International Variations in the Incidence of Childhood Carcinomas

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Abstract
In the study of international childhood cancer incidence coordinated by the International Agency for Research on Cancer, carcinomas were generally rare, with an annual incidence for most sites nearly always under 1/1 million. Liver carcinoma was most common in parts of East Asia, Oceania, and Africa, where it is also common among adults and hepatitis B infection is widespread. Adrenocortical carcinoma had an incidence in Sao Paulo, Brazil, of 1.5/1 million, more than three times the rate in most other registries, indicating the presence of either a specific environmental risk factor acting before or around the time of birth or a concentration of genetically susceptible persons. Thyroid carcinoma seldom had a recorded incidence of more than 1/1 million, and variations in recorded rates may reflect differences in frequency of diagnosis rather than variations in risk. In East Asian populations, who have the highest incidence of nasopharyngeal carcinoma among adults, the childhood incidence of this cancer was moderately elevated. By far the highest incidence in children was found in North Africa, a region of intermediate risk for adults. In the United States the incidence among Black children was nine times that among Whites. Genetic and environmental factors may both be involved in the striking ethnic and geographical distribution. Oral carcinoma in childhood had a high relative frequency in Bangladesh. In the United States, the incidence among Black children was three times that among Whites. Skin carcinoma had an exceptionally high frequency in Tunisia, associated with the unusually high prevalence of xeroderma pigmentosum. The other common carcinomas of adulthood, those of breast, lung, and digestive tract, were extremely rare among children in all regions of the world.

Introduction
Carcinomas account for the great majority of malignant disease in adults, but the common carcinomas of adulthood, those of breast, lung and digestive tract, are rarely seen among children. Although carcinomas in these and other sites are sometimes diagnosed below age 15, embryonal tumors, sarcomas, and germ cell tumors are considerably more frequent. It is therefore impossible to obtain information on the incidence of most childhood carcino-

Materials and Methods
The methods used in collecting and coding the data are described in detail in the monograph on the IARC study (1). The series in the study all contained at least 200 cases of childhood cancer and wherever possible were drawn from population-based registries. For some regions in Africa, Asia, and Oceania, however, population-based data were not available, and large series from hospital- or histopathology-based registries were included. The period during which the cases were diagnosed was chosen to correspond as closely as possible to the decade of 1970–1979. Diagnoses were classified according to the method of Birch and Marsden (3). The present paper is concerned with all carcinomas of childhood.

Average annual rates were calculated for population-based registries with reasonably complete ascertainment and good knowledge of the populations at risk. Age standardization was performed by the direct method, using the world standard population for age groups under 15 (4). Relative frequencies of carcinomas as a percentage of all childhood cancers could be calculated for all registries since the population at risk was not required.

Because of the rarity of carcinomas in childhood, non-overlapping data sets from registries within the same country were combined, as were the four registries covering Chinese populations in Shanghai, Taipei, Hong Kong, and Singapore, and those from four Nordic countries, Denmark, Finland, Norway, and Sweden.

Results
The results are presented for each primary site in the same order as they appear in the classification. Table 1 shows the ASRs among males and females and the total number of registrations for the most common sites in eight large population-based series.

Kidney. The data on renal carcinoma have been presented previously (5). Carcinoma was extremely rare in compari-
son to Wilms' tumor, and hardly any large series had an annual ASR greater than 0.2/1 million; there was little sign of variation between regions of the world or ethnic groups.

**Liver.** Most series with substantial numbers of cases of hepatic carcinoma had ASRs of under 0.5/1 million. In the United States, the incidence was similar among White and Black children. The highest rates by a considerable margin were found in Chinese populations, particularly among boys. The Chinese series also contained substantial numbers of liver cancers of unspecified types. The two principal types of childhood liver cancer, hepatoblastoma and carcinoma, have very different age distributions and so the unspecified cases can be redistributed to these two categories on the basis of the proportions of cases specified as hepatoblastoma or hepatic carcinoma among the two sexes at ages 0, 1–4, 5–9, and 10–14. This procedure yielded an ASR for hepatic carcinoma of 2.0/1 million in all four Chinese series combined, although the estimated incidence among Singapore Chinese was lower than in the other three series (0.6/1 million).

