National Cancer Institute

Melding Epidemiology and Genomics

Program Review

Division of Cancer Epidemiology and Genetics

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Melding Epidemiology and Genomics

From High-Risk Families to Populations

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Malignant Bladder Tumors in a Man and His Three Sons

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ASSOCIATION OF WILMS'S TUMOR WITH ANIRIDIA, HEMIHYPERTROPHY AND OTHER CONGENITAL MALFORMATIONS*

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WHEN, through epidemiologic study of persons or families, diseases are found to be associated, the opportunities for determining their etiology may be very much increased. The association of leukemia and mongolism[1] is an example. An accumulation of case reports in the past decade suggests a link between another childhood cancer, Wilms's tumor, and a rare congenital defect, total hemihypertrophy.[2-8] In addition, isolated cases of Wilms's tumor in horseshoe kidneys have been reported.[9] The purpose of this presentation is to define more fully the relation between Wilms's tumor and congenital defects by study of the diagnoses contained in the medical records of 440 children hospitalized for such a tumor.

RESULTS

The patients were about equally distributed by sex: 223 boys and 217 girls. All but 20 were Caucasian. The distribution according to age at diagnosis was as follows: under four years, 287 cases; four to six years, 116 cases; and seven to eighteen years, 37 cases. The major congenital defects among 440 patients with Wilms's tumor are listed in Table 1.

Aniridia and Its Associated Defects

Congenital aniridia was recorded for 6 of the children; the rate among patients with Wilms's tumor, 1:73, is markedly greater than the at-birth incidence of 1:50,000 estimated by Shaw, Falls and Neel[10] for Michigan. The aniridic children tend-

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Soft-Tissue Sarcomas, Breast Cancer, and Other Neoplasms

A Familial Syndrome?

