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Update on Evidence that Support a Role of Solar Ultraviolet-B Irradiance in Reducing Cancer Risk

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Abstract: The ultraviolet-B (UVB)–vitamin D–cancer hypothesis was proposed in 1980 yet has not been fully accepted. Ecological studies based on geographical variations of cancer rates with respect to solar UVB doses have supported the hypothesis for about 20 cancers. This paper reviews the evidence from studies of personal or group UVB irradiance. Studies have associated personal UVB irradiance with reduced risk for breast, colon, endometrial, prostate, and renal cancer, as well as non-Hodgkin's lymphoma (NHL). However, some studies have also found increased risk of NHL from UV irradiance, probably due to immunosuppression by UVA near 370 nm. Several related approaches have also been used to study the hypothesis. Studies in Norway and the UK found that diagnosis in summer or fall is associated with increased survival rates for breast, colon, lung, and prostate cancer, as well as Hodgkin's lymphoma. Diagnosis of nonmelanoma skin cancer is associated with reduced risk of several cancers in sunny countries, but not often in high-latitude countries. Living at higher surface elevation is associated with reduced risk of some cancers. In a recent analyzed study of cancer rates for 54 occupations in Nordic countries, a UVB index based on standardized incidence ratios of lip cancer less those for lung cancer was inversely correlated with 15 types of cancer for males, but only four types for females. This ecological study provides additional evidence that UVB doses at high latitudes are adequate to reduce the risk of cancer, but requires considerable time outside to produce sufficient vitamin D. Because only vitamin D production has been proposed to explain the UVB–cancer link, studies reviewed in this paper should be considered strong evidence for the hypothesis.

Keywords: Breast cancer, Colon cancer, Ecological study, Endometrial cancer, Hill's criteria for causality, Immunosuppression, Melanoma, Non-Hodgkin's lymphoma, Nonmelanoma skin cancer, Nordic countries, Observational study, Randomized controlled trial, Renal cancer, Ultraviolet-A, Ultraviolet-B, Vitamin D.

INTRODUCTION

In 1980, the brothers Cedric and Frank Garland proposed the ultraviolet-B (UVB)–vitamin D–cancer hypothesis after they saw a map of the geographical variation of U.S. colon cancer mortality rates and recognized that the regions of low and high rates were inversely correlated with annual sunlight doses [1]. The hypothesis has since garnered considerable support from additional ecological studies based on geographical variations of cancer incidence and/or mortality rates with respect to indices of solar UVB doses [2-4], observational studies of serum 25-hydroxyvitamin D [25(OH)D] and cancer incidence [5-7], some studies of cancer incidence and/or mortality rates with respect to solar UVB irradiance [8], and randomized controlled trials (RCTs) [9,10]. Also, a good understanding exists of the ways in which vitamin D reduces cancer risk [11-13].

The UVB–vitamin D–cancer hypothesis generally satisfies the criteria for causality in a biological system that A. Bradford Hill [14] established for several types of cancer [15]. The important criteria are strength of association, consistency, temporality, biological gradient, plausibility (mechanisms), coherence, and experiment (RCT). Later work added accounting for confounding factors and removing bias [16]. Not all criteria need be satisfied to claim causality, but the more that are, the better. The evidence supporting the hypothesis has strengthened since the review in 2009. Nonetheless, the UVB–vitamin D–cancer hypothesis has not been widely accepted in medical or public health practice [17,18]. The primary barriers to general acceptance of the hypothesis are the low regard for ecological studies, the limited number of RCTs supporting the hypothesis [9,10], and the failure of many observational studies to find evidence supporting the hypothesis [5,19]. However, the failure of observational studies often relates to the use of a single serum 25(OH)D concentration measured at the time of enrollment, with follow-up periods extending as long as 28 years [20]. Serum 25(OH)D concentrations change over time; a study in Norway found a regression coefficient of 0.42 for measurements in a cohort made 14 years apart [21]. Some reviews have also suffered from reviewer bias [17,22].

Most approaches for studying and evaluating the UVB–vitamin D–cancer hypothesis have been the subject of many reviews. One not reviewed in depth is the relation of personal UVB irradiance cancer risk—which this review addresses.

