An Ecologic Study of Dietary Links to Prostate Cancer

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Abstract

Background: The etiology of prostate cancer has not been fully resolved in the scientific and medical literature, although the non-fat portion of milk and calcium are emerging as leading dietary risk factors, with lycopene (found in tomatoes) and vitamin D apparently being risk reduction factors.

Methods: The ecologic (multi-country statistical) approach is used to study dietary links to prostate cancer. Mortality data from 1986 for various age groups in 41 countries are compared with national consumer macronutrient supply values for 1983 and tomato supply values for 1985.

Results: For 28 countries with more than five Kcal/day of tomatoes in the consumer supply, a linear combination of non-fat milk (risk factor) and tomatoes (risk reduction factor) was found to have the highest statistical association with prostate cancer mortality rates for men over the age of 35, with the Pearson regression coefficient – r^2 – for those aged 65-74 years = 0.67 and $p < 0.001$. For the 13 countries with fewer than six Kcal/day of tomatoes, non-fat milk had the highest association ($r^2 = 0.92$, $p < 0.001$ for men aged 65-74 years). For 41 countries combined, the non-fat portion of milk had the highest association with prostate cancer mortality rates ($r^2 = 0.73$, $p < 0.001$ for men aged 65-74 years).

Conclusions: These results support the results of several cohort studies which found the non-fat portion of milk to have the highest association with prostate cancer, likely due to the calcium, and tomatoes to reduce the risk of prostate cancer, most likely due to lycopene.

(Altern Med Rev 1999;4(3):162-169)

Introduction

Investigation of dietary links to prostate cancer appears to be reaching an important stage after years of effort. A number of studies have found high correlations between prostate cancer and diet, of which the most significant correlations as risk factors are total fat,[1,2] animal fat,[3-8] milk,[6,9-18] and red meat,[19] while the most significant correlations with risk-reduction factors are vitamin A,[13] vegetarian diet,[20] and lycopene and tomatoes.[21-26] In addition, there appears to be a link to testosterone in the etiology of prostate cancer.[27-31] While the prior ecologic studies did not reach a strong conclusion (Table 1), the cohort and case-control studies seem to have

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reached the conclusion that the non-fat portion of milk, along with calcium from milk or alone, is the highest risk factor (Table 2). In addition, tomatoes have been found to be a risk-reduction factor.

Methods

In this study, the ecologic approach is used to investigate dietary links to prostate cancer mortality. In this approach, mortality data for a number of countries are compared statistically with various components of national dietary supply. While morbidity data would be preferable, since not everyone who develops prostate cancer dies as a result, the mortality data are much more readily available. The ecologic approach previously served as the first way to link macronutrients to chronic disease, such as dietary fat to breast[1] and colon cancer.[1,32] The ecologic approach has also been used to find dietary links to coronary heart disease (CHD) and ischemic heart disease (IHD). The first use was by Keys, in which the CHD mortality rate versus fat calories was plotted for men aged 55-59 in six countries.[33] Yerushalmy and Hilleboe[34] pointed out if all 22 countries for which available comparable data were used, animal fat and animal protein calories, each divided by total calories, yielded a higher correlation with CHD than did fat. As a result, Keys conducted a cohort study in seven countries, with the finding that animal fat had the highest association with CHD.[35] This result has been the guiding principle in dietary recommendations for heart disease ever since. The ecologic approach has also linked lactose to IHD[36-40] for a number of years. Recently, sweeteners, primarily fructose, have been linked to IHD for women aged 35-64.[38-41] Unfortunately, no case-control or cohort studies have been conducted to test the ecologic findings regarding sugars, although a number of recent papers provide indirect support for these findings. The ecologic approach works well if approached with an open mind about which dietary factors might be involved, but it has yielded some discarded findings. Case-control and cohort studies in which investigations were limited to single factors have also resulted in some incorrect findings. The best epidemiologic results seem to be those that can be confirmed using case-control, cohort, and ecologic approaches.

