Ultraviolet B Irradiance and Vitamin D Status are Inversely Associated With Incidence Rates of Pancreatic Cancer Worldwide

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Objectives: To determine if an inverse association exits between latitude, ultraviolet B (UVB) irradiance and incidence rates of pancreatic cancer worldwide.

Methods: Multiple linear regression was used to investigate the relationship and between UVB irradiance incidence rates of pancreatic cancer and while controlling for cigarette, alcohol and sugar consumption, and proportion overweight. Serum 25-hydroxyvitamin D [25(OH)D] levels were estimated, and their association with incidence rates also was analyzed.

Results: Incidence rates were higher at higher latitudes (R^2 for latitude for men, 0.51; $P < 0.001$; R^2 for latitude for women, 0.32; $P < 0.001$). Ultraviolet B irradiance also was independently inversely associated with incidence in men ($P < 0.01$) and women ($P = 0.02$). Alcohol ($P < 0.0001$) and cigarette ($P \leq 0.01$) consumption were positively associated with incidence in men (R^2 for overall model for men, 0.76; $P < 0.0001$). Alcohol ($P < 0.0001$) and sugar ($P = 0.001$) consumption were positively associated with incidence rates in women (R^2 for overall model for women, 0.64; $P < 0.0001$). Incidence rates were half as high in countries with estimated serum 25(OH)D >30 ng/mL (75 nmol/L) than in those with ≤30 ng/mL.

Conclusions: Countries with lower UVB irradiance had higher incidence rates of pancreatic cancer in both hemispheres, with occasional exceptions.

Key Words: pancreatic neoplasms, incidence, vitamin D, alcohol, smoking, multiple regression

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Approximately 232,000 new cases and 227,000 deaths occur worldwide annually from pancreatic cancer,[1] including 37,700 cases and 34,200 deaths in the United States.[2] The case-fatality rate is 98%.[2] Risk factors include cigarette smoking,[3–6] intake of alcohol[6,7] and red meat,[6,8,9] and history of type 2 diabetes,[3–6] although pancreatic cancer is enigmatic and most of the substantial worldwide differences in incidence cannot be readily accounted for by known factors. The possibility that vitamin D might play a role in the etiology of pancreatic cancer was raised by studies showing that populations living at higher latitudes or having lower prediagnostic serum 25-hydroxyvitamin D [25(OH)D] levels have higher incidence rates of various cancers, including those of breast,[10–14] colon,[14–19] and ovary.[20]

While dietary and lifestyle factors are well established and highly relevant to risk of pancreatic cancer,[3–9] an inverse association between ultraviolet B (UVB) irradiance and pancreatic cancer mortality was identified in an ecological study in the United States by Grant.[18] The association persisted after controlling for per capita alcohol intake, a proxy estimate of cigarette consumption in the region, and several other covariates.[21] Two studies identified a positive association between latitude and pancreatic cancer mortality rates in Japan[22,23] and Spain.[24] These results suggest that exposure to solar UVB irradiance and resulting vitamin D photosynthesis may be associated with lower incidence of pancreatic cancer, although a worldwide analysis of incidence rates by latitude and UVB irradiance has not been performed.

To further investigate whether there may be an inverse association between UVB irradiance and incidence of pancreatic cancer, this study examined the associations of UVB irradiance, cloud cover, per capita cigarette consumption, intake of alcohol and sugar, and proportion of population overweight, with age-standardized incidence rates of pancreatic cancer in all countries of the world that had data available on all covariates.

MATERIALS AND METHODS

Data Sources

Age-standardized incidence rates of pancreatic cancer were obtained for 175 countries from the International Agency for Research on Cancer (IARC) Global Cancer (GLOBOCAN) database.[1] GLOBOCAN uses national registries and registration of vital events to estimate annual age-standardized incidence rates per 100,000 population in these countries. The latest year for which complete data were available was 2002. Data also were obtained on solar UVB irradiance at the top of the atmosphere at the vernal equinox, adjusted for cloud cover; alcohol, cigarette, and sugar consumption; and proportion of population overweight. Data on these covariates were available for 104 countries and were the basis for the multiple regression analyses in this study.

