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An ecological study of cancer incidence and mortality rates in France with respect to latitude, an index for vitamin D production

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France has unexplained large latitudinal variations in cancer incidence and mortality rates. Studies of cancer rate variations in several other countries, as well as in multicountry studies, have explained such variations primarily in terms of gradients in solar ultraviolet-B (UVB) doses and vitamin D production. To investigate this possibility in France, I obtained data on cancer incidence and mortality rates for 21 continental regions and used this information in regression analyses with respect to latitude. This study also used dietary data. Significant positive correlations with latitude emerged for breast, colorectal, esophageal (males), lung (males), prostate, both uterine cervix and uterine corpus, all and all less lung cancer. Although correlations with latitude were similar for males and females, the regression variance for all and all less lung cancer was about twice as high for males than for females. Lung cancer incidence and mortality rates for females had little latitudinal gradient, indicating that smoking may have also contributed to the latitudinal gradients for males. On the basis of the available dietary factor, micro- and macronutrient data, dietary differences do not significantly affect geographical variation in cancer rates. These results are consistent with solar UVB's reducing the risk of cancer through production of vitamin D. In the context of serum 25-hydroxyvitamin D level–cancer incidence relations, cancer rates could be reduced significantly in France if everyone obtained an additional 1,000 IU/day of vitamin D. Many other benefits of vitamin D exist as well.

Introduction

France has large geographical variations in cancer incidence and mortality rates, with rates generally increasing with increasing latitude.[1-11] Incidence rates for all cancers are 40% higher for males in the north than in the south and are 25% higher for females, whereas mortality rates are 30% and 15% higher, respectively, on the basis of quadric regression fits with respect to latitude.[11] However, despite more than 25 years of study of geographic variations in cancer rates in France, no comprehensive explanations for these variations appear to exist.

However, studies have linked such geographic variations to variations in solar ultraviolet-B (UVB) doses and irradiances in several countries, including the United States,[12-16] Japan,[17,18] Australia,[19-21] Spain[22] and China.[23] The literature includes one randomized, controlled trial of vitamin D supplementation with sufficient amount to have a significant effect, finding a 35% reduction in all-cancer incidence for 1,100 IU/day of vitamin D.[24] Recent publications have reviewed the ecological and observational evidence for a beneficial role of UVB and vitamin D in reducing the risk of cancer.[25-29]

Although many of these studies investigated only the effects of solar UVB in producing vitamin D, recent studies included several other factors—including smoking, alcohol consumption, ethnic background, urban/rural residence and poverty—finding that UVB and smoking were the two most important factors in explaining the variance.[15,22] Although dietary factors are not thought to generate important variances in single-country studies, they do so in multicountry studies.[30-35] Some regional differences are apparent in dietary factors important in cancer risk in France,[36,37] and such data may also relate to regional differences in cancer rates.

The evidence in general that UVB irradiance and vitamin D reduce the risk of cancer continues to strengthen. The International Agency for Research on Cancer found the evidence convincing only for colorectal cancer.[38] However, their Working Group report committed several serious errors and omissions, including dismissing the only randomized, controlled trial of sufficient vitamin D to significantly reduce the risk of cancer;[24] evidence is reasonably strong for breast and several other cancers.[39] Also, UVB and vitamin D, as agents to reduce the risk of cancer, generally satisfy the criteria for causality in a biological system

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Table 1. Regression results for breast and colorectal cancer[6] with respect to latitude

Cancer	Sex	Year	Incidence (*r*, p)	Mortality (*r*, p)
Breast	F	1985	0.53, 0.01	
		1990	0.62, 0.002	
		1992	0.65, 0.002	0.69, 0.001
		1995	0.62, 0.003	
Colorectal	M	1985	0.54, 0.01	
		1990	0.56, 0.008	
		1992	0.56, 0.008	0.53, 0.01
		1995	0.56, 0.008	
	F	1985	0.74, 0.000	
		1990	0.72, 0.000	
		1992	0.65, 0.001	0.46, 0.04
		1995	0.49, 0.02	

F, female; M, male.

