Robert Carachi
Jay L. Grosfeld
*Editors*

# The Surgery of Childhood Tumors

Third Edition

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# A Brief History of Pediatric Oncology

1

Robert Carachi and Jay L. Grosfeld

Dr Odile Schweisguth was born during the turbulent period of the first world war in Vosges (France) in 1913. Her first contact with medicine was at the Red Cross Nursing School and with the mentoring and support of one of her teachers there, was admitted to the medical school in Nancy in 1932, graduating in Paris in 1936. Her early training was carried out in "Hopital des Enfants Malades" in Paris. She became the first pediatric oncologist when she was appointed to the Consultant post in 1948 at the Institute Gustave Roussy to establish a new paediatric section at this renowned Cancer centre in France. She set up over her working life until she retired in 1978, a separate paediatric oncology ward fully staffed caring for children with cancer and to look after the dying children. The volume of patients increased to 350 per year once it was fully established. Her visit in 1959 for 2 months to the Sidney Farber at the Boston Children's Hospital established a lifelong friendship and a strong voice for children's cancer. Her interest was on long term morbidity because the main treatment modality available at that time was radiation and radiotherapists had no means of scaling down the treatment for children. She was a strong advocate for the rights of childhood cancer survivors. An initial meeting on childhood cancers in 1959 was organised and Odile Schweisguth was its director. This led to comprehensive pediatric oncology care worldwide with the formation of the new society called Societe International d'Oncologie Pediatrique, at a meeting in Madrid in 1969. She was elected as the first Present of SIOP, with a membership worldwide of over a thousand members. Odile died at the age of 89 in March 2002.

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## About SIOP

### History

On 3 July 1967, a small group of paediatricians, surgeons, pathologists and others met in the Paediatric Department "Service Milhit" of the Institut Gustav in Villejuif/Paris, France. Everyone there knew SIOPs now honorary member Dr Odile Schweisguth, and shared a keen interest in paediatric oncology.

A decision was taken at this meeting, to form the Club d'Oncologie Pediatriquie (Paediatric Oncology Club). During the second meeting of the Club, held at IGR in 1668, participants agreed to convene the following year in Madrid, hosted by the late Dr J Monereo, Paediatric Surgeon. It was during this memorable assembly that it became obvious that there was a clear and widespread interest in paediatric oncology and the Club was transformed to the Societe International d'Oncologie Pediatrique (SIOP) on 6 November 1969.

The Founding Members of the Society who were present at the founding meeting of the Society in Madrid and voted for the constitution, were Doctors Bouchon, Boureau, Brunat, Carton, Delemarre, Gerard-Marchant, Gompel, Gubler, Hitzig, Hurtado, Kaser, Lemerle, Massimo, Maurus, Monero, Neidhardt, Noel, Pages, Payan, Pellerin, Pluss, Orsini, Raybaud, Schlienger, Schweisguth, Sullivan, Voute and Wagner. SIOP was initially a bilingual Society; French and English were both used at meetings. According to the statutes, it is still bilingual; however English has taken over as the conference language, but a French flavour remains!

Furthermore, SIOP has fulfilled its original intention of becoming a truly international society and not restricting its influence and membership to one continent or part of a continent. Over the years, most of the annual meetings have been



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held in Europe, the saying "doing Europe with SIOP", but this policy has been changed and at the moment, the majority of our members are from Europe and North America.

In the early years, the Society was mostly clinically orientated, promoting involvement in clinical studies and trials, such as medulloblastoma, neuroblastoma and rhabdomyosarcoma, for example. Eminent surgeons, pathologists, paediatricians and radiotherapists met together. In recent years, more basic scientific aspects of paediatric oncology have featured at the annual meetings.

SIOP continues to work in the interest of our patients, children with cancer, who wish to be cured to lead normal lives alongside other healthy children.

SIOP was legally established in 1969. Under the name of International Society of Paediatric Oncology there exists an association governed by the present statutes and by the provisions of articles 60 ff. of the Swiss Civil Code. Its registered office is in Zurich, Switzerland.

The first annual general meeting was held in Madrid (Spain) in 1969 and was devoted to neuroblastoma, nephroblastoma, lymphoscarcoma and immunology. Beginning with a few enthusiastic members to more than 1400 active Ordinary Members, SIOP remains a friendly Society in which all the challenges of treating patients with malignancies are discussed in depth. The central secretariat of SIOP is established in The Netherlands where one can receive detailed information on the Society. Address of the Secretariat is:

**SIOP Secretariat c/o Kenes Associations Worldwide**
**1 – 3 Rue de Chantepoulet**
**1211 Geneva, Switzerland**
**Email:** irah@kenes.com

## Societe Internationale D'Oncologie Pediatrique- International Society of Paediatric Oncology

### Constitution

1. The official name of this organisation shall be the Societe Internationale d'Oncologie Pediatrique with the acronym SIOP. It is also to be known by the English translation; namely the International Society of Paediatric Oncology. The name of the organisation and its acronym SIOP may only be used by a member for professional identification or in a curriculum vitae. A member shall not use the name or acronym for any commercial purpose or to advertise his services without the express approval of the Board. A violation of this prohibition may subject the member to censure, suspension or expulsion from the Society by the Board.

   The Society was founded in 1969. Under the name of "International Society of Paediatric Oncology" there exists an association governed by the present statutes and by the provisions of articles 60 ff. of the Swiss Civil Code.
2. SIOP has its domicile where its administration is domiciled.
3. The financial year starts with the annual Congress of the Society in October each year or as may be decided by the Board.

Article II: Vision and Mission of SIOP and charitable status of the Society

SIOP is a non-profit organisation and acts in a selfless manner. Members do not receive funds or additional benefits. SIOP aims for a charitable tax exempt status.

1. Vision
   No child should die of cancer
2. Mission
   The mission of the international Society of Paediatric Oncology (SIOP) is :
   (a) To ensure that each child and young adult with cancer has access to state of the art treatment and care
   (b) To ensure that all involved in childhood cancer worldwide have access to the latest progress through meetings, networking and continuing professional development
   (c) To support those caring for children and young adults with cancer to provide the best curative and palliative therapies.
   (d) To advocate for appropriate longterm follow up for children and young adults after treatment for cancer.

## The International Society of Paediatric Surgical Oncology (IPSO)

IPSO is an international society of surgeons who specialise in the surgical care of children with cancer.
**IPSO's aims are**:

- To set up a global standard for surgical care of children with cancer
- To provide a forum and enhance communication between surgeons who specialise in children's cancer
- To promote and support clinical trials aimed at improving the outcome in the treatment of children's cancer
- To encourage co-operation with other organisations concerned with children's cancer

IPSO is a truly global organisation with an expanding membership from all parts of the world. At the last count, 48 coun-

tries were represented. Membership is open to all surgeons who have a demonstrable commitment to paediatric surgical oncology, and we are always keen to attract new members.

IPSO meets once a year in conjunction with our sister organisation SIOP (The International Society of Paediatric Oncology) and has regular joint meetings with other international organisations who represent specialist children's surgery.

IPSO strongly supports the continuing professional development of surgeons who care for children who have cancer, and to this end IPSO runs an annual course in paediatric surgical oncology, in collaboration with EUPSA (the European Paediatric Surgeons Association).

## Historical Background

### IPSO

#### Aims

To:

Further knowledge, promote research and set standards in paediatric surgical oncology :

Facilitate communication between various surgical disciplines (orthopaedics, neurology, plastic surgery etc) and also other medical specialties involved in the treatment of paediatric cancer. Maintain a forum for discussion and/or advice on problems relevant to paediatric surgical oncology.

Exchange and diffuse information on paediatric cancer in general which may impact surgical practice. Be involved in the formulation and implementation of requirements for postgraduate training and education as well as specialist recognition on an international level.

