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Cloud cover-adjusted ultraviolet B irradiance and pancreatic cancer incidence in 172 countries

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ABSTRACT

Background: Controversy exists regarding whether vitamin D deficiency could influence the etiology of pancreatic cancer. Several cohort studies have found that high serum 25-hydroxyvitamin D [25(OH)D] concentrations are associated with low risk of pancreatic cancer, while others have not.
Hypothesis: Low ultraviolet B irradiance is associated with high incidence of pancreatic cancer.
Methods: Age-standardized pancreatic cancer incidence rates were obtained from GLOBOCAN in 2008. The association between cloud-adjusted UVB irradiance and age-standardized incidence rates of pancreatic cancer was analyzed using regression.
Results: Overall, the lower the cloud-adjusted UVB irradiance, the higher the incidence rate of pancreatic cancer. Residents of countries with low UVB irradiance had approximately 6 times the incidence rates as those in countries with high UVB irradiance ($p < 0.0001$ for males and $p < 0.0001$ for females). This association persisted after adjustment for traditional risk factors of pancreatic cancer ($p = 0.0182$ for males and $p = 0.0029$ for females).
Conclusions: There was an inverse association of cloud-adjusted UVB irradiance with incidence of pancreatic cancer that persisted after adjustment. This result is consistent with an inverse association of overall vitamin D deficiency in countries with lower UVB irradiance with risk of pancreatic cancer. Further research on the role of 25(OH)D in reduction of pancreatic cancer in individuals would be desirable to expand the limited avenues available for prevention of this highly fatal disease.
This article is part of a Special Issue entitled '17th Vitamin D Workshop'.

1. Introduction

There were estimated 337,872 new cases of pancreatic cancer and 330,372 deaths in 2012 [1]. In the US, there were 42,885 new cases and 41,509 deaths [1]. Smoking, excessive alcohol consumption, and intake of large amounts of red meat have been reported as being associated with higher than usual risk of pancreatic cancer [2–8]. A previous ecological study in 2002 found an inverse association between latitude and a measure of solar ultraviolet B (UVB) irradiance and incidence rates of pancreatic cancer worldwide [9]. Exposure to solar UVB irradiance is the source of approximately 95% of circulating 25-hydroxyvitamin D, the principal vitamin D metabolite [10]. Vitamin D and its metabolites have been linked to lower incidence and mortality of several cancers [11–14], but the results have been mixed, with some studies failing to detect benefit [15,16].

Six years have passed since the earlier analysis using the 2002 data from GLOBOCAN [9]. An updated analysis is needed since more recent data are available and many rates have changed due to shifts in cultural, political, and economic factors. It is also desirable since a new method for display of the association of solar UVB with incidence rates has been created that reveals a clearer association between UVB irradiance and risk than has been shown before: a stratified method according to hemisphere and cancer incidence [17]. This new method allows visualization of the symmetry of this association in two hemispheres. It could be useful for future studies of association between UVB irradiance and risk of any disease.

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2. Methods

We obtained age-standardized incidence rates of pancreatic cancer from the International Agency for Research on Cancer (IARC) GLOBOCAN 2008 database [18], a recent source of age-standardized incidence and mortality rates by country. Intake of energy from animal sources and alcohol consumption were obtained from the United Nations Food and Agriculture Organization [19]; prevalence of obesity, sex-specific smoking prevalence, and per capita health expenditure data were obtained from the World Health Organization [20]; and prevalence of diabetes was obtained from the International Diabetes Federation [21].

Total solar UVB irradiance, adjusted for cloud cover, was calculated using data from the National Aeronautics and Space Administration (NASA) International Satellite Cloud Climatology Project (ISCCP) satellite [22], which provided astronomical data on geographic variation in solar irradiance [23]. The total noon solar irradiance at the top of the atmosphere for each country on the date of the winter solstice was calculated using the formula $A' = A \times \cos(x + 23.5^\circ)$ in the northern hemisphere; and $A' = A \times \cos(x - 23.5^\circ)$ in the southern hemisphere; where x = latitude of the population centroid of the country in degrees, A = total solar radiation at the equator in Watts (W) per square meter (m^2) (i.e., the solar constant, 1366 W/m^2), and A' = total solar radiation in W/m^2 for the country on the date of the winter solstice [23]. Since UVB is approximately 0.4% of total solar irradiance, total solar irradiance was multiplied by 0.004 to obtain the estimated UVB irradiance at the top of the atmosphere. UVB was then corrected for percentage cloud cover, according to data from the ISCCP satellite, using the following formula: UVB irradiance × (1 − fractional cloud cover). Population centroids were calculated by the Columbia University Center for International Earth Science Information Network [24].

