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Germ Cell Testicular Cancer Incidence, Latitude and Sunlight Associations in the United States and Australia

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ABSTRACT

International patterns suggest germ cell testicular cancer (GCTC) incidence may be lower in lower latitudes. To investigate this possibility, we examined GCTC incidence by latitude (population-centroid in 2000) for men ≥15 years within two reasonably homogeneous countries, the United States (US) and Australia. In the US, we examined age-adjusted

incidence/latitude trends using data from states (2001-2010) and local-area registries (1980-2011). In Australia, we evaluated incidence/latitude trends in 61 Statistical Divisions (2000-2009). In White US men (68,566 cases), state incidences increased by latitude, rising 5.74% (4.45-7.05%) per 5°North latitude increment. Similar trends were found for seminoma and non-seminoma subtypes (p<0.001). In Black US men (2,256 cases), the association was also seen (4.9%; 0.2 to 9.7%). In local US data, similar increases in incidence with latitude were present in each of the last three decades. In Australia (6,042 cases), the incidence increased by 4.43% (95% CI: 1.54-7.39%) per 5°South, and trends for subtypes were similar. Thus, we found that incidence of GCTC in both White and Black men increased significantly with distance from the equator, approximately 1% per degree within the range of latitudes studied.

INTRODUCTION

The epidemiology of germ cell testicular cancer (GCTC) is unusual. Although infrequent, incidence peaks sharply to dominate cancer risk in 15-30 year old males, an age-range when cancer incidence is otherwise low (1-3). Recognized risk factors support *in utero*/neonatal influences on incidence, including strong associations with gonadal dysgenesis and cryptorchidism (4), but other postnatal environmental factors have been proposed, such as undetermined social/economic influences (5) and diet (6-9). Geographically, GCTC incidence is higher in northern/north-western than southern Europe, wherein Norway and Denmark have the highest national incidences (9-13). The lowest GCTC incidences are found in southeast Asia and Africa (9,14,15), although reporting/surveillance comparability have been questioned (15). Finally, there is also a strong genetic association between testicular cancer incidence and carriage of the G allele of KITLG, which confers a 3-fold increased risk (16-19). The KITLG G variant is also associated with lighter-skin coloration through an

effect on melanin production and more frequent in areas farther from the equator (19). In the United States (US), Blacks have a remarkably low GCTC incidence compared to Whites (1) and also much lower G allele carriage than Whites (19).

However, there are inconsistencies within these geographic and pigmentation patterns. For example, GCTC incidence in Finland, a northern nation, is intermediate for Europe (9-13), and in New Zealand, the darker-skinned Maori have higher incidence than local-area Whites (20). These variations suggest that the etiology is multi-factorial and that additional important but unknown risk factors exist. The heterogeneous cultures of different countries and in distinct subsets within societies make it difficult to ascertain reasons for the geographic and societal variations in incidence internationally. We therefore examined GCTC incidence in White and Black men by the latitude in the US and Australia. Both countries are geographically vast, economically well-developed countries with similar lifestyles, and both have comprehensive population-based registration of cancer by well-defined constituent sub-regions. *A priori*, we hypothesized higher incidences in areas away from the equator, i.e., North (N) in the US and South (S) in Australia.

We were primarily interested seasonal variation in visual light, for which latitude is an excellent surrogate (21). We reasoned that greater cyclical variation in reproductive cycles might affect testicular cancer incidence via retinal-pituitary interactions. Seasonal variation affects reproductive cycles in many species (22-27) and probably humans (28,29). Retinal effects would be mediated mainly by light in the visual spectrum since little UV spectrum light penetrates to the retina (21). We also evaluated if GCTC incidence variation in Australia correlated better than latitude with directly measured ultraviolet radiation (UVR), which takes

into account variation in regional cloud cover. Light in the visual spectrum will follow the same cloud-cover pattern as UVR (21). Finally, we evaluated GCTC incidence in by latitude in US Black men, reasoning that retinal exposure to visual light would be similar whereas cutaneous effects would differ because of pigmentation.

MATERIALS AND METHODS

United States. Anonymous grouped cancer data in White (including Hispanics) and Black men from 2001 through 2010 by state and the District of Columbia were obtained from the North American Association of Central Cancer Registries (NAACCR); Minnesota, Vermont and Kansas did not provide data, and individual states were missing data for specific years (average annual incidence used). The extraction received exempt status from the NAACCR Institutional Review Board on Human Subjects. Hispanics have a slightly lower GCTC incidence than non-Hispanic Whites (30) but were included with Whites for comparability with Australia, which does not distinguish subgroups in cancer patients but has significant Mediterranean-origin populations. We examined GCTC incidence trends with latitude, based on the latitude of the population-centroid of each state in 2000, for total GCTC and for seminoma and non-seminoma cancers, defined by International Classification of Diseases—Oncology 2nd Edition (ICD-O-2) codes (31) as described below. Comparisons were made to the incidence of all cancers excluding GCTC in the same populations.