METHOD AND MATERIALS

Papers for inclusion in this review were sought through a search of the National Library of Medicine's PubMed database (pubmed.gov). The following search terms were used: *ultraviolet cancer* (specific types of cancer were also specified); *skin cancer second cancer*; and *altitude* or *elevation, cancer, risk*. This paper also reports results from my own unpublished work. The papers discussed should be considered representative rather than comprehensive.

RESULTS

The results are given first for several types of cancer, followed by discussions of using survival as a function of season of diagnosis, diagnosis of nonmelanoma skin cancer (NMSC), elevation of residence, and outdoor occupation as an index of solar UVB dose and vitamin D production.

Colon Cancer

Colon cancer has the strongest evidence that solar UVB and vitamin D reduce risk [5,6,11]. Two U.S. studies reported colon or colorectal cancer rates with respect to solar UV irradiance.

The first study significantly inversely correlated colon cancer mortality rates with indices of UV doses. For residence in areas with high versus low solar UV doses, the odds ratio (OR) was 0.73 (95% confidence interval [CI], 0.71–0.74). For outdoor occupation, the OR was 0.90 (95% CI, 0.86–0.94) [8].

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The second study, from the Women's Health Initiative, significantly inversely correlated ambient solar UVB doses in summer with colorectal cancer incidence (OR = 0.40 [95% CI, 0.17–0.93]) for those who had never used hormone replacement therapy or who had before but were not currently. Although personal UV exposure was not (OR = 0.64 [95% CI, 0.30–1.34]), combined personal and ambient UV exposure marginally insignificantly correlated with colorectal cancer incidence (OR = 0.50 [95% CI, 0.24–1.03]) [8]. The study was limited by the small number of cases (47).

Breast Cancer

Breast cancer has the second-strongest support for a beneficial role of vitamin D in reducing risk [5,6]. Many papers reported breast cancer incidence, survival, or mortality rate with respect to indices of UVB irradiance (see Table **1** for representative findings).

The studies reported significant inverse correlations for breast cancer outcome with respect to UV irradiance (except for one study in Norway). Because vitamin D production is the only mechanism proposed to explain sunlight's role in summer in reducing breast cancer risk, these studies strongly support vitamin D's role in this risk reduction. However, melatonin also reduces the risk of breast cancer: one paper noted that breast cancer diagnoses peak in spring and fall, with vitamin D production in summer and melatonin production in winter probably accounting for the findings [30].

Prostate Cancer

Several papers reported risk of prostate cancer incidence or mortality rate with respect to indices of solar UVB doses (Table **2**).

However, meta-analyses of prediagnostic serum 25(OH)D concentration find no significant correlation with prostate cancer incidence [5,6]. Reviews also find little to no effect of 25(OH)D concentrations on prostate cancer incidence [34-36]. However, lower UV irradiance and vitamin D deficiency increases the risk of more advanced prostate cancer [33,36]. U.S. studies found inverse correlations between UV level at place of residence [8,32] but not with respect to outdoor occupation [8]. However, a meta-analysis of several studies found a marginally insignificant benefit of solar UV doses. Ethnic background as a confounding factor may explain some of the correlation in the U.S. studies with UV at place of residence. As explained previously, the U.S. geographical variation of prostate cancer mortality rates [37] correlates reasonably well with ethnic background, as evidenced by country of greatest prevalence by county in 2000 [38]. Prevalence of the apolipoprotein E ε4 allele and diet might explain the geographical variation of prostate cancer in both the U.S. and the world [39].

Non-Hodgkin's Lymphoma

In general, papers report increased incidence rates for NHL for sun exposure in high-latitude countries but reduced rates for sun

Table 1. Breast Cancer Incidence, Survival, or Mortality with Respect to Indices of UVB Irradiance

