Original Article

Multilevel analysis of solar radiation and cancer mortality using ecological data in Japan

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Summary **A preventive effect of solar radiation on cancer has been suspected. This study aimed to compare the statistical relationship between solar radiation and cancer mortality according to hierarchical models and adjustment for confounding factors, and then to demonstrate the relationship with main site-specific cancer mortalities in Japan. We examined the relationship between all-site and main site-specific cancer mortalities and global solar radiation using Poisson regression with municipal data around 2000. The models included single-level (municipality) and multilevel (municipality and prefecture) with/without potential confounding factors (lifestyle and socioeconomic variables). For all-site cancer, single-level analysis showed a significant, strong negative association with solar radiation. However, multilevel analysis showed a moderate or no association. In multilevel analysis with potential confounding factors, solar radiation was significantly negatively associated with most site-specific cancers, but not with gallbladder and liver cancer in men and stomach and breast cancer in women. Our findings support the preventive effective of solar radiation on several types of cancer. However, to show a concrete relationship, a statistical model with an appropriate hierarchy and adjustment for potential confounding factors is required.**

Keywords: Malignant neoplasm, Solar radiation, Vitamin D, Multilevel analysis, Ecological study

1. Introduction

The influence of solar radiation on cancer has recently received attention (*1*). Some epidemiological studies have suggested a preventive effect of solar radiation on several types of cancer, such as colonic (*2-4*), breast (*5,6*), lung (*7,8*), pancreatic (*9,10*), prostatic (*11*), and ovarian cancer (*12*). In addition to epidemiological studies in western countries, a few studies in Asian countries including Japan (*13-15*) support the protective effect of solar radiation against cancer.

Investigation of the relation between solar radiation and cancer mortality predominantly depends on ecological studies, since individual-level exposure to solar radiation is difficult to measure (*16,17*). Ecological studies, however, have several critical weaknesses in providing causal evidence, including confounding and ecological fallacy (*18*). Waltz and Chodick suggested that the association of solar radiation with cancer mortality resulted from confounding effects caused by ecological study design (*19*). In Japan, prefectural-level analysis has a small unit size (n = 47), and thus, possible confounders might not be sufficiently considered. Municipal-level analysis with a large number of units (about 2,000) can deal with several possible confounders, although some kinds of important data such as life-style related variables are not available. There has been little discussion to compare results among different study designs and to elucidate which study design is suitable to detect the true relationship between solar radiation and cancer mortality.

Multilevel analysis has been used for various public

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health and epidemiological studies (*20,21*). It detects the influence of hierarchical levels (*e.g.*, individual and neighborhood levels) and their interaction. Multilevel analysis can also be applied to not only individual data but also ecological data (*20,22,23*). However, it is not clear whether multi-level analysis demonstrates different and more valid evidence than single-level analysis.

This study compared the results of different types of ecological studies, including single-level and multilevel models with and without adjustment for possible confounding variables, on the relationship between solar radiation and cancer mortality in Japan. In addition, its relationship with major sites of cancer was examined using multilevel ecological analysis.

2. Methods

2.1. *Data*

The unit of analysis was basically municipalities: cities, towns, villages, and wards ("ku") of several designated cities. In 2002, there were 3,000 municipalities in Japan. The local governments of Japan have two hierarchical systems: prefectures and municipalities. There are 47 prefectures, which consist of a few tens of municipalities.

Mortality was based on deaths from 1998 to 2002 (*24*). The expected number of deaths in municipalities was estimated using the sex-age (five-year interval)-specific population and the national mortality rate in 2002. We estimated empirical Bayes estimates of local standardized mortality ratio (EBSMR) from all-site cancer of municipalities using maximum likelihood method of Poisson-Gamma model with the secondary medical care zones as groups of municipalities to estimate empirical prior distribution (*22,23,25*). The estimation of EBSMR was conducted by a window based program developed by Nakaya (*26*).

The data on solar radiation for this study were constructed as population-weighted mean annual global solar radiation of municipalities (MJ/m^2). According to the Standard Grid Square (*27*), the population as of 2000 based on the national population census and climate summary statistics including annual mean solar radiation during the period of 1971-2000 were compiled as grid square statistics based on a small square unit defined as 30" latitude × 45" longitude (approximately 1 square kilometer). Overlaying these gridded data with a municipality zoning layer, we calculated the population-weighted average value of global solar radiation for each municipality in a GIS environment. The original gridded data of 30-year mean climate summaries are provided as Mesh Climatic Data 2000 (*28*) in which the amount of global solar radiation was computed by the gridded duration of sunshine, which was interpolated by applying a multiple regression technique to the records of meteorological stations with elevation and urban indices. It should also be noted that adjustment for the effect of elevation, that is, shadowing of land features, was made for computing the gridded data of global solar radiation.