Elsewhere in East Asia, hepatic carcinoma was apparently rare. In Japan, the ASR was 0.5/1 million for specified cases alone, or 0.8 when a redistributed proportion of unspecified liver cancers was included. Hepatic carcinoma accounted for under 1% of childhood cancer in the Philippines and Thailand, and there were no cases of any type of liver cancer in a hospital series from Vietnam. The four cases in a pathology series from Indonesia accounted for 1.9% of all cancers but this is likely to be an overestimate of the true frequency because the series included no cases of leukemia and only one brain tumor. In other parts of Asia the incidence was also low.

High incidence rates or relative frequencies for liver carcinoma were observed among indigenous populations of Oceania. In Papua New Guinea, the 20 cases accounted for 8.5% of all childhood cancers, and for 10.4% when Burkitt’s lymphoma was excluded. In Fiji, the four registrations among children of Fijian ethnic origin gave a relative frequency of 3.8% and an ASR of 2.3/1 million, which is probably a considerable underestimate of the true incidence because registration is believed to be very incomplete. In New Zealand, the two cases (1.2%) registered among Maori children gave an ASR of 1.5/1 million.

In Africa, only the Bulawayo Cancer Registry in Zimbabwe had a relative frequency of more than 1%, with 18 registrations representing 3.3% of all childhood cancers; 15 of these cases were in boys aged 10–14.

**Gonadal.** Gonadal carcinomas were very rare, and in population-based series with five or more cases, the ASR for each sex was always well below 1/1 million. Gonadal carcinomas were more than twice as frequent among girls compared with boys. The age distribution of cases registered among boys, with 33 of 41 (80%) occurring below age 5, suggests that many were in fact germ cell tumors which were at one time commonly called adenocarcinoma of the infant testis or embryonal carcinoma. Among girls, 74 of 113 (65%) ovarian carcinomas occurred at ages 10–14; 52 (83%) of the 63 cases of specified histological subtype were cystic, serous, or mucinous adenocarcinomas.

**Adrenal Cortex.** In most registries, the ASR for ACC was under 0.5/1 million. From all series combined, 49% of the cases among boys and 70% of those among girls occurred below age 5. Overall ACC was 1.5 times as common among girls as boys. The sex ratio (male:female) was less than 0.5:1 in the 0–4 age group, whereas at ages 5–14 there were similar numbers of registrations for the two sexes. Among registries with more than five registrations for ACC, the highest incidence was in Sao Paulo, Brazil, where the ASRs were 1.0/1 million for boys, 2.0 for girls, and 1.5 for both sexes combined; the incidence was particularly high among girls aged 0–4, with an annual rate of 4.7/1 million, compared with 0.6 among United States Whites and 0.8 in Great Britain.

**Thyroid.** The thyroid is the most common site for carcinoma in children in many regions of the world, but even so the annual incidence was under 1.0/1 million in most population-based registries. Thyroid carcinoma was more common among girls than boys, and the incidence increased sharply with age in both sexes. In series with more than 20 registrations, the ASR ratio (male:female) was in the range of 0.2:1 to 0.4:1. The female excess was most marked among older children, and in the same registries, cases occurring at ages 10–14 accounted for 72–100% of the cumulative incidence among girls compared with 50–79% among boys. Papillary tumors were the most common histological subtype, accounting for 40–50% of the registrations in many series, with 10–20% being follicular, 10–40% mixed papillary and follicular, and 10–15% medullary carcinomas. In the two largest series, United States Whites and Great Britain, mean age did not vary significantly with histological type.

Relatively high rates were observed in North America. In the United States, the ASRs for both sexes combined were 1.3:1 million among Whites, 0.9 among Blacks, and 1.4 among Los Angeles Hispanics, whereas in Canada the incidence was 0.9/1 million. The ASR for both sexes combined in the Nordic countries was 0.9/1 million, and none of these four countries had a rate below 0.6/1 million. There

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**Table 1 ASRs per million and the total number of cases (n) of carcinomas of principal sites other than skin for males (M) and females (F) among large population-based series**

<table>
<thead>
<tr>
<th>Site</th>
<th>United States, white</th>
<th>United States, black</th>
<th>Brazil</th>
<th>Chinese</th>
<th>Japan</th>
<th>Germany</th>
<th>Nordic countries</th>
<th>United Kingdom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>0.4</td>
<td>0.4</td>
<td>0.2</td>
<td>0.3</td>
<td>1.7</td>
<td>0.7</td>
<td>2.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Adrenal cortex</td>
<td>0.6</td>
<td>0.6</td>
<td>0.3</td>
<td>0.3</td>
<td>3</td>
<td>0.7</td>
<td>1.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1.5</td>
<td>0.4</td>
<td>0.1</td>
<td>0.1</td>
<td>3</td>
<td>0.4</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>0.6</td>
<td>0.6</td>
<td>0.3</td>
<td>0.3</td>
<td>1</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Other oral</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

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Table modified for readability and clarity.
was little consistency in incidence rates elsewhere in Europe. Torino, Italy had the highest observed incidence, 1.3/1 million, but this was based on only 11 cases. The former German Democratic Republic had an ASR of 0.8/1 million, but other large registries including England and Wales, Western Germany, Slovakia, and Hungary had rates below 0.4.

