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

Fangyi Gu1,2, Shangda Xu1,3, Susan S. Devesa1, Fanni Zhang4, Elizabeth B. Klerman5, Barry I. Graubard1, and Neil E. Caporaso1

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.

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 SEERStat 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).
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 intra-hepatic 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 (PITZ) 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 approx.

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 PITZ as continuous variable, where the weights were the county population sizes. The analyses adjusted for latitude, pov-

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 × 10−6) for men and 1.039 (95% CI, 1.027–1.051; P = 3.8 × 10−6) for women. Chronic lymphocytic leukemia rates also increased significantly among men (RR = 1.134; 95% CI, 1.076–1.196; P = 3.1 × 10−4) and women (RR = 1.118; 95% CI, 1.052–1.189; P = 3.7 × 10−4).

Among women 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 × 10−5), liver cancer (RR = 1.110; 95% CI, 1.046–1.177; P = 6.0 × 10−4), prostate cancer (RR = 1.042; 95% CI, 1.018–1.066; P = 4.8 × 10−3), and non-Hodgkin lymphoma (RR = 1.059; 95% CI, 1.028–1.091; P = 1.6 × 10−3).

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 × 10−5) and specifically HR+ breast cancer (RR = 1.055; 95% CI, 1.026–1.084; P = 1.8 × 10−4). Also elevated were esophageal cancer (RR = 1.163; 95% CI, 1.075–1.258; P = 1.8 × 10−3), colorectal cancer (RR = 1.045; 95% CI, 1.024–1.066; P = 1.8 × 10−3), lung cancer (RR = 1.046; 95% CI, 1.017–1.076; P = 1.6 × 10−3), and corpus uteri cancer (RR = 1.1; 95% CI, 1.067–1.135; P = 2.4 × 10−3).

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
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.
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

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 \times 10^{-3} (0.05/28) for men (blue square) and less than 1.7 \times 10^{-2} (0.05/30) for women (red dot).
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 bedtime) 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

Acknowledgments
We thank David Check of the Biostatistics Branch, DCEG, for figure development.

Grant Support
This work was supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics of the National Cancer Institute. E.B. Klerman was supported by K24-CA135664.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received December 21, 2016; revised February 20, 2017; accepted April 6, 2017; published OnlineFirst April 27, 2017.
Longitude Position in a Time Zone and Cancer Risk in the United States

Fangyi Gu, Shangda Xu, Susan S. Devesa, et al.


Updated version
Access the most recent version of this article at:
doi:10.1158/1055-9965.EPI-16-1029

Supplementary Material
Access the most recent supplemental material at:
http://cebp.aacrjournals.org/content/suppl/2017/04/27/1055-9965.EPI-16-1029.DC1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, use this link http://cebp.aacrjournals.org/content/26/8/1306. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.