International variations in the incidence of childhood renal tumours

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Summary The International Agency for Research on Cancer has coordinated a worldwide study of childhood cancer incidence, with data from over 50 countries. We present here the results on renal tumours. Wilms’ tumour was the most common malignant kidney tumour in all regions. It is sometimes considered to be an ‘index cancer of childhood’ but it is clear from the present study that there is at least a threefold difference in incidence between the age-standardised annual rates of over 10 per million in the Black populations in the United States and Nigeria and those of around three per million in several East Asian populations. In White Caucasian populations, Wilms’ tumour had an annual incidence of 6–9 per million, accounting for 5–7% of all childhood cancer. It was almost everywhere equally common in boys and girls, but the sex ratio in East Asia was M:F = 1.4:1. Age distributions were similar among White Caucasian and Black populations, with the peak incidence in the second year of life. In East Asia, however, 25–40% of the total incidence occurred in infants aged under 1 year, compared with around 15% in many Western series. Other studies have shown that, in the United States, Wilms’ tumour has a lower incidence among Asian children than among Whites or Blacks and tends to occur at a younger age. The variation in patterns of incidence of Wilms’ tumour along ethnic rather than geographical lines suggests that genetic predisposition is important in its aetiology. Renal carcinoma in childhood is rare throughout the world, with little sign of international variation. It accounted for a higher proportion of childhood renal tumours in East Asia but this was attributable to the lower incidence of Wilms’ tumour in that region.

The International Agency for Research on Cancer (IARC) recently coordinated the first comprehensive worldwide study of childhood cancer incidence in which data were collected wherever possible from population based registries and diagnostic groups were defined according to histology (Parkin et al., 1988a). The study included data from some 50 countries and a summary of some of the principal findings has been given elsewhere (Parkin et al., 1988b).

Wilms’ tumour is by far the commonest form of malignant kidney tumour in childhood. At one time it was believed to have a relatively constant incidence throughout the world and was thus proposed as an ‘index tumour’ of childhood (Innis, 1972). It was clear from the IARC study, however, that there is a three- to four-fold variation in the incidence of Wilms’ tumour between different regions and ethnic groups. In this paper we present a more detailed account of the results for Wilms’ tumour and other childhood renal tumours.

Materials and methods

A detailed description of the methods used in collecting and coding the data is given in the monograph on the IARC study (Parkin et al., 1988a). The series included in the monograph all contained at least 200 cases of childhood cancer. Wherever possible, series were used from population-based registries which were believed to be reasonably complete. For some regions, however, predominantly in large parts of Africa and Asia, such data were not available and large series deriving from hospital-based or histopathology-based registries were included. The time period to which the data referred was chosen to correspond as closely as possible to the decade 1970–79. A classification scheme was developed with diagnostic groups defined largely according to histological type (Birch & Marsden, 1987). The present paper is concerned with the category of renal tumours within this classification; Table I lists the diagnoses included within this category, defined by their codes in the International Classification of Diseases for Oncology (ICD-O).

Average annual incidence rates were calculated for population-based registries where ascertainment was believed to be reasonably complete and there was a good knowledge of the population at risk. Age standardisation was performed by the direct method, using the world standard population for age groups under 15 (Doll & Smith, 1982). Relative frequencies of Wilms’ tumour and of all renal tumours as a percentage of all childhood cancers within the same registry were also calculated; since the population at risk was not required, these calculations could be done for all registries.

Results

We consider first the results for Wilms’ tumour, which accounted for over 90% of cases of known histological type in most series. Results are then presented for the much rarer renal carcinomas. The category of ‘other and unspecified renal tumours’ consisted almost entirely of tumours of unspecified type. In population based registries, over 70% of these were without histological verification. They were presumably mainly Wilms’ tumours and we have therefore considered this possibility when presenting the data from those registries, mainly in Asia, where they comprised a substantial proportion of all registrations for renal tumours.

Wilms’ tumour

Figure 1 shows the age-standardised annual incidence rates (ASR) per million for Wilms’ tumour together with other and unspecified renal tumours in 22 population-based series. In predominantly White Caucasian populations in Europe, North and South America and Oceania the ASR is generally around 6–9 per million (corresponding to a cumulative incidence of 80–120 per million by age 15), with Wilms’ tumour accounting for 5–7% of all childhood cancers. The highest rates were found in Black populations. Combining data from four series in the United States (Figure 1), the ASR was 30% higher in Blacks than in Whites. Incidence rates for Blacks were higher than those for Whites in three of the individual series; in the fourth, New York, Blacks and Whites had similar rates, but there was a substantial excess in Blacks of ‘other and unspecified renal tumours’, many of which were presumably in fact Wilms’ tumours. Incidence

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found in Asia, and especially in East Asia. Some registries
with very low incidence rates, including Shanghai, Taipei and
the Philippines, had relatively large numbers of ‘other and
unspecified renal tumours’ but even the ASR for this
category and Wilms’ tumour combined in these three regist-
ries were respectively 1.5, 2.8 and 3.8 per million, all substan-
tially below the rates commonly seen in White Caucasians.

