Cloudiness and Breast Cancer

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Abstract

Traditional risk factors for breast cancer explain only a fraction of cases. Causes for trends in breast cancer incidence are not fully understood. Breast cancer incidence and mortality rates decrease with environmental conditions that promote Vitamin D synthesis in human skin including lower latitude and higher personal exposure to sunlight. Association of temporal variability in breast cancer incidence with changes in cloudiness, which decrease human Vitamin D synthesis is investigated. Association between temporal changes in breast cancer incidence and in the autumn cloudiness for preceding years is computed using data for the United States. There is a correlation of 0.96 (95%CI=0.92-1) between the time series of breast cancer incidence in the age group of 70-79 years and the average cloudiness in October during preceding 20 years. An empirical model for breast cancer incidence using autumn cloudiness in preceding years captures a rapid increase in breast cancer incidence in the 1980s and some of its year-to-year variability. Increased autumn cloudiness is associated with increased subsequent breast cancer incidence. Proposed mechanism includes blocking of solar ultraviolet radiation by thick clouds and decreasing the synthesis of Vitamin D in human skin. The findings suggest a new connection between climate variability and human health.

Introudction

Breast cancer incidence rates for several representative US regions have been recorded by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (SEER, 2007) since 1973. Time series of age-adjusted incidence rates $f_1(t)$, $f_2(t)$,…, $f_5(t)$ for five age groups of women are shown in Figure 1. The incidence rates for women diagnosed between 70 and 79 years of age ($f_4(t)$: magenta curve) climbed rapidly from mid 1970s to mid 1980s and declined from 1999 to 2004. The introduction of screening mammography, which allows earlier detection of cancer, contributed to the former increase (Miller et al., 1993), but it cannot account for the entire observed increase (White et al., 1990). A decline in the use of hormone replacement therapy (HRT) (Glass et al., 2007) or saturation in screening mammography (Li and Darling, 2007) may

have contributed to the latter decline in cancer incidence. Age, early menarche, nulliparity, late age of first full-term pregnancy, late age and short length of lactation, late menopause, genetic mutations, use of HRT, radiation exposure, alcohol consumption, higher educational level and higher socioeconomic status are among risk factors for breast cancer, many of which are related to cumulative exposure to estrogens (Coyle, 2004). However, causes for trends and year-to-year variations in breast cancer incidence are not fully understood (Garfinkel, 1993; Ghafoor et al., 2003).

Low vitamin D status is a risk factor for the development of breast cancer (Coyle, 2004; John et al., 1999). Synthesis in the skin exposed to solar UV radiation is a major source of Vitamin D in humans (Holick, 2004). Breast cancer incidence and mortality are higher in geographic regions with lower UV radiation (Gorham et al., 1990; Garland et al., 1990; Grant, 2002; Grant and Garland, 2006). In the extratropics low wintertime UV amounts may be
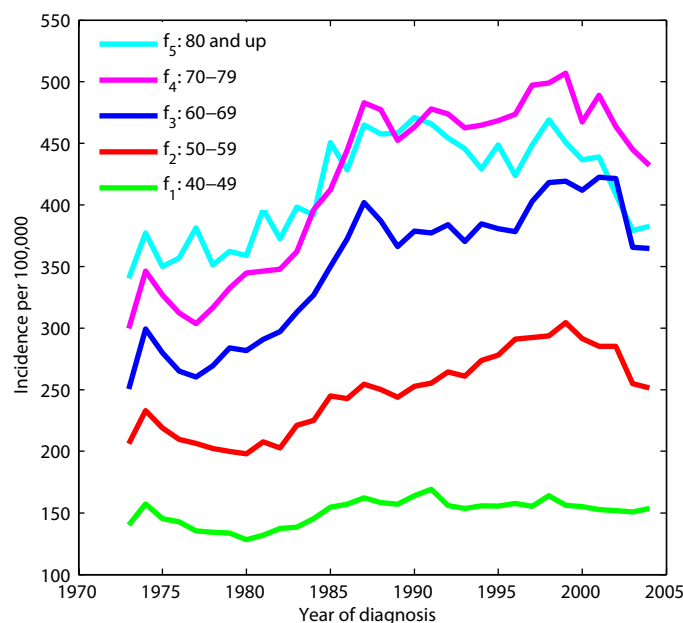

Figure 1: Breast cancer incidence. Annual rates per 100,000 females of any race are shown by the age at diagnosis: f_1 (age 40-49 years), f_2 (age 50-59), f_3 (age 60-69), f_4 (age 70-79) and f_5 (age 80 and above). Age adjusted incidence rates to standard US population in year 2000 are shown (SEER, 2007). Statistics were generated from malignant cases only.