Chinese populations had a combined ASR of 0.7/1 million. In Japan, the ASR was substantially lower, 0.2/1 million based on seven cases; the addition of the two registrations for unspecified thyroid cancer would only increase this rate to 0.3. Elsewhere in Asia, Jews in Israel were the only population-based series with more than 10 registrations for thyroid carcinoma and they had an ASR of 1.2/1 million from 11 cases.

**Nasopharynx.** Among predominantly White populations of Europe, North America, and Oceania, NPC seldom had an incidence above 0.4/1 million and it accounted for well under 1% of all childhood cancer. In the United States, Blacks had an ASR for both sexes combined of 1.1/1 million compared with 0.1 for Whites. In both ethnic groups, NPC was extremely rare below age 10 and the incidence among boys was twice that among girls.

Table 2 shows the percentage of all childhood cancers accounted for by NPC in series from Africa and Asia, together with incidence rates where these could be calculated. Reliable rates could not be calculated in Africa but the incidence was clearly very high in Tunisia and among both the Arab and Sudanic ethnic groups in Sudan; in all these series, the relative frequency of NPC was in the range of 7–15% overall and 19–29% at ages 10–14. In Morocco, NPC apparently had a lower incidence but the relative frequency was still much higher than among Western populations. In most of the sub-Saharan African registries, including those where there was a high incidence of Burkitt’s lymphoma, NPC was very rare; in this region the highest relative frequency was in Uganda but this was based on only four cases in the combined data from Kampala and the West Nile District, and when Burkitt’s lymphoma was included NPC still represented only 1.6% of all childhood cancers and 4.5% of those diagnosed at ages 10–14.

NPC in Japan had a low incidence, 0.1/1 million, similar to that found in most Western countries. The Chinese populations of Taipei, Hong Kong, and Singapore combined had a higher ASR of 0.7/1 million. There were no registrations for NPC from Shanghai, the fourth Chinese series, but the nine registrations for unspecified nasopharyngeal cancer gave an ASR of 0.8/1 million and accounted for 1.1% of all cancers. In South East Asia the relative frequency of NPC was at least as high. The number of cases in individual registries were small but the relative frequency of NPC was 3.1% at ages 10–14 and 1.3% at ages 0–14 in the series from the Philippines, Thailand, Vietnam, and Indonesia combined. There was also a high relative frequency in Bangladesh. In Bombay, childhood NPC had low incidence rates and relative frequencies in the Cancer Registry series, but at the Tata Memorial Hospital the relative frequencies were higher. In Israel, Jews had a moderately raised incidence and in both Israel and Iraq, NPC accounted for well over 1% of cancers at ages 10–14.

No cases of NPC were registered in Papua New Guinea or Fiji, or among Maori children in New Zealand.

**Other Sites.** Carcinomas in other sites in children are generally even rarer than those discussed above; consequently, it is only possible to identify with any confidence the most marked geographical or ethnic variations in incidence. By far the highest incidence of carcinomas of the mouth and oral cavity (other than nasopharynx) appeared to be in Bangladesh. Incidence rates could not be calculated, but the 42 registrations for this group of sites accounted for 3.2% of all childhood cancers, and an additional 7 (0.5%) registrations were for unspecified malignant tumors in the same site. Oral carcinoma also had a high relative frequency in Sudan, where it accounted for 2.2% of all childhood cancers, with similar frequencies among Arabs and Sudanese. The incidence among Western populations is presumably very much lower; for example, in Great Britain the relative frequency was 0.2% based on 26 cases and the
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ASR was 0.2/1 million. In the United States, oral carcinoma was about three times as common among Black children as among Whites.

Colorectal carcinoma was extremely rare virtually everywhere in the world. The great majority of registrations, including all 49 in Sweden, consisted of cases coded as malignant carcinoid of the appendix. When this diagnosis was excluded, the incidence was well under 0.1/1 million almost everywhere, although somewhat higher among Hispanic children in Los Angeles (ASR, 0.6/1 million based on 4 cases).

