ALL as an adult. ALL was diagnosed in 6020 persons and AML in 18,860 persons in the United States in 2014.

The preponderance of evidence suggests that Hodgkin's lymphoma is of B-cell origin. The incidence of Hodgkin's lymphoma appears fairly stable, with 9190 new cases diagnosed in 2014 in the United States. Hodgkin's lymphoma is more common in whites than in blacks and more common in males than in females. A bimodal distribution of age at diagnosis has been observed, with one peak incidence occurring in patients in their twenties and the other in those in their eighties. Some of the late age peak may be attributed to confusion among entities with similar appearance such as anaplastic large cell lymphoma and T-cell–rich B-cell lymphoma. Patients in the younger age groups diagnosed in the United States largely have the nodular sclerosing subtype of Hodgkin's lymphoma. Elderly patients, patients infected with HIV, and patients in Third World countries more commonly have mixed-cellularity Hodgkin's lymphoma or lymphocyte-depleted Hodgkin's lymphoma. Infection by HIV is a risk factor for developing Hodgkin's lymphoma. In addition, an association between infection by EBV and Hodgkin's lymphoma has been suggested. A monoclonal or oligoclonal proliferation of EBV-infected cells in 20–40% of the patients with Hodgkin's lymphoma has led to proposals for this virus having an etiologic role in Hodgkin's lymphoma. However, the matter is not settled definitively.

For unknown reasons, non-Hodgkin's lymphomas increased in frequency in the United States at the rate of 4% per year and increased 2–8% per year globally between 1950 and the late 1990s. The rate of increase in the past few years seems to be decreasing. About 70,800 new cases of non-Hodgkin's lymphoma were diagnosed in the United States in 2014 and nearly 360,000 cases worldwide. Non-Hodgkin's lymphomas are more frequent in the elderly and more frequent in men. Patients with both primary and secondary immunodeficiency states are predisposed to developing non-Hodgkin's lymphomas. These include patients with HIV infection; patients who have undergone organ transplantation; and patients with inherited immune deficiencies, the sicca syndrome, and rheumatoid arthritis.

The incidence of non-Hodgkin's lymphomas and the patterns of expression of the various subtypes differ geographically. T-cell lymphomas are more common in Asia than in Western countries, while certain subtypes of B-cell lymphomas such as follicular lymphoma are more common in Western countries. A specific subtype of non-Hodgkin's lymphoma known as the angiocentric nasal T/natural killer (NK) cell lymphoma has a striking geographic occurrence, being most frequent in Southern Asia and parts of Latin America. Another subtype of non-Hodgkin's lymphoma associated with infection by human T-cell lymphotropic virus (HTLV) 1 is seen particularly in southern Japan and the Caribbean **(Chap. 225e)**.

A number of environmental factors have been implicated in the occurrence of non-Hodgkin's lymphoma, including infectious agents, chemical exposures, and medical treatments. Several studies have demonstrated an association between exposure to agricultural chemicals and an increased incidence of non-Hodgkin's lymphoma. Patients treated for Hodgkin's lymphoma can develop non-Hodgkin's lymphoma; it is unclear whether this is a consequence of the Hodgkin's lymphoma or its treatment. However, a number of non-Hodgkin's lymphomas are associated with infectious agents **(Table 134-4)**. HTLV-1 infects T cells and leads directly to the development of adult T-cell lymphoma in a small percentage of infected patients. The cumulative lifetime risk of developing lymphoma in an infected patient is 2.5%. The virus is transmitted by infected lymphocytes ingested by nursing babies of infected mothers, bloodborne transmission, or sexually. The median age of patients with adult T-cell lymphoma is ~56 years, emphasizing the long latency. HTLV-1 is also the cause of tropical spastic paraparesis—a neurologic disorder that occurs somewhat more frequently than lymphoma and with shorter latency and usually from transfusion-transmitted virus **(Chap. 225e)**.