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inadequate for vitamin D synthesis (Webb et al., 1988) causing seasonal variability in serum Vitamin D status (Lappe et al., 2006; Kull et al., 2009). Due to Vitamin D half-life of 1-2 months (Vieth, 1999), a deficiency is common at the end of the winter (Holick, 2004). Assuming that autumn vitamin D synthesis modulates subsequent Vitamin D minima (Figure 2), we ask: Is interannual variability in the autumn surface UV radiation related to breast cancer incidence?

High quality, multi-decadal observations of surface UV are needed to examine temporal association between UV radiation and breast cancer incidence. However, ground-based observations providing time series since 1960s are of insufficient quality to establish trends (Weatherhead et al., 1997). A newer network of ground based stations has been collecting UVB observations since 1990s (Bigelow et al., 1998), but their record is too short at the time of this writing. Assuming that exposure is relevant over about two decades from initiation to detection of breast cancer, about 50 years of UV data are needed to evaluate association with the 30 years of subsequent SEER breast cancer incidence rates. Satellite estimates of surface UV have difficulties over polluted sites (McKenzie et al., 2001), where they do not capture reduction in UV radiation caused by urban aerosols near the ground (Herman et al., 1999). Solar UV radiation is scattered and absorbed in the atmosphere by clouds, ozone, aerosols, and nitrogen dioxide (WMO, 2003). Thick clouds can reduce UV-B radiation at wavelengths of 290-320 nm by 80% (Frederick and Steele, 1995). The focus of this study is on interannual variability in cloudiness due to its large impact on surface UV.

Materials and Methods

For 1987 and earlier years we use monthly mean daylight cloud amounts from an edited record of all US ground stations (Karl and Steurer, 1990), which was used to study cloudiness trends over the United States. Due to changes in observing practices spurious trends may exist between late 1930s and late 1940s. An increasing trend in cloudiness and a consistent decrease in
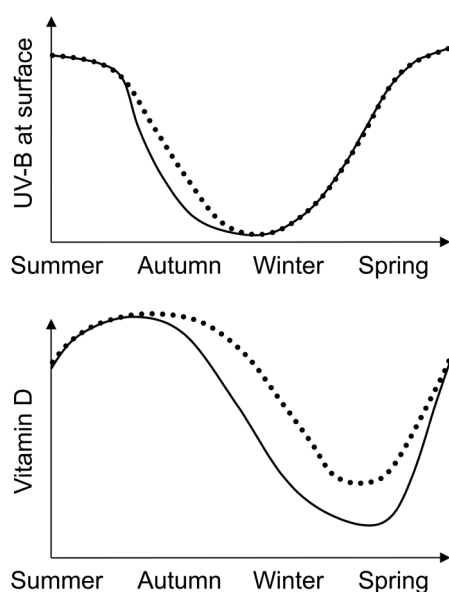

Figure 3: Average cloudiness for each month for the preceding 20 years. Months are marked by season: winter (circles), spring (squares) and summer (triangles). Autumn months are shown by thicker lines: September (brown), October (red) and November (violet).

temperature range were found since 1948. From each of the nine SEER regions we selected one ground station with complete records from 1948 to 1987. Two stations are available in Iowa; Sioux City is very close to the state border, so Des Moines was selected to represent this state. Only one station has a complete record in each of the other four SEER states: Hartford in Connecticut, Albuquerque in New Mexico, Salt Lake City in Utah, and Honolulu in Hawaii. For each of the four SEER metropolitan areas (San Francisco, California; Seattle, Washington; Detroit, Michigan; and Atlanta, Georgia) there is a ground station for that metropolitan area.

Variability in cloudiness over several years is examined using the spatial average over the nine stations in SEER regions. For each month this cloudiness was averaged for 20-year intervals. From the 20-year interval ending in 1967 to the 20-year interval ending in 1987 the largest increase in cloudiness is seen for October (5%), followed by September (4%), and November (3.5%, Figure 3). Due to this substantial increase in cloudiness in the autumn months, we focus the remaining analysis on the autumn months.

