

A Multicountry Ecological Study of Risk-modifying Factors for Prostate Cancer: Apolipoprotein E ε4 as a Risk Factor and Cereals as a Risk Reduction Factor

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Abstract. *The primary risk-modifying factors for prostate cancer are still a matter of debate. This work proposes and examines the hypothesis that the apolipoprotein E ε4 (ApoE4) allele and diet are important risk factors for prostate cancer. The hypothesis was evaluated in an ecological study involving 122 countries for which prostate cancer rates for 2002, ApoE4 allele prevalence, dietary supply values, and per capita gross domestic product (GDP) data were available, and for which there were at least 250,000 inhabitants. In addition, a subset of 102 countries with ApoE4 prevalence of less than 30% was also used. In the full data set, per capita GDP, lack of cereal consumption, milk protein and ApoE4 were significantly correlated with incidence, explaining 60% of the variance. In the 102-country subset of 102, per capita GDP, ApoE4 prevalence, and milk protein explained 62% of the variance of prostate cancer incidence, while lack of cereal consumption, ApoE4 prevalence and per capita GDP explained 55% of the variance of prostate cancer mortality rates. Cholesterol has been identified as an important risk factor for prostate cancer. The ApoE4 allele increases cholesterol production and cereal consumption lowers serum cholesterol levels. The ApoE4 allele is an important risk factor for Alzheimer's disease, and cholesterol is a risk factor and cereals a risk reduction factor. The ApoE4-diet-GDP hypothesis may explain the higher risk of prostate cancer for African Americans and should form the basis for further studies.*

Despite the many years of research on the epidemiology and etiology of prostate cancer, several puzzling facts remain regarding risk-modifying factors and ethnic and geographical

variations. Diet plays an important role, with milk – especially the nonfat portion (1-3) – and animal products associated with risk, whereas vegetable products in general are associated with risk reduction (4, 5). Other factors associated with risk of prostate cancer include oxidative stress (inflammation (7, 8), insulin (9), insulin-like growth factor 1 (10), and cholesterol (11, 12).

The geographical variation of prostate cancer mortality rates in the United States generally increases with increasing latitude, with somewhat higher rates in the northwest than in the northeast, and lowest in the southern states, especially in the southeast (13). This geographical pattern was used to develop the hypothesis that solar ultraviolet-B (UVB) irradiance, through production of vitamin D, reduced the risk of prostate cancer incidence and the mortality rate (14-16). However, the geographic variation for prostate cancer mortality rates differs from that for the 14 types of cancer with the strongest evidence for a beneficial role of UVB and vitamin D (17-20). For these 14 types of cancer, rates are highest in the northeastern states and lowest in the southwest, except for gastric cancer, for which those with Hispanic heritage near the Mexican border have higher rates, probably because of poor sanitation in Mexico (21). This pattern is the inverse of solar UVB doses in summer (22). The asymmetry is due to two factors: the generally high surface elevation from the Rocky Mountains to the west and the thinner stratospheric ozone layer there due to the prevailing westerly winds raising the tropopause height as the air masses prepare to cross the Rocky Mountains.

Prostate cancer mortality rates increase with increasing latitude in France (23), Italy (24), and Spain (20). The reasons for the variations in France and Italy have not been explained, although prostate cancer screening is more frequent in the north central region of Italy (25). In Spain, prostate cancer was not significantly inversely correlated with nonmelanoma skin cancer, an index of solar UVB irradiance, although 10 other types of cancer were in multiple linear regressions that included latitude and lung cancer (20, 26).

More support exists for the hypothesis that vitamin D is not important in prostate cancer incidence or progression.

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Table I. ApoE4 prevalence for various countries used in this study (values rounded to the nearest whole percent).