Incidence rates of sex-specific, age-adjusted rates of pancreatic cancer were plotted against cloud cover-adjusted UVB irradiance. A polynomial trend line was added to show the best fit. UVB values in the northern hemisphere were plotted as positive numbers. To stratify the hemispheres, UVB values for countries in the Southern hemisphere were plotted as negative numbers, a common convention in cartographic analyses. This method of plotting is analogous to the plotting approach we have previously used for latitude. It provides a parabola when the highest incidence rates are in countries far from the equator and the lowest are in countries nearest the equator. It would be a flat line if there were no association of UVB with incidence rates. No attempt was made to correct for ozone thickness, since it was found in preliminary analyses to be strongly positively correlated with percentage cloud cover. All calculations for these graphs were performed using JMP, version 10.0.0 (Cary NC: SAS Institute).

Multiple linear regression was used to investigate the association between cloud cover-adjusted UVB irradiance and age-adjusted pancreatic cancer incidence rates, while controlling for prevalence of obesity and diabetes; per capita consumption of animal protein and alcohol; sex-specific smoking prevalence, and per capita health expenditure. One regression model was created for males (Table 1) and another was created for females (Table 2). All analyses were performed using SAS Version 9.3 (Cary NC: SAS Institute).

3. Results

Incidence rates of pancreatic cancer were generally higher in countries with lower UVB irradiance. This is illustrated in Figs. 1 and 2, where values to the left of the center are for countries in the Southern hemisphere, and values to the right of the center are for countries in the Northern hemisphere.

UVB irradiance adjusted for cloudiness was inversely associated with pancreatic cancer in the multiple regression model for males (Table 1) and the multiple regression model for females (Table 2). Consumption of animal protein was positively associated with incidence of pancreatic cancer in both sexes (Tables 1 and 2). Each of the regression models in this study explains approximately three-quarters of the variation in pancreatic cancer incidence worldwide (Tables 1 and 2). The relationship between UVB irradiation and pancreatic cancer incidence persisted in both sexes despite controlling for six covariates. This is consistent with other regression results on the relationship between UVB irradiation and cancer incidence [25,26].

4. Discussion

We are not aware of any previous studies that have used cloud cover-adjusted UVB irradiance as the independent variable for incidence of pancreatic cancer. Instead, latitude or clear-air UVB irradiance has been used, due to the historical difficulty of estimating cloud cover worldwide before the existence of the NASA–ISCCP satellite data set. The data from this satellite have now made this feasible [22]. This is a worthwhile advance, since there are many places in the world where UVB irradiance reaching the surface is strongly influenced by cloud cover. A previous paper on pancreatic cancer did not plot incidence rates according to cloud-adjusted UVB irradiance [9]. It had greater dispersion of the points around the prediction line that was based on latitude. Use of latitude as the independent variable accounts for the major effect of solar zenith angle on UVB irradiance, but does not take variations in cloud cover into account. While that study used cloud cover-adjusted UVB for some analyses, it did not use it constructing graphs of incidence rates, which this study does. The new approach to analyzing the association between UVB irradiance and age-standardized incidence rates yield far fewer outliers and a much smoother curve. The new data display methodology used here helps to confirm the inverse association of solar UVB with incidence rates

Table 1
Multiple linear regression models for age-standardized pancreatic cancer incidence rates according to cloud-adjusted UVB irradiance, males, 111 countries, 2008.

Covariate	Regression coefficient	Standard error	t	p
Solar UVB irradiance (W/m^2)	−0.18905	0.07883	−2.40	0.0182
Animal protein consumption (kcal/capita/year)	0.00216	0.00090	2.38	0.0190
Diabetes prevalence (%)	0.02986	0.05378	0.56	0.5800
Obesity prevalence (%)	0.00551	0.01177	0.47	0.6408
Alcohol consumption (kcal/capita/year)	0.01409	0.00295	4.77	<0.0001
Male smoking Prevalence (%)	0.04205	0.01477	2.85	0.0053
Health expenditure (US dollars/person/year)	0.00001	0.00030	0.04	0.9679
Intercept	1.75413	1.31371	1.34	0.1847

$R^2 = 0.71$; $p < 0.0001$.