EBV is associated with the development of Burkitt's lymphoma in Central Africa and the occurrence of aggressive non-Hodgkin's lymphomas in immunosuppressed patients in Western countries. The majority of primary central nervous system (CNS) lymphomas are associated with EBV. EBV infection is strongly associated with the occurrence of extranodal nasal T/NK cell lymphomas in Asia and South America. Infection with HIV predisposes to the development of aggressive, B-cell non-Hodgkin's lymphoma. This may be through overexpression of interleukin 6 by infected macrophages. Infection of the stomach by the bacterium *Helicobacter pylori* induces the development of gastric MALT (mucosa-associated lymphoid tissue) lymphomas. This association is supported by evidence that patients treated with antibiotics to eradicate *H. pylori* have regression of their MALT lymphoma. The bacterium does not transform lymphocytes to produce the lymphoma; instead, a vigorous immune response is made to the bacterium, and the chronic antigenic stimulation leads to the neoplasia. MALT lymphomas of the skin may be related to *Borrelia* sp. infections, those of the eyes to *Chlamydophila psittaci*, and those of the small intestine to *Campylobacter jejuni*.

Chronic hepatitis C virus infection has been associated with the development of lymphoplasmacytic lymphoma. Human herpesvirus 8 is associated with primary effusion lymphoma in HIV-infected persons and multicentric Castleman's disease, a diffuse lymphadenopathy associated with systemic symptoms of fever, malaise, and weight loss.

In addition to infectious agents, a number of other diseases or exposures may predispose to developing lymphoma **(Table 134-5)**.

TABLE 134-4 INFECTIOUS AGENTS ASSOCIATED WITH THE DEVELOPMENT OF LYMPHOID MALIGNANCIES

Infectious Agent	Lymphoid Malignancy
Epstein-Barr virus	Burkitt's lymphoma
	Post–organ transplant lymphoma
	Primary CNS diffuse large B-cell lymphoma
	Hodgkin's lymphoma
	Extranodal NK/T-cell lymphoma, nasal type
HTLV-1	Adult T-cell leukemia/lymphoma
HIV	Diffuse large B-cell lymphoma
	Burkitt's lymphoma
Hepatitis C virus	Lymphoplasmacytic lymphoma
Helicobacter pylori	Gastric MALT lymphoma
Human herpesvirus 8	Primary effusion lymphoma
	Multicentric Castleman's disease

Abbreviations: CNS, central nervous system; HIV, human immunodeficiency virus; HTLV, human T-cell lymphotropic virus; MALT, mucosa-associated lymphoid tissue; NK, natural killer.

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All lymphoid cells are derived from a common hematopoietic progenitor that gives rise to lymphoid, myeloid, erythroid, monocyte, and megakaryocyte lineages. Through the ordered and sequential activation of a series of transcription factors, the cell first becomes committed to the lymphoid lineage and then gives rise to B and T cells. About 75% of all lymphoid leukemias and 90% of all lymphomas are of B-cell origin. A cell becomes committed to B-cell development when it begins to rearrange its immunoglobulin genes. The sequence of cellular changes,

TABLE 134-5 DISEASES OR EXPOSURES ASSOCIATED WITH INCREASED RISK OF DEVELOPMENT OF MALIGNANT LYMPHOMA

Inherited immunodeficiency disease	Autoimmune disease
Klinefelter's syndrome	Sjögren's syndrome
Chédiak-Higashi syndrome	Celiac sprue
Ataxia-telangiectasia syndrome	Rheumatoid arthritis and systemic lupus erythematosus
Wiskott-Aldrich syndrome	Chemical or drug exposures
Common variable immunodeficiency disease	Phenytoin
Acquired immunodeficiency diseases	Dioxin, phenoxy herbicides
Iatrogenic immunosuppression	Radiation
HIV-1 infection	Prior chemotherapy and radiation therapy
Acquired hypogammaglobulinemia	