ApoE4 prevalence (%)	Countries
6	Thailand
7	Egypt, Kuwait
8	Cyprus, India, Iran, Iraq, Sri Lanka
9	Algeria, Bangladesh, Cambodia, China, Columbia, Greece, Italy, Jordan, Lebanon, Morocco, Pakistan, Portugal, Spain, Tunisia, Turkey, United Arab Emirates, Vietnam
10	Azerbaijan, Croatia, Indonesia, Japan, Former Yugoslav Republic of Macedonia, Myanmar, Paraguay, Philippines, Singapore, Slovakia, Slovenia, Tajikistan, Turkmenistan, Uzbekistan, Yemen
11	Armenia, Bulgaria, Ecuador, Georgia, Kazakhstan, Korea, Kirgizstan, Malaysia, Mauritius, Mexico, Switzerland
12	Belarus, Israel, Romania, Ukraine
13	Argentina, Bolivia, Costa Rica, France, Hungary, Nicaragua, Norway, Panama, Peru, Poland, Surinam, Venezuela
14	Austria, Brazil, Czech Republic, Russia, Uruguay
15	Australia, Belgium, Dominican Republic
16	Canada, Chile, Ethiopia, Germany, Mongolia, Netherlands, Saudi Arabia, United Kingdom
17	Guyana, Ireland (Eire), New Zealand, United States
18	Denmark, Iceland, Latvia, Trinidad and Tobago
20	Estonia, Lithuania, Sweden,
22	Cuba, Finland
23	Gambia
25	South Africa, Tanzania, Uganda
26	Barbados
28	Jamaica
30	Angola, Botswana, Cameroon, Congo, Gabon, Guinea, Ivory Coast, Lesotho, Malawi, Mali, Mozambique, Namibia, Niger, Nigeria, Senegal, Swaziland, Zambia, Zimbabwe
32	Kenya
40	Papua New Guinea

Prediagnostic serum 25-hydroxyvitamin D [25(OH)D] has little relation to prostate cancer incidence (27-30). These findings contrast sharply with the findings for breast and colon cancer, for which serum 25(OH)D dose–cancer incidence have well-defined relations (31, 32). Some studies have reported a difference in grade of tumor, nonaggressive or aggressive, with respect to prediagnostic serum 25(OH)D (33). Although some studies report that early-life solar UVB irradiance is associated with reduced risk of prostate cancer (34), the finding could be related to ethnic background linked to geographic location. Some studies also report inverse correlations between diagnosis of nonmelanoma skin cancer and prostate cancer (35, 36), suggesting that long-term UVB irradiance has some benefit in reducing the risk of prostate cancer. Vitamin D does seem to increase prostate cancer survival, with a recent study reporting that higher serum 25(OH)D levels were associated with increased survival rates (37) and noting that vitamin D metabolite reduces signal transducer and activator of transcription 3 (Stat3), which is involved in prostate cancer metastasis (38).

There are important differences in incidence and mortality rates associated with ethnic heritage. For reasons that are not understood, those with African heritage have much higher rates than those with Asian or European heritage (39, 40). Inspection of the map of largest ancestry by county of the United States in 2000 (41) in comparison with the map of

prostate cancer mortality rates (13) indicates that many of the variations in mortality rates are correlated with ethnic background. For example, on the map at the state economic area resolution (504 units, composed of one or more counties) for 1950-1969, those of Finnish ancestry in northern Michigan have lower prostate cancer mortality rates than do those with German ancestry in the neighboring counties. Those with British ancestry in and near Utah have higher rates than those in the surrounding regions. Italians on and near Long Island, New York, have lower rates than the Irish in Massachusetts, who in turn have lower rates than the English in New Hampshire and Vermont. Those with Spanish ancestry in northeast New Mexico have the lowest mortality rates in the surrounding area.

The fact that African-Americans have an incidence rate of prostate cancer that is 2.5-3.0 times greater than that of Caucasian-Americans strongly suggests a genetic factor. African-Americans also have higher rates of Alzheimer's disease than Caucasian-Americans (42), as well as coronary heart disease (CHD) (43), and both diet and genetics are implicated. Diets high in fat and total energy are important risk factors for Alzheimer's disease (44, 45). The apolipoprotein E ε4 (ApoE4) allele is the important gene affecting risk of Alzheimer's disease (46) and CHD (47). Thus, it is a candidate gene to explain the prostate cancer disparity between the races.

