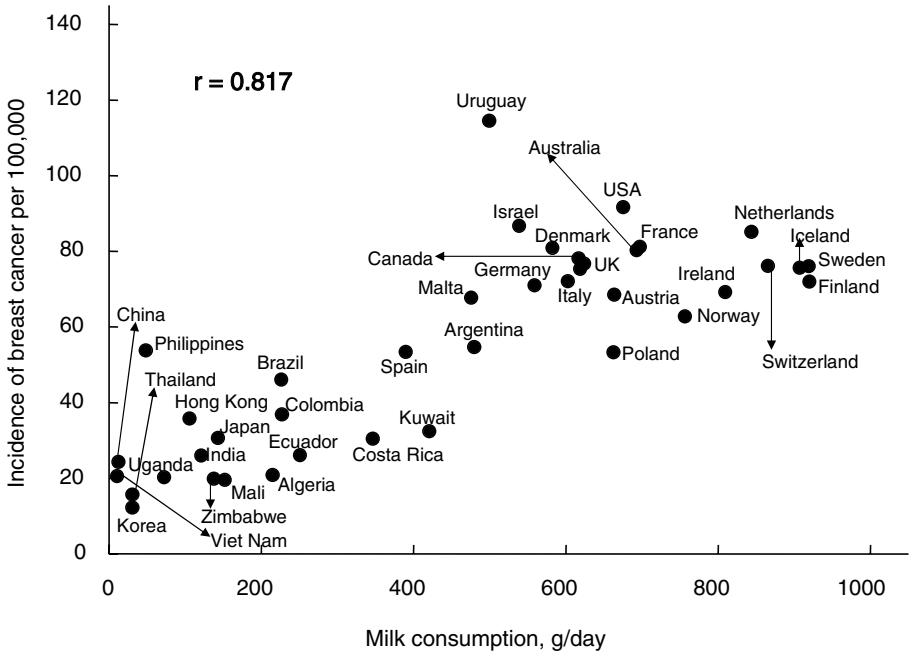

Figure 2 Correlation between the age-adjusted incidence rates of breast cancer (1993–97) and *per capita* milk consumption (1961–97) in 40 countries.

40 countries are shown in Table 1. Of the food items examined, meat was the most closely correlated with incidence of this cancer incidence ($r = 0.827$) (Fig. 1), followed by milk (0.817) (Fig. 2) and cheese (0.751). By contrast, cereals (−0.467) and pulses (−0.438) were negatively correlated with the incidence of breast cancer.

Table 1 Correlation coefficients between female cancer incidence rates (1993–97) and food consumption (average values during 1961–97)

	Correlation coefficient		
	Breast	Ovary	Corpus uteri
Animal fats	0.650**	0.717**	0.713**
Butter	0.584**	0.576**	0.543**
Cheese	0.751**	0.697**	0.787**
Eggs	0.660**	0.589**	0.703**
Meat	0.827**	0.575**	0.782**
Fish	0.055	0.226	0.115
Milk	0.817**	0.779**	0.814**
Cereals	−0.467**	−0.520**	−0.422**
Pulses	−0.438**	−0.465**	−0.437**
Fruits	0.297	0.357*	0.297
Vegetables	0.222	0.068	0.211
Vegetable oils	0.515**	0.396*	0.580**
Alcohol	0.517**	0.399*	0.497**
Coffee	0.537**	0.621**	0.626**
Tea	0.322*	0.045	0.126

* $p < 0.05$.
** $p < 0.01$.

Stepwise multiple-regression analysis revealed that meat (1961–97) contributed most to the incidence of breast cancer in 1993–97 (standardized regression coefficient [R] = 0.862) (Table 2).

The correlation coefficient between the age-adjusted incidence rate and age-adjusted mortality rate of breast cancer in the 40 countries examined was $r = 0.872$. The age-adjusted mortality rates of breast cancer had the highest correlation with cheese consumption ($r = 0.725$), followed by fats (0.670) and butter (0.595) (Table 3).

Incidence of ovarian cancer and food intake

Iceland had the highest ovarian cancer incidence at 16.2 per 100,000, followed by Sweden (15.2) and the United Kingdom (13.7) (Fig. 3). The lowest rate per 100,000 was for Korea (1.6), followed by Mali (2.1), China (4.0), and Brazil (4.0).

