MAPPING VITAMIN D DEFICIENCY, BREAST CANCER, AND COLORECTAL CANCER

SHARIF B. MOHR[1]

CEDRIC F. GARLAND[1,2]

EDWARD D. GORHAM[1,2]

WILLIAM B. GRANT[3]

ROBYN M. HIGHFILL[1]

FRANK C. GARLAND[1,2]

(1) Naval Health Research Center, San Diego CA 92186

(2) Department of Family and Preventive Medicine, School of Medicine, University of California San Diego, La Jolla, CA

(3) Sunlight, Nutrition, and Health Research Center, San Francisco, CA

ABSTRACT

Breast and colorectal cancer incidence rates are highest in countries distant from the equator and lowest in near-equatorial countries. It is known that adequate levels of vitamin D, which require sunlight for synthesis in the skin, tend to be associated with lower age-adjusted incidence rates of these cancers. Residents of near-equatorial areas synthesize far more vitamin D than those living at high latitudes. To describe the associations of these cancers with ultraviolet B (UVB) irradiance, we obtained sunlight measurements from the National Aeronautics and Space Administration (NASA), and age-adjusted breast and colorectal cancer incidence rates for 175 countries from the International Agency for Research on Cancer Global Cancer Database (GLOBOCAN). We created Geographic Information Systems displays of the association between sunlight levels and disease rates using three-dimensional analysis. Countries that received the lowest solar irradiance had rates of breast and colorectal cancer that were several times greater than those of countries with the highest solar irradiance. Countries with intermediate irradiance had intermediate rates of colorectal and breast cancer incidence. Dietary differences might explain some but not all of this association.

INTRODUCTION

Age-adjusted breast and colorectal cancer incidence rates exhibited a strong latitudinal gradient, with highest incidence rates in countries distant from the equator. By contrast, countries closer to the equator experienced much lower incidence rates. This may implicate inadequate levels of ultraviolet B (UVB), which is needed for photosynthesis of vitamin D and its metabolites. Low levels of serum 25-hydroxyvitamin D (25[OH]D) are associated with increased risk of colorectal cancer (1-4). Other factors related to sunlight and ultraviolet B exposure, such as amount of anthropogenic sulfate-carbon pollution in the troposphere (5), urbanization, population density, and proportion of the population engaged outdoors in agriculture may also play an important role. Previous epidemiological studies have found a statistically significant beneficial effect of vitamin D or its markers on colorectal and breast cancer risk (1-20). Further evidence is provided here for the protective effect of solar irradiance and photosynthesized vitamin D for these cancers.

Residents of areas distant from the equator photosynthesize less vitamin D than those living at lower latitudes (21). Equatorial countries receive much more UVB than countries more distant from the equator, which accounts for the latitudinal difference. Areas nearer the equator also tend to have a higher proportion of their population engaged in outdoor occupations where individuals would have high occupational exposure to UVB. This is in contrast to countries at higher absolute latitudes, where most work tends to be performed indoors.

METHODS

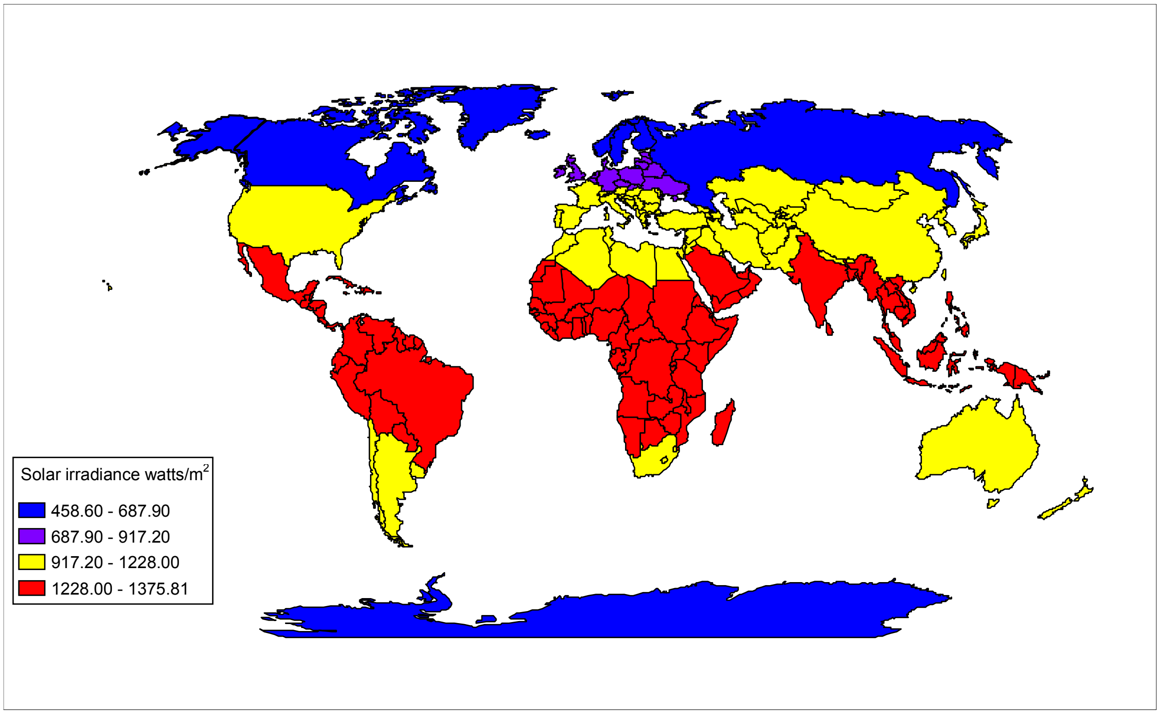
Geographic Information Systems (GIS) displays were created of colorectal and breast cancer incidence rates, total solar irradiance during the vernal equinox, and ground level UVB flux, the latter based on a map created by Lubin et al (22). Multiple linear regression was performed using JMP 5.1.2 (Cary NC: SAS Institute) to examine the association of age-adjusted incidence rates of colorectal and breast cancer with the above factors and with total percentage cloud cover, anthropogenic sulfate aerosol optical depth, stratospheric ozone thickness, population density, urbanization, and proportion of the population engaged in agriculture. The International Agency for Research on Cancer (IARC) GLOBOCAN database (23) provided estimated age-adjusted incidence rates for colorectal and breast cancer for 175 countries. The rates were adjusted by the direct method to the world standard population. Columbia University provided total solar radiation at solar noon at the top of the atmosphere on the date of the vernal equinox in each hemisphere (24). Column sulfate aerosol optical depth at 550 nm and total proportion of cloud cover data were obtained through the National Aeronautics and Space Administration (NASA) from various United States and European satellite packages (25, 26). Countries that were not industrialized were categorized for this study as not having anthropogenic sulfate aerosols. The proportion of the labor force engaged in agriculture in each country was obtained from Federal Government sources (27). Data on urbanization and population density were obtained from the United Nations statistics division (28-30). Population density was defined as the number of individuals per km2. Adjustment for population density was performed using the following heuristic formula: adjusted incidence rate = unadjusted incidence rate * (e-1*[(ln population density)/10]).