Skin carcinoma accounted for 9% of all registrations in Tunisia, by far the highest relative frequency recorded anywhere. Of the 81 cases registered, 72 (89%) were in children with xeroderma pigmentosum; 57 were squamous cell carcinomas. In Morocco there was only 1 registration for skin carcinoma, whereas in Sudan there were 13 cases accounting for 1.7% of all childhood cancers. 12 of these being specified as squamous cell.

In Malawi, there were 3 recorded cases of carcinoma of the bladder, an exceptionally high relative frequency of 1.3%, even allowing for the fact that this series did not include leukemia or brain tumors. Carcinomas of the other sites common among adults, breast, lung, esophagus, stomach, and small intestine, were not registered in substantial numbers among children anywhere in the world.

Discussion

The highest incidence rates and relative frequencies for liver carcinoma were found in parts of East Asia, Oceania, and Africa where this tumor is also common among adults and hepatitis B infection is widespread. Many, if not all, of the children with liver carcinoma in these regions are chronic hepatitis B surface antigen carriers (6, 7). In Western countries, where hepatocellular carcinoma is rare in childhood, the proportion of affected children who are hepatitis B surface antigen positive is smaller, although still larger than in the general population (8, 9). Adrenocortical carcinoma is a conspicuous component of the Li-Fraumeni family cancer syndrome (10). This syndrome, and hence the greatly increased susceptibility to ACC, can sometimes be attributed to inherited germ line mutations in the p53 tumor suppressor gene on chromosome 17p13 (11), although such mutations have not been found in all cases (12). In a population-based series of 14 children with adrenocortical tumors, 4 (28%) were probably members of Li-Fraumeni families (13). The remarkably high incidence of ACC in Sao Paulo, Brazil in the present study relates to the period of 1969-1978, but a high relative frequency was also found in a large hospital series from the same city during 1952-1965 (14). The especially marked excess among young girls has not previously been noted. The raised incidence in Sao Paulo appears to be a geographically isolated phenomenon. The incidence rates from the northern Brazilian registries of Fortaleza and Recife in the present study were unremarkable, and even among cases diagnosed in other parts of Brazil there is an unusual preponderance of children born in Southeastern Sao Paulo state (15), indicating the presence of either a specific environmental risk factor acting before or around the time of birth, or a high proportion of genetically susceptible persons in that area.

Previous radiation treatment is a known risk factor for thyroid carcinoma in childhood (16) but it probably only accounts for a small proportion of cases in most series. Papillary carcinoma is a slow growing tumor which can be undetected in a large proportion of cases, as shown by an autopsy study in Finland in which the incidence greatly exceeded that of clinically diagnosed tumors (17). The recorded incidence can also be markedly affected by screening programs (18). A recent dramatic rise in the incidence of childhood thyroid cancer, especially papillary carcinoma, to around 80/1 million has been reported in Belarus, which received high levels of radioactive fallout following the Chernobyl nuclear reactor explosion (19, 20). Without any indication of the proportion of tumors which might not have been detected without screening, these data are extremely hard to interpret. It is not known whether the very low recorded incidence in Japan represents a genuinely low risk rather than less frequent clinical diagnosis. Medullary thyroid carcinoma occurs in persons with multiple endocrine neoplasia type 2 (21), although often in adulthood rather than below age 15. However, cases also occur outside known multiple endocrine neoplasia type 2 families.