In this study, 1986 mortality rates for prostate cancer for various age groups from 41 countries[42] are compared statistically with various components of the national consumer food supply for 1982-1984.[43] The U.S. Department of Agriculture estimates 25 percent of food in the U.S. consumer supply is not consumed. It is assumed similar loss factors apply to the countries used in this analysis. Since

Table 1. Statistical findings in other works based on age-adjusted prostate cancer mortality data.

Macronutrient	Years, number of countries	SROCC	r^2	Reference
Meat	1964-5, 36	0.74		57
Milk	1964-5, 36	0.73		57
Fats	1964-5, 36	0.70		57
Total fat	1964-5, 32		0.55	1
Fat & oils	1964-5, 32		0.49	1
Milk	1964-5, 32		0.36	1
Animal fat	1978-9, 30		0.48	3
Total fat	1973-7, 20*		0.48	2
Animal fat/cal.	? , 28		0.50	5

* incidence
SROCC = Spearman Rank Order Correlation Coefficient

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Figure 1. 1986 prostate cancer mortality rates for males aged 65-74 years in countries with > 5 Kcal/day of tomatoes in the consumer food supply vs. 1983 non-fat milk and tomatoe supply according to the equation y=0.341 non-fat milk (Kcal/day) - 0.884 tomatoes (Kcal/day).

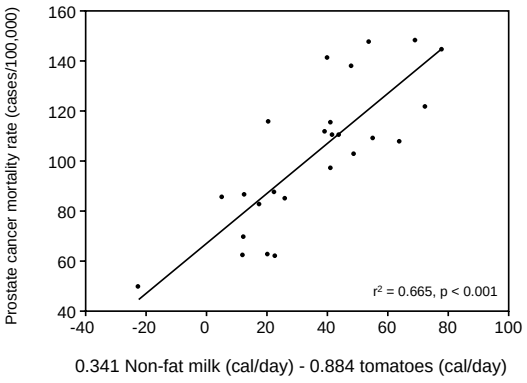


Figure 2. 1986 prostate cancer mortality rates for males aged 65-74 years in countries with< 6 Kcal/day of tomatoes in the consumer food supply vs. 1983 non-fat milk supply (Kcal/day).

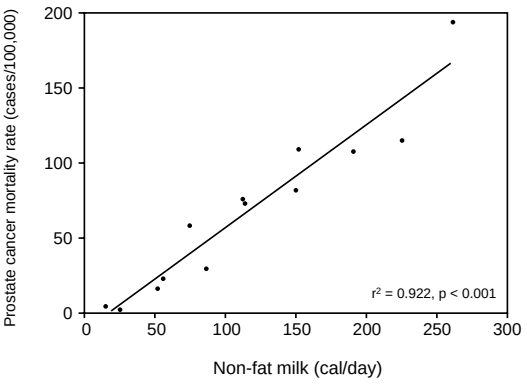
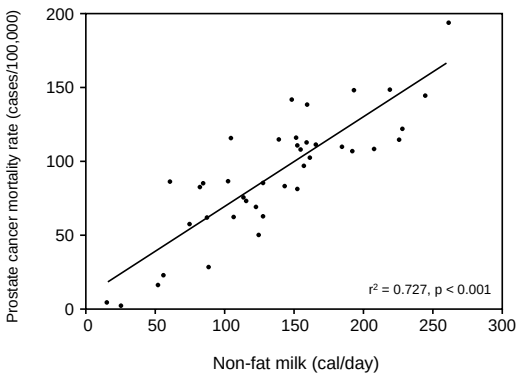


Figure 3. 1986 prostate cancer mortality rates for males aged 65-74 vs. 1983 non-fat milk supply (Kcal/day).



supply values for countries included in the study vary greatly (non-fat milk, for example, varies from 14 to 244 Kcal/day for the data reported here), the differences between supply and consumption are relatively unimportant. Some other difficulties with the data are the fact that micronutrients, such as vitamins and minerals are difficult to quantify using national dietary data.[20] Moreover, mortality rate data are also subject to non-dietary factors. The level of health care can play a major role, as well as the criteria and care with which mortality data are recorded. Finally, the level of physical exercise common to each country is not considered. The data shortcomings are not thought to affect the conclusions.