#### Development

**1989**: First full surgical symposium back to back with SIOP meeting Prague.

Main topic Surgical Oncology (local organisers J Snadjauf J, Koutecky)

**1990**: Second surgical symposium back to back with SIOP meeting Rome, 1990. (Local organisers C Boglino, R Cozzi, M Castello)

**1991**: Letter of intent to form an independent society sent to all participants of above symposia and other pediatric surgeons known or shown to have special interest in surgical oncology. Number 179. (D Hays)

**1991**: Draft constitution prepared by A Gentil-Martins

**1992**: Positive response received from 1010 replies (List of names and countries available)

IPSO Officially founded as independent society in 1991 at Rhodes SIOP meeting (Again including a separate surgical symposium Local Organiser – D Keramidas).

Constitution and executive council approved at first general assembly

Membership: All surgeons attending any of the three above symposia considered as members (numbers) see attached list.

Executive 1991

Founding President – J Plaschkes

Secretary/treasurer – R Spicer

F Cattalliotti

A Gentil-Martins

P Exelby (SIOP scientific committee representative)

## A Brief History of Modern Pediatric Oncology in the United States

Following WWII, as many medical specialists returned to civilian practice, an increased interest in improving the dismal outcome for children with leukemia and other malignant conditions was observed. Early use of then sparsely available chemotherapy in leukemic children was spearheaded by the work by Sidney Farber in Boston in 1948. Implementation of postoperative radiotherapy for children with Wilms tumor was reported by Gross and Neuhauser in 1949. However, the relatively low incidence of childhood cancer cases managed at any single center made it difficult to determine the most appropriate treatment and stimulated interest in developing collaborative efforts to accrue an adequate number of patients for clinical studies. It soon became obvious that in order to carry out randomized prospective and controlled clinical trials would require cooperative group studies implementing multidisciplinary care including, surgery, radiotherapy and chemotherapy.

In 1955, the Acute Leukemia Cooperative Chemotherapy Study Group A was formed. This was mainly an adult study group that also cared for some children with leukemia. The group's activities expanded somewhat to include patients with solid tumors including cases of Wilms tumor and neuroblastoma. In 1967, childhood cases split off with formation of the Children's Cancer Study Group A (CCSG-A). Subsequently, the name was shortened to the Children's Cancer Group (CCG). In 1968, the National Wilms tumor Study Group (NWTSG) was formed led by Dr. Giulio D'Angio (a radiotherapist). The other founding members included Drs. Daniel Green, Audrey Evans (Hematologist-Oncologists), J. Bruce Beckwith (pathologist), and Norman Breslow (statistician). Drs. Harry Bishop (pediatric surgeon) and Willard Goodwin (urologist) joined the initial group. Since then this highly successful group has carried out a total of five different major Wilms tumor studies leading to an overall survival rate of near 90 %. Full details concerning Wilms tumor are covered in detail in Chap. 12.

During the same period, in 1956 the Southwest Cancer Chemotherapy Study Group (SWOG) was organized with a small pediatric component based at the MD Anderson Cancer Hospital in Houston, TX. In 1973 SWOG merged with the Cancer and Acute Leukemia Group B (CALG-B) which included both adult and pediatric oncologists. In 1979 the pediatric oncologists split off and developed the Pediatric Oncology Group (POG) led by Dr. Teresa Vietti of St Louis, MO.

In 1970 the Intergroup Rhabdomyosarcoma Study Goup (IRSG) was formed with members from both CCG and POG. Dr. Harold Mauer (Hematology-Oncology) was the lead physician supported by Drs. William Newton (pathology), Ruth Heyn, Milton Donaldson (Hematology-Oncology), Daniel Hays and Walter Lawrence (Surgeons) and Melvin Tefft (radiotherapy).

In 2000, The NWTSG, IRSG, CCG and POG merged into a single group named the Children's Oncology Group (COG).

## Children's Oncology Group (COG)

The Children's Oncology Group founded in 2000, is the largest Cooperative Cancer group in the world including the United States, Canada, and a number of international sites (Australia, New Zealand, and areas of Europe). COG sites care for more than 90 % of the 13,500 pediatric cancer patients seen in the US annually.

COG is primarily funded by grants from the US National Cancer Institute (NCI) and other granting agencies as well as philanthropic sources through gifts to the COG Foundation.

There are two types of COG centers:

1. COG Phase I consortium consisting of 21 premier pediatric oncology program centers that carry out early clinical cancer trials, and
2. the Community Cancer Oncology Program (CCOP) centers that manage patients in assigned clinical protocols

Two hundred member institutions in COG carry out nearly 100 clinical trials at any given time. The group manages pediatric patients with hematologic malignancies (leukemias and lymphomas), solid tumors (including bone tumors), central nervous system tumors and rare cancers. Approximately 8000 cancer experts work and perform research at COG facilities. In addition to disease specific clinical research, COG members conduct studies in cancer drug development, supportive care, epidemiology, stem cell transplantation, behavioral sciences and survivorship. The group maintains a vigorous long-term follow up outcomes and guidance program that monitors late effects of treatment.

Scientific research collaboration occurs at a world-wide level in areas such as molecular genetics, molecular biology, immunology, proteomics, targeted therapies, antiangiogenesis, cellular proliferation, apoptosis and tumor vaccine development.

Children's Oncologic Surgeons represent one of the key multidisciplinary groups that compose the COG. There is a COG Executive Committee and the Chair of the Surgery Discipline Committee is the surgical representative to that Committee. When COG was initially formed in 2000, Dr. Gregory Reaman (National Children's Hospital, Washington, DC) was the overall COG Chairman and Dr.

Robert Shamberger of Boston, MA (Boston Children's Hospital) was the first Chair of the Surgery Discipline committee. Dr. Peter Adamson of Philadelphia, PA (CHOP) is the current COG Chairman and the Chair of the COG Surgery Discipline Committee is Dr Michael LaQuaglia of (Memorial Sloan-Kettering Cancer Center), New York, NY. Within the Surgical Committee there is a surgical leadership Group whose members are often appointed to the various solid tumor Committees and other relevant Committees in COG by the Chair. Some examples include:

**Neuroblastoma**: Dr Jed Nuchtern (Houston, TX) Vice-Chair, and others that are members of the senior surgery investigator group including Drs. Michael LaQuaglia, Andrew Davidoff, Daniel vonAllmen and Stanton Adkins.

**Rhabdomyosarcoma**: Dr. David Rodeberg (Vice-Chair), Dr. Andrea Hayes-Jordan-other soft tissue sarcomas.

**Wilms Tumor**: Dr. Peter Ehrlich (Vice-Chair), with Drs. Robert Shamberger, Thomas Hamilton and Michael Richey – senior surgery investigators.

**Rare tumors**:

- **Hepatoblastoma**: Dr. Rebecka Meyers lead investigator, Drs Max Langham and Gregory Tijan – senior investigators
- **Germ Cell Tumors**: Drs. Frederick J. Rescorla and Deborah F. Billmire Co-Principle investigators
- **Adrenocortical tumors**: Drs. Michael LaQuaglia and Christopher Weldon-Co-Principle investigators

**Informatics**: Dr. John Doski

Many of the aforementioned individuals are contributors to this 3rd edition of *Surgery of Childhood tumors*.


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|---|---|

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# Epidemiology of Childhood Tumours

2

Charles A. Stiller

## Classification

Traditionally, descriptive data on cancers occurring in people of all ages combined have been presented with the diagnoses categorised according to the International Classification of Diseases (ICD), in which cancers other than leukaemias, lymphomas, Kaposi sarcoma, cutaneous melanoma and mesothelioma are classified purely on the basis of primary site. The malignant solid tumours 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) [1–3]. The current scheme is the International Classification of Childhood Cancer, Third Edition (ICCC-3), based on the third edition of ICD-O [3]. ICCC-3 contains 12 main diagnostic groups:

I. Leukaemias, 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 tumours
V. Retinoblastoma
VI. Renal tumours
VII. Hepatic tumours
VIII. Malignant bone tumours
IX. Soft tissue and other extraosseous sarcomas
X. Germ cell tumours, trophoblastic tumours, 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 non-malignant intracranial and intraspinal tumours since they are usually recorded by cancer registries.

