Introduction

Cancer is, in general, associated with aging. In the United States, cancer incidence rates per 100,000 persons per year rise almost 100-fold, from 23.4 in the first year of life to 2177.2 in the 85th year and beyond. Among adults, the four most common cancers are solid tumors of the prostate, breast, colon, and lung. Hematologic malignancies, leukemias and lymphomas, are much less common. However, among children, leukemias and lymphomas account for a much larger share of all malignancies (Fig. 1.1). At ages 2–14 years, the hematologic malignancies account for more than 40% of new cancer diagnoses. At ages 15–19 years, they account for 40.1% of malignant diseases among males but only 33.3% among females. At ages 20–39 years, hematologic malignancy incidence rates are slightly lower among females than males, but all-site incidence rates are much higher among females, primarily due to breast, cervical, and thyroid cancer. As a result, by the late 1930s, hematologic malignancies account for 18.6% of newly diagnosed cancers per year among males but only 6.7% among females (Table 1.1).

Leukemia is a set of diseases of the blood or bone marrow (in which blood cells originate), involving an abnormal proliferation of (white) blood cells. The acute leukemias involve the rapid proliferation of immature blood cells, crowding the bone marrow and spreading through the bloodstream into other organs. The chronic leukemias involve a more gradual increase in more mature blood cells. The acute leukemias are the most common hematologic malignancies in children; incidence rates peak among 2–3-year-olds.

Lymphoma is a term used for cancers that originate in lymphocytes, usually within lymph nodes, but, unlike lymphoid leukemias, which involve only circulating blood and bone marrow, lymphomas typically present as solid tumors of the lymph nodes. More than 40 types of lymphoma have been identified, but most can be classified as involving T-cells, B-cells, or NK cells. Lymphomas are very rare among young children; incidence rates are lower than 1/100,000 per year among children younger than 8 years, but are as high as leukemia rates by the early teens and rise considerably higher by the early 1920s (Figs. 1.2A–B).

The Leukemias

Among children aged 0–14 in the United States, leukemias are responsible for 33% of cancers and 30% of cancer deaths. Incidence rates of leukemia are 5.0 per 100,000 per year in that age range, age-specific rates rise from birth to age 2 and then fall; the association
with age is driven by acute lymphoblastic leukemia (ALL), the most commonly diagnosed leukemia of children (Fig. 1.1). Untreated acute leukemias are uniformly fatal. However, leukemia was the first cancer in which chemotherapy was successful, and in the past 35 years, combination chemotherapy has achieved dramatic results (Fig. 1.3). Overall 5-year survival among children and adolescents with leukemia has risen from 50% to nearly 80%. Several etiologic factors...
in leukemia in children and young adults are summarized in Table 1.2.

Some childhood leukemias have been linked to certain genetic disorders, including Down syndrome (trisomy 21). Children with Down syndrome (DS) have a 10- to 20-fold increased risk of developing acute leukemia, compared to children without DS. A large case control study from the Children’s Cancer Group found significantly increased risk of ALL (odds ratio 4.85) and dramatically increased risk of acute myelogenous leukemia (AML) (odds ratio 76.80) among children with DS. However, children with DS account for only 2% of cases of pediatric ALL, and 15% of cases of pediatric AML. Among children with acute leukemia, children with DS differ substantially from those without DS in leukemia-related cytogenetics and acquired gene mutations. Children with DS also have more than a 400-fold increased risk for acute megakaryoblastic leukemia (AMKL), the most common subtype of DS-associated AML. AMKL is frequently preceded by a preleukemic myelodysplastic syndrome (MDS) in children with DS. Kleinfelter syndrome (XXY) has been inconsistently associated with ALL.