The idea that genetics could play a role in prostate cancer risk is also supported based on studies of twins, although the predisposing genetic risk factor has not yet been identified (48). For example, in a cohort of 31 848 veteran twins born in 1917-1927 in which a total of 1009 prostate cancer cases were identified, probandwise concordance for prostate cancer was substantially higher among monozygous twin pairs, 27.1%, than among dizygous twin pairs, 7.1% ($p < 0.001$). These data suggest that genetic influences account for approximately 57%, and environmental influences for 43%, of the variability in twin liability for prostate cancer. (49) A study in the Nordic countries reported 42% heritability (95% confidence interval (CI), 29%-50%) (50).

Many ecological studies of dietary risk factors for chronic diseases have used dietary supply data from the Food and Agriculture Organization (FAO) (2, 4, 5, 44, 51). The findings in Armstrong and Doll (51) that animal fat or total fat was the most important dietary risk factor for breast and other types of cancer was disputed for years. Then it was finally realized that ecological studies include the effects of diet on the entire lifespan from conception to death, whereas observational studies such as cohort studies are most sensitive to the period of life after enrollment, and much of the risk for breast cancer due to diet comes from early life (52, 53). However, earlier studies of cancer trends among recent migrants (54) gave strong support for the Armstrong–Doll (51) findings.

This report examines the association between the ApoE4 allele by ethnic or country background, dietary supply factors, and per capita gross domestic product (GDP) for males with prostate cancer incidence and mortality rates for 122 countries in an ecological study.

Materials and Methods

Values of ApoE4 by country or ethnic background were obtained from data for individual countries, as well as several summaries of such values (55-80). For Europe, the data were graphed with respect to the latitude of the population center for each country, and the regression value was used for each country. For countries with mixed ethnicity, the value was a proportional combination of the values for the ethnic backgrounds in the countries of origin. Table I summarizes the ApoE4 prevalence values used in this study.

The uncertainties in the ApoE4 prevalence values are estimated to be 10%-25% of the value. One contribution to the uncertainty is that ApoE4 prevalence is not a well-determined value in that it is determined from targeted studies. For several countries, no determinations were made, so estimates were made on the basis of values from other countries. It was noted that for ApoE4 prevalence below 30%, prostate cancer rates generally increased but that rates were very low for countries with prevalence of 30% or higher. This effect is similar to that observed for the prevalence of Alzheimer's disease (44) and largely relates to dietary differences between developing and Western developed countries. Thus, a subset of 102 countries with ApoE4 prevalence less than 30% was used in a second regression analysis.

Table II. *Correlations between independent data factors for 102 countries with ApoE4 prevalence <30%. The animal and cereals supply data are for 1992-4, the milk protein for 1989-91, lung cancer incidence rates for 2002, and the per capita GDP for 2000.*

Factor	Animal fat (β P)	Cereal (β P)	Milk protein (β P)	SqRt (GDP) (β P)	Lung cancer (β P)
ApoE4	-0.48*	-0.48*	0.20, 0.04	0.07, 0.46	-0.01, 0.89
Animal fat		-0.56*	0.81*	0.73*	0.63*
Cereal			-0.52*	-0.49*	-0.21, 0.03
Milk protein				0.65*	0.49*
GDP					0.33, 0.001

* $p < 0.001$; SqRt, square root.

Per capita GDP has been suggested as a risk-modifying factor for several types of cancer (81). Data for per capita GDP for 2000 were obtained from an almanac (82). Because of the large range of GDP, the square root of the value was used in the regression analyses to reduce the effect of extreme values.

The prostate cancer data used are incidence and mortality rates for 2002 from GLOBOCAN 2002 (83). The criteria for inclusion were that the population of the country had to exceed 250,000 inhabitants, that the data had to be of high quality, that dietary supply data had to be available (84), and, generally, per capita GDP data had to be available for 2000. Data for several other types of cancer were also obtained to investigate the findings for various risk-modifying factors for prostate cancer: breast, colorectal, endometrial, ovarian, pancreatic, and renal cancer, with lung cancer incidence data for 2002 used to determine the role of smoking in risk for each type of cancer (17).

