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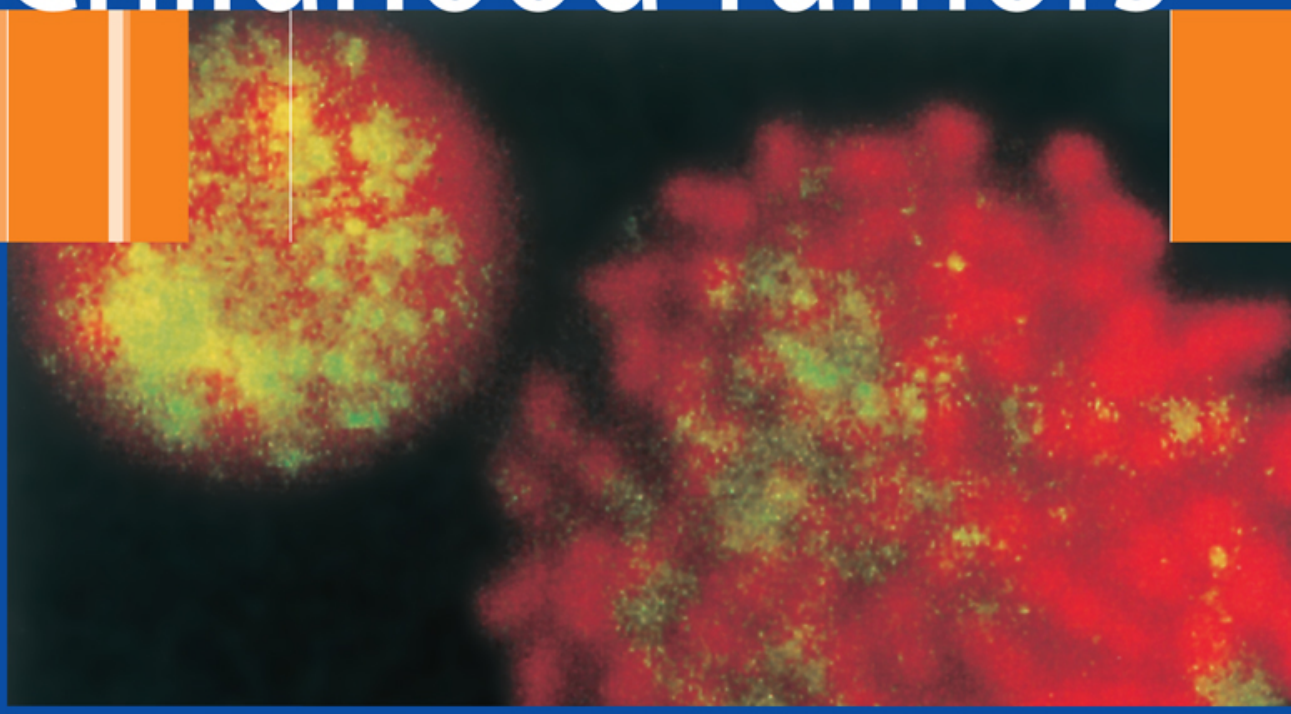
The Surgery of Childhood Tumors



Second Edition

Springer

Robert Carachi · Jay L. Grosfeld · Amir F. Azmy

The Surgery of Childhood Tumors

Robert Carachi · Jay L. Grosfeld · Amir F. Azmy (Eds.)

The Surgery of Childhood Tumors

Second Corrected and Enlarged Edition

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This photograph was taken in Glasgow (March, 1998) when Professor Jay Grosfeld was awarded the Honorary Fellowship of The Royal College of Physicians and Surgeons of Glasgow. The three editors in the picture with their wives are, from left to right, Robert and Annette Carachi, Jay and Margie Grosfeld, Amir and Fatima Azmy.

This volume is dedicated to our wives,
our children, and our grandchildren.

Foreword

Surgery was at one time the only modality of treatment which was capable of curing children unfortunate enough to develop cancer. Then along came radiotherapy, chemotherapy, and now even immunotherapy; however, surgery still retains an important place and in some instances good surgery is a prerequisite for cure.

In Europe and the UK, as in the US, much of the early treatment for children with solid tumors was led by and often given by surgeons. We now, however, have multidisciplinary teams with each member having a key role to play.

Survival for childhood cancer has improved dramatically over the last 50 years and although we continue to make progress the rate of improvement has inevitably slowed down. In developed countries the major scope for improvement still lies in the organization of care. Ensuring that the pathway to diagnosis is as short as possible and ends at the team that can deliver best modern treatment, preferably in a clinical trial setting, has to be a goal for all countries. One of the biggest hurdles, however, remains getting on to that diagnostic journey in the first place and there remains a great deal to be done in education of both parents and primary care physicians to take lumps and bumps seriously. Even within Europe there are marked disparities in outcome in spite of similar treatments. Social factors and access to and compliance with care must also be considered.

The role of the surgeon is important in the direct management of children with cancer but they also play a huge supportive role. The advent of central venous lines to facilitate access for chemotherapy has revolutionized the giving of treatment. Insertion of these lines is a skilled procedure and needs to be done in a timely fashion. The oncology team surgeon usually plays this vital role.

I am delighted to see the second edition of this important book. The editors have done an excellent job in drawing together a real team of experts. This book will facilitate the education of young surgeons, keen to join the pediatric oncology team, and provide refreshment and stimulation for those already in the field.

Professor Sir Alan W. Craft

Foreword

In managing a child thought to have a malignant tumor, the day starts in the operating room, literally and figuratively. The surgeon is the key figure, whether in taking a biopsy or undertaking a major extirpation. Much depends on how that procedure is done, starting with the incision. Is it correctly placed – whether for a biopsy or a radical procedure – or will it make for problems in subsequent management? Even at this perhaps simplest of levels, it is obvious that the surgeon from the beginning plays a pivotal role in ensuring success in pediatric oncology. A trans-scrotal biopsy of a subsequently proven testicular or paratesticular malignant tumor complicates matters. How best to deal with the unnecessarily contaminated hemi-scrotal sac?

It is also inherent in the example given that modern management of the child with cancer entails working as a member of a coordinated, multimodal team. Long gone are the days when any specialist could embark on a solo course of action. The pediatric radiation therapist and chemotherapist along with the surgeon make up that team, each depending on the skill and expertise of the other.

Modern multimodal care in pediatric oncology has led to the rapid rise in survival rates of the various malignant entities to the present astonishing levels. Effective anticancer drugs have been credited with much of that progress – and rightly so. That has, however, also led in recent decades to an unfortunate undervaluation of the part surgeons have played and continue to play in contributing to that success. The surgeon's role too often is being taken for granted. It must be more appreciated and understood that the day does indeed start in the operating room. I feel this perhaps more keenly because I had the privilege of working as an intern under two great pioneering pediatric surgeons: Drs. William E. Ladd and Robert E. Gross. They were the Fathers of Pediatric Surgery in the USA, and were responsible for major steps forward in the management of children with cancer. Their surgical skills were remarkable, and made a deep impression, of course, as did their willingness to look beyond accepted techniques and methods. They were ready to explore the new and promising; Dr. Ladd, for instance trying and then advocating the transperitoneal approach to Wilms' tumors. Dr. Gross did so for routine postoperative radiation therapy for that neoplasm, thus forging the first link in the chain of interdisciplinary care. Even more memorable and important was their systematic, careful method for moving forward. Their innovations were not capricious. They came about only after careful thought, observation, and even laboratory experimentation when appropriate. Their textbooks were models of building on the logical conclusions. From the organization of those books, I first began to understand the meaning of the "scientific method."

Despite the fact that some of the best survival rates in the world resulted from what they were doing, the chemotherapist was quickly added to the radiotherapist to form the modern multimodal team. Great credit is due Drs. Ladd, Gross, and other surgeons like them, in so quickly embracing a pattern of care that was completely new, and helping to pave the path to progress.