Several inherited marrow failure syndromes, including Fanconi anemia (FA), Schwachman–Diamond Syndrome (SDS), and to a lesser extent Diamond Blackfan anemia (DBA) are associated with increased risk of MDS and AML. FA is a rare, genetic disorder, usually with an autosomal recessive pattern of inheritance, affecting some 1–5 per million. The incidence of FA is considerably higher among Spanish Gypsies, white Afrikaners in South Africa, and Ashkenazi Jews than among other groups, probably due to founder mutations in small, isolated populations. FA is associated with progressive marrow failure, numerous congenital abnormalities, and high incidence of cancer. Among patients with FA, approximately 8% develop AML by age 20, and 22% by age 36. SDS is a rare, autosomal recessive disorder (approximately 1.33 per 100,000 live births) characterized by marrow failure, pancreatic insufficiency, and skeletal abnormalities; some 30% of SDS patients develop MDS or AML. DBA is a rare disorder characterized by macrocytic anemia and erythroblastopenia, associated with several mutations in genes encoding for ribosomal proteins. Familial DBA seems to be autosomal dominant with incomplete penetrance and an incidence rate of approximately 1 in 100,000. DBA is associated with increased risk of hematologic malignancies, particularly MDS and AML, as well as solid tumors. However, the incidence of AML and MDS in children with DBA is considerably lower than in children with FA or SDS.

Children and adolescents who have received chemotherapy or radiation therapy for a prior malignancy are at increased risk for acute leukemia (usually AML) and other myeloproliferative disorders, compared to individuals of similar age who have not been treated for cancer. It is not clear whether genetic factors play a role in this association. Patients treated with mechlorethamine or cyclophosphamide for Hodgkin lymphoma (HL), have a more than 300-fold or 100-fold, respectively, increased risk of acute leukemia compared to that in the general population. Patients receiving mechlorethamine-containing combination chemotherapy (the MOPP regimen) for HL have a cumulative 3.4–9.5% risk of leukemia in the 15 years following treatment. Such cases of AML are often preceded by MDS and tend to occur 5–7 years after the primary diagnosis. Other chemotherapeutic agents used in the treatment of childhood hematologic or solid cancers, such as the epipodophyllotoxins (e.g. etoposide, teniposide) and the anthracyclines (e.g. doxorubicin, daunorubicin), also increase the risk of secondary AML significantly; these cases of AML tend to occur more acutely, without antecedent MDS, at a mean of 2–3 years following the primary diagnosis. The dose of
epipodophyllotoxins and the frequency of dosing are positively associated with increased risk of secondary AML.15

Children exposed to ionizing radiation also face an increased risk for hematological and other malignancies, including the leukemias. Among more than 86,000 survivors of the 1945 atomic bomb blasts in Hiroshima and Nagasaki, long-term follow-up has suggested that 103 leukemia deaths were attributable to radiation exposure; about 28 of these deaths occurred in children, adolescents and young adults under age 30. A dose-response relationship between radiation dose and excess leukemia risk was observed; individuals who received radiation doses > 2 Gy, 10.4, 14.5, and 59.1 times the risk of ALL, AML, and chronic myelogenous leukemia (CML), respectively, compared to those receiving only background levels of radiation exposure.16 The therapeutic use of ionizing radiation also predisposes patients to ALL, AML, and CML, with risk greatest 5–9 years following exposure. For example, among 10,000 patients receiving 25 Gy of radiotherapy for testicular cancer, an excess of nine leukemias is predicted over 15 years.17 Patients treated with combination chemotherapy and total body irradiation (mean: 12.6 Gy) for non-Hodgkin lymphoma (NHL) had a 17% risk of AML in 15 years of follow-up.18

**Acute lymphoblastic leukemia**

Acute lymphoblastic leukemia is an aggressive, malignant neoplasm of B- or T-lymphocyte precursor cells (lymphoblasts) (see Chapters 11 and 12). Unlike other leukemias, ALL is primarily a disease of childhood, with a median age at diagnosis of 13 years. In the United States, ALL is the most common malignancy of children aged 0–14, representing 26% of all cancers and 79% of all leukemias.2 Among children aged 0–14, the incidence of ALL is 4.0 per 100,000 per year, peaking at 9.4 per 100,000 per year at age 3. In 2002–2006, an estimated 5,760 individuals per year, approximately 3,500 of them under the age of 20, were diagnosed with ALL.

