International trends in the incidence of brain tumours in children and young-adults and their association with indicators of economic development

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List of Abbreviations

Abbreviation	Definition
AAPC	Average annual percentage change
CBT	Childhood brain tumours
CI	Confidence interval
CI5	Cancer Incidence in Five Continents
CNS	Central nervous system
CT-scan	Computerised tomography scan
GDP	Gross domestic product
GWAS	Genome wide association studies
HIC	High-income countries
ICD	International Statistical Classification of Diseases and Related Health Problems
IRR	Incidence rate ratio
LIC	Low-income countries
LMIC	Low-middle income countries
MIC	Middle-income countries
MRI	Magnetic resonance imaging
NOC	N-nitroso compounds
NF	Neurofibromatosis
SE	Standard error
TSC	Tuberous Sclerosis
WHO	World Health Organisation

Abstract

Introduction: Childhood brain tumours (CBTs) are the second most common type of cancer in individuals aged 0-24 years globally and cause significant morbidity and mortality. CBT aetiology remains poorly understood, however previous studies found higher CBT incidence in high-income countries (HIC) compared to low-middle income countries (LMIC), suggesting a positive relationship between incidence and wealth.

Materials & Methods: Aggregated data from Cancer Incidence in Five Continents (CI5) were used to explore CBT epidemiology. Incidence rate ratios (IRR) compared CBT rates between twenty-five geographically and economically diverse countries. The relationship between incidence and economic development was explored using linear regression models and Spearman's rank correlation tests. Trends in CBT incidence between 1978 and 2012 were investigated using average annual percentage changes (AAPC).

Results: CBT incidence was highest in North America and lowest in Africa. CBT incidence rates increased significantly with increasing GDP per capita ($p=0.006$). Gini index was significantly negatively associated with CBT incidence. Incidence decreased with increasing income inequality within countries, indicated by higher Gini indices ($p=0.040$). Increasing and decreasing CBT incidence trends were observed within individual countries, although only Italy ($p=0.02$) and New Zealand ($p<0.005$) experienced statistically significant changes over time.

Conclusions: The excess disease found in HIC may be explained by environmental risk factor exposure increasing CBT risk in wealthy populations. However, systematic limitations of substandard cancer detection and reporting in LMIC may mean incidence disparities result from misinformation bias rather than genuine differences in risk factor exposure. Further research is required to comprehensively describe CBT epidemiology and explain study findings.

Keywords: childhood brain tumours; childhood cancer; cancer epidemiology; socioeconomic risk factors; health inequalities

1. Introduction

Brain and central nervous system (CNS) tumours are the second most common type of cancer and the leading cause of cancer-related deaths in children and young-adults(1). Approximately one-eighth of brain/CNS cancers occur in 0-24 year-olds and are collectively named childhood brain tumours (CBTs). The World Health Organisation (WHO) classifies tumours using histological, molecular and pathological parameters, and grades them on severity(2). Tumours are identified with neuroimaging technology; MRI/CT-scans, and treated with resection surgery, radiotherapy and/or chemotherapy(3). Medical advances have improved outcomes; survival ranges from <5% for glioblastomas to >95% for low-grade gliomas, and is often accompanied with increased risk of subsequent neoplasms(4-6).

CBT's aetiology remains poorly understood, although the heterogenous nature suggests complex interactions between biological and environmental factors. Increased CBT risk has been linked to genetic variants; Neurofibromatosis (NF1/2) and Tuberous Sclerosis (TSC1/2), European ancestry, congenital abnormalities and high foetal growth(7). Robust evidence exists demonstrating a causal relationship between CBTs and ionising radiation: CT-scans and radiotherapy(7). Environmental exposures, such as N-nitroso compounds (NOCs), pesticides, petrochemical/diesel-exhausts, farm-life and infectious agents may alter tumour susceptibility. However, no association has been found between CBTs and non-ionising radiation, including mobile phones(7).

Three studies have recently analysed WHO's Cancer Incidence in Five Continents (CI5) database(8). Authors found geographical disparities in brain/CNS tumour incidence between countries and significant changes over time between 1993 and 2007(3, 9, 10). Further national analyses reported similar findings, where affluent populations were disproportionately impacted, possibly attributable to genetic and/or environmental factors(1, 11, 12). However, in addition to ecological fallacy, findings may be influenced by case-ascertainment bias(13). Study results might be confounded by differing clinical and reporting practices between countries and time-periods(9). The relationships between CBT incidence and Gross Domestic Product (GDP) per capita and Gini index, as indicators of wealth and wealth inequality respectively, remain unknown(14, 15). It is unclear whether findings from adult studies would translate to children, as CBTs show distinctly different distribution patterns to adult tumours. Younger populations must therefore be explored specifically(4).