Total solar UVB irradiance at the top of the atmosphere on the vernal equinox was calculated using a standard algorithm.[25] The vernal equinox is March 21 in the Northern hemisphere and September 21 in the Southern hemisphere. The total noon solar irradiance at the top of the atmosphere for each country on the date of the vernal equinox was calculated using the formula ($A' = A \times \cos x$) where x is the latitude of the country in degrees, A is the total solar radiation at the equator in W/m^2, and A' is the total solar radiation for the country on the date of the vernal equinox in W/m^2.[25] Because UVB irradiance is approximately

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0.42% of the total solar irradiance, the total solar irradiance was multiplied by 0.0042 to obtain the estimated UVB irradiance.

To account for the influence of percentage of cloud cover on transmission of UVB through the atmosphere, solar UVB at the top of the atmosphere (TOA) was adjusted for mean December percentage cloud cover by multiplying the UVB at TOA by the following factor: (1 − mean percentage cloud cover). This was done for each country by using data from a NASA cloud cover measurement instrument, the International Satellite Cloud Climatology Project satellite that measures cloud cover from space.[26] Relative ground level UVB irradiance at solar noon on the equinox in each country also was evaluated using UVB data from Lubin et al.[27]

The latitude of the population centroid of each country was determined by the Columbia University Center for International Earth Science Information Network.[25] Intakes of alcohol and sugar were obtained from the United Nations Food and Agriculture Organization, as daily energy in kilocalories, for 132 countries.[28] Data on per capita cigarette consumption during 1980–1982 were obtained from the World Health Organization (WHO).[29] Data on the proportion of population of overweight (obese) individuals during 2002 also were obtained from the World Health Organization.[30]

Serum 25(OH)D was modeled using measured levels of serum 25(OH)D during winter obtained from 28 regions in 18 countries (Appendix Table 1, Supplemental Digital Content 1, http://links.lww.com/MPA/A20) as the dependent variable, and UVB irradiance adjusted for cloudiness and skin pigmentation levels in the areas where the studies were performed as the independent variables. The initial regression model that was based on the known values of all variables provided regression coefficients that were used in a separate multiple regression prediction equation. That equation used known UVB and skin pigmentation and the regression equation derived above to estimate mean winter serum 25(OH)D levels in countries where measurements were not available. The prediction equation included an empirically determined scaling constant. The measured 25(OH)D levels were used in the final calculations for

