Regional Correlation Between Estimated UVB Levels and Skin Cancer Mortality in Japan

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Most ecological studies investigating the relationship between incidence and/or mortality of skin cancer and surrogate measures of ultraviolet radiation B (UVB) have been conducted among the Caucasian population. The objective of the present study was therefore to assess the geographical correlation between ambient UVB estimates and regional mortality rates for skin cancer in Japan. The standardized mortality ratio (SMR) for malignant melanoma and other malignant neoplasms of the skin was calculated by sex, region and time-period for all deaths occurring in the period 1973-1994. The Spearman's correlation coefficient was calculated between estimated ambient UVB and regional SMRs for the two types of skin cancer. There was no geographical correlation between UVB and skin cancer mortality, except for a significantly negative correlation in malignant melanoma among males and a significantly negative correlation in other malignant neoplasms of the skin confined to unexposed anatomic sites of the body among females. The characteristic ecological relationship adds to the importance of conducting further epidemiological studies at the individual level in Japan. (165 words)
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The International Agency on Research on Cancer (IARC) has concluded that there is sufficient evidence in humans for the carcinogenicity of solar radiation in causing cutaneous malignant melanoma and nonmelanocytic skin cancer [1]. Ultraviolet radiation B (UVB) is implicated as an important, if not the sole, causal component of solar radiation. Many ecological studies, along with case-control studies, have been included in the evaluation of human carcinogenicity data and considered to be supporting evidence for the relationship. These epidemiologic studies are unanimously based on the Caucasian population with fair complexion.

In the Japanese population, the relationship between UVB exposure and skin cancer risk has been investigated to only a limited extent. This is related to the fact that incidence and mortality rates of skin cancer are relatively low, and presumably, acceptance of the general notion that the complexion of Japanese, with more pigmentation than Caucasians, protects against harmful effects of UVB exposure. However, this is yet to be substantiated. Moreover, the human health effects of UVB increase triggered by depletion of the ozone layer warrant scientific investigation from various perspectives in the respective populations.

For the purpose of utilization in ecological and/or environmental epidemiological studies, we previously reported ambient UVB estimates based on meteorological data for various regional points of Japan [2]. The objective of the present study was to utilize these estimates to assess geographical correlation between ambient UVB estimates and regional mortality rates for skin cancer in Japan.

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METHODS

Measurement of ambient UVB has been carried out since 1990 or 1991 at four weather stations in Japan, Sapporo, Tsukuba, Kagoshima and Naha. In conducting an ecological study, however, UVB levels need to be estimated spanning a wider area and a longer period, to the extent possible. Thus a formula was developed to estimate ambient UVB from meteorological data accumulated over the past in weather stations distributed throughout Japan. Details of the formula and its fitness have been reported elsewhere [2]. Briefly, the formula was empirically determined on the basis of observed UVB data in the four weather stations in relation to latitude, global solar radiation and total ozone of the observation point. With this formula, we produced a list of ambient UVB estimates for the successive periods 1961-1969, 1970-1979, 1980-1989, and 1990 for 46 to 62 weather stations, depending on the availability of previous meteorological data.

Mortality data were obtained from a digital file of the national registry of individual death records for the period 1973-1994. Death counts were accumulated by cause (coded by the International Classification of Diseases, ninth revision), region or municipality, sex and five-year age group for the periods 1983-1992 and 1973-1994. For malignant melanoma of the skin and other malignancies of the skin, standardized mortality ratios (SMRs) were calculated for the respective regions or municipalities and time periods, adjusted to the national mortality rate by sex and five-year age group of the corresponding period.

The selection of regions for the calculation of SMR was twofold: i) the "conventional" regional blocks dividing the entire country into eleven regions, *i.e.*, Hokkaido, Tohoku, Kanto, Koushinetsu, Hokuriku, Toukai, Kinki, Chugoku, Shikoku, Kyushu and Okinawa, and ii) cities with a population greater than 100,000 (*i.e.*, "large" city) nearest to a weather station with available UVB data. In cases where the same "large" city had to be linked to more than one weather station, the data of remote weather stations were precluded from further analysis to avoid duplicate linkage. The number of cities that fulfilled this criteria was 40 (with the UVB estimate of the year 1990 available) or 33 (with the UVB estimate for the periods 1961-1969, 1970-1979, 1980-1989, and 1990 available), both of which are smaller than the number of weather stations where UVB level was estimated. Such a procedure was deemed necessary to ensure direct proximity of the estimated UVB data to the mortality data.