But the day for the multimodal team nonetheless starts with the surgeon, who ideally should be a member of an experienced, interdisciplinary unit. If not, and such a well-staffed and competent pediatric cancer center is available locally, the child should be referred there. This is so because childhood cancers are very different from those that occur in the adult. Few surgeons accumulate sufficient personal experience to feel confident in undertaking the care of a child with a malignant tumor. To help them understand the intricacies of the pediatric surgical oncology, the editors have brought together in these pages the experience and expertise of an international array of surgeons and other authorities. The Table of Contents shows the wide range topics covered. They start with basic considerations such as the epidemiology of childhood tumors. The roles of associated specialties are then discussed along with a review of specific tumor types. Supportive and palliative care – extremely important topics sometimes neglected in "how to" books – are not neglected. Chapter 29 adds information concerning how best to interact with parents' groups and other psychosocial support associations. Such groups are

making their voices heard more and more, and it is appropriate and proper that they should. The surgeon must be ready to meet with such associations, to discuss their problems and to answer their questions. The second edition of this book thus brings detailed and up-to-date informing concerning what needs to be done not only before surgery, but also at the operating table and thereafter. It does more than that: It provides a blue print of how the surgeon can best fit within the modern practice of pediatric oncology.

Emeritus Professor J. Giulio D'Angio

Preface

The first edition of The Surgery of Childhood Tumors was published in 1999. The purpose of the book was to produce a comprehensive illustrated reference book on the management of childhood solid tumors focusing on those neoplasms of specific interest to pediatric surgeons. It was also intended for use by pediatricians, pediatric and adult medical oncologists, general and pediatric urologists, orthopedic surgeons, otolaryngologists and neurosurgeons. Each chapter was written by an authority in that field of pediatric oncology. Authors were selected from Europe, the United States, and Asia. Most were members of the major cancer study groups worldwide. This book was well received and the editors believed that a second edition was due because of the new important knowledge that has become available in the last few years. There have been new developments in epidemiology, tumor biology, molecular genetics of cancer, concepts of risk in relation to pediatric surgical pathology, diagnostic imaging techniques, radiation and chemotherapy. In particular, there are new surgical concepts in the evolution of minimally invasive surgery in the diagnosis and management of surgical oncology as well as the problem of vascular access provided by the surgeon and the interventionalist. Novel methods of treatment in cancer patients have advanced with the increased knowledge of the molecular biology of the cancer cell. As a consequence, the 2nd edition has had to include chapters on new therapies and technologies and up-to-date literature reviews. We trust that the readers will find these changes valuable.

We have retained our main aim in the 1st edition to have the book well illustrated with clinical images as well as detailed operative techniques and up-to-date references. The book consists of three sections:

Part A consists of eight chapters dealing with epidemiology of childhood cancer, tumor biology, and environmental carcinogens, the genetics of cancer including inherited syndromes and counseling, tumor markers and results of tumor screening programs, tumor imaging, the general pathologic principles of childhood solid tumors, and information regarding chemotherapy, radiation therapy, and immunotherapy in pediatric cancer.

Part B consists of seven chapters concerning tumors encountered in the neonatal period, and the contemporary management of Wilms' tumor and other renal neoplasms, neuroblastoma and other adrenal lesions, malignant hepatic tumors, germ cell tumors, soft tissue sarcomas, and Hodgkin's and non-Hodgkin's lymphoma.

Part C deals with some tumors managed by the specialist surgeons and other members of the cancer team and consists of fourteen chapters including chapters about malignant bone tumors, and head and neck tumors with extensive coverage of medullary thyroid cancer and multiple endocrine neoplasia syndromes. The chapter on brain tumors has been altered to include orbital and periorbital tumors. The other chapters in this section cover thoracic tumors (lung, chest wall, and mediastinum), other rare tumors observed in children, and unique aspects of reconstructive surgery following extensive procedures (limb salvage, chest wall replacement, etc.). Surgical and other complications of cancer treatment, patient and family support and counseling at diagnosis and during early postoperative care in potential survivors, palliative and terminal care, and bereavement, as well as the late effects of cancer treatment in long-term survivors are also covered in detail. This chapter also includes an extensive review on fertility in children treated for cancer. Four other new chapters have been included on minimal invasive surgery, new treatments and new strategies, central venous access and pain management. There is occasional overlap in some chapters when dealing with tumors in anatomical regions, and this was intentionally left in place and cross-referenced.

The editors wish to thank all the contributing 47 authors for taking valuable time from their busy schedules to participate in the development of this text and for submitting their manuscripts in a timely manner.

Robert Carachi
Jay L. Grosfeld
Amir F. Azmy

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We are grateful to Professor Dr. Giulio D'Angio and Sir Alan Craft for writing the Foreword to this 2nd edition of 'The Surgery of Childhood Tumors'. We would also like to thank our secretaries Kay Byrne (Glasgow) for the tremendous amount of work in corresponding with the authors of all the chapters and collating all the material to hand over to the publishers as well as Karen Jaeger (Indianapolis) for her help in preparing the manuscripts during the production of this text. Our gratitude goes to Gabriele Schröder, Editorial Director and Stephanie Benko, Desk Editor Clinical Medicine of Springer Verlag for their help and support in the production of this book.

Finally we would like to thank our wives and children for their continuing support and understanding while we were editing this book.

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Glossary of Terms

Alleles
Alternative forms of a gene or DNA sequence occuring at the same locus an homologous chromosomes.

Aneuploid
Chromosome number that is not an exact multiple of the haploid set – for example, 2n – 1 or 2n × 1.

Clone
All cells arising by mitotic division from a single original cell and having the same genetic constitution.

Diploid
Normal state of human somatic cells, containing two haploid sets of chromosomes (2n).

DNA polymerase
Enzyme concerned with synthesis of double-stranded DNA from single-stranded DNA.

Haploid
Normal state of gametes, containing one set of chromosomes (n).

Heritability
The contribution of genetic as opposed to environmental factors to phenotypic variance.

Hybridization
Process by which single strands of DNA with homologous sequence bind together.

Oncogene
Gene with potential to cause cancer.

Polymerase chain reaction (PCR)
Method of amplification of specific DNA sequences by repeated cycles of DNA synthesis to permit rapid analysis of DNA restriction fragments subsequently.

Polyploid
Chromosome numbers representing multiples of the haploid set greater than diploid – for example 3n.

Probe
Labeled DNA fragment used to detect complementary sequences in DNA sample.

Southern blotting
Process of transferring DNA fragments from agarose gel to nitrocellulose filter or nylon membrane.

Translocation
Transfer of chromosomel material between two non-homologous chromosomes.

Triploid
Cells containing three haploid sets of chromosomes (3n).

Deletion
A deletion occurs when a section of a chromosome either terminal or intestitial is lost.

Proto-oncogene
First recognized as viral oncongenes (*v-onc*) carried by RNA viruses. Subsequent ones found in the human genome are called cellular oncogenes *(c-onc*). More than 60 such proto-oncognes have been described. Their normal function is the control of cell growth and differentiation. Mutation results in appropriate expression leading to neoplasia.

Northern blotting
Blotting for analysis from RNA detects gene expression.

FISH
Fluorescent in situ hybridization. DNA probe labeled with fluorochrome and hybridized direct with a metaphase chromose spread. A fluorescent signal produced by the hybridization to the relevant chromosome is visualized using a fluorescent microscope.