Monthly cloudiness records for the nine stations in SEER regions were extended to year 2004 using monthly total cloud amounts from satellite based International Satellite Cloud Climatology Project (ISCCP) data (Rossow and Schiffer, 1999). Measurements from geostationary and polar orbiting satellites are combined every 3 hours and subsequently averaged to produce ISCCP monthly total cloud amounts. Multiple satellites provide measurements over some locations. Thus, ISCCP uses a hierarchy of preferred sources of satellite data that based on satellite observing geometries, with preference for data from the satellite

Figure 2: Schematic annual cycle. Idealized annual cycle is shown for a) UV-B at the surface for cloud-free conditions (dotted) and for cloudy autumn (solid) and for b) corresponding serum 25-hydroxyvitamin D [25(OH)D] concentration.
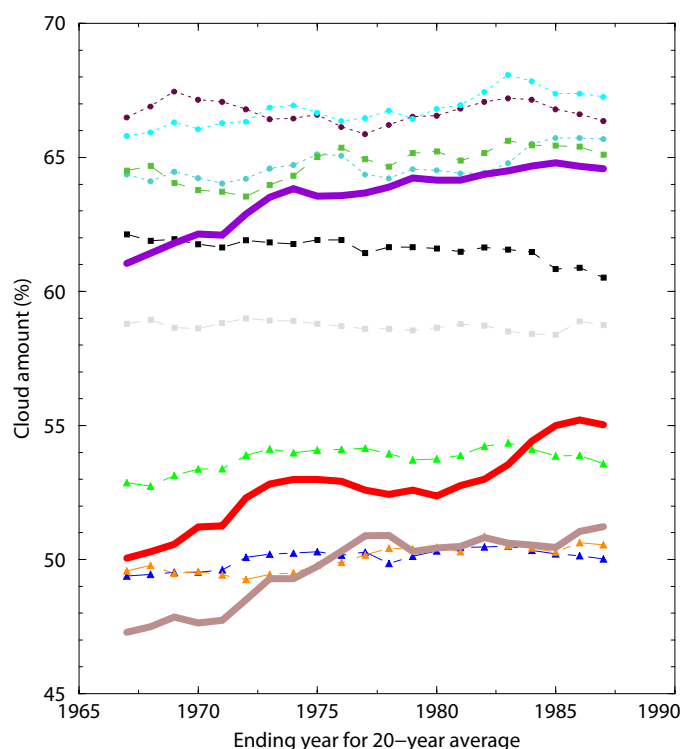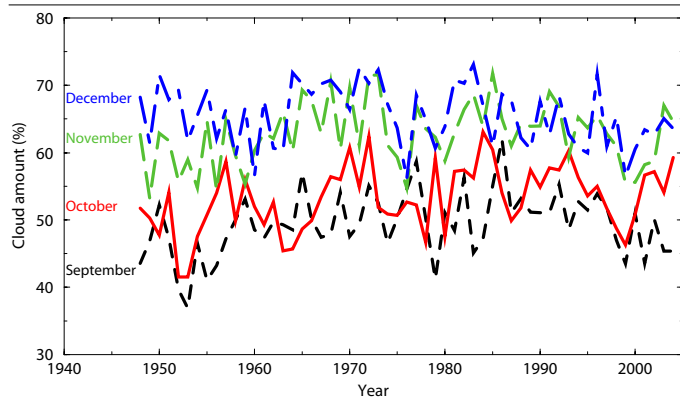
Figure 4: Monthly average cloudiness. Average cloud amounts for the nine ground stations in SEER regions are shown for September (g_9: black), October (g_{10}: red), November (g_{11}: green) and December (g_{12}: blue).

closest to being overhead rather than low on the horizon. For the 48 contiguous United States and Hawaii the primary data sources are geostationary satellites (Geostationary Operational Environmental Satellite (GOES)-East and GOES-West). The monthly maps of cloudiness from ISCCP allow us to examine how well cloudiness over chosen stations represents cloudiness over SEER regions. For example, the October cloudiness from 1983 to 2004 over Des Moines and the cloudiness over a rectangular area representing Iowa both vary from <60% to >75%; even though cloudiness for Des Moines is 1.8% lower, there is a correlation of 0.95 between their time series. Differences between ground-based and satellite observations during the 1980-1987 overlap period are typically smaller than the interannual variability in the records at each of the nine stations. Figure 4 shows the time series of the nine-station average of the cloud amounts for September, October, November, and December, which are denoted by g_9, g_{10}, g_{11}, and g_{12}, respectively.