GCTC data also were obtained from the Surveillance, Epidemiology, and End Results (SEER) Registries using web-accessible records (32,33), defined in Figure 2 and accessed April 11, 2016. Although geographically limited, the smaller size of SEER registries

provided greater specificity for the population-centroid latitude. For example, while California extends over a thousand miles North-to-South, SEER registries exist for three more-localized areas: Los Angeles, San Francisco and San Jose/Monterey. Cases from 1980-2011 were defined by ICD-O-2 (31). The SEER data also contained more delineated population descriptors. We examined incidence patterns in White men excluding Hispanics and Black men from 17 areas available in SEER 18, 2001-2011 to align with NAACRR and Australia evaluation-periods. Alaskan data were excluded because SEER data were for Native Americans only. The consistency of the latitude association was evaluated in decade intervals using SEER 9 data for Whites including Hispanics, required for consistency because Hispanics were not identified as a subgoup in SEER until 1992.

Australia. After review and approval, anonymous grouped cancer data between 2000 and 2009 (considered complete) were obtained from the Australian Institute of Health and Welfare (AIHW). Analysis examined incidence for Statistical Divisions, stable administrative units smaller than states that encompass Australia completely and without overlap. The corresponding populations were obtained from the Australian Bureau of Statistics (34). For data stability, the small populations of the Australia Capital Territory and the Northern Territory (each with two Statistical Divisions) were collapsed into single entities. The northern and central Statistical Divisions are sparsely populated but cover vast areas, resulting in unstable point estimates which can give misleading impressions on the map representation (map in the Supporting Information), but the estimate variability was accommodated in statistical analysis of trend which considered population size.

Cases were defined using the same ICD-O-2 codes (31) as in the US analyses. Trends for incidence by population-centroid latitude of the Statistical Division were examined for GCTC and its major subtypes and for overall cancer incidence trends, excluding GCTC. We also excluded melanoma, considered well documented in Australia, because incidence increased strongly in northern areas and was sufficiently common to impact on the all-cancer trends with latitude. Indigenous Australians (Aborigines/Torres Straits Islanders) constitute 3% of all Australians but tend to live in central and equatorial Statistical Divisions (34). One report, using indirect methods to evaluate a small database, suggested that Indigenous Australians might have a lower GCTC incidence (35), possibly biasing our associations. We could not exclude them because, according to the AIHW, the ethnic classification of cancer patients is not reliable in some Australian states. Therefore, we evaluated the impact of their inclusion by a sensitivity analysis described in Results.

We also investigated the impact of solar UVR in Australia (here defined as bandwidth 280-400 nm) intensity. We used UVR measurements (watts/m^2) obtained from a UVR database developed at Queensland University of Technology (Brisbane, Australia) using an established UVR modeling protocol (36). Modeled assessments of ground-level UVR measures adjusted for cloud cover/pollution were made in half-degree latitude and longitude increments, and the nearest referent point to the population-centroid of each Statistical Division was accepted to represent the ambient UVR exposure. Seasonal assessment examined directly measured average monthly UVR exposure, a measure of the annual average solar exposure that includes variation in cloud cover, to determine if summer (January) and winter (June) exposures conferred more importance.

Analysis. Cancers were initially classified by ICD-O-2 codes as all invasive cancers, melanoma (C44, M872-M879), and GCTC (M9060 to 9102, except M9063). Cancer incidence trends by latitude were then examined for GCTC, all cancers except GCTC (and melanoma in Australia), and for subtypes of seminoma (M9061, M9062 and M9064) and non-seminoma cancers (M9065-M9102). In both the US (state and SEER registries) and Australia Statistical Districts, directly age-standardized incidence rates (ASR) per 100,000 person-years were calculated for men ≥15 years old (Stata 13.0 for Windows; StataCorp, College Station, TX, 77845, USA) using the 2000 US Census distribution as the standard for both countries. Age-adjusted incidence changes (percent) for every 5° increase in latitude are presented with 95% confidence intervals (CI), which was based on population size, using on a log-linear model generated by negative binomial regression. This model had the age-specific number of incident cancers as the outcome variable and the log of the age-specific population as the offset variable. We used data-driven joinpoint analysis (Joinpoint 4.1.0; Statistical Research and Applications Branch, National Cancer Institute, USA) to evaluate if a log-linear model was appropriate. The population-centroid latitude (continuous) and age-at-diagnosis (categorical, five-year age groups) were included in the model. SEER data were analyzed independently using R version 3.0 (The R Project, Auckland, New Zealand). In SEER data, percent changes per 5° latitude were also assessed using the age-adjusted incidence and the log of each registry population as the offset. Trends assessed the relationship of incidence to the population-centroid latitude of each registry using Poisson regression.

