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SOLAR ULTRAVIOLET EXPOSURE AND MORTALITY FROM SKIN TUMORS

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Abstract

Solar UV radiation (UVR) exposure is clearly associated with increased mortality from nonmelanoma skin cancer—usually squamous cell carcinoma. However, the association with cutaneous melanoma is unclear from the evidence in ecologic studies and several analytic studies have conflicting results regarding the effect of high levels of intermittent UV exposure prior to diagnosis on mortality. Understanding this conundrum is critical to present coherent public health messages and to improve the mortality rates from melanoma.

INTRODUCTION

Solar Ultraviolet Exposure

Solar ultraviolet radiation (UVR) exposure can be measured in a multitude of ways, but there is no “gold standard” applicable to epidemiologic studies of incidence and mortality at the moment. This problem leads to the lack of consistent observations regarding mortality from skin cancer that currently exist in the literature. Solar UVR exposure consists of two broad types of wavelengths—UVB (280–320 nm) and UVA (320–400 nm). UVB at ground level is reduced by its passage through the thin stratospheric ozone shield around the earth at 10–16 km above the earth’s surface and by factors in the atmosphere, such as cloud cover, pollution and water vapor. UVA is not substantially modified by stratospheric or atmospheric conditions and accounts for approximately 90% of UVR reaching the earth’s surface. Another measure utilized is erythemal UV irradiance, a measure of spectral irradiance between 250 and 400 nm weighted for UV by erythema-inducing capacity in human skin.

Measurement

Multiple studies use an “ecological” approach to assessing the role of sunlight and mortality from cancer, particularly melanoma. However, both latitude and satellite measures can only measure **potential** exposure at the site and do not take into account a particular individual’s characteristics or behavior. Using latitude alone also ignores the complexity of other

geographic factors that modify solar UV exposure, such as altitude and cloud cover. On the other hand, latitude is a static variable and is readily available for ecological analyses.

Ground Level Meter Readings

Robertson-Berger meters have been placed at ground level at various weather stations throughout the world and give readings for the erythral action spectrum. Unfortunately, these are not often calibrated and so the readings are somewhat suspect.

Satellite Measures and Mathematical Algorithms

Several algorithms using satellite measures have been used and are generally considered more accurate than the Robertson-Berger meter readings. Satellite measures and mathematical algorithms have advantages over latitude in that they also can take into account variations in the Earth-Sun distance, cloud cover, ozone column and surface elevation.

Self-Reported Outdoor Activities

Occupationally associated UV exposure is generally determined by a combination of an individual's self-reported occupation—either as a history or as that occupation engaged in for the longest period. This information is then often converted by an occupational hygienist into an exposure matrix and a summary variable of exposure is generated. Recreational UV radiation exposure is also determined from numerous self-reported activities, time outdoors, and combinations thereof.

Combination of Satellite Measures and Self-Reported Outdoor Activities

Perhaps the most rigorous estimation has been published by Kricker et al.¹ where a number of types of exposures are presented in relation to risk of melanoma, including: potential lifetime and early life ambient erythral UV exposure estimated using lifetime residential history and a satellite-based model, and history of sunburns, holiday hours in sunnier climates, and hours in outdoor beach and waterside recreational activities. Less rigorous algorithms often use latitude of current residence **combined** with beach activities, or another similar combination.

OBSERVED RELATIONSHIPS FOR NONMELANOMA SKIN CANCER

The relationships for solar exposure and mortality in nonmelanoma skin cancer—squamous cell carcinoma and basal cell carcinoma—seem to be more straightforward than for melanoma skin cancer. That said, it should be pointed out that most deaths from nonmelanoma skin cancer are from squamous cell carcinoma; few individuals die of basal cell carcinoma. Possibly because there is a somewhat linear relationship between solar UV light exposure and squamous cell carcinoma, there is a consistent association between any of the measures of solar UV radiation and mortality from squamous cell carcinoma. However, this relationship is not so clear for melanoma skin cancer.