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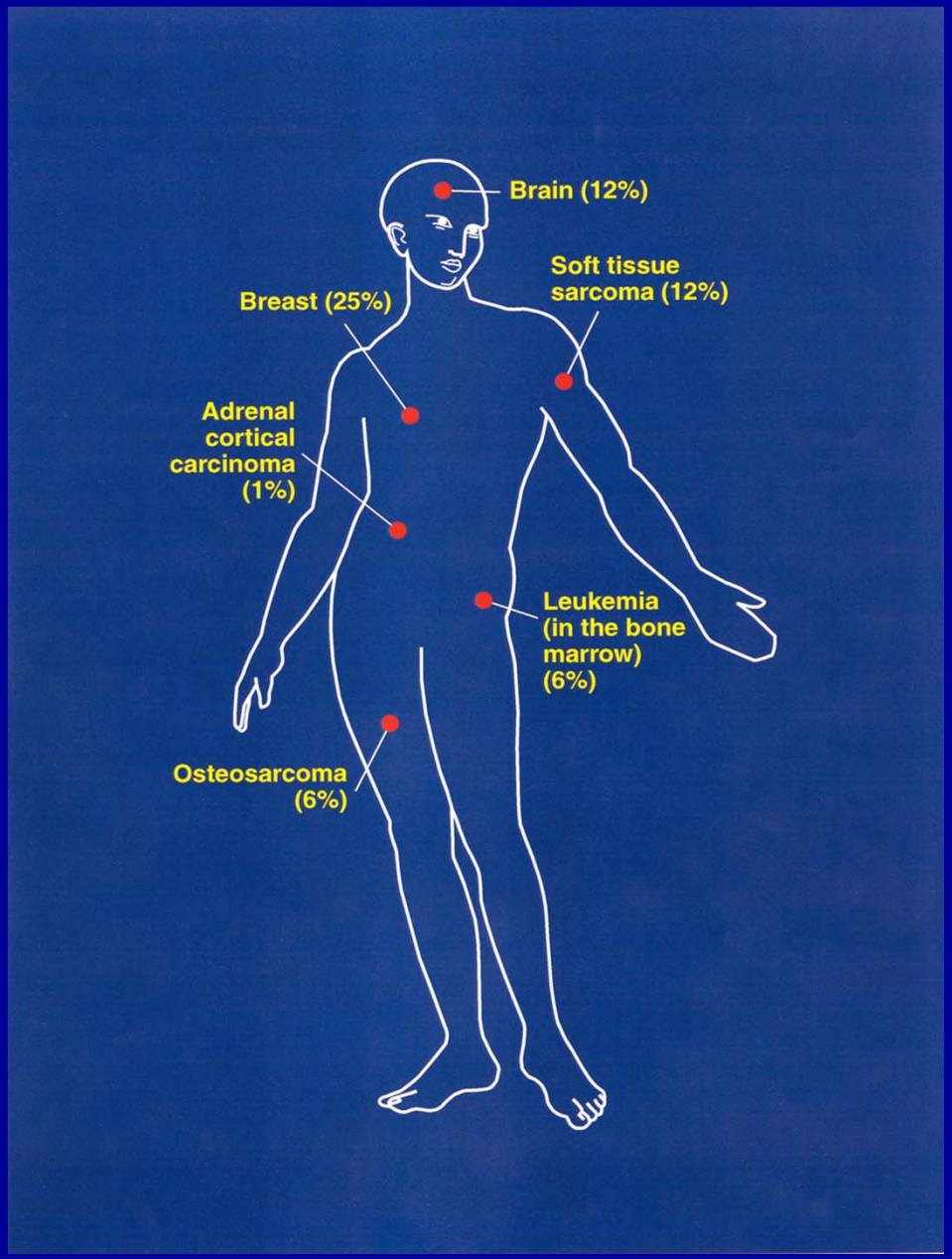
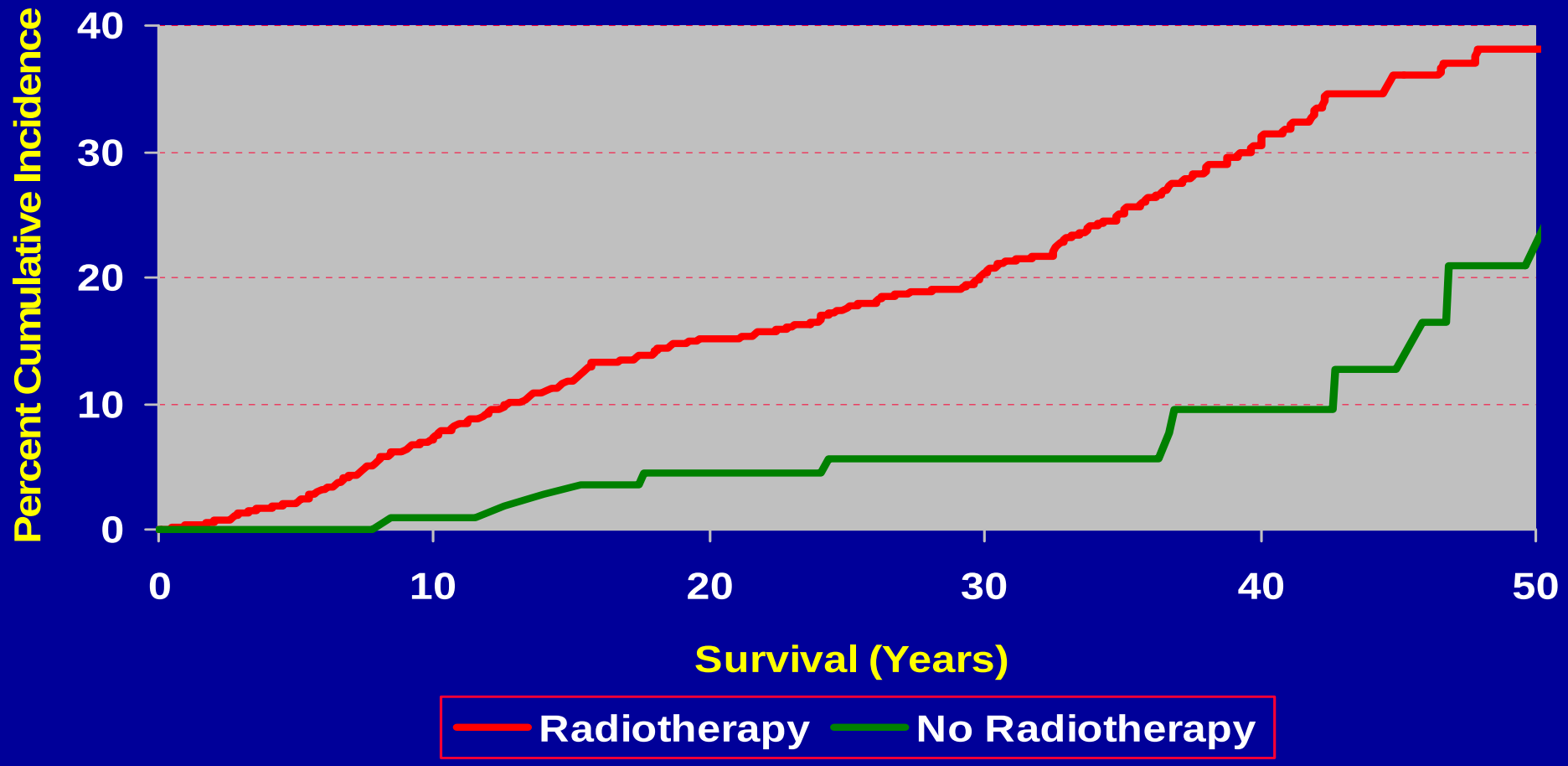


Li-Fraumeni Syndrome

- Dominantly inherited
- Striking variety of early-onset tumors
- Predisposition to second primaries
- Germline mutations of p53

Cumulative incidence of second cancer after hereditary retinoblastoma



Cloned Familial Tumor Suppressor Genes

Retinoblastoma	RB1	13q14	1986
Wilms' tumor	WT1	11p13	1990
Li-Fraumeni syndrome	p53	17p13	1990
Neurofibromatosis 1	NF1	17q11	1990
Neurofibromatosis 2	NF2	22q12	1993
von Hippel-Lindau syndrome	VHL	3p25	1993
Familial melanoma 1	p16	9p21	1994
Familial breast cancer 1	BRCA1	17q21	1994
Familial breast cancer 2	BRCA2	13q12	1995
Basal cell nevus syndrome	PTC	9q22	1996

Inherited Mutations vs Polymorphisms

Characteristics	Mutations	Polymorphisms*
Penetrance	High (familial)	Low (sporadic)
Absolute/relative risk	High	Low
Attributable risk	Low	High
Gene frequency	Uncommon	Common (>1%)
Number of genes	Usually one	Usually multiple
Role of environment	Minor	Major
Testing	Diagnostic	Susceptibility
Target tissue	Mainly cancer cells	Cancer and stromal cells
Study design	Family (linkage)	Population (association)

* Cancer susceptibility (modifier) genes

Melding Epidemiology and Genomics

From high-risk families to populations (J. Fraumeni)

Key epidemiologic challenges (R. Hoover)

Clues from the pathway-driven approach (M. Garcia-Closas)

The promise of genome-wide association studies (S. Chanock)