RESULTS

Countries distant from the equator had the lowest total solar irradiance at the top of the atmosphere (Figure 1) and UVB (Figure 2).

Figure 1

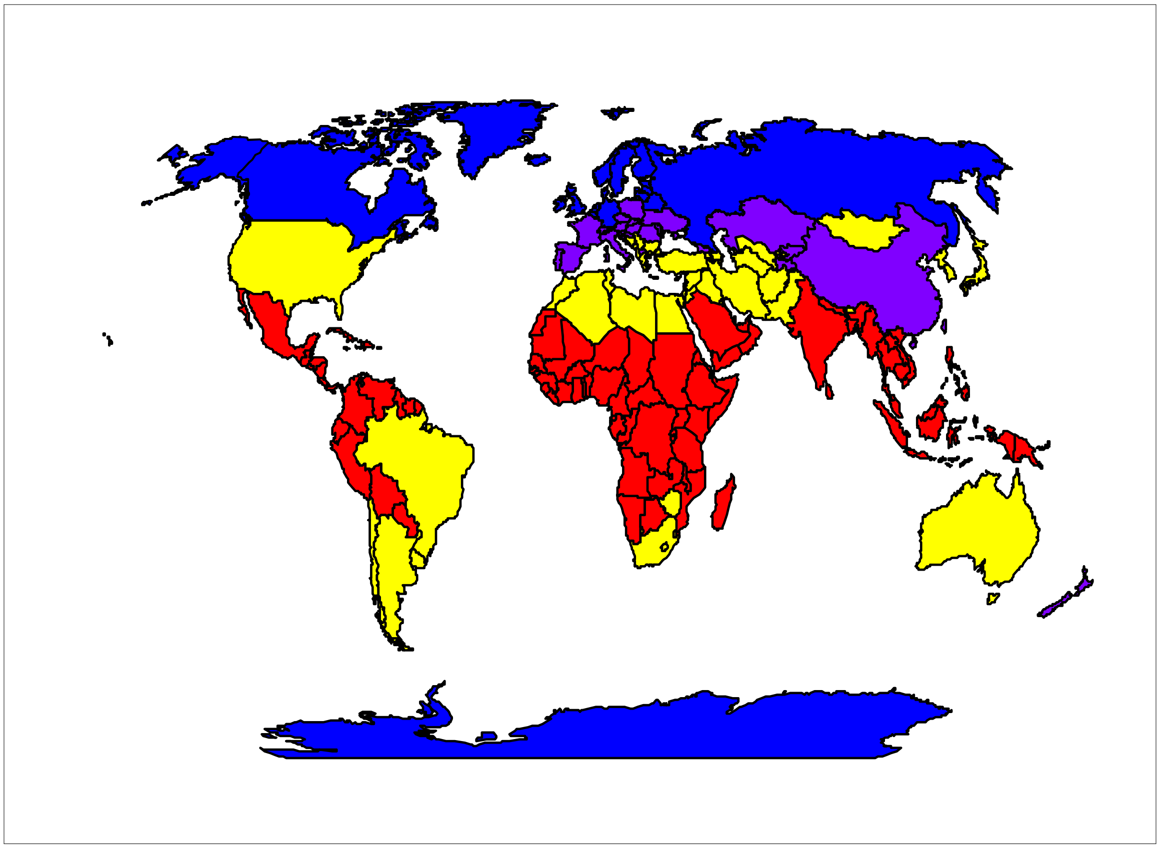
Total solar irradiance at the vernal equinox at the top of the atmosphere, solar noon, Watts/meter^2



Source: Columbia University (19)

Figure 2

Estimated equinoctial ultraviolet B flux (280-315 nm) at ground level, solar noon, Watts/meter^2. The measurements were integrated over the UVB range.

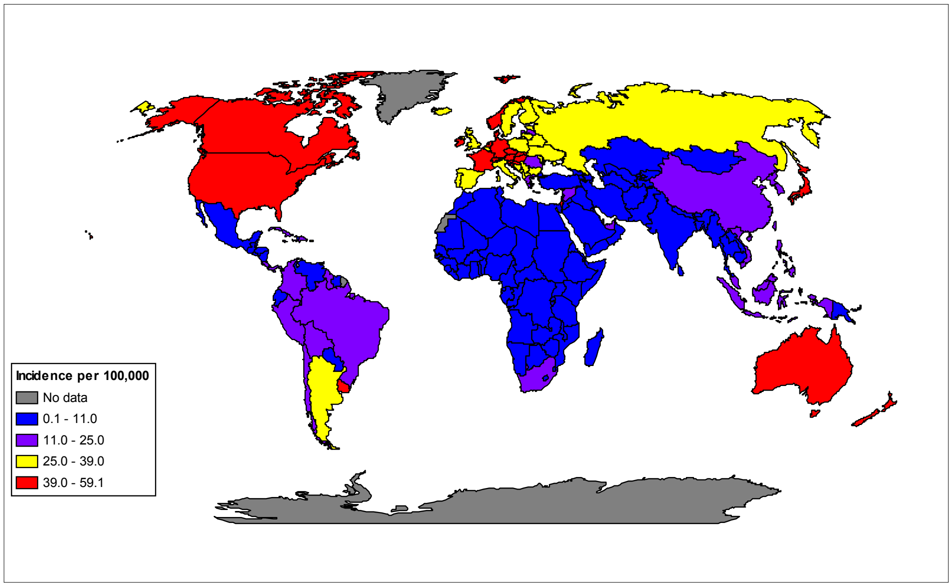


Source of data used for creation of this map: Dan Lubin and associates, California Space Institute, Scripps Institution of Oceanography, University of California San Diego (22)

The maps of colorectal and breast cancer by country (Figures 3-5) revealed the highest incidence rates of colorectal and breast cancer in areas of low total solar irradiance and UVB.

Figure 3

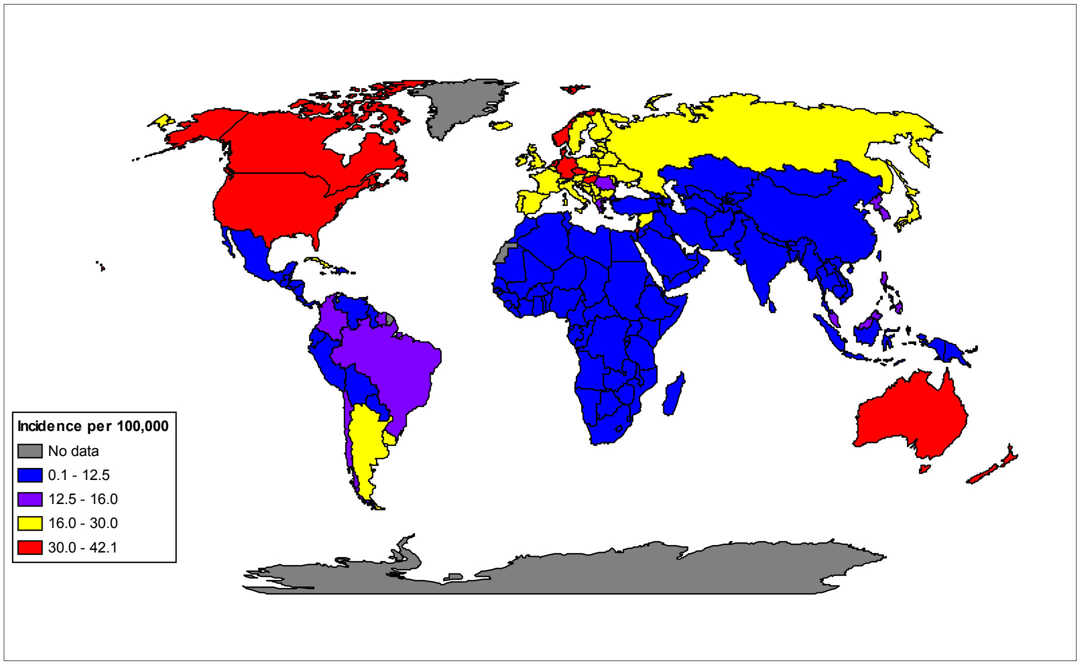
Age-adjusted colorectal cancer incidence rates, by country, males, 2000.