For the conventional regional blocks having more than one weather station (with available UVB data) within the region, UVB levels in each weather station within the region were averaged for the respective periods. When only one weather station (with available UVB data) existed within the region, the UVB estimate of the particular weather station was considered to represent that of the region. For the "large" cities, the UVB level of the corresponding weather station was considered to represent that of the city.

The geographical correlation between estimated ambient UVB levels and SMR was assessed by calculating Spearman's (rank) correlation coefficient and its p-value by EPILOG on a personal computer. Zero values obtained for SMRs were precluded from the calculation of the correlation.

RESULTS

Table 1 shows the estimated ambient UVB levels in eleven regional blocks. Similar data were obtained for "large" cities with corresponding meteorological data (data not shown). For the eleven regions, the gradient in UVB level corresponds roughly with latitude, *e.g.*, Okinawa has a twofold higher level than Hokkaido, Shikoku and Kyushu have higher levels than Honshu regions (Tohoku, Kanto, Koushinetsu, Hokuriku, Toukai, Kinki and Chugoku), and a mild gradient is present within Honshu (Table 1). It should be noted that ambient UVB levels are primarily determined by latitude but they are also affected, although to a lesser extent, by meteorological conditions. This is reflected in the change in rankings of UVB levels over the years in regions excluding Hokkaido and Okinawa.

The observed number and SMR of malignant melanoma of the skin (ICD 172) in the eleven regional blocks are shown in Table 2. There is a consistent trend in males showing that, Hokkaido, Tohoku, Hokuriku and Kyushu have elevated and Okinawa and Kinki decreased SMR values, while in females, Hokkaido, Koushinetsu, and Kyushu have elevated and Okinawa and Kinki decreased SMR values. Similarly, the observed number and SMR of other malignant neoplasms of the skin (ICD 173) in the eleven regional blocks are shown in Table 3. There is a consistent trend in males showing that, Okinawa and Tohoku have elevated and Koushinetsu and Chugoku decreased SMR values, while in females, Tohoku has elevated and Hokuriku and Kanto decreased SMR values. The observed numbers of deaths due to the two types of skin cancer for the large cities with corresponding meteorological data were small, particularly for the shorter observation period (data not shown).

The geographical correlation between ambient UVB and SMR for malignant melanoma and other malignant neoplasms of the skin is summarized in Table 4. For malignant melanoma, a negative correlation is present in the analysis of eleven regions, which is statistically significant for males ($r=-0.66$, $p=.03$ to $r=-0.74$, $p=.01$) but not significant for females. In the analysis of large cities with corresponding meteorological data, there is no statistically significant correlation for males or females. For other malignant neoplasms of the skin, there is no statistically significant correlation for males or

Table 1. Estimated ambient UVB level (10J/m²/yr) in eleven regional blocks for several time periods.

Region	Weather stations[1] N	Period			
		1961-1969	1970-1979	1980-1990	1990
Hokkaido	7	1,039	1,049	1,033	1,188
Tohoku	9	1,373	1,366	1,338	1,407
Kanto	2	1,456	1,396	1,405	1,416
Koushinetsu	1	1,460	1,349	1,356	1,424
Hokuriku	1	1,290	1,472	1,414	1,494
Toukai	1	1,547	1,639	1,577	1,701
Kinki	5	1,655	1,594	1,621	1,678
Chugoku	3	1,636	1,703	1,696	1,735
Shikoku	4	1,854	1,851	1,841	1,921
Kyushu	9	1,876	1,734	1,792	1,864
Okinawa	4	2,241	2,292	2,422	2,399

[1] Number of weather stations in the region where UVB estimates were averaged

Table 2. Observed number and SMR[1] of malignant melanoma of skin (ICD172) in eleven regional blocks.