Table 2. Regression results for cancer mortality rates for 1998–2000[11] vs. latitude x latitude

Cancer	Sex	Incidence rate (*r*, adjusted R^2, p)	Mortality rate (*r*, adjusted R^2, p)
All	M	0.86, 0.73*	0.80, 0.65*
	F	0.79, 0.60*	0.78, 0.59*
All less lung	M	0.83, 0.67*	0.78, 0.30*
	F	0.79, 0.60*	0.76, 0.55*
Breast	F	0.60, 0.33, 0.004	0.66, 0.40, 0.001
Colorectal	M	0.50, 0.21, 0.02	0.49, 0.20, 0.02
	F	0.66, 0.40, 0.001	0.65, 0.39, 0.001
Esophageal	M	0.86, 0.72*	0.81, 0.64*
	F	-	0.64, 0.38, 0.002
Lung	M	0.71, 0.48*	0.54, 0.25, 0.01
	F	NS	NS
Prostate	M	0.64, 0.37, 0.002	0.68, 0.44, 0.001
Uterine, cervix	F	0.60, 0.32, 0.004	
Uterine, corpus	F	0.71, 0.32, 0.004	0.64, 0.37, 0.002

*p < 0.001; F, female; inc, incidence rate; M, male; NS, not significant.

that A. Bradford Hill established in reducing the risk of cancer very well for breast and colorectal cancer and well for several other types of cancer including bladder, esophageal, gallbladder, gastric, ovarian, rectal, renal and uterine corpus cancer, plus Hodgkin's and non-Hodgkin's lymphoma.[40] Other recent reviews also discuss the evidence.[41-43] In addition, meta-analyses have found reasonable serum 5-hydroxyvitamin D [25(OH)D] level–cancer incidence relations for breast and colorectal cancer.[44-47] and a recent observational study in Finland found a nearly statistically significant reduced risk of ovarian cancer for those with serum 25(OH)D levels >57.8 nmol/L (23.1 ng/mL) compared to <31.5 nmol/L (12.6 ng/mL): the adjusted odds ratio (OR) for those followed between 3 and 13 years after serum draw was 0.43 (95% confidence interval, 0.18–1.05).[48]

However, a recent pooled analysis from ten studies on three continents of incidence of seven rarer types of cancer, endometrial, esophageal, gastric, kidney, ovarian and pancreatic cancer and non-Hodgkin's lymphoma (NHL) with respect to prediagnostic serum 25(OH)D with cases followed for a mean observation time of about 10 years, failed to find any beneficial effect of higher serum 25(OH)D levels.[49] The number of cancer cases varied from 516 for ovarian cancer to 1,353 for lymphoma. Many of the smaller studies on breast and colorectal cancer had fewer than 500 cases, so case number does not seem to be the problem. It has been suggested that the single serum 25(OH)D level measurement is not a good representation of the value of serum 25(OH)D level at the time when it had the greatest impact on cancer incidence.[50] Serum 25(OH)D levels are likely to be significantly different than at time of serum draw due to competing trends: reduced solar UVB irradiance due to concerns about skin cancer[51] and increased oral intake of vitamin D due to rising public awareness of the health benefits of vitamin D. Two recent papers suggest that a single draw can not be relied upon as an indication of serum 25(OH)D level 7–14 years later.[52,53]

This report investigates the possible role of solar UVB through production of vitamin D in affecting the geographic variation of cancer incidence and mortality rates in France.

Results

Table 1 shows regression results for breast and colorectal[6] cancer incidence and mortality rates. Both cancers had significant correlations with increasing latitude for at least one period. The correlation decreased with time for colorectal cancer for females.

Table 2 presents the regression results for incidence and mortality rates for FNORS[11] data. Latitude strongly correlated with incidence and mortality rates for all, all less lung cancer, breast, colorectal, esophageal (males), lung (males), prostate and both uterine cervix and uterine corpus cancers. Neither lung cancer nor dietary factors[36,37] significantly correlated with cancer incidence or mortality rates when included with latitude.