Location	Condition(s)	Outcome	Findings (95% CI)	Reference
U.S.	Combined recreational and occupational sun exposure	Incidence	RR = 0.50 (0.29–0.86)	[23]
U.S.	High UV residence	Mortality	OR = 0.74 (0.72–0.76)	[8]
	Outdoor occupation	Mortality	OR = 0.82 (0.70–0.97)	[8]
Norway	Diagnosis in fall vs. winter	3-year survival	RR = 0.70 (0.65–0.75)	[24]
California	Light pigmentation, high vs. low sun exposure	Incidence	OR = 0.53 (0.31–0.91)	[25]
Ontario, Canada	Time outdoors >21 h/wk vs. <6 h/wk, teenage years	Incidence	OR = 0.71 (0.60–0.85	[26]
	20s–30s	Incidence	OR = 0.64 (0.53–0.76)	
	40s–50s	Incidence	OR = 0.74 (0.61–0.88)	
	60s–70s	Incidence	OR = 0.50 (0.37–0.66)	
Norway	Vitamin D dose (kJ/m^2)	Incidence	RR = 1.17 (0.94–1.43)	[27]
France	Mean daily UVR dose exposure at place of residence	Incidence	HR = 0.91 (0.82–0.99)	[28]
Nordic countries	Occupation, lip cancer less lung cancer	Incidence	$r = -0.73$, adjusted $r^2 = 0.53$, $p < 0.001$	[29; Grant, submitted]

HR, hazard ratio; OR, odds ratio; RR, relative risk.

Table 2. Prostate Cancer Incidence or Mortality with Respect to Indices of Solar UVB Doses

Location	Condition(s)	Outcome	Findings (95% CI)	Reference
U.S.	High UV residence	Mortality	OR = 0.90 (0.87–0.93)	8
	Outdoor occupation	Mortality	OR = 1.00 (0.96–1.05)	
Norway	Diagnosis in fall vs. winter	3-year survival	RR = 0.70 (0.66–0.74)	24
U.S.	Predicted serum 25(OH)D based in part on solar UVB	Advanced cancer incidence	RR = 0.8 (0.5–1.2)	31
U.S.	High solar UV in state of birth and high solar UV in state of longest residence vs. low and low	Nonfatal and fatal cases	RR = 0.66 (0.47–0.93)	32
	Physician-assessed sun exposure	Nonfatal and fatal cases	RR = 0.78 (0.52–1.17)	32
Meta-analysis multi-country	High vs. low sun exposure	Incidence	OR = 1.13 (0.98–1.28)*	33
	High vs. low sun exposure	Advanced or fatal cancer	OR = 1.14 (0.98–1.33)*	33
Nordic countries	Occupation, lip cancer less lung cancer	Incidence	$r = -0.65$, adjusted $r^2 = 0.41$, $p < 0.001$	29; Grant, submitted

OR, odds ratio; RR, relative risk; *OR > 1.00 indicates beneficial sun exposure.

Table 3. Personal Sun Exposure and Risk of NHL Incidence

Location	Condition(s)	Findings	Reference
UK	Association with solar UV radiation levels	RR = 1.27 (95% CI, 1.24–1.29), rising to 1.34 (95% CI, 1.32–1.37) after adjustment for social class and employment in agriculture	[40]
Sweden	High-exposure in the construction industry	RR = 1.3 (95% CI, 0.9–1.9)	[41]
SW and ACT, Australia	Reported sun exposure hours	ORs for successively higher quarters were 0.72 (95% CI, 0.53–0.98), 0.66 (95% CI, 0.48–0.91), and 0.65 (95% CI, 0.46–0.91) (p_{trend} = 0.01). The association of sun exposure on nonworking days with NHL was stronger; OR for highest quarter was 0.47 (95% CI, 0.34–0.66) (p_{trend} = 0.0001). Risk also fell with sun exposure on vacations; OR for highest quarter 0.60 (95% CI, 0.43–0.85) (p_{trend} = 0.003).	[42]
World	Composite measure of increasing recreational sun exposure,	Pooled OR = 0.76 (95% CI, 0.63–0.91) for the highest exposure category (p_{trend} = 0.01). Protective effect of recreational sun exposure was statistically significant at 18–40 years of age and in the 10 years before diagnosis, and for B-cell, but not T-cell, lymphomas.	[43]
Greece	Children (aged 0–14 years), for an increment of 15 days of sunbathing at seaside resorts	OR = 0.60 (95% CI, 0.43–0.83)	[44]
U.S.	Women residing in areas of high ambient UV radiation (UVB flux >113 R-B count × 10(–4)) compared with those with lower exposure (<113)	Multivariable-adjusted RR for high-UV area at age 15 was 1.21 (95% CI, 1.00–1.47; p_{trend} < 0.01).	[45]
California	Residential UVR levels for teachers	RR for highest vs. lowest statewide quartile of minimum UVR (≥ 5100 vs. < 4915 W-h/m^2], 0.58; 95% CI, 0.42–0.80), especially diffuse large B-cell lymphoma (RR = 0.36; 95% CI, 0.17–0.78)	[46]