Abbreviations

Organizations

CCG	Children's Cancer Group
CCLG	Children's Cancer and Leukemia Group
CESS	German Cooperative Ewing's Sarcoma Study
CLGB	Cancer and Leukemia Group B
CWS	German Cooperative Sarcoma Group
EC	European Community
ENSG	European Neuroblastoma Study Group
IACR	International Association of Cancer Registries
IARC	International Agency for Research and Cancer
ICDO	International Classification of Disease for Oncology
INSS	International Neuroblastoma Staging System
IRS	Intergroup Rhabdomyosarcoma Study Group
NCI	National Cancer Institute (USA)
NWTS	National Wilms' Tumor Study
POG	Pediatric Oncology Group (USA)
SEER (Program)	Surveillance, Epidemiology and End-Results Program
SIOP	International Society of Pediatric Oncology (Society Internationale Oncologie Pediatrique)
SWOG	Southwest Oncology Group
UKW	United Kingdom Wilms' Tumor Trials
WHO	World Health Organization

Common Abbreviations Used in the Text

ABMT	Autologous Bone Marrow Transplant
ACTH	Adrenocorticotropic Hormone
ADEPT	Antibody Directed Enzyme Prodrug Therapy
AFP	Alpha-Fetoprotein
AIDS	Acquired Immunodeficiency Syndrome
ALL	Acute Lymphoblastic Leukemia
ALL	Acute Lymphocytic Leukemia
AML	Acute Myelogenous Leukemia
ANLL	Acute Nonlymphoblastic Leukemia
APUD	Amine Precursor Uptake and Decarboxylation
ARDS	Adult Respiratory Distress Syndrome
ASR	Age Standardized Rate
ASRM	Age Standardized Mortality Rate
bFGF	Basic Fibroblast Growth Factor
BMRTC	Bone Metastasing Renal Tumor of Childhood
CFS	Congenital Fibrosarcoma
CK	Creatine Kinase
CMN	Congenital Mesoblastic Nephroma
CMV	Cytomegalovirus
CNS	Central Nervous System
COMT	Catechol-O-Methyltransferase
CPDN	Cystically Partially Differentiated Nephroblastoma
CT	Computed Tomography
CUM	Cumulated Incidence Rate
DDC	DOPA Decarboxylase
DGH	dopamine β-hydroxylase
DNET	Dysembryoplastic Neuroepithelial Tumor
DOPA	3, 4-Dihydroxyphenylalanine
EBV	Epstein-Barr virus
EMG	Exomphalos, Macroglossia and Gigantism Syndrome
FAP	Familial Adenomatous Polyposis
FISH	Fluorescent In Situ Hybridization
FNA	Fine Needle Aspiration
FRC	Functional Residual Capacity
FSH	Follicle Stimulating Hormone
5-FU	5-Fluorouracil
FVC	Forced Vital Capacity
G-CSF	Granulocyte Colony Stimulating Factor
GCT	Germ Cell Tumors
GLC	Gas Liquid Chromatography
GM	Granulocyte Macrophage
HAL	Hepatic Artery Ligation
HCG	Human Chorionic Gonadotropin

HIV	Human Immunodeficiency Virus
HMMA	Hydroxymethoxymandellic Acid
HPLC	High Performance Liquid Chromatography
HSV	Herpes Simplex Virus
HVA	Homovanillic Acid
IGF	Insulin-Like Growth Factor
IR	Incidence Rate
ITP	Idiopathic Thrombocytopenic Purpura
LCH	Lens Culinaris Hemagglutinin
LDH	Lactic Dehydrogenase
LH	Luteinizing Hormone
LT	Linear Trend
Mab	Monoclonal Antibodies
MAO	Monoamine Oxidase
MDP	Methylene Diphosphonate
MDR	Multiple Drug Resistance
MEN	Multiple Endocrine Neoplasia
Mesna	2-Mercaptoethane Sulfate
MFH	Malignant Fibrous Histiocytoma
MIBG	Meta-Iodo-Benzylguanidine
MKI	Mitosis/Karryorrhexis Index
6-MP	6-Mercaptopurine
MPNST	Malignant Peripheral Nerve Sheath Tumors
MR	Mortality Rate
MRA	Magnetic Resonance Angiography
MRP	Multiple Drug Resistance Associated Protein Gene
MTC	Medullary Thyroid Carcinoma
NGF	Nerve Growth Factor
NHL	Non-Hodgkin's Lymphoma
NPY	Neuropeptide Y
NRSTS	Non-Rhabdomyosarcoma Soft Tissue Sarcomas
NSE	Neuron-Specific Enolase
OMIM	On-line Mendelian Inheritance in Man
OPSI	Overwhelming Post-Splenectomy Infection
PAS	Periodic Acid-Schiff
PCA	Patient-Controlled Analgesia
PCNA	Proliferating Cell Nuclear Antigen
PCR	Polymerase Chain Reaction
PEFR	Peak Expiratory Flow Rate
PEI	Percutaneous Ethanol Injection
PNET	Primitive Neuroectodermal Tumor
PNMT	Phenylethanolamine-N-Methyl-transferase
RMS	Rhabdomyosarcoma
SIR	Standardized Incidence Rate
SMN	Second Malignant Neoplasms
SMR	Standardized Mortality Rate
SPECT	Single Photon Emission Computed Tomography
TBI	Total Body Irradiation
TGF	Transforming Growth Factor
TLC	Total Lung Capacity
RMN	Third Malignant Neoplasms
TNM	Tumor-Node-Metastasis
TRK	Tyrosine Kinase Receptor
TS	Tuberous Sclerosis
TSH	Thyroid-Stimulating Hormone
VIP	Vasoactive Intestinal Polypeptide
VLA	Vanillactic Acid
VMA	Vanillylmandelic Acid
WAGR	Wilms' Tumor, Aniridia, Genitourinary Abnormalities (or Gonadoblastoma), Abnormalities and Mental Retardation

Acronyms of Drug Combinations

ABVD	Adriamyciri (Doxorubicin) Bleomycin, Vinblastine, Dacarbazine
Adria-VAC	Adriamycin (Doxorubicin), Vincristine, Actinomycin-D, Cyclophosphamide
BEP	Bleomycin, Etoposide, Cisplatin
BiCNU	Carmustine (Bischloroethyl-N-Nitro-surea)
CADO	Cyclophosphamide, Adriamyciri (Doxorubicin)
CCNU	Lomustine (Chloroethyl-N-Cyclohexyl-N-Nitrosurea)
Ch1VPP	Chlorambucil, Vinblastine, Procarbazine, Prednisone
COMP	Cyclophosphomide, Vincristine (Oncovin) Methotrexate, Prednisone
IVA	Ifosfamide, Vincristine, Adriamycin (Doxorubicin)
JEB	Carboplatin, Etoposide, Bleom Cin
MOPP	Mustine, Vincristine (Oncovin) Procarbazine, Prednisolone
OPEC	Vincristine (Oncovin) Cisplatin or
OJEC	Etoposide, Carboplatin
PEI	Cisplatin, Etoposide, Ifosfamide
PVB	Cisplatin, Vinblastine, Bleomycin
PLADO	Cisplatin, Adriamyciri (Doxorubicin)
VA	Vincristine, Actinomycin-D
VAC	Vincristine, Actinomycin-D, Cyclophos-phamide
VAdriaC	Vincristine, Adriamyciri (Doxorubicin), Cyclophosphamide
VIA	Vincristine, Ifosfamide, Actinomycin-D
VIE	Vincristine, Ifosfamide, Etoposide

Part A

Epidemiology of Childhood Tumors

Charles A. Stiller

1

Contents

1.1 Classification

Traditionally, descriptive data on cancers occurring in people of all ages combined have been presented with the diagnoses categorized according to the International Classification of Diseases (ICD), in which cancers other than leukemias, lymphomas, Kaposi's sarcoma, cutaneous melanoma, and mesothelioma are classified purely on the basis of primary site. The malignant solid tumors of children are histologically very diverse and a substantial proportion consists of characteristic entities that are rarely seen in adults. Therefore, it is appropriate to group childhood cancers in a way which more fully takes morphology into account, and standard classifications have been devised with the categories defined according to the codes for topography and morphology in the International Classification of Diseases for Oncology (ICD-O) [4, 25, 59]. The current scheme is the International Classification of Childhood Cancer, Third Edition (ICCC-3), based on the third edition of ICD-O [59]. ICCC-3 contains 12 main diagnostic groups:

I Leukemias, myeloproliferative diseases, and myelodysplastic diseases
II Lymphomas and reticuloendothelial neoplasms
III CNS and miscellaneous intracranial and intraspinal neoplasms
IV Neuroblastoma and other peripheral nervous cell tumors
V Retinoblastoma
VI Renal tumors
VII Hepatic tumors
VIII Malignant bone tumors
IX Soft tissue and other extraosseous sarcomas
X Germ cell tumors, trophoblastic tumors, and neoplasms of gonads
XI Other malignant epithelial neoplasms and malignant melanomas
XII Other and unspecified malignant neoplasms

All of the groups except retinoblastoma are split into subgroups, and the most heterogeneous subgroups are in turn split into divisions. Most groups contain only malignant neoplasms, but groups III and X also include nonmalignant intracranial and intraspinal tumors since they are usually recorded by cancer registries.

