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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Longitude Position in a Time Zone and Cancer Risk in the United States

Fangyi Gu[1,2], Shangda Xu[1,3], Susan S. Devesa[1], Fanni Zhang[4], Elizabeth B. Klerman[5], Barry I. Graubard[1], and Neil E. Caporaso[1]

Abstract

Background: Circadian disruption is a probable human carcinogen. From the eastern to western border of a time zone, social time is equal, whereas solar time is progressively delayed, producing increased discrepancies between individuals' social and biological circadian time. Accordingly, western time zone residents experience greater circadian disruption and may be at an increased risk of cancer.

Methods: We examined associations between the position in a time zone and age-standardized county-level incidence rates for total cancers combined and 23 specific cancers by gender using the data of the Surveillance, Epidemiology, and End Results Program (2000–2012), including four million cancer diagnoses in white residents of 607 counties in 11 U.S. states. Log-linear regression was conducted, adjusting for latitude, poverty, cigarette smoking, and state. Bonferroni-corrected *P* values were used as the significance criteria.

Results: Risk increased from east to west within a time zone for total and for many specific cancers, including chronic lymphocytic leukemia (both genders) and cancers of the stomach, liver, prostate, and non-Hodgkin lymphoma in men and cancers of the esophagus, colorectum, lung, breast, and corpus uteri in women.

Conclusions: Risk increased from the east to the west in a time zone for total and many specific cancers, in accord with the circadian disruption hypothesis. Replications in analytic epidemiologic studies are warranted.

Impact: Our findings suggest that circadian disruption may not be a rare phenomenon affecting only shift workers, but is widespread in the general population with broader implications for public health than generally appreciated. *Cancer Epidemiol Biomarkers Prev; 26(8); 1306–11. ©2017 AACR.*

Introduction

Disturbances of circadian rhythm may produce health consequences including metabolic syndrome (1–3), psychiatric conditions (4), and cancer (5, 6). Circadian rhythms are disrupted by night light exposure or night shift work, but disruption may also occur due to misalignment between environmental/social time and internal circadian timing, including "social jet lag" (7), defined as the change of sleep/wake timing individuals experience between days when they have a free choice and those days when their sleep/wake timing is determined by school or work schedules. Because circadian rhythms are entrained and synchronized by light exposure (8), the misalignment may be more severe in the western region of a time zone where solar time and hence circadian time is delayed relative to clock hour, resulting in increased exposure to light during later circadian "night" similar to "late" chronotypes (9). Shift work has been classified as a probable human carcinogen (Group 2A) by the International Agency for Research on Cancer (6), based on sufficient evidence in experimental animals and epidemiologic studies of breast cancer in female shift workers and flight attendants. However, health consequences of more subtle circadian misalignment due to a relatively delayed circadian clock as would occur in the western part of a time zone have not been well studied. Social jetlag has been associated with increased body mass index (3) in the U.S. population. In Russia and China, residence in the western border of a time zone was reported to have higher cancer incidence and mortality rates as well as lower life expectancy (9). Here we conducted the first investigation of time zone position in the United States in relation to incidence of total and specific cancers.

Materials and Methods

Cancer incidence data

We calculated county-specific age-adjusted (2000 U.S. standard) cancer incidence rates by gender for malignant neoplasms diagnosed during the years 2000 to 2012 from the Surveillance, Epidemiology and End Results (SEER) program, using SEER*Stat software (10). We restricted analyses to whites to reduce confounding by race. We included 607 counties in 11 states of the continental United States: California, Connecticut, Georgia, Iowa, Kentucky, Louisiana, New Mexico, New Jersey, Utah, the Detroit metropolitan area of Michigan and the Seattle-Puget Sound area of Washington. Seven counties that encompassed 2 time zones were excluded. Cancers were defined using ICD-O-3 site and morphology codes as used in SEER (10).