Countries included are in the footnotes to Tables 3 and 4. The criteria for including a country were a life expectancy of age 69+ in the 1980s and a population in excess of one million. Eastern European countries were included even though they were found to be outliers in the IHD studies.[38-41]

The dietary components chosen for analysis are primarily those linked to prostate cancer in other studies, such as cereals, fat, fructose (sweeteners), milk, and tomatoes. Since the literature suggests that milk seems to play an important role in the etiology of prostate cancer, the various components of milk were treated separately. Implicit in this analysis is the assumption the various components can be considered independently, even though they are usually consumed in combination. Multiple linear regressions can be used to investigate any interactions, as was done successfully for Alzheimer's disease, in which countries were segregated according to general dietary type.[44,45]

Results

The results of the regression analyses confirm the non-fat portion of milk is a risk factor for prostate cancer, while tomatoes reduce the risk. For the 28 countries for which

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Table 2. Relative risk ratios for milk and prostate cancer.

Drinks/day	Relative risk ratio	Reference
<1 1-2 3+	1.0 1.8 2.4	9
<5 days/week ≥5 days/week	1.0 2.46-2.58	10
0 1-2 ≥2	1 1.2 5.0-5.1	11
Whole milk Skim milk Whole + skim	1.0 2.2 1.2	13
>2 (83% skim, low fat)	1.6	14
>2.5 2.5-3.4 3.5-4.4 >4.5	1.00 (age adjusted) 1.24 1.37 1.53	15

the supply of tomatoes in the national dietary supply exceeded five Kcal/day, a multiple linear regression using non-fat milk and tomatoes had the highest association with prostate cancer mortality for those aged 65+ years (r^2 = 0.67 for those aged 65-74) (Table 3). The r^2 value is generally regarded as the fraction of the data that can be explained by the model. Thus, two-thirds of prostate cancer mortality for those over the age of 65 in the 28 countries can be attributed to non-fat milk as a risk factor and tomatoes as a risk reduction factor. For those aged 45-54 years, non-fat milk had the highest association with prostate cancer mortality. The r^2 for non-fat milk is only 0.35, while that for the multiple linear regression for non-fat milk and tomatoes is 0.53. However, since the student t-test, represented by F in Table 3, is higher for non-fat milk alone, it is the better statistical result. For the 13 countries with less than six Kcal/day of tomatoes in the national dietary supply, non-fat milk alone gave the highest association with prostate cancer mortality (r^2 = 0.92 for those aged 65-74) (Table 4). For the combined 41-country data set, the non-fat portion of milk was also found to have the highest association with prostate cancer mortality (r^2 = 0.73 for those aged 65-74) (Table 5). The statistical associations with the non-fat portion of milk with or without tomatoes are much higher than those with dietary fat.

In order to check whether the period used for the dietary data was appropriate, statistical analyses were also performed for the non-fat portion of milk for all 41 countries for the years 1976-1978 and 1979-1981. The correlation coefficients were about five percent lower, suggesting diet a few years prior to prostate cancer mortality is more important than diet earlier in life.

Table 3. Regression analyses for 28[1] countries with tomatoes > 5 Kcal/day in the consumer supply in 1985 along with milk from 1982-1984.