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Table 2
Multiple linear regression models for age-standardized pancreatic cancer incidence rates according to cloud-adjusted UVB irradiance, females, 111 countries, 2008.

Covariate	Regression coefficient	Standard error	*t*	*p*
Solar UVB irradiance (W/m^2)	−0.15378	0.05049	−3.05	0.0029
Animal protein consumption (kcal/capita/year)	0.00151	0.00062	2.46	0.0156
Diabetes prevalence (%)	0.02103	0.03604	0.58	0.5608
Obesity prevalence (%)	0.0084	0.00784	1.13	0.2622
Alcohol consumption (kcal/capita/year)	0.00365	0.00206	1.78	0.0784
Female smoking prevalence (%)	0.03061	0.01652	1.85	0.0668
Health expenditure (US dollars/person/year)	0.00014	0.00021	0.69	0.4939
Intercept	2.42139	0.74589	3.25	0.0016

$R^2 = 0.71$; $p < 0.0001$.

of pancreatic cancer by showing that the curves are similar in the Northern and Southern hemispheres. The similarity of the association in the two hemispheres helps to rule out solely cultural explanations for the higher rates in countries with low UVB irradiance, and is a point in favor of a geophysical factor such as solar UVB irradiance.

These results support the hypothesis that vitamin D levels account for a large amount of global variation in pancreatic cancer. However, it should be noted that certain countries with high dietary vitamin D intake (notably Norway and Sweden) have persistently high rates of pancreatic cancer [27,28]. As this suggests, low serum vitamin D is not the sole contributor to pancreatic cancer risk. For this reason, the regression analyses in this study have controlled for animal protein consumption, diabetes prevalence, obesity prevalence, alcohol consumption, sex-specific smoking prevalence, and healthcare expenditures. Several further behavioral factors may protect against pancreatic cancer, including higher folate consumption [29] or possibly the use of non-steroidal anti-inflammatory drugs [30]. Certain genetic polymorphisms may also increase risk, although several of these polymorphisms influence the vitamin D pathway, such those for the CYP2R gene [31].

4.1. Weaknesses

Complete data on all variables were not available for all countries, which may have biased the results. However, missing data for covariates were mostly for countries near the equator that have low incidence rates of pancreatic cancer. In general, missing data for some countries would tend to weaken measures of association between UVB irradiance and age-adjusted incidence rates of pancreatic cancer. This study could not account for all possible confounders and the regression model cannot account for all variables that have an impact on vitamin D photosynthesis in humans, such as type of clothing worn, misdiagnosis rate, or time spent outdoors. Therefore, some degree of misclassification may have occurred. On the other hand, UVB irradiance may affect a broad range of individuals, and an independent negative association between UVB irradiance and incidence rates of pancreatic cancer by country was still present in this study, despite the possibility of exposure misclassification.

Results of ecological studies are generally used to stimulate the formation of novel hypotheses. This is because findings from ecological analyses may not be applicable to individuals. For inherently ecological variables, such as exposure to sunlight,