The association between latitude and lower UVR in areas more distant from the equator is well known, but UVR intensity at the same latitude could be impacted by the Antarctic "ozone hole" which overlaps southern Australia (37). To assess an independent role for UVR

on cancer incidence in Australia, we first examined latitude and UVR measures, finding a high co-linearity. We therefore used a two-stage modeling process to investigate the separate effects of latitude and UVR. The first model was a simple comparison of incidence trend by latitude, as described above. The second model had the same outcome variable but included the UVR measurement as the explanatory variable and the fitted values from the first model as the offset variable. A similar approach has been used for other latitude-related studies (38).

RESULTS

United States

In US White men, (68,566 cases), the overall age-standardized incidence of GCTC was 7.9 cases/100,000 person-years (95% CI: 7.8-8.0). For all GCTC, incidence increased with increasing latitude (Figure 1), 5.74% (4.45-7.05%) per 5°N latitude increment (p<0.001, Table 1). Incidence increases for seminoma (38,695 cases) and non-seminoma (29,871 cases) were 7.38% (5.75 to 9.03%) and 4.09%, (2.57 to 5.64%) per 5°N, respectively. Joinpoint analysis showed no significant deviation from a log-linear relationship at any latitude. Hawaii (21°N) was noted to be an outlier, but its influence was negligible because of its small population. For all invasive cancers except GCTC; (5,928,111 cases), incidence decreased non-significantly with latitude (p=0.18; Table 1 and Figure 1). In Black men (2,256 cases), the age-standardized incidence, 1.5 cases/100,000 (95% CI: 1.4 to 1.8), was low compared to White men. However, the incidence of GCTC in Black men also increased with latitude, 4.9% (0.2- 9.7%) per 5°N, which was approximately the same slope as in White men. The map in the Supporting Information illustrates the average annual age-standardized GCTC incidence by state, showing higher GCTC incidence in northern than southern states in both the East and West of the US.

To examine long-term trends, we used SEER Registry data, as defined and presented in Figure 2, for GCTC incidence from 1980 through 2011. In Seer 9 data, incidence in White men including Hispanics increased with latitude (per 5°N) in every time period: in 1980-89 (5,027 cases): 4% (95% CI: 1-7%); in 1990-1999 (6,185 cases): 5% (2-7%); and in 2000-2011 (8,442 cases): 4% (1-6%) (Figure 2A). In the SEER 18 data, 2001-2011, we examined non-Hispanic men White men only (17,196 cases) to assure that trends were not attributable to admixed Hispanic populations, finding the GCTC incidence trend with latitude were increased to 8% (7-10%) per 5°N latitude (Figure 2B). Excluding Hawaii (173 cases) as an outlying point, the GCTC incidence rate trend by latitude among non-Hispanic White men in SEER 18 was 10% (8-11%) per 5°N. Trend increases were also present in seminomas and, less strongly, in non-seminomas. In Black men in SEER 18 (643 GCTC cases), the association between GCTC incidence and latitude were similar (8% increase per 5°N) although having wide confidence intervals (-1 to 17%), the trend was not statistically significant (p=0.10).

Australia

In Australian men ≥15 years old, 6,042 GCTCs were reported from 2000 through 2009. The overall age-standardized incidence was 7.1/100,000 person-years (95% CI: 6.8-7.8%), being 5.9 in the most equatorial northern band, <21.0°S, and 8.2 in the most southern band (>36°S). For all GCTC, incidence increased 4.43% (1.54-7.39%) per 5°S latitude increment (p=0.002, Table1). Joinpoint analysis suggested a possible flattening of the trend in the northern (equatorial) regions (inflection at 27°S). Incidences increases for seminoma (3,365 cases) and non-seminoma (2,377 cases) were statistically similar: 4.86% (1.25 to 8.61%; p=0.008) and 2.54% (-1.77 to 7.04%; p=0.252) per 5°S, respectively.

