Another interpretation for the geographical gradient of cancer mortality rate

M Yokoya*

Abstract

Introduction
Many epidemiologic studies indicate that cancer mortality rate tends to increase at higher latitudes. One proposed hypothesis explaining this geographical gradient is that vitamin D, which is produced after exposure to solar radiation, has anti-carcinogenic effects. However, the association between solar radiation and cancer risk is not fully explained.

The Hypothesis
A number of recent studies have provided support for a link between photoperiodic environment and cancer. Accumulating epidemiological and genetic evidence indicates that the disruption of circadian rhythms might be directly linked to cancer. It is possible that part of the latitudinal gradient of cancer mortality rates is due to the effects of vitamin D but to circadian rhythm amplitude reduction.

Evaluation of Hypothesis
In previous study, the author proposed effective day length (duration of photoperiod exceeding the threshold light intensity) as a climatic element indicating ambient daylight intensity and length. While day lengths are shorter in winter in the north than in the summer, on average, the possible sunshine duration is exactly the same at all points of the globe. However, effective day length is essentially a photoperiod that takes into account the intensity of light; it becomes shorter with decreases in solar radiation. The effective day length at more than 1000 lx increases in almost direct proportion to the intensity of solar radiation. This shows that the effects of solar radiation, which generates vitamin D, and effective day length, which reinforces amplitude of circadian rhythm, are essentially undistinguishable in ecological studies.

Conclusion
This result supports the hypothesis of circadian disruption from a meteorological standpoint. This indicates the possibility that part of the latitudinal gradient of cancer mortality rates is not due to the effects of vitamin D but to circadian rhythm amplitude reduction.

Introduction
Many epidemiologic studies also known as ecological studies indicate that the rate of incidence and mortality for certain cancers tends to increase at higher latitudes, indicating a relationship between geographical latitude and the rates of cancer incidence or mortality. These studies have shown the existence of a geographical (latitudinal) gradient in cancer incidence or mortality rates, including the United States[1,2,3,4,5], Australia[6,7,8], Spain[9], France[10], China[11], and Japan[12,13].

One hypothesis explaining these geographical gradients is that vitamin D, which is produced after exposure to solar radiation, has anti-carcinogenic effects[14]. However, the association between solar radiation and cancer risk is not fully explained.

A number of observational studies have investigated whether people with higher vitamin D levels or intake have lower risk of cancer, but these studies have yielded inconsistent results[15,16,17,18]. Even those studies based on the measurement of blood levels of 25-hydroxyvitamin D, which avoid some of the limitations of assessing dietary intake, have been conflicting[19,20,21,22,23,24,25,26]. Additionally, some studies indicate that residential concentration of 25-hydroxyvitamin D does not depend on latitude and sunlight exposure[27,28]. Furthermore, as modern humans spend much of the day indoors, it is unlikely that difference in ambient solar radiation has a direct impact on any biological processes. Some studies indicate that variations in the amount of solar radiation exposure at the individual level are primarily the result of lifestyle rather than geographical differences[29,30,31,32]. Based on these results, the National Cancer Institute makes no recommendation for or against the use of vitamin D supplements to reduce the risk of colorectal or any other type of cancer[33].

Despite the existence of many reports mentioning a geographical gradient in cancer incidence and mortality rates, most research results are inconsistent, and the hypothesis that increased exposure to solar radiation helps to prevent cancers and causes this geographical gradient is dubious. There are other sunlight-potentiated and vitamin D-independent pathways, such as modulation of the immune system and circadian rhythm, which might play a role in reduced cancer risk[34].

Certainly, it is natural to consider environmental factors in relation to this geographical gradient when social or economic conditions or other eating habits are homogeneous in the region. However, solar radiation is not the only climatic factor related to the latitudinal gradient.

The hypothesis
The photoperiodic environment has recently been attracting attention from various fields as it affects the physiological processes of all living organisms and initiates many biological and behavioural changes. A number of recent studies have provided support

*Corresponding author
Email: m.yokoya@shimonoseki-jc.ac.jp

1 Shimonoseki Junior College, Shimonoseki, Yamaguchi, Japan

License OAPL (UK) 2014. Creative Commons Attribution License (CC-BY)

for a link between photoperiodic environment and cancer. It is well known that a circadian clock is involved in the regulation of photoperiodism and governs a remarkable variety of metabolic and physiological functions. Accumulating epidemiological and genetic evidence indicates that the disruption of circadian rhythms might be directly linked to cancer\textsuperscript{35}. It is possible that part of the latitudinal gradient of cancer mortality rates is not due to the effects of vitamin D but to circadian rhythm amplitude reduction.

**Evaluation of the hypothesis**

The authors have referenced some of their own studies in this hypothesis. The protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. A number of recent studies have provided support for a link between changes in photoperiodic environment and risk of developing cancer. There is increasing interest in the possibility that circadian rhythm disruption increases the risk of developing cancer.

For example, persons who engage in nightshift work may exhibit altered night-time melatonin levels and reproductive hormone profiles that could increase the risk of many diseases, including cancer\textsuperscript{36,37}.

The International Agency for Research on Cancer Working Group concluded that shift work that involves circadian disruption is probably carcinogenic to humans (Group 2A)\textsuperscript{37}.

Circadian rhythms govern a remarkable variety of metabolic and physiological functions. Rhythmicity is observed in transcriptional expression of a wide range of clock-controlled genes that regulate a variety of normal cell functions, such as cell division and proliferation. Asynchrony of this rhythmicity seems to be implicated in several pathologic conditions, including tumorigenesis and cancer progression\textsuperscript{36}. Intriguingly, several molecular gears constituting the clock machinery have been found to establish functional interplays with regulators of the cell cycle, and alterations in clock function could lead to aberrant cellular proliferation. In addition, connections between the circadian clock and cellular metabolism, which are regulated by chromatin remodelling, have been identified. This suggests that abnormal metabolism in cancer could also be a consequence of a disrupted circadian clock\textsuperscript{36}.

