Age Distribution of Wilms' Tumor: Report from the National Wilms' Tumor Study

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ABSTRACT

Median ages at diagnosis were 36.5 and 42.5 mo for 1523 males and 1678 females with unilateral Wilms' tumor registered between October 1969 and December 1985; they were 23.5 mo and 30.5 mo for 100 males and 141 females with bilateral disease. The median age for multicentric, unilateral cases was intermediate between the bilateral and unicentric median. Patients with hemihypertrophy in addition to their Wilms' tumor had a typical age distribution, whereas those with aniridia or characteristic genitourinary anomalies were substantially younger. Patients with perihlobar nephroblastomatosis had a median age of 35.5 mo and those with intralobar nephroblastomatosis, a median age of 18.5 mo. Most of the bilateral disease occurred in the presence of one or both of these precursor lesions. These findings suggest heterogeneity in the pathogenesis of Wilms' tumor, having implications for genetic counselling, and call into question certain aspects of Kndons and Strong's two-stage mutational model for the origin of Wilms' tumor.

INTRODUCTION

Studies of the age and gender distributions of childhood and adult cancers have provided important epidemiological clues regarding their etiology and pathogenesis (1, 2). By delineating the period of risk, they are also important for genetic counselling of families of individuals who may be particularly susceptible to cancer development by virtue of an associated congenital condition, for example, aniridia or hemihypertrophy in the case of Wilms' tumor (3). This report presents a detailed descriptive analysis of the frequency distributions of age at diagnosis for 3442 children with Wilms' tumor registered on the NWTS. It extends and refines the results of an earlier study of 1905 patients (4). Particular attention is paid to the shape, spread (variability), and location of the age distributions and how they vary between males and females, between those with unilateral and bilateral disease, and between those with and without specific congenital anomalies and precursor lesions of the kidney.

MATERIALS AND METHODS

Patients in the study were registered on the NWTS between October 1969 and December 1985. Ages were calculated as the number of months between birth and diagnosis. Those whose final diagnosis was not Wilms' tumor were excluded from the statistical analyses, as were those identified by the NWTS Pathology Center as having clear cell or rhabdoid sarcoma of the kidney (5) and a few patients who were 16 yr of age or older at the time of diagnosis. This left 3442 patients of whom 241 were identified as having bilateral disease either at the time of initial diagnosis (204 cases) or subsequently (37 cases). The Pathology center scored 377 of the 3201 unilateral cases as having multicentric lesions either by microscopic review, using a criterion of separate tumor nodules of distinct histology, or else from the gross description given by the pathologist making the initial diagnosis. NWTS pathologists also classified cases diagnosed since May 1979, and for whom sufficient histologic material was available, as to the presence or absence of perihlobar and intralobar nephroblastomatosis. Congenital anomalies were ascertained from the registration card submitted by the registering institution, from a questionnaire submitted by the patient's family, or from the operative note submitted by the surgeon. For 29 of 37 cases of familial Wilms' tumor also identified by this process, pathology reports were obtained confirming the diagnosis in at least one relative. Three more were identified as familial cases from published reports, and the remaining five were judged to be "very probably familial."

Frequency distributions of the age at diagnosis for each subgroup were estimated by three separate methods: (a) the histogram; (b) smoothed, nonparametric density estimation; and (c) parametric maximum likelihood. Three-mo intervals were used to construct the histograms. Silverman's (6) penalized likelihood log-density estimator, with smoothing parameter chosen in most cases by cross-validation, was used for nonparametric estimation. The three parameter (a, 0, 0) generalized "/i-distribution (7) was used for parametric analysis; a and 0 denote the location and scale parameters on the log scale and denote the shape of the error distribution (0 = 0 for log-normal and 0 = 1 for Weibull). Most computations were carried out using the S statistical language (8), which was supplemented with special routines for the nonparametric and parametric analyses. Significance testing of age differences between subgroups was performed using the Wilcoxon statistic, the analysis of variance, or via comparison of estimated a values. Goodness-of-fit of the parametric model was evaluated by comparing observed and expected numbers of cases in 11 intervals using the x^2 statistic.