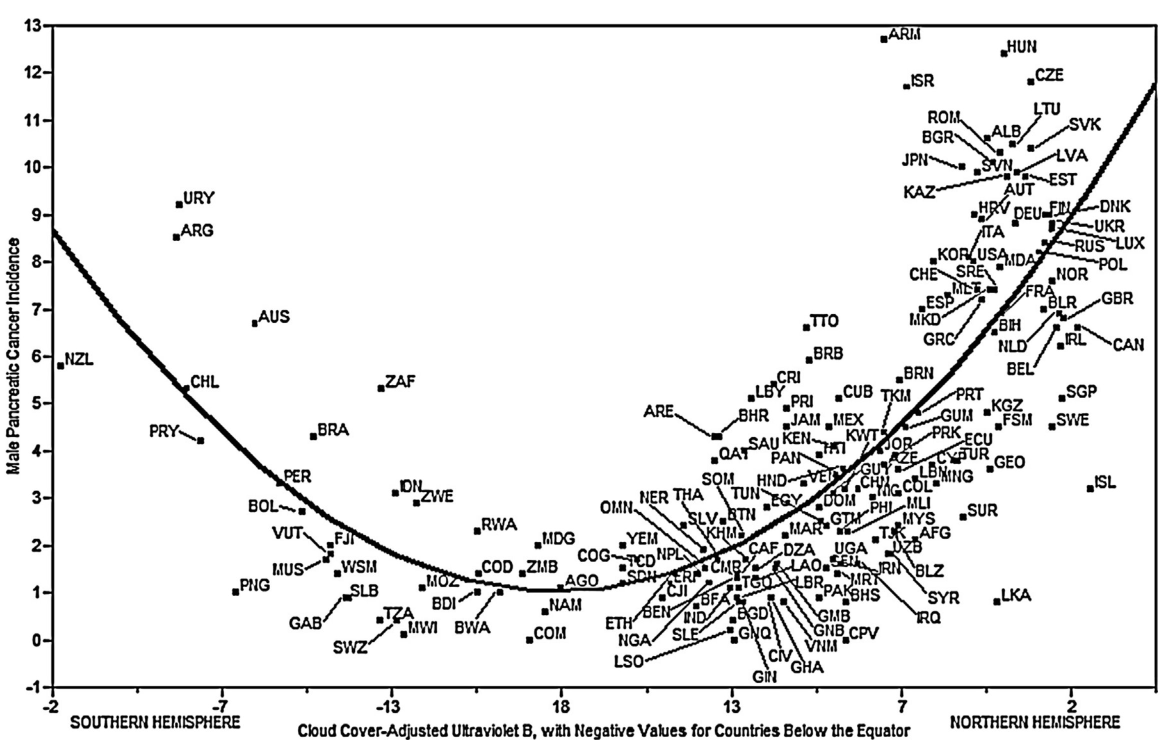

Fig. 1. Rates of age-standardized pancreatic cancer incidence (cases per 100,000) in males according to cloud cover-adjusted UVB irradiance (W/m^2), 172 countries, 2008.

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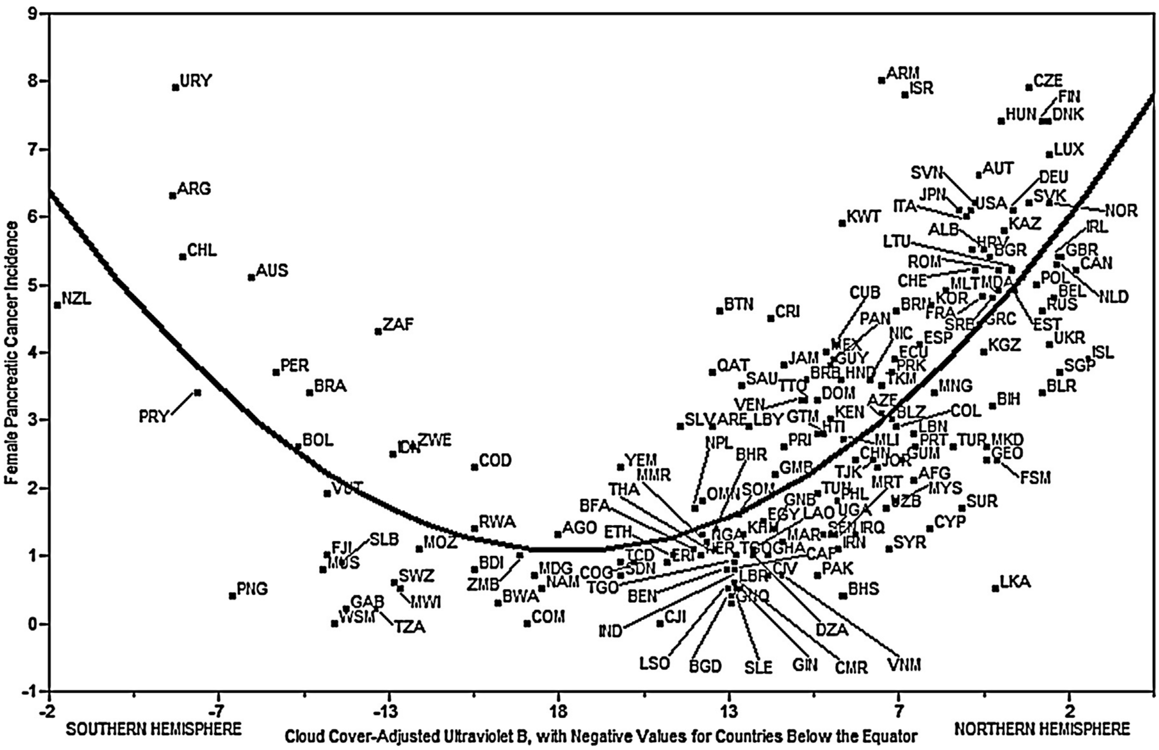