Successive classifications have been designed to have as much continuity as possible with their predecessors, while recognizing advances in understanding of tumor pathology and biology. Although the nomenclature of many groups and subgroups has changed since the previous version of the classification, their contents are largely the same.

1.2 Incidence

The annual incidence of cancer in children under 15 years of age is usually between 100 and 160 per million. There is a risk of 1 in 650 to 1 in 400 that a child will be affected during the first 15 years following birth. Table 1.1 shows annual incidence rates per million children in Great Britain for the decade 1991–2000 [61]. The total incidence, just under 140 per million, was slightly lower than in many industrialized countries, but the relative frequencies of the different groups and subgroups were fairly typical. In Table 1.1, the ICCC-3 subgroups for Burkitt lymphoma and other non-Hodgkin lymphoma (NHL) have been combined because they are usually considered together clinically, and data for some other subgroups and divisions are not shown separately because of small numbers.

Table 1.1 Registration rates for cancers diagnosed at age 0–14 years in Great Britain, 1991–2000. Source: National Registry of Childhood Tumors [61]

ICCC-3 categories	Total registrations	Annual rates per million children for age group (years)				Age standardized rates per million (world standard population)		
		0	1–4	5–9	10–14	Boys	Girls	Children
I-XII. All cancers	14,659	187.9	185.9	108.3	110.8	150.5	127.4	139.2
I. Leukemias	4,695	38.3	78.2	34.4	24.8	50.1	40.7	45.5
(a) Lymphoid leukemias	3,715	18.0	66.7	28.3	17.0	39.9	32.1	36.1
(b) Acute myeloid leukemias	693	13.5	7.9	4.4	5.8	7.1	6.1	6.6
(c) Chronic myeloproliferative diseases	63	-	0.3	0.5	1.1	0.6	0.5	0.6
(d) Myelodysplastic syndrome and other myeloproliferative	173	4.9	2.7	1.0	0.6	1.9	1.5	1.7
(e) Other and unspecified	51	2.0	0.6	0.2	0.3	0.5	0.5	0.5
II. Lymphomas, etc.	1424	1.1	7.9	12.9	20.1	17.0	13.9	12.5
(a) Hodgkin lymphoma	584	-	1.3	4.2	11.1	6.5	3.4	5.0
(b, c) Non-Hodgkin lymphomas	815	0.8	6.4	8.5	8.8	10.2	4.3	7.3
(d, e) Other and unspecified	25	0.3	0.2	0.2	0.3	0.3	0.1	0.2
III. CNS, intracranial, intraspinal	3,605	35.2	36.0	35.4	28.3	34.7	32.3	33.5
(a) Ependymomas & choroid plexus tumors	352	6.9	5.5	2.2	1.7	4.0	2.9	3.5
1. Ependymomas	261	1.8	4.2	1.9	1.6	2.7	2.2	2.5
2. Choroid plexus tumors	91	5.0	1.4	0.3	0.1	1.3	0.6	1.0
(b) Astrocytomas	1,551	10.4	15.1	15.8	13.0	13.3	15.4	14.3
(c) Intracranial & intraspinal embryonal tumors	697	9.0	8.1	7.2	3.7	7.8	5.4	6.6
1. Medulloblastomas	509	4.1	5.4	6.0	2.9	5.9	3.6	4.8
2. Primitive neuroectodermal tumor	161	3.8	2.3	1.1	0.7	1.7	1.5	1.6
4. Atypical teratoid/ rhabdoid tumor	24	1.1	0.3	0.1	0.1	0.2	0.2	0.2
(d) Other gliomas	380	2.0	3.2	4.5	3.0	3.5	3.5	3.5
(e) Other specified	452	3.9	2.8	4.3	5.2	4.5	3.7	4.1
2. Craniopharyngioma	201	0.7	1.2	2.3	2.2	2.0	1.6	1.8
4. Neuronal, neuronal-glial	142	2.4	0.8	1.4	1.4	1.4	1.2	1.3
5. Meningiomas	48	0.1	0.3	0.4	0.7	0.5	0.3	0.4
(f) Unspecified	173	3.1	1.4	1.4	1.7	1.7	1.6	1.6
IV. Neuroblastoma etc	897	36.0	17.5	3.0	0.6	10.3	8.4	9.3
(a) Neuroblastoma & ganglioneuroblastoma	886	36.0	17.3	2.9	0.5	10.2	8.3	9.2
(b) Other peripheral nervous cell	11	-	0.1	0.1	0.1	0.1	0.1	0.1

Table 1.1 *(Continued)* Registration rates for cancers diagnosed at age 0–14 years in Great Britain, 1991–2000. Source: National Registry of Childhood Tumors [61]

ICCC-3 categories	Total registrations	Annual rates per million children for age group (years)				Age standardized rates per million (world standard population)		
		0	1–4	5–9	10–14	Boys	Girls	Children
V. Retinoblastoma	430	25.4	7.9	0.5	0.1	4.5	4.6	4.6
VI. Renal tumors	811	15.9	17.4	3.9	1.3	8.3	8.3	8.3
(a) Nephroblastoma & other nonepithelial	787	15.6	17.3	3.8	0.9	8.0	8.1	8.1
1. Nephroblastoma (Wilms tumor)	732	13.2	16.4	3.6	0.8	7.2	7.8	7.5
2. Rhabdoid	24	2.0	0.3	-	-	0.4	0.2	0.3
3. Sarcomas	24	0.3	0.6	0.1	-	0.4	0.1	0.3
4. Peripheral neuroectodermal tumor	7	0.1	-	0.1	0.1	0.1	0.1	0.1
(b) Renal carcinoma	19	-	0.1	0.1	0.4	0.2	0.2	0.2
(c) Unspecified	5	0.3	-	0.1	-	0.1	0.0	0.1
VII. Hepatic tumors	138	5.9	2.2	0.3	0.6	1.7	1.1	1.4
(a) Hepatoblastoma	112	5.9	2.1	0.1	0.1	1.5	0.9	1.2
(b) Hepatic carcinoma	25	-	0.1	0.2	0.4	0.2	0.2	0.2
(c) Unspecified	1	-	0.0	-	-	0.0	-	0.0
VIII. Malignant bone tumors	563	0.7	0.9	4.1	10.8	4.7	4.9	4.8
(a) Osteosarcoma	307	-	0.2	2.4	6.1	2.4	2.7	2.6
(c) Ewing sarcoma family	217	0.1	0.7	1.6	4.0	2.0	1.8	1.9
(b, d, e) Other & unspecified	39	0.6	0.0	0.1	0.8	0.3	0.4	0.3
IX. Soft tissue & extraosseous sarcomas	1028	14.7	11.1	8.1	8.6	10.6	8.7	9.7
(a) Rhabdomyosarcoma	547	6.6	8.5	4.6	2.3	6.3	4.3	5.3
(b) Fibrosarcoma etc	80	2.2	0.3	0.5	1.1	0.6	0.9	0.7
(c) Kaposi's sarcoma	5	-	-	0.1	0.1	0.0	0.1	0.0
(d) Other specified	340	4.5	2.0	2.5	4.5	3.2	3.0	3.1
1, 2. Ewing sarcoma family	122	1.4	1.1	0.9	1.3	1.0	1.2	1.1
7. Synovial sarcoma	56	-	0.1	0.4	1.2	0.6	0.4	0.5
(e) Unspecified	56	1.4	0.3	0.4	0.7	0.5	0.5	0.5
X. Germ cell, trophoblastic & gonadal	486	11.2	4.2	2.2	5.7	4.2	4.9	4.5
(a) Intracranial & intraspinal germ cell	165	2.0	0.6	1.1	2.6	1.7	1.2	1.5
(b) Other malignant extragonadal	107	6.3	1.8	0.1	0.2	0.7	1.6	1.1
(c) Malignant gonadal germ cell	204	3.1	1.8	0.9	2.7	1.8	2.0	1.9
(d, e) Other & unspecified gonadal	10	0.1	-	0.1	0.2	0.1	0.1	0.1