An analysis of solar UV radiation and nonmelanoma skin cancer comes from a death certificate based study² in which usual occupation derived from death certificates was the

surrogate for occupational sunlight exposure, and 24 states were categorized as low, medium or high residential exposure using data from the United States Weather Bureau. Analyses were controlled for age, sex, race, physical activity and socioeconomic status. These data show for Caucasians that living in a state with “high” UV radiation increased mortality from nonmelanoma skin cancer significantly (Odds Ratio [OR] 1.23, 95% Confidence Interval [CI] 1.14–1.33) and that having an outdoor occupation also increased the mortality from nonmelanoma skin cancer significantly (OR 1.30, 95% CI 1.14–1.47). This study illustrates the problems with ecological analyses, even though it was based on individual death certificates. There is always the potential misclassification of underlying cause of death, occupation, and residential exposure. Lifetime residential history, individual behaviors, and accurate measures of ground level UV radiation are unavailable in such a study.

A more sophisticated analysis of cancer mortality and latitude was conducted by Grant³ using Spanish data. He concluded that data on the latitudinal gradient for melanoma and nonmelanoma skin cancer distinctly differentiates the two cancers, and that nonmelanoma skin cancer mortality is a good proxy for chronic solar exposure, whereas melanoma is due to intermittent sun exposure and thus an analysis based on latitude alone will not capture this type of exposure. Further, in Spain at least, latitude seems to correlate more strongly with smoking than with sun exposure in the association with nonmelanoma skin cancer. In Spain, melanoma mortality was inversely but not significantly associated with latitude. An important and highly salient point made by Grant, using the 2002 International Agency for Cancer Research Globocan data, is that melanoma mortality rates increase with increasing latitude from those living in their ancestral homelands, but rates decrease with increasing latitude for pale-skinned populations who have migrated to countries such as Australia, New Zealand, Israel and the United States.

Interest has focused on nonmelanoma skin cancer among subgroups such as blacks. Pennello et al.⁴ compared non melanoma skin cancer rates among whites and blacks using Robertson-Berger meter readings as the exposure variable. Although there is a trend for mortality among whites by UVB tertile, there is no clear trend for blacks. White males move from 0.83 deaths per 100,000 in the lowest tertile to 1.19 in the highest and, similarly, white females move from 0.39 in the lowest tertile to 0.49 in the highest. However, although black males do move from 0.58 deaths per 100,000 in the lowest tertile to 0.68 in the highest, the trend is not linear. The trend is even flatter for black females moving from 0.37 in the lowest tertile to 0.39 in the highest.

OBSERVED RELATIONSHIPS FOR CUTANEOUS MELANOMA

Ecologic Studies

As stated above, ecologic studies are subject to many unknown biases. However, they can also provide insights into scientific problems and so have some utility. In the area of melanoma mortality there are few large studies that have been conducted, so the large databases maintained by the US. SEER program and the WHO database can be helpful to evaluate trends over time and by latitude. Lemish et al.⁵ observed that survival from melanoma increased with increasing melanoma incidence among several populations and suggested that high levels of ambient sun exposure might induce a more biologically benign

type of melanoma. Recent data evaluating a very large number of populations support this association between the positive temporal and geographic association with incidence and survival.⁶

Conflicting analyses, however, occur. For example, two studies have found **no** association between latitude or other measures of UV exposure and mortality from melanoma in the US,^{7,8} and Bulliard et al.⁹ reported a positive association between increasing latitude (decreasing UV) and increasing melanoma rates in New Zealand. The mean percentage increase in mortality rates per degree of latitude ranged from 0.27% to 4.01%. On the other hand, two other studies have found a **positive** (or inverse) association^{10,11} between melanoma mortality and latitude. An important difference among these studies, however, is that Lachiewicz evaluated individual tumor characteristics whereas Boscoe and Schymura only evaluated latitude and mortality without adjustment for critical covariates that can be obtained from the SEER registries, as their analysis evaluated multiple cancers. Clearly, the more refined and specific data analysis is likely to be more informative. Finally, WHO data, Garland et al.¹² found a strong **negative** association between melanoma mortality and UVA as well as UVB in 45 countries.