Dietary supply data were obtained from the Food Balance Sheets of the FAO (84). These data represent food disappearance in the population. Although food consumption by individuals accounts for only about 70% of the food that disappears, the factor is similar in most populations and therefore serves as a reliable index. The data examined in this study were animal and vegetable fat, cereals, fish, milk, milk protein, milk fat, onions, sweeteners (added sugar), and tomatoes. Only animal fat, cereals, and milk protein were studied in detail because the other factors did not have significance in preliminary analyses for prostate cancer.

The data were processed in multiple linear regression analyses using SPSS Grad Pack 16.0 (SPSS, Chicago, IL, USA).

Table II gives the cross-correlation coefficients for the most important variables for 102 countries. Most factors used in this study are highly correlated with each other, so there is the danger of interference among the various factors in multiple linear regression analysis.

Results

Table III gives the regression results for prostate cancer for 122 countries that satisfy the general criteria for inclusion in this study. The results for various combinations of factors are provided to demonstrate that even though the factors are highly correlated, one can in general determine which factors

Table III. Regression results for prostate cancer rates for all 122 countries with data as in Table II.

Cancer outcome	Cereals (β P)	ApoE4 (β P)	SqRt of GDP (β P)	Milk protein (β P)	Animal fat (β P)	Adjusted R^2 , F, P
Incidence	-0.29*	0.18, 0.012	0.41*	0.26, 0.003		0.60, 46*
	-0.30*	0.18, 0.013	0.41*	0.26, 0.02	-0.009, 0.94	0.60, 37*
	-0.39*		0.34*	0.22, 0.011		0.58, 57*
		0.32*	0.50*	0.34*		0.55, 50*
	-0.39*	0.08, 0.26		0.48*		0.53, 49*
	-0.38*	0.08, 0.29			0.47*	0.51, 43*
		0.26*		0.38, 0.003	0.36, 0.004	0.46, 36*
	-0.64*	-0.11, 0.14				0.37, 37*
Mortality	-0.40*	0.25, 0.004			0.22, 0.015	0.37, 25*
	-0.38*	0.28, 0.002	0.13, 0.29	-0.02, 0.87	0.12, 0.44	0.37, 15*
	-0.43*	0.23, 0.006		0.18, 0.04		0.36, 24*
	-0.53*	0.16, 0.04				0.35, 33*
	-0.58*					0.33, 60*
		0.43*			0.44*	0.27, 24*
		0.32*				0.09, 13*

* $p < 0.001$; SqRt, square root.

are more important. The factors for which the β value is little changed depending on which other factors are included have the most strength—here, cereals, GDP, and milk protein. ApoE4 and animal fat vary widely and have little statistical strength.

For incidence, per capita GDP, milk protein, and ApoE4 were significantly correlated, whereas cereals were inversely correlated; the highest adjusted R^2 value was 0.60. For mortality, only cereals and GDP were significantly correlated, and the adjusted R^2 dropped to 0.37.

Table IV gives the regression results for 102 countries with ApoE4 prevalence less than 30%. For incidence, ApoE4, cereals, and GDP vary by up to a factor of 2 depending on which other factors are included, with larger variations for milk protein and animal fat compared to no additional factors. ApoE4 and GDP are essentially independent factors, with the adjusted R^2 value for the pair approximating the sum of the individual adjusted r^2 values. Adding cereals to the pair makes the largest additional gain in the β value but reduces the β values for the first two factors, suggesting that all three factors are important. For mortality rate, ApoE4, cereals and GDP per capita accounted for nearly all of the maximum adjusted R^2 value for any combination of factors. The adjusted R^2 values for this set of results are higher than those in Table III because this dataset excluded the low cancer rates with respect to the higher ApoE4 values.