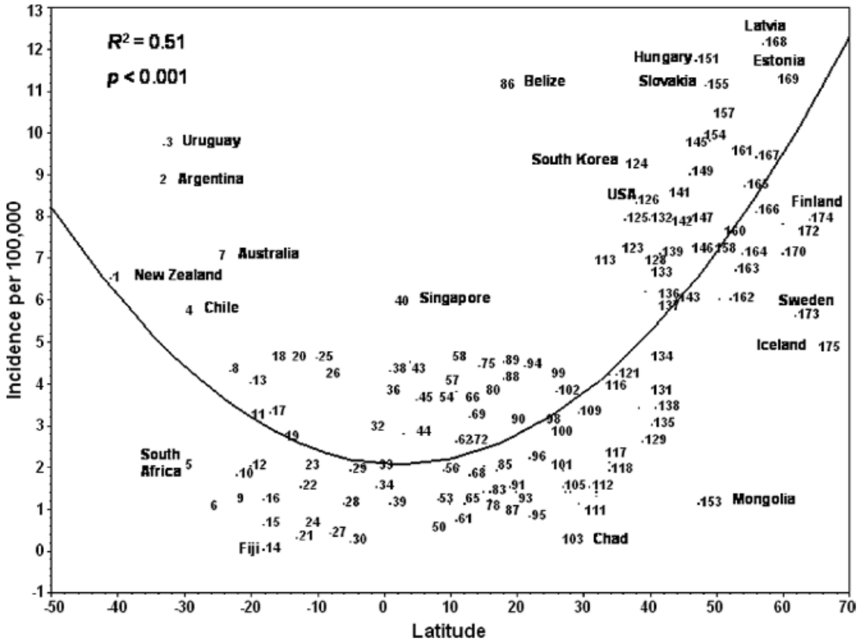

FIGURE 1. Incidence rates of pancreatic cancer per population of 100,000 men. Source: Data from GLOBOCAN.[1] 1. New Zealand; 2. Argentina; 3. Uruguay; 4. Chile; 5. South African Republic; 6. Swaziland; 7. Australia; 8. Paraguay; 9. Namibia; 10. Botswana; 11. Mauritius; 12. Madagascar; 13. Zimbabwe; 14. Fiji; 15. Mozambique; 16. Vanuatu; 17. Bolivia; 18. Polynesia; 19. Zambia; 20. Samoa; 21. Melanesia; 22. Angola; 23. Comoros; 24. Malawi; 25. Peru; 26. Brazil; 27. Solomon Islands; 28. Tanzania; 29. Indonesia; 30. Papua New Guinea; 32. Rwanda; 33. Congo Brazzaville; 34. Gabon; 36. Ecuador; 38. Kenya; 39. Uganda; 40. North Korea; 43. Suriname; 44. Brunei; 45. Guyana; 50. Sri Lanka; 53. Togo; 54. Venezuela; 56. Ethiopia; 57. Panama; 58. Costa Rica; 61. Guinea; 64. Djibouti; 65. Guinea-Bissau; 66. Philippines; 68. Cambodia; 69. Nicaragua; 72. Guam; 74. Senegal; 75. Guatemala; 78. Sudan; 80. Yemen; 83. Niger; 85. Viet Nam; 86. Belize; 87. Laos; 88. Jamaica; 89. Puerto Rico; 90. Dominican Republic; 91. Haiti; 93. Mauritania; 94. Cuba; 95. Myanmar; 96. Oman; 98. Bahamas; 99. Qatar; 100. Saudi Arabia; 101. United Arab Emirates; 102. Bahrain; 103. Bangladesh; 105. Libya; 109. Kuwait; 111. Pakistan; 112. Jordan; 113. Israel; 116. China; 117. Iraq; 118. Afghanistan; 121. Cyprus; 123. Malta; 124. Japan; 125. Slovakia; 126. United States of America; 128. Greece; 129. Turkey; 131. Armenia; 132. Korea, Republic of; 133. Spain; 134. Turkmenistan; 135. Azerbaijan; 136. Albania; 137. Kyrgyzstan; 138. Uzbekistan; 139. Macedonia; 141. Italy; 142. Bulgaria; 143. Serbia and Montenegro; 145. Croatia; 146. France; 147. Romania; 149. Singapore; 151. Hungary; 153. Mongolia; 154. Kazakhstan; 155. Sierra Leone; 157. Czech Republic; 158. Luxembourg; 160. Germany; 161. Poland; 162. Netherlands; 163. Ireland; 164. United Kingdom; 165. Belarus; 166. Denmark; 167. Lithuania; 168. Latvia; 169. Estonia; 170. Canada; 172. Norway; 173. Sweden; 174. Finland; 175. Iceland. Legend for countries not labeled on graph: 31. Burundi; 35. Congo; 37. Equatorial Guinea; 41. Malaysia; 42. Colombia; 46. Benin; 47. Cameroon; 48. Liberia; 49. Central African Republic; 51. Cote d'Ivoire; 52. Ghana; 55. Slovenia; 59. Nigeria; 60. Somalia; 62. Micronesia; 63. Trinidad and Tobago; 67. Burkina Faso; 70. Barbados; 71. Gambia; 73. El Salvador; 76. Chad; 77. Honduras; 79. Thailand; 81. Eritrea; 82. Cape Verde; 84. Mali; 92. India; 97. Mexico; 104. Egypt; 106. Bhutan; 107. Algeria; 108. Nepal; 110. Lesotho; 114. Iran; 115. Morocco; 119. Lebanon; 120. Tunisia; 122. Syria; 127. Tajikistan; 130. Portugal; 140. Georgia; 144. Bosnia Herzegovena; 148. Switzerland; 150. Moldava; 152. Austria; 156. Ukraine; 159. Belgium; 171. Russian Federation.