These results indicate a strong latitudinal gradient in cancer risk, although for some cancers, little change occurs in incidence or mortality rates between 43.5° and 46.5° for females. For males, lung cancer rates have a minimum value near 46°, increasing rapidly after 47.5°, but other cancers increase monotonically from 44°. Several factors, including more sun exposure and smoking by males, may contribute to the higher ratio of high-latitude to low-latitude rates for males than for females.

To further evaluate whether the gradient could be due to solar UVB, one can use data from the eastern United States. Solar UVB is an important contributor to cancer risk in the United States,[13,15,16] but other factors such as smoking, alcohol consumption, limited dietary factors, urban/rural residence and air pollution from coal-fired power plants also play a role.[15,54] Unfortunately, lung cancer rates are higher in the Southern states, so all-cancer mortality rates are not so useful, nor are cancers strongly linked to smoking. One can use, for example, two cancers for which smoking may be only a minor risk factor: breast and colorectal, as well as all-cancer-less-lung cancer for females. For breast cancer for white females for 1950–1969,[55] an extrapolation of the second-order regression fit indicates a 20% increase between 43.5° and 50.5°, which is two-thirds of that for France. The scatter plots for all-cancer-less-lung cancer for females is shown in **Figure 1**.

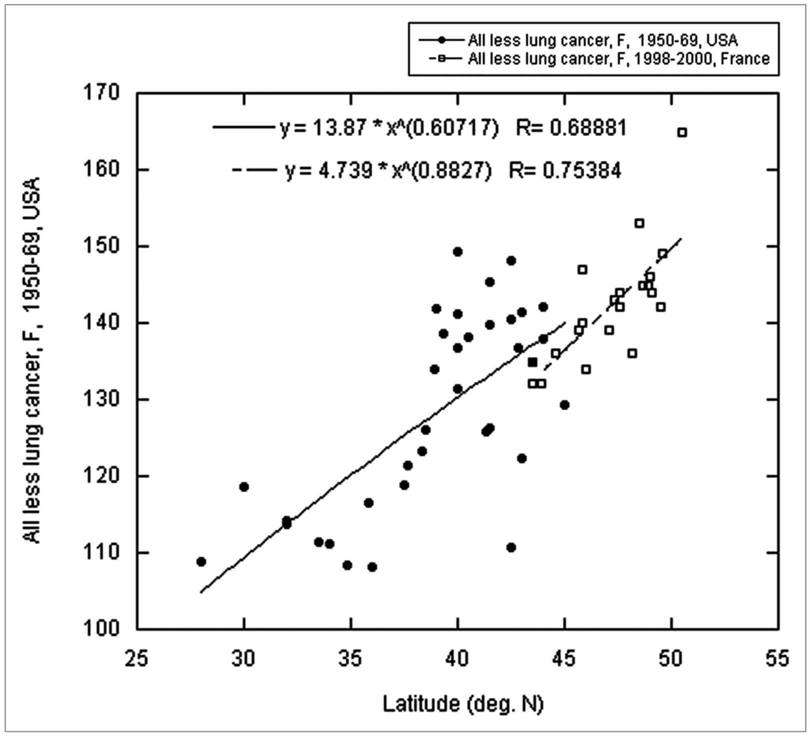

Figure 1. All cancer less lung cancer vs. latitude. Shown are data for females in the United States,[55] 1950–69 (dots) and females in France,[11] 1998–2000 (squares).

Discussion

The results presented in **Tables 1–3** are consistent with solar UVB, through the production of vitamin D, in reducing the risk of cancer incidence and mortality rates in France. Other studies had found that all cancers with significant correlations with latitude were vitamin D sensitive, although the evidence for cervical cancer is weak. For colorectal cancer,[11] rates for females have a nearly monotonic increase in rate with increasing latitude, whereas rates for males have high rates in a band near the middle of France, suggesting the involvement of an unmodeled factor.