We examined all-cancer (invasive) incidence, excluding GCTC (Table 1) and also melanoma (474,192 cases) because melanoma incidence was very high in equatorial areas (trend with latitude: -11.81; 95% CI: -12.87 to -10.74 per 5°S increase); being frequent, its inclusion would have biased all-cancer incidence trends with latitude. For all other cancers, there was a non-significant decrease in incidence with increasing latitude (-0.72%; -1.55 to 0.13 per 5°S increment).

To evaluate the possible impact of including Indigenous Australian men, we undertook a sensitivity analysis that assumed a 50% lower GCTC incidence in the proportion of the population identified as being Indigenous in each Statistical Division by the Australian Bureau of Statistics (19). We estimated cases arising in Indigenous Australians using 50% incidence reductions of patients and the Indigenous population of men in the Division by proportion. For example, if 100 testicular cases were observed in a Division with 10% Indigenous men, 5 cases (50% of expected by proportion) would be excluded and the Division population reduced by 10%, thereby increasing the incidence in the remaining population. In this conservative model, trends of increasing incidence at higher latitude trends were found but at borderline significance (p=0.074).

UVR exposures for the Division centroids were closely correlated with latitude by several measures: monthly average annual UVR (ρ=-0.95), July UVR (ρ=-0.97) and January UVR (ρ=-0.49). After inclusion of latitude, analysis of residual effects from UVR variation found no independent associations with GCTC incidence, regardless of UVR exposure assessment approach: monthly average (p=0.904), January (summer) (p=0.699) and July (winter) measurements (p=0.828).

DISCUSSION

To our knowledge, a relationship between latitude and GCTC incidence has not been reported within the US or Australia. We observed increasing incidence, approximately 1% increasing per degree latitude in both countries, with similar trends observed in both White and Black (US) populations. Evaluations within the consistent-area SEER 9 registries showed that the association has been present at least since the 1980s. As with other risk factors, associations were seen in both seminomas and non-seminomas and attributed to both having a common precursor lesion (39).

Our approach differs from others by examining within-country incidences for two vast countries, US and Australia. The populations of each country are homogeneous and share many characteristics throughout both countries, including predominately European-origin populations, relatively affluent lifestyles, similar diets, well-developed medical care systems, and strong cancer surveillance/reporting infrastructures. This relative uniformity provides a large advantage over the previous reports that examined areas where development, economy, culture, medical coverage, and cancer reporting all differ. In both countries, a similar incidence/latitude association was observed.

The more geographically-localized high-quality SEER data reinforce the relationship between latitude and GCTC incidence in US state data. We also confirmed the results applied to non-Hispanic White men. However, Hawaii is a persistent and remarkable outlier in both NAACRR state and SEER local area data. Studies of GCTC incidence have shown first-generation immigrant populations tend to keep the incidences of their previous residence (40-

42). Immigration of US White men to Hawaii is not likely to explain this outlying status because no US state has as high an incidence as Hawaii. As noted, the generally higher incidence variation in northern Europe is also not completely consistent. This variation indicates that multiple factors affect GCTC genesis and suggest Hawaii would be a good study site to identify other risk factors.

We acknowledge that the association with latitude is ecological. Any risk factor correlated with latitude might be responsible. GCTC incidence has been associated with other exposures and environmental risk factors (e.g., chemicals, diet, higher socio-economic status) that are reviewed extensively elsewhere (1-9). Many accepted associations pertain to *in utero*/early life events (4), supporting the critical impact of events in these years on subsequent GCTC incidence. Persons born in an area will likely have grown up there, but we lacked data about birthplace and residence duration. However, we are unaware of any latitude associations with known early-life risk factors. Furthermore, if the association with latitude is attributable to an early life exposure, better refinement of early-life residence would only strengthen the association.

While discussion of lifestyle factors is beyond our scope, skin color merits consideration because it is closely associated with latitude, darkening with greater exposure to UVR. In our study, latitude (a surrogate for visual-spectrum light) and UVR patterns were so similar that we could not discern independent effects on GCTC incidence. The relationship between UVR and cancer incidence has been evaluated for other cancers (43), generally showing lower incidence in high UVR areas, but testicular cancer has not been previously examined to our knowledge. Some investigators have suggested UVR-influenced high vitamin D levels might

lower cancer risk in general (44,45). Vitamin D has been reported to have anti-proliferative effects on GCTC cells *in vitro* (46,47), and low vitamin D levels have been associated with hypogonadism in older men (48) We did not find a relationship with UV light that was independent of sunlight. We note that US Black men have lower vitamin D levels than Whites (49), yet they also had an exceptionally low incidence of GCTC, both in our study and elsewhere (1-3). This finding is inconsistent with a protective UVR/latitude effect linked to high vitamin D or any solar effect mediated through skin.