The three Japanese registries all had rates for Wilms’
tumour of 4.0 per million or less, with a maximum for
Wilms’ with other and unspecified renal tumours of 4.5 per
million in Osaka. The cumulative incidence of Wilms’
tumour by age 15 in Japan was 43 per million from the three
registries combined.

Few population-based data were available for the rest of
Asia and incidence rates were mostly calculated on the basis
of small numbers of cases. In the largest population based
Asian series outside Japan, the Bombay Cancer Registry,
Wilms’ tumour had an ASR of 3.8 per million based on 75
cases; the addition of nine cases of other and unspecified
renal tumours, all aged under five, increases the ASR to 4.2
per million.

In Israel, Jews had a similar incidence to White Caucasians
(ASR 6.8 per million) while the rate for non-Jews (ASR 4.6
per million based on 12 cases) was closer to those observed
elsewhere in Asia. The relatively high rate of 6.0 per million
for non-Kuwaitis in Kuwait was also based on only 12 cases.

There were only two series of registrations among
indigenous populations in Oceania. In New Zealand Maoris,
Wilms’ tumour had an ASR of 8.7 per million, accounting
for 5.6% of all childhood cancers. In Fiji the ASR for Fijians
was 6.1 per million, but ascertainment is probably very
incomplete; 10.4% of all registrations were for Wilms’
tumour. The corresponding ASR and relative frequency for
Indians in Fiji were both substantially lower, 1.6 per million
and 4.9% respectively. All of these rates for Oceania were
based on fewer than 10 cases.

Wilms’ tumour appears to be almost everywhere equally
common in boys and in girls. Among the 25 large series with
at least 50 cases, the sex ratio of incidence rates (M/F) was
generally in the range 0.8:1 to 1.3:1. The highest ratio among
these large series, however, was in Osaka, where it was 1.5:1,
and this male excess appeared to obtain throughout East
Asia: the ratio of the total of numbers of cases in 11 series
ranging from Japan in the north to Singapore in the south
was M/F = 1.4:1.

There were few registries with large numbers of cases for
which the population was available by single year of age.
Figure 2, however, shows incidence rates by single year of
age for New York Whites and Japan. In general, age distrib-
tutions were similar among the predominantly White
Caucasian populations of Europe, the Americas and Oceania
and among Blacks both in the United States and in Nigeria,
with the largest number of cases occurring in the second year
of life and 70–75% of the total incidence before age five. In
East Asia, a larger proportion of the total occurred in infants
aged under 1 year (42% in Osaka and 25% in the four series
from Chinese populations, compared with around 15% in
many American and European series). There was no syste-
matic difference in age distribution between the sexes in any
region.

Laterality of Wilms’ tumour was recorded in only a few
registries. Bilateral cases accounted for around 3–6% of

Table 1 Classification of malignant renal tumours

| Diagnostic group | First 4 digits | 5th digits | ICD-O | T code |
|------------------|---------------|-----------|-------|--------|
| (a) Wilms’ tumour | 8960          | 3, 6, 9   |       |        |
| (b) Renal carcinoma | 8010–8041, 8043, 8050, | 3, 6, 9 | 189.0 |
|                  | 8120, 8122, 8130, 8140, |        |       |
|                  | 9230, 8231, 8260, 8310, |        |       |
|                  | 8312          | 3, 6, 9   |       |        |
| (c) Other and unspecified | 8961, 8962 | 3, 6, 9   | 189.0 |
|                  | 8000–8004, 9990 |        |       |