RESULTS

Age, Gender, and Bilaterality. Fig. 1 graphs the cumulative proportion of cases not yet diagnosed as a function of age by gender and bilaterality. All four subgroups show substantial curvature on the semilogarithmic plot. Ninety-five--% of bilateral (unilateral) cases are diagnosed before 82 mo (116 mo). The best fitting Weibull distributions (0 = 1) for unilateral cases have - = 3.85 for males and 3.96 for females, with 0 = 0.72 and 0.70. The log-normal distributions (0 = 0) for bilateral disease have = 3.10 and 3.24 for males and females, with = 0.81 and 0.87.

Females are on average about 6 mo older at diagnosis than males, and bilateral cases are approximately 1 yr younger than unilateral cases (Table 1). There is strong evidence that the age distributions differ between the two genders for unilateral cases (P < 0.0001); this difference is not significant for the bilateral cases, probably because of smaller numbers.

Fig. 2 contrasts the fitted parametric age distributions with the histograms and smoothed nonparametric estimates. Although formally rejected by the x^2 test (Table 1), the parametric models fit the data for males reasonably well. For females with unilateral disease, the "peak" in the distribution, estimated to occur at 24 mo according to the parametric model, in fact extends to 48 mo of age. There is some suggestion that the...
bilateral age distributions may be bimodal, but this cannot be confirmed with the present limited data.

Relative log-likelihoods for the shape parameter \( \theta \) (Fig. 3) show that, within the generalized \( \gamma \) family, the unilateral distributions are consistent with the Weibull and the bilateral distributions with the log-normal, but not vice-versa. Fitted cumulatives based on these two standard distributions are shown in Fig. 1 for possible use in genetic counselling. However, discrepancies may be noted, especially in the upper tails of the distributions for bilateral cases.

Centricity. Table 2 shows that on average the ages are younger for multicentric cases than unincentric ones for both males (\( t = 2.42, P = 0.02 \)) and females (\( t = 3.95, P < 0.0001 \)). The shapes of the age distributions for unilateral cases of each gender and centricity were similar, with the maximum likelihood estimates of \( \theta \) closely concentrated in the range 0.9 to 1.1 for all four subgroups.

Gender. A surprising feature of the NWTS data is the slight preponderance of females. Table 3 summarizes the results of statistical tests used to compare the sex ratios observed in each subgroup and to test each for equality with a hypothesized 1:1 ratio. The evidence for a female excess among multicentric and bilateral cases is strong (\( P = 0.01 \)). There is some evidence that the female percentage for unincentric cases, although still higher than 50% (\( P = 0.06 \)), is less than that for multicentric and bilateral cases.

Congenital Anomalies and Familiality. Table 4 characterizes the age and gender distributions for subgroups of NWTS patients having selected congenital anomalies or family members with Wilms’ tumor. Except for the males with cryptorchidism and/or hypospadias, the subgroups are not further broken down by gender, since to do so would overly fragment the data. There is some overlap among these categories, and rates of bilaterality very substantially between them. For example, 9 of the 26 aniridics are males with cryptorchidism and/or hypospadias. The other genital anomalies include (pseudo) hermaphroditism, ambiguous genitalia, hypo- or dysplastic testis, streak ovary, and chordee syndrome.

The age distributions for patients with hemihypertrophy and familial Wilms’ tumor are roughly comparable to those for the unilateral cases; average ages of the familial cases are younger, but not significantly so. By contrast, patients with aniridia, cryptorchidism/hypospadias, and other genital anomalies are substantially younger, and their age distributions otherwise resemble more closely those of the bilateral cases. Due to the small numbers in most subgroups, however, these data are consistent with a wide range of distributional shapes. The fitted parameters for the small group of aniridia cases were heavily influenced by one case diagnosed at 190 mo of age: the remainder had ages of 51 mo or less.

