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Gender Disparity in the Incidence of Childhood Central Nervous System Cancers among Different Asian Pacific Islander Populations

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Abstract

Childhood nervous system cancers are among the most prevalent and lethal cancers worldwide. Prior research suggests their incidence varied significantly among race/ethnicities. However, little has been done to systematically survey the gender disparities and temporal trends in the incidence of childhood nervous system cancers among Asian Pacific Islander (API) populations in multiple jurisdictions. Age-standardized Incidence Rates (ASR) per million person-years of Brain and Central Nervous System (CNS) cancers in API children and adolescents aged 0-19 in Hong Kong, Japan, the Republic of Korea, Thailand, and the USA National Program of Cancer Registries (NPCR) API population between 1999 and 2010 were extracted from the Cancer Incidence in Five Continents Time Trends database (CI5plus) published by the International Agency for Research on Cancer (IARC) and analyzed. A generally increasing trend in male ASRs can be observed consistently across the jurisdictions, while there are no consistent trends in females. ASRs in Thailand for both genders were significantly lower than ASRs in all other jurisdictions. Both male and female ASR in the USA NPCR API population were significantly higher than those in all other jurisdictions except males in Hong Kong. Males had significantly higher ASRs than females in Hong Kong, Japan, and the Republic of Korea. This study identified a significant gender disparity in incidence of childhood CNS cancers between API male and female in developed jurisdictions, with male incidence increasing over time and significantly higher than female incidence. Further work is needed to discern the underlying shared factors, such as environmental factors including the state of economic development of a country, that contribute to gender differences in the incidence of childhood nervous system cancers among API populations in developed and developing jurisdictions.

Keywords*:* cancer, gender difference, Asian Pacific Islander, pediatric neuro-oncology, childhood cancer, central nervous system, incidence, epidemiology

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Introduction

Cancer is a leading cause of death in children and adolescents (ages 0-19) (1). Of these, childhood nervous system cancers have the highest mortality rate (2-6). Such cancers are also the most common form of childhood solid tumors (7-11) and have the second-highest incidence (one-fifth) (12) among all childhood cancers (3, 5, 6).

Previous studies on the incidence of childhood cancer (including or specific to nervous system cancers) were mostly limited to single country/ location (13-14), occasionally compared with one or two other jurisdictions (15-17), or among regions within the same country (18). Gender differences and temporal trends in the incidence of childhood cancer were examined but they were likewise limited to single country (19). While there were studies that analyzed the incidence of childhood cancer across multiple jurisdictions, the target jurisdictions comprised diverse races/ethnicities (20). Studies that examined gender differences in incidence presented the trends observed by countries (21) or by continents (22), and did not control for race/ethnicity. When the race/ethnicity variable was controlled, the study involved all ages and all cancers rather than focusing on childhood nervous system cancers, and the gender disparities in incidence were not analyzed (23). In short, there is very limited investigation on gender differences and temporal trends in the incidence of childhood nervous system cancers among populations of the same race/ethnicity across multiple jurisdictions. Additionally, prior research suggested that males have a greater genetic predisposition to CNS cancers than females due to a greater inactivation of tumor suppressor RB (24). Thus, this study seeks to investigate whether such genetic predisposition translates into statistically significant differences in incidence. Since there is no record of epigenetic influence on the RB gene, this study may also shed light on whether economic development contributes to gender disparity in the incidence of childhood CNS cancers among API populations.

Comparing incidence using data from the same race/ethnicity is important as cancer rates differ significantly between such groups (25). Also, comparing incidence rates across multiple jurisdictions is useful to provide a more comprehensive picture of the trends associated with different environments. This study seeks to achieve these objectives simultaneously by examining the temporal trends and gender disparities in the incidence of childhood CNS cancers (age 0-19) in the Asian Pacific Islander (API) populations in and across five jurisdictions: the United States of America (USA), Hong Kong, Japan, the Republic of Korea, and Thailand. This study serves to raise awareness of temporal trends and gender differences in the incidence of childhood CNS cancers. Identifying and acknowledging such trends and differences is a critical first step to formulate effective policies and allocate adequate resources to tackle these cancers.