Table V gives the regression results for dementia mortality rates and both incidence and mortality rates for seven types of cancer. Because the purpose of this analysis was to quickly determine significant risk-modifying factors for various types of cancer for comparison with the results for prostate cancer, the regressions were run for all six factors

without trying to optimize the choice of factors to include. Results for the full set of 122 countries are given; the results using the 102 countries with ApoE4 prevalence less than 30% were similar to those for the 122 countries.

Several findings are noteworthy: i. Consumption of cereals is significantly inversely correlated only with colorectal and endometrial cancer incidence. ii. For incidence, GDP is significantly correlated only with colorectal (directly) and ovarian (inversely) cancer and marginally insignificantly with breast (directly) and endometrial (inversely) cancer, based on the Bernoulli criterion ($p < 0.05/n$, where n is the number of factors included in the analysis). GDP is also inversely correlated with ovarian cancer mortality rate. iii. ApoE4 prevalence is not significantly correlated with any type of cancer, but it is significantly correlated with dementia mortality rates. iv. Lung cancer is significantly directly correlated with incidence rates for all types of cancer and mortality rates for colorectal, ovarian, pancreatic, and renal cancer. v. Milk protein is significantly correlated with incidence for four types of cancer (breast, endometrial, ovarian, and renal) and mortality rates for two types (ovarian and renal). vi. Animal fat consumption is directly correlated with incidence and mortality rates for lung and ovarian cancer incidence and mortality rates.

Discussion

Lung cancer was directly correlated with incidence and mortality rates for nearly all types of cancer considered in Table V, in general agreement with the literature (85). Animal fat was directly correlated with incidence of breast

Table IV. Regression results for prostate cancer rates for 102 countries with ApoE4 prevalence less than 30% with data as in Table II.

Cancer outcome	Cereals (β P)	ApoE4 (β P)	SqRt (GDP) (β P)	Milk protein (β P)	Animal fat (β P)	Lung cancer (β P)	Adjusted R^2 , F, P
Incidence	-0.30*	0.30*	0.38*	0.14, 0.09			0.67, 52*
	-0.30*	0.29*	0.37*	0.18, 0.07	0.19, 0.85	-0.11, 0.15	0.67, 35*
		0.42*	0.47*	0.21, 0.012			0.62, 57*
	-0.47*		0.30, 0.001	0.16, 0.07			0.61, 53*
		0.46*	0.60*				0.60, 77*
	-0.70*						0.49, 97*
			0.64*				0.40, 68*
				0.60*			0.36, 57*
					0.60*		0.35, 55*
			0.50*				0.24, 33*
Mortality	-0.44*	0.34, 0.05			0.20, 0.05	-0.18, 0.04	0.56, 33*
	-0.44*	0.35*	0.07, 0.50	-0.08, 0.52	0.20, 0.20	-0.17, 0.07	0.55, 22*
	-0.44*	0.37*	0.37*				0.55, 42*
	-0.51*	0.35*					0.54, 61*
	-0.68*						0.45, 84*
		0.60*					0.35, 55*
			0.36*				0.12, 14*

* $p < 0.001$; SqRt, square root.

and lung cancer, and mortality rates of breast, lung, and ovarian cancer, in general agreement with the literature (51). The Colli solar UVB index (5) was not significantly correlated with any type of cancer except renal cancer mortality rates (data not shown). However, more sophisticated multicountry ecological studies have found inverse correlations for all these types of cancer (86, 87).

ApoE4 is much more common among hunter-gatherer populations than among agrarian populations. Its role is to facilitate the storage of excess food as fat to ensure survival between feasts. This efficient utilization of ingested food is why ApoE4 is an important 'thrifty' gene (60). The important mechanisms of ApoE4 are to increase production of cholesterol in the liver (88) and of insulin in the pancreas (89, 90). For example, ApoE4 tended to reduce high-density lipoprotein (HDL) C and increase the low-density lipoprotein (LDL) C level in a high-fat intake population in Vietnam (91).