Recent studies show that the circadian amplitude of melatonin is shown to relate both to cancer risk and to the presence of cancer, while no differences are found in the 24-hour average of melatonin secretion\textsuperscript{38,39,40,41,42}. Clinical studies show that melatonin tends to be depressed in patients with primary tumours of different histological types including both hormone-related (breast, uteri and prostate cancer) and non-hormone-related tumours (lung, stomach and colorectal cancer)\textsuperscript{41,42}.

The circadian amplitude of melatonin was reduced by more than 50\% in patients with breast cancer versus patients with nonmalignant breast disease\textsuperscript{43,44}. High urinary melatonin has been found in breast cancer patients in the morning, suggesting circadian disorganization\textsuperscript{43,45}.

Circadian amplitude of melatonin was reduced by two-thirds in patients with prostate cancer versus patients with prostate disease, and similar phenomena were observed in colorectal cancer patients\textsuperscript{43,44}. Circadian disruption accelerates cancer progression, whereas circadian rhythm reinforcement could halt it\textsuperscript{43,47}. Similar to night light, daylight and meal timing have a strong influence on melatonin amplitude. Exposure to light at night inhibits melatonin secretion.

Dim light exposure during daytime decreases melatonin secretion by increasing light sensitivity at night\textsuperscript{48,49,50}. It has been reported that the suppression of melatonin secretion after the exposure to light was significantly greater in winter than in summer. The results suggest that the increase in suppression of melatonin by light is due to lower exposure to daytime ambient light in winter\textsuperscript{50}. This also indicates that, if living hours (time of sleep) is equal, the geographical difference of the melatonin suppression rate at night will increase with decreasing ambient day-light intensity and length. In fact, affective and sleep disorders due to circadian rhythm disruption frequently occur at high latitudes in the winter. This is believed to be due to weakened circadian rhythms triggered by dim daylight at high latitudes in winter\textsuperscript{51,52,53}.

According to the hypothesis of circadian disruption, external factors that disturb the function of the circadian system can increase the risk of malignant neoplasm and reduce the lifespan\textsuperscript{54,55}. Given that dim ambient light increases the incidence of circadian rhythm disruption, it is natural that cancer risk increases at high latitudes with decreasing daylight intensity and length.

In previous study, the author proposed effective day length (duration of photoperiod exceeding the threshold light intensity) as a climatic element indicating ambient daylight intensity and length\textsuperscript{56}. Effective day length at any light intensity can be estimated using solar radiation data. While day lengths are shorter in winter in the north than in the summer, on average, the possible sunshine duration is exactly the same at all points of the globe. However, effective day length is essentially a photoperiod that takes into account the intensity of light; it becomes shorter with decreases in solar radiation. The effective day length at more than 1000 lx increases in almost direct proportion to the intensity of solar radiation\textsuperscript{56,57}. This shows that the effects of solar radiation, which generates vitamin D, and effective day length, which reinforces amplitude of circadian rhythm, are essentially indistinguishable in ecological studies.

This result supports the hypothesis of circadian disruption\textsuperscript{54,55} from a meteorological standpoint. Moreover, in this case, we cannot distinguish what intensity of effective day length influences the distribution of cancer.
mortality rate the most. However, geographical differences in effective day length decrease with decreases in light intensity, and geographical differences in effective day length at low light intensities (< 1000 lx) are too small to produce a geographical difference in cancer mortality rates. Furthermore, human photoperiodic sensitivity is not so sensitive, and light intensity of indoor environments is generally less than 10% of that outdoors, so relatively strong daylight will be needed.

**Discussion**

The mechanisms for the entrainment of human circadian rhythms remain unclear. There is great difference across individuals in sensitivity to light environment, varying by race, age, sex, and lifestyle. Additionally, human reaction to light varies depending on the intensity, wavelength, duration of exposure, and the history of previous light exposure. As the impact of environmental factors on the human body varies according to many elements, the use of group-level phenomenon has limited utility when evaluating environmental factors affecting health.

All ecological studies are potentially prone to the ecological fallacy, and our study findings should thus be interpreted cautiously. Additionally, our study does not deny the clinical effects of vitamin D. Laboratory studies have shown that vitamin D promotes cellular differentiation, decreases cancer cell growth, and stimulates apoptosis. Vitamin D deficiency is surprisingly common, especially among the elderly, African American, and residents of northern climates.

Further research is required to judge the plausibility of our hypothesis as an explanation for the inverse association between effective day length and cancer mortality rates.

**Conclusion**

The distribution of solar radiation, which generates vitamin D, and the distribution of effective day length, which reinforces circadian rhythm amplitude, are essentially undistinguishable in ecological studies. The results indicate the possibility that part of the latitudinal gradient of cancer mortality rates is not due to the effects of vitamin D but to circadian rhythm amplitude reduction. This result supports the hypothesis of circadian disruption from a meteorological standpoint. Humans who live in high latitudes may have a higher risk of cancer because of the weakening of circadian rhythm amplitude due to the shortage of bright light.

**Acknowledgement**

The author would like to thank the faculty and students of Shimonoseki Junior College for their assistance with the research.

**References**

Hypothesis


48. Takasu NN, Hashimoto S, Yamanaka Y, Tanahashi Y, Yamazaki A, Ishibashi S, Matuda T. Less exposure to daily ambient light in winter increases}

Licensee OAPL (UK) 2014. Creative Commons Attribution License (CC-BY)