Acute lymphoblastic leukemia incidence rates are higher among males than among females at all ages. Among children aged 0–14, incidence rates are 4.4 per 100,000 in boys and 3.5 per 100,000 in girls. ALL is more common in whites (1.7 per 100,000) than in blacks (0.9 per 100,000) across all age groups. Acute lymphoblastic leukemia incidence is highest among children aged 1–4 in both groups, but is substantially higher in whites (8.5 per 100,000) than blacks (3.3 per 100,000). From 1975 to 2006, the incidence of childhood ALL increased by nearly 50% in children aged 0–14; the average annual increase was 0.8%.

Aneuploidy is the most commonly observed acquired abnormality in ALL, occurring in some form in 92% of cases of childhood ALL.19 Specific genetic abnormalities have been observed in childhood ALL, including the TEL-AML1 gene fusion generated by a translocation involving chromosomes 12 and 21 (see Chapters 5 and 6). This fusion gene is present in approximately 25% of cases of ALL; studies by the Children’s Oncology Group and others suggest the TEL-AML1 gene carries positive prognostic significance.20 However, although approximately 1% of children are born with the TEL-AML1 translocation, only approximately 1 in 8000 of those with the translocation will develop childhood ALL.21 Translocations involving chromosome 11q23, with resulting arrangement of the MLL gene, may occur in utero and are found in some infants with ALL; such translocations are also frequently observed in secondary AML following therapy with topoisomerase II inhibitors, including etoposide and doxorubicin.22 The Philadelphia chromosome, generated by translocation involving chromosomes 9 and 22, is observed in 3–5% of children with ALL and is associated with poor prognosis; in one large retrospective study, only 28% of patients achieved 5-year event-free survival. Matched sibling donor allogeneic stem cell transplantation and good response to initial glucocorticoid therapy were associated with superior outcomes in these patients.23

Several investigators have hypothesized an infectious etiology for childhood ALL. Greaves has postulated that two genetic events — one occurring in utero and a second following antigenic stimulation — may underlie childhood ALL. He suggests that among infants whose exposure to pathogens is delayed, proliferation may occur in the preleukemic clone.24 Kinlen believes that exposure to a yet-unidentified viral infection leads to ALL as a rare outcome, particularly when infectious and susceptible populations come into contact. He has identified several studies demonstrating a significantly increased incidence of leukemia in situations where different populations mix, such as urban and rural populations or groups with very different socioeconomic backgrounds.25 These hypotheses are not wholly inconsistent; abnormal immune responses to infection could be leukemogenic. Although numerous small clusters of childhood ALL have been observed in the United States, no specific environmental etiology has been identified.26
However, a recent meta-analysis has demonstrated an association of daycare attendance before age 2 with reduced risk of pediatric ALL; investigators have suggested that the hygiene hypothesis, originally proposed as a risk factor for asthma, may also apply to ALL; early daycare attendance is hypothesized to be a marker of early exposure to pathogens, which may protect against ALL.

Treatment of childhood ALL consists of several phases of combination chemotherapy to induce remission, to eradicate leukemia cells in the central nervous system, and ultimately to suppress leukemic cell growth. Sibling or unrelated donor stem cell transplantation may be employed for children with relapsed or refractory ALL and for those with other poor prognostic features, as will be discussed in subsequent chapters (see Chapters 11, 12 and 20). Five-year survival for ALL has increased substantially in the past 35 years and is currently 89.2% for children aged 0–14 and 85.9% for children and adolescents aged 0–19.

**Acute myelogenous leukemia**

Acute myelogenous leukemia (AML) is an aggressive cancer of myeloid precursor cells that crowd the bone marrow and interfere with normal hematopoiesis (see Chapter 13). It is estimated that 12,810 individuals, more than 800 of whom were younger than 20 years, were diagnosed with AML in the United States in 2009. AML is primarily a disease of older adults, with a median age at diagnosis of 67 years. AML incidence rates have a J-shaped age distribution. Among children aged 0–14 years, the AML incidence rate is 0.8 per 100,000 per year, but among infants (<1 year old), the rate is 2.1 per 100,000 per year. In adolescents (15–19 years), the incidence rate is 1.0 per 100,000 per year and continues to rise through middle and older age groups, peaking at 22.9 cases per 100,000 among those aged 80–84. AML is the second most common leukemia in childhood, representing 16% of leukemias in children and adolescents aged 0–19.