Figure 1 Age-standardised annual incidence rates per million for
Wilms’ tumour and other and unspecified kidney tumours (except
carcinoma) in childhood, both sexes combined. *Rates for United
States from combined data of Greater Delaware Valley, Los
Angeles, New York and SEER Program. + Rates for Chinese
from combined data of Shanghai, Taipei, Hong Kong and Singa-
pore. Chinese *Rates for Japan from combined data of
Kanagawa, Miyagi and Osaka.
tumours with known laterality in the United States (SEER Whites and Blacks) and Europe (Finland, Great Britain and Hungary) and among Israeli Jews. Data on laterality were not available for large series in any other part of the world. Bilateral tumours occurred with almost exactly equal frequency in boys and girls (M/F = 1.02). They tended to occur slightly earlier than unilateral Wilms’ tumour. Only two series, United States SEER Whites and England and Wales, had 10 or more bilateral cases. In the American series, 50% of bilateral cases were aged under 2 years compared with 34% of unilateral, while in England and Wales 58% of bilateral and 32% of unilateral cases occurred before age 2. No cases of bilateral Wilms’ tumour above age 8 were recorded from any registry in the study.

Renal carcinoma

Renal carcinoma was everywhere rare in children, and no large series had an ASR greater than 0.2 per million. In Europe, carcinomas accounted for 1.5–3% of all childhood renal tumours. Similar proportions were observed in United States Whites and Blacks. Among Chinese populations, where Wilms’ tumour had a lower incidence, carcinoma accounted for 10% of all childhood kidney tumours but its incidence was similar to that in other regions. Figure 3 shows the distribution by age and sex of all 153 registrations for renal carcinoma in the study. Only eight cases (5%) were not stated to be histologically verified. The numbers of cases at each year of age were similar until around age 12, with a moderate rise thereafter. Renal carcinoma was registered approximately twice as frequently in boys as in girls during the first decade of life, but equal numbers of cases occurred in the two sexes among children aged 10 and over.

Discussion

Since the publication of Innis’s paper in 1972, the view that Wilms’ tumour is an ‘index cancer of childhood’ with approximately constant incidence worldwide has gained wide currency (Davies, 1976; Breslow & Beckwith, 1982; Lucas & Fischer, 1990). It is clear, however, from the results of the present study that there is a considerable variation in the incidence of Wilms’ tumour between different regions and ethnic groups.

The highest rates in this study were found among Blacks, in both Africa and the United States. Blacks were on average 3.6 months older than Whites in the United States National Wilms’ Tumour Study (NWTS), which included 528 Black children (Breslow et al., 1988). We could find little evidence for any difference but there were only 163 United States Blacks in the present study. The incidence in predominantly White Caucasian populations was lower than for Blacks and was similar in all regions from which data were available. The lowest incidence was found in Asia, and especially in the eastern part of that continent, though the area of low incidence appears to extend at least as far west as India. In many of the east Asian series, Wilms’ tumour occurred at a much earlier age than elsewhere, indeed the highest incidence was found in infancy. Incidence rates for Wilms’ tumour were not available for children of East Asian ethnic groups in the United States, but the Asian children in the NWTS had a mean age of 29.1 months compared with 43.7 months for Whites (Breslow et al., 1988). The ASR for all childhood renal tumours among Asians in Los Angeles, San Francisco and Hawaii during 1972–82 was 2.2 per million (Waterhouse et al., 1982; Muir et al., 1987) though this was based on only four cases. During 1960–84, the incidence of renal tumours in Asian children in Hawaii was less than two thirds of that in Whites (Goodman et al., 1989).

In Israel the relationship between the rates for Jews and non-Jews is hard to interpret. In the present study, the non-Jews appeared to follow the Asian pattern, while the incidence among Jews was similar to that in White Caucasians. The rate for non-Jews was, however, based on small numbers, and in a previous series covering 1961–65, with a total of 35 cases of Wilms’ tumour, Israeli Arabs had an ASR of 16 per million, twice that of Jews (Virag & Modan, 1969). Underlying risks to the predominantly Arab, non-Jewish population may have changed with time, but combining the results for the two periods produces a rate very similar to that for Jews.

The results presented here, though based on small numbers of cases, suggest that Wilms’ tumour is relatively common among the indigenous peoples of Oceania. The Hawaiian ethnic group in Hawaii, however, had a low incidence of childhood renal tumours but this was again based on only eight cases (Goodman et al., 1989).