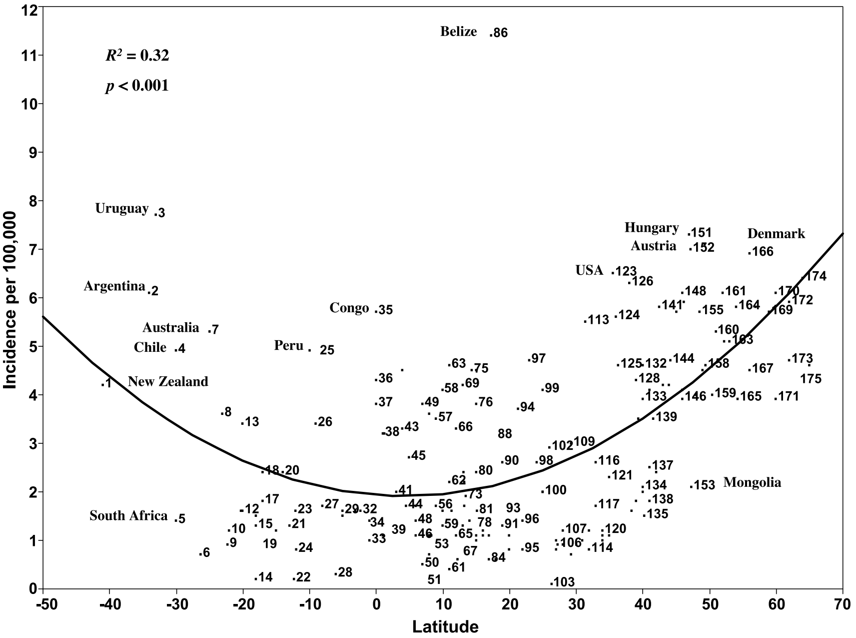

FIGURE 2. Incidence rates of pancreatic cancer per population of 100,000 women. Source: Data from GLOBOCAN.[1] Labels for countries are the same as in Figure 1. Legend for countries not labeled on graph: 11. Mauritius; 16. Vanuatu; 30. Papua New Guinea; 31. Burundi; 40. North Korea; 47. Cameroon; 52. Ghana; 54. Venezuela; 55. Slovenia; 60. Somalia; 64. Djibouti; 68. Cambodia; 70. Barbados; 71. Gambia; 72. Guam; 74. Senegal; 77. Honduras; 79. Thailand; 82. Cape Verde; 83. Niger; 85. Viet Nam; 87. Laos; 92. India; 101. United Arab Emirates; 104. Egypt; 105. Libya; 108. Nepal; 110. Lesotho; 111. Pakistan; 112. Jordan; 118. Afghanistan; 119. Lebanon; 122. Syria; 127. Tajikistan; 129. Turkey; 130. Portugal; 131. Armenia; 136. Albania; 140. Georgia; 142. Bulgaria; 143. Serbia and Montenegro; 145. Croatia; 147. Romania; 149. Singapore; 150. Moldava; 154. Kazakhstan; 156. Ukraine; 157. Czech Republic; 162. Netherlands; 168. Latvia.

the 18 countries, and the values modeled from the regression procedures described above were used for the 156 other countries.

Skin pigmentation scores were based on an anthropological analysis of population skin pigmentation levels using skin reflectometry to ascertain mean constitutive skin worldwide.[31] When the population consisted of several different pigmentary groups, the mean pigmentation score was used.