Region	Male				Female			
	1983-1992		1973-1994		1983-1992		1973-1994	
	Observed	SMR	Observed	SMR	Observed	SMR	Observed	SMR
Hokkaido	97	123.2	180	113.2	96	153.5	163	128.3
Tohoku	172	121.8	321	118.9	124	104.0	237	102.0
Kanto	422	89.9	823	93.2	325	87.8	674	95.1
Koushinetsu	51	103.6	105	111.2	44	108.1	97	121.9
Hokuriku	61	128.8	106	116.8	40	99.3	74	94.3
Toukai	188	98.5	362	100.0	160	104.5	314	106.4
Kinki	238	88.5	438	85.1	205	91.2	384	88.2
Chugoku	116	94.6	234	98.9	107	102.8	211	103.6
Shikoku	61	88.7	142	106.4	57	96.4	110	94.6
Kyushu	238	120.6	420	110.5	200	114.6	365	107.2
Okinawa	9	66.3	18	71.0	7	55.7	16	66.2
Total	1,653	100.0	3,149	100.0	1,365	100.0	2,645	100.0

[1] standardized mortality ratio

Table 3. Observed number and SMR[1] of other malignant neoplasms of skin (ICD173) in eleven regional blocks.

Region	Male				Female			
	1983-1992		1973-1994		1983-1992		1973-1994	
	Observed	SMR	Observed	SMR	Observed	SMR	Observed	SMR
Hokkaido	91	108.0	220	95.6	71	105.5	194	105.9
Tohoku	187	121.2	454	113.5	179	130.7	466	131.2
Kanto	471	97.9	1,144	93.0	349	87.6	876	85.7
Koushinetsu	37	65.2	131	89.0	53	104.1	142	108.7
Hokuriku	50	94.5	133	96.8	31	64.4	106	84.9
Toukai	194	95.0	495	94.0	198	114.6	462	103.8
Kinki	276	96.7	749	101.3	250	99.0	630	96.7
Chugoku	131	91.4	336	90.0	127	94.7	296	86.4
Shikoku	90	110.0	231	108.0	74	96.0	198	100.2
Kyushu	232	102.2	667	112.9	235	106.5	643	114.5
Okinawa	20	131.1	64	166.3	19	100.6	52	114.0
Total	1,779	100.0	4,624	100.0	1,586	100.0	4,065	100.0

[1] standardized mortality ratio

Table 4. Summary of geographical correlation for malignant melanoma of skin (ICD172) and other malignant neoplasms of the skin (ICD173).

	SMR[1] [period]	11 Regions (UVB period)				Large cities[2]
		(1961-1969)	(1970-1979)	(1980-1989)	(1990)	(1990)
Malignant melanoma of the skin (ICD162)						
Male						
	[1983-1992]	-0.736 (p=0.010)	-0.609 (p=0.047)	-0.664 (p=0.026)	-0.600 (p=0.051)	-0.238 (p=0.169)
	[1973-1994]	-0.664 (p=0.026)	-0.573 (p=0.066)	-0.627 (p=0.039)	-0.555 (p=0.078)	-0.155 (p=0.352)
Female						
	[1983-1992]	-0.364 (p=0.272)	-0.455 (p=0.160)	-0.482 (p=0.133)	-0.373 (p=0.259)	-0.073 (p=0.668)
	[1973-1994]	-0.373 (p=0.259)	-0.509 (p=0.110)	-0.527 (p=0.096)	-0.427 (p=0.190)	-0.090 (p=0.584)
Other malignant neoplasms of the skin (ICD173)						
Male						
	[1983-1992]	0.245 (p=0.467)	0.282 (p=0.401)	0.209 (p=0.537)	0.155 (p=0.650)	0.151 (p=0.358)
	[1973-1994]	0.409 (p=0.212)	0.464 (p=0.151)	0.409 (p=0.212)	0.364 (p=0.272)	0.268 (p=0.099)
Female						
	[1983-1992]	0.027 (p=0.937)	-0.155 (p=0.650)	-0.236 (p=0.484)	-0.145 (p=0.670)	0.135 (p=0.431)
	[1973-1994]	0.245 (p=0.467)	0.018 (p=0.958)	-0.027 (p=0.937)	0.045 (p=0.894)	0.282 (p=0.082)

[1] standardized mortality ratio; [2] large cities with corresponding meteorological data (see text)

females in either the eleven regional blocks or the large cities with corresponding meteorological data.

The relationship between estimated ambient UVB level during 1961-1969 and the SMR during 1983-1992 for each type of skin cancer among males are plotted in the figure. The figure shows the opposite direction of the geographical correlation for malignant melanoma of the skin, *i.e.*, significantly negative, and other malignant neoplasms of the skin, *i.e.*, non-significantly positive, among males.