This study explored CBT epidemiology in young people aged 0-24 years. Our aims were; 1) to describe international geographical patterns of CBT incidence and trends over time; 2) to investigate the relationship between CBT incidence and economic development, uniquely using GDP per capita and Gini index. Understanding disease spread will support generating aetiological hypotheses and could help improve health and reduce inequalities.

2. Materials & Methods

2.1. Data Collection

All cases of primary malignant brain/CNS cancers (C70-72) in individuals aged 0-24 years were extracted from CI5's volumes five through eleven; 1978 to 2012(16-22). From 1993 (volume eight), tumours were defined using the tenth International Statistical Classification of Diseases and Related Health Problems: ICD-10. Prior to this, ICD-9 was used(23). Benign/unspecified tumours were excluded from volume seven (1988) onwards, meaning volumes five and six may contain such cases. Race/ethnicity and histological data were unavailable and no formal ethics were required as data is publicly available.

We explored geographical patterns of CBT incidence between 2008 and 2012 (volume eleven) and investigated time trends from 1978 to 2012 (volumes five to eleven). 25 countries were selected to reflect diverse geographical regions and economic development stages: high (HIC), middle (MIC) or low-income countries (LIC). Data from 15 of these countries were available in all seven volumes and were therefore incorporated into trend analyses. Algeria was absent from volume five, however was retained to provide trend data from Africa, and was included from 1983.

To investigate associations between CBT incidence and economic development, GDP per capita (US$) and Gini index (%) data were extracted from the World Bank and considered as continuous variables(14, 15). 2012 GDP per capita data were used to indicate country's wealth, corresponding to the final data collection year(14). Current Gini index estimates were extracted, although the calculation year ranged from 2011 to 2018(15). Gini index indicates income inequality within countries; Gini=0% signifies perfect equality and higher coefficients indicate greater inequality. Gini indices were unavailable for Saudi Arabia and New Zealand, possibly due to not satisfying World Bank's quality criteria, and were excluded from analyses(15).

2.2. Statistical Analysis

Aggregated data (case and population numbers) were used to estimate crude incidence rates between 2008 and 2012 and are expressed per 100,000 persons per year. Crude rates and CI5's age-standardised rates were found to be very similar. Total incidence (male and female

combined) was calculated, alongside separate male and female rates. Incidence rate ratios (IRR) compared rates between two countries, using the USA as the comparator country as it had the largest population. Ratios above one indicated the country had a higher rate than the USA. IRRs were also calculated comparing male and female incidence within countries, where ratios above one indicate higher male incidence. To explore economic relationships, linear regression analyses were conducted with incidence and GDP per capita and Gini index individually. Spearman's rank correlation was performed as a complimentary non-parametric test. Saudi Arabia and New Zealand were omitted from Gini analyses due to data unavailability. Additional sensitivity analyses explored smaller age-groups (0-14yrs and 15-24yrs), HIC and European countries. Model checking confirmed regression assumptions were met; data showed linear relationships between continuous variables, showed homoscedasticity and residuals were normally distributed(24). Analyses were conducted using STATA.16 to a 0.05 predefined significance(25).

Similarly, CBT incidence rates were calculated for the previous six volumes for 15 countries. Joinpoint was used to calculate the average annual percentage changes (AAPC) in total, male and female incidence between 1978 and 2012(26). Algeria was only investigated from 1983. The permutation method, as described by Kim was used to identify models of trend changes and a piecewise approach was assumed(27, 28).

3. Results

3.1. Comparing CBT incidence between countries [2008 – 2012]

Between 2008 and 2012, overall CBT incidence was 3.54 per 100,000 persons per year for individuals aged 0-24 years in the 25 countries considered. Females had lower rates (3.27) compared to males (3.79) and North America showed the highest overall incidence (2.32), followed by Oceania (2.06) and Europe (2.05). South America and Asia had lower rates of 1.96 and 1.41 per 100,000 respectively, and Africa had the lowest incidence (0.66).