Source: GLOBOCAN (18)

Figure 4

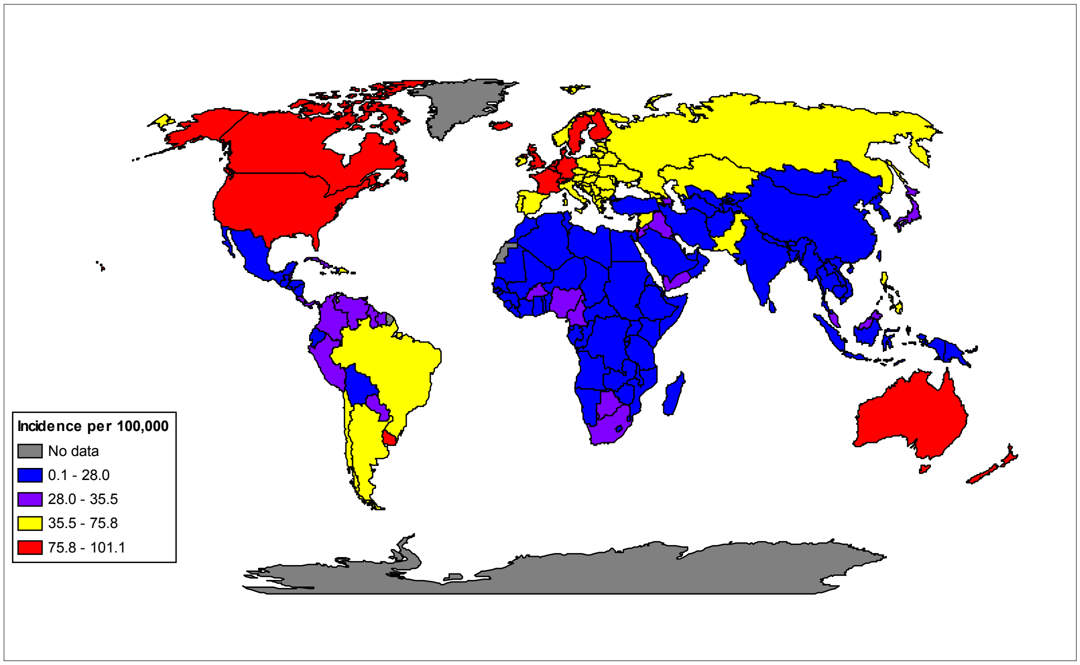
Age-adjusted colorectal cancer incidence rates, by country, females, 2000



Source: GLOBOCAN (18)

Figure 5

Age-adjusted breast cancer incidence rates, by country, females, 2000

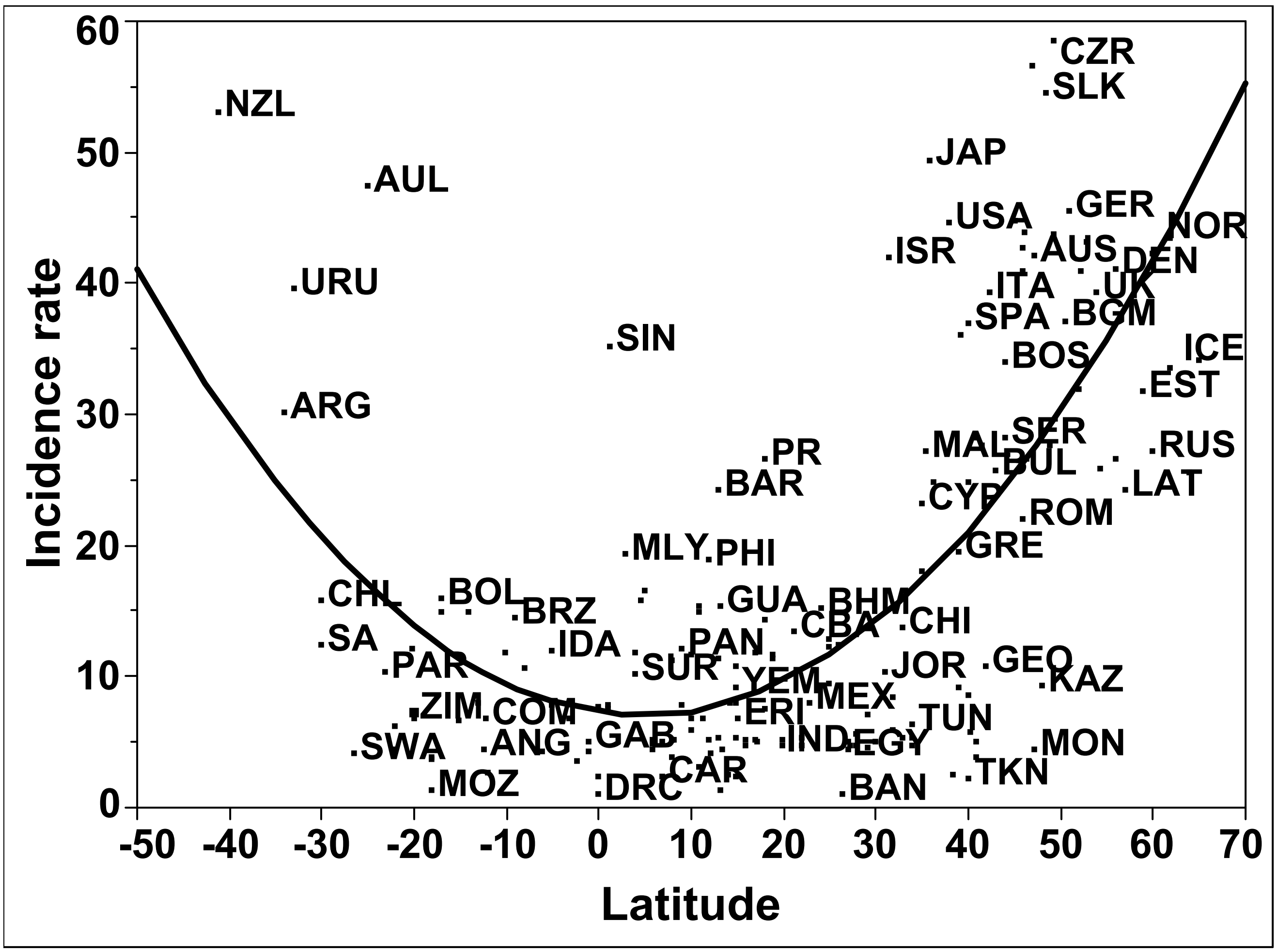


Source: GLOBOCAN (18)

Male colorectal cancer was highly correlated with latitude $R^2 = 0.47$ (Figure 6), a correlation that persisted and was strengthened by adjustment for population density (Figure 7). Abbreviations for countries shown in figures are provided in Appendix Table 1.