Precursor Lesions. Table 4 also examines the ages and genders of patients with “rest associated” tumors. Of 1466 recently diagnosed patients with sufficient histologic material for diagnosis of intralobar nephroblastomatosis, it was found in 197 (13.4%). These cases had young ages whose distributional shape tended towards the log-normal. Perilobar nephroblastomatosis was diagnosed in 336 of 1462 cases (23.0%). These were only slightly younger and had a typically shaped age distribution. Rates of bilaterality were elevated in both subgroups; only 14 of 940 cases (1.5%) evaluated as negative for both types of nephroblastomatosis were bilateral.

Race, Calendar Time, and Institution. Analysis of variance demonstrated no trends in the average age of diagnosis by calendar year (1969 to 1985) and only slightly more variation among the 102 participating institutions than expected by chance (\( r^2 = 0.038, F_{101,1490} = 1.29, P = 0.03 \)). However, there was substantial evidence (\( P = 0.002 \)) that blacks were older at

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**Table 1 Summary statistics and parameter estimates for the age distributions, by sex and bilaterality**

<table>
<thead>
<tr>
<th></th>
<th>Unilateral</th>
<th></th>
<th>Bilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>No. of patients</td>
<td>1523</td>
<td>1678</td>
<td>100</td>
</tr>
<tr>
<td>Age (mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>42.7 ± 31.4</td>
<td>47.6 ± 33.9</td>
<td>29.8 ± 22.7</td>
</tr>
<tr>
<td>Median</td>
<td>36.5</td>
<td>42.5</td>
<td>23.5</td>
</tr>
<tr>
<td>Parameter estimates*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shape (( \theta ))</td>
<td>0.9</td>
<td>0.9</td>
<td>0.4*</td>
</tr>
<tr>
<td>Location (( \alpha )) ± SE</td>
<td>3.810 ± 0.020</td>
<td>3.927 ± 0.018</td>
<td>3.262 ± 0.078</td>
</tr>
<tr>
<td>Scale (( \sigma )) ± SE</td>
<td>0.731 ± 0.014</td>
<td>0.762 ± 0.013</td>
<td>0.776 ± 0.056</td>
</tr>
<tr>
<td>Goodness-of-fit**</td>
<td>18.3</td>
<td>35.8</td>
<td>4.9</td>
</tr>
</tbody>
</table>

* See Ref. 7 for definitions.

** See Ref. 7 for definitions.

* The value of \( \theta \) that maximized the likelihood was close to 0.4 for bilateral cases of both genders, and a common value was used so that location and scale parameters for males and females would be comparable (see Fig. 3).

** Goodness-of-fit statistics that may be taken, very roughly, to have a \( \chi^2 \) distribution on 8 degrees of freedom.
WILMS' TUMOR AGE DISTRIBUTION

Table 2 Characteristics of the age distributions by sex and centricity (unilateral cases only)

<table>
<thead>
<tr>
<th></th>
<th>Unicentric</th>
<th></th>
<th>Multicentric</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>No. of patients</td>
<td>1361</td>
<td>1463</td>
<td>162</td>
<td>215</td>
</tr>
<tr>
<td>Age (mo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>43.4 ± 31.9</td>
<td>48.8 ± 34.7</td>
<td>36.5 ± 25.3</td>
<td>39.1 ± 26.6</td>
</tr>
<tr>
<td>Median</td>
<td>36.5</td>
<td>43.5</td>
<td>35.5</td>
<td>37.5</td>
</tr>
</tbody>
</table>