In order to examine the relationship between multi-annual averages of cloudiness in one of the autumn months and the breast cancer incidence, we formulate the following model h to compare with breast cancer incidence f_i:

$$h(t) = c + \frac{b}{l} \sum_{k=a}^{a+l-1} g_j(t-k) \text{, for } j = 9, 10, 11, 12.$$

In this model monthly cloud amounts g_j are averaged over l years, with a lag of a years. In order to match ranges of f_i and h, linear stretching is controlled by parameter b and offsets by c.

For example, for $j=10$, g_j is cloudiness for October. Cloudiness is averaged over several (l) years because cancer may be influenced by conditions that occurred over decades before its detection. The lag parameter a is introduced to allow a possibility that cloudiness in the last few years may be irrelevant, e.g. if the cancer is too advanced to be influenced by saddle changes in Vitamin D sources. All cloudiness attains values between 0 (clear sky) and 100 (cloud covered sky), so by construction, averages of cloudiness will produce numbers between 0 and 100. In order to fit breast cancer incidence (which e.g. varies from ~300/100,000 to ~500/100,00 for women in the age group 70-79 as seen in Figure 1) parameter b allows adjusting the range of variability, and the parameter c allows vertical offsets to bring curves closer together.

Using least-squares norm we determine the best fit $h_i(t)$ to $f_i(t)$, for $i=1,2,…,5$, $j=9,10,11,12$, $a \geq 0$, $l \geq 1$ and $a+l \leq 25$. The causality limits a to be positive. Total temporal shifts $(a+l)$ do not exceed 25 years to avoid artificial offsets in cloudiness data in 1930s and 1940s caused by changes in cloud measurement techniques (Karl and Steurer, 1990).

Results

For the age group 70-79 the best least-squares fit to f_4 is provided by h_4 using cloudiness in October ($j=10$) and the following parameters:

$a = 1$, $l = 20$, $b = 58.78$, and $c = -2764.9$.

Thus, the best fit uses October cloudiness for 1 to 20 (a to $a+l-1$) years before the cancer incidence. Note the importance of parameter b: it quantifies the increase of cancer incidence rate per 100,000 individuals corresponding to a 1% increase in the average cloudiness over the l years in the model h. Cloudiness for October or November provided best fit for all five age groups, with the parameters in Table 1. The correlation coefficients between the incidence and best fit models range from 0.84 (95%CI=0.70-0.95) to 0.96 (95%CI=0.92-1). The time series of best fit models in Figure 5 capture the strong increases in breast cancer incidence rates during 1980s and more stable rates since 1987.

Spatial association between cloudiness and breast cancer was investigated as well. There is a correlation of 0.815 between 20-year average (1983-2002) of October cloudiness (Rossow and Schiffer, 1999) over regions included in the SEER program and the breast cancer incidence in 2003 for white women older than

Age group	Group index i	Month j	Number of years l	Lag a	Sensitivity to change In Cloudiness b	Offset c	Correlation between f_i and h_i	95% confidence interval
40-49	1	10	19	1	7.9513	-280.8	0.8408	0.6962-0.9537
50-59	2	10	17	2	26.3441	-1182.2	0.9342	0.8684-0.9924
60-69	3	10	20	1	46.3609	-2151.3	0.9483	0.8958-0.9953
70-79	4	10	20	1	58.7847	-2764.9	0.9599	0.9187-0.9972
80+	5	11	23	2	47.8014	-2636.2	0.8704	0.7490-0.9698

Table 1: The parameters for model h_i that provide best fit using least square norm to the breast cancer incidence f_i for five age groups.
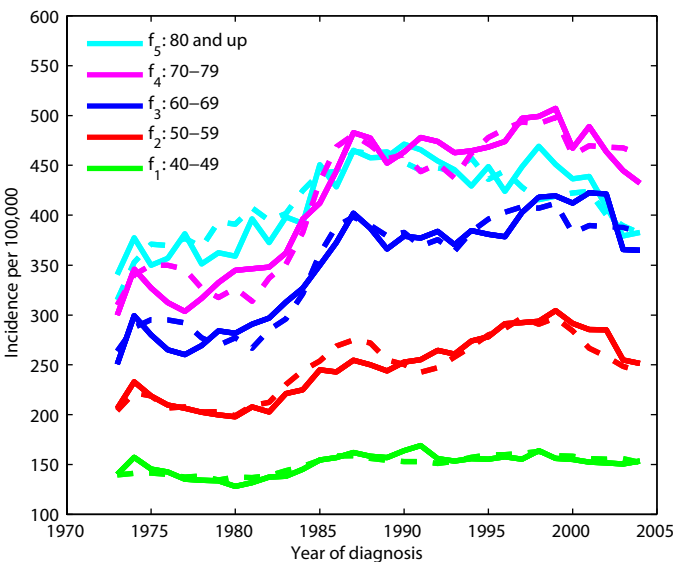
Figure 5: Empirical model using best fit parameters. Breast cancer incidence f_1 to f_5 for women of ages 40-49, 50-59, 60-69, 70-79, 80 and older (solid: colors as in Figure 1) and the fit functions h_1 to h_5 (dashed) with parameters given in Table 1.