Adequate support exists for an important role of cholesterol in the etiology of prostate cancer. The Health Professionals Follow-Up Study found that low cholesterol levels reduced the risk of high-grade prostate cancer (odds ratio=0.61; 95% CI=0.39-0.98) (11). A recent large-scale cohort study in Japan found that total cholesterol was associated with increased risk of prostate cancer (multivariate hazard ratio (HR)=1.26; 95% CI=1.09-1.46) for a 1-standard deviation increment, and a reduced risk of liver cancer cases (HR=0.45; 95% CI=0.35-0.59) (12). For CHD for males, the HR was 1.34 (95% CI=1.17-1.53). No significant correlations with total cholesterol were found for any other type of cancer in this study.

A recent report proposed the hypothesis that cholesterol-rich domains, known as lipid rafts, in the membrane microdomains of the prostate process biochemical signals for tumor cell survival, proliferation, and migration (92).

Statin use reduces cholesterol production in the liver (93). Statin use is inversely correlated with risk of prostate cancer (94-101). Statin use has also been associated with reduced risk of dementia (102). For cognitive decline, elderly African-Americans with the ApoE4 allele who used statins had lower levels of cognitive decline (103).

Higher insulin levels are associated with increased risk of prostate cancer (104). Hyperinsulinemia stimulates liver production of insulin-like growth factor 1 and plays a role in the promotion of prostate cancer (105). A higher frequency of insulin receptors is found on malignant than on benign prostate epithelial cells (106). An observational study also found a significant increase in serum insulin levels in a prostate cancer risk group (107).

Fasting insulin level was significantly correlated with triglyceride ($r=0.404$; $p=0.037$) and HDL cholesterol ($r=-0.474$; $p=0.013$). The present study concludes that hyperinsulinemia associated with reduced insulin sensitivity may play a role in the pathogenesis of prostate carcinoma (108).

Other supporting evidence for a role of ApoE4 in prostate cancer risk. Several previous studies investigated the association between ApoE4 and prostate cancer. One in New York involving 35 patients with prostate cancer found an increased frequency of ApoE4 (prevalence=0.24) (109). However, a study in Finland found no difference in ApoE4

Table V. Regression results for dementia for 63 countries and several types of cancer for up to 122 countries with data as in Table II.

Cancer, gender, N	Lung Cancer (β P)	Cereals (β P)	ApoE4 (β P)	Milk protein (β P)	SqRt of GDP (β P)	Animal Fat (β P)	Adjusted R ² , F, P
Incidence							
Breast, F, 122	0.22*	-0.14, 0.015	0.003, 0.95	0.34*	0.19, 0.012	0.18, 0.06	0.78, 71*
Colorectal, M, 122	0.44*	-0.16, 0.006	0.03, 0.56	0.06, 0.50	0.38*	0.10, 0.38	0.77, 70*
Endometrial, F, 122	0.25, 0.002	-0.19, 0.009	-0.05, 0.42	0.46*	-0.25, 0.008	0.29, 0.02	0.64, 38*
Lung, M, 45	0.62*	0.13, 0.28	0.03, 0.77	-0.27, 0.08	-0.21, 0.10	0.77*	0.71, 19*
Lung, F, 45	0.81*	0.15, 0.17	0.14, 0.13	-0.27, 0.06	-0.10, 0.43	0.57*	0.75, 23*
Ovarian, F, 122	0.25, 0.001	-0.16, 0.03	-0.10, 0.15	0.39*	-0.28, 0.005	0.36, 0.003	0.63, 36*
Pancreatic, M, 121	0.58*	-0.10, 0.09	-0.04, 0.55	0.13, 0.14	-0.05, 0.52	0.23, 0.05	0.75, 59*
Renal, M, 122	0.47*	-0.12, 0.04	0.04, 0.47	0.30, 0.001	0.03, 0.68	0.16, 0.16	0.76, 64*
Mortality							
Dementia, 63***			0.29, 0.005	0.26, 0.03	0.37, 0.001		0.46, 19*
Dementia, 63***		-0.10, 0.46	0.25, 0.03	0.22, 0.11	0.31, 0.03	0.05, 0.72	0.45, 11*
Breast, F, 122	0.05, 0.65	-0.09, 0.36	0.10, 0.27	0.25, 0.08	-0.08, 0.56	0.37, 0.03	0.32, 11*
Colorectal, M, 121	0.50*	-0.13, 0.04	0.05, 0.47	-0.008, 0.93	0.14, 0.12	0.29, 0.02	0.70, 48*
Endometrial, F, 122	-0.009, 0.94	-0.16, 0.15	-0.13, 0.21	0.39, 0.02	-0.47, 0.001	0.22, 0.25	0.15, 4.6*
Lung, M, 45	0.55*	0.11, 0.38	0.02, 0.83	-0.22, 0.16	-0.19, 0.13	0.79*	0.70, 18*
Lung, F, 45	0.78*	0.12, 0.33	0.09, 0.39	-0.32, 0.05	-0.11, 0.41	0.64*	0.69, 17*
Ovarian, F, 122	0.23, 0.008	-0.09, 0.25	0.03, 0.68	0.44*	-0.29, 0.005	0.38, 0.005	0.57, 27*
Pancreatic, M, 121	0.51*	-0.10, 0.11	-0.02, 0.79	0.18, 0.04	-0.04, 0.62	0.25, 0.03	0.73, 56*
Renal, M, 122	0.50*	-0.09, 0.19	-0.01, 0.88	0.28, 0.004	-0.18, 0.04	0.26, 0.05	0.69, 46*