A different measure of previous sun exposure derived for ecologic study is season of diagnosis. Seasonality of mortality has been shown to be associated with melanoma mortality in one study. Boniol et al.¹³ found that in Australia those diagnosed in the summer had a significantly reduced risk of dying from melanoma compared with those diagnosed in the winter (HR = 0.72, 95% CI = 0.65–0.81). In contrast, Shipman and colleagues¹⁴ evaluated melanoma mortality in Europe in terms of sunhours. They reported that there was an inverse association, so that there is higher mortality at higher latitudes. These conclusions are more in line with a report from Spain¹⁵ which showed a significant association between diagnosis in July and August (the Spanish summer) and mortality from melanoma. In the United States, Woodall et al.¹⁶ found no difference in survival between individuals from the Sunbelt Trial who lived in Northern States or Southern States. Finally, another report from Australia¹⁷ also found that no association between season of diagnosis and survival from melanoma in Victoria. These authors point out that Victoria is further from the equator than New South Wales and that any strong relationship between season of diagnosis and melanoma survival should be even more marked than found by Boniol et al. Clearly, the weight of the evidence for melanoma in these ecological studies does not support a role for diagnosis during the summer and improved survival.

Occupation is sometimes used as a surrogate for solar exposure. Gass¹⁸ reported that in Switzerland, occupation outdoors was slightly protective for mortality from melanoma, whereas indoor workers had an increased risk, consistent with meta-analyses of incidence.^{19–21}

It is clear that despite the complexity and inherent bias in ecologic studies that the preponderance of the evidence upholds Lee's^{22,23} projections - that the upward gradient noted by Elwood in 1974 has been decreasing since 1950 and that rates of mortality in the contiguous US would be unaffected by latitude by the early 21st Century. A study by Fears et al.²⁴ suggests that ecological data assigning UV exposure to an individual based on the

place of diagnosis (or by inference death) is more likely to be measuring current rather than lifetime UV exposure. He found that among melanoma patients studied at sites in Philadelphia and San Francisco only 13% had spent their life at the residence of diagnosis. Most participants had spent only about half their life at the place of diagnosis.

No particular associations between measures of UV and melanoma mortality were noted by Page²⁵ when evaluating deaths from melanoma among WWII veterans of the Pacific and the European theaters, or by Larsen²⁶ in evaluating associations among histology, survival and solar elastosis—a marker of sun damage and a large study of mortality among children and UV levels found no association with UV irradiance and the hazard of dying from melanoma.

So, in summary, the ecologic studies are mixed in their results, but the weight of the evidence no longer supports a strong positive association between latitude or UV exposure, regardless of how measured, and mortality from melanoma (Table 1).

Analytic Studies

Unfortunately, few analytic studies have interviewed patients for sun exposure and residential histories and then followed subjects for mortality (Table 1).

Berwick et al.²⁷ reported an inverse association between measures of solar exposure and melanoma mortality among a population of 528 subjects who had been interviewed within 3 months of diagnosis and then followed for a mean of 5 years for mortality. Variables associated with sun exposure over a lifetime were inversely and significantly associated with mortality from melanoma in univariate analyses: A history of ever having been severely sunburned, a history of high levels of intermittent sun exposure and the presence of any solar elastosis in the matrix surrounding the lesional biopsy. This study was unique in that individual level characteristics of surveillance were carefully and thoroughly collected: skin self-examination practices, physician skin examination and skin examination by a partner, as well as “awareness” of skin. A self-reported awareness of skin for cosmetic or medical reasons resulted in a reduced risk of dying from melanoma. The authors suggested that this provocative finding might be related to this beneficial effect of sun exposure in relationship to survival with melanoma could be mediated by vitamin D. Alternative hypotheses were also offered: that previous sun exposure might induce more indolent melanomas through increased melanization and DNA repair capacity.