As a possible genetic basis for a latitude correlation, a recent report describes variation in the KITLG gene, in which 80% of Europeans have a single-nucleotide polymorphism, the G allele, compared to only 24% of Africans (19). In the context of our results, the mutant G allele interacts with p53, with two important consequences: first, an increase in testicular cancer incidence, attributed to proliferation of germ line cells (19); and second, a reduction in melanin production (19), which helps to produce vitamin D in low UVR areas. In US Black men, GCTC incidence also increased significantly with latitude. While they are less likely to carry the G allele (19), N-S variation in KITLG allele frequency has not yet been reported within US Black men.

As an alternative sunlight-exposure hypothesis, incidence could be influenced by an effect from photobiology on reproductive cycles. Farther from the equator, birth in spring/summer is common in a wide variety of species, timed to maximize survival. Control appears to be mediated by visual input affecting hypothalamic regulation of hormone production. Studies done in frogs (22), birds (23-25) and mammals (26,27) have all shown seasonal variation in testicular activity, as measured by testosterone levels, testicular size, or sperm counts. In

humans, salivary testosterone levels were highest in December and lowest in April (28), whereas sperm counts were highest in September (29). In line with these observations, it is possible that more pronounced cyclical variation in reproductive preparedness at higher latitudes, mediated visually, increases GCTC incidence modestly.

We acknowledge important limitations to interpreting the association between incidence and latitude. Latitude is associated with temperature, diet and many lifestyle factors, as extensively reviewed elsewhere (1-9). We lacked detailed personal information on our populations, including skin coloration, personal habits, and population stability. Furthermore, our cohorts were defined by location at cancer diagnosis, not birthplace or residential history.

CONCLUSIONS

We observed a statistical association between latitude exposure and GCTC incidence in largely European-origin populations of two economically well-developed countries that have similar lifestyles. The association was present at the population level, unlike most risk factors for which risk increases apply only to small subsets of exposed subjects. If the effect is indirect, i.e., from risk factors associated with latitude and also with GCTC incidence, then our findings will help to direct attention to those risk factors. However, we are not aware of any risk factors that correlate closely with latitude at every latitude. Alternatively, the association could be directly with latitude, perhaps mediated via KITLG G allele distribution, or the interaction of photobiology and reproduction.

SUPPORTING INFORMATION

Additional Supporting Information may be provided in the online version of this article:

Figure S1. Maps illustrating the average, annual, age-standardized germ cell testicular cancer incidence by state in the United States (US) and Australia.

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Table 1. Linear incidence rate trends (IRT) per 5° increase in latitude for various cancers among White men (including Hispanics) in the United States (2001-2010) and men in Australia (2000-2009).

Type of Cancer	**United States** **IRT (95% CI)**[‡,§] ***(per 5° latitude North)***	**Australia** **IRT (95% CI)** [‡,§] ***(per 5° latitude South)***
Testicular cancer	5.74 (4.45, 7.05) $p<0.001$	4.43 (1.54, 7.39) $p=0.002$
Seminomas	7.38 (5.75, 9.03) $p<0.001$	4.86 (1.25, 8.61) $p=0.008$
Non-seminomas	4.09 (2.57, 5.64) $p<0.001$	2.54 (-1.77, 7.04) $p=0.252$
Invasive melanoma	(Not evaluated)	-11.81 (-12.87, -10.74) $p<0.001$
Remaining cancers[‖]	-0.37(-0.91, 0.18) $p=0.184$	-0.72 (-1.55, 0.13) $p=0.096$

‡ Adjusted for age group at diagnosis.

§ % change (95% confidence interval), significance.

‖ All cancers combined excluding testicular cancer (United States) and melanoma and testicular cancer (Australia).

Figure 1. All cancer and germ cell testicular cancer incidences and population-centroid latitude in US States (White men including Hispanics: 2001-2010) and Australia (2000-2009). Age-standardized rates (ASR) per 100,000 were directly standardized to the US 2000 population. Note different y-axis scales. The central and northern areas of Australia are particularly sparcely populated (reflected by their smaller circle size, which is proportional to population size).

Figure 2. Germ cell testicular cancer incidence in SEER Registries by population-centroid latitude: (a) SEER 9[1] (three periods during 1980-2011) in White men including Hispanics for population consistency; and (b) SEER 18 (2001-2011) in non-Hispanic White men. Relative population size is indicated by the size of the circle.