Lung cancer rates for males were much more important in the analysis than lung cancer rates for females because in France males smoke much more than females. Smoking is generally associated with risk for the cancers for which this study identified correlations with lung cancer.[56,57]

The fact that the increase between low and high latitude for all-cancer and all-cancer-less-lung-cancer is twice as high for males compared to females (**Table 3**) suggests that lung cancer may contribute to this finding even though lung cancer did not have a significant correlation in conjunction with latitude for any of the cancers or all-cancer-less-lung cancer.

Per several studies in the United States, summertime solar UVB doses seem to be much more important than those in wintertime.[13,15] A UK study offers evidence that solar UVB doses are high enough in summer to produce some vitamin D. A study of 45-year-old British found that serum 25(OH)D levels increased from 35 nmol/L in winter to 75 nmol/L in summer from casual solar UVB irradiance.[58] However, vitamin D production efficiency decreases with increasing age,[59] so older French citizens would not experience such large changes. Indeed, a recent study found that about 45% of elderly French women have serum 25(OH)D levels <50 nmol/L and 90% have <80 nmol/L.[60]

One can use several reports in the literature to estimate the variation in vitamin D obtained from solar UVB. A study of the US Male Health Professionals cohort, using a vitamin D index based on oral-intake and UVB-produced vitamin D, estimated that 1,500 IU of vitamin D/day or an increase of 25 nmol/L in 25(OH)D could reduce male cancer mortality rates by 29%.[14]

The body can make at least 10,000 IU of vitamin D/day with whole-body UVB irradiance.[61] However, since most people no longer spend much time in the sun with few clothes on, and solar UVB doses in France are somewhat weak due to its location. For comparison, in the eastern United States, which ranges from 26° to 48° N, the variation of colorectal cancer mortality rates for 1970–1994 is 30%, whereas that for all cancers for females varies by 20%. Smoking attenuates both values, whereas urban residence enhances them. France lies between 42.5° and 51° N. Northern France is more urbanized than Southern France. Thus, risk-modifying factors in addition to solar UVB and vitamin D are probably involved in the latitudinal gradients.

Although this analysis did not include several factors that could also affect cancer risk, such as diet, alcohol consumption, air pollution and degree of urbanization,[13,15,54] a more comprehensive analysis should do so. However, the explanation that much of the increased risk of cancer with respect to increased latitude is related to UVB irradiance and vitamin D production is consistent with several US study findings. Those that included only indices for solar UVB[13] yielded similar results to those that included other factors.[15,16]

Vitamin D also has many other health benefits, including reduced risk of cardiovascular disease and type 2 diabetes mellitus;[62] autoimmune diseases such as multiple sclerosis;[63] bone conditions and diseases;[64] and infectious diseases such as type A influenza,[65,66] pneumonia,[67] and sepsis/septicemia.[68] Several recent reviews describe the benefits of vitamin D for diseases other than cancer[69,70] as well as pregnancy outcomes.[71] Previous work indicates that the health benefits of UVB and vitamin D greatly outweigh the adverse health effects of UV irradiance.[72] Modeling studies estimate that increasing mean population serum 25(OH)D levels to more than 100 nmol/L could reduce

Table 3. Ratio of high latitude to low latitude regression fit for cancer data for 1998–2000[11]

Cancer	Male incidence	Male mortality	Female incidence	Female mortality
Breast			1.32	1.29
Cervical			1.42	
Colorectal	1.20	1.18	1.24	1.21
Esophageal	2.74	2.04	1.91	
Lung	1.64	1.51	NS	NS
Prostate	1.26	1.25		
Uterine corpus			1.38	
Uterine cervical + corpus				1.32
All	1.42	1.30	1.24	1.16
All less lung	1.40	1.28	1.23	1.15

NS, not significant.

the all-cause mortality rate by 15%–20%.[72-75] It is encouraging to see growing interest in vitamin D in France.[76]

These results strongly suggest that solar UVB irradiance significantly affects cancer rates in France. While France now fortifies some of its food with vitamin D, reductions in cancer risk would probably manifest if foods such as milk and grain products were fortified to provide at least 1,000 IU/day of vitamin D3 (cholecalciferol) and if officials encouraged people to take vitamin cholecalciferol supplements when they were not getting adequate vitamin D from diet or solar UVB. Thus, a better vitamin D policy in France would result in many important health benefits.