Interestingly, Heenan²⁸ published a somewhat similar analysis among 486 subjects diagnosed with melanoma in 1980/1981. In their univariate analyses, they found that solar elastosis was of borderline significance (P for trend = 0.07) and inversely associated with death from melanoma: Mild solar elastosis resulted in a rate ratio of 0.64 (95% CI = 0.30–1.37) and severe solar elastosis a rate ratio of 0.46 (95% CI = 0.19–1.12), and because of the borderline significance, this variable was not included in multivariate analyses. This study is the only other epidemiologic study evaluating melanoma mortality and solar elastosis in the literature and, interestingly, had very similar findings to the Berwick paper.

Rosso et al.²⁹ have also suggested that intense intermittent sun exposure prior to the diagnosis of melanoma is associated with an improved survival. They found that intermittent

sun exposure (time spent over a lifetime at the beach) was inversely associated with risk of death from melanoma (HR = 0.41 95% CI = 0.17 to 0.98).

A study from the UK measured serum vitamin D at diagnosis and found that those with the highest level of serum vitamin D had the best survival.³⁰

To add to the confusion, Berwick and colleagues³¹ have now analyzed survival data from a very large international cohort of melanoma patients and find that there is no association between sun exposure prior to diagnosis and melanoma survival. This study, GEM (Genes, Environment and Melanoma) used similar measures to the Connecticut study as well as new and well-validated measures of sun exposure. This seems like a reasonable conclusion given the mixed evidence presented above.

In summary, the analytic studies evaluating mortality in relationship to solar exposure prior to diagnosis have quite mixed results. The discrepancy among studies is worth of further investigation. Analytic studies are generally considered to be more valid than ecologic studies and could come up with different interpretations of data because they may suffer less from misclassification of solar UV and the measures of individual sun exposure are more precise than those estimated by latitude.

POTENTIAL MECHANISMS

If UV exposure prior to a diagnosis of melanoma is protective, then there are multiple hypotheses as to how that could happen. Sun exposure prior to the diagnosis of melanoma, i.e., lifetime exposure, may lead to the development of less aggressive melanomas,⁵ and potentially increases DNA repair,³² and possibly the higher levels of serum Vitamin D stimulated by the UVB exposure delay tumor onset. In addition, sun exposure after diagnosis—or near the time of diagnosis—may increase serum levels of Vitamin D that may limit tumor progression. To know how UV is associated with incidence and mortality we need to rely on a more clear understanding of the biology of melanoma progression. Thus, none of the ecological studies are necessarily in conflict if in fact the temporal relationship of sun exposure to melanoma differs by incidence and mortality. Unfortunately, this is an area where we have little hard evidence. There is evidence both for and against the hypothesis that sun exposure plays a protective role.

Vitamin D. 25-hydroxy vitamin D₃ has antiproliferative and proapoptotic effects.^{33,34} UVB induces serum vitamin D yet it also plays an important role in the development of melanoma. Possibly the circulating vitamin D levels are insufficient to reduce the risk of developing melanoma, particularly as melanocytes may have been programmed toward the development of melanoma quite early on. However, perhaps sun exposure does increase the protective reaction³⁵ of tanning and enhanced DNA repair capacity, in combination with the antiproliferative and proapoptotic effects of vitamin D, so that in combination, these factors are able to keep the invasive lesion “in check.” Evidence for the vitamin D theory suggests vitamin D limits tumor progression—perhaps people with melanoma stay out of the sun during and following melanoma diagnosis; thus they do not receive the survival benefit (this would correspond to Boscoe’s study examining **current** environment risk factors, all ecological). Since migration is so frequent, we would expect ecological data (like assigning

UV to SEER sites) to measure current sun exposure as well. Garland's study, on the other hand, although ecological as well, might be capturing lifetime exposure as well as current exposure if people are less likely to migrate between countries than within countries.

Thus, none of the ecological studies are necessarily in conflict with the Berwick study finding that solar elastosis may be an independent indicator of better survival, if in fact they are measuring two different temporal aspects of sun exposure.