Among adults, the highest risk of nasopharyngeal carcinoma is found in populations of southern Chinese origin and incidence is also raised, but to a lesser extent, in South-East Asia. There is a region of intermediate risk in North Africa which in the east of that continent extends as far south as northern Uganda (22). The pattern in childhood is somewhat different. In East Asia (other than Japan), the incidence is moderately elevated. The relative frequency for nasopharyngeal cancer of 0.6% at ages 0–14 in the Korean Central Cancer Registry (23) was slightly lower than in Chinese populations but substantially higher than in Japan. By far the highest incidence of NPC in childhood clearly occurs in North Africa, corresponding to a markedly bi-modal age distribution with the first peak occurring during adolescence. Within this region, the highest recorded relative frequencies of nasopharyngeal cancer at ages 15–24 are 18% in Tunisia (24) and 17% in Sudan (25), which are also the countries with the highest relative frequency for childhood NPC. The true relative frequencies may be somewhat lower, however, as the data were contributed by radiotherapy centers which would treat a particularly high proportion of patients with this diagnosis. Within Sudan, the pattern of higher risk for childhood NPC among Sudanese tribes compared with Arabs was similar to that among adults (26). Incidence rates for NPC in North Africa could not be calculated in the present study. In a histopathology series from Algeria (27), however, cancers of the nasopharynx, of which the great majority would be carcinomas, accounted for 4% of registrations at ages 0–14, giving a minimum estimate for the crude annual incidence of 2.5/1 million, 20 times the ASR among most White populations. In childhood, the region of increased risk appears to extend into the extreme west of Africa. Jews in Israel had a moderately raised incidence, and among Israeli-born Jews under 25 years of age, the highest incidence of NPC is among those whose parents were born in North Africa (28). In Jordan, the minimum estimated crude annual incidence from a national pathology series was 1.2/1 million (29). It seems unlikely that the area of raised incidence for childhood NPC extends any further east because this tumor had a much lower relative frequency in Iraq. The high relative frequency in the Tata Hospital series from Bombay probably results from this center’s particular interest and expertise in treating oral cancer (30). The excess of NPC among Black children in the United States had previously been noted in

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mortality data (31), with particularly high rates in the rural south. Genetic and environmental factors may both be involved in the striking ethnic and geographical distribution of NPC. The EBV has been implicated in its etiology since the 1960s, and case-control studies in many parts of the world have shown consistent relationships between tumor burden and the presence of the EBV in undifferentiated NPC (32). Since the EBV is almost ubiquitous, however, any part that it has in the etiology of NPC must be in association with other unknown factors which vary markedly between populations.

The extremely high frequency of oral cancer in Bangladesh, where it accounts for 15% of all cancers among adults, has been linked to the frequent chewing of tobacco and betel (33), and the exceptionally large number of cases in children may represent the lower end of the age distribution of cancers with this cause. The practice is common in India, Southeast Asia, and parts of Oceania (34), with relatively elevated incidence rates for oral cancer observed in the same populations. It is not generally known whether the habit is common among children, although it is thought to be so in at least some rural areas of India. There was, however, little evidence of a correspondingly high incidence of oral carcinoma in childhood in other Asian countries. The raised incidence among Black children in the United States is similar to that among Black adults, whose incidence rates for oral cancer are typically double those for Whites. Much of the higher incidence among Black adults can be accounted for by their greater use of tobacco and alcohol, the latter in mouthwashes as well as beverages (35), and some American childhood cases may have a similar etiology.

The association of skin carcinoma with xeroderma pigmentosum, which has an unusually high prevalence in Tunisia, is well documented. In a histopathology series from Algeria (27), 6.1% of all the registrations in children were for nonmelanoma skin cancer. The prevalence of xeroderma pigmentosum in Algeria is unknown, but it seems likely that this condition was linked to many of the cases, especially because Constantine, one of the three large contributing centers, is close to the border with Tunisia.

The unusually high relative frequency of bladder carcinoma among children in Malawi, although based on only three cases, may be related to schistosomiasis infection which is endemic in this area; in Zimbabwe, Iraq, and Kuwait, all regions where relatively high frequencies of bladder cancer in adults are ascribed to the same cause, there was no sign of an excess incidence of bladder cancer among children.

In conclusion, the incidence of hepatocellular carcinoma in childhood is closely related to an environmental factor, namely, the level of hepatitis B infection in the population. Susceptibility to the carcinogenic effects of sunlight on the skin is greatly heightened in persons with xeroderma pigmentosum; the combination of this condition with skin carcinoma thus represents a marked example of the interaction between genetic predisposition and an environmental factor. A combination of environmental and genetic factors may well also be responsible for variations in the incidence of childhood nasopharyngeal carcinoma, and possibly of oral carcinoma. The incidence of adrenocortical carcinoma showed little variation throughout most of the world, but many cases have a known genetic basis as part of the Li-Fraumeni syndrome. Detailed information on individual cases would be necessary to elucidate the contribution of possible genetic and environmental factors to the very localized high incidence of this tumor in Sao Paulo. Because of their extreme rarity, there is little evidence from variations in incidence for likely genetic or environmental components in the etiology of carcinomas of other sites in childhood, although the tendency for tumors occurring in young adults to be more frequently associated with family history suggests that genetic predisposition is likely to be important.

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