Total CBT incidence rates (male and female combined) for individuals aged 0-24yrs are displayed in *figure 1*. Canada and the USA had the highest rates of 3.02 and 2.97 per 100,000 respectively. The remaining HIC, with the exception of Seychelles, had rates between 1.5 and 2.6 and MIC incidence ranged from 0.18 in South Africa to 2.20 in Brazil. MIC did not consistently record lower incidence than HIC, however African countries generally had lower rates. Uganda, the only LIC included, had the second-lowest incidence of 0.54 per 100,000.

IRRs comparing total CBT incidence between countries and the USA (comparator country) are displayed in *table 1*. Canada uniquely reported a greater incidence than the USA, with an IRR of 1.02 (95% CI: 0.95, 1.09). However, the difference was not statistically significant. With the exception of Seychelles, the remaining countries had significantly lower incidence rates compared to the USA. Gender IRRs suggested CBT incidence was typically higher in males than females, however, differences were only significant in Chile, Canada, USA, Japan, Korea, Saudi Arabia, UK, Australia, Argentina, China, India and Ukraine. Seychelles was excluded as no male cases occurred here during the time-period.

0-14 year-olds typically showed higher CBT incidence, compared to 15-24 year-olds (Table A3). Overall, compared to 0-24 year-olds, similar geographical patterns were observed for younger children (0-14yrs), where all countries apart from Canada had lower CBT incidence than the USA. Individuals aged 15-24yrs showed some discrepancies, where 7 additional countries had greater incidence rates than the USA (Table A4).

3.1.1. The relationship between CBT incidence and economic development

GDP per capita was lowest in the LIC category, represented only by Uganda ($784), and highest in HIC (mean= $41,990). South Africa had the highest Gini index of 63.0%,

representing greater income inequality, compared to lower figures in Ukraine (26.1%) and Algeria (17.6%). CBT incidence between 2008 and 2012 was analysed against GDP per capita and Gini index individually, and results for total incidence are displayed in *table 2* and *figure 2*.

Total CBT incidence increased by 1.41 per 100,000 with every $100,000 increase in GDP per capita (95%CI: 0.46, 2.37 per 100,000 [p=0.006]), as shown in *table 2A*. The Spearman's correlation test produced a coefficient of 0.635 for total CBT incidence (p<0.001) *(table 2B)*. Both analyses found a significant positive relationship between CBT incidence and GDP per capita. An inverse relationship between CBT incidence and Gini index was found, where incidence decreased with increasing income inequality (indicated by larger Gini coefficients). Every percentage increase in Gini index resulted in a decrease in total incidence by 0.036 per 100,000 (95% CI: -0.070, -0.002 [p=0.040]). Associations were statistically significant for total and female rates, but non-significant for males (*table 2A)*. Spearman's rank test found a significant correlation of -0.4136 (p= 0.0498) for total incidence and non-significant relationships for male and female incidence *(table 2B)*. Furthermore, sensitivity analyses found non-significant relationships between incidence and economic development. Total CBT incidence was not significantly associated to GDP per capita (HIC: p=0.170 and European countries: p=0.775) or Gini index (HIC: p=0.143 and European countries p=0.342).

3.2. Changes in CBT incidence between 1978 and 2012

The trends in CBT incidence between 1978 and 2012 were explored in 15 countries. Only HIC and MIC are present as no LIC were consistently included in CI5 volumes. *Figure 3* displays trends for total incidence: HIC *(3A)* and MIC *(3B)*. For clarity, *figure 3A* is split into two graphs: HIC from North America, Asia and Oceania, and those from Europe. *Table 3* presents AAPCs for total incidence.

Negative AAPCs were found in five countries, indicating a decrease in total CBT incidence over time. The largest declines were in New Zealand, where AAPC was -2.04% (95% CI: -2.79, -1.29 [p<0.005]), followed by Italy, where AAPC was -1.31% (95% CI: -2.36, -0.26 [p=0.02]). These trends were statistically significant. The USA had the largest magnitude of change, despite being non-significant, with an AAPC of 6.6% (95%CI: -1.74, 15.66 [p=0.10]), followed by Algeria (2.6%), New Zealand and Italy. All other countries expressed non-

significant AAPC<1%. Total AAPCs did not differ between genders or income levels.

4. Discussion

This study identified geographical disparities in CBT incidence between countries and found higher GDP per capita and lower Gini index to be associated with higher incidence. Both increasing and decreasing incidence trends were observed between 1978 and 2012, however, changes were only significant in New Zealand and Italy. Findings may primarily be explained by environmental risk factor exposure, although also reflect the complex gene-environment interactions involved in tumour progression(3, 9).