We used socioeconomic and lifestyle data as potential confounding factors. Since municipality-level data of dietary and nutritional intake were not available, we used prefecture-level data of these variables (*29*). Using principle component analysis with eighteen items of dietary consumption (*e.g.*, rice, potato, beans, fruit and green vegetables, and egg) (*30*), we drew five components and thus we used the factor scores of these components. An additional lifestyle variable was smoking rate, which was obtained from the Comprehensive Survey of the Living Conditions of People on Health and Welfare ("Kokuminseikatu Kiso Chosa") in 2004 conducted by the Japanese Ministry of Health, Labour and Welfare (*31*). The socioeconomic variables consisted of per capita income, unemployment rate, and population density, which were municipality-level data. Previous studies have demonstrated a strong relationship between these factors and all-cause and main leading causes of death in Japan (*22,23*).

2.2. *Analysis*

The relationship between mortality and solar radiation was evaluated by Poisson regression analysis, which is described in previous studies (*22,23*). We used the following six models: Model 1 was single-level (municipality) analysis without adjustment; Model 2 was single-level analysis with adjustment for socioeconomic variables; Model 3 was single-level analysis with adjustment for socioeconomic and municipal variables; Model 4 was multilevel (municipality and prefecture) analysis without adjustment; Model 5 was multilevel analysis with adjustment for socioeconomic variables; and Model 6 was multilevel analysis with adjustment for prefectural and municipal data.

The equation for Poisson regression was as follows; O_{ij} is the observed death number, E_{ij} expected death number, x_{nj} a variable of a potential confounder of j prefecture, x_{nij} that of i municipality in j prefecture, and u is a random effect among prefectures.

Single-level:

$$\log(O_{ij}) = \log(E_{ij}) + \beta_0 + \beta_{1j}x_{1j} + \ldots + \beta_{nj}x_j + \beta_{1i}x_{1ij} + \ldots + \beta_{ni}x_{nij}$$

Multilevel:

$$\log(O_{ij}) = \log(E_{ij}) + \beta_0 + u_j + \beta_{1j}x_{1j} + \ldots + \beta_{nj}x_{ij} + \beta_{1i}x_{1ij} + \ldots + \beta_{ni}x_{nij}$$

We used SPSS 15.0J (Chicago, SPSS Inc.) for principle component analysis and MLwiN 2.0 (London, Centre for Mutilevel Modelling, Institute of Education, University of London) for Poisson regression analysis.

3. Results

Figure 1 is a map showing all-site cancer mortality (EBSMR) and global solar radiation of municipalities. The EBSMR and the global solar radiation ranged from 0.44 to 1.48 and from 11.1 to 15.8 (MJ/m^2), respectively. The southern part and mountainous areas had higher solar radiation. In contrast, the northeast part showed a lower level of solar radiation.

Figure 2 shows the results of Poisson regression of the relation between all-cause mortality and solar radiation. Model 1 to Model 3 are single-level models with a single regression line, while Model 4 to Model 6 are multilevel models with prefectural specific regression lines (n = 47). Single-level analysis (Models 1, 2 and 3) showed a significant relationship regardless of adjustment for potential confounding factors. However, Model 4 of multilevel analysis did not show a significant relationship. When the municipal data (socioeconomic variables) were adjusted for (Model 6), mortality and solar radiation showed a significant negative association.

Table 1 shows the results of analysis of the relationship between solar radiation and male cancer mortality using three models of Poisson regression. In Model 1, a significant negative relationship was found for all cancer mortalities except for liver cancer. Model 4 showed a significant negative relationship for esophageal and pancreatic cancer, and a significant