Although age-adjusted AML incidence rates are higher among males than among females (4.3 per 100,000 in males and 2.9 per 100,000 in females), age-specific rates are similar in males and females younger than 30 years. AML is slightly more common in whites (3.6 per 100,000) than blacks (3.0 per 100,000) overall. Like that of childhood ALL, childhood AML incidence increased significantly between 1975 and 2006 (63.3% in children aged 0–14), with an average annual increase of 1.4%.

Treatment of AML employs combination chemotherapy to induce disease remission. Consolidation therapy for pediatric AML generally consists of high-dose chemotherapy or stem cell transplantation. Treatment regimens will be reviewed in subsequent chapters (see Chapters 13 and 20). Like that of patients with ALL, the survival of patients with AML has increased substantially in the past 35 years; five-year survival is currently 60.2% for children aged 0–14 and 55.0% for children and adolescents aged 0–19. Although pediatric AML carries a less favorable prognosis than ALL, children and adolescents with AML have a far better 5-year survival rate than the general population of AML patients, whose 5-year survival is only 23.8%.

**Chronic myelogenous leukemia**

Chronic myelogenous leukemia (CML) is a neoplasm of pluripotent stem cells still capable of terminal differentiation (see Chapter 15). It is uniformly associated with the presence of the *BCR-ABL* fusion gene; 95% of patients have a translocation involving chromosomes 9 and 22. Some 5,050 Americans, of whom approximately 120 were aged 0–19 years, were diagnosed with CML in 2009; the median age at diagnosis is 66 years. The incidence of CML approaches 0.1 per 100,000 in children aged 0–14 years and increases to 0.2 per 100,000 among those aged 15–19 years. CML accounts for approximately 3% of leukemias in children and adolescents aged 0–19. Like the acute leukemias, CML has a male predominance; incidence rates are 1.9 per 100,000 among males and 1.1 per 100,000 among females. In children and adolescents, however, CML is similarly rare in both sexes.

Chronic myelogenous leukemia is associated with slow progression from indolent growth in chronic phase, through an acute phase characterized by treatment failure and worsening hematologic derangements, to a blast crisis similar to that in the acute leukemias. Historically, busulfan, hydroxyurea, and interferon-α were used for cytodestruction in chronic phase CML. However, the development and success of tyrosine kinase inhibitors (such as imatinib) that target the *Bcr-abl* fusion protein has changed the treatment of CML. Upfront therapy with imatinib has become the standard care for most patients with pediatric CML. Although tyrosine kinase inhibitors are not curative therapy, they achieve very high rates of cytogenetic response and can extend survival substantially. Allogeneic stem cell transplantation offers the potential for cure,
although it entails substantial risks of morbidity and mortality, particularly for unrelated donor transplants. Children with CML undergoing matched sibling donor transplantation in chronic phase have had 60–75% 5-year relapse-free survival, while those undergoing matched unrelated donor transplantation have had less favorable 5-year survival rates, approximately 55% in one recent large study. In some pediatric patients, such as those in whom tyrosine kinase inhibitors fail to control disease, or those in accelerated phase or blast crisis, allogeneic stem cell transplant from related or unrelated donors may clearly be indicated. Subsequent chapters will review the therapeutic approach to childhood and adolescent CML. Significant unresolved questions remain regarding the ideal front-line treatment of CML in this population.

**Chronic lymphocytic leukemia**

Chronic lymphocytic leukemia (CLL) is a clonal proliferation of B lymphocytes arrested in differentiation. Although CLL is the most common leukemia, with 15,490 new diagnoses among Americans in 2009, it primarily affects older adults; the median age at diagnosis is 72. Cases of CLL in children and adolescents are vanishingly rare. Those described in case reports may be associated with a translocation involving chromosomes 2 and 14.