Figure 6

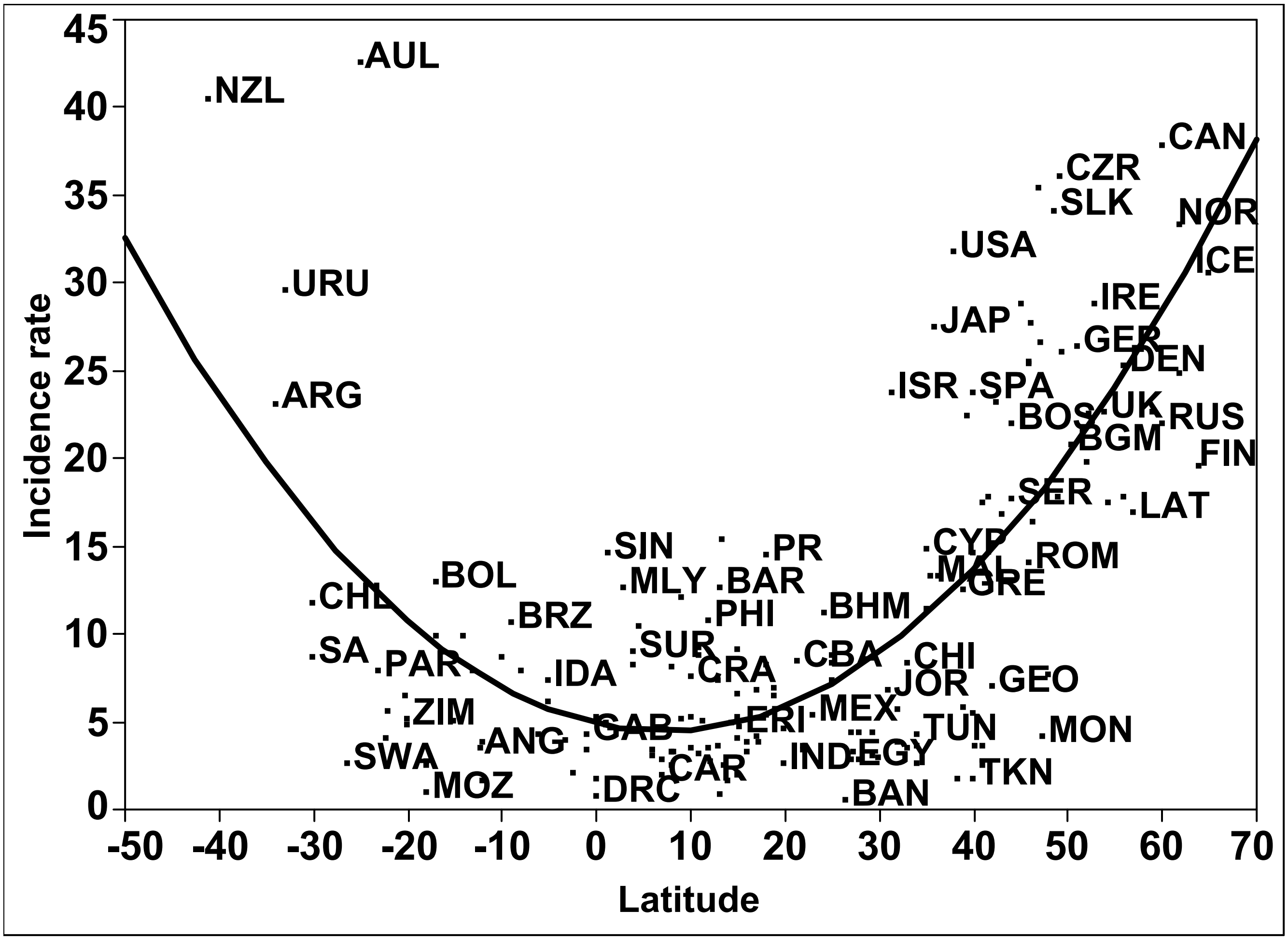
Colorectal cancer incidence rates, by latitude, males, 2000



Source: GLOBOCAN (18)

Figure 7

Colorectal cancer incidence rates, by latitude adjusted for population density, males, 2000