Fig. 2. Rates of age-standardized pancreatic cancer incidence (cases per 100,000) in females according to cloud cover-adjusted UVB irradiance (W/m^2), 172 countries, 2008.

ecological studies may be less prone to error that might occur for non-ecological covariates such as physical activity [32]. However, despite the substantial limitations of the ecological approach, analysis of the global differences in pancreatic cancer incidence and UVB irradiance provides a large-scale natural experiment. Such large-scale natural experiments have identified important associations of great public health impact, including studies of water fluoridation and incidence of dental carries [33].

4.2. Strengths

This study is consistent with findings for analyses of cancer incidence in the United States [34,35] and the world [36,37]. It is the first study to analyze variations in pancreatic cancer incidence according to ultraviolet B when adjusting for cloud cover using NASA satellite data. The significant negative association between age-standardized pancreatic cancer incidence and cloud cover-adjusted UVB persisted even after adjustment for six known confounders.

4.3. Conclusion

Further observational studies of individuals on the relationship between serum 25(OH)D and risk of pancreatic cancer are needed to fully assess a possible beneficial effect of vitamin D on risk of pancreatic cancer. To avoid missing this possible benefit, it may be prudent to correct vitamin D deficiency whenever detected in the population. Serum 25(OH)D can be tested for this purpose. The recommended target concentration of 25(OH)D is currently 40–60 ng/ml (100–150 nmol/L), according to a letter signed by many respected vitamin D scientists and physicians [11].

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The positions expressed in this article are solely those of the authors, and do not represent official positions of the Bureau of Medicine and Surgery, Department of the Navy, Department of Defense, or the U.S. Government.

Appendix A

See Table A1.

Table A1
Countries included in this study, including three-letter country code, country name, age-standardized male pancreatic cancer incidence (cases per 100,000), age-standardized female pancreatic cancer incidence (cases per 100,000), and cloud cover-adjusted ultraviolet B (W/m^2).

Three-letter country code	Country name	Male pancreatic cancer incidence	Female pancreatic cancer incidence	Cloud cover-adjusted ultraviolet B
AFG	Afghanistan	2.1	2.1	7.18578
ALB	Albania	10.6	5.5	5.08767
DZA	Algeria	1.5	1	11.90406
AGO	Angola	1.1	1.3	17.62383
ARG	Argentina	8.5	6.3	6.28936

Table A1 (*Continued*)