**Myelodysplastic syndromes**

The myelodysplastic syndromes (MDS) are a group of disorders characterized by clonal proliferation of pluripotent hematopoietic stem cells, resulting in disordered and ineffective hematopoiesis (see Chapter 15). MDS in the setting of the congenital marrow failure syndromes, severe aplastic anemia, or prior chemotherapy or radiation therapy is known as secondary MDS. MDS/AML observed in the setting of DS is considered to be a separate entity, as previously discussed. Other cases of MDS are considered “primary” or “de novo,” but may still be associated with genetic predisposition. Monosomy 7 or loss of the long arm of chromosome 7 occurs in approximately 30% of childhood MDS cases and 50% of therapy-related MDS. Abnormalities of chromosome 5 are frequently observed in adult MDS but are very rare in childhood MDS.

Childhood MDS is very rare; in the United Kingdom, which has an MDS registry, the incidence rate of non-DS-related MDS among children under 15 is estimated at 0.81 per million (0.66 per million for de novo MDS). In Denmark and British Columbia, incidence rates are estimated at 2.1 per million and 1.4 per million, respectively.

Myelodysplastic syndrome may progress to AML. Different subtypes of MDS demonstrate differing rates of progression; patients with the subtype of MDS known as refractory anemia with excess blasts (i.e. 5–20% marrow blasts) have approximately 50% risk of developing AML within 5 years; patients with less than 5% marrow blasts have a 20% 5-year risk of progression to AML.

**Juvenile myelomonocytic leukemia**

Juvenile myelomonocytic leukemia (JMML) is a rare hematopoietic disorder of early childhood characterized by uncontrolled proliferation of monocytes and granulocytes, as well as myelodysplastic features of anemia and thrombocytopenia (see Chapter 14). According to the UK MDS registry, the JMML incidence rate is estimated at 0.69 per million among children under 15. In Denmark and British Columbia, estimates are 1.3 and 1.0 per million, respectively. JMML usually presents in children younger than 6 years; the median age at diagnosis is 2 years. Later presentation of disease is an adverse prognostic indicator.

About 11% of JMML patients have neurofibromatosis type 1, an autosomal dominant disorder found in 1 in 4,000 births and characterized by café au lait spots on the skin and predisposition to neurofibromas, and schwannomas. A genetic defect in the NF1 gene underlies neurofibromatosis type 1; NF1 is a negative regulator of the Ras signal transduction pathway. For children born with one defective copy of Ras, a second somatic mutation in NF1 can lead to uncontrolled Ras activation and cell proliferation. Indeed, the pathogenesis of JMML is related to abnormalities in the Ras signaling pathway. Similar to MDS, JMML is associated with monosomy 7, which is found in approximately 25% of cases. However, many cases are associated with a normal karyotype. Standard chemotherapy is generally ineffective in treating JMML and allogeneic stem cell transplantation offers the only potential for cure. Even with stem cell transplantation, the high risk of leukemic relapse lowers 5-year event-free survival to only 50%.

**The Lymphomas**

The lymphomas are cancers of the lymphatic system, which consists of lymph (interstitial fluid similar to blood
plasma, containing white blood cells and other components) and the lymphatic vessels, lymph nodes, and other lymphatic organs (tonsils, spleen, thymus, and Peyer patches on the small intestine) through which the lymph circulates (SEER training). Lymphomas are categorized by cell type as T-cell, representing about 10% of lymphomas, or B-cell, representing the other 90%. Chapter 2 of this volume deals with the 2008 World Health Organization (WHO) classification of lymphomas.

Lymphoma incidence rates rise with age, although patterns of incidence vary by cell type. All the lymphomas diagnosed among children are more common among adults; some types found among adults are virtually unknown among children. These include the chronic/small/prolymphocytic/mantle and B-cell NHLs, which account for more than 15% of adult lymphomas. Malignant lymphoma is the most common cancer affecting adolescents.46 Overall, lymphoma incidence has been rising in the past few decades.47 Although lymphomas have generally been more common among whites than non-whites, the recent increase is greater and the age distribution is younger among blacks than among whites. Lymphomas are overall more common among males than females, although the gender difference is smaller among adults than among children.