CONCLUSION

Clearly, there is much more to understand about the specific wavelengths involved in the development and progression of cutaneous melanoma and clearly sun exposure is a classic "two-edged sword." Data to date are only provocative and not convincing. If we assume that most ecological studies are measuring current UV exposure rather than lifetime exposure, the null or positive associations between melanoma mortality and UV exposure could be due to (1) a tendency for melanoma patients to tend to avoid sun exposure following diagnosis so they are not getting the benefit from Vitamin D, (2) a lack of variability in Vitamin D levels among melanoma patients (e.g., light pigmentation or sun avoidance) to detect any association with vitamin D levels, or (3) the fact that melanoma is a cancer, like renal cell carcinoma, more responsive to immune system response than other cancers; thus the rationale for interferon therapy and the occurrence of vitiligo among melanoma patients. It is possible that the effect of a UV-induced decrease in cellular immunity negates any benefit from Vitamin D antiproliferative and proapoptotic effects.

Much more work needs to be performed to elucidate the effects of solar UV on melanoma development and progression before any conclusions can be drawn. Unfortunately, these data indicate that our public health messages—which are already confusing ("wear sunscreen all the time and stay out of the sun"—vs. "some sun is good for you")—are not biologically driven and in order to stem the rising incidence of melanoma, it is critically important to understand better the basic biology of the disease.

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Table 1

Melanoma mortality and sun exposure

Author, Year	Country or Population	Time Period	Number Followed	Number of Deaths or Mortality Rate /100,000	Comments
Jayeskara 2011	Australia Victoria	1986–2004	26,060		Summer to winter ratio 1.46 (95% CI 1.41, 1.52) (opposite findings to Bontiol)
Shipman 2011	Europe	2002	Population of European countries	Differed by country. Correlation of -0.43 F, -0.37 Mortality by latitude	Concluded that sunlight has a minor role in melanoma mortality
Woodall 2009	United States	1997–2003	2,025		This study divided patients with 1 mm by No or So residence and found no difference in survival
Bontiol 2006	Australia New South Wales	1989–1998	10,869 F 14,976 M	2,710 (10.5%)	Fatality for melanoma lower for that diagnosed in summer than winter 0.72 (0.65–0.81)
Boscoe FP 2006	United States	1993–2002	3 million Incidence 0.72 M 0.78 F	Mortality 0.7 M 0.83 F	Paper relates UV exposure and cancer incidence on population bases. UV exposure was positively associated with melanoma.
Lasithiotakis K G 2006	Germany	1976–2003	1980	1.5–0.8 M 2.6–0.8 F	Incidence of cutaneous melanoma tripled, mortality was reduced. Superficial spreading melanoma (associated w/ intermittent sun exp) increased. Lentigo maligna melanoma (as w/ hvy chronic exp) didn't show trend.
Coory, M 2006	Queensland	1982–2002	33,393 invasive melanoma 12,313 in situ lesion	200/yr	In situ lesions increased at faster rate than invasive melanomas. Thin-invasive, increased faster than thick-invasive melanomas. Mortality rates: flat trend in males and decreased for females.
Whiteman DC 2006	Queensland		154 superficial spreading 76 Head and neck 76 Lentigo maligna and lentigo maligna melanoma		Melanomas of head and neck are associated with chronic patterns of sun exposure whereas trunk melanomas are associated with intermittent patterns of sun exposure, supporting hypothesis that melanomas may arise through divergent causal pathways.
Stang A 2006	Lithuania	Incidence 1978–2002 Mortality 1990–2002	3485 skin melanoma	1.2–2.3 M 1.7–2.2 F	Incidence rates increased. Mortality rates increased. Relative 5 year survival rates among men were 10% lower than women. Favorable survival for women 60–74 years age.
Cockburn M 2006	Hispanic population of California	1988–2001	1520 M 2234 F with melanoma	1–1.3 M 0.6–0.8 F	Increase in mortality for M and F Hispanics. Slight declines in melanoma mortality in non-white Hispanics. Increase incidence of invasive and in situ melanoma in M and F
de Vries E 2006	European children	1978–1997	1419 melanoma 485 skin carcinoma	Incidence 4.1% melanoma	British Isles had highest incidence of skin cancers. In Europe, melanomas were more common in North