Table 3 Comparison of sex ratios according to centricity and laterality

<table>
<thead>
<tr>
<th></th>
<th>Unicentric</th>
<th>Multicentric</th>
<th>Bilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>2824</td>
<td>377</td>
<td>241</td>
</tr>
<tr>
<td>% Female</td>
<td>51.8</td>
<td>57.0</td>
<td>58.5</td>
</tr>
<tr>
<td>Test of M:F equality (P)</td>
<td>0.06</td>
<td>0.007</td>
<td>0.010</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td>1.0</td>
<td>1.23</td>
<td>1.31</td>
</tr>
<tr>
<td>Test of odds ratio = 1 (P)</td>
<td>0.06</td>
<td>0.054</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

In order to calculate age incidence rates, one ideally utilizes all disease cases diagnosed in a specified population and has access to age-specific denominators of persons at risk. Although such data are not analyzed here, there is reason to believe that the age distributions presented serve as good approximations (in the sense of proportionality) to the underlying age-specific incidence curves. (a) Due to a slowly changing birthrate and the fact that over 98% of children born alive survive to their 16th birthday, with most mortality occurring in the immediate postnatal period, the numbers of children at risk in the United States were fairly constant between 0 and 15 yr of age during the study period. In 1980, for example, these numbers stood in the ratio 1.00:1.02:1.12 for the 0 to 4, 5 to 9, and 10 to 14 age groups (9). (b) The NWTS has from the outset requested that participating institutions register all patients with a diagnosis of Wilms' tumor, regardless of their participation in the randomized trial. The enrollment of United States patients on study increased from 84 of an estimated 450 cases (19%) occurring nationally in 1970 (10) to 313 of an estimated 350 cases (89%) occurring in 1980 (9, 11). The study currently enrolls a very substantial fraction of the total United States incidence, plus a few foreign children, and there are no obvious selection biases. We believe, therefore, that studies of the NWTS patient population reasonably reflect what is happening in the country as a whole.

Differences between the age distributions in specific subgroups should closely parallel the corresponding comparisons of age incidence patterns. A tendency of some primary care physicians to refer girls with Wilms' tumor to NWTS institutions and boys to other institutions conceivably could explain the female excess. However, this seems most implausible. It is even less likely that differential selection of patients into the NWTS on the basis of both gender and age operates to produce the clear age difference for males and females. Since boys aged 0 to 14 in 1980 outnumbered girls by a ratio of 1.05 to 1, moreover, the NWTS observations are all the more suggestive of a slight excess incidence among girls in the United States. By contrast, data from a large number of cancer registries worldwide show the sex ratio to be almost exactly unity (11). The subgroups that have the most atypical age distributions consist of patients with bilateral disease, characteristic genito-urinary abnormalities, aniridia, and intralobar nephroblastomatosis, which features all tend to overlap to some extent. In each of these subgroups the patients are substantially younger at diagnosis, and the shape of the age distribution (on the log
and location. These latter two characteristics are also

distributions for patients with hemihypertrophy and perilobar

scale) tends toward the symmetry of the log-normal as opposed
to the skewness of the Weibull. On the other hand, the age
distributions for patients with hemihypertrophy and perilobar
nephroblastomatosis are rather typical as regards both shape
and location. These latter two characteristics are also
associated: 23 of 336 = 6.8% of the cases with perilobar
nephroblastomatosis had hemihypertrophy as opposed to 29 of
1126 = 2.6% of those without (P = 0.0004).

These observations lend further support to the concept of
heterogeneity in the pathogenesis of Wilms’ tumor (4). For
some cases, an event early in embryogenesis may have led to
the development of a precursor lesion (intralobar nephroblas-
tomatosis) that put the patient at high risk of a subsequent
Wilms’ tumor. Such cases have a histológica! spectrum typical
of the increasing numbers of survivors and their offspring. One

In the final analysis, accurate estimation of the fraction of
Wilms’ tumors that are truly hereditary will come from study
of the increasing numbers of survivors and their offspring. One
such study (14) failed to turn up a single case of cancer among
179 liveborn children of 99 patients treated for unilateral