Age	Dietary Factors	r^2	F	p
75+	Non-fat milk + tomatoes[2]	0.606	19.2	<0.001
	Non-fat milk	0.419	18.8	<0.001
	Tomatoes	0.370	15.3	<0.001
	Animal fat	0.290	10.6	<0.003
	Fat	0.135	4.1	<0.054
65-74	Non-fat milk + tomatoes[3]	0.665	24.8	<0.001
	Non-fat milk	0.488	24.7	<0.001
	Animal fat	0.411	18.1	<0.001
	NFM + tomatoes + cereals	0.679	16.9	<0.001
	Tomatoes	0.377	15.7	<0.001
	Fat	0.172	5.4	0.028
55-64	Non-fat milk	0.346	17.1	<0.001
	Non-fat milk + tomatoes	0.526	13.9	<0.001
45-54	Non-fat milk	0.200	6.3	0.019

1. Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Chile, Cuba, Denmark, England/Whales, France, Germany, Greece, Hungary, Israel, Italy, Mexico, Netherlands, New Zealand, Norway, Panama, Portugal, Romania, Spain, Sweden, Switzerland, United States, Uruguay.
2. Prostate cancer mortality = 253.56 ± 1.211skim milk - 3.561 tomatoes.
3. Prostate cancer mortality = 67.35 ± 0.341 skim milk - 0.884 tomatoes.

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Table 4. Regression analyses for 13 countries[1] with tomatoes < 6 Kcal day in the consumer supply in 1985 along with milk from 1982-1984.

Age	Dietary Factors	r^2	F	p
75+	Non-fat milk	0.673	22.6	<0.001
	Non-fat milk + tomatoes	0.730	13.5	0.001
	Animal fat	0.284	4.4	0.061
65-74	Non-fat milk	0.922	129.7	<0.001
	Non-fat milk + tomatoes	0.923	60.0	<0.001
	NFM + tomatoes + cereals	0.924	36.6	<0.001
55-64	Non-fat milk	0.576	14.9	0.003
	Non-fat milk + tomatoes	0.658	9.6	0.005
45-54	Non-fat milk	0.661	19.5	0.001
	Non-fat milk + tomatoes	0.673	9.3	0.007

1. Costa Rica, Czechoslovakia, Ecuador, Finland, Hong Kong, Iceland, Ireland, Japan, Korea, Poland, Singapore, Sri Lanka, Venezuela.

Discussion

The results reported in Tables 3-5 add strong support to the papers which have already reported a statistical association between consumption of milk, especially the non-fat portion, and prostate cancer.[9-16] Giovannucci et al previously reported that calcium, from the diet or supplements, is a risk factor for prostate cancer.[14] Tables 3-5 seem to support this, as each 230 g of milk contains 300 mg of calcium. In addition, the results for the countries in which tomatoes comprise a significant portion of the diet strongly support previous research which found dietary and plasma lycopene to be a significant risk reduction factor for the development of prostate cancer.[22-26] The equations in the footnotes to Table 3 provide the information to determine the amount of tomatoes required to counter the effect of milk. The ratio of skim milk to tomatoes (Kcal) is 2.6-2.9. Thus, one cup of non-fat milk, with 86 Kcal and 300 mg calcium, would require 29-33 Kcal of tomatoes to fully counter the effects of the calcium. Note that Greece had 73 Kcal/day of tomatoes in the national dietary supply in 1983, and 122 Kcal/day of skim milk. The next highest tomato-eating country was Italy with 35 Kcal/day. The prostate cancer mortality rate for Greek men aged 65-74 in 1986 was 50 cases per year per 100,000 population. In Hungary, where the skim-milk supply was 102 Kcal/day and the tomato supply was 16 Kcal/day, the comparable mortality rate was 117 cases per year.

While not shown, no support could be given for the finding that fructose reduces the risk of prostate cancer.[14] The data used for this analysis included sweeteners and fruit, which are significant sources of fructose, but included other sugars and carbohydrates as well. That does not, however, rule out fructose as a possible risk reduction factor for prostate cancer.

No support is found, either, for the suggestion that dietary fat is a risk factor for prostate cancer. Animal studies have also shown a high-fat diet does not influence the growth of prostate cancer in rats.[46] Again, this does not rule out the possibility that fat is a risk factor for prostate cancer, but if it does, it appears to be much less important than skim milk and calcium.