Table 1.1 *(Continued)* Registration rates for cancers diagnosed at age 0–14 years in Great Britain, 1991–2000. Source: National Registry of Childhood Tumors [61]

ICCC-3 categories	Total registrations	Annual rates per million children for age group (years)				Age standardized rates per million (world standard population)		
		0	1–4	5–9	10–14	Boys	Girls	Children
XI. Other malignant epithelial & melanoma	483	1.4	1.6	2.9	9.1	3.7	4.7	4.2
(a) Adrenocortical carcinoma	24	0.3	0.5	0.1	0.1	0.2	0.3	0.2
(b) Thyroid carcinoma	71	-	0.2	0.5	1.4	0.4	0.8	0.6
(c) Nasopharyngeal carcinoma	24	-	-	0.1	0.6	0.3	0.1	0.2
(d) Malignant melanoma	154	1.0	0.7	1.1	2.5	1.1	1.6	1.4
(e) Skin carcinoma	82	0.1	0.2	0.5	1.6	0.7	0.7	0.7
(f) Other & unspecified carcinomas	128	-	0.1	0.6	2.9	1.0	1.2	1.1
XII. Other & unspecified	99	2.1	1.1	0.5	0.9	0.8	1.1	0.9
(a) Other specified	17	0.3	0.3	0.0	0.2	0.2	0.2	0.2
(b) Unspecified	82	1.8	0.8	0.5	0.7	0.7	0.9	0.8

Leukemia formed the most frequent diagnostic group, about one third of the total incidence. The lymphoid subgroup, which in childhood consists almost entirely of precursor cell acute lymphoblastic leukemia (ALL), accounted for about 80% of leukemias and one quarter of all childhood cancers; nearly all the remaining leukemias were acute myeloid (AML). The most numerous solid neoplasms were CNS and other intracranial and intraspinal tumors, accounting for just under a quarter of total cancer incidence. The next most frequent diagnostic groups were, in descending order of incidence, lymphomas, soft tissue sarcomas, neuroblastoma and other peripheral nervous cell tumors, and renal tumors, each accounting for 6–9% of the total. The remaining groups together accounted for 15%. Overall, incidence in the first 5 years of life was about 1.7 times that at 5–14 years of age. Boys were affected 1.2 times as often as girls. There were, however, pronounced differences in age distribution and sex ratio between different types of childhood cancer. The principal embryonal tumors, namely those of the CNS (including medulloblastoma and other primitive neuroectodermal tumors), neuroblastoma, retinoblastoma, nephroblastoma (Wilms tumor) and hepatoblastoma, all had their highest incidence in early childhood, and about 40% of the cumulative incidence of retinoblastoma and hepatoblastoma were observed in the first year of life. Contrastingly, incidence of some diagnostic categories increased with age, and more than two thirds of the cumulative childhood incidence of Hodgkin lymphoma and osteosarcoma occurred at age 10–14 years. Incidence was higher among boys than girls in most diagnostic categories and NHL had a male:female ratio of more than 2:1, but for a few cancers, notably germ cell tumors of certain sites, thyroid carcinoma and malignant melanoma, there was a marked excess of girls.

Table 1.2 shows the distribution by morphology of childhood cancers in selected anatomical sites, based on the same data as Table 1.1. The proportions of lymphomas in some sites are probably underestimates, as some cases coded to less specific or multiple sites may in fact have arisen in one of the sites listed. While most cancers of most sites in adults are carcinomas, the pattern in childhood is strikingly different. Tumors of the head and neck included substantial numbers of lymphomas and sarcomas. Lymphomas predominated among cancers of the gastro-intestinal tract. Most cancers of the liver, kidney, and eye were characteristic childhood embryonal tumors. Cancers of the ovary were nearly all germ cell tumors. The majority of testicular cancers were germ cell tumors, but there were also substantial numbers of paratesticular rhabdomyosarcomas. Rhabdomyosarcoma was the most common type of childhood cancer in other genito-urinary sites of both sexes.

In addition to the diseases included in ICCC-3, children can also develop many types of nonmalignant

Table 1.2 Histological types of cancers of selected primary sites diagnosed at age 0–14 years in Great Britain, 1991–2000. Source: National Registry of Childhood Tumors

Primary site (ICD-O–3)	Type	Number of registrations
Major salivary glands (C07–08)	Total	46
	Lymphoma	8 (17%)
	Rhabdomyosarcoma	4 (9%)
	Other sarcoma	2 (4%)
	Germ-cell tumor	1 (2%)
	Carcinoma	30 (65%)
	Unspecified	1 (2%)
Other mouth (C00–06)	Total	38
	Lymphoma	4 (11%)
	Rhabdomyosarcoma	14 (37%)
	Other sarcoma	10 (26%)
	Carcinoma	9 (24%)
	Unspecified	1 (3%)
Tonsil (C09)	Total	35
	Lymphoma	34 (97%)
	Rhabdomyosarcoma	1 (3%)
Nasopharynx (C11)	Total	97
	Lymphoma	27 (28%)
	Rhabdomyosarcoma	44 (45%)
	Other sarcoma	2 (2%)
	Carcinoma	24 (25%)
Other upper aerodigestive (C10, 12–14, 30–32)	Total	68
	Lymphoma	8 (12%)
	Neuroblastoma	2 (3%)
	Esthesioneuroblastoma	5 (7%)
	Rhabdomyosarcoma	38 (56%)
	Other sarcoma	7 (10%)
	Germ cell	3 (4%)
	Carcinoma	2 (3%)
	Unspecified	3 (4%)
Stomach (C16)	Total	11
	Lymphoma	4 (36%)
	Sarcoma	2 (18%)
	Germ cell	2 (18%)
	Carcinoma	1 (9%)
	Unspecified	2 (18%)
Small intestine (C17)	Total	51
	Lymphoma	45 (88%)
	Carcinoma	4 (8%)
	GIST	2 (4%)
Colon, rectum (C18–19)	Total	53
	Lymphoma	39 (74%)
	Carcinoma	12 (23%)
	Unspecified	2 (4%)
Liver (C22)	Total	171
	Lymphoma	6 (4%)
	Hepatoblastoma	112 (65%)
	Carcinoma	25 (15%)
	Sarcoma	22 (13%)
	Germ cell	5 (3%)
	Unspecified	1 (1%)
Pancreas (C25)	Total	9
	Lymphoma	2 (22%)
	Sarcoma	1 (11%)
	Carcinoma	2 (22%)
	Pancreatoblastoma	4 (44%)

Table 1.2 *(Continued)* Histological types of cancers of selected primary sites diagnosed at age 0–14 years in Great Britain, 1991–2000. Source: National Registry of Childhood Tumors

Primary site (ICD-O–3)	Type	Number of registrations
Lung (C34)	Total	28
	NHL	6 (21%)
	Sarcoma	3 (11%)
	Carcinoid/bronchial adenoma	8 (29%)
	Other carcinoma	2 (7%)
	Pleuropulmonary blastoma	7 (25%)
	Unspecified	2 (7%)
Ovary (C56)	Total	126
	Lymphoma	6 (5%)
	Neuroblastoma	1 (1%)
	Germ cell	112 (89%)
	Carcinoma	6 (5%)
	Mesothelioma	1 (1%)
Other female reproductive (C52–55,57)	Total	37
	Rhabdomyosarcoma	19 (51%)
	Other sarcoma	1 (3%)
	Germ cell	12 (32%)
	Carcinoma	5 (14%)
Prostate (C61)	Total	18
	Rhabdomyosarcoma	18 (100%)
Male genital (C62–63)	Total	160
	Lymphoma	6 (4%)
	Neuroblastoma	2 (1%)
	Rhabdomyosarcoma	55 (34%)
	Other sarcoma	2 (1%)
	Germ cell	92 (58%)
	Carcinoma	1 (1%)
	Unspecified	2 (1%)
Kidney (C64)	Total	829
	Lymphoma	5 (1%)
	Neuroblastoma	12 (1%)
	Nephroblastoma (Wilms)	728 (88%)
	Rhabdoid	24 (3%)
	Clear cell sarcoma	24 (3%)
	pPNET	7 (1%)
	Other sarcoma	4 (<0.5%)
	Germ cell	1 (<0.5%)
	Carcinoma	19 (2%)
	Unspecified	5 (1%)
Bladder (C67)	Total	47
	Lymphoma	1 (2%)
	Rhabdomyosarcoma	36 (77%)
	Other sarcoma	3 (6%)
	Carcinoma	6 (13%)
	Unspecified	1 (2%)
Orbit (C69.6)	Total	57
	Chloroma	2 (4%)
	Lymphoma	3 (5%)
	Rhabdomyosarcoma	47 (82%)
	Other sarcoma	4 (7%)
	Unspecified	1 (2%)
Other eye (C69.0–69.5, 69.7–69.9)	Total	443
	Lymphoma	1 (<0.5%)
	Astrocytoma	2 (<0.5%)
	Medulloepithelioma	1 (<0.5%)
	Retinoblastoma	430 (97%)
	Melanoma	8 (2%)
	Unspecified	1 (<0.5%)