Successive classifications have been designed to have as much continuity as possible with their predecessors, while recognising advances in understanding of tumour 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.

## 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 2.1 shows annual incidence rates per million children in the UK for 1998–2007 based on data from the population-based National Registry of Childhood Tumours. The total incidence, just under 150 per million, and the relative frequencies of the different groups and subgroups were typical of those in industrialised countries. In the table, 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.

Leukaemia 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

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**Table 2.1** Registration rates for cancers diagnosed at age 0–14 years in the UK, 1998–2007

| | | Annual rates per million children for age group (years) | | | | Age standardised rates per million (World standard population) | | |
|---|---|---|---|---|---|---|---|---|
| ICCC-3 categories | Total registrations | 0 | 1–4 | 5–9 | 10–14 | Boys | Girls | Children |
| I-XII. All Cancers | 15,729 | 209.5 | 198.2 | 112.5 | 119.9 | 158.3 | 138.6 | 148.7 |
| I. Leukaemias | 4971 | 45.5 | 81.6 | 36.8 | 26.7 | 52.4 | 44.2 | 48.4 |
| (a) Lymphoid leukaemias | 3884 | 19.7 | 69.2 | 30.1 | 18.4 | 41.6 | 34.3 | 38.0 |
| (b) Acute myeloid leukaemias | 742 | 17.5 | 8.3 | 4.7 | 5.6 | 7.4 | 6.8 | 7.1 |
| (c) Chronic myeloproliferative diseases | 114 | 1.3 | 0.5 | 0.7 | 1.7 | 1.0 | 1.0 | 1.0 |
| (d) Myelodysplastic syndrome and other myeloproliferative | 188 | 5.7 | 2.9 | 1.0 | 0.8 | 2.1 | 1.6 | 1.9 |
| (e) Other and unspecified | 43 | 1.3 | 0.6 | 0.3 | 0.2 | 0.3 | 0.5 | 0.4 |
| II. Lymphomas etc | 1621 | 1.6 | 8.1 | 13.5 | 23.2 | 18.2 | 9.0 | 13.7 |
| (a) Hodgkin lymphoma | 733 | – | 1.6 | 4.4 | 13.7 | 7.3 | 4.5 | 5.9 |
| (b, c) Non-Hodgkin lymphomas | 862 | 1.0 | 6.2 | 8.9 | 9.3 | 10.5 | 4.4 | 7.6 |
| (d, e) Other and unspecified | 26 | 0.6 | 0.3 | 0.2 | 0.2 | 0.4 | 0.1 | 0.2 |
| III. CNS, intracranial, intraspinal | 3992 | 37.4 | 42.5 | 36.5 | 31.4 | 38.8 | 35.0 | 36.9 |
| (a) Ependymomas and choroid plexus tumours | 399 | 9.1 | 6.3 | 2.4 | 1.9 | 4.6 | 3.3 | 4.0 |
| 1. Ependymomas | 292 | 2.6 | 4.8 | 2.0 | 1.7 | 3.3 | 2.4 | 2.8 |
| 2. Choroid plexus tumours | 107 | 6.6 | 1.5 | 0.3 | 0.2 | 1.3 | 0.9 | 1.1 |
| (b) Astrocytomas | 1700 | 9.4 | 17.7 | 18.0 | 13.9 | 15.1 | 16.1 | 15.6 |
| (c) Intracranial and intraspinal embryonal tumours | 743 | 9.3 | 9.4 | 6.9 | 4.3 | 8.5 | 5.6 | 7.1 |
| 1. Medulloblastomas | 546 | 3.3 | 6.4 | 5.9 | 3.4 | 6.5 | 3.6 | 5.1 |
| 2. Primitive neuroectodermal tumour | 129 | 3.4 | 1.8 | 0.8 | 0.7 | 1.2 | 1.3 | 1.3 |
| 3. Atypical teratoid/rhabdoid tumour | 65 | 2.6 | 1.2 | 0.1 | 0.2 | 0.8 | 0.6 | 0.7 |
| (d) Other gliomas | 400 | 1.1 | 4.1 | 4.5 | 2.9 | 3.8 | 3.5 | 3.7 |
| (e) Other specified | 543 | 3.3 | 3.5 | 4.6 | 6.6 | 4.9 | 4.6 | 4.7 |
| 1. Pituitary adenoma and carcinoma | 52 | – | 0.1 | 0.2 | 1.1 | 0.4 | 0.5 | 0.4 |
| 2. Craniopharyngioma | 189 | 0.3 | 1.0 | 2.3 | 2.0 | 1.7 | 1.5 | 1.6 |
| 3. Pineal parenchymal tumours | 53 | 0.9 | 0.7 | 0.3 | 0.4 | 0.5 | 0.5 | 0.5 |
| 4. Neuronal, neuronal-glial | 204 | 2.1 | 1.5 | 1.6 | 2.3 | 1.9 | 1.7 | 1.8 |
| 5. Meningiomas | 45 | – | 0.3 | 0.3 | 0.7 | 0.3 | 0.4 | 0.4 |
| (f) Unspecified | 207 | 5.1 | 1.5 | 1.7 | 1.8 | 2.0 | 1.9 | 1.9 |
| IV. Neuroblastoma etc | 946 | 44.2 | 17.7 | 3.0 | 0.8 | 10.3 | 9.9 | 10.1 |
| (a) Neuroblastoma and ganglioneuroblastoma | 930 | 44.2 | 17.6 | 2.9 | 0.6 | 10.1 | 9.8 | 10.0 |
| (b) Other peripheral nervous cell | 16 | – | 0.2 | 0.1 | 0.2 | 0.2 | 0.1 | 0.1 |
| V. Retinoblastoma | 417 | 24.8 | 7.9 | 0.5 | 0.1 | 4.3 | 4.8 | 4.6 |
| VI. Renal tumours | 862 | 16.3 | 19.3 | 4.3 | 1.3 | 8.3 | 9.8 | 9.0 |
| (a) Nephroblastoma and other non-epithelial | 844 | 16.3 | 19.3 | 4.3 | 0.9 | 8.2 | 9.6 | 8.9 |
| 1. Nephroblastoma (Wilms tumour) | 771 | 12.3 | 18.1 | 4.1 | 0.8 | 7.2 | 9.0 | 8.1 |
| 2. Rhabdoid | 31 | 3.0 | 0.3 | 0.0 | – | 0.3 | 0.3 | 0.3 |
| 3. Sarcomas | 34 | 0.9 | 0.9 | 0.1 | 0.0 | 0.5 | 0.2 | 0.4 |
| 4. Peripheral neuroectodermal tumour | 8 | 0.1 | 0.0 | 0.0 | 0.1 | 0.1 | 0.1 | 0.1 |
| (b) Renal carcinoma | 16 | – | 0.0 | 0.0 | 0.4 | 0.1 | 0.1 | 0.1 |
| (c) Unspecified | 2 | – | – | 0.1 | – | 0.0 | 0.0 | 0.0 |
| VII. Hepatic tumours | 182 | 8.4 | 3.1 | 0.4 | 0.6 | 2.0 | 1.8 | 1.9 |
| (a) Hepatoblastoma | 146 | 7.8 | 2.9 | 0.2 | 0.1 | 1.7 | 1.4 | 1.6 |
| (b) Hepatic carcinoma | 32 | 0.1 | 0.2 | 0.2 | 0.5 | 0.3 | 0.3 | 0.3 |
| (c) Unspecified | 4 | 0.4 | – | – | 0.0 | 0.0 | 0.0 | 0.0 |