The simple correlation coefficient, r, showed the greatest correlation between milk and ovarian cancer ($r = 0.779$), followed by animal fats (0.717) and cheese (0.697) (Table 1). By contrast, cereals ($r = -0.520$) and pulses (−0.465) were negatively correlated with the incidence of ovarian cancer.

The results of stepwise multiple-regression analysis are presented in Table 2. The analysis identified ''milk + cheese'' as the factor contributing most to the incidence of ovarian cancer (standardized regression coefficient [R] = 0.767), while it

Table 2 Stepwise-multiple-regression analysis (forward) on the consumption of selected food items (independent variables[a]) affecting incidence/mortality rates of female cancers (dependent variables)

	Coefficient	Standard error	R^{2b}	*F*-to-remove
Breast cancer incidence vs. 11 independent variables (1961–1998)				
Meat	0.251	0.025	0.862	13.724
Breast cancer mortality vs. 11 independent variables (1961–1998)				
Milk and cheese	0.022	0.003	0.814	68.527
Ovary cancer incidence vs. 11 independent variables (1961–1998)				
Milk and cheese	0.009	0.001	0.767	48.619
Ovary cancer mortality vs. 11 independent variables (1961–1998)				
Fats and butter	0.059	0.008	0.796	60.416
Corpus uteri cancer incidence vs. 11 independent variables (1961–1998)				
Milk and cheese	0.014	0.003	0.861	72.242
Corpus uteri cancer mortality vs. 11 independent variables (1961–1998)				
Milk and cheese	0.001	0.001	0.517	12.746

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

Table 3 Correlation coefficients between female cancer mortality rates (2000) and food consumption (average values during 1961–97)

	Correlation coefficient		
	Breast	Ovary	Corpus uteri
Animal fats	0.670**	0.818**	0.403**
Butter	0.595**	0.651**	0.330*
Cheese	0.725**	0.731**	0.406**
Eggs	0.615**	0.655**	0.223
Meat	0.517**	0.600**	0.434**
Fish	0.110	0.047	−0.140
Milk	0.536**	0.790**	0.545**
Cereals	−0.401*	−0.391**	−0.384*
Pulses	−0.395*	−0.367*	−0.345*
Fruits	0.292	0.246*	0.381*
Vegetables	0.189	0.185	−0.036
Vegetable oils	0.435**	0.372*	0.339*
Alcohol	0.463**	0.491**	0.249
Coffee	0.547**	0.569**	0.349*
Tea	0.316*	0.186	0.256

* $p < 0.05$.
** $p < 0.01$.

identified cereals as a factor contributing to a decreased incidence.

The correlation coefficient between mortality and incidence of ovarian cancer was as high as $r = 0.808$. The food most closely correlated with mortality due to ovarian cancer was fats ($r = 0.818$), followed by milk (0.790) and cheese (0.731). Cereals, by contrast, were negatively correlated with the mortality (−0.391) (Table 3).

Incidence corpus uteri cancer and food intake

The age-adjusted incidence rate (per 100,000) of corpus uteri cancer was highest in the United States (18.4), followed by Malta (16.3) and Canada (14.4). Viet Nam had the lowest incidence rate at 1.6, followed by Mali (1.7) and Korea (1.9) (Fig. 4).

Milk was most closely correlated with the incidence of corpus uteri cancer ($r = 0.814$), followed by cheese (0.787) and meat (0.782) (Table 1). Conversely, pulses were negatively correlated with the incidence of this cancer (−0.437).

Stepwise multiple-regression-analysis identified ''milk + cheese'' as the factor contributing most to an increased incidence of corpus uteri cancer (standardized regression coefficient [*R*] = 0.861) (Table 2).

The mortality rates of corpus uteri cancer were weakly correlated with its incidence rate ($r = 0.251$). The highest age-adjusted mortality rate was 4.4 for Uruguay, and Mali had the lowest rate of 0.24. As with the incidence data, the age-adjusted mortality rates of this cancer had the highest correlation with milk consumption ($r = 0.545$), followed by cheese (0.406) and animal fats (0.403).