4.1. Comparing CBT incidence between countries [2008 – 2012]

The geographical pattern found of higher CBT incidence in North America and lower rates in Africa supports existing literature(3, 9, 10). The significant association between CBT incidence and GDP per capita (p=0.006) suggests a relationship between incidence and wealth, where HIC had higher rates compared to low-middle income countries (LMIC)(29, 30).

HIC may experience greater environmental risk factor exposures, increasing CBT risk. For example, greater medical technology (CT-scans) use increases both exposure to ionising radiation, an established CBT risk factor, and cancer detection(7). In 2017, the USA conducted the greatest number of CT scans, and Pearce suggests CT exposure may triple CBT risk(31). Varied CT use may explain HIC differences, possibly correlating to private vs public healthcare systems(32, 33). CBT risk may be further increased by higher levels of air pollution, pesticide use and NOC consumption in HIC, or correlate to higher birthweights in wealthy populations(7). Alternatively, HIC may show greater European ancestry, increasing their brain cancer risk(34). Mobile phone use may also be higher here, however the literature reports no link between CBTs and non-ionising radiation(7). Alternatively, seasonal variation in underlying environmental factors, such as higher infection levels accompanying colder temperatures, may explain northern countries having higher incidence(35, 36). HIC may experience greater CBT susceptibility through children's reduced exposure to infectious agents, resembling the association between greater sanitation and atopic conditions suggested in the 'hygiene hypothesis'(37, 38). Nevertheless, the role of infection in CBT aetiology remains unclear. Other unidentified factors could be involved, including genetic contributions. Longer telomere length, or a predisposition for this, was found to significantly increase the risk of adolescent and adult-onset ependymoma, however associations weren't significant in children (<12-years)(39).

This study identified a significant relationship between total CBT incidence and Gini index (p=0.04). Higher rates were observed in countries with low Gini coefficients, indicating less income inequality. As Gini index in relation to CBTs has rarely been studied, this finding cannot be directly compared to literature. Higher GDP per capita may correlate with income equality, however this relationship was non-significant. The lower CBT incidence found in LMIC may be from genuinely lower risk factor exposures, however, can be plausibly explained by case-ascertainment bias. Substandard diagnostic and reporting practices, due to fewer healthcare services limiting cancer detection, leads to incidence underestimation in LIC(9, 40). HIC' greater detection inflates incidence and amplifies income-level differences. Countries' differing CT use, or MRIs for asymptomatic cases, and varying surveillance system sensitivities may also explain differences(32). Additionally, sensitivity analyses found no significant associations between incidence and wealth and income inequality for HIC/European countries, suggesting relationships may result from case-ascertainment differences(9).

CBT incidence was greater in males, however, only eleven countries showed significant differences. This gender disparity is commonly noted in literature, possibly explained by males experiencing greater exposures to environmental risk factors(3, 29, 41). Some LIC may show case-ascertainment bias for genders, where girls are less frequently taken to healthcare settings(42). We contrastingly found higher female incidence in Africa. Sensitivity analyses suggested CBT incidence patterns were clearer in younger children (0-14yrs), compared to adolescents (15-24yrs), and further analyses of smaller age-groups may better explain the observed patterns(1).

4.2. Changes in CBT incidence between 1978 and 2012

Between 1978 and 2012, CBT incidence increased in ten countries and decreased in five. The only significant changes were in Italy (p= 0.02) and New Zealand (p<0.005) where incidence decreased. Small fluctuations may result from changing demographics, clinical practices and registry reporting methods or random variation(9). Despite lacking significance, the increasing trends support previous studies(1, 3, 43). Increasing trends may be explained by environmental risk factors becoming more prevalent in populations or improved cancer detection over time from increased MRI/CT use(4, 7, 29, 44). These likely occurred at different times and rates across the world, perhaps with steeper changes in affluent countries(3). This confounds time-

trends, where average changes may not accurately reflect genuine variations in disease rates or risk factor exposure, but instead show improved detection. Furthermore, positive trends were non-significant here.

Declining rates are unlikely due to case-ascertainment issues due to increased cancer detection over time(3, 29, 44). Presently, CI5 only considers malignant cases however benign tumours were included before volume seven. CBT incidence may therefore be inflated between 1978 and 1987, resulting in false decreasing trends. Nevertheless, it is unclear why five countries presented opposing trends. Trends did not differ between income levels, although this may result from no LIC being analysed(7).