DISCUSSION

There was no consistent, statistically significant geographical correlation between estimated ambient UVB level and SMR for malignant melanoma of the skin or other malignant neoplasms of the skin for either sex in Japan. However, a negative correlation between UVB and mortality for malignant melanoma was found, which was statistically significant among males in the analysis of eleven regional blocks. The corresponding mortality among females also had a negative correlation, but it was not statistically significant. The correlation in the analysis of major cities for mortality of malignant melanoma was not significant for either sex. In contrast, the geographical correlation between UVB and mortality of other malignant neoplasms of the skin was positive but statistically non-significant among males, and inconsistent among females. A geographical correlation between UVB and skin cancer mortality is therefore unlikely in Japan. However, the absence of a positive geographical correlation does not negate the possibility of a causal relationship at the individual level and the results of the present study should be viewed in this context.

In general, skin cancer is a rare disease in Japan. The estimated incidence of skin cancer (malignant melanoma and other malignant neoplasms of the skin combined) in Japan in 1992 is 5.1 and 4.8 per 100,000 among males and females, respectively [3]. These figures are based on cancer registries of confined areas and thus do not represent the entire country. Further, skin cancer may be underreported in these registries. Efforts have just begun to collect valid incidence data regarding skin cancer on a nation-wide basis. On the other hand, the use of mortality data from the national vital statistics, as in the present study, had its own constraints. Diagnosis on death certificates may not be accurate and/or lack pathological evidence. Mortality is also affected by the natural course of disease as well as treatment after onset and is therefore a poor measure of risk. Despite these limitations, basic information on the time-

trend, as well as the geographical distribution of skin cancer mortality and its possible association with UVB exposure, warrant description in view of the paucity of such information.

In the present analysis, the national mortality data for skin cancer were accumulated up to a 22-year period covering 1973-1994. During this period, deaths from malignant melanoma among both sexes combined increased 80% from 182 in 1973 (0.2 per 100,000) to 325 (0.3 per 100,000) in 1994, while deaths from other malignant neoplasms of the skin among both sexes combined decreased 40% from 568 cases in 1973 (0.5 per 100,000) to 342 cases in 1994 (0.3 per 100,000). Hence, the total number of skin cancer deaths combined remained fairly stable over this period. This time-trend may be real, but it is also possible that increased recognition and/or improved pathologic diagnosis led to increased reporting of malignant melanoma deaths over the years while the total number remained stable.

The SMR of skin cancer by different regional blocks in the present study corroborate an earlier report in which SMR was calculated by prefecture for two three-year periods (1979-1981 and 1984-1986) [4]. It was concluded in this report that "skin cancer mortality seemed not to be related to latitude, but the Kyushu region showed higher SMR." The present study also showed an elevated mortality for both skin cancer types in Kyushu (second lowest latitude) among both sexes (Tables 2, 3 and Figure). However, the relationship between skin cancer mortality and latitude is not linear-negative, since Hokkaido (highest latitude) shows consistently elevated SMRs for both skin cancer types in both sexes, and Okinawa (lowest latitude) shows consistently elevated SMRs for malignant melanoma but consistently decreased SMRs for other malignant neoplasms of the skin in both sexes.

In comparison to the Caucasian population where most of the ecological relationships have been assessed, the Japanese population differs in complexion or pigmentation characteristics, among many other ethnic and socio-cultural characteristics. As one of the earliest studies, Lancaster showed a positive relationship (negative correlation) between latitude and mortality rate of malignant melanoma among the white population of Australia [5,6]. Subsequently within various nations, many ecological studies showed increasing skin cancer incidence and/or mortality with latitude or other surrogate measures of ultraviolet radiation [1,6]. The study by Scotto *et al.* evaluated incidence data from the National Cancer Institute's (NCI) Surveillance Epidemiology and End-Results (SEER) program in relation to the NCI R-B meter measurements of accumulated dose in eight locations in the United States, and found a strong positive association [6,7]. Based on the evaluation of all available scientific evidence from ecological as well as case-control studies, the International Agency on Research on Cancer (IARC) concluded that solar radiation causes malignant melanoma and other malignant neoplasms of the skin [1]. Currently UVB is implicated as the causal component of solar radiation.