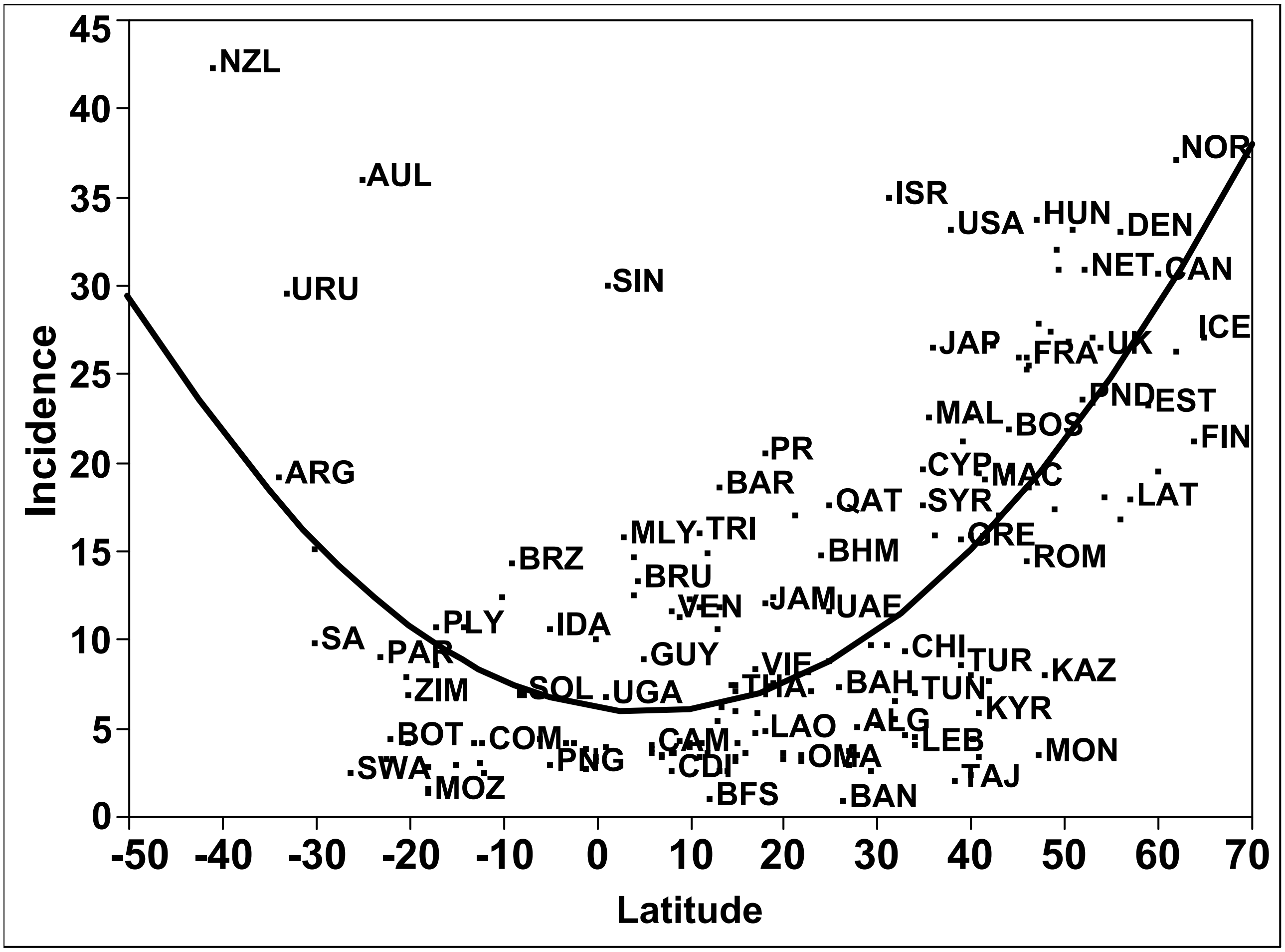


Source: GLOBOCAN (18)

Female colorectal cancer incidence rates and latitude had an unadjusted R^2= 0.45 (Figure 8) and a population-density adjusted R^2 = 0.49 (Figure 9).

Figure 8

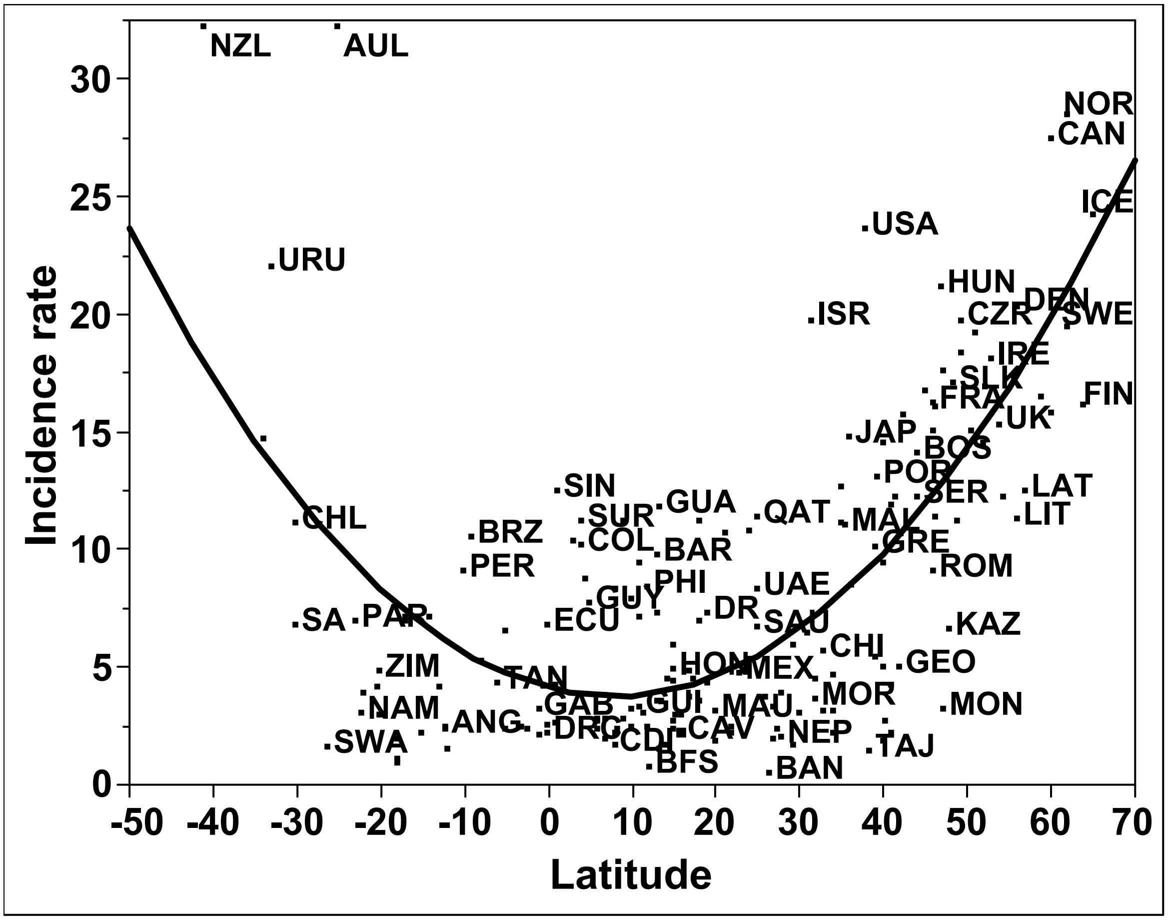
Colorectal cancer incidence rates, by latitude, females, 2000



Source: GLOBOCAN (18)

Figure 9

Colorectal cancer incidence rates, by latitude adjusted for population density, females, 2000