OR, odds ratio; RR, relative risk.

exposure in low-latitude countries (see Table **3** for representative study results). Direct correlations with solar UVB were found for the UK, the U.S., and Sweden, whereas inverse correlations were found for Australia, California, Greece, and in a multicountry study—that is, direct correlations in high-latitude countries, inverse correlations in low-latitude countries.

A recent letter to the editor [47] suggested that two effects of UV irradiance are at work with respect to risk of NHL: vitamin D production and immunosuppression. UV can impair the systemic immune system [48,49]. UVA's immunosuppression effects are probably stronger than those of UVB. The action spectrum for immunosuppression includes peaks at 300 and 370 nm [50]. The solar UV dose at 370 nm is much higher than at 300 nm. Sweden and the UK have high ratios of UVA to UVB [51], which may explain the different findings by country in Table **3**. Immunocompromised people have higher risk of NHL [52]. Another recent paper demonstrated that p53 haploinsufficient mice developed B-cell lymphoma by UVB irradiance [53].

Endometrial Cancer

A study in Sweden found that women who used sunbeds more than three times per year reduced their hazard risk (HR) of endometrial cancer by 50% after adjustment for body mass index or physical activity (HR = 0.5 [95% CI, 0.3–0.9]), and those women who were sunbathing during summer reduced their risk by 20% (HR = 0.8 [95% CI, 0.5–1.5]) compared with women who did not expose themselves to the sun or to artificial sun (i.e., sunbeds). Sunbed use in winter may have compensated for lack of sun in winter [54]. Sunbeds used in winter in Norway increased serum 25(OH)D concentrations by 15 nmol/l per session [55].

Renal Cancer

A study in four countries of Central and Eastern Europe (Czech Republic, Poland, Romania, and Russia) found an OR of 0.76 (95% CI, 0.58–1.00), p = 0.05, for renal cell carcinoma for men with the highest tertile of cumulative sun exposure compared with the lowest tertile [56]. A nonsignificant increase was found for women, but the dividing lines between the first and third tertiles varied by only 29%, and the absolute value of the upper tertile was lower than the cutoff for the lowest tertile for men. For Moscow alone, the OR for men was 0.27 (95% CI, 0.15–0.47) for highest versus lowest tertile of sun exposure, with no significant results for women.

Cancer Survival as a Function of Season of Diagnosis in Norway

For most people, solar UVB is the primary source of vitamin D. This is mostly the case in high-latitude countries in Europe [57] due to the 5-month vitamin D winter [58]. It is reasonable that season of diagnosis would play a role in cancer survival in Norway because serum 25(OH)D concentrations are higher in summer than winter, and higher serum 25(OH)D concentrations are associated with better cancer survival for several cancers, including colorectal [59], breast [60], lung [60], and lymphoma [60]. The first paper finding a seasonal variation of cancer survival with respect to season of diagnosis was reported in 2004 for breast, colon, and prostate cancer, with diagnosis in fall providing about a 30% reduction in 3-year survival rate compared with winter diagnosis [24]. These findings were extended to Hodgkin's lymphoma [61] and lung cancer [62], and repeated for colon [63], breast [64], and prostate [65] cancer. Several reviews have presented the findings of these studies [66-68]. Similar findings were reported in England for breast and lung cancer [69].

Nonmelanoma Skin Cancer as an Index of UV Irradiance

Solar UV irradiance is the most important risk factor for NMSC. Integrated lifetime UVB irradiance is the most important risk factor for squamous cell carcinoma (SCC) [70], with smoking also playing a role [71]. Sporadic UV irradiance seems to be more important for basal cell carcinoma (BCC), but chronic UV irradiance also plays a role [70], with smoking apparently not playing a role [71]. Thus, personal or cohort diagnosis of NMSC can serve as an index of integrated UVB irradiance. Diagnosis of melanoma cannot, partly because UVA [70] and sunburning [72] are important risk factors, whereas chronic UVB irradiance can reduce risk [73,74], as can vitamin D [75].