**Table 2.1** (continued)

| | | Annual rates per million children for age group (years) | | | | Age standardised rates per million (World standard population) | | |
|---|---|---|---|---|---|---|---|---|
| ICCC-3 categories | Total registrations | 0 | 1–4 | 5–9 | 10–14 | Boys | Girls | Children |
| VIII. Malignant bone tumours | 620 | 0.3 | 1.1 | 4.8 | 10.8 | 5.2 | 4.9 | 5.0 |
| (a) Osteosarcoma | 322 | – | 0.3 | 2.2 | 6.0 | 2.6 | 2.5 | 2.6 |
| (c) Ewing sarcoma family | 262 | 0.1 | 0.7 | 2.2 | 4.2 | 2.2 | 2.1 | 2.2 |
| (b, d, e) Other and unspecified | 36 | 0.1 | 0.1 | 0.3 | 0.5 | 0.3 | 0.3 | 0.3 |
| IX. Soft tissue and extraosseous sarcomas | 993 | 12.0 | 10.4 | 7.4 | 9.0 | 10.1 | 8.1 | 9.2 |
| (a) Rhabdomyosarcoma | 499 | 5.3 | 7.4 | 4.5 | 2.4 | 5.5 | 4.1 | 4.8 |
| (b) Fibrosarcoma etc | 72 | 1.9 | 0.3 | 0.2 | 1.1 | 0.7 | 0.6 | 0.6 |
| (c) Kaposi sarcoma | 4 | – | 0.0 | 0.0 | 0.1 | 0.0 | 0.0 | 0.0 |
| (d) Other specified | 356 | 3.4 | 2.1 | 2.3 | 4.9 | 3.3 | 2.9 | 3.1 |
| 1, 2. Ewing sarcoma family | 147 | 0.9 | 1.1 | 1.1 | 1.8 | 1.1 | 1.5 | 1.3 |
| 3. Extrarenal rhabdoid tumour | 20 | 1.4 | 0.2 | 0.1 | 0.1 | 0.3 | 0.2 | 0.2 |
| 4. Fibrohistiocyytic tumours | 46 | 0.4 | 0.1 | 0.4 | 0.7 | 0.5 | 0.3 | 0.4 |
| 5. Synovial sarcoma | 71 | – | 0.3 | 0.4 | 1.3 | 0.7 | 0.4 | 0.6 |
| (e) Unspecified | 62 | 1.4 | 0.6 | 0.4 | 0.6 | 0.6 | 0.5 | 0.6 |
| X. Germ cell, trophoblastic and gonadal | 518 | 16.4 | 3.7 | 2.1 | 5.8 | 4.3 | 5.3 | 4.8 |
| (a) Intracranial and intraspinal germ cell | 176 | 1.7 | 0.6 | 1.1 | 2.7 | 1.9 | 1.0 | 1.5 |
| (b) Other malignant extragonadal | 144 | 11.7 | 1.6 | 0.2 | 0.3 | 1.0 | 2.1 | 1.5 |
| (c) Malignant gonadal germ cell | 189 | 3.0 | 1.5 | 0.6 | 2.7 | 1.4 | 2.0 | 1.7 |
| (d, e) Other and unspecified gonadal | 9 | – | – | 0.1 | 0.1 | 0.0 | 0.1 | 0.1 |
| XI. Other malignant epithelial and melanoma | 517 | 1.4 | 1.9 | 2.9 | 9.1 | 3.6 | 5.0 | 4.3 |
| (a) Adrenocortical carcinoma | 28 | 0.6 | 0.6 | 0.1 | 0.1 | 0.2 | 0.4 | 0.3 |
| (b) Thyroid carcinoma | 118 | – | 0.4 | 0.7 | 2.1 | 0.7 | 1.3 | 1.0 |
| (c) Nasopharyngeal carcinoma | 28 | – | – | 0.0 | 0.7 | 0.3 | 0.1 | 0.2 |
| (d) Malignant melanoma | 129 | 0.9 | 0.5 | 0.7 | 2.2 | 0.8 | 1.3 | 1.1 |
| (e) Skin carcinoma | 108 | – | 0.2 | 0.7 | 2.0 | 0.8 | 0.9 | 0.9 |
| (f) Other and unspecified carcinomas | 106 | – | 0.1 | 0.7 | 2.0 | 0.7 | 1.0 | 0.8 |
| XII. Other and unspecified | 90 | 1.3 | 0.9 | 0.3 | 1.1 | 0.8 | 0.8 | 0.8 |
| (a) Other specified | 20 | 0.6 | 0.3 | 0.0 | 0.2 | 0.2 | 0.2 | 0.2 |
| (b) Unspecified | 70 | 0.7 | 0.6 | 0.3 | 1.0 | 0.6 | 0.6 | 0.6 |

Source: National Registry of Childhood Tumours

acute lymphoblastic leukaemia (ALL), accounted for 78 % of leukaemias and one quarter of all childhood cancers; nearly all the remaining leukaemias were acute myeloid (AML). The most numerous solid neoplasms were CNS and other intracranial and intraspinal tumours, accounting for one 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 tumours and renal tumours, each accounting for 5.5–10 % 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 1.1 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 tumours, namely those of the CNS (including medulloblastoma and other primitive neuroectodermal tumours), neuroblastoma, retinoblastoma, nephroblastoma (Wilms tumour) 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 tumours of certain sites, thyroid carcinoma and malignant melanoma, there was a marked excess of girls.

Table 2.2 shows the distribution by morphology of childhood cancers in selected anatomical sites, based on the same data as Table 2.1. 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. Tumours 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 tumours. Cancers of the ovary were nearly all germ cell tumours. The majority of testicular cancers were germ cell tumours, 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.

**Table 2.2** Histological types of cancers of selected primary sites diagnosed at age 0–14 years in the UK, 1998–2007

| Primary site (ICD-O-3) | Type | Number of registrations |
|---|---|---|
| Major salivary glands (C07-08) | Total | 52 |
| | Lymphoma | 8 (15 %) |
| | Rhabdomyosarcoma | 4 (8 %) |
| | Carcinoma | 40 (77 %) |
| Other mouth (C00-06) | Total | 34 |
| | Lymphoma | 2 (6 %) |
| | Rhabdomyosarcoma | 9 (26 %) |
| | Other sarcoma | 5 (15 %) |
| | Germ-cell tumour | 1 (3 %) |
| | Carcinoma | 14 (41 %) |
| | Unspecified | 3 (9 %) |
| Tonsil (C09) | Total | 45 |
| | Lymphoma | 45 (100 %) |
| Nasopharynx (C11) | Total | 72 |
| | Lymphoma | 13 (18 %) |
| | Rhabdomyosarcoma | 30 (42 %) |
| | Other sarcoma | 1 (1 %) |
| | Carcinoma | 28 (39 %) |
| Other upper aerodigestive (C10,12-14,30-32) | Total | 71 |
| | Lymphoma | 15 (21 %) |
| | Neuroblastoma | 1 (1 %) |
| | Esthesioneuroblastoma | 8 (11 %) |
| | Rhabdomyosarcoma | 33 (46 %) |
| | Other sarcoma | 5 (7 %) |
| | Germ cell | 2 (3 %) |
| | Carcinoma | 3 (4 %) |
| | Unspecified | 4 (6 %) |
| Stomach (C16) | Total | 6 |
| | Lymphoma | 2 (33 %) |
| | Germ cell | 3 (50 %) |
| | Carcinoma | 1 (17 %) |
| Small intestine (C17) | Total | 44 |
| | Lymphoma | 39 (89 %) |
| | Carcinoma | 4 (9 %) |
| | GIST | 1 (2 %) |
| Colon, rectum (C18-19) | Total | 51 |
| | Lymphoma | 30 (59 %) |
| | Carcinoma | 19 (37 %) |
| | Unspecified | 2 (4 %) |
| Liver (C22) | Total | 224 |
| | Lymphoma | 10 (4 %) |
| | Hepatoblastoma | 146 (65 %) |
| | Carcinoma | 32 (14 %) |
| | Sarcoma | 30 (13 %) |
| | Germ cell | 2 (1 %) |
| | Unspecified | 4 (2 %) |
| Pancreas (C25) | Total | 5 |
| | Lymphoma | 2 (40 %) |
| | Sarcoma | 1 (20 %) |
| | Pancreatoblastoma | 2 (40 %) |
| Lung (C34) | Total | 36 |
| | Lymphoma | 6 (17 %) |
| | Sarcoma | 6 (17 %) |
| | Carcinoid/bronchial adenoma | 6 (17 %) |
| | Other carcinoma | 5 (14 %) |
| | Pleuropulmonary blastoma | 11 (31 %) |
| | Mesothelioma | 1 (3 %) |
| | Unspecified | 1 (3 %) |
| Ovary (C56) | Total | 135 |
| | Lymphoma | 4 (3 %) |
| | Neuroblastoma | 1 (1 %) |
| | Sarcoma | 2 (1 %) |
| | Germ cell | 120 (89 %) |
| | Carcinoma | 4 (3 %) |
| | Sertoli-Leydig | 2 (1 %) |
| | Mesothelioma | 1 (1 %) |
| | Unspecified | 1 (1 %) |
| Other female reproductive (C52-55,57) | Total | 27 |
| | Rhabdomyosarcoma | 13 (48 %) |
| | Other sarcoma | 1 (4 %) |
| | Germ cell | 11 (41 %) |
| | Carcinoma | 2 (7 %) |
| Prostate (C61) | Total | 8 |
| | Rhabdomyosarcoma | 8 (100 %) |
| Male genital (C62-63) | Total | 124 |
| | Lymphoma | 1 (1 %) |
| | Rhabdomyosarcoma | 51 (41 %) |
| | Germ cell | 70 (56 %) |
| | Sertoli cell | 1 (1 %) |
| | Unspecified | 1 (1 %) |