Discussion

Epidemiological studies that correlate cancer incidence and mortality rates with the dietary practices in various geographical areas have certain

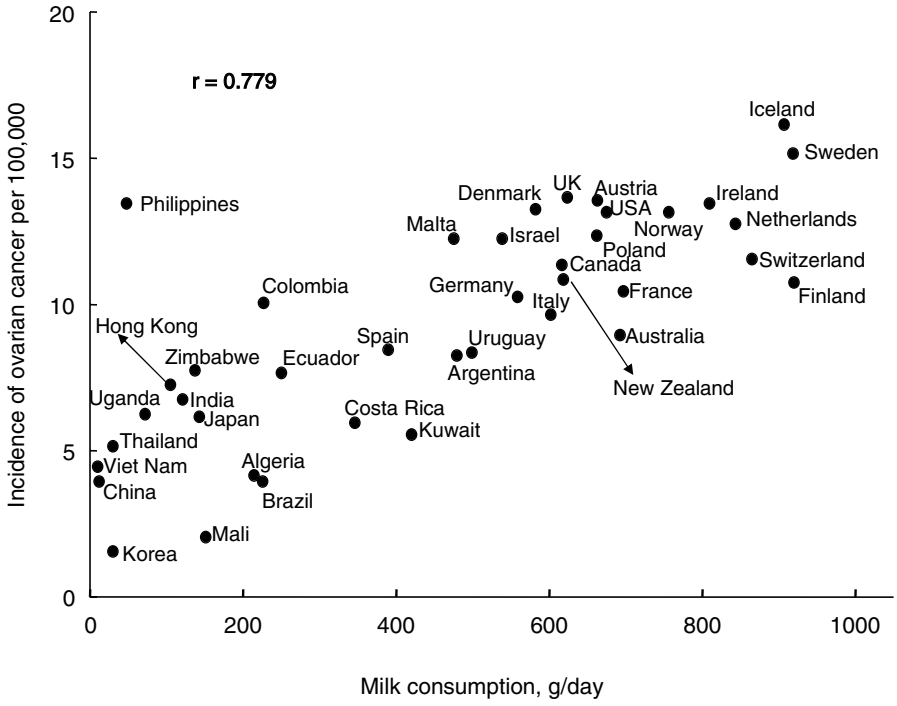

Figure 3 Correlation between the age-adjusted incidence rates of ovarian cancer (1993–97) and *per capita* milk consumption (1961–97) in 40 countries.

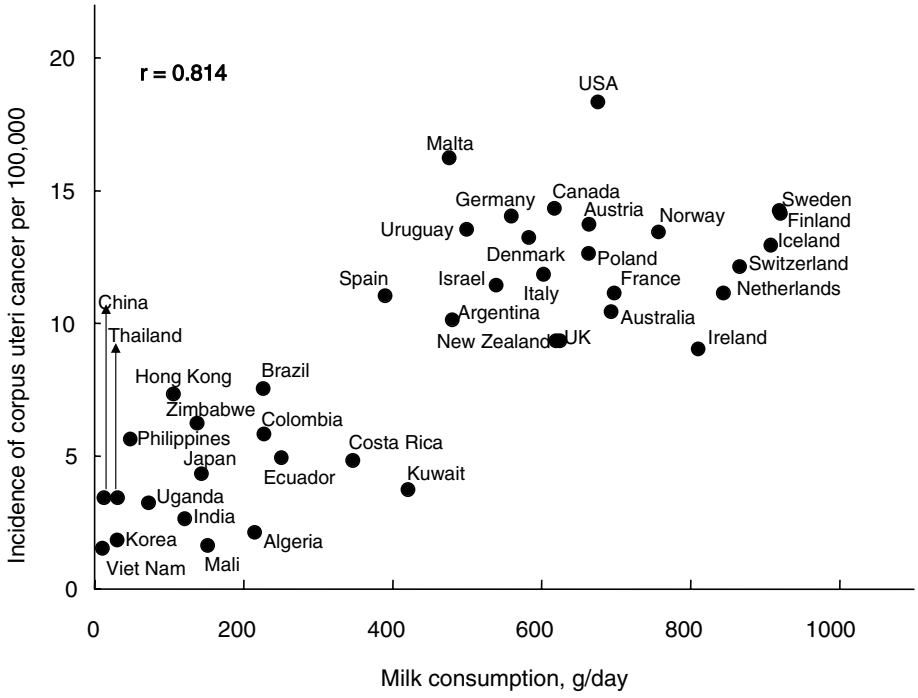

Figure 4 Correlation between the age-adjusted incidence rates of corpus uteri cancer (1993–97) and *per capita* milk consumption (1961–97) in 40 countries.