65 years (Table 2). Note that solar zenith angle, cloudiness and ozone, which all decrease surface UV-B, typically increase with increasing latitude, so the correlation is not likely to be due to changes in cloudiness alone. Latitude of SEER cities and geographic centers for SEER states is also given in Table 2. There is a negative correlation of -0.366 between latitude and breast cancer incidence rates, indicating that latitude alone does not explain variability in breast cancer incidence rates. The surprising negative correlation is due to Hawaii data. When correlations are computed for 8 SEER regions, excluding Hawaii, there is a positive correlation of 0.564 between latitude and breast cancer incidence. Correlation between cloudiness and breast cancer is much less sensitive to exclusion of Hawaii data; it drops only slightly to 0.813.

Discussion

High temporal correlations between autumn cloudiness and breast cancer incidence exist, which do not imply causality. However, we assert that synthesis of Vitamin D in human skin is the linking mechanism, which is consistent with earlier studies of environmental exposure to solar radiation (John et al., 1999;

Gorham et al., 1990; Garland et al., 1990; Grant, 2002). Dietary supplementation provides an alternative source of Vitamin D and another mode of intervention in order to reduce the burden of breast cancer. Randomized trials of daily Vitamin D and calcium supplementation in postmenopausal women showed mixed results: 400 IU of Vitamin D and 1000 mg of elemental calcium did not reduce colon cancer incidence (Wactawski-Wende et al., 2006), but 1100 IU of Vitamin D plus 1400-1500 mg of calcium substantially reduced incidence of breast, colon, and several other cancers (Lappe et al., 2007). The latter trial, which is consistent with our findings, had a smaller sample population, but its strengths lie in the higher dose of Vitamin D and a better adherence to treatment.

This is the first study into factors influencing autumn synthesis of Vitamin D and subsequent cancer incidence. Several factors modulating surface UV radiation in the autumn may be important. This study focuses on the large variability caused by clouds. Spatial correlation of 0.815 was found between autumn cloudiness and subsequent breast cancer incidence, which is much stronger than the spatial correlation that was found between latitude and breast cancer incidence. Correlations between breast cancer incidence and annual mean of the total solar radiation (-0.75, Gorham et al., 1990) are weaker. Correlations between breast cancer mortality and annual mean of the total solar radiation (-0.80, Garland et al., 1990) or summertime UV radiation (-0.67, Grant, 2002) are weaker as well. Wintertime UV radiation may be inadequate for synthesis of Vitamin D (Webb et al., 1988), making autumn the key period for synthesis of Vitamin D that is used during winter. In contrast, cloudiness in the spring is not expected to have a lasting effect because UV radiation is generally increasing during this season.

High temporal correlations of up to 0.96 were found between cloudiness in the autumn months, especially October, and subsequent breast cancer incidence. This temporal correlation is stronger than any of the previously discussed spatial correlations. Variability in cloudiness is a major factor causing interannual variability in UV radiation at the surface. Other factors include variability in ozone, aerosols or nitrogen dioxide (WMO, 2003). Interannual ozone variability in the northern middle latitudes is the lowest in the autumn (September to November) among all the seasons (WMO, 2003). Changes in atmospheric aerosol concentrations may have caused a 5% decline in the solar radiation

	New Mexico	**Utah**	**Atlanta**	**Connecticut**	**Seattle**	**Detroit**	**Iowa**	**San Francisco**	**Hawaii**
Cloudiness in October 1983-2002 [%]	38.8	42.65	50.55	56.425	59.925	60.875	61	64.075	66.225
Latitude [degrees N]	34.50	39.38	33.65	41.60	47.45	42.42	41.96	37.62	20.95
Breast cancer incidence rate per 100,000 for 65+	368.4	374.4	413.2	419.7	490.5	430.4	409.2	472.4	542.5

Table 2: Average cloudiness, latitude (of geographic center for states), and breast cancer incidence for white females older than 65 years in 9 SEER regions.

incident at the Earth's surface from 1960 to 1990 and a later increase through 1990s (Wild et al., 2005). Aerosol variability could also be related to breast cancer incidence, and is a topic for future research.