**Table 2.2** (continued)

| Primary site (ICD-O-3) | Type | Number of registrations |
|---|---|---|
| Kidney (C64) | Total | 895 |
| | Lymphoma | 12 (1 %) |
| | Neuroblastoma | 17 (2 %) |
| | Nephroblastoma (Wilms) | 767 (86 %) |
| | Rhabdoid | 31 (3 %) |
| | Clear cell sarcoma | 34 (4 %) |
| | pPNET | 8 (1 %) |
| | Other sarcoma | 7 (1 %) |
| | Germ cell | 1 (<0.5 %) |
| | Carcinoma | 16 (2 %) |
| | Unspecified | 2 (<0.5 %) |
| Bladder (C67) | Total | 43 |
| | Lymphoma | 1 (2 %) |
| | Rhabdomyosarcoma | 32 (74 %) |
| | Other sarcoma | 6 (14 %) |
| | Carcinoma | 3 (7 %) |
| | Paraganglioma | 1 (2 %) |
| Orbit (C69.6) | Total | 65 |
| | Chloroma | 3 (5 %) |
| | Lymphoma | 5 (8 %) |
| | Rhabdomyosarcoma | 56 (86 %) |
| | Other sarcoma | 1 (2 %) |
| Other eye (C69.0-69.5,69.7-69.9) | Total | 432 |
| | Lymphoma | 1 (<0.5 %) |
| | Medulloepithelioma | 1 (<0.5 %) |
| | Retinoblastoma | 417 (97 %) |
| | Melanoma | 8 (2 %) |
| | Sarcoma | 4 (1 %) |
| | Unspecified | 1 (<0.5 %) |
| Thyroid (C73) | Total | 124 |
| | Lymphoma | 3 (2 %) |
| | Differentiated carcinoma | 91 (73 %) |
| | Medullary carcinoma | 27 (22 %) |
| | Unspecified | 3 (2 %) |

Source: National Registry of Childhood Tumours

In addition to the diseases included in ICCC-3, children can also develop many types of non-malignant 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, or have been the subject of special studies. The incidence of Langerhans cell histiocytosis (LCH) has recently been reported as around 6 per million in Germany [4] and Switzerland [5] and 4 per million in the UK and Ireland [6]. Mesoblastic nephroma accounted for 3 % of all renal tumours in North-west England [7], 4 % in Germany [4] and 6 % in the West Midlands of England [8], indicating an annual incidence of about 0.4 per million. In North-west England 61 % of all extracranial germ cell tumours were non-malignant [9]; they represented 48 % of germ cell tumours in the testes, 60 % in the ovaries and 69 % in other sites. In the West Midlands of England, all 49 extracranial germ cell tumours diagnosed in the first 3 months of life were benign teratomas, though four did recur as malignant tumours [10]; 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 tumours in North-west England [11], implying an annual incidence of about 0.1 per million. It is not always possible to distinguish morphologically between benign and malignant adrenocortical tumours, however, and they should perhaps be regarded as lying on a continuum of clinical behaviour [12]. Carcinoid tumours of the appendix had an annual incidence of 1.1 per million children in the West Midlands of England [13].

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 industrialised 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 [14–17]. Mostly the changes have been quite small, often no more than 1 % per year [14]. 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 [18–20]. The very large increase in childhood Kaposi sarcoma in some sub-Saharan African countries is linked to the AIDS epidemic, through immunosuppression consequent on HIV infection allowing HHV-8 viral load to increase uncontrollably [21]. 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 [22]. Incidence has fallen to lower levels among children who were born after the Chernobyl accident [23].

Increases in the incidence of CNS tumours, especially low-grade gliomas, are consistent with improved detection following the introduction of computed tomography (CT) and magnetic resonance imaging [17, 24]. 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 [16, 17].

## Aetiology

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 [25–27]. 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 leukaemia. Germline mutations of TP53 carry a raised risk of various cancers including soft tissue sarcoma, osteosarcoma, adrenocortical carcinoma, brain tumours and leukaemia, as well as pre-menopausal 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 tumour, including Beckwith-Wiedemann, Denys-Drash, WAGR, and Simpson-Golabi-Behmel syndromes [28]. Constitutional chromosomal abnormalities are implicated in about 1 % of all childhood cancers [29]. The most important is Down syndrome, which carries a greatly raised risk of leukaemia and almost certainly an increased risk of germ cell tumours, though the total excess of cancer is reduced by an apparent protective effect against several other types of solid tumours [30]. 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 [31]. 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 [32]. In a series of 900 childhood cancers other than leukaemia from the National Cancer Institute in Tunisia, 8 % were skin carcinomas associated with XP [33].

The largest study of parental age as a risk factor for childhood cancer found positive linear trends in risk with maternal age for several diagnostic groups but there was little evidence of any effect of paternal age after adjustment for maternal age [34]. It was not possible to determine the mechanisms whereby cancer risk increased with mother's age, but it seemed likely to involve germline mutations.

An enormous number of exogenous or environmental exposures have been investigated as possible risk factors for childhood cancer [35, 36]. 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 [37]. 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. A large national study of cancer following CT scans before the age of 22 years found that a cumulative dose of 50 mGy might almost triple the risk of leukaemia and cumulative dose of 60 mGy might triple the risk of a CNS tumour [38]. 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 [39]. It has been estimated that around 15 % of childhood leukaemia in Britain may be attributable to natural background ionising radiation [40].

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 more than two decades. A moderately raised risk of leukaemia has consistently been found for the highest exposure levels experienced by fewer than 1 in 20 children in industrialised countries but the reasons for this are unclear [41–45]. There is little evidence for an association between magnetic field exposure and childhood brain tumours [44, 46, 47].

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 sarcoma (HHV-8) [48]. The introduction of universal vaccination against hepatitis B has been followed by reductions of around 70 % in the occurrence of childhood hepatocellular carcinoma in Taiwan and South Korea [49, 50].

Many epidemiological studies support the suggestion that infection is involved in the aetiology of some childhood leukaemias [51]. Most of these studies are relevant to either or both of two hypotheses. Kinlen's hypothesis that leukaemia 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 [52]. 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 [53–55].