Statistical Analysis

Incidence rates were standardized to the 2000 world standard population by IARC using the direct method.[1] Incidence rates for 175 countries were plotted by latitude of the population centroid of each country. The best fit to the data points was obtained using a polynomial trend line. A standard pharmacologic dose-response curve was plotted using a conventional algorithm (Prism) (GraphPad Software, San Diego, Calif). Multiple linear regression was used to investigate the relationship of age-standardized incidence rates of pancreatic cancer with UVB irradiance at the top of the atmosphere adjusted for mean cloud cover. The covariates were alcohol, cigarette and sugar consumption, and proportion of population of overweight

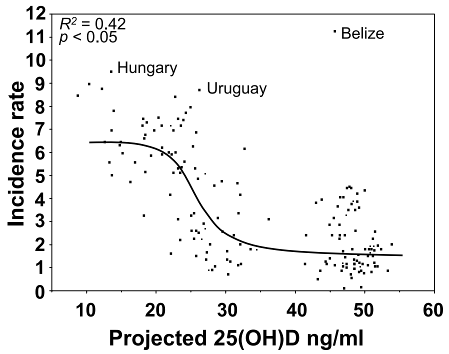

FIGURE 3. Dose-response relationship between modeled serum 25(OH)D and pancreatic cancer incidence rates per 100,000 population in 175 countries, 2002. Data points represent countries that reported incidence data to IARC GLOBOCAN. Source: Data from GLOBOCAN.[1]

TABLE 1. Solar Ultraviolet B Irradiance and Other Covariates Associated With Pancreatic Cancer Incidence Rates; Multiple Regression, 104 Countries, Men, 2002

Variable	Regression Coefficient	SE	t	P
Solar UVB irradiance*	−0.1456	0.0542	−2.68	<0.01
Alcohol intake†	0.0145	0.0022	6.49	<0.0001
Sugar intake†	0.0014	0.0012	1.23	0.22
Cigarette consumption‡	0.0006	0.0002	2.63	<0.01
Proportion of population overweight§	0.0267	0.0201	1.33	0.19
Intercept	2.3719	0.7784	3.05	0.003

R^2 = 0.76, $P < 0.0001$.

*Watts/m^2, adjusted for cloud cover.

†Source: United Nations Food and Agriculture Organization.[32]

‡Source: United Nations Tobacco Atlas.[33]

§Source: United Nations WHO Global InfoBase.[34]

TABLE 2. Solar Ultraviolet B Irradiance and Other Covariates Associated With Pancreatic Cancer Incidence Rates; Multiple Regression, 104 Countries, Women, 2002

Variable	Regression Coefficient	SE	*t*	*P*
Solar UVB irradiance*	−0.1090	0.0470	−2.32	0.02
Alcohol intake†	0.0081	0.0020	4.08	<0.0001
Sugar intake†	0.0038	0.0011	3.35	<0.001
Cigarette consumption‡	0.0003	0.0002	1.60	0.11
Proportion of population overweight	−0.0101	0.0108	−0.93	0.35
Intercept	1.9810	0.6790	2.92	0.004

R^2 = 0.64, $P < 0.0001$.

*Watts/m^2, adjusted for cloud cover.

†Source: United Nations Food and Agriculture Organization.[32]

‡Source: United Nations Tobacco Atlas.[33]

§Source: United Nations, WHO Global InfoBase.[34]

individuals. The analyses were performed using SAS Version 9.1 and JMP Version 5.1.2 (SAS Institute, Cary, NC).