Materials and Methods

Data Collection

This study examined the incidence of CNS cancer in children and adolescents among the API populations in 5 jurisdictions: the USA National Program of Cancer Registries (NPCR) API, Hong Kong, Japan, the Republic of Korea (5 registries), and Thailand (4 registries). The age bracket included in this study is age 0-19. Data between 1999 and 2010 are used in this

study since data is available for all five jurisdictions during this time frame. Hence, potential confounding variables created by different data gathering/collection methods are controlled. Prior research suggested that the incidence of childhood nervous system cancer incidence vary significantly among race/ ethnicities (25). To eliminate the differences in cancer incidence due to race/ethnicity, jurisdictions that are either located in Asia (Hong Kong, Japan, Republic of Korea, Thailand) or jurisdictions outside of Asia with cancer data for their API populations (the USA) were selected. Annual incidence data on "Brain, Central Nervous System" cancers, corresponding to code C70-72 in the International Classification of Diseases Tenth Revision (ICD-10, Version 2010) (26), were collected from the Cancer Incidence in Five Continents Time Trends database (CI5plus) of the International Agency for Research on Cancer (IARC). The exact cancers included in this study are detailed in Table 1.

The potential extraneous factors pertaining to differences in non-malignant and histologically unclassified tumors between countries (e.g., under-registration of non-malignant tumors in certain countries, or differences in the proportion of histologically unclassified tumors between countries) are all eliminated (27), as the data included in this study is strictly filtered and controlled according to the exact definitions outlined in Table 1.

Data from the same international cancer database rather than local registries was used to eliminate potential differences in classification and data quality between different datasets (14). In other words, any potential extraneous factors when comparing data between countries (e.g., different categorizations of tumors in different countries) are eliminated, since only a single database is used with uniform categorizations for all countries.

Statistical Analysis

Temporal trends of Age-Standardized Rates (ASR) per million person-years were identified and compared between different jurisdictions, for each gender and both genders respectively. Sub-analyses were performed to compare temporal trends of annual incidence rate between males and females within each jurisdiction. T-tests were used to determine the statistical significance of differences between incidence in males and females for each jurisdiction and between jurisdictions. Specifically, one-tailed t-test was used as it is well established that males have a higher incidence of childhood CNS cancers than females (13). Paired two samples for means were used for data with temporal trends. Unpaired t-tests were used for data without temporal trends, after conducting F-tests that indicated equal variance. Linear regression was used to analyze trends in annual incidence over time for each gender and jurisdiction. The statistical significance of the linear regression models was evaluated using p-values.

Results

Temporal Trends in Incidence by Gender in Different Jurisdictions

In the Republic of Korea, both male ($p = .029$) and female ($p = .042$) ASRs increased significantly over time. In Thailand, male ASR's increase over time was nearing significant ($p = .063$) while female ASR significantly decreased over time ($p = .014$).

Table 1: International Classification of Diseases Tenth Revision (ICD-10) Version 2010: Official Definitions of Code C70-72 Cancers

C70-72: "Malignant neoplasms [of] brain and other parts of central nervous system," "stated or presumed to be primary, of specified sites"	
C70: "of meninges"	C70.0: "Cerebral meninges"
	C70.1: "Spinal meninges"
	C70.9: "Meninges, unspecified"
C71: "of brain, excluding cranial nerves (C72.2-C72.5) and retrobulbar tissue (C69.6)"	C71.0: "Cerebrum, except lobes and ventricles; Supratentorial (Not Otherwise Specified)"
	C71.1: "Frontal lobe"
	C71.2: "Temporal lobe"
	C71.3: "Parietal lobe"
	C71.4: "Occipital lobe"
	C71.5: "Cerebral ventricle, excluding fourth ventricle (C71.7)"
	C71.6: "Cerebellum"
	C71.7: "Brain stem; Fourth ventricle; Infratentorial (Not Otherwise Specified)"
	C71.8: "Overlapping lesion of brain"
	C71.9: "Brain, unspecified"
C72: "of spinal cord, cranial nerves and other parts of central nervous system, excluding meninges (C70.-), peripheral nerves and autonomic nervous system (C47.-)"	C72.0: "Spinal cord"
	C72.1: "Cauda equina"
	C72.2: "Olfactory nerve; olfactory bulb"
	C72.3: "Optic nerve"
	C72.4: "Acoustic nerve"
	C72.5: "Other and unspecified cranial nerves; Cranial nerve (Not Otherwise Specified)"
	C72.8: "Overlapping lesion of brain and other parts of central nervous system; Malignant neoplasm of brain and other parts of central nervous system whose point of origin cannot be classified to any one of the categories C70-C72.5"
	C72.9: "Central nervous system, unspecified; Nervous system (Not Otherwise Specified)"

Among USA API, there was a strong and significant positive correlation between years and ASR of childhood CNS cancers for males, but an insignificant correlation for females. Temporal trends in Hong Kong and Japan populations were insignificant for both genders. Oscillatory behavior in temporal trends across the jurisdictions appears to be the result of

random variations and not indicative of any discernable cycles. Nonetheless, general trends can be observed and are statistically significant as discussed above (Table 2A, 2B; Figure 1).