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland. [2]Roswell Park Cancer Institute, Buffalo, New York. [3]Harvard University, Cambridge, Massachusetts. [4]Information Management Services, Inc., Rockville, Maryland. [5]Division of Sleep and Circadian Disorders, Brigham and Women's Hospital and Division of Sleep Medicine, Harvard Medical School, Boston, Massachusetts.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Neil E. Caporaso, Room 7E102, 9609 Medical Center Drive, Rockville, MD 20850. Phone: 240-276-7228; Fax: 240-276-7835; E-mail: caporasn@mail.nih.gov

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We included 23 types of cancer: 20 most common cancers among males and females in the United States [breast, lung and bronchus, prostate, colon and rectum, urinary bladder, melanoma of the skin, non-Hodgkin lymphoma, thyroid, kidney and renal pelvis, corpus uteri and uterus NOS, pancreas, oral cavity and pharynx (excluding lip and salivary glands), liver and intrahepatic bile duct, myeloma, stomach, brain, ovary, acute myeloid leukemia, chronic lymphocytic leukemia, esophagus; ref. 11], as well as larynx, cervix uteri, and gallbladder cancers, which have been associated with cigarette smoking (12), alcohol drinking (13), or obesity (14).

We also evaluated cancer subgroups for breast cancer (hormone receptor positive/negative (HR^+/HR^-; ref. 15), esophagus cancer (adenocarcinoma, squamous cell carcinoma; ref. 16), and lung and bronchus cancer (adenocarcinoma, small cell carcinoma, and squamous cell carcinoma; ref. 17). Coding for subgroups of each cancer was described previously (15–17).

Position in a time zone data

Geographical coordinates of each county's population centroid, which is defined as the latitude and longitude of the population balance point (official Census definition) of each county using 2010 U.S. Census data, were obtained from the United States Census Bureau (http://www.census.gov/geo/reference/centersofpop.htm). The position in a time zone (PTZ) is calculated as the distance (in degrees longitude) between the population centroid of each county and the central meridian of longitude of the respective time zone. In the United States, time zones correspond to approximately 15 degrees of longitude, and the central meridians of the Eastern, Central, Mountain, and Pacific time zones are 75, 90, 105, and 120 degrees longitude west, respectively.

Statistical analysis

For total cancer and each specific cancer, we used a weighted least squares linear regression to examine the associations between the natural logarithm of age-adjusted county-level cancer rates and PTZ as continuous variable, where the weights were the county population sizes. The analyses adjusted for latitude, poverty percentage (the American Community Survey, 2008–2013-Census Planning Database http://www.census.gov/research/data/planning_database), prevalence of cigarette smoking (18), and state. Latitude was included as it is related to degree and intensity of solar exposure, which influences vitamin D levels, day length, solar zenith angle (in winter at high latitudes, more UVB radiation is absorbed), and sleep (19, 20). Latitude also subsumes climatic factors such as temperature that influence overall mortality and may impact cancer (21). Smoking is related to diverse cancers. Poverty and state relate to health care quality and access. Covariate-adjusted rate ratios (RR) per 5 degrees difference in longitude, corresponding to 20 minutes, were estimated by exponentiating five times the regression coefficients estimated in the model. Analyses were conducted in men and women separately.

To check whether an association could be explained by obesity, urbanization, and Hispanic ethnicity, we further adjusted for obesity prevalence (BMI > 30, from Centers for Disease Control and Prevention for 2010; ref. 22), and an urban/rural index (2013 Rural-Urban Continuum Codes, http://www.ers.usda.gov/data-products/rural-urban-continuum-codes.aspx). Sensitivity analyses were conducted by restricting to non-Hispanic whites. To adjust for multiple comparisons, we used Bonferroni-corrected two-sided P values as the significance criteria [i.e., $P < 1.8 \times 10^{-3}$ (0.05/28) for men, and $<1.7 \times 10^{-3}$ (0.05/30) for women]. R software version 3.2.2 was used for statistical analysis. For each gender, age-adjusted cancer rates were calculated for position tertiles across the four time zones.

Results

After adjustment for age and county-level covariates, the total cancer incidence rates for counties increased significantly from eastern to western locations within time zones (Table 1; Figs. 1, and 2). The RR per five degrees of longitude toward the west (corresponding to 20 minutes' delay of sunrise) was 1.029 [95% confidence intervals (CI), 1.017–1.041, $P = 2.7 \times 10^{-6}$] for men and 1.039 (95% CI, 1.027–1.051; $P = 3.8 \times 10^{-10}$) for women. Chronic lymphocytic leukemia rates also increased significantly among men (RR = 1.134; 95% CI, 1.076–1.196; $P = 3.1 \times 10^{-6}$) and women (RR = 1.118; 95% CI, 1.052–1.189; $P = 3.7 \times 10^{-4}$).