Stratification of cloudiness-cancer correlations by age group or time period provides insight into possible roles of Vitamin D. First, among all age groups correlations are the highest for ages 70-79, when occurrence of estrogen receptor positive (ER+) breast cancer peaks (Anderson and Matsuno, 2006). Given that temporal variability of less common estrogen receptor negative cancer differs (Glass et al., 2007) from that of ER+, this suggests a stronger link between cloudiness and ER+ breast cancer. Second, restricting the analysis to periods receding widespread estrogen-plusprogestin replacement therapy (EPRT), the highest correlation of 0.972 is found between 1973-1988 breast cancer incidence for ages 70-79 and cloudiness for 12 Decembers at least 13 years before the cancer detection. This suggests a preventative role of vitamin D in initial phases of cancerogenesis. Third, inclusion of data for 1990s shifts best fit to October cloudiness. Estrogen therapy alone raises levels of the highly active 1,25-dihydroxyvitamin D, but the addition on progestin lowers its levels (Bikkle et al., 1992). Vitamin D requirements might increase during EPRT shifting the sensitivity to October cloudiness, when UV radiation is stronger, and to the years closer to the cancer detection, when vitamin D may play a role in suppressing the growth of still undetected cancer that is fueled by the EPRT (Dietel et al., 2005).

Since the release of Women's Health Initiative trial results, the use of EPRT has declined substantially. Ravdin et al., (2007) attributed the subsequent reduction of breast cancer incidence rates to the decline in the use of EPRT. However, it is plausible that vitamin D supplementation increased concurrently and also contributed to the reduction of breast cancer incidence rates. Such increase in vitamin D supplementation would be consistent with recent trends that show almost five-fold increase in vitamin D prescriptions from year 2006 to year 2008 (Drug Topics, 2009). Additional data are needed on recent trends in serum vitamin D levels. Note that a marked decrease in serum 25(OH) D levels was observed from the 1988-1994 to the 2001-2004 National Health and Nutrition Examination Survey (NHANES) data collections (Ginde et al., 2009).

It is recognized that factors other than ambient UV light exposure, such as personal behavior, melanin content, and age, have impact on Vitamin D synthesis and Vitamin D status (Holick, 2004; McCarty, 2008). Avoidance of UV radiation in order to decrease risk of skin cancer is common and it may be leading to Vitamin D deficiency. For example, sunscreen efficiency and use have increased. Under very controlled conditions the sunscreen can completely suppress cutaneous Vitamin D synthesis. However, when subjects were allowed to apply their own sunscreen no significant changes in serum concentrations of Vitamin D were found (McCarty, 2008). A limitation of the present study is that associations were observed in groups and may not apply to individuals within these groups. Thus, further study of individual exposure, serum vitamin D levels and breast cancer risk is needed. Higher personal exposure to sunlight determined by physician assessment or self-reported frequent recreational or occupational exposure were shown to lower breast cancer risk (John et al., 1999). Analysis of personal skin pigmentation mea-

surements showed a reduced risk of advanced breast cancer among women with naturally light skin pigmentation and higher pigmentation on the forehead, which indicates higher exposure to sunlight (John et al., 2007). Furthermore, several recent case-control studies found an inverse association between serum vitamin D levels and breast cancer risk (Blackmore et al., 2008; Abbas et al., 2008; Crew et al., 2009; Rossi et al., 2009). A future study that takes measurements of Vitamin D status at the end of the winter following varying autumn cloudiness over several years could provide further information about the asserted connection among cloudiness and Vitamin D status, and potential links to breast cancer incidence.

High temporal correlations between autumn cloudiness and subsequent breast cancer incidence offer an alternative to previously proposed explanations of breast cancer trends (Miller et al., 1993; White et al., 1990; Glass et al., 2007; Li and Darling, 2007; Garfinkel, 1993; Ghafoor et al., 2003). The length of breast cancer incidence time series is a limitation of the study. Its strengths lie in the use of independently collected datasets, focus on the autumn season, and on cloudiness as a major modulator of the solar UV reaching the Earth's surface. The proposed mechanism of action through modulation of Vitamin D synthesis in human skin provides a new example of possible interaction between climate variability and human health on decadal scales.

Acknowledgment

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