* $p < 0.001$; **cigarettes for lung cancer; ***ApoE4 prevalence less than 30%; F, female; M, male; N, number of countries included; SqRt, square root.

alleles between those with prostate cancer and those with benign hyperplasia or controls; however, plasma LDL-C and HDL-C were 10%-20% higher (110). A study in Norway also found no significant difference in ApoE4 allele prevalence. A study in Italy found that ApoE expression correlates directly with the Gleason score in tissue sections (111).

Because ApoE4 is associated with risk of Alzheimer's disease (46), the significant correlation of ApoE4 with dementia mortality rates shown in Table V provides support that the values of ApoE4 prevalence used in this study are reasonable. Although several dietary factors (fat and total energy (both directly correlated) and fish and cereals (both inversely correlated)) correlated with the prevalence of Alzheimer's disease in a previous study (44), it did not include ApoE4 prevalence, and no dietary factors correlated with mortality rates for dementia in the present study.

Dietary factors. Dietary supply of cereals inversely correlated with prostate cancer incidence and mortality rates in this study. The effect is not merely a displacement of other dietary factors such as animal products because the fraction of energy derived from cereals did not give as high a correlation as energy derived from cereals. Cholesterol levels are lower in countries with higher cereal consumption (112). Cholesterol levels increased dramatically for Japanese men over a 40-year period as the fraction of carbohydrates in the diet decreased (113). Rice bran oil, not fiber, lowers cholesterol in healthy, moderately hypercholesterolemic

adults (114). A recent study involving Native American Indians found that eating oat cereal significantly reduced LDL cholesterol (115). Although cereals may well account for a good fraction of serum cholesterol levels, a recent study did not correlate fiber from cereals with prostate cancer risk (116). However, fiber may not be the active ingredient in cereals in reducing the risk of prostate cancer (114).

Milk, especially the nonfat portion, has long been associated with risk of prostate cancer. The first report came from the Seventh Day Adventists Study (117), followed by a report from Italy (118), one in Sweden (119), and, later, an ecological study (2). An analysis of 13 cohort studies found a relative risk (RR) comparing high and low dairy product consumption of 1.13 (95% CI=1.02-1.24) (120). A recent meta-analysis of case-control studies reported a RR of 1.14 (95% CI=1.00-1.29) for milk or dairy product consumption, although the risk ratio from cohort studies was insignificantly increased (RR=1.04; 95% CI=0.90-1.15) (121). Part of the problem with these meta-analyses is that total consumption of dairy or milk products was considered, not the nonfat portion. As noted in a study in Hawaii, low-fat/nonfat milk was related to an increased risk; and whole milk, to a decreased risk of total prostate cancer (3).