RESULTS

Incidence rates of pancreatic cancer were higher at higher latitudes in men (R^2 = 0.51, P < 0.001; Fig. 1) and women (R^2 = 0.32, P < 0.001; Fig. 2), generally with a curvilinear gradient rising from a low in countries near the equator to a high in those most distant from it. There was an inverse dose-response relationship between modeled serum 25(OH)D and incidence rates of pancreatic cancer in both sexes combined (Fig. 3). Modeled serum 25(OH)D levels above 30 ng/mL (75 nmol/L) were associated with substantially lower incidence rates, with the exception of Belize, which is at a low latitude but had an unusually high incidence rate.

Ultraviolet B irradiance at ground level was independently inversely associated with incidence rates of pancreatic cancer in men (P < 0.01; Table 1). Per capita alcohol consumption (P < 0.0001) and cigarette consumption (P < 0.01) were positively associated with incidence rates (R^2 for full model in men = 0.76, P < 0.0001). In women, UVB irradiance at ground level was also independently inversely associated with incidence rates (P = 0.02; Table 2). Alcohol consumption (P < 0.0001) and sugar intake (P < 0.001) were positively associated with incidence rates (R^2 for full model in women = 0.64, P < 0.0001).

DISCUSSION

This is the first report of the inverse association of incidence rates of pancreatic cancer with UVB irradiance by country, to our knowledge. Pancreatic cancer incidence rates were higher in countries located at latitudes distant from the equator, where UVB irradiance is low, than in countries closer to the equator, where it is high. Ultraviolet B irradiance varies inversely with latitude[32] and is the source of approximately 95% of circulating vitamin D and its metabolites.[33] The incidence curve corresponded approximately to the reciprocal of the cosine of the latitude, multiplied by a constant that may be different for each disease. The cosine of the latitude is the strongest single correlate of total solar irradiance at noon on the equinoxes. At the latitude of Boston, 42°, for example, the cosine of the latitude is 0.74 at the latitude of Helsinki, 60°, the cosine is 0.5.

The dose-response gradient between modeled serum 25(OH)D levels and incidence rates of pancreatic cancer followed a sigmoid inverse dose-response curve (Fig. 3). There was a flat portion at the upper left that suggested that there is no effect of serum 25(OH)D level below approximately 30 ng/mL (75 nmol/L) on incidence rates of pancreatic cancer. The diagonal portion of the dose-response curve suggests that increasing increments in serum 25(OH)D levels in the range from approximately 30 to 36 ng/mL (75–90 nmol/L) were associated with incrementally lower incidence rates of pancreatic cancer. The ratio of the median of the highest incidence rates on the curve to the lowest points was approximately 2.3-fold.

Cigarette and alcohol consumption were positively associated with incidence rates, as expected from previous studies.[3–7] In women, sugar intake was positively associated with rates. This result is in agreement with previous studies that have found a positive association between sugar intake and the risk of pancreatic cancer.[34]

A cohort study by Giovannucci et al[35] reported that higher estimated serum 25(OH)D levels were associated with lower incidence rates of pancreatic cancer. Higher dietary intake of vitamin D also was associated with lower incidence rates of pancreatic cancer in the Harvard Health Professionals Follow-up Study[36] and the Nurses Health Study.[37] Despite these important findings, the literature on the association of vitamin D and 25(OH)D with pancreatic cancer is mixed because of a positive association in men with winter 25(OH)D in a cohort of Finnish smokers.[38] The Finnish population regularly consumed pickled and processed herring that may have been contaminated with environmental carcinogens and are known to contain carcinogenic nitrosamines.[39] This ecological analysis confirms that higher UVB irradiance, a correlate of serum 25(OH)D, is associated with lower incidence of pancreatic cancer. This finding is reassuring and is a new line of evidence that helps to confirm the validity of the inverse association of oral vitamin D intake and serum 25(OH)D levels with pancreatic cancer that has been found in previous research.[36,37]

Strengths

This study had several strengths. It is the first, to our knowledge, to analyze incidence rates in a large number of countries located at widely different latitudes and to account for variation among countries using multiple linear regression. The latitude part of the study included virtually all countries of the world. The regression model accounted for 76% of the variation in age-standardized incidence rates of pancreatic cancer in men and 64% in women. The regression revealed that there was an independent inverse association of UVB irradiance with incidence rates of pancreatic cancer while controlling for several potential confounders.