neoplasm. They are not generally notified to cancer registries, hence estimates of their incidence are difficult to obtain. A few categories, however, have been routinely ascertained by some specialist population-based registries, namely the Manchester Children's Tumour Registry (MCTR) and West Midlands Regional Children's Tumour Registry (MWRCTR), both in England, and the German Childhood Cancer Registry (GCCR). The incidence of Langerhans cell histiocytosis (LCH) has been reported as around 6 per million in the GCCR [12] and 2–3 per million in the MCTR [3]. Mesoblastic nephroma accounted for 3% of all renal tumors in the MCTR, 4% in the GCCR, and 6% in the WMRCTR [2, 12, 33], indicating an annual incidence of about 0.4 per million. In the MCTR 61% of all extracranial germ cell tumors were nonmalignant [32]; they represented 48% of germ cell tumors in the testes, 60% in the ovaries and 69% in other sites. In the WMRCTR, all 49 extracranial germ cell tumors diagnosed in the first 3 months of life were benign teratomas, though four did recur as malignant tumors [45]; benign teratomas represented 29% of all registered neoplasms in this age group, making them more numerous than neuroblastomas. Adrenocortical adenoma accounted for 29% of adrenocortical tumors in the MCTR [14], implying an annual incidence of about 0.1 per million. It is not always possible to distinguish morphologically between benign and malignant adrenocortical tumors, however they should perhaps be regarded as lying on a continuum of clinical behavior [51]. Carcinoid tumors of the appendix had an annual incidence of 1.1 per million children in the WMRCTR [44].

There are pronounced variations in the occurrence of different types of childhood cancer between ethnic groups and world regions. ALL is less common among less affluent populations, including not only those of developing countries but also African-Americans in the USA. The deficit is largely due to the attenuation or even the absence of the early childhood peak that has been characteristic of western industrialized countries since the mid-twentieth century. Lymphomas, on the other hand, tend to be more frequent in less developed countries, the most extreme example being the very high incidence of Burkitt lymphoma in a broad band across equatorial Africa and also in Papua New Guinea.

Increases in the incidence of various childhood cancers have been recorded in many countries during past decades [20, 49]. Mostly the changes have been quite small, often of the order of 1% per year [20]. There have, however, been a few examples of much larger increases. Where population screening for neuroblastoma in infancy was offered either as a service or in the context of a scientific study, there was a dramatic increase in incidence resulting from detection of additional cases that would otherwise never have presented clinically [17, 54, 72]. The very large increase in childhood Kaposi's sarcoma in some sub-Saharan African countries is linked to the AIDS epidemic, probably through immunosuppression consequent on HIV infection allowing HHV8 viral load to increase uncontrollably [46]. The equally spectacular rise in thyroid cancer among children in regions most severely contaminated with radioactive fallout from Chernobyl was certainly due in part to radiation exposure, though intensive screening also contributed [71].

Recent increases in the incidence of ALL among young children in former socialist countries of central and eastern Europe, resulting in the more marked early childhood peak that has been characteristic of western countries for decades, seem likely to reflect improved socioeconomic conditions [18, 58]. An increase in the incidence of CNS tumors, especially low-grade gliomas, in the USA in the mid-1980s was attributed to improved detection with the introduction of magnetic resonance imaging (MRI) [56]. While an increase in low-grade gliomas in Sweden could also have resulted from improved detection [16, 57], it has been argued that increases in childhood CNS tumors in north-west England and in Denmark represent a true increase in risk [37, 47]. It is difficult to apportion the relative contributions of improved detection and diagnosis, improved registration and genuine increases in risk to the rather small increases in incidence of most other childhood cancers.

1.3 Etiology

Despite intensive research over several decades, very little is known about the causes of most childhood cancers. Some of the most well-established risk factors are genetic in nature. An increasingly long list of hereditary syndromes, mostly associated with identified single gene defects, carry a raised risk of specific childhood cancers [64, 67]. Germline mutations or deletions of RB1 give rise to heritable retinoblastoma. Children with neurofibromatosis 1 have an increased risk of gliomas, soft-tissue sarcomas, and juvenile myelomonocytic leukemia. Germline mutations of TP53 carry a raised risk of various cancers including soft tissue sarcoma, osteosarcoma, adrenocortical carcinoma, brain tumors, and leukemia, as well as premenopausal breast cancer; Li-Fraumeni syndrome is the resulting aggregation of specific combinations of these cancers within a family. An especially wide range of genetic disorders, both heritable and sporadic, is associated with Wilms tumor, including Beckwith-Wiedemann, Denys-Drash, WAGR, and Simpson-Golabi-Behmel syndromes [55]. Constitutional chromosomal abnormalities are implicated in about 1% of all childhood

cancers [65]. The most important is Down syndrome, which carries a greatly raised risk of leukemia and almost certainly an increased risk of germ cell tumors, though the total excess of cancer is reduced by an apparent protective effect against several other types of solid tumors [15]. Risks associated with other, usually isolated, congenital abnormalities will be discussed towards the end of this section.

In 1991 it was estimated that genetic conditions were responsible for about 3% of all childhood cancer [42]. That figure will now be higher, not least because the 1991 estimate did not include Li-Fraumeni syndrome, but the proportion attributable to known genetic disorders is probably still under 5% in most populations. The main exception must be North African populations with high frequencies of the recessive DNA repair disorder xeroderma pigmentosum (XP), which carries a 1000-fold increased risk of skin cancer among children and adolescents [24]. In a series of 900 childhood cancers other than leukemia from the National Cancer Institute in Tunisia, 8% were skin carcinomas associated with XP [39].

An enormous number of exogenous or environmental exposures have been investigated as possible risk factors for childhood cancer [30, 63]. The only ones to which more than a handful of cases can be attributed worldwide are ionising radiation and certain infectious agents.

The relationship between in utero radiation exposure from obstetric x-rays and subsequent cancer in the child was established almost half a century ago [60]. At that time as many as 1 in 20 cases of childhood cancer may have been attributable to obstetric irradiation but the proportion nowadays must be much lower since ultrasound has largely supplanted x-rays. The use of x-rays to treat certain benign conditions produced an increased risk of cancer but this practice is also obsolete and therefore responsible for virtually no new cases of childhood cancer. Radiotherapy treatment for childhood cancer is itself carcinogenic but the numbers of subsequent malignancies occurring within childhood are relatively small. Large numbers of thyroid carcinomas occurred among children in the areas of Ukraine, Belarus, and Russia most heavily exposed to radioactive iodine as a result of the Chernobyl nuclear power station explosion in 1986, but there is little evidence of increased risk in less severely contaminated regions [7]. It is plausible that some childhood cancers are caused by naturally occurring gamma rays and radon, but there is limited consistency between studies and the numbers of attributable cases must be small [9, 22, 26, 69].

Ultraviolet (UV) radiation from the sun causes malignant melanoma and skin carcinomas, mainly in adults. The excess of skin cancers in children with XP results from UV exposure of a highly susceptible group. The possibility of carcinogenic effects of electromagnetic fields arising from electric power cables has caused public concern for two decades. A moderately raised risk of leukemia has consistently been found for the highest exposure levels experienced by fewer than 1 in 20 children in industrialized countries, but the reasons for this are unclear [1, 21, 38].