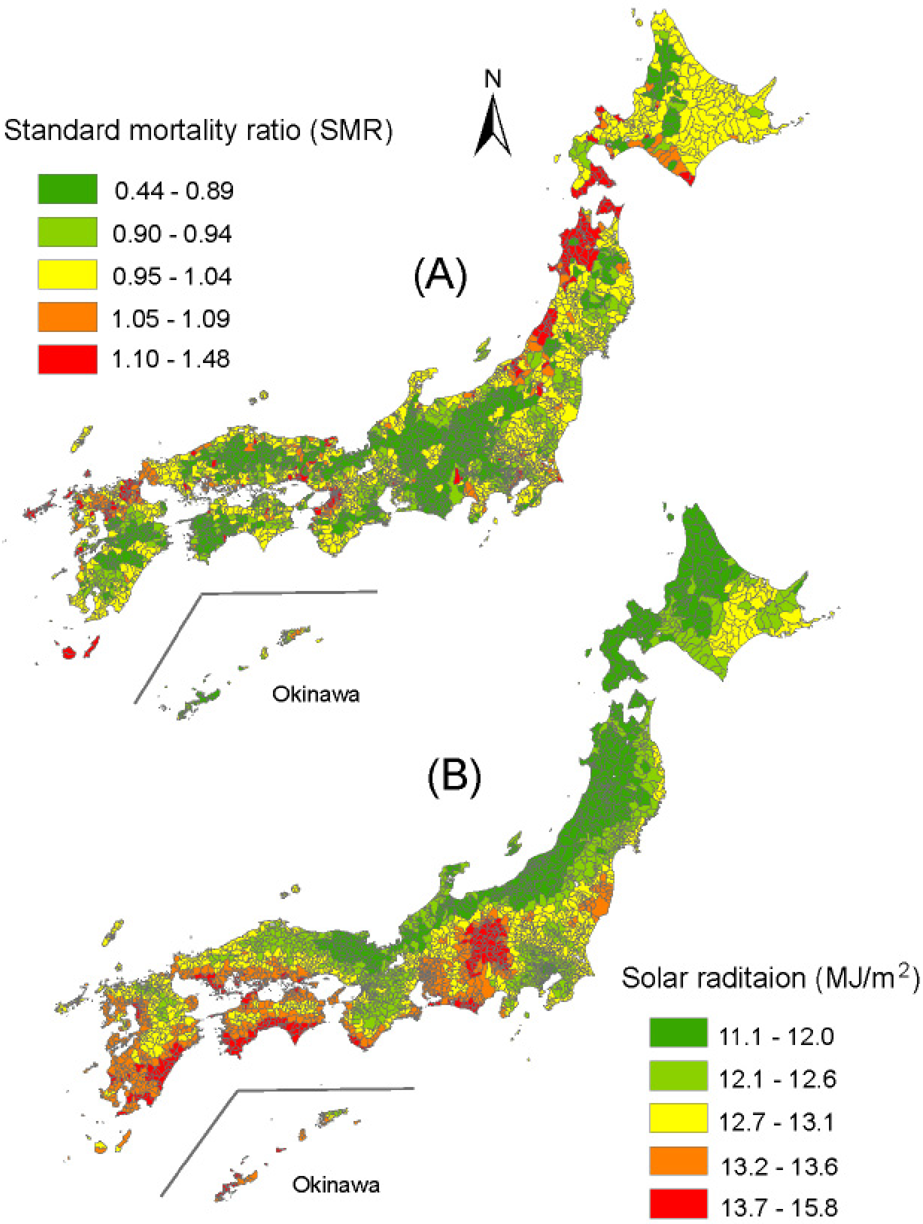

Figure 1. Mapping of mortality empirical Bayes estimates of SMR of all-site cancer (A) and global solar radiation (B) by municipality in Japan.