Three-letter country code	Country name	Male pancreatic cancer incidence	Female pancreatic cancer incidence	Cloud cover-adjusted ultraviolet B
ARM	Armenia	12.7	8	8.11503
AUS	Australia	6.7	5.1	8.59460
AUT	Austria	8.9	6.6	5.25448
AZE	Azerbaijan	3.7	3.1	8.11503
BHR	Bahrain	4.3	1.4	12.98325
BGD	Bangladesh	0.4	0.4	12.55048
BRB	Barbados	5.9	3.6	10.32185
BLR	Belarus	7	3.4	3.39654
BEL	Belgium	6.6	4.8	3.03030
BLZ	Belize	2.3	3	7.82842
BEN	Benin	1.3	0.9	12.45062
BTN	Bhutan	2.5	4.6	12.87090
BOL	Bolivia	2.7	2.6	9.97535
BIH	Bosnia & Herzegovina	6.5	3.2	4.84953
BWA	Botswana	1	0.3	15.82686
BRA	Brazil	4.3	3.4	10.30337
BRN	Brunei	5.5	4.6	7.67480
BGR	Bulgaria	10.1	5.4	4.93038
BFA	Burkina Faso	0.7	1.1	13.65886
BDI	Burundi	1	0.8	15.15248
KHM	Cambodia	1.7	1.3	12.19855
CMR	Cameroon	1.4	0.6	12.45062
CAN	Canada	6.6	5.2	2.40765
CPV	Cape Verde	0	0.4	9.25750
CAF	Central African Republic	1.4	0.8	12.42605
TCD	Chad	1.5	0.9	15.81391
CHL	Chile	5.3	5.4	6.56992
CHN	China	3.2	2.4	8.88426
COL	Colombia	3.1	2.9	7.68544
COM	Comoros	0	0	16.69626
COG	Congo	1.7	0.9	15.40896
COD	Congo, DRC	1.4	2.3	15.17040
CRI	Costa Rica	5.4	4.5	11.38116
CIV	Cote d'Ivoire	0.9	0.7	11.44416
HRV	Croatia	9	5.5	5.44768
CUB	Cuba	5.1	4.1	9.44034
CYP	Cyprus	3.7	1.4	6.70565
CZE	Czech Republic	11.8	7.9	3.79092
DNK	Denmark	9	7.4	3.23106
CJI	Djibouti	0.9	0	14.65293
DOM	Dominican Republic	2.8	3.3	10.01616
ECU	Ecuador	3.6	3.9	7.70448
EGY	Egypt	2.8	1.5	11.58381
SLV	El Salvador	2.4	2.9	14.01645
GNQ	Equatorial Guinea	0	0.3	12.51978
ERI	Eritrea	1.2	0.9	14.41857
EST	Estonia	9.8	5.1	3.96816
ETH	Ethiopia	1.4	1	14.26740
FJI	Fiji	2	1	10.82256
FIN	Finland	9	7.4	3.37736
FRA	France	6.7	4.8	4.95053
GAB	Gabon	0.9	0.2	11.37780
GEO	Georgia	3.6	2.4	5.00976
DEU	Germany	8.8	6.1	4.24242
GHA	Ghana	0.9	1	11.44416
GRC	Greece	7.2	4.4	5.23908
GUM	Guam	4.5	2.4	7.50680
GTM	Guatemala	2.4	2.8	9.81152
GIN	Guinea	0.8	0.5	12.28955
GNB	Guinea-Bissau	1.5	1.4	11.30388
GUY	Guyana	3.1	3.8	9.59350
HTI	Haiti	3.9	2.8	10.01616
HND	Honduras	3.6	3.6	9.30230
HUN	Hungary	12.4	7.4	4.59767
ISL	Iceland	3.2	3.9	2.03490
IND	India	1.1	0.8	12.66944
IDN	Indonesia	3.1	2.5	12.75372
IRN	Iran	1.6	1.1	9.39194
IRQ	Iraq	1.6	1.3	8.88426
IRL	Ireland	6.2	5.4	2.89800
ISR	Israel	11.7	7.8	7.42959
ITA	Italy	8.1	6	5.63472
JAM	Jamaica	4.5	3.8	10.99056
JPN	Japan	10	6.1	5.84325
JOR	Jordan	4	2.3	8.25510
KAZ	Kazakhstan	9.8	5.8	4.51094

Table A1 (*Continued*)