Several specific infections are known to increase the risk of cancer. Among children worldwide, the types of cancer with the largest numbers of cases attributable to infectious agents are Burkitt lymphoma, Hodgkin lymphoma, and nasopharyngeal carcinoma (all associated with Epstein-Barr virus, with malaria as a cofactor for Burkitt lymphoma in the region of highest incidence), hepatocellular carcinoma (hepatitis B), and Kaposi's sarcoma (HHV8) [46]. The incidence of childhood hepatocellular carcinoma fell dramatically in Taiwan following the introduction of universal vaccination against hepatitis B [27], and a similar decrease would also be expected in other countries of hitherto high incidence as they introduce immunization.

Many epidemiological studies support the suggestion that infection is involved in the etiology of some childhood leukemias [36]. Most of these studies are relevant to either or both of two hypotheses. Kinlen's hypothesis that leukemia is a rare response to a specific, but unidentified infection is supported by the finding of increased incidence in many situations of population mixing which could have led to impaired herd immunity [6, 23]. Greaves's hypothesis that common ALL can arise as an abnormal response to infectious challenge, especially in children with weaker immunity, is supported by studies showing a protective effect of breast feeding and early daycare attendance [6, 13, 34].

Some medical treatments are undoubtedly carcinogenic. The excess risk from radiotherapy has already been mentioned. Some chemotherapeutic drugs used to treat cancer produce an increased risk of subsequent cancers but relatively few of these occur in childhood. Daughters of women who took diethylstilboestrol (DES) in pregnancy had an increased risk of clear cell carcinoma of the vagina or cervix but most of these tumors occurred in early adulthood and DES ceased to be used more than 30 years ago. Despite considerable public concern generated by a positive finding in one early study, there is no consistent evidence that intramuscular vitamin K given neonatally to prevent hemorrhagic disease of the newborn is a risk factor for childhood cancer [10, 52]. Many studies have found associations between exposure to other medical treatments in utero or postnatally and various childhood cancers but there has been little consistency between reports. With the increasing use of assisted reproductive technology (ART), there has been a succession of anecdotal reports of cancer in children born following

ART. Follow-up of cohorts of children born after ART has so far failed to reveal any significant increase in the risk of cancer [28, 48], but the expected numbers of cancers are still relatively small and follow-up is as yet short for children born after some types of ART.

A wide range of other exogenous exposures to the child, to the mother antenatally, or to the father preconceptionally, have been suggested as contributing to the etiology of childhood cancer. Mostly the evidence comes from a small number of studies or is inconsistent between studies [29]. There are two exposures for which the evidence seems relatively strong, though it is still short of conclusive and further research is needed to clarify the nature of any etiological relationship. A possible role for benzene in relation to leukemia has not only been found in several childhood studies but is also supported by its acceptance as a risk factor for AML in adults [6, 29]. Maternal consumption of cured meats during pregnancy has been repeatedly linked to increased risk of a brain tumor in the child [29], perhaps as a result of increased exposure of the fetus to N-nitrosamides [8].

Malformations and other physical characteristics associated with certain childhood cancers could be markers for underlying genetic or environmental causes. In a large population-based study, more than 4% of children with malignant solid tumors also had a congenital anomaly, in many cases not as part of any recognized syndrome [41]. Such an occurrence could result from an unknown genetic defect or, as seems more likely, for example, in the association of inguinal hernia with Ewing sarcoma, have a common environmental cause [70].

1.4 Survival

Table 1.3 shows actuarial 5-year survival rates for children in Great Britain with cancer diagnosed during 1996–2000 [61]. More than three quarters of children survived for 5 years, and the survival rate comfortably exceeded 80% for several important diagnostic groups. Five-year survival rates above 75% are seen in many other industrialized countries [49, 53]. Survival tended to be lower in less affluent countries of Eastern Europe [53], and lower still in developing countries [40]. The prognosis for many childhood cancers has improved dramatically over past decades. In Great Britain, 5-year survival of children diagnosed in 1971–1975 was 39%, compared with 77% for those diagnosed a quarter century later [61]. This means that the risk of death within 5 years from diagnosis has been reduced by 63%. Figures 1.1–1.3 show that survival for all major diagnostic groups increased in Europe between 1978–1982 and 1993–1997, though the timing of the largest increases varied between diagnostic groups [31]. Broadly similar trends have been observed in the USA [49].

Table 1.3 Five-year survival of children in Great Britain with cancer diagnosed during 1996–2000. Source: National Registry of Childhood Tumors [61]

	Five-year survival (%)
All cancers	77
Leukemia	79
ALL	83
AML	65
Lymphomas	86
Hodgkin	94
Non-Hodgkin (incl. Burkitt)	81
CNS tumors	71
Ependymoma	69
Astrocytoma	81
Embryonal	55
Other glioma	43
Craniopharyngioma	99
Neuroblastoma	59
Retinoblastoma	96
Renal tumors	88
Nephroblastoma (Wilms tumor)	91
Hepatic tumors	66
Hepatoblastoma	79
Bone tumors	64
Osteosarcoma	62
Ewing sarcoma family	63
Soft tissue sarcoma	66
Rhabdomyosarcoma	68
Germ cell and gonadal	87
CNS germ cell	81
Other extragonadal germ cell	79
Gonadal germ cell	96
Other epithelial and melanoma	87
Thyroid carcinoma	100
Malignant melanoma	85

The results quoted here are derived from cancer registry data and estimate survival rates at the population level. Survival data can also be found in countless publications from clinical trials and single or multi-institutional case series. Very often the results appear better than those from population-based data, but they could well be unrepresentative of all cases in the population because of selective exclusion of those with a poor prognosis or not offered most effective treat-

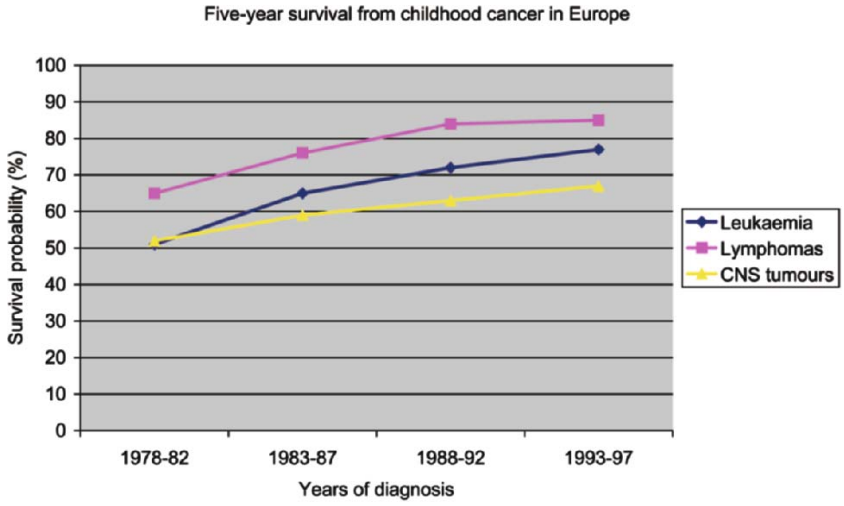

Fig. 1.1 Five-year survival of children in Europe with leukemias, lymphomas and CNS tumors diagnosed 1978–1997. Source: Automated Childhood Cancer Information System [31]