<table>
<thead>
<tr>
<th>Table 4 Characteristics of the sex, age, and bilaterality distributions in selected subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptorchidism and/or hypospadias</td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>%</td>
</tr>
<tr>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Bilateral</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>%</td>
</tr>
<tr>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Age (mo)</td>
</tr>
<tr>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Shape of age distribution*</td>
</tr>
<tr>
<td>Wilcoxon test* (P)</td>
</tr>
</tbody>
</table>

* Test for equality of sex distributions for patients with and without the indicated anomaly/condition.
* s Test for equality of bilaterality distributions for patients with and without the indicated anomaly.
* s Best-fitting value of i; see Ref. 7.

It is of interest to examine the NWTS observations for
agreement with epidemiological data used by Knudson and
Strong (12) to develop a two-stage mutational model for the
origin of Wilms’ tumor. According to this model, a tumor may
arise from two (or more) events. The first is either a germ cell
or a somatic cell mutation, whereas the second event is always
postzygotic. Hereditary cases, i.e., those in which the initial
mutation is germinal, are likely to be multicentric or bilateral
and to be diagnosed at a younger age since all cells are at risk
of the second event from the moment of conception. The
evidence cited (12) in support of this model included the
younger ages at diagnosis of bilateral and familial cases com-
piled from the world literature. Cases with aniridia were iden-
tified as hereditary largely on the basis of a younger age distrib-
ution, whereas those with hemihypertrophy and most of the
rather small number of cases with genitourinary anomalies were
presumed to be sporadic.

The NWTS data confirm the younger ages and atypical age
distributions of the bilateral and aniridia cases. They further
suggest that patients with characteristic genitourinary anom-
alies should be included in this group. However, it is not obvious
that such cases are exclusively of “genetic” origin. The small
but important group of familial cases does not, or at least not
yet, provide clear evidence of the younger ages and higher rates
of bilaterality that are predicted by the model. Most perplexing
is the rather large group of patients with multicentric disease,
who according to the model should also be carriers of the
prezygotic mutation. Their age distributions differ only slightly
from those of unicuscent cases. Furthermore, they are consid-
erably more numerous than the bilateral cases (377 versus 241),
whereas one would expect less than half of the patients with
multiple primary tumors to have unilateral, multicentric disease
if target cells in both kidneys had a constant probability of
experiencing the second event. This suggests either that a
substantial number of the multicentric, unilateral tumors do
not represent two or more independent primaries, but rather
the spread of disease within the kidney, or else that some other
mechanism is responsible for at least some of these cases. For
example, if the first mutation occurred in a somatic cell in the
developing embryo after the division into two halves but prior
to the induction of the renal blastema (now recognized as
perilobar nephroblastomatosis) that has been suggested as the
substrate for Wilms’ tumor (13), this would place the tissues of
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Wilms' tumor, some of whom may have carried the putative Wilms' gene. Another study of 46 offspring of childhood kidney tumor survivors, with 278 person-yr of observation before 15 yr of age, turned up a single bilateral case of Wilms' tumor (15). It is hoped that continued follow-up of the large NWTS series, many members of which are just now approaching the child-bearing years, will ultimately resolve the issue.

In spite of the failure of the NWTS data to confirm completely the epidemiological observations made by Knudson and Strong in the development of their model, recent laboratory studies leave little doubt that a two-stage mutational mechanism is indeed operative at the cellular level. The first clue came from the observation that most children with the rare aniridia/Wilms' tumor syndrome have a constitutional deletion at the 11p13 locus (16). Molecular analysis using DNA probes then suggested that expression of a recessive mutant allele at this same locus is involved in tumor production (17–20). Evidently, an abnormal somatic segregation event results in production of a cell that is homozygous or hemizygous for the mutant allele. This is a beautiful example where the statistical study of events at the population level led to a hypothesized pathogenetic mechanism that was later confirmed in the laboratory.

ACKNOWLEDGMENTS

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