In men only, the east–west gradients in risk within a time zone were elevated for stomach cancer (RR = 1.087; 95% CI, 1.035–1.142; $P = 9.6 \times 10^{-4}$), liver cancer (RR = 1.110; 95% CI, 1.046–1.177; $P = 6.0 \times 10^{-4}$), prostate cancer (RR = 1.042; 95% CI, 1.018–1.066; $P = 4.8 \times 10^{-4}$), and non-Hodgkin lymphoma (RR = 1.059; 95% CI, 1.028–1.091; $P = 1.6 \times 10^{-4}$).

Among women only, the east–west gradients in risk within a time zone were increased for breast cancer overall (RR = 1.037; 95% CI, 1.019–1.055; $P = 6.5 \times 10^{-5}$) and specifically HR^+ breast cancer (RR = 1.055; 95% CI, 1.026–1.084; $P = 1.8 \times 10^{-4}$). Also elevated were esophageal cancer (RR = 1.163; 95% CI, 1.075–1.258; $P = 1.8 \times 10^{-4}$), colorectal cancer (RR = 1.045; 95% CI, (1.024–1.066; $P = 1.8 \times 10^{-5}$), lung cancer (RR = 1.046; 95% CI, 1.017–1.076; $P = 1.6 \times 10^{-3}$), and corpus uteri cancer (RR = 1.1; 95% CI, 1.067–1.135; $P = 2.4 \times 10^{-9}$). None of the subgroups for esophagus cancer was significantly associated with the position in a time zone.

The age-adjusted cancer incidence rates and 95% CI for each tertile of the PTZ combined across the four time zones are provided in Supplementary Table S1. A strong east-to-west gradient was observed for all cancers and chronic lymphocytic leukemia among both males and females. Similar, but less strong trends, also appear in other cancers, such as colorectal and prostate cancer.

Further adjusting the models for urban–rural characteristic and the prevalence of obesity, and restricting to non-Hispanic whites did not change the findings.

Discussion

In 607 counties of the continental United States, involving more than four million cancer diagnoses among whites, we found that residents in the western regions of time zones had increased rates of overall cancer and many specific cancers, in accord with the circadian disruption hypothesis. These observations might implicate a novel source of circadian disruption that occurs as one proceeds westward in each time zone due to the increased divergence between social time and internal circadian time.

Our findings on breast, corpus uteri, and prostate cancer are consistent with a previous report based on a small ecologic database of 59 regions in European population in Russia (9). We also identified new associations that will require follow-up: increased risk of chronic lymphocytic leukemia in both genders, stomach cancer, liver cancer, and non-Hodgkin lymphoma in males, and esophageal, colorectal, and lung cancer in females associated with western time zone position. In particular, the

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association with chronic lymphocytic leukemia is the strongest and most robust; the association was consistent in each time zone, and in both men and women.

The associations with female breast cancer are only significant for HR^+ breast cancer. The positive findings in the hormone-related malignancies are generally concordant with a body of previous work that reported elevated risk in shift workers of breast cancer (15, 23), prostate cancer (24), and uterine corpus cancer (25), all hormone-responsive tumors. Epidemiologic studies have also reported increased risks of colon (26, 27) and non-Hodgkin lymphoma (28) associated with shift work.

The unexpectedly broad pattern of associations across multiple tumor types that we observed accords with the evidence in animal models, studies of shift workers, and mechanistic studies that indicate circadian rhythm alterations have manifold biological consequences. Increased cancer risks in animal models have been documented in a broad group of tumors including blood, liver, ovary, intestine, colon, and skin (29–31). Mechanistically, many nonhormone-related pathways involved in carcinogenesis are under circadian control (32), such as cell proliferation, DNA repair (33), apoptosis (34), and immune response (35). Therefore, it is possible that circadian disruption has effects across a wider group of tumors than previously thought.