shortcomings. The rates of incidence and mortality of any cancer are affected by regional differences in diagnosis, registration and certification, and the fatality rate of the cancer. The cancer incidence and mortality data from developing countries are clearly less complete than those from developed countries because of problems with under diagnosis and under certification due to the

local medical and economic background, together with problems enumerating the population. In addition, the consumption data for each food item in a country are not based on actual nutrition surveys, but are roughly estimated using the following equation: food supply per capita = (production + import + stock changes − export − feed − seed − processing − waste − other uses)/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 [10,14].

Breast cancer

Early diagnosis (mammography, fine-needle biopsy), treatment (lumpectomy, radiotherapy, chemotherapy) and increasing public awareness of breast cancer may have contributed to its relatively stable mortality rates despite its increasing incidence. Starting in the 1990s, breast cancer mortality began to decline in the United States and in some European countries [8]. Since the 1950s, however, both incidence and mortality rates have been increasing in a number of other countries, including low-risk countries such as China [15] and Japan [16]. Lifestyle changes in these countries, such as diet, likely account for much of this increase.

In this study, the food that was most closely correlated with the incidence of breast cancer was meat, followed by milk and cheese. Many other epidemiological studies have found positive correlations between breast cancer risk and the consumption of meat, milk, and dairy products [14,17–21]. According to La Vecchia and Pampallona [18], who found a significantly positive correlation between breast cancer mortality and meat and milk consumption, milk and cheese were the only dietary variables to remain significantly positive after the correlation was adjusted for the women's age at the birth of their first child and economic variables.

Since dietary fat has long been considered a major risk factor for breast cancer, special attention has been given to the high fat content of milk [17,19,21–23]. However, milk fat cannot account for all of the breast cancer risk related to milk consumption. In fact, consumption of whole milk has declined steadily since the 1950s, and been replaced by fat-reduced milk [24], yet the incidence of breast cancer has increased worldwide over the last 50 years [25].

Estrogens and progesterone are breast cancer promoters because of their physiological roles stimulating the mammary gland [26]. The major sources of animal-derived estrogens in the human diet are milk and dairy products, which account for 60–80% of the estrogens consumed [27]. Most milk for human consumption is obtained from heifers in the latter half of pregnancy, when the estrogen levels in cows are markedly elevated [28].

Although the oral bioactivity of free estradiol and estrone may be relatively low, estrone sulfate, which is a major estrogen in milk, has high oral bioactivity. Once inside the body it can be readily converted to estrone and estradiol. Postmenopausally, estrone is the source of most circulating estradiol, and estrone sulfate is the most abundant circulating estrogen [29]. In addition to the long plasma half-life of estrone sulfate, it is absorbed in the intestinal mucosa either virtually unchanged [30,31] or by enterohepatic circulation. Remesar et al. [32] calculated estrone intake in a standard human diet and found that 46.6% of estrone came from dairy products.

Recently, we confirmed that commercially available low-fat milk promotes the development of 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced mammary tumors in rats [33]. In order to specify the role of estrogens on the development of mammary tumors, an aqueous estrone sulfate solution was used as a positive control in this study. The degree of tumor promotion by cows' milk was almost comparable to that of 100 ng estrone sulfate per milliliter.

Some human studies have also demonstrated that milk consumption increases the circulating estrogen level. South African black males who had switched from a vegetarian diet to a Western diet with milk, butter, and meat showed an increase in circulating estrogen levels [34]. The relationship between milk consumption and plasma estrogen concentrations is also supported by the fact that Asian women, whose consumption of milk and dairy products is low, have lower plasma estrogen concentrations than those of Caucasian women, whose dairy product consumption is high [35].

In addition to estrogens, milk also contains insulin-like growth factor I (IGF-I) in nanomolar concentrations [36]. IGF-I plays a role in the growth and incidence of neoplastic pathology [37] by regulating the growth of cancer cells and it stimulates the proliferation of human breast cancer cell line MCF-7 [38]. Further, estrogen and IGF-I have mutually favorable actions on breast cancer cell proliferation. In a human study, plasma IGF-I concentration increased by 10% when healthy subjects consumed cows' milk [39]. In fact, the consumption of commercial milk pasteurized by heat at 125–130 °C was confirmed to increase the plasma level of IGF-1 in rats [33].