The percentage of the variation among countries that was explained for pancreatic cancer was similar to that for cancers for which a role of vitamin D has been more fully established in observational studies of individuals, such as those of the breast (R^2 = 0.55, P < 0.0001),[40] colon (R^2 = 0.68, P < 0.0001),[41] and ovary (R^2 = 0.60, P < 0.0001).[42]

Limitations

Studies of this type should be considered as hypothesis generating or confirmatory rather than as definitive in isolation. Findings that apply to aggregates, such as countries, may not apply to individuals.[43] For example, all individuals living in areas of high UVB irradiance may not have high exposure to it because of indoor urban lifestyle,[44] air pollution,[45] and regular use of chemical sunscreens.[46] On the other hand, regional solar UVB irradiance may affect a broad range of individuals, and the association reported here was present despite the possible misclassification of exposure. This is important because nondifferential misclassification of exposure generally obscures associations rather than creating them.[47]

The model does not account for all variables that have an impact on vitamin D production such as amount of clothing worn, resulting in some degree of misclassification The main geophysical and pigmentary determinants of solar photosynthesis of vitamin D were included in the regression model for points that required estimation of 25(OH)D.[31,48,49] There are no accepted international measures of the proportion of skin surface area typically exposed to solar irradiance, so it was not possible to include this clothing factor in regression. The estimated 25(OH)D levels that were used in this model may have been overestimates in countries where cultural factors prevent exposure of most of the skin to solar irradiance, especially Muslim countries. In these countries, 25(OH)D levels, particularly in women wearing a hijab, may be quite low.[50,51] However, most women worldwide do not wear such clothing and the modeling is more directly applicable to them.

Despite the limitations of the ecological approach, the great differences that exist in UVB irradiance among countries worldwide provide a natural experiment on a global scale. Natural experiments have been of value in the past identifying potentially relevant etiological factors for disease.[52]

This study could not account for all possible confounders. For example, although a history of type 2 diabetes mellitus has been a mild risk factor for pancreatic cancer in previous studies,[3–6] the present study could not adjust for differences in prevalence among countries. No comprehensive database on type 2 diabetes prevalence by country is available.

Previous research has identified relatively mild associations between lower levels of physical activity and higher risk of pancreatic cancer[53] and possible associations with high consumption of animal fat[54] and red meat.[6,8,9] The present study did not attempt to control dietary factors other than alcohol and sugar consumption, the most prominent dietary risk factors. However, a covariate was included for proportion of the population overweight, which is a marker for risk of type 2 diabetes. No association was found in the present study between the percentage of population overweight and incidence rates of pancreatic cancer.

While there were departures from the parabolic least-squares trend line for many countries, none was as great as for Belize (17 degrees North), formerly British Honduras. Incidence rates in Belize could represent a chance fluctuation, but a similar association for brain cancer (S. B. Mohr, unpublished) suggests there is a carcinogen present in the environment or diet of Belize.

Further investigation is warranted to confirm the new line of evidence described in this study regarding UVB irradiance and vitamin D.

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14. ABSTRACT (maximum 200 words)
A brief (approximately 200 words) factual *summary* of the most significant information.

Approximately 232,000 new cases and 227,000 deaths occur worldwide annually from pancreatic cancer, including 37,700 cases and 34,200 deaths in the US alone. The possibility that Vitamin D might play a role in the etiology of pancreatic cancer was raised by studies showing that populations living at higher latitudes, or having lower prediagnostic serum 25-hydroxyvitamin D [25(OH)D] levels, have higher incidence rates of various cancers. Countries with lower UVB irradiance had higher incidence rates of pancreatic cancer in both hemispheres, with occasional exceptions.

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Pancreatic neoplasms, incidence, vitamin D, alcohol, smoking, multiple regression

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