It is noteworthy that when anatomic site was considered, the geographical correlation for other malignant neoplasms of the skin showed distinctive trends by anatomic site among females (data not shown). Consistent, statistically significant negative correlations were present for other malignant neoplasms of the skin of trunk (ICD 173.5) and skin of lower limb including hip (ICD 173.7), while the correlations for other anatomic sites

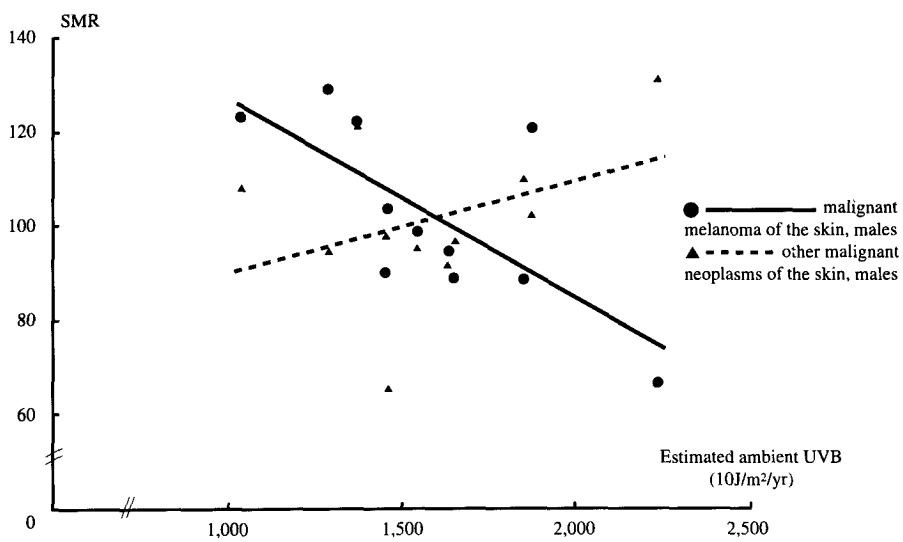

Figure. Geographical correlation between estimated ambient UVB during 1961-1969 and standardized mortality ratio (SMR) of malignant melanoma of the skin and other malignant neoplasms of the skin among males during 1983-1992 in eleven regional blocks.

(ICD 173.0, 173.1, 173.2, 173.4, 173.6) were inconsistent. The two aforementioned anatomic sites are usually covered with clothing and in this relationship, if real at the individual level, an indirect, protective effect of UVB exposure cannot be ruled out. It was not possible to analyze the mortality of malignant melanoma by anatomic site because nearly 80% of deaths was categorized into the "unspecified" category (ICD 172.9).

Among the many limitations of a geographical correlation study, several points merit particular attention in this study: i) regional differences in diagnostic and/or coding practices; ii) regional differences in pigmentation characteristics; and iii) compensating behavior to avoid or engage in sunlight exposure. First, the problem of regional differences in diagnostic and/or coding practice may be substantial if the above speculation on increased reporting of malignant melanoma deaths due to improved recognition of the disease is true, and if a regional gap exists in this trend. Second, it is generally accepted that the Japanese population has a notable range of fair to dark complexion with a north-south gradient. Although speculative, the negative correlation found for malignant melanoma and UVB may reflect the higher susceptibility of fair-skinned populations in the north, and vice-versa. Hence, the present result may be in line with analyses of European cancer registries showing a significant trend of increasing melanoma incidence with increasing latitude, accompanied by high incidence and mortality rates in Sweden and Norway [8, 9]. IARC [10] and Armstrong [11] attributed this to differences in complexion between Mediterranean and Scandinavian populations [6]. Third, as discussed by Teppo *et al.* [12], compensating behavior to avoid or engage in sunlight exposure may reverse a positive relationship. However, these points are merely speculative and difficult to factor into an ecological study.

In conclusion, there is no geographical correlation between UVB and skin cancer mortality in Japan, except for a significantly negative correlation in malignant melanoma among males and a significantly negative correlation in other malignant neoplasms of the skin confined to unexposed anatomic sites of the body among females. Although inferences are limited, the characteristic ecological relationship adds to the importance of conducting further epidemiological studies at the individual level in Japan.

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