Data and Methods

Cancer incidence and mortality rate data came from several sources. Breast and colorectal cancer incidence rate data—age adjusted for the European age distribution for 21 continental regions of France for 1985, 1990, 1992 and 1995, as well as mortality rate data for 1992—come from Colonna et al.[6]

Cancer incidence and mortality rate data also come from a publication of the Fédération Nationale des Observatoires Régionaux de la Santé (FNORS).[11] Mortality rate data for 1998–2000, age adjusted to the French population, were presented for all, breast, colorectal, esophageal, lung, prostate and uterine cancer and melanoma. Incidence data for these cancers were presented as estimates for 2000; thus, they are not deemed as reliable as the mortality rate data. Cancer registries have been established in only 12 departments. Incidence data issued from twelve administrative areas with cancer registries participating in the Francim network. These twelve areas which cover about 15% of the surface area of France were: Bas-Rhin, Calvados, Côte-d'Or, Doubs, Haut-Rhin, Hérault, Isère, Loire-Atlantique, Manche, Saône-et-Loire, Somme and Tarn.[9] Thus, the values for the other nine departments would be based on data from the 12 departments as this study used the data for the 21 continental regions of France.

Three sets of data served as independent factors in this study: latitude of the population center of the region, lung cancer incidence and mortality rates and dietary factors. Latitude is assumed to be primarily the index of solar UVB dose, which is assumed to represent vitamin D production rates. Solar UVB doses at the surface have been developed using data from NASA's Total Ozone Mapping Spectrometer (TOMS), which show quasi-linear variation in latitude unless mountains affect the dose due to elevated surface level or changing the stratospheric ozone layer.[77-79] In the US, summertime UVB doses east of the Rocky Mountains are much lower than at the same latitude to the west,[77] owing to differences in surface elevation and stratospheric ozone layer due to the prevailing winds rising to cross the Rocky Mountains, thereby pushing the tropopause higher.

This study used the square of latitude because cancer rates appear to increase with the square of latitude, although using latitude gave very similar results. This index has worked well in several studies, especially when the UVB doses have a uniform latitudinal variation in the country and no large differences in skin phenotype or indoor/outdoor occupation exist, such as in Australia[19-21] and China.[23,79] However, in winter, when viral infections are more common, latitude squared worked well for multiple sclerosis.[80] In Spain, evidently significant differences exist in indoor versus outdoor occupation.[22] France has some variation in surface elevation, and although differences in indoor and outdoor occupation ratios likely occur by region, this study does not include them. Solar UVB appears to be the primary source of vitamin D in France,[81] and no public policies designed to ensure that residents have adequate serum 25(OH)D levels seem to exist.[82-86]

Lung cancer rates have correlated highly with other smoking-related cancers in several studies.[15,22,87] Thus, this study uses those lung cancer rates as the index of smoking. Lung cancer is vitamin D sensitive to some extent, as well as ambient air pollution, so variations in lung cancer rates could also reflect differences in solar UVB irradiance.

The dietary data in reference 36 were for food types as well as macro- and micronutrients for women in eight regions of France with questionnaires mailed out between June 1993 and July 1995. The dietary data in reference 37 were only for macro- and micronutrients for four regions, gathered between 1995 and 2000.

All regression analyses were conducted using the SPSS 16.0 statistical package (SPSS, Chicago, IL) as discussed in reference 15.

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Note

After this paper was submitted, two papers reported reduced risk of breast cancer with respect to vitamin D.[88,89] The second[89] found a hazard ratio 0.90 (95% confidence interval: 0.82–0.98) for latitude <45.8° N compared to >48.6° N. Since ecological studies generally find lower inverse correlations for cancer incidence compared to cancer mortality rates,[16,79] the results of the two studies are in good agreement.

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