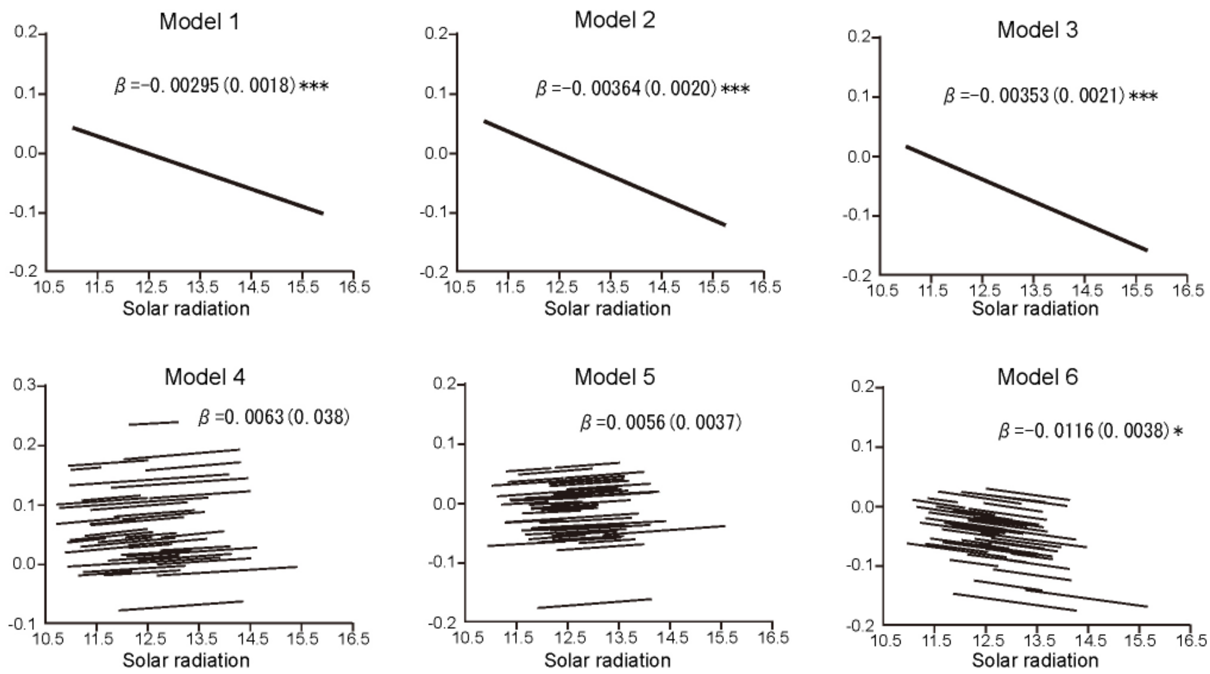

Figure 2. Relationship between solar radiation and all-site cancer mortality for men. The x axis is solar radiation (MJ/m^2) and the y axis is log RR (= SMR) predicted by Poisson regression. Model 1: single-level without adjustment; Model 2: single-level with adjustment for prefectural data; Model 3: single-level without adjustment for prefectural and municipal data; Model 4: multilevel without adjustment; Model 5: multilevel with adjustment for prefectural data; Model 6: multilevel with adjustment for prefectural and municipal data. * $p < 0.05$, *** $p < 0.001$.

positive relationship for stomach and liver cancer. In the final model (Model 6), a significant negative relationship with solar radiation was found for all cancers except for gallbladder and liver cancers.

Table 2 shows the results for female cancer. In single-level analysis (Model 1 and Model 2), all mortalities were significantly negatively associated with solar radiation. In Model 4, colorectal, gallbladder, and pancreatic cancers showed a significant negative relationship. In addition to these three cancers, all-site cancer and lung cancer showed a significant negative relationship with solar radiation.

4. Discussion

This study demonstrated that the statistical relationship between solar radiation and all cancer mortality differed among statistical models. For male all-site cancer, a single-level model showed a significant negative relationship regardless adjustment for potential confounders. In a multilevel model, however, this relationship was not found. This difference suggests that the relationship in the single-level model is not true, since the true relationship should be independent of the hierarchical model. The relationship in the single-level (municipal level) model might be confounded by unknown and unavailable factors of prefectural level variables. It is suggested that the negative association between solar radiation and cancer mortality in a previous study using single (prefecture) level analysis (*15*) might be influenced by confounding factors and fallacies.

The relationship between all-site cancer mortality and solar radiation was similar among models with and without lifestyle-related variables. This similarity was also found in most site-specific cancer mortality. It is suggested that these variables, which were used in a previous study (*15*), are not useful as variables for adjustment. In contrast, adjustment for socioeconomic variables (municipal level) greatly modified the relationship between mortality and solar radiation. These socioeconomic variables are useful potential confounders, although it might be dummy variables including unknown and unavailable factors. Even in the final model adjusting lifestyle and socioeconomic variables, there was large variation among prefectures, as shown in Figure 2. This suggests that the variation might depend on other unknown factors, such as medical resources.

One study in Japan investigating pancreatic cancer mortality and solar radiation did not consider any kind of factors related to lifestyle (*14*). Even if the study had shown a negative association between solar radiation and mortality, the result would seem incredible. Another Japanese study considered some possible confounding factors related to lifestyle (*15*). The adjustment, however, hardly changed the relationship, and thus it might not have included important confounding factors.

Concerning methodological issues, our analysis has three advantages compared with previous studies. First, the use of multilevel analysis could adjust for unknown and measurable confounding factors. Second, we used

Table 1. Results of Poisson regression analyses for solar radiation and cancer mortality in Japan according to various models: men