Alternatively, the findings may be due to confounding, or other bias. Geographical regions could subsume many cancer-related factors, such as the degree of rural/urban, tax policies affecting smoking, poverty levels, cancer screening and hospitalization, as well as behavior and lifestyles. Although we adjusted for many of these community-level factors, given the limitations of ecologic studies, study of individual-level subjects is needed to confirm these findings.

We note that our strongest and most consistent effect was observed for chronic lymphocytic leukemia, a tumor that lacks strong extrinsic environmental risk factors and which has recently been a focus of studies of dysregulation, altered expression (36, 37) and methylation (38) of specific circadian genes. Further investigation of this association along with other categories of lymphoproliferative malignancies is warranted.

Table 1. Association between position in a time zone[a] and age-adjusted county-level cancer incidence in 11 states within the continental United States, SEER program 2000–2012[b]

	Male			Female		
Cancer[c]	**Cases**	**RR (95% CI)[f]**	***P***	**Cases**	**RR (95% CI)[f]**	***P***
All cancers	2,095,394	1.029 (1.017–1.041)	$\mathbf{2.7 \times 10^{-6}}$	1,972,514	1.039 (1.027–1.051)	$\mathbf{3.8 \times 10^{-10}}$
Oral cavity and pharynx[d]	54,889	1.037 (0.997–1.078)	0.07	23,199	1.086 (1.029–1.145)	2.6×10^{-3}
Esophagus	30,956	1.003 (0.960–1.049)	0.89	8,751	1.163 (1.075–1.258)	$\mathbf{1.8 \times 10^{-4}}$
Adenocarcinoma	21,355	1.000 (0.947–1.056)	1	3,448	1.054 (0.946–1.175)	0.34
Squamous cell	6,570	1.024 (0.942–1.114)	0.57	4,150	1.071 (0.956–1.201)	0.24
Stomach	35,990	1.087 (1.035–1.142)	$\mathbf{9.6 \times 10^{-4}}$	21,924	1.039 (0.974–1.107)	0.24
Colon and rectum	205,056	1.023 (1.002–1.044)	0.03	193,349	1.045 (1.024–1.066)	$\mathbf{1.8 \times 10^{-5}}$
Liver and intrahepatic bile duct	39,276	1.110 (1.046–1.177)	$\mathbf{6.0 \times 10^{-4}}$	15,796	1.099 (1.028–1.175)	6.0×10^{-3}
Gallbladder	2,834	0.875 (0.763–1.003)	0.06	6,683	1.030 (0.943–1.124)	0.51
Pancreas	51,150	1.041 (1.008–1.075)	0.015	50,553	1.047 (1.013–1.083)	0.01
Larynx	24,578	0.997 (0.951–1.045)	0.9	6,158	1.077 (0.996–1.165)	0.07
Lung and bronchus	288,452	1.002 (0.977–1.028)	0.87	256,618	1.046 (1.017–1.076)	$\mathbf{1.6 \times 10^{-3}}$
Adenocarcinoma	89,166	1.006 (0.967–1.047)	0.75	94,771	1.058 (1.019–1.100)	3.8×10^{-3}
Squamous cell	65,665	1.003 (0.965–1.043)	0.87	38,324	1.029 (0.974–1.087)	0.31
Small cell	35,852	0.985 (0.941–1.031)	0.51	35,834	1.037 (0.986–1.090)	0.16
Melanoma of the skin	119,304	1.050 (0.998–1.103)	0.06	85,934	1.023 (0.967–1.083)	0.43
Breast	4,463	1.074 (0.972–1.187)	0.16	593,753	1.037 (1.019–1.055)	$\mathbf{6.5 \times 10^{-5}}$
HR positive	3,713	1.038 (0.932–1.156)	0.49	435,649	1.055 (1.026–1.084)	$\mathbf{1.8 \times 10^{-4}}$
HR negative	141	0.450 (0.134–1.514)	0.2	92,225	1.025 (0.995–1.056)	0.1
Cervix uteri	0	—	—	34,283	1.031 (0.985–1.080)	0.19
Corpus and uterus NOS[e]	0	—	—	113,344	1.100 (1.067–1.135)	$\mathbf{2.4 \times 10^{-9}}$
Ovary	0	—	—	62,958	1.011 (0.977–1.045)	0.54
Prostate	578,119	1.042 (1.018–1.066)	$\mathbf{4.8 \times 10^{-4}}$	0	—	—
Urinary bladder	147,266	1.012 (0.986–1.038)	0.39	47,073	1.025 (0.983–1.070)	0.24
Kidney and renal pelvis	80,453	1.020 (0.989–1.052)	0.2	47,964	1.009 (0.972–1.047)	0.64
Brain	32,043	1.019 (0.978–1.061)	0.37	24,808	0.995 (0.949–1.042)	0.82
Thyroid	24,274	1.042 (0.976–1.112)	0.22	73,382	1.063 (1.008–1.121)	0.02
Non-Hodgkin lymphoma	95,143	1.059 (1.028–1.091)	$\mathbf{1.6 \times 10^{-4}}$	80,861	1.039 (1.010–1.070)	0.01
Myeloma	26,959	0.980 (0.935–1.027)	0.39	20,839	1.064 (1.013–1.118)	0.01
Chronic lymphocytic leukemia	25,251	1.134 (1.076–1.196)	$\mathbf{3.1 \times 10^{-6}}$	17,072	1.118 (1.052–1.189)	$\mathbf{3.7 \times 10^{-4}}$
Acute myeloid leukemia	17,990	1.030 (0.975–1.089)	0.28	14,815	1.045 (0.987–1.106)	0.13