Obesity has been linked with breast, corpus uteri and ovarian cancers, probably via its effect on

circulating estrogens [40,41]. This finding is biologically plausible, since a greater amount of fat results in greater conversion of androstenedione to estrone by aromatase and lower levels of sex hormone-binding-globulin (SHBG), which leads to higher levels of bioavailable estrone and estradiol [42]. We should pay particular attention to the sex hormone in modern cows' milk, because epidemiological studies of large scale have repeatedly confirmed the increased incidence of breast cancer in postmenopausal women who are currently undergoing hormone replacement therapy [43,44].

Ovarian cancer

The strong correlation between ovarian cancer and per capita milk consumption led to the hypothesis that consumption of lactose is a risk factor for ovarian cancer [8]. In the Iowa Women's Health Study, a prospective study of 41,836 women, high lactose consumption was associated with an increased risk of ovarian cancer ($r = 1.60$) [45]. Cramer [46] proposed that galactose, a component sugar of lactose, is a risk factor for ovarian cancer, as galactose is toxic to oocytes. Hypogonadism or ovarian failure in response to gonadotropin stimulation has been found in women who are deficient in the enzyme galactose-1-phosphate uridyltransferase (GALT) [47]. In one case-control study, GALT activity was significantly lower in cases of ovarian cancer [48]. Nevertheless, most case-control studies that have examined the risk of ovarian cancer in relation to lactose intake have not reported a substantial association between the two [49,50]. A recent prospective cohort study in Sweden [51] indicated that high intakes of lactose and dairy products, particularly milk, are associated with an increased risk of serious ovarian cancer but not of other subtypes of ovarian cancer.

Several research groups have reported associations between ovarian cancer and the intake of specific milk products, such as butter [52,53], whole milk [53—55], skim milk [45], yogurt [48—55], cottage cheese [48], and ice cream [53]. One study found a threefold greater risk of ovarian cancer among women who drank at least one glass of whole milk per day compared with those who did not [54]. Risk was also elevated for non-fat milk, eggs and cheese, and dairy products in general [45].

In our study, the stepwise multiple-regression analysis revealed that ''milk + cheese'' contributed the most to the incidence of ovarian cancer. Our results are consistent with previous ecological studies that found an association between ovarian cancer and milk consumption [14]. The etiology of ovarian cancer is still poorly understood, although it is clear that hormonal factors are involved. Higher IGF-I levels and reduced IGF-I binding protein levels have also been found in patients suffering from ovarian cancer [56,57]. Epidemiological observations and experimental data indicate that estrogens have an adverse effect on the ovarian epithelium [7]. It is not unreasonable to presume that estrogens and growth factors in milk and dairy products are associated with the development of ovarian cancer by changing the hormonal environment in the ovaries.

Corpus uteri cancer

Cancer of the corpus uteri is a typical model of hormone-related carcinogenesis. Indeed, the effect of estrogens is so direct and strong that the widespread use of hormone therapy increased the incidence of this cancer in the United States to almost epidemic proportions [8]. Most of the risk factors for corpus uteri cancer can be explained within the framework of the unopposed estrogen hypothesis, which holds that exposure to estrogens leads to increased mitotic activity of endometrial cells, an increased number of DNA replication errors, and somatic mutations resulting in a malignant phenotype [58,59].

In our study, the incidence of corpus uteri cancer was most closely correlated with the consumption of milk and cheese. As discussed in the section on breast cancer, milk and dairy products contain considerable amounts of estrogens and growth factors. Estrogens induce various tumors in laboratory animals and have been recognized as carcinogens in humans, raising the risk for uterine cancer, in addition to breast and ovarian cancers [60]. Several trials have established a link between endometrium cancer and the IGF system [61—63], including the stimulating effect of IGF-I in vitro on endometrial cancer cells, and increased circulating levels of serum IGF-I and decreased insulin-like growth-factor-binding protein (IGFBP-1) in women with corpus uteri cancer.

In conclusion, we hypothesize that female sex hormones in milk and dairy products have a common effect on the development of breast, ovarian and corpus uteri cancers. Further epidemiological and mechanistic studies are needed to verify this hypothesis.

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