Site of cancer	Model 1		Model 2		Model 4		Model 6	
	Coefficient	(SE)	Coefficient	(SE)	Coefficient	(SE)	Coefficient	(SE)
All sites	-0.0295	(0.0018)***	-0.0364	(0.0020)***	0.0067	(0.0038)	-0.0116	(0.0038) **
Esophagus	-0.2226	(0.0082)***	-0.1606	(0.0093) ***	-0.1099	(0.0173) ***	-0.1160	(0.0175) ***
Stomach	-0.1546	(0.0040)***	-0.0723	(0.0046) ***	0.0259	(0.0087) **	-0.0255	(0.0089) **
Colorectum	-0.0885	(0.0053)***	-0.0625	(0.0060) ***	-0.0189	(0.0103)	-0.0267	(0.0100) **
Gallbladder	-0.0149	(0.0089)	-0.0079	(0.0099)	-0.0160	(0.0161)	-0.0180	(0.0133)
Pancreas	-0.0686	(0.0073) ***	-0.0617	(0.0083) ***	-0.0410	(0.0130) **	-0.0357	(0.0113) **
Liver	0.1209	(0.0048) ***	0.0656	(0.0055) ***	0.0637	(0.0107)***	0.0293	(0.0110) **
Lung	-0.0183	(0.0037) ***	-0.0507	(0.0043) ***	-0.0024	(0.0077)	-0.0299	(0.0076) ***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
Model 1: Single-level (prefecture) without adjustment
Model 2: Single-level (prefecture) with adjustment for dietary factors and smoking rate
Model 4: Multi-level (prefecture and municipality) without adjustment
Model 6: Multi-level (prefecture and municipality) with adjustment for dietary factors, smoking rate and socioeconomic conditions

Table 2. Results of Poisson regression analyses for solar radiation and cancer mortality in Japan according to various models: women

Site of cancer	Model 1		Model 2		Model 4		Model 6	
	Coefficient	(SE)	Coefficient	(SE)	Coefficient	(SE)	Coefficient	(SE)
All sites	-0.0474	(0.0022)***	-0.0369	(0.0026)***	-0.0021	(0.0045)	-0.0146	(0.0044)***
Stomach	-0.0745	(0.0055)***	-0.0644	(0.0065)***	-0.0052	(0.0115)	-0.0121	(0.0118)
Colorectum	-0.1035	(0.0058)***	-0.0724	(0.0069)***	-0.0529	(0.0108)***	-0.0516	(0.0110)***
Gallbladder	-0.0359	(0.0080)***	-0.0244	(0.0094)**	-0.0338	(0.0146)*	-0.0373	(0.0138)**
Pancreas	-0.0736	(0.0078)***	-0.0478	(0.0094)***	-0.0494	(0.0128)***	-0.0316	(0.0118)**
Breast	-0.1014	(0.0079)***	-0.0255	(0.0096)**	-0.0089	(0.0155)	0.0165	(0.0131)
Lung	-0.0384	(0.0060)***	-0.0382	(0.0073)***	0.0069	(0.0124)	-0.0226	(0.0112)*

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
Model 1: Single-level (prefecture) without adjustment
Model 2: Single-level (prefecture) with adjustment for dietary factors and smoking rate
Model 4: Multi-level (prefecture and municipality) without adjustment
Model 6: Multi-level (prefecture and municipality) with adjustment for dietary factors, smoking rate and socioeconomic conditions

potential confounding factors as much as possible. Last, Poisson regression analysis could compare not the correlation coefficient, but the regression coefficient. Because of these three advantages, our analysis approached the true relationship between solar radiation and cancer mortality.

Using the final model, multilevel analysis with adjustment for socioeconomic and dietary variables, we examined the relationship between solar radiation and cancer mortality of main sites. Solar radiation was significantly negatively associated with most gastrointestinal cancers and male lung cancer. These findings agree with previous studies, which showed a beneficial effect of solar radiation on these cancers (*1*).

The beneficial effect of solar radiation on cancer is partly explained by vitamin D. Epidemiological studies including a cohort study and intervention study demonstrated evidence that high serum levels of vitamin D are associated with lower risk of some cancers (*1*). The evidence suggested that the beneficial effects of sunlight against cancer might be mediated by its role in vitamin D production.

This study found an inverse effect of solar radiation on liver cancer. Since it is not reasonable that solar radiation increases the risk of liver cancer, even the final model seems to suffer from remaining confounding factors. For female breast cancer, on which solar radiation has been demonstrated to have a beneficial effect in western countries (*5,6*), the final model of this study showed no relationship with solar radiation. This inconsistency suggests that differences in the incidence/mortality and the strength of other risk factors among countries could contribute to the impact of solar radiation.

In conclusion, this study attempted to examine the suitability of different statistical models in relation to solar radiation and cancer mortality, and demonstrated that multilevel analysis with adjustment for relevant possible confounding factors is more suitable than single-level analysis. Using multi-level analysis, our findings support the preventive effective of solar radiation on several types of cancer, especially gastrointestinal cancer.

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