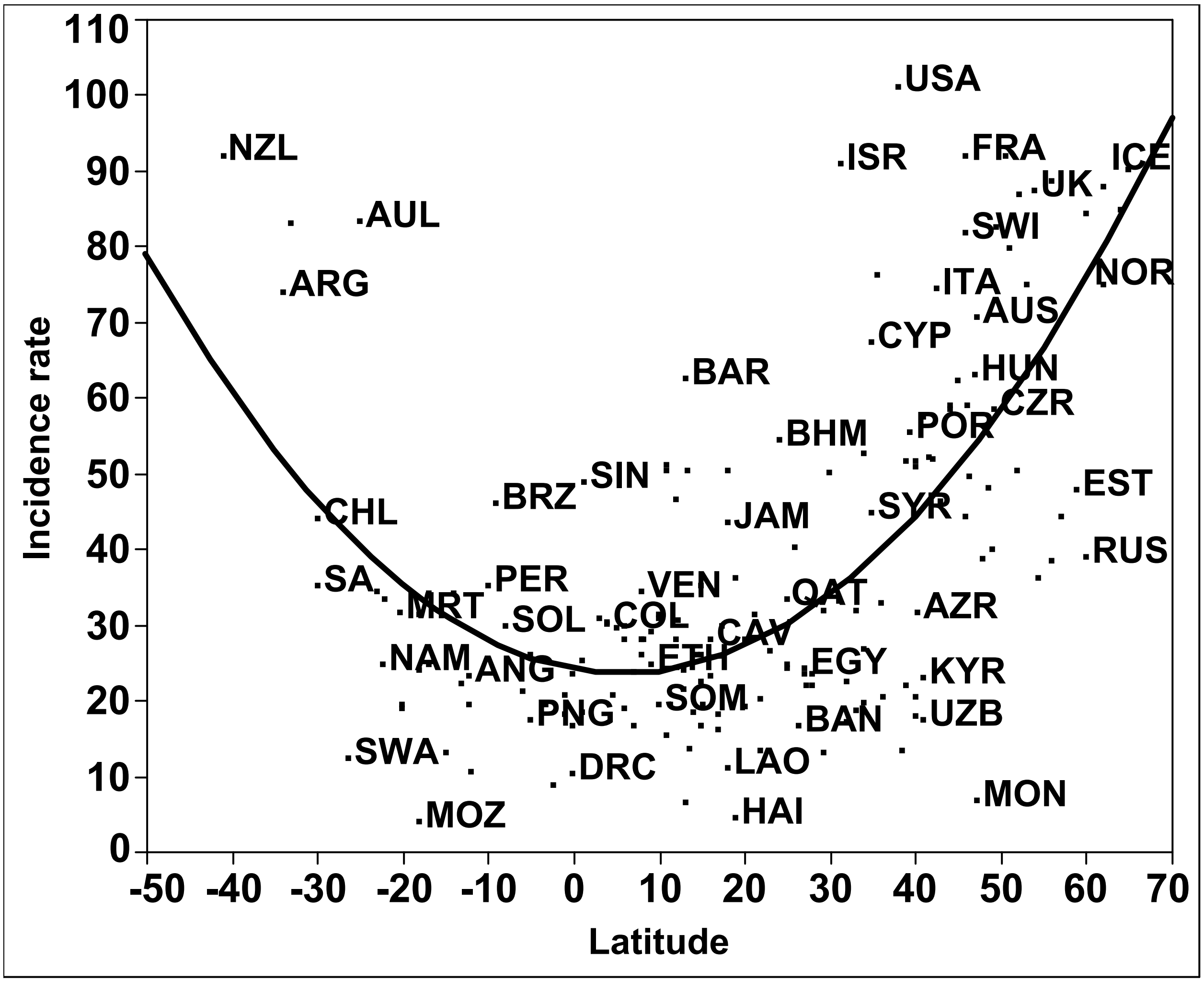


Source: GLOBOCAN (18)

Female breast cancer incidence rates were also highly associated with latitude and latitude adjusted for population density, R^2= 0.43 (Figure 10), and 0.46 (Figure 11) respectively.

Figure 10

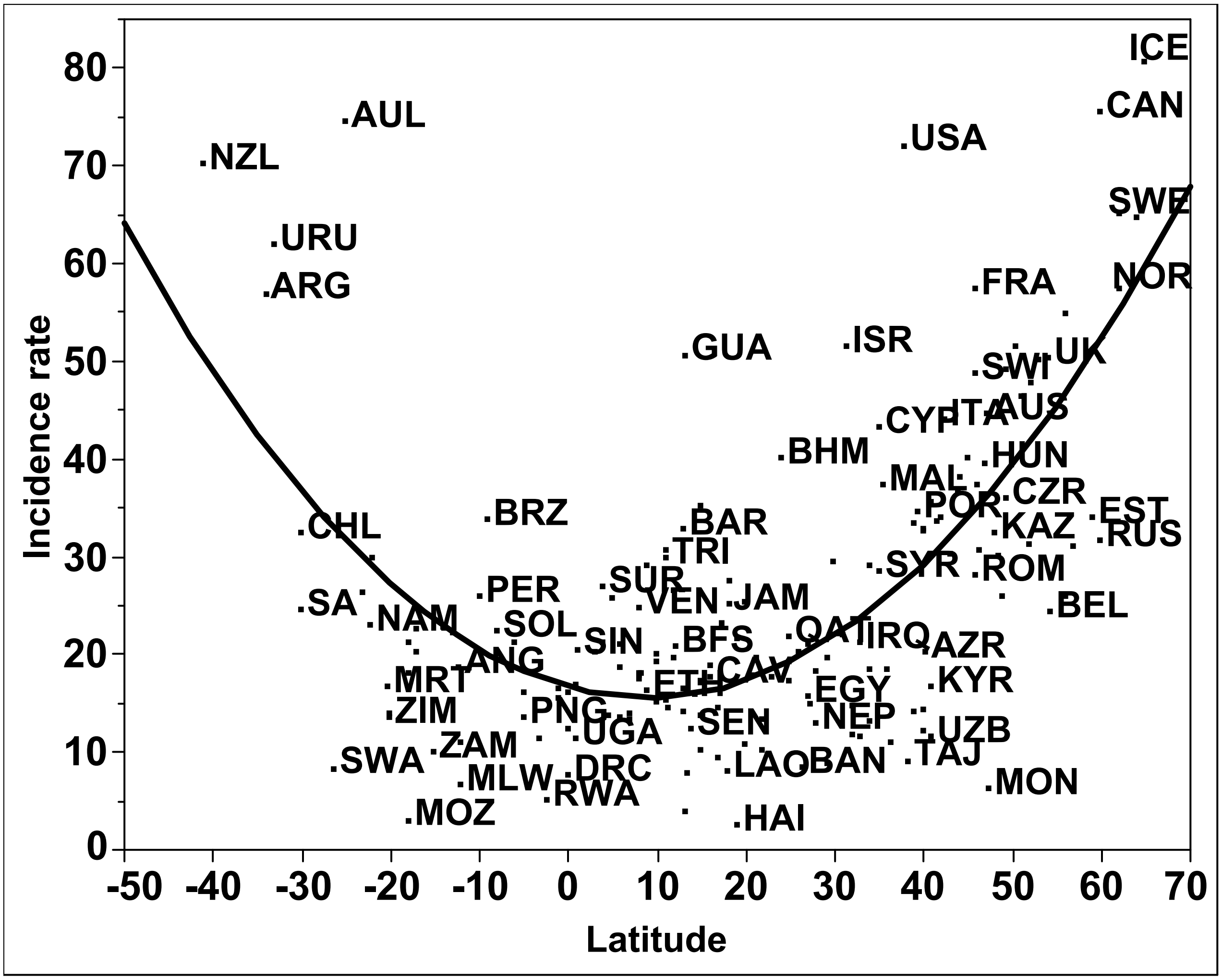
Breast cancer incidence rates, by latitude, females, 2000



Source: GLOBOCAN (18)

Figure 11

Breast cancer incidence rates, by latitude adjusted for population density, females, 2000



Source: GLOBOCAN (18)

A regression model for male colorectal cancer incidence accounted for 68% of the variation in rates ($R^2 = 0.68$) (Table 1). Total solar irradiance at the top of the atmosphere ($p = 0.0004$) and proportion of the population engaged in agriculture ($p = 0.002$), were statistically significantly inversely associated with colorectal cancer incidence, while total cloud cover ($p = 0.002$) and anthropogenic sulfate aerosol optical depth ($p = 0.0003$) were positively associated. Stratospheric ozone thickness was not significantly related to incidence rates of colorectal or breast cancer, and was therefore not included in further regressions.

Table 1. Association of total solar irradiance and other variables with age-adjusted incidence rates of colorectal cancer per 100,000 population, males, 175 countries, 2000

Variable	Regression coefficient	Standard error	*t*	*p*
Total solar irradiance, W/m^{2*}	-0.0181	0.005	-3.53	0.0004
Total cloud cover, proportion	19.9350	6.203	3.21	0.002
Anthropogenic sulfate aerosol optical depth	19.0711	5.116	3.73	0.0003
Proportion of population living in urban areas	0.0195	0.061	0.32	0.75
Population density, individuals/km^2	0.0016	0.001	1.16	0.25
Proportion of population engaged in agriculture	-0.1668	0.053	-3.12	0.002

R^2 for model = 0.68

p for model < 0.0001

*At equinox.