A meta-analysis of cancer incidence in cohorts with respect to diagnosis of BCC and/or SCC—corrected for smoking in the cohort using lung cancer incidence rates as the index of smoking—found inverse correlations for several types with NMSC for several cancers [76]. As stated in the abstract:

For a diagnosis of squamous cell carcinoma, RRs for subsequent colon, gastric, and rectal cancers were significantly reduced, with that for renal cancer being marginally insignificant. For NMSC, RRs for cervical, esophageal, gastric, and rectal cancer were significantly reduced; those for colon and gallbladder cancer were marginally insignificant, while those for female breast, laryngeal, ovarian, renal, and uterine corpus cancers were insignificantly reduced; RRs for lip and salivary gland cancers and melanoma were significantly increased [76].

A record-linkage study of BCC, SCC, and melanoma with solid cancers was reported for sunny countries (Australia, Singapore, and Spain) and less sunny countries (Canada, Denmark, Finland, Iceland, Norway, Scotland, Slovenia, and Sweden). For the sunny countries, diagnosis of NMSC significantly inversely correlated with later diagnosis of liver, pancreatic, and prostate cancer, and insignificantly inversely correlated with bladder, colon, gastric, ovarian, rectal, and renal cancer [77]. All cancers included in that study were directly correlated with BCC and SCC in less sunny countries. Both smoking and ambient temperature, which influenced the amount of body surface area exposed to the sun, may have affected the findings [78]. A later review noted that few studies found an inverse correlation between diagnosis of NMSC and other cancers [79]. Most of those studies were from less sunny countries, in agreement with the findings by Tuohimaa and colleagues [77]. However, two studies did find significant inverse correlations for colorectal and prostate cancer for those diagnosed with NMSC in the Netherlands [80,81]. A recent study from Sweden found slightly increased risks for colon, prostate, breast, and ovarian cancer for those diagnosed with BCC, with no increased risk for pancreatic and gastric cancer [82].

Residence Elevation as an Index of UVB Irradiance

Solar UVB doses increase by 15% per kilometer of elevation [83]. Rising 1 km in elevation is approximately the same as moving south by about 4º latitude (280 miles) in the middle of the U.S. in summertime [84]. Thus, we would expect that those living at higher elevations would have lower cancer rates, other factors being equal. Hayes [83] explored this hypothesis. He reviewed seven epidemiological studies, primarily ecological, reporting that higher residential elevation was associated with lower cancer mortality rates. One study in that review, for lung cancer with respect to elevation of counties in the U.S., proposed "carcinogenic effect of higher absolute oxygen concentration in the inspired air at lower elevations" [85], which has not been confirmed in subsequent studies.

OCCUPATION AND CANCER RISK IN NORDIC COUNTRIES

Solar UVB doses in Nordic countries are relatively low, and the region has about a 5-month vitamin D winter [58]. Thus, finding studies showing a beneficial effect of solar UV irradiance in reducing risk of cancer is more difficult. Such studies in Nordic countries have generally found limited benefits, if any [86,87]. Studies of cancer survival with respect to season of diagnosis have found benefits for several cancers, as already noted. Recently I found a paper tabulating cancer standardized incidence ratios (SIRs) for many cancers by sex and 54 occupation categories on the basis of 1.4 million male and 1.36 million female cancer cases for 1961–2005 in the five Nordic countries [29]. An ecological study used a UVB index based on the data in that study. Lip cancer SIRs less lung cancer SIRs (to correct for smoking) for men were the best index of solar UVB dose, which was inversely correlated with both melanoma and NMSC SIRs for males. Lung cancer SIRs were used as the index of the effects of smoking. For men, the UVB index was significantly inversely correlated with 14 types of internal cancers: bladder, breast, colon, gallbladder, kidney, laryngeal, liver, lung, oral, pancreatic, pharyngeal, prostate, rectal, and small intestine cancer. For women, the same UVB index was inversely correlated with bladder, breast, colon, and rectal cancer [29]. These results generally agree well with findings from ecological and other studies.