Hodgkin lymphoma

Hodgkin lymphoma, first described by the British pathologist Thomas Hodgkin in 1832, is usually distinguished from the many and collectively more common NHLs. Four cell types of HL have been identified: nodular sclerosing (NS), lymphocyte predominant (LP), lymphocyte depletion (LD), and mixed cellularity (MD) (see Chapter 18). Most, but not all, HL involves B cells. Although rare among young children, HL is the most common cancer of young adults and the most common hematologic malignancy among males and females aged 15–30 years (Figs. 1.2A–B) (see Chapter 3). Incidence rates are less than 1.0 per 100,000 per year among children younger than 10 years, 1.0 among those aged 10–14 years, and rise to 4.0 per 100,000 among those aged 15–30 years (The age distribution of HL incidence is bimodal, peaking for the second time among persons aged > 55 years.). Among children < 15 years, HL is at least twice as common in males as in females. In older age groups, the gender difference is not evident (Figs. 1.2A–B). Unlike the incidence rates of the NHLs, those of HL had been relatively stable in the final decades of the 20th century, but they now appear to be rising overall, especially among individuals aged 20–29 years.

Family history is a strong risk factor for HL, especially among relatives of young probands. In a study conducted in the Swedish and Danish cancer registries, linked to other registries, first-degree relatives of cases diagnosed at age < 40 years had a fourfold increased risk compared to relatives of controls; the associations were stronger for siblings than for parents or offspring and for male than for female relatives of probands,48 although the latter association may reflect the generally higher risk in males than in females.

For more than a decade, the Epstein–Barr virus (EBV) has been understood to play a causal role in HL, especially among young children.49 EBV has been identified in close to 50% of patients < 15 years and 25% of those aged 15–35 years.50 In specimens from those patients, the multinucleated Reed–Sternberg cells that confirm the diagnosis of HL contain the EBV genome, and EBV gene products are expressed in those cells. Other viruses have also been associated with HL. An association with human immunodeficiency virus (HIV) is well established, but most HL patients with HIV also appear to have EBV (see Chapter 19).51 Measles virus has been associated with HL41 in some, but not all, studies.42

In the 0–14 age group, patients diagnosed with HL have more siblings and come from families of lower socioeconomic status (SES) than controls. Incidence rates are higher in developing countries than in industrialized countries43–44; they are highest in Western Asia and North Africa. Among adolescents and young adults 15–35 years of age, those associations are generally reversed. The socioeconomic risk factor pattern among young children is consistent with an etiology involving infectious agents (viruses) and underdevelopment of the immune system that may be genetic in origin. The pattern among adolescents and young adults may reflect a relative lack of exposure to infectious agents in childhood among individuals of higher SES, and the expansion of social networks that leads to EBV and infectious mononucleosis among college-age youth and young adults. In a study of EBV and lymphoma among 18,642 organ transplant recipients in Europe, North America, and Australia, 40% of kidney transplant patients aged 0–9 years, 70% of those 10–19 years, 85% of those 20–29 years, and ≥ 90% of older patients were EBV-seropositive prior to transplant.45 EBV prevalence among transplant recipients may not be representative...
of EBV prevalence in the general population, but its association with age is unlikely to be very different.

Among young children, the histology of HL, especially EBV-related HL, is most commonly of mixed cellularity; among adolescents and young adults, it is predominantly nodular sclerosis.

Autoimmune disorders, notably rheumatoid arthritis and systemic lupus erythematosus, sarcoidosis, and immune thrombocytopenic purpura have been associated with HL, but their relevance to adolescents and young adults is difficult to establish because of the very small numbers of cases and controls in that age group with a history of such disorders.