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Lee EY 2006	Brisbane, Australia	1998–1999	141	2.5% skin carcinoma	and West. Skin carcinomas in South and East. High levels of sun exposure strongly predicted dermal elastosis for head and neck melanomas but not of the back. Results: melanomas w/ different histological characteristics have different risk factor profiles, particularly on head and neck; melanomas arise through different causal pathways.
Strouse, JJ 2005	US children (age < 20yrs)	1973–2001	1,255 children 2,673 young adults	Incidence increased 46% per yr of age and 2.9% per yr.	Incidence rates lower in M than F. increased ambient radiation was associated with higher risk. The hazard ratio of death increased with male sex and older age.
Buettner PG 2005	Germany	1976–2000	45,483 cutaneous melanoma	Adjusted survival rates Females did not increase ($p = 0.1561$) Males did increase ($p < 0.0001$)	Median tumor thickness decreased 1.81–0.53mm. % of ulcerated CM decreased ($p < 0.0001$). superficial spreading melanoma increased, nodular melanoma decreased ($p < 0.0001$)
Cayuela A 2005	Spain	1975–2001		0.3–1.4 M. No corresponding date for F	Survival of W 84.3%, M 74.8%
Stracci F 2005	Umbria, Italy	1978–82 1994–98		Incidence rates per 100,000 Italy 1994–98 M8.5; F1.9 Australia and NZ M27.9; F25 N America M10.9; F7.7	
Levi Fab 2005	Vaud and Neuchatel, Switzerland	1978–2002		Age-standardized world incidence increased 5.7–16.8 M 7.9–18.7 F	Upward trends observed for lentigo maligna and superficial spreading melanoma. Increased survival rates b/c of rise in superficial spreading which are thinner.
Eide MJ, 2005	US Nonwhite populations	1992–2001	1515 white Hispanics 293 black, 57 Native American, 492 Asian/Pacific Islanders, 2167 unknown race	Age-adjusted incidence rate 4.1 white hispanics, 1.0 blacks, 2.0 for Native Americans, 1.5 Asian/Pacific Islanders	Negative, not significant, correlations with incidence were observed in blacks ($r = -0.53, p = 0.10$) Hispanics ($r = -0.43, p = 0.19$) Asians ($r = -0.28, p = 0.41$). Latitude had a significant correlation with incidence on in non-hispanic whites ($r = -0.85, p = 0.001$)
Siskind V 2005	Queensland	1982–1990	2360 cutaneous melanoma		Observed in study was heterogeneity for melanoma risk by anatomical site, lending weight to the hypothesis that cutaneous melanomas may develop through multiple causal pathways.
Gass R 2005	Switzerland males			Mortality rates 1979/83 and 1997/2001 in M (35–44 years) diminished by 66% ($p < 0.02$)	Analysis of mortality by occupational groups shows indoor workers males have increased risk. Outdoor workers with chronic sunlight exposure are slightly protected.