NOTE: *P* values less than 1.8×10^{-3} (0.05/28) for men and less than 1.7×10^{-3} (0.05/30) for women are in bold and indicate statistical significance using Bonferroni correction.

[a]The position in the time zone (PTZ) is calculated as the distance (in degrees longitude) between the population centroid of each county and the middle meridian of the located time zone (EST:75, CST:90, MST:105, and WST:120).

[b]A weighted (by population size) logarithmic linear regression was used between PTZ and age-adjusted (2000 U.S. standard population) county-level cancer incidence rate. Model adjusted for latitude, poverty percentage, smoking and state.

[c]Ordered by organ systems, based on SEER Statistics Review 1975 to 2013.

[d]Excluding lip and salivary glands.

[e]Not otherwise specified.

[f]RRs are per five degrees of longitude difference, equivalent to 20 minutes.

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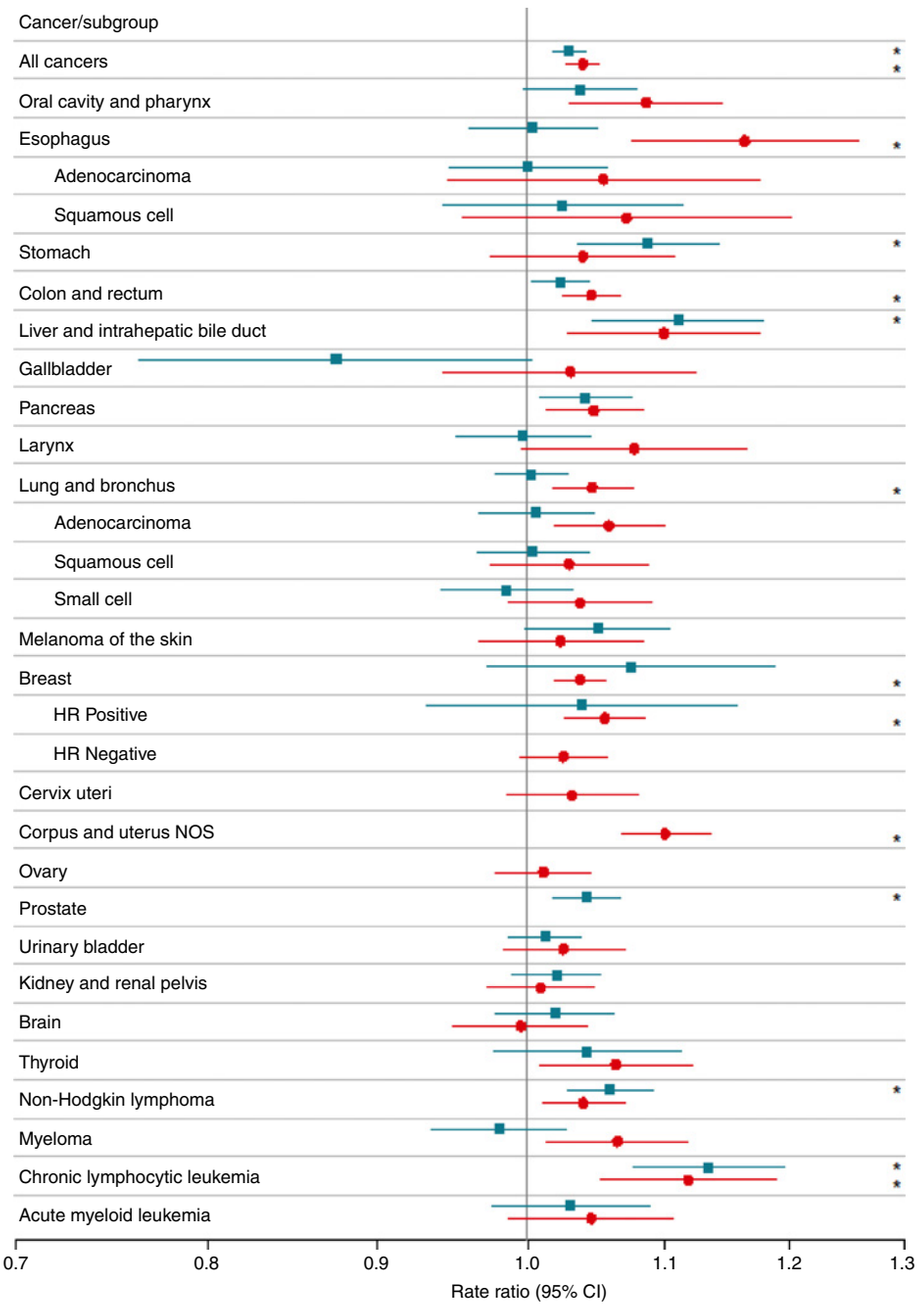

Figure 1.
Adjusted cancer RRs and 95% CIs in 11 states within the continental United States, SEER program 2000 to 2012, by gender and cancer type. The adjusted cancer RRs are per five degrees of longitude difference, equivalent to 20 minutes. *, *P* value less than 1.8×10^{-3} (0.05/28) for men (blue square) and less than 1.7×10^{-3} (0.05/30) for women (red dot).

The hypothesis that exposure to light at night contributes to circadian disruption, previously associated with breast (39), and prostate (40) cancers, is generally concordant with our findings. There is evidence that exposure to light at night suppresses melatonin production, which has anti-oncotic properties (41). Consistent with this is the finding of reduced breast cancer in blind women, in whom light does not suppress melatonin because the pathway for light-induced suppression is via the eye (42).

Our study has several strengths. Using position in a time zone to study circadian misalignment is a unique design. The SEER registry is closely monitored and controlled, and therefore has high data quality (10). The opportunity to link the SEER registry with substantial numbers of cancer cases (2,095,394 in men, 1,972,514 in women) with geographic information allowed us to explore multiple cancer sites. Other independent variables are derived from high-quality government data allowing us to consider several important potential confounders.

As mentioned above, the ecologic study is limited by the inability to adjust for person-level risk factors, although we were able to adjust for county-level data on cigarette smoking, latitude, poverty, and state to partially mitigate these limitations. Separately, we examined obesity, Hispanic make-up of counties and