Survival among young people with HL is one of the great success stories of hematology and oncology in the latter part of the 20th century and HL treatment has played a key role in the development of the field. In the 1940s, the effects of nitrogen mustard and radiation therapy on the lymphatic system were discovered; the implications of the discoveries for HL were quickly explored in clinical trials. Subsequently, chemotherapy was introduced and steadily improved. Five-year survival among children, adolescents, and young adults is now >90%. However, the increasing numbers of HL survivors have found themselves at risk for second cancers and other late effects of treatment (see Chapter 24). Many patients who received radiation therapy prior to puberty before standard doses were lowered, have experienced bone or soft tissue hypoplasia. Doxorubicin has been found to have greater cardiotoxicity among children than among adults. Treatment can also have adverse effects on fertility. Second malignant neoplasms associated with prior HL and its treatment include leukemias, sarcomas, and breast, thyroid, gastrointestinal, and lung carcinomas; overall, HL survivors have more than a 10-fold higher risk of those malignancies than the general population. These increased risks may be due in part to the HL or to the exposures that caused it, but they are also clearly related to treatment. Both overall and HL-specific mortality risk have been associated with low SES and non-white race. Improvements in long-term survival and quality of life for patients with HL depend on modifying existing treatments, facilitating access to care, and developing new treatments with fewer side effects.

**Non-Hodgkin lymphoma**

The past few decades have seen a dramatic rise in the incidence of NHL, except in the youngest age groups. In the United States, from the 1970s to the 1990s, rates increased by 3–4% each year, and NHL became the fifth most commonly diagnosed malignancy. However, among children, adolescents, and young adults < 30 years of age, NHL is still less common than HL (Figs. 1.2A–B).

Like HL, NHL is associated with the male gender, family history, infectious agents, autoimmune disorders, immunosuppression, birth order (at least for some cell types) and perhaps some chemical exposures, mainly in the setting of occupational exposures (Table 1.3). An association with white race has also been observed. The most common NHLs are diffuse large B-cell lymphoma, lymphoblastic lymphoma, anaplastic large cell lymphoma, and Burkitt lymphoma (see Chapters 16 and 17).

<table>
<thead>
<tr>
<th>Table 1.3. Etiologic factors in lymphoma.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subtype</strong></td>
</tr>
<tr>
<td>HL</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>NHL</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>DLBCL</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>BL</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>LL</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>ALCL</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>PMBCL</td>
</tr>
</tbody>
</table>
**Diffuse large B-cell lymphoma (DLBCL)**

Diffuse large B-cell lymphoma (DLBCL) is the most common NHL among adolescents and young adults in industrialized countries, and the second most common, after Burkitt lymphoma, among children. Nearly 40% of new lymphoma cases in adolescents and about 20% in children under 14 years are DLBCL. However, incidence rates are lower than 1 per 100,000 per year for those aged 0–20 years and rises above 1 per 100,000 only for those older than 25 years. Pediatric patients have better outcomes than older patients, possibly because treatment strategies or tumor biology vary by age group. Birth order (having many older siblings) has been associated with DLBCL. Congenital immunodeficiency syndromes, including ataxia telangiectasia and Wiskott–Aldrich syndrome are associated with a 10–15% risk of DLBCL.

**Burkitt lymphoma (BL)**

Burkitt lymphoma (BL) is the most common childhood cancer in much of tropical Africa; it is much less common in industrialized countries, including the United States; incidence rates hover around 0.6 per 100,000 per year among males and 0.2 per 100,000 among females aged 0–30 years. Among children, it is 3–4 times as common among males as among females. Overall, BL has been found to have a trimodal age-specific incidence pattern, with peaks near ages 10, 40, and 75 years among males; the peak near age 40 years is much less pronounced among females than males. From 1982–1985 to 2002–2005, incidence rates in the US population aged 0–20 years increased from 0.41 to 0.55 per 100,000 or 34%, but the increase in older age groups was much greater. Data from Surveillance Epidemiology and End Results (SEER) for those aged 0–29 years illustrate the increase and the peak around age 10 years. In Africa, BL also has almost the same geographical distribution as *Plasmodium falciparum* malaria; mosquito eradication programs and sickle cell trait are associated with reduced risk of BL. Most adult-onset BL also appears to be AIDS-related. Both DLBCL and BL are also associated with EBV.