Results were similar for females (Table 2) with the main difference being the larger coefficient of variation ($R^2 = 0.73$). The proportion of the population living in urban areas was associated with the colorectal cancer incidence rate in females but not males.

Table 2. Association of total solar irradiance and other variables with age-adjusted incidence rates of colorectal cancer per 100,000 population, females, 175 countries, 2000

Variable	Regression coefficient	Standard error	*t*	*p*
Total solar irradiance, W/m^{2*}	-0.0096	0.003	-3.02	0.003
Total cloud cover, pro-portion	14.8314	3.856	3.85	0.0002
Anthropogenic sulfate aerosol optical depth	9.6355	3.181	3.03	0.003
Proportion of population living in urban areas	0.0792	0.038	2.08	0.04
Population density, individuals/km^2	0.0012	0.001	1.38	0.17
Proportion of population engaged in agriculture	-0.0988	0.033	-2.97	0.004

R^2 for model = 0.73

p for model < 0.0001

*At equinox.

Total solar irradiance ($p = 0.0003$) and proportion of the population engaged in agriculture ($p = 0.05$) were statistically significantly inversely associated with incidence rates of female breast cancer (Table 3). Total cloud cover ($p = 0.02$) and the proportion of the population living in urban areas ($p = 0.05$), were statistically significantly positively associated with incidence rates.

Table 3. Association of total solar irradiance and other variables with age-adjusted incidence rates of breast cancer per 100,000 population, females, 175 countries, 2000

Variable	Regression coefficient	Standard error	*t*	*p*
Total solar irradiance, W/m^{2*}	-0.0327	0.009	-3.69	0.0003
Total cloud cover, proportion	26.0517	10.723	2.43	0.02
Anthropogenic sulfate aerosol optical depth	13.2226	8.844	1.5	0.14
Proportion of population living in urban areas	0.2067	0.106	1.95	0.05
Population density, individuals/km^2	-0.0001	0.002	-0.04	0.97
Proportion of population engaged in agriculture	-0.1818	0.092	-1.97	0.05

R^2 for model =0.63

p for model < 0.0001

*At equinox.

CONCLUSIONS

Countries with persistently high percentage of cloud cover had significantly higher incidence rates of breast and colon cancer. This is the first report to our knowledge of an adverse association between persistent cloud cover and incidence of any disease. Consistent with the association with cloud cover, places that had the lowest solar irradiance had incidence rates of breast and colorectal cancer that were several times greater than those with the highest. Countries with intermediate irradiance had intermediate incidence rates. Countries with high levels of anthropogenic sulfate aerosols (acid haze) also had significantly higher incidence rates of breast and colon cancer than those with lower levels, consistent with previous research (5). Such aerosols are the cause of acid precipitation. Their geographic distribution is nearly identical to that of acid rain (5, 20).

The aerosol optical depths reported by the MODIS package on the Terra satellite were higher than expected. This suggests the possibility that attenuation of solar radiation may have been greater than anticipated due to the presence of optically-absorbing particles, such as elemental carbon (soot) in association with sulfate particles, and possibly optically-absorbing sulfuric and sulfurous acid droplet aerosols. This is consistent with recent reports of extensive, thick, and highly persistent atmospheric brown clouds in the northern hemisphere. The brown clouds are due to the combustion of high sulfur content bituminous (soft) coal in Asia and the U.S., mainly for electric power generation. Sulfate-carbonaceous acid haze air pollution is almost exclusively due to burning of soft coal, and it strongly attenuates UVB (5). However more research is needed to determine the extent to which the brown cloud and other anthropogenic aerosols are contaminated with particles that absorb UVB.

The lack of a statistically significant association of stratospheric ozone thickness with incidence rates was apparently due to the relative uniformity of ozone thickness among countries, particularly at the equinox. It may have a greater effect at other times of year, when the distribution of stratospheric ozone could be less uniform. The graphs of incidence rates were presented according to latitude, which is directly related to total solar irradiance at the top of the atmosphere. This type of display allows comparison of the associations with breast and colon cancer in the northern hemisphere compared to the southern. Similar associations were observed when the incidence rates were plotted according to total solar irradiance, but, as expected from the earth's approximately spherical shape, the least-squares lines for the associations tended to be straight or mildly curvilinear (not shown). The purpose of the maps presented here is to allow comparisons among countries. The data on which the maps are based generally provided more geographic resolution than was shown, namely overall estimates for entire countries. Studies that can take advantage of regional differences in incidence rates within countries should geocode the data provided in the original sources cited in the references, rather than use these maps.

The regression models presented here used total solar irradiance at the top of the atmosphere, and atmospheric characteristics that reduce transmission of UVB and tend to vary considerably by location, namely cloud cover and column aerosol optical depth, as the predictor variables. Total solar irradiance at the top of the atmosphere was used since existing estimates of UVB irradiance derived from remote sensing platforms such as TOMS and ERBE do not adequately account for the effect of clouds on UVB extinction (Jay R. Herman, personal communication, 2005). If more information were available on cloud-cover parameters, including the extinction by clouds at UVB wavelengths, it is likely that the explanatory power of the regression models that were used could be enhanced. The regression models did not include Rayleigh scatter, whose attenuation varies as the inverse of the fourth power of the wavelength. As a result of this wavelength dependence, extinction due to Rayleigh scatter, although probably relatively minor, would be greater for UVB than for visible light. The models might have accounted for slightly more of the variance in incidence rates if Rayleigh scatter had been taken into account.

More research is clearly needed on absorption and reflection of UVB by clouds, on a global basis. Above all, more numerous and evenly dispersed ground photometer stations are needed to measure ultraviolet radiation (290-400 nm) in nanometer increments, and to provide measurements that are difficult or impossible to accomplish by remote sensing, such as UVB irradiance in cities, where the UVB absorptive effects of sulfate-carbonaceous aerosol "dust domes" may be prominent. High-resolution remote sensing and ground based spectrophotometer measurements are complementary, and expansion of both types of sensing is needed to adequately understand and monitor the prominent effects of ultraviolet radiation on human health.

Previous studies have reported associations between dietary factors and risk of colorectal cancer incidence or mortality, such as an adverse association of intake of animal protein as a proportion of total energy intake with mortality, and of regular intake of red meat with incidence (31-32). These associations are thought to be due to intake of carcinogenic polyamines (32). The present analysis did not include these dietary factors in the regression models. However, it is likely that variation between countries in them could account for variance that was not accounted for by total solar irradiance or UVB. Differences in age at first pregnancy might explain some of the unexplained variance in incidence rates of breast cancer. However it is unlikely that differences in age at first pregnancy could account for the inverse association with solar irradiance, which is stronger. Differences in sex hormone concentrations in women among countries are generally minor, and could not account for these findings. All incidence rates were age-adjusted to the same world standard (23), so differences in age distributions among the countries could not explain any of the associations.