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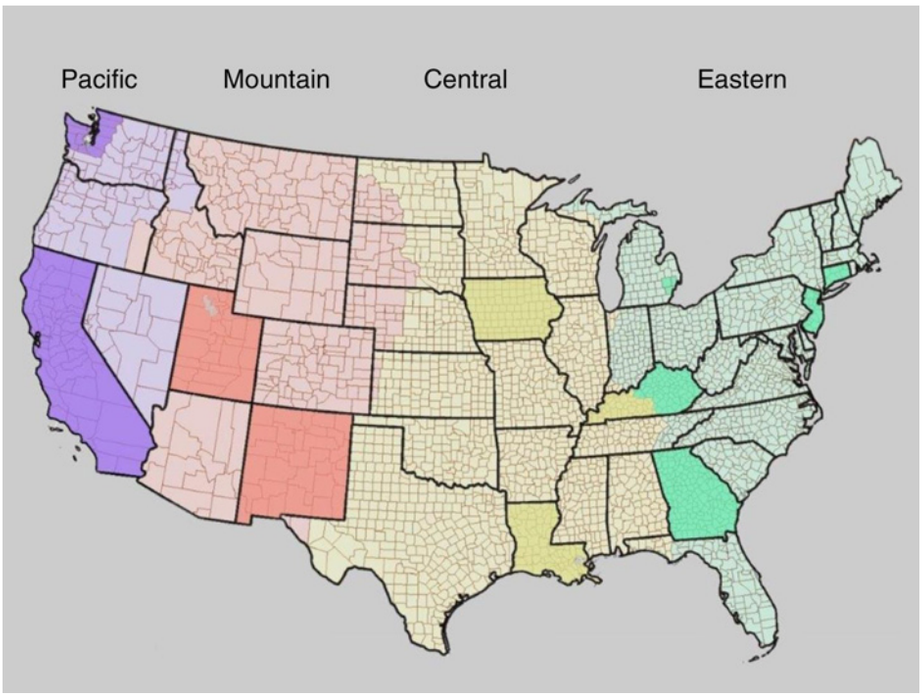

Figure 2.
Map of the Continental United States showing the four time zones (Pacific—purple, Mountain—peach, Central—yellow, Eastern—green) with each of the 11 SEER states (California, Connecticut, Georgia, Iowa, Kentucky, Louisiana, New Mexico, New Jersey, Utah) and registries (the Detroit metropolitan area of Michigan and the Seattle-Puget Sound area of Washington) shaded a darker shade. The 607 counties are also indicated.

urbanicity in sensitivity analyses. None of these variables had a noteworthy effect on the findings.

The inability to track migration and the impact of temporal lag between exposure and outcome are limitations. The United States is a relatively mobile society, and residence may have changed one or more times, but such changes would tend to bias data towards the null, making real differences harder to detect. It has been hypothesized that the natural seasonal adaptation is disrupted by Daylight Savings Time (43) but because all the states included in our study are equally affected, this would not influence our findings.

If these findings are verified, what measures should be considered to reduce their potential public health impact? It is worth noting that the magnitudes of risks are in a very small range (generally RR < 1.1 per 5 degrees longitude). Measures to reduce environmental vs. circadian misalignment such as improved sleep hygiene (reducing light at night, earlier bedtimes) and promoting later and more flexible school and work schedules have been advocated by the United States Centers for Disease Control and Prevention and others (19). The tendency for later sleep times and chronotypes to increase with westward movement across the time zone is well documented on the basis of questionnaire and personal device data from Europe, Russia, China, South Africa, and the United States (44–46). Increased misalignment may cause shorter sleep episodes, which may also contribute to adverse health outcomes. Further studies to investigate the relationship of time zone position to diabetes, obesity, cardiovascular endpoints, and overall mortality, as well as follow-up of the cancer findings reported here, are needed. Our findings suggest that circadian disruption is not a rare phenomenon affecting only shift workers or international travelers but is common in the general population and therefore has broader implications for public health than generally appreciated.

In summary, this ecologic study shows residency in the western part of a time zone is associated with increased rates of total cancer and many specific cancers, in accord with the circadian disruption hypothesis. Replication in analytic epidemiology studies is warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S. Xu, S.S. Devesa, N.E. Caporaso
Development of methodology: F. Gu, S. Xu, S.S. Devesa, B.I. Graubard, N.E. Caporaso
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Xu, S.S. Devesa, N.E. Caporaso
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): F. Gu, S. Xu, S.S. Devesa, F. Zhang, E.B. Klerman, B.I. Graubard, N.E. Caporaso
Writing, review, and/or revision of the manuscript: F. Gu, S. Xu, S.S. Devesa, F. Zhang, E.B. Klerman, B.I. Graubard, N.E. Caporaso
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N.E. Caporaso
Study supervision: N.E. Caporaso

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