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. Children who receive a solid organ transplant are especially vulnerable to neoplasms, of which post-transplant lymphoproliferative disorder and skin carcinomas are the most frequent [56]. Daughters of women who took diethylstilboestrol (DES) in pregnancy had an increased risk of clear cell carcinoma of the vagina or cervix [57] but most of these tumours occurred in early adulthood and DES ceased to be used more than 30 years ago. 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. Combined data from studies up to 2005 of children born after ART failed to reveal any significant increase in the risk of cancer [58, 59], but the expected numbers of cancers were relatively small and follow-up was short for children born after some types of ART. A more recent study in Sweden found a significantly increased odds ratio of 1.34 for cancer (excluding LCH) in children born after in vitro fertilization, but there were fewer than 50 cases of cancer of all types combined [60]. In the same study there were 6 cases of LCH compared with 1.0 expected [60]. No other study has reported an association of LCH with 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 aetiology of childhood cancer. Mostly the evidence comes from a small number of studies or is inconsistent between studies [61, 62].

Malformations and other physical characteristics associated with certain childhood cancers could be markers for underlying genetic or environmental causes. In large population-based studies, 3–4 % of children with malignant solid tumours also had a congenital anomaly, in many cases not as part of any recognised syndrome [63, 64]. The overall relative risk is about 3 for all anomalies [65] , and about 1.5 for non-chromosomal anomalies [64]. Such occurrences could result from an unknown genetic defect or, as seems more likely, for example, in the association of hernia with Ewing sarcoma, have a common environmental cause [66].

High birth weight has been associated with raised risk of several types of childhood cancer, notably leukaemia [67, 68], CNS tumours [69], and neuroblastoma [70], perhaps resulting from increased growth rate *in utero*. By contrast, infants with very low birth weight have a greatly increased risk of hepatoblastoma which may be attributable to exposures in neonatal intensive care units but there is as yet no conclusive evidence [71]. Children who are twins have consistently been found to have a risk of cancer around 80 % of that in singleton children [72, 73]. The reasons for this are unknown but possible explanations include lower birth weight, earlier restriction of growth in twin pregnancies, and higher *in utero* death rates of embryos in which tumorogenesis is initiated shortly after conception [73]. Patients with osteosarcoma are significantly taller than the general population, indicating a role of accelerated long bone growth around puberty [74].

## Survival

Table 2.3 shows actuarial 5-year survival rates for children in Great Britain with cancer diagnosed during 2003–2007 [75]. 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 industrialised countries [76, 77]. Survival tends to be lower in less affluent countries of Eastern Europe [77], and lower still in developing countries [78]. 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 [75]. This means that the risk of death within 5 years from diagnosis was reduced by 63 %. Figures 2.1, 2.2 and 2.3 show that survival for all major diagnostic groups increased in Britain between 1983 and 1987 and 2003–2007, though the timing of the largest increases varied between diagnostic groups. Broadly similar trends have been observed in other industrialised countries [79–83].

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

**Table 2.3** Five year survival of children in Great Britain with cancer diagnosed during 2003–2007

| | Five-year survival (%) |
|---|---|
| All cancers | 79 |
| Leukaemia | 86 |
| ALL | 90 |
| AML | 68 |
| Lymphomas | 89 |
| Hodgkin | 94 |
| Non-Hodgkin (incl. Burkitt) | 85 |
| CNS tumours | 71 |
| Ependymoma | 70 |
| Astrocytoma | 81 |
| Embryonal | 53 |
| Other glioma | 43 |
| Craniopharyngioma | 95 |
| Neuroblastoma | 63 |
| Retinoblastoma | 99 |
| Renal tumours | 84 |
| Nephroblastoma (Wilms tumour) | 90 |
| Hepatic tumours | 71 |
| Hepatoblastoma | 78 |
| Bone tumours | 64 |
| Osteosarcoma | 63 |
| Ewing sarcoma family | 63 |
| Soft tissue sarcoma | 68 |
| Rhabdomyosarcoma | 65 |
| Germ cell and gonadal | 92 |
| CNS germ cell | 89 |
| Other extragonadal germ cell | 87 |
| Gonadal germ cell | 99 |
| Thyroid carcinoma | 100 |
| Malignant melanoma | 91 |

Source: National Registry of Childhood Tumours [75]

most effective treatment. Increases in survival have, nevertheless, occurred concurrently with the development of paediatric oncology clinical trials groups and increased referral to specialist treatment centres 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 [84, 85]. A recent national study in Britain found that for a wide range of childhood cancers changes in population-based survival between the eras of successive clinical trials paralleled those reported by the relevant trials [86].

Improved survival has resulted in increasing numbers of long-term survivors of childhood cancer. The cumulative risk of a second primary malignancy is about 3.6 % within 25 years of diagnosis [87] and about 5 % by the age of 40 years [88]. Many other aspects of the health of long-term survivors and their offspring are the subject of several large epidemiological studies [89–98].

## Mortality

Population mortality rates from childhood cancer in western countries have fallen dramatically since the mid twentieth century, in line with the moderate increase in incidence and very marked improvements in outcome. Table 2.4 shows estimated age standardised mortality rates for childhood cancer by world region in 2008 [99]. In wealthy industrialised countries, mortality was typically around 20–30 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 [100].

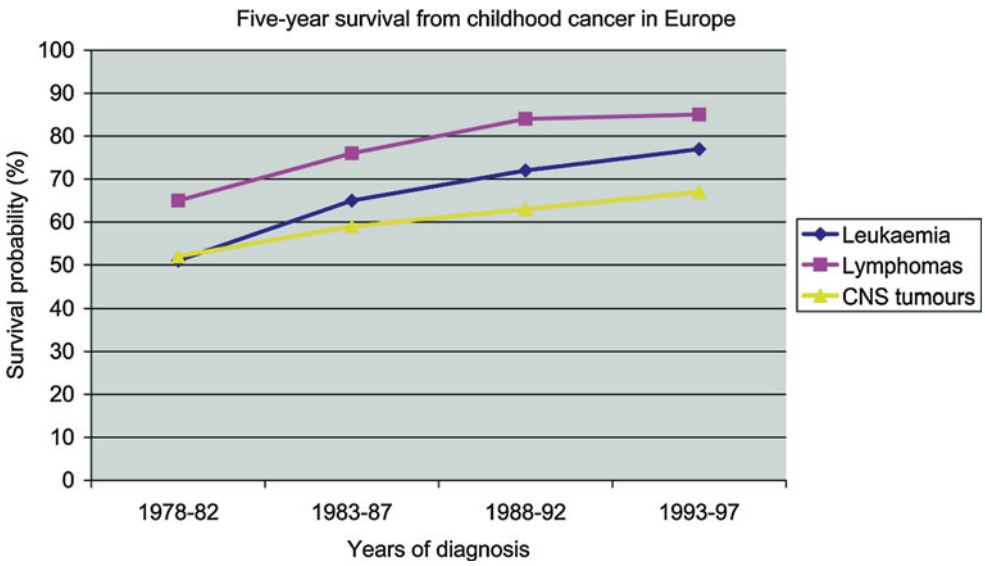


**Fig. 2.1** Five year survival of children in Great Britain with leukaemias, lymphomas and CNS tumours diagnosed 1983–2007 (Source: National Registry of Childhood Tumours)