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Hu S 2004	US Blacks and Hispanics		64,305	Incidence was positively associated with UV index, negatively associated w/ latitude of residency.	Statistically significant correlation between melanoma and UV index ($R = 0.93$; $p = 0.01$) and latitude, ($R = -0.8$; $p = 0.05$) in blacks
Hallberg Ö 2004	Sweden	1910–2000		Deaths increased 22% in 1955	Paper shows strong correlation between the start of FM broadcasting and increased mortality from melanoma. The environmental factor to radio frequency is electromagnetic radiation.
de Vries E 2004	Europe	2000	26,100 M 33,300 F	8,300 M 7,600 F Deaths	In the US a person dying of melanoma would die approx 17 years before age 65, in Denmark 14–15 years and in Belgium 6–8 years. Incidence rates increased markedly for the intermittently exposed body sites (trunk and legs) whereas increases on face and neck were moderate. Mortality rates have stabilized in high incidence countries: Australia, US, Sweden, Norway and Germany. Changes in biology of the melanoma w/ less aggressive lesions could be consistent with a continuing increase in incidence, with moderation in mortality rates.
Ulmer MJ 2003	Saskatchewan	1970–1999			# of patients registered increased during study period. Increase was greatest for thin lesions in all age groups. Head and neck tumors showed continual risk w/ increasing age. Mortality rates in F have been stable over time but increased for M in 1990s.
Pennello G 2000	US Blacks	1970–1994			Age-adjusted risk of mortality for 50% increase in UVB radiation significantly above 1 for malignant melanoma for M. for both M and F relative risk of incidence was not significantly elevated 1973–94.
Page WF 2000	WWII Veterans of Pacific and European theaters	50 year follow up	9237 male	18	Prisoner Of War (POW) status is associated with high levels of solar radiation. POW higher cumulative risk of melanoma death.
Jemal A 2000	White population United States	1950–1959 1990–1995		0.08–0.01 F 0.11–0.12 M	Mortality reflects sun-protection behaviors, geographic region, geographic mobility of population and risk awareness and early detection.
Bulliard JL 2000	New Zealand	1968–1993	16,117 cases 3,150 death records	Age-standardized rates highest for trunk in M and lower limbs in F.	Melanomas occurred at a substantially younger age on intermittently exposed sites than chronically exposed one. Age and latitude influence rates in sex- and site-specific fashion. Results confirm that intermittent exposure is probably more effective than continuous exposure in producing an early onset melanoma.

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Gruijl FR 1999					Skin cancer is most common type of cancer in US and Australia, a result of unnatural displacement of people with sun sensitive skin to sub-tropical regions.
Hall HL 1999	US whites	1973–1994			Incidence increased 120.5% Mortality increased 38.9%. M have higher incidence and mortality than F. largest increases by site was on trunk of M and F
Lee JA 1997	US whites	1950–1992			Upward gradient of mortality from north to south has been decreasing since 1950. rates of mortality in contiguous US expected to be unaffected by latitude.
Thom M 1992	Sweden	1953–1987	6,324	Age-standardized rates increase 1.1–4.0 M 1.0–2.6 F	Risk of dying increased in M for birth cohorts up to 1932, in F rise continued for cohorts of 1947. Avg annual increase leveled off in M to 2% in 1978–1987; in F to 0%
Roush GC 1992	US, Connecticut				Long-term patterns of change are best described by birth cohort. In M and F evidence for change in slope begins in cohort born in early 1930s. Decline in rates in F cohort begins early 1930s; in M cohorts since 1950s. incidence rates showed persistent increase in cohort born 1955–1965. Analysis suggest downward trend in death rates.
Scotto J 1991	Whites in US	1950–84			Risk of dying peaked in M born cohorts in 1950s; F born in 1930s. Incidence data from 1973–84 shows age-specific rates are comparable to those observed for mortality during overlapping time period.
Suarez-Varlea MM 1990	Spain	1975–1983			Statistically significant relation observed (p less than 0.05) in mortality and solar radiation during July and August. Paper suggests intermittent, intense sun exposure is important risk factor. Increased mortality 8.5% during time period. Mortality higher in M.
Devesa SS 1987	Whites in US	1940–1984			Melanoma and multiple myeloma increased greatly until early 1980s in male and female. Greater increase of melanoma incidence in males than that for lung cancer. Increased rate of multiple myeloma mortality in females, exceeded that of lung cancer.
Holman CD 1980	Australia	1931–1977		Age-standardized rates increase 0.8–4.2 M 0.6–2.5F	Mortality rates highest in Queensland. Its suggested that the cohort-based increase in mortality resulted from life-style changes.
Lee JAH 1979	England, Wales, Canada and US whites.	1951–1975			Increase in age adjusted death rates by 3%/yr.

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Larsen TE 1979	Scandinavia		669 w/ primary cutaneous malignant melanoma stage I.		Study does not permit conclusions about possible causal relationship between 3 types of melanoma and previous sun-exposure b/c of lack of clinical info and control series concerning solar elastosis in normal pop.
Elwood JM 1974	US and Canada	1950–1967			The rates of mortality rate w/ latitude are similar in each sex, greater in males than females. Strong negative assoc w/ latitude, similar degree of correlation w/ mortality rates.