4.3. Limitations

This study was strengthened by using high-quality data and innovatively considering economic measures as continuous variables to increase data sensitivity and minimise misclassification/information loss(8, 13, 45). However, a major caveat was case-ascertainment bias, where incidence disparities may have been exaggerated leading to false associations between CBT incidence and wealth. 25 countries were selected based on their geography and income level to obtain a sample representative of all global countries. Nevertheless, as they weren't randomly chosen, there is an element of selection bias where trends and patterns may have been missed or falsely displayed(46). Aggregated data optimised statistical power, however incidence calculations were less stable in early CI5 volumes and some countries, such as Seychelles, due to small populations *(Table A1 & A2)*(46). This study was subject to ecological fallacy, whereby inferences cannot be assumed for individuals based on population-level findings, and registries may be incomplete due to undiagnosed or excluded cases(9, 10, 46).

Tumour misclassification may be present between countries or time-periods, as any ICD version or WHO's brain tumour classification system could have been used(2, 3). This would skew incidence rates if for example low-grade tumours are regarded as benign in some populations, but malignant in others. This suggests CBT's geographic distribution depends on malignant/benign classification(12). LIC may be less likely to satisfy CI5's rigorous quality checks on completeness, comparability and validity, leading to their exclusion from volumes and underrepresentation in this study. African registries and those in early CI5 volumes had the lowest coverage and standards: lacked mortality data, had low proportions of

microscopically verified cases and were marked by CI5 for data-quality concerns(8). Registry standards influence the reliability of incidence estimates, and so direct comparisons between time-periods or countries may be inappropriate due to differences in healthcare systems, population demographics or cancer surveillance system sensitivities. Similarly, LIC may be less able to provide molecular/imaging evidence required for diagnosis, amplifying incidence underestimation(9). Additionally, associations between incidence and economic development were stronger between continents (large-scale), and weaker when comparing countries, suggesting the disparities may more reflect improvements in detection, rather than genuine differences in incidence driven by environmental factors(47).

5. Conclusions

This study identified geographical disparities and trends over time in CBT incidence in individuals aged 0-24 years and found significant associations between incidence and wealth and income inequality. The excess disease in HIC may be attributed to environmental factors increasing CBT risk; such as elevated ionising radiation exposure from CT-scans, which have been previously reported to triple CBT risk(31). Genetic contributions likely result from CBT predisposing genes interacting with oncogenic environments(7). Nevertheless, the study's systematic limitation of case-ascertainment bias may mean incidence disparities reflect cancer detection disparities, rather than genuine risk factor differences(3).

Findings can be used to form aetiological hypotheses to help guide future policy, enhance cancer prevention and treatment. However, results must be interpreted with caution and further research is required to comprehensively describe CBT epidemiology, explain disparities and improve aetiological knowledge. There is a need for large-scale epidemiological research on brain tumours, particularly those focusing on children. Importantly, to minimise systematic limitations, LMIC require support in developing their infrastructure to improve cancer detection and reduce global inequalities(3).

Data Availability

The data that support the findings of this study are openly available in Cancer Incidence in Five Continents (CI5) at https://ci5.iarc.fr/Default.aspx, reference number 8.

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Table 1. Incidence rate ratios (IRR) with 95% confidence intervals comparing the incidence of childhood brain tumours (CBTs), in individuals aged 0-24 years, between countries and the USA, as the comparator country [2008 – 2012].

Table 2. Association between CBT incidence and countries' GDP per capita and CBT incidence and countries' Gini index in individuals aged 0-24 years between 2008 and 2012; using linear regression models (A) and Spearman's rank correlation test (B).

Table 3. Average annual percentage change (AAPC) in total CBT incidence rates, in individuals aged 0-24 years (male and female combined), in countries between 1978 and 2012.

Figure 1. Countries' total CBT incidence rates expressed per 100,000 persons per year with standard error bars, for individuals aged 0-24 years (male and female combined), between 2008 and 2012.

Figure 2. Association between total CBT incidence and GDP per capita and CBT incidence and Gini index between 2008 and 2012.

Figure 3. Trends in countries' total CBT incidence rates, expressed per 100,000 persons per year, between 1978 and 2012: high income countries (A) and middle income countries (B).

→ Include appendix tables in this list?