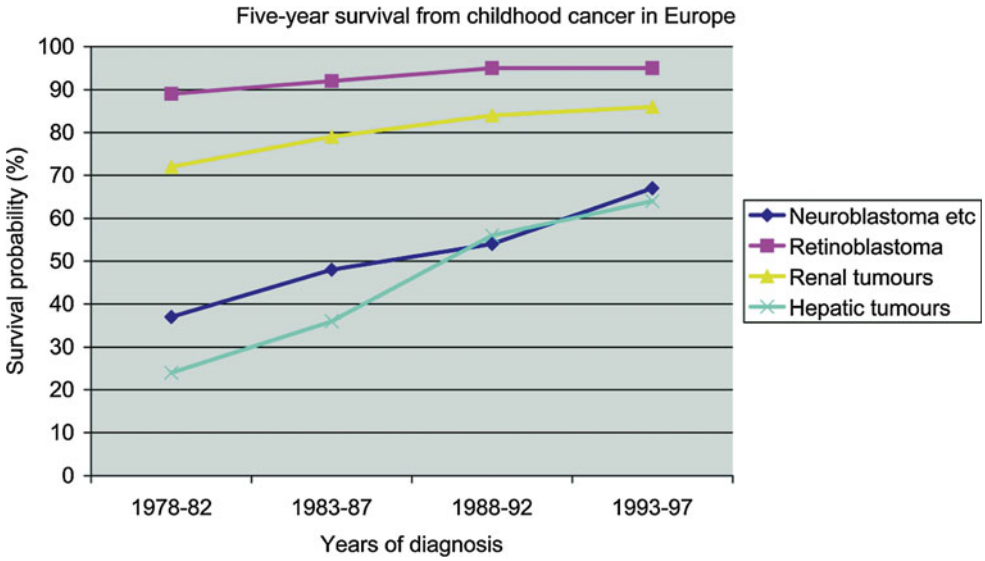


**Fig. 2.2** Five year survival of children in Great Britain with neuroblastoma and other peripheral nervous cell tumours, retinoblastoma, renal tumours and hepatic tumours diagnosed 1983–2007 (Source: National Registry of Childhood Tumours)

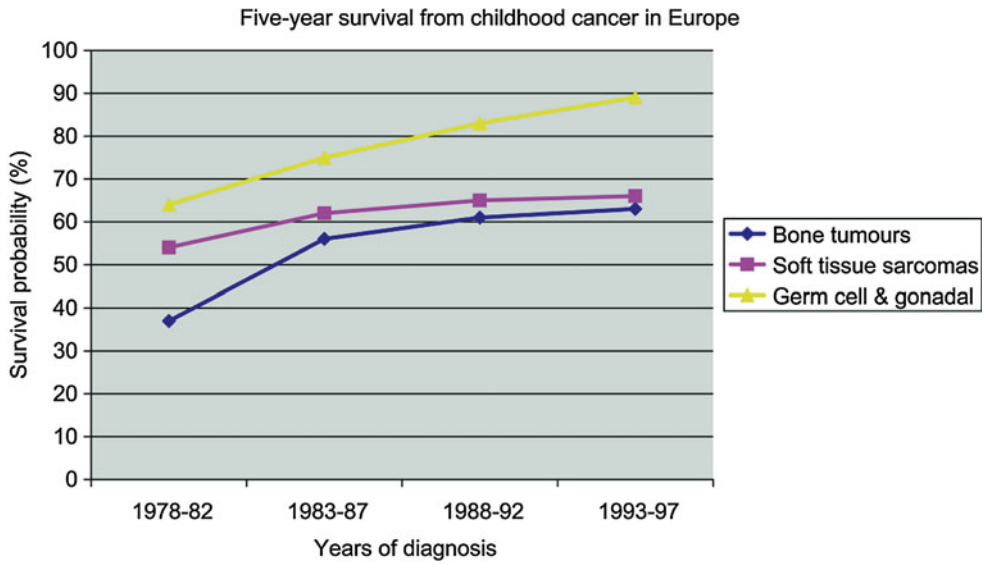


**Fig. 2.3** Five year survival of children in Great Britain with bone tumours, soft tissue sarcomas and germ cell and gonadal tumours diagnosed 1983–2007 (Source: National Registry of Childhood Tumours)

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 2.4** Estimated age-standardised mortality rates per million for cancer at age 0–14 years, 2008, by world region

| | Total | Leukaemia | Lymphoma | Brain/nervous system | Renal |
|---|---|---|---|---|---|
| Northern Africa | 78 | 19 | 17 | 9 | 9 |
| Sub-Saharan Africa | 68 | 8 | 21 | 2 | 8 |
| USA/Canada | 24 | 7 | 1 | 7 | 1 |
| Central America | 63 | 32 | 5 | 9 | 1 |
| South America | 46 | 19 | 3 | 9 | 2 |
| Western Asia | 77 | 29 | 16 | 10 | 5 |
| India | 37 | 13 | 4 | 5 | 1 |
| Other South and Central Asia | 59 | 20 | 9 | 6 | 3 |
| China | 46 | 25 | 2 | 10 | 1 |
| Japan | 19 | 7 | 1 | 5 | <1 |
| South-Eastern Asia | 70 | 34 | 6 | 8 | 3 |
| Nordic Countries | 28 | 10 | 1 | 9 | 1 |
| British Isles | 27 | 7 | 1 | 9 | 1 |
| Former USSR in Europe | 41 | 12 | 2 | 12 | 2 |
| Other Eastern Europe | 36 | 12 | 3 | 12 | 1 |
| Western Europe | 21 | 6 | 1 | 9 | 1 |
| Southern Europe | 30 | 10 | 1 | 9 | 1 |
| Australia/New Zealand | 25 | 8 | <1 | 10 | 1 |

Source: GLOBOCAN 2008 [99]

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# Tumor Biology and Environmental Carcinogenesis

3

Andrew M. Davidoff

## Introduction

During normal development and self-renewal, cells evolve to perform highly specialized functions to meet the physiologic needs of the organism. These processes involve tightly regulated activities 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 forms the basis for that control, but 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, 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.

## Cell Fate

### Stem Cells

The development and maintenance of the tissues that comprise an organism are 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 [133]. 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.

## Programmed Cell Death

Multicellular organisms have developed a highly organized and carefully regulated mechanism of cell death in order to maintain cellular homeostasis. Normal development and morphogenesis are often associated with the production of excess cells, which are removed by the genetically programmed process called apoptosis. Apoptosis is a highly regulated event which can be effected by either death receptor-mediated or mitochondrial pathways by activating specific signaling molecules. Both pathways converge onto a group of effector caspases, leading to morphologic and biochemical changes characteristic of apoptosis. Cells undergoing apoptosis have distinct morphologic features (plasma membrane blebbing, reduced volume, nuclear condensation), and their DNA is subjected to endonucleolytic cleavage.

Receptor-mediated apoptosis is initiated by the interaction of "death ligands" such as tumor necrosis factor α (TNFα), Fas, and TNF-related apoptosis-inducing ligand (TRAIL) with their respective receptors. This interaction is followed by aggregation of the receptors and recruitment of adaptor proteins to the plasma membrane, which activate caspases [92]. Caspases are a large family of proteases that function in both the initiation of apoptosis in response to proapoptotic signals and in the subsequent effector pathway

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**Table 3.1** Proto-oncogenes and tumor suppressor genes in pediatric malignancies

| *Oncogene family* | *Proto-oncogene* | *Chromosome location* | *Tumors* |
|---|---|---|---|
| Growth factors and receptors | | | |
| | erb B2 | 17q21 | Glioblastoma |
| | trk | 9q22 | Neuroblastoma |
| Receptor tyrosine kinase | | | |
| | alk | 2p23 | Neuroblastoma |
| | ret | 10q11.2 | Medullary thyroid carcinoma, Multiple endocrine neoplasia 2A/B, pheochromocytoma |
| Signal transducers | | | |
| | H-ras | 11p15.1 | Neuroblastoma |
| Transcription factors | | | |
| | c-myc | 18q24 | Burkitt lymphoma |
| | N-myc | 2p24 | Neuroblastoma |
| *Syndrome* | *Tumor suppressor gene* | *Chromosome location* | *Tumors* |
| Familial polyposis coli | APC | 5q21 | Intestinal polyposis, colorectal cancer |
| Familial retinoblastoma | RB | 13q24 | Retinoblastoma, osteosarcoma |
| WAGR[a] | WT1 | 11p13 | Wilms tumor |
| Denys-Drash[b] | WT1 | 11p13 | Wilms tumor |
| Beckwith-Weidemann[c] | WT2 (?) | 11p15 | Wilms tumor, hepatoblastoma, adrenal tumors |
| Li-Fraumeni | p53 | 17q13 | Multiple |
| Neurofibromatosis type 1 | NF1 | 17q11.2 | Sarcomas, breast cancer |
| Neurofibromatosis type 2 | NF2 | 22q12 | Neurofibroma, neurofibrosarcoma, brain tumor |
| Von Hippel-Lindau | VHL | 3p25-26 | Renal cell cancer, pheochromocytoma, retinal angioma, hemangioblastoma |

Reprinted with permission from Davidoff and Krasin [31]
[a]WAGR: Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation
[b]Denys-Drash: Wilms tumor, pseudohermaphroditism, mesangeal sclerosis, renal failure
[c]Beckwith-Weidemann: multiple tumors, hemihypertrophy, macroglossia, hyperinsulinism

that disassembles the cell. Thus, apoptosis limits cellular expansion and counters cell proliferation. Because cell survival signals may also be activated through parallel pathways, the fate of a cell is determined by the balance between death signals and survival signals [65]. Other signals arising from cellular stress (e.g., DNA damage, hypoxia, oncogene activation) may also effect cell cycle arrest or apoptosis.