Table 2A: C70-72 Cancers in Children: Age-Standardized Rates (ASR) per million person-years

Year	Jurisdiction									
	Hong Kong		Japan		Republic of Korea		Thailand		USA API (NPCR)	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
1999	18	14	19	14	18	12	9	13	19	20
2000	25	19	14	17	18	17	7	13	22	23
2001	23	15	17	19	18	18	7	18	24	27
2002	33	11	16	14	21	13	17	14	18	18
2003	19	14	19	16	20	21	13	13	21	21
2004	26	25	21	19	15	14	19	10	17	24
2005	27	9	22	21	17	18	12	8	21	27
2006	20	21	21	16	17	20	14	7	24	20
2007	24	21	29	19	20	22	12	12	27	21
2008	20	18	18	16	24	21	21	6	26	20
2009	28	18	23	20	25	18	21	11	24	26
2010	18	15	18	15	24	19	11	8	24	14
R^2	.009	.047	.233	.055	.394	.352	.304	.467	.340	.057
p	.769	.499	.112	.464	**.029****	**.042****	**.063***	**.014****	**.047****	.456

Note: $p < .01$(***), $p < .05$(**), $p < .1$ (*)

Gender Differences in Incidence across Jurisdictions

Results of the t-tests indicate that the ASRs of childhood CNS cancers in Thailand for both genders were significantly lower than all other jurisdictions. Female ASR of the USA API population was significantly higher than all other jurisdictions. Male ASR in USA API was significantly higher than all other jurisdictions except Hong Kong. Male ASR

Table 2B: Incidence of Childhood CNS Cancers: Temporal Trends by Gender in Different Jurisdictions

Jurisdiction	**Gender**	***R***	***P***
Hong Kong	Female	.217	.499
	Male	.095	.769
Japan	Female	.234	.464
	Male	.483	.112
Republic of Korea	**Female**	**.593**	**.042****
	Male	**.627**	**.029****
Thailand	**Female**	**.683**	**.014****
	Male	**.551**	**.063***
USA NPCR API	Female	.238	.456
	Male	**.583**	**.047****

Note: $p < .01$(***), $p < .05$(**), $p < .1$ (*)

in Hong Kong was significantly higher than all other jurisdictions except USA API. (Table 3, Figure 2).

Gender Differences in Incidence within Jurisdictions

As demonstrated by the one-tailed t-tests, the male ASRs of childhood CNS cancers in Hong Kong, Japan, and the Republic of Korea were consistently, significantly higher than female ASRs over the years, while there were no significant gender differences in Thailand and the US API populations (Table 4, Figure 3).

Discussion

A generally increasing trend in male ASRs can be observed consistently across the jurisdictions: the Republic of Korea (p = .029) and the USA API (p = .047) both increased significantly over the years, and Thailand increased near-significantly (p = .063). However, no consistent trends in female ASRs can be observed across the jurisdictions: the Republic of Korea significantly increased (p = .042) while that of Thailand significantly decreased (p = .014). As the USA and the Republic of Korea are developed countries while Thailand is a developing country, their populations live in vastly differently environments. However, the male API populations in those 3 populations exhibited an increasing trend of incidence over time, possibly suggesting that environmental factors might not be a significant contributor

Table 3: Incidence of Childhood CNS Cancers: Gender Differences among Jurisdictions

Jurisdiction	**Gender**	***T***	***P***
Hong Kong vs. Japan	Female	-0.338	.370
	Male	**2.098**	**.024****
Hong Kong vs. Republic of Korea	Female	-0.672	.254
	Male	**2.254**	**.017****
Hong Kong vs. Thailand	**Female**	**3.392**	**.001*****
	Male	**5.013**	**< .001*****
Hong Kong vs. USA NPCR API	**Female**	**-2.954**	**.004*****
	Male	0.721	.239
Japan vs. Republic of Korea	Female	-0.502	.310
	Male	0.000	.500
Japan vs. Thailand	**Female**	**5.036**	**< .001*****
	Male	**3.389**	**.001*****
Japan vs. USA NPCR API	**Female**	**-3.503**	**.001*****
	Male	**-1.734**	**.048****
Republic of Korea vs. Thailand	**Female**	**4.225**	**.001*****
	Male	**4.577**	**<.001*****
Republic of Korea vs. USA NPCR API	**Female**	**-2.744**	**.006*****
	Male	**-2.726**	**.0098*****
Thailand vs. USA NPCR API	**Female**	**-7.133**	**< .001*****
	Male	**-5.038**	**< .001*****

Note: $p < .01$(***), $p < .05$(**), $p < .1$ (*)

Table 4: Incidence of Childhood CNS Cancers: Gender Differences within Jurisdictions

Jurisdiction	***T***	***P***
Hong Kong	**3.602**	**<.001*** **
Japan	**1.966**	**.031** **
Republic of Korea	**1.864**	**.045** **
Thailand	1.186	.130
USA NPCR API	0.348	.366