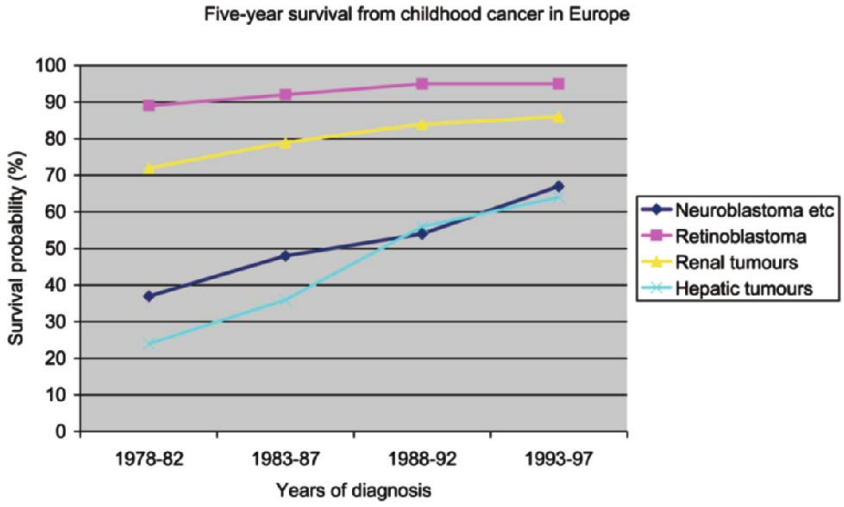

Fig. 1.2 Five-year survival of children in Europe with sympathetic nervous system tumors (neuroblastoma etc.), retinoblastoma, renal tumors and hepatic tumors diagnosed 1978–1997. Source: Automated Childhood Cancer Information System [31]

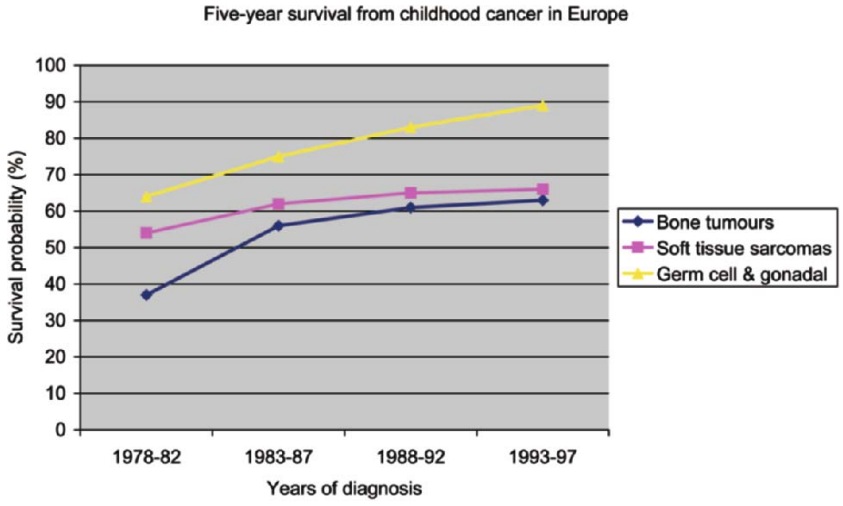

Fig. 1.3 Five-year survival of children in Europe with bone tumors, soft tissue sarcomas, and germ cell and gonadal tumors diagnosed 1978–1997. Source: Automated Childhood Cancer Information System [31]

ment. Increases in survival have, nevertheless, occurred concurrently with the development of pediatric oncology clinical trials groups and increased referral to specialist treatment centers in many countries. Several studies have found that survival was higher for children who were treated at large or specialist centres or entered in clinical trials [62, 66].

Improved survival has resulted in increasing numbers of long-term survivors of childhood cancer. The risk of a second primary malignancy within 25 years of the original childhood cancer diagnosis is about 4% [19, 43]. Many other aspects of the health of long-term survivors and their offspring are the subject of several large epidemiological studies [5, 50, 68].

1.5 Mortality

Population mortality rates from childhood cancer in western countries have fallen dramatically since the mid-20th century, in line with the moderate increase in incidence and very marked improvements in outcome. Table 1.4 shows estimated age-standardized mortality rates for childhood cancer by world region in 2002 [11]. In wealthy industrialized countries, mortality was typically around 25–30 per million. It was considerably higher in Eastern Europe, reflecting the lower survival rates still obtained in that region. Results for other world regions are harder to interpret because of incompleteness and inaccuracy in the data for many countries [35]. Overall, and for cancers other than those of the brain and nervous system, mortality rates tended to be highest in developing countries, reflecting their generally lower survival rates. Mortality from cancers of the brain and nervous system showed a different pattern with low rates in developing countries outside the Americas and Western Asia; since survival is lower in these countries, the lower mortality must be a result of under-recording and lower incidence.

Table 1.4 Estimated age-standardized mortality rates per million for cancer at age 0–14 years, 2002, by world region. Source: GLOBOCAN 2002 [11]

	Total		Leukemia		Lymphoma		Brain/nervous system		Other	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
North Africa	72.8	52.7	20.6	12.2	17.1	9.1	6.8	4.0	28.3	27.4
Sub-Saharan Africa	74.2	52.5	11.1	6.6	23.2	13.7	3.3	3.6	36.6	28.6
USA/Canada	26.5	23.2	8.6	7.1	1.4	0.8	7.5	7.1	9.0	8.2
Central America	60.6	52.2	31.9	28.2	6.2	3.0	8.2	7.1	14.3	13.9
South America	63.5	51.9	26.8	21.4	6.9	3.6	11.7	9.5	18.1	17.4
Western Asia	72.7	58.2	29.4	22.1	14.3	9.6	12.7	9.4	16.3	17.1
India	36.2	23.2	15.0	9.8	4.6	1.5	5.4	3.0	11.2	8.9
Other South Asia	55.5	36.5	16.9	13.3	9.6	3.1	7.1	4.9	21.9	15.2
China	52.3	38.9	32.2	23.0	3.4	1.7	7.8	7.9	8.9	6.3
Japan	27.6	18.5	11.5	8.2	1.5	1.1	5.1	3.5	9.5	5.7
South East Asia	68.7	54.7	33.0	25.5	8.8	4.9	8.3	7.4	18.6	16.9
Nordic Countries	27.1	24.5	7.9	7.5	2.8	0.0	8.4	7.9	8.0	9.1
British Isles	33.8	25.4	11.6	10.4	1.1	1.0	10.7	7.7	10.4	6.3
Former USSR in Europe	57.3	47.9	18.5	14.8	6.2	2.7	13.7	12.1	18.9	18.3
Other Eastern Europe	50.5	40.0	15.5	11.3	4.6	2.2	14.0	12.8	16.4	13.7
Western Europe	30.9	22.1	9.9	6.3	1.3	0.9	9.9	6.5	9.8	8.4
Southern Europe	34.7	30.4	12.3	10.3	2.6	1.9	9.8	6.9	10.0	11.3
Australia/New Zealand	37.0	26.7	12.2	10.1	1.8	1.1	12.4	6.0	10.6	9.5

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Tumor Biology and Environmental Carcinogenesis

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2

Contents

2.1 Introduction

During normal development and renewal, cells evolve to perform highly specialized functions to meet the physiologic needs of the organism. Development and renewal involve tightly regulated processes that include continued cell proliferation, differentiation into specialized cell types, and programmed cell death (apoptosis). An intricate system of checks and balances ensures proper control over these physiologic processes. The genetic composition (genotype) of a cell determines which pathway(s) will be followed and exerting that control. The environment also plays a crucial role in influencing cell fate. Cells use complex signal transduction pathways to sense and respond to neighboring cells and their extracellular milieu. In addition, however, environmental factors may have a direct impact on cell phenotype and fate by causing DNA damage that permanently alters the host genome. Cancer is a genetic disease whose progression is driven by a series of accumulating genetic changes influenced by hereditary factors and the somatic environment. These genetic changes result in individual cells acquiring a phenotype that provides those cells with a survival advantage over surrounding normal cells. Our understanding of the processes that occur in malignant cell transformation is increasing with many discoveries in cancer cell biology having been made using childhood tumors as models.

2.2 Cell Fate

2.2.1 Stem Cells

The development and maintenance of the tissues that comprise an organism are processes driven by stem cells. These are cells with the potential for both self-renewal and terminal differentiation into one or more cell types. They, therefore, play a critical role in normal tissue turnover and repair. The fate of most of these stem cells is generally one of terminal differentiation and either quiescence or apoptosis. However, a small percentage of stem cells maintain their pleuripotent capacity. It is becoming increasingly recognized that these same stem cells that are essential for maintaining an organism are also central to the development of malignancy and therapy resistance [116]. Cancer stem cells, like normal stem cells, possess remarkable proliferative and self-renewal capacities, while the larger portion of partially differentiated tumor cells possess quite limited reproductive potential.