An alternative to cell death mediated by receptor-ligand binding is cellular senescence, which is initiated when chromosomes reach a critical shortened length. Eukaryotic chromosomes have DNA strands of unequal length, and their ends—telomeres—are characterized by species-specific nucleotide repeat sequences. Telomeres stabilize the ends of chromosomes, which are otherwise sites of significant instability [121]. Over time and with each successive cycle of replication, chromosomes are shortened by failure to complete replication of their telomeres. Thus, telomere shortening acts as a biologic clock, limiting the lifespan of a cell. Germ cells, however, avoid telomere shortening by using telomerase, an enzyme capable of adding telomeric sequences to the ends of chromosomes. This enzyme is normally inactivated early in the growth and development of an organism. Persistent activation or the reactivation of telomerase in somatic cells appears to contribute to the immortality of transformed cells.

## Malignant Transformation

Alteration or inactivation of any of the components of normal cell regulatory pathways may lead to the dysregulated growth that characterizes neoplastic cells. Malignant transformation may be characterized by cellular dedifferentiation or failure to differentiate, cellular invasiveness and metastatic capacity, and/or decreased drug sensitivity. Tumorigenesis reflects the accumulation of excess cells that results from increased cell proliferation and decreased apoptosis or senescence. Cancer cells do not replicate more rapidly than normal cells, but they show diminished responsiveness to regulatory signals. Positive growth signals are generated by proto-oncogenes, so named because their dysregulated expression or activity can promote malignant transformation. These proto-oncogenes may encode growth factors or their receptors, intracellular signaling molecules, and nuclear transcription factors (Table 3.1). Conversely, tumor suppressor genes, as their name implies, control or restrict cell growth and proliferation. Their inactivation, through various mechanisms, permits the dysregulated growth of cancer cells. Also important are the genes that regulate cell death. Their inactivation leads to resistance to apoptosis and allows accumulation of additional genetic aberrations.

Cancer cells carry DNA that has point mutations, viral insertions, or chromosomal or gene amplifications, deletions, or rearrangements. Each of these aberrations can alter the context and process of normal cellular growth and differentiation. Although genomic instability is an inherent property of the evolutionary process and normal development, it is through genomic instability that the malignant transformation of a cell may arise. This inherent instability may be altered by inheritance or exposure to destabilizing factors in the environment. Point mutations may terminate protein translation, alter protein function, or change the regulatory target sequences that control gene expression. Chromosomal alterations create new genetic contexts within the genome and lead to the formation of novel proteins or to the dysregulation of genes displaced by aberrant events.

Genetic abnormalities associated with cancer may be detected in every cell in the body or only in the tumor cells. Constitutional or germline abnormalities are either inherited or occur de novo in the germ cells (sperm or oocyte). Interestingly, despite the presence of a genetic abnormality that might affect growth regulatory pathways in all cells, specific genetic abnormalities generally predispose only to certain tumor types. This selectivity highlights the observation that gene function contributes to growth or development only within a particular milieu or physiologic context.

Specific tumors occur earlier and are more often bilateral (in paired organs) when they result from germline mutations than when they result from sporadic or somatic alterations. Such is often the case in two pediatric malignancies, Wilms tumor and retinoblastoma. These observations led Alfred Knudson to propose a "two-hit" model of carcinogenesis in which the first genetic defect, already present in the germ line, must be complemented by an additional spontaneous mutation before a tumor can arise [62]. In sporadic cancer, cellular transformation occurs only when two (or more) spontaneous mutations take place in the same cell. The critical features of the Knudson model – the small number of mutations required for malignant transformation, the possible inheritance of a first mutation and the gradual disappearance of transformable target cells with increasing age, provide a conceptual framework for mutational theories of the genetics of most childhood tumors. In this scheme familial tumors will present earlier than sporadic tumors of the same histologic type; inheritance of a tumorigenic mutation will also predispose to multiple tumor occurrences.

Much more common, however, are somatically acquired chromosomal aberrations, which are confined to the malignant cells. These aberrations affect growth factors and their receptors, signal transducers, and transcription factors. The general types of chromosomal alterations associated with malignant transformation are shown in Fig. 3.1. Although a low level of chromosomal instability exists in a normal population of cells, neoplastic transformation occurs only if these alterations affect a growth-regulating pathway and confer a growth advantage.

## DNA Content

Normal human cells contain two copies of each of 23 chromosomes; therefore, a normal "diploid" cell has 46 chromosomes. Although cellular DNA content, or ploidy, is accurately determined by karyotypic analysis, it can be estimated by the much simpler method of flow cytometry. The DNA index (DI) is defined as the ratio of the number of chromosome copies per cell to that of a normal cell (i.e., 46). Diploid cells have a DI of 1.0, whereas near-triploid cells have a DNA index ranging from 1.26 to 1.76. The majority (55 %) of primary neuroblastoma cells are triploid or near triploid, having between 58 and 80 chromosomes, whereas the remainder are near diploid (35–57 chromosomes) or near tetraploid (81–103 chromosomes) [57]. Neuroblastomas consisting of near-diploid or near-tetraploid cells usually have structural genetic abnormalities (e.g., chromosome 1p deletion and amplification of the *MYCN* oncogene), whereas those consisting of near-triploid cells are characterized by three almost complete haploid sets of chromosomes with few structural abnormalities [12]. The DI can have prognostic significance; patients with near-triploid tumors typically have favorable clinical and biologic prognostic factors, and excellent survival rates, compared with those who have near-diploid or near-tetraploid tumors [75].

## Chromosomal Translocations

Many pediatric cancers, particularly soft-tissue neoplasms and hematologic malignancies, have recurrent, nonrandom abnormalities in chromosomal structure, typically chromosomal translocations (Table 3.2). The most common result of a nonrandom translocation is the fusion of two distinct genes from different chromosomes. The genes are typically fused within the reading frame and express a functional, chimeric protein product that has transcription factor or protein kinase activity. These fusion proteins contribute to tumorigenesis by activating genes or proteins involved in cell proliferation. For example, in Ewing sarcoma the consequence of the t(11;22)(q24;q12) translocation is the fusion of *EWS*, a transcription factor gene on chromosome 22, and *FLI-1*, a gene encoding a member of the ETS family of transcription factors on chromosome 11 [81]. The resultant chimeric protein, which contains the DNA-binding region of FLI-1 and the transcription activation region of EWS, has greater transcriptional activity than does EWS alone [82]. The EWS:FLI-1 fusion transcript is detectable in approximately 90 % of Ewing sarcomas. At least four other EWS fusions have been identified in Ewing sarcoma; fusion of EWS with ERG (another ETS family member) accounts for an additional 5 % of cases [124]. Alveolar rhabdomyosarcomas have characteristic translocations between the long arm of chromosome 2 (75 % of cases)