Three-letter country code	Country name	Male pancreatic cancer incidence	Female pancreatic cancer incidence	Cloud cover-adjusted ultraviolet B
KEN	Kenya	4.1	3	9.62920
KWT	Kuwait	3.2	5.9	9.26541
KGZ	Kyrgyzstan	4.8	4	5.08767
LAO	Laos	1.3	1.1	11.90644
LVA	Latvia	9.9	4.9	4.19608
LBN	Lebanon	3.4	2.8	7.18578
LSO	Lesotho	0.2	0.5	12.63465
LBR	Liberia	0.9	0.6	12.45062
LBY	Libya	5.1	2.9	12.01284
LTU	Lithuania	10.5	5.2	4.30808
LUX	Luxembourg	8.7	6.9	3.15910
MKD	Macedonia	7.4	2.6	5.00976
MDG	Madagascar	2	0.7	16.93090
MWI	Malawi	0.1	0.5	12.98598
MYS	Malaysia	2.4	1.8	7.69384
MLI	Mali	2.3	2.7	9.20990
MLT	Malta	7.3	4.9	6.23280
MRT	Mauritania	1.4	1.3	9.50208
MUS	Mauritius	1.7	0.8	10.69320
MEX	Mexico	4.5	4	9.75128
FSM	Micronesia	4.5	2.4	4.72675
MDA	Moldova	7.9	4.9	4.68293
MNG	Mongolia	3.3	3.4	6.56810
MAR	Morocco	2.2	1.2	11.02532
MOZ	Mozambique	1.1	1.1	13.52820
MMR	Myanmar	1.5	1.3	13.39380
NAM	Namibia	0.6	0.5	17.14577
NPL	Nepal	1.4	1.7	13.60464
NLD	Netherlands	6.9	5.3	2.96450
NZL	New Zealand	5.8	4.7	2.86272
NIC	Nicaragua	3	3.6	8.44515
NER	Niger	1.9	1	13.42338
NGA	Nigeria	1.2	1.2	13.27802
PRK	North Korea	3.9	3.7	7.79100
NOR	Norway	7.6	6.2	3.16491
OMN	Oman	1.5	1.8	13.39380
PAK	Pakistan	0.9	0.7	10.00860
PAN	Panama	3.5	3.9	9.51160
PNG	Papua New Guinea	1	0.4	8.03012
PRY	Paraguay	4.2	3.4	6.98320
PER	Peru	3.3	3.7	9.33940
PHL	Philippines	2.3	1.8	9.41990
POL	Poland	8.2	5	3.55740
PRT	Portugal	4.8	2.6	7.11018
PRI	Puerto Rico	4.9	2.6	10.99056
QAT	Qatar	3.8	3.7	13.09245
ROM	Romania	10.3	5.2	4.68293
RUS	Russia	8.4	4.6	3.37071
RWA	Rwanda	2.3	1.4	15.16368
WSM	Samoa	1.4	0	11.04180
SAU	Saudi Arabia	4	3.5	12.21962
SEN	Senegal	1.5	1.3	9.81152
SRB	Serbia & Montenegro	7.4	4.8	4.84953
SLE	Sierra Leone	0.8	0.5	12.39784
SGP	Singapore	5.1	3.7	2.88876
SVK	Slovakia	10.4	6.2	3.79092
SVN	Slovenia	9.9	6.2	5.35192
SLB	Solomon Is.	0.9	0.9	11.26860
SOM	Somalia	2.2	1.6	12.32959
ZAF	South Africa	5.3	4.3	12.31860
KOR	South Korea	8	4.7	6.63957
ESP	Spain	7	4.1	7.00844
LKA	Sri Lanka	0.8	0.5	4.77925
SDN	Sudan	1.2	0.7	15.81391
SUR	Suriname	2.6	1.7	5.76408
SWZ	Swaziland	0.4	0.6	12.78480
SWE	Sweden	4.5	4.1	3.16491
CHE	Switzerland	7.4	5.2	5.35192
SYR	Syria	1.8	1.1	7.88900
TJK	Tajikistan	2.1	2.4	8.34757
TZA	Tanzania	0.4	0.2	12.26043
THA	Thailand	1.7	1.1	13.02322
BHS	The Bahamas	0.8	0.4	9.23748
GMB	The Gambia	1.6	2.2	11.26020
TGO	Togo	1.1	1	12.39784
TTO	Trinidad & Tobago	6.6	3.3	10.39885
TUN	Tunisia	2.5	1.9	9.98025

Table A1 (*Continued*)

Three-letter country code	Country name	Male pancreatic cancer incidence	Female pancreatic cancer incidence	Cloud cover-adjusted ultraviolet B
TUR	Turkey	3.8	2.6	5.98752
TKM	Turkmenistan	4.4	3.5	8.11503
UGA	Uganda	1.7	1.3	9.62920
UKR	Ukraine	8.8	4.1	3.15910
ARE	United Arab Emirates	4.3	2.9	13.09245
GBR	United Kingdom	6.8	5.4	2.83045
USA	United States	8	6.1	5.50181
URY	Uruguay	9.2	7.9	6.36272
UZB	Uzbekistan	1.8	1.7	7.99491
VUT	Vanuatu	1.8	1.9	10.82256
VEN	Venezuela	3.3	3.3	10.49048
VNM	Vietnam	0.8	0.7	11.05188
YEM	Yemen	2	2.3	15.81391
ZMB	Zambia	1.4	1	16.48836
ZWE	Zimbabwe	2.9	2.6	13.36650

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