Some cases of Wilms’ tumour have been explicitly described as heritable in origin. These include bilateral tumours, those which occur in association with aniridia and certain other congenital abnormalities, and the small number of cases which form part of familial aggregations. Fewer than one in 15 cases of Wilms’ tumour are bilateral and the other classes of ‘genetic’ Wilms’ tumour account for even smaller proportions (Breslow & Beckwith, 1982; Pastore et al., 1988). The frequency of associated congenital abnormalities is higher in Blacks, who have a higher incidence of Wilms’ tumour, than in Whites (Kramer et al., 1984). The genetic damage which is postulated to give rise to Wilms’ tumour in some cases could of course itself be caused by environmental factors. Aetiological factors for Wilms’ tumour have been investigated in many studies, sometimes as part of larger studies of all childhood cancers. Much attention has been focused on various occupational associations but these have...
generally only been found in a small proportion of all studies (Arundel & Kinnier Wilson, 1986; Bunin et al., 1989). The age distribution of Wilms' tumour is strong evidence of the association. The lack of consistency in reports of environmental risk factors together with the ethnic variations and genetic associations described above strongly suggest that the risk of Wilms' tumour may be predominantly genetically determined at the population level with predisposition varying between populations of different ethnic origins. Though the familial element appears to be small. The series of Wilms' tumour reported here will have included small numbers of cases of two other tumours which are now regarded as distinct entities. The first of these is the bone-metastasising renal tumour of childhood or clear cell sarcoma of the kidney. This is a rare tumour, accounting for around 4–5% of cases in clinical trials (Marsden et al., 1984; D'Angio et al., 1989). It has a similar age distribution to Wilms' tumour but occurs very much more frequently in boys than in girls; in the largest reported series the sex ratio was M:F = 6:6:1 (Marsden & Lawler, 1980). We could find no published references to the aetiology of this tumour. The second rare tumour now distinguished from Wilms' tumour is the rhabdoid renal tumour, which accounts for around 2% of all tumours formerly classified as Wilms' (D'Angio et al., 1989). Rhabdoid renal tumour tends to occur in younger children than Wilms' tumour, with a median age of 1 year in the NWTSS and 100 cases (Wecks et al., 1989). The sex ratio in the NWTSS series was M:F = 1.47:1. The association of rhabdoid tumour with medulloblastoma and other embryonally unrelated brain tumours in the same patient is well documented (Bonnin et al., 1984; Weeks et al., 1989), suggesting that there may be a large heritable component to its aetiology. Nothing is known of international variations in the incidence of either of these tumours.

Another type of renal tumour seen predominantly in very young children is the mesoblastic nephroma. This is not a malignant tumour, and thus it is not generally recorded systematically by cancer registries. The Manchester Children's Tumour Registry ascertained five cases over a 30-year period (Marsden & Newton, 1986). All were in infants aged under 6 months, and all but one aged under 3 months. They accounted for half of all renal tumours in children aged under 6 months, and 17% of those under 1 year of age.

Many tumours at one time described as Wilms' in infants would in fact have been mesoblastic nephromas (Boland, 1974). It was not possible to tell how far this phenomenon contributed to the apparent excess of Wilms' tumour in infants in east Asian registries, but of the 32 infants registered in Osaka with Wilms' tumour only four (13%) were aged under 3 months, suggesting that few of these tumours were really mesoblastic nephromas. The markedly lower average age for American Asians (of mostly east Asian extraction) in the NWTSS, in which the pathology was reviewed centrally, also suggests that the excess of Wilms' tumour among Asian infants is real.

Carcinoma of the kidney is predominantly a disease of adults. There was little sign of any variation in incidence rates in childhood in the present study, with very low rates in all regions. There were roughly constant numbers of cases at each year of age below 12, after which point there could be observed the start of the steady increase in incidence which continues through early adulthood. In the first decade of life there were twice as many boys affected as girls, whereas among older children there was a slight excess of girls. These patterns contrast with those for Wilms' tumour, which occurs largely in the first 5 years of life and is equally common in the two sexes.

Patterns of incidence for renal cancer (mainly carcinoma) in adults can be found in Cancer Incidence in Five Continents (Muir et al., 1987). From the truncated standardised rates (for persons aged 35–64), it seems that the disease is in general about twice as common in males as females. The lowest rates are recorded in Asia, particularly in India but also in Japanese and Chinese populations. Rates in North America and the Nordic countries are somewhat higher than those for other parts of Europe. In the United States, the incidence is similar for Blacks and Whites. These patterns contrast with the recorded incidence of renal carcinoma in later childhood as regards age-standardised distribution. This suggests either that renal carcinoma in children has a different aetiology from tumours of the same morphology in adults, or that some of the childhood cases were misclassified. It is not clear, however, why Wilms' tumours should be more likely to be misclassified as carcinomas if they occur in boys rather than girls.

While incidence of Wilms' tumour varies predominantly by ethnic group rather than geographically, suggesting that genetic predisposition is important in its aetiology, the causes of renal carcinoma in childhood remain more completely a mystery.

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