In order for a statistical association to be seriously considered as a causal one, there are a number of criteria which should be satisfied.[47] These are broadly described as strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy. Most importantly, there has to be some likely mechanism to link the suspected

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agent with the observed effect. For milk, the most likely mechanism may be related to calcium. For men aged 65-74 years in the set of 41 countries, skim milk had the highest statistical association ($r^2 = 0.73$), with milk protein ($r^2 = 0.70$) and lactose ($r^2 = 0.65$) having lower associations. Giovannucci et al[14,17] found a significant increase in advanced prostate cancer and metastatic prostate cancer in subjects consuming over 2000 mg calcium per day, compared to individuals ingesting less than 500 mg calcium per day. The authors propose that high calcium intake suppresses the conversion of 25(OH) vitamin D (the primary form of vitamin D in the circulation) to $1,25(OH)_2$ vitamin D, which has an anti-tumor effect for prostate cancer.[48-51] This inhibition of vitamin D conversion by high calcium intake subsequently could reduce the body's ability to suppress cancer.

Additional support for the vitamin D hypothesis comes from the geographical distribution of prostate cancer mortality rates in the United States. A 1980 study revealed a linear trend in prostate cancer mortality rates among white men in the years 1970-1979, increasing from 19.8-20.1 in the southwest, to 20.7-21.0 in the northeast.[52] Surface UV-B radiation is predicted to decrease from 34-43 in the southwest to 10-18 in the northeast. Since the study did not include the geographic distribution of calcium and milk consumption, it cannot be considered conclusive. On the other hand, a recent cohort study involving 3,737 Japanese-American men in Hawaii of serum vitamin D metabolite levels and prostate cancer failed to find a strong correlation between vitamin D metabolites and lack of prostate cancer.[53]

Lycopene has also received much support in the literature as a risk reduction factor.[22-26] While lycopene is a strong antioxidant, the role it plays in reducing the risk of prostate cancer remains a mystery.[54] A recent cohort study among male smokers in Finland found that long-term supplementation with alpha-tocopherol substantially reduced prostate cancer incidence and mortality, while long-term supplementation with beta-carotene was associated with increased prostate cancer incidence and mortality.[55]

Prostate cancer likely has several contributing factors which may vary in relative importance as they affect individuals. However, calcium and the non-fat portion of milk

Table 5. Regression analyses for 41 countries for milk in 1982-1984 and tomatoes in 1985.

Age	Dietary Factors	r^2	F	p
75+	Non-fat milk	0.566	50.9	<0.001
	Non-fat milk + tomatoes	0.584	22.5	<0.001
	Animal fat	0.340	20.1	<0.001
65-74	Non-fat milk	0.727	104.0	<0.001
	Non-fat milk + tomatoes	0.731	51.6	<0.001
	Animal fat	0.499	38.8	<0.001
55-64	Non-fat milk	0.466	34.0	<0.001
	Non-fat milk + tomatoes	0.466	16.6	<0.001
45-54	Non-fat milk	0.383	23.0	<0.001
	Non-fat milk + tomatoes	0.394	11.7	<0.001

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appear to be the highest dietary risk factors for prostate cancer, while tomatoes or lycopene and vitamin D appear to be important risk reduction factors. Saturated fat may also be a risk factor, but there is only weak support for that possibility currently.

Acknowledgments

The author thanks E. Giovannucci (Channing Laboratory, Harvard Medical School) for helpful discussions, A. M. Moore (Williamsburg, VA) for technical editing, two anonymous referees for helpful comments, and the staffs of the Moorman Memorial Library of the Eastern Virginia Medical School (Norfolk, VA), the Health Sciences Library of the Riverside School of Professional Nursing (Newport News, VA), the Tomkins-McCaw Library of the Virginia Commonwealth University (Richmond, VA) and the Louise M. Darling Biomedical Library, UCLA (Los Angeles, CA) for use of their facilities.

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