DISCUSSION

Studies of personal or cohort UV irradiance and cancer outcome offer an important bridge between ecological studies based on geographical location and observational studies based on serum 25(OH)D concentrations. From the analysis presented in this review and its citations, very good evidence exists that solar UVB irradiance reduces the risk of many cancers. Those cancers with the strongest evidence tend to be those with higher incidence and/or mortality rates because it is easier to obtain enough cases to yield robust statistics [88].

On the basis of relations between serum 25(OH)D concentrations and breast and colorectal cancer incidence, the apparent optimal serum 25(OH)D concentration for cancer prevention is 100 nmol/l [5]. Because the global 25(OH)D concentration is around 50–55 nmol/l [89], and because many cancers have similar geographical variations in U.S. mortality rates [90,91], raising serum 25(OH)D concentrations would greatly reduce cancer incidence and mortality rates. Because vitamin D also reduces the risk of other chronic and infectious diseases, raising serum 25(OH)D concentrations at the population level to more than 100 nmol/l would reduce mortality rates by an estimated 10%–20% and increase life expectancy by 2 years [92]. A meta-analysis of all-cause mortality rate with respect to premortality serum 25(OH)D concentrations [93] supports this hypothesis.

The results from personal UV irradiance agree well with those from ecological studies [4]. However, prospective observational studies with respect to prediagnostic serum 25(OH)D concentration often fail to find a significant inverse correlation, such as for breast cancer with follow-up times greater than about 3 years [20] or rarer types of cancer [19]. Such prospective studies can fail to find a significant inverse correlation with respect to serum 25(OH)D concentration because serum 25(OH)D concentrations change with time [20]. In one study, the correlation coefficient between measurements of a cohort measured 14 years apart in Sweden was 0.4 [21]. A recent update of this suggestion found that the inverse correlation between all-cause mortality rate and prediagnostic serum 25(OH)D concentration [94] varied from 0.72 (95% CI, 0.50–1.03) with 5 years of follow-up to 0.92 (95% CI, 0.89–0.95) for the average of the 12 studies [95].

No factor other than vitamin D production has been proposed to explain the link between solar UVB irradiance and cancer risk. A large body of observational studies and two randomized controlled studies support the role of vitamin D in reducing risk of cancer [5,9,10,15,20]. However, it is conceivable that other effects of sunlight are involved. One possible confounding factor is physical activity because when in the sun, people are generally active. Physical activity does lower the risk of cancer [96,97]. However, geographical variations in cancer incidence and/or mortality rates have not been reported as significantly correlated with physical activity levels in general.

NOTE

After submission of this paper, a paper was published providing additional support to the role of solar UVB in reducing risk of cancer [98]. The paper reported results of a prospective study of cancer incidence with respect to solar erythemal (includes both UVA and UVB) doses in July for people living in seven U.S. states. During a mean follow-up period of 9.07 years, there were 75,917 incident cancer cases arising from 450,934 included participants. Significant inverse correlations were found for bladder, colon,

adeno and squamous cell lung, pleural, prostate, kidney cancer and non-Hodgkin's lymphoma. Indications of reduced risk were also found for pancreatic and thyroid cancer. As expected, melanoma rates were significantly increased as solar UV doses increased.

SUMMARY AND CONCLUSION

This brief review found strong evidence for a beneficial role UVB irradiance in reducing risk of many cancers. The findings from UVB irradiance studies generally agree well with those from ecological studies. However, these results are not always well supported by observational studies with respect to prediagnostic serum 25(OH)D concentrations, probably due to using only a single serum 25(OH)D value from the time of enrollment with a long follow-up time. Further reflection on findings to date and additional research results should soon lead to acceptance of the UVB–vitamin D–cancer hypothesis.

DISCLOSURE

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CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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Declared none.

ABBREVIATIONS

25(OH)D	=	25-hydroxyvitamin D
BCC	=	Basal cell carcinoma
CI	=	Confidence interval
HR	=	Hazard ratio
NHL	=	Non-Hodgkin's lymphoma
NMSC	=	Nonmelanoma skin cancer
OR	=	Odds ratio
RR	=	Relative risk
SCC	=	Squamous cell carcinoma
SIR	=	Standardized incidence ratio
UV	=	Ultraviolet
UVA	=	315–400 nm
UVB	=	290–315 nm

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