Note: $p < .01$(***), $p < .05$(**), $p < .1$ (*)

to the gender difference in temporal trends, and other confounding variables might be involved. The male ASR of childhood nervous system cancers in Hong Kong did not significantly increase, the reason of which requires further investigation. While the increase in Japan's male ASR was not statistically significant, its *p*-value (.112) is much smaller compared to females in Hong Kong, Japan, and USA API. In other words, there was still a relatively strong increase in the male incidence of childhood Brain and CNS cancers in Japan. As a whole, these results have shown that incidence of childhood CNS cancers among API males in these 5 jurisdictions increased over time while no consistent temporal trends were observable in females.

The ASR of childhood CNS cancers in Thailand was significantly lower than all other jurisdictions for both genders ($p \leq .001$) (Table 3, Figure 2). These results suggest that a jurisdiction's state of economic development might be a significant contributor to the differences in childhood CNS cancer incidence regardless of gender, since Thailand is the only developing country among the jurisdictions studied. This finding is consistent with the earlier observation that environmental factors might have a limited impact on the gender disparities in incidence, as the ASRs between Thailand and all other jurisdictions were significantly different for both females and males. In other words, the state of economic development is an environmental factor that was negatively correlated with the incidence of childhood CNS cancers generally irrespective of gender, but did not appear to be a significant contributor to the gender difference in incidence. A contrary correlation has been observed in other studies involving non-API populations (27). Moreover, both male ($p \leq .048$) and female ($p \leq .006$) US API incidence of childhood CNS cancers were found to be significantly higher than those in all other jurisdictions except males in Hong Kong, which could potentially be attributed to the relatively more advanced healthcare and reporting systems in the US and Hong Kong, or greater gender inequality in healthcare access in

the rest of Asia. This potential reason of high incidence observed is corroborated by previous studies reporting that rigor in child health checks affects incidence (28). Male ASRs in Hong Kong and US API had no significant difference, indicting they were statistically similar.

Hong Kong ($p < .001$), Japan ($p = .031$), and the Republic of Korea ($p = .045$) all had significant gender differences in the incidence of childhood CNS cancers, with males having a higher incidence overall, a finding in line with past literature on sex differences in the incidence of general childhood cancers (18, 19, 23). Adding to prior understanding, these results demonstrate that there were significant gender differences in incidence of childhood CNS cancer generally, not just in developing countries but also in developed countries. There may be one or more shared factors among developed API jurisdictions that leads males to have a higher incidence. No significant difference between female and male incidence was observed in Thailand, however, which is not in line with previous studies that developing countries had greater gender differences in the incidence of childhood cancers in general (21, 23). This finding suggests that the underdiagnosis or underreporting of female cancer incidence, or females' lacking access to healthcare might not be universal among developing countries. Alternatively, the gender difference in the incidence of childhood CNS cancers in developing countries might have a cause distinct from other cancers, which has yet to be identified. The fact that no significant difference was found between female and male incidence of childhood nervous system cancers in both Thailand and USA NPCR API might point to one or more underlying factors that is present in both the API populations in developing jurisdictions and non-API populations in developed jurisdictions.

Despite attempts to control for confounding variables by using the same database and studying data relating to only one specific race/ethnicity group (specifically, API), this study has its limitations. First, the number of jurisdictions studied was relatively small. For instance, only one jurisdiction (Thailand) is a developing economy. This was a particular challenge in studying childhood cancer incidence data because most developing countries lacked registries in general, especially ones with complete and high-quality data. Hence, the extraneous factor of data being regional/metropolitan versus encompassing the whole country is hard to eliminate (29). This study had sought to minimize this extraneous factor by including the maximum number of registries for Korea and Thailand, making their regional data comparable to the country-wide data of the USA, Hong Kong, and Japan. Additionally, this study was limited by the availability of long-term, comprehensive data. Future studies can consider other datasets, such as the International Incidence of Childhood Cancer (IICC), and include data on more API populations, and to validate the findings in this study. Future research can also investigate whether and how economic development contributes to gender differences in the incidence of childhood nervous system cancers. Finally, the gender differences and temporal trends, particularly the increasing incidence of male childhood nervous system cancers, require further analysis to determine potential causes, and provide the necessary scientific grounding

to formulate sound, gender-specific policies targeting childhood nervous system cancers.

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Abbreviations

API	Asian Pacific Islander
ASR	Age-Standardized Rates (Incidence per million person-years)
CNS	Central Nervous System
NPCR	National Program of Cancer Registries (USA)
CI5plus	Cancer Incidence in Five Continents Time Trends database
IARC	International Agency for Research on Cancer

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