Since the ability of a country to detect and report cancer incidence may depend to a degree on level of economic development, this possibility was tested by including per capita health expenditure by country in further regression models. While this variable had some explanatory power, total solar irradiance and the variables that reduced UVB irradiance, such as total cloud cover and anthropogenic aerosol optical depth, had the most powerful effects. These findings support previous research indicating that solar irradiance, UVB, and photosynthesized vitamin D are associated with lower incidence of cancers of the colon (1-4, 6-15) and breast (5, 14-20). Preventive measures should include elimination of anthropogenic sulfate-carbonaceous (acid haze) aerosols that interfere with photosynthesis of vitamin D. Elimination of these anthropogenic aerosols would also reduce cloud cover, as cloud cover tends to be associated with sulfate aerosols that provide condensation nuclei. Ten to fifteen minutes per day of exposure to sunlight between 10:00 AM and 2:00 PM should be encouraged, without sunscreen, at all ages. At least one square foot of skin should be exposed for adequate vitamin D photosynthesis, preferably not the face. Such exposure would prevent nine or more cases of potentially fatal internal cancers for each possible case of skin cancer that it might cause.

Vitamin D is also available in oral form, but only in acceptable doses far lower than those associated with 10-15 minutes of solar exposure. Individuals wishing to consume vitamin D for reduction of risk of colon and breast cancer should consume at least 1,000 IU/day of vitamin D3 (33), but should not, according to present U.S. guidelines, exceed 2,000 IU/day (34). According to a consensus of observational studies conducted over a period of 20 years, adequate exposure of the population to moderate amounts mid-day sunlight or oral vitamin D_3 could reduce the incidence of colon cancer by at least 50% (35).

The worldwide geographic distribution of breast cancer incidence rates (Figure 5) was highly similar to the distribution of colorectal cancer incidence rates (Figures 3 and 4). Rates tended to be lowest in regions of high solar radiation (Figures 1 and 2), and highest in areas with low solar radiation. This effect is probably due to vitamin D status in childhood and early adolescence. If initiated in early childhood, the preponderance of epidemiological evidence suggests that moderate amounts mid-day sunlight or oral vitamin D_3 could similarly reduce the incidence of breast cancer (5, 16, 18-20).

Delays in implementing simple and inexpensive preventive actions to improve vitamin D status would be unwise, considering that annually there are 357,000 new cases and 106,000 deaths from breast and colorectal cancers in the U.S. (36) and 2.2 million new cases and 940,000 deaths in the world (37), at least half of which could be prevented.

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APPENDIX

Table 1. Abbreviations for countries

AFG	Afghanistan	CRA	Costa Rica
ALB	Albania	CRO	Croatia
ALG	Algeria	CYP	Cyprus
ANG	Angola	CZR	Czech Republic
ARG	Argentina	DEN	Denmark
ARM	Armenia	DJI	Djibouti
AUL	Australia	DR	Dominican Republic
AUS	Austria	DRC	Congo
AZR	Azerbaijan	ECU	Ecuador
BAH	Bahrain	EGY	Egypt
BAN	Bangladesh	ELS	El Salvador
BAR	Barbados	EQG	Equatorial Guinea
BEL	Belarus	ERI	Eritrea
BEN	Benin	EST	Estonia
BFS	Burkina Faso	ETH	Ethiopia
BGM	Belgium	FIJ	Fiji
BHM	Bahamas	FIN	Finland
BHU	Bhutan	FRA	France
BLZ	Belize	GAB	Gabon
BOL	Bolivia	GAM	Gambia
BOS	Bosnia Herzegovena	GEO	Georgia
BOT	Botswana	GER	Germany
BRU	Brunei	GHA	Ghana
BRZ	Brazil	GIB	Guinea-Bissau
BUL	Bulgaria	GRE	Greece
BUR	Burundi	GTA	Guatemala
CAM	Cameroon	GUA	Guam
CAN	Canada	GUI	Guinea
CAR	Central African Republic	GUY	Guyana
CAV	Cape Verde	HAI	Haiti
CBA	Cuba	HON	Honduras
CBD	Cambodia	HUN	Hungary
CDI	Cote d'Ivoire	ICE	Iceland
CGB	Congo Brazzaville	IDA	Indonesia
CHD	Chad	IND	India
CHI	China	IRE	Ireland
CHL	Chile	IRN	Iran, Islamic Republic of
COL	Colombia	IRQ	Iraq
COM	Comoros	ISR	Israel

ITA	Italy
JAM	Jamaica
JAP	Japan
JOR	Jordan
KAZ	Kazakhstan
KEN	Kenya
KUW	Kuwait
KYR	Kyrgyzstan
LAO	Laos
LAT	Latvia
LBY	Libya
LEB	Lebanon
LES	Lesotho
LIB	Liberia
LIT	Lithuania
LUX	Luxembourg
MAC	Macedonia
MAD	Madagascar
MAL	Malta
MAU	Mauritania
MEL	Melanesia
MEX	Mexico
MIC	Micronesia
MLI	Mali
MLW	Malawi
MLY	Malaysia
MOL	Moldava
MON	Mongolia
MOR	Morocco
MOZ	Mozambique
MRT	Mauritius
MYA	Myanmar
NAM	Namibia
NEP	Nepal
NET	Netherlands
NGA	Nigeria
NIC	Nicaragua
NIG	Niger
NKO	Korea, Democratic Republic of
NOR	Norway
NZL	New Zealand
TUN	Tunisia
TUR	Turkey
OMA	Oman
PAK	Pakistan
PAN	Panama
PAR	Paraguay
PER	Peru
PHI	Philippines
PLY	Polynesia
PND	Poland
PNG	Papua New Guinea
POR	Portugal
PR	Puerto Rico
QAT	Qatar
ROM	Romania
RUS	Russian Federation
RWA	Rwanda
SA	South African Republic
SAM	Samoa
SAU	Saudi Arabia
SEN	Senegal
SER	Serbia and Montenegro
SIN	Singapore
SKO	Korea, Republic of
SLK	Slovakia
SLN	Sierra Leone
SLV	Slovenia
SOL	Solomon Islands
SOM	Somalia
SPA	Spain
SRL	Sri Lanka
SUD	Sudan
SUR	Suriname
SWA	Swaziland
SWE	Sweden
SWI	Switzerland
SYR	Syrian Arab Republic
TAJ	Tajikistan
TAN	Tanzania
THA	Thailand
TKN	Turkmenistan
TOG	Togo
TRI	Trinidad and Tobago

UAE	United Arab Emirates
UGA	Uganda
UK	United Kingdom
UKR	Ukraine
URU	Uruguay
USA	United States of America
UZB	Uzbekistan
VAN	Vanuatu
VEN	Venezuela
VIE	Viet Nam
YEM	Yemen
ZAM	Zambia
ZIM	Zimbabwe

CORRESPONDING AUTHOR INFORMATION

Cedric F. Garland, Dr.P.H., F.A.C.E.
Professor
Department of Family and Preventive Medicine
University of California, San Diego
9500 Gilman Drive, Dept. 0631C
La Jolla CA 92093-0631, and
Naval Health Research Center
P.O. Box 85122
San Diego CA 92186-5122

Telephone (858) 534-0520/(619) 553-9016
E-mail: cgarland@ucsd.edu
Fax: (858) 534-3777

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