**Lymphoblastic lymphoma**

Lymphoblastic lymphoma is a T-cell lymphoma that overlaps in many respects with T-cell lymphoblastic leukemia. It is the second most common NHL among patients younger than 15 years, but is less common in older adolescents and young adults. Incidence rates are 0.4 per 100,000 among children younger than 5 years but close to 0.1 per 100,000 in older age groups. It is similar to pediatric T-cell acute lymphoblastic leukemia in gender and age, but generally does not present with bone marrow involvement. In Africa, LL has been associated with HIV.

**Anaplastic large cell lymphoma (ALCL)**

Anaplastic large cell lymphoma (ALCL) is a relatively rare NHL, with incidence rates of about 0.2 per 100,000 per year overall. About 13% of NHL among children, and somewhat more among adolescents, but much less among adults is ALCL.

**Primary mediastinal B-cell lymphoma (PMBCL)**

Primary mediastinal B-cell lymphoma (PMBCL) is another rare NHL that has been classified by WHO as a subtype of DLBCL but appears to be a distinct entity that also has some features of classical HL. Although the varying descriptive features of the various cell types suggest differences in etiology, their rarity makes it difficult to study them, and their commonalities also appear to be informative.

For example, an important clue to the etiology of the NHLs among children is the occurrence of post-transplant lymphoproliferative (usually B-cell) disease, a relatively common complication of organ transplantation, probably due to the immunosuppression that transplantation requires. Risk is greatest among children who are EBV- or CMV-negative prior to receiving a transplant from an EBV- or CMV-positive donor. A similar risk factor is atopic dermatitis treated with topical steroids. Immunosuppression favors infectious agents, perhaps in the presence of a genetic factor or factors that also facilitate malignant transformation.

Other environmental factors that may play a role in pediatric lymphomas as well as other cancers are agricultural chemicals and occupational exposures of parents. Future studies with larger samples may make it possible to home in on these exposures and to develop effective interventions to improve outcomes for children, adolescents, and young adults at risk.

As Figs. 1.4A–B shows, survival continues to improve for most lymphoma subtypes, but is better for children and adolescents than for young adults. Tai et al. suggest that lack of health insurance leading to late...
diagnosis contributes to the inferior survival of young adult patients.

Conclusions

If childhood cancers were as common as adult cancers, their etiology would be much better understood. The example of lung cancer and smoking illustrates the contrast. The rise in smoking prevalence preceded the identification of the causal role of smoking in lung cancer by about 20 years; without that increase, lung cancer would still be rare and the association might still be controversial. Childhood cancers, by definition, take less than 20 years from initial exposure to diagnosis, but because cancers in the young are, fortunately, rare it has generally been difficult to identify and recruit enough cases for well-designed epidemiologic studies. Even to the extent that etiologic agents are known, the rarity of childhood cancer is a deterrent to effective prevention. For example, EBV is now implicated in HL as well as several NHL, but EBV infection is almost ubiquitous. The pathway by which it increases the risk of lymphoma, the co-factors in that pathway, and their relationship to specific lymphoma subtypes need to be much better understood. Other infectious agents, genetic factors, and other environmental factors, such as nutrition, are likely to affect individual risk and specific disease outcome. Age at exposure may also play a role, as it does in the hygiene hypothesis invoked to explain the rise of asthma. However, childhood ALL rates have not risen in parallel with asthma rates. The crossover association between socioeconomic status and HL is also suggestive of a similar pattern.

The acquired immune deficiency (AIDS) epidemic and the related rising rates of lymphoma among children and young adults, especially in the third world, are tragic. However, they give us the opportunity to observe whether AIDS treatment increases risk by prolonging life or reduces risk by addressing the immunocompromised state; and the role of concomitant tuberculosis and other co-infections and their treatment may also be instructive. Studying these patterns may help us to improve outcomes for all children and young adults with hematologic malignancies. The dramatic successes in treating patients with these diseases have not depended on knowledge of etiology, but they have come at a cost in long-term morbidity and risk of second malignancies. Epidemiologic studies now in progress are identifying etiologic factors, teasing out interactions between infectious agents, and other associations that may provide a basis for more targeted treatments. Such treatments may lead to further improvement in outcomes for young patients and those at risk for hematologic malignancies.

References