The present study found that milk protein, which is primarily casein, had the highest correlation with prostate cancer incidence and mortality rates for the 2002 data. Milk protein became the important dietary risk factor for prostate cancer incidence in the this period. It is not clear whether

this is due to casein, the primary protein in cow's milk, or some other component such as calcium or hormones. A higher circulating serum calcium level was recently reported as being inversely correlated with prostate cancer survival rates (122). A recent review found that calcium intake is generally protective against many types of cancer, with mixed results noted for prostate cancer (123).

Interestingly, a case-control study of African and Caucasian American men found that animal fat was a significant risk factor for African-Americans but not Caucasian-Americans, although animal fat was a risk factor for advanced prostate cancer for both groups (124). Several recent studies found no link between animal fat and prostate cancer risk (3), but that may be because they investigated only recent dietary history.

Trends in prostate cancer mortality rates. Prostate cancer mortality rate trends in various countries depend on several factors such as diet and medical delivery systems. The advent of prostate-specific antigen screening for prostate cancer diagnosis doubled prostate cancer incidence rates and led to a 30% increase in mortality rates in many countries in the early 1990s. Nonetheless, countries with a greater degree of economic development can better provide medical interventions that increase survival once prostate cancer is diagnosed. Thus, such countries would have better survival rates than less developed countries. In light of this fact, the incidence data are more reliable in recent periods, although mortality rate data from earlier periods are adequate. As countries adopt diets more aligned with the Western Developed Country diet (84), prostate cancer rates increase, as in Japan and Spain (125): in both countries, dietary supply of animal products more than doubled from 1962 to 1980.

Geographical variation in the United States. The ranking of prostate cancer mortality rates in the United States on the basis of ancestry (41) and data from Devesa *et al.* (13) appears to be in this order: African, Norwegian, English, German, Irish, French, Dutch, Italian, Spanish, Mexican, and Finnish. Other than for the Finnish, who constitute the most populous country group in northern Michigan, and the Dutch, who make up a small region of southwest Michigan, the order is generally in line with ApoE4 allele frequency in the respective ancestral countries. This conclusion assumes that the diet is largely the same for all ancestries, although that assertion is not likely to be entirely correct. For example, the highest cardiovascular disease and lung cancer mortality rates for Caucasian Americans occur in the southeast (126).

Thus, on the basis of the results and interpretations of this study, it can be concluded that solar UVB does not explain the geographical variation of prostate cancer mortality rates in the United States. No conclusion can be reached for other countries such as France (23), Italy (24), and Spain (20);

however, examining latitudinal variations in ApoE4, diet, and prostate cancer screening in these countries would be useful.

Hill's criteria for causality. Correlations between risk-modifying factors and disease outcome indicate that a causal link might exist. However, establishment of a causal link generally requires much additional work. Hill (127) laid out the criteria for causality in a biological system. For this study, the most important criteria were strength of association, consistency from study to study, dose-response relationship, mechanisms, and experiment. Not all criteria must be satisfied, but the more that are, the more convincing the link. The ApoE4-diet-cholesterol-prostate cancer hypothesis seems to satisfy all the preceding criteria except consistency and experiment. Although consistency is lacking, some inconsistent studies did not control for all the factors at once, *e.g.* diet but not genetics or cholesterol levels. Further observational and experimental investigations are therefore warranted.

Conclusion

The ApoE4-diet-cholesterol-prostate cancer hypothesis seems to explain the geographical variation of prostate cancer mortality rates in 122 countries. It also seems to explain much of the geographical variation of prostate cancer mortality rates in the United States. Although vitamin D does not seem to affect risk of prostate cancer, serum 25(OH)D does seem to increase survival for those diagnosed with the disease (37). The ApoE4-diet-cholesterol-prostate cancer hypothesis should be easy to test by using existing data on those enrolled in several cohort studies, adding measurement of ApoE allele frequencies to the studies. If the hypothesis is substantially correct, it should lead to more accurate identification of those at greatest risk of prostate cancer, as well as improving preventive and treatment approaches.

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