chapter 1

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Epidemiology of hematological malignancies

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incidence rates

Hematological malignancies comprise a collection of heterogeneous conditions, all originating from cells of the bone marrow and the lymphatic system. There are three major groups: leukemia, lymphoma, and plasma cell neoplasms. In general, in Western countries the overall incidence of hematological malignancies appears to be rising but it is very difficult to describe in a consistent and uniform way their epidemiological behavior, especially in Europe. The number of European Union (EU) Member States has increased and this expansion enlarged the Union to incorporate a diversity of peoples with a much larger degree of heterogeneity in lifestyle habits and disease risk, as well as in cancer incidence and mortality (either overall or site-specific). Moreover, there is not a unique European reporting system or registry for hematological cancers, so the estimation of the exact number of patients is difficult. In addition, the comparison of the incidences reported by various European registries may be biased because their populations can be predominantly either urban or rural, or because there are differences in the methodology and accuracy of registration.

The number of new patients in Europe diagnosed with hematological malignancies in 2005 can be estimated in ~230 000 patients. These new cases of leukemia, Hodgkin's and non-Hodgkin's lymphoma (NHL) and myeloma account for ~8% of all the new cancer patients diagnosed in Europe and the estimated deaths from these tumors account for ~7% of the cancer-related deaths in 2005. Incidence rates for the main hematological cancers in Europe and the United States are summarized in Tables 1 and 2.

leukemia

Worldwide, over 250 000 people are diagnosed with leukemia each year, accounting for 2.5% of all cancers. An estimated 75 700 new patients of leukemia will be diagnosed in Europe in 2005. All age groups can be affected; leukemias are the most common pediatric tumor (~35% of cancers in children aged 0–14 years). Most cases, however, occur in older adults; more than half after 65 years of age.

In the United States SEER registries, from 1998 to 2002, the median age at diagnosis for leukemia was 67 years. Approximately 11% were diagnosed under age 20; 11% between 20 and 44; 10% between 45 and 54; 14% between 55 and 64; 21% between 65 and 74; 23% between 75 and 84; and 10% after 85 years of age.

Leukemias are usually divided into four major categories, with different clinical features and prognosis: acute lymphocytic leukemia, chronic lymphocytic leukemia, acute myelogenous leukemia, and chronic myelogenous leukemia.

The incidence rates for all types of leukemia are slightly higher among males than among females. There are also geographical and ethnic variations in leukemia rates. In the United States, the incidence is higher in Caucasians than in Afro-Americans and Hispanics. The American Indians/Alaskan natives have the lowest incidence rates. Trends in overall incidence of leukemia have generally been stable or slowly increasing. A substantial reduction in death rates from acute lymphoblastic leukemia (ALL), particularly in childhood, however, have been observed since the 1970s, thanks to advances in treatment and subsequent improvement in survival.

acute myelogenous leukemia (AML)

AML is mainly an adult's disease with a median age at presentation of 64 years. It accounts for ~30% of all leukemias in adults, and ~18 000 new patients are diagnosed in Europe each year, representing ~0.6% of all cancers. The annual incidence rate in Europe ranges from two per 100 000/year to four per 100 000/year. In the past decade, the trend in overall incidence of AML has generally been stable or slowly increasing in most European countries. Incidence in England and Wales, however, has risen by ~70% in both sexes since 1971.

chronic myelogenous leukemia (CML)

Most cases of CML occur in adults with a median age at presentation around age 60. CML comprises only ~2%–3% of all the leukemias diagnosed in patients <20 years of age but the incidence increases with age slowly until the mid-40s, then more rapidly from about one per 1000 000/year in children <10 years to two per 100 000 in people in the fifth decade to one per 10 000 at age ≥80. The disease is more common in males. There is no clear evidence of geographical or ethnic background that predisposes to CML; however, in the United States the incidence is slightly higher in Caucasians than in Blacks or Hispanics.

acute lymphoblastic leukemia

ALL is uncommon in adults, where it represents ~15% of leukemias, but is the most common form of leukemia in people

Table 1. Estimated new cases of hematological cancers in 2005

	Europe	EEA[a]	European Union	United States
	No. of cases	No. of cases	No. of cases	No. of cases
Lymphomas	121 200	104 600	101 400	63 740
Non-Hodgkin's lymphoma	ND[b]	64 400	62 300	56 390
Hodgkin's lymphoma	ND[b]	10 500	10 300	7350
Multiple myeloma	ND[b]	29 700	28 700	15 980
Leukemia	75 700	55 800	54 400	34 810

[a]EEA plus Switzerland: 25 European Union countries plus Iceland, Liechtenstein, and Norway.
[b]Could not be estimated with adequate precision due to coding classification used in some countries.
Europe: EEA plus Albania, Belarus, Bosnia and Herzegovina, Bulgaria, Macedonia, Moldova, Romania, Russian Federation, Serbia and Montenegro, Switzerland, and Ukraine.
EEA, European economic area; ND, not determined.

Table 2. Age-adjusted SEER incidence and United States death rates and 5-year relative survival rates by cancer type, sex and time period

Type	Incidence[a] 1998–2002			United States mortality[b] 1998–2002			Survival[c] 1995–2001		
	Total	Males	Females	Total	Males	Females	Total	Males	Females
Lymphoma	21.8	26.3	18.2	8.6	10.8	7.0	64.2	62.3	66.6
Hodgkin's lymphoma	2.7	3.0	2.4	0.5	0.6	0.4	85.3	83.8	87.0
Non-Hodgkin's lymphoma	19.1	23.2	15.8	8.1	10.2	6.6	60.2	58.2	62.6
Myeloma	5.5	6.9	4.5	3.8	4.7	3.2	32.4	36.1	28.4
Leukemia	12.2	15.9	9.4	7.6	10.2	5.8	47.6	48.3	46.7
Lymphocytic	5.6	7.5	4.0	2.2	3.1	1.6	71.4	71.2	71.7
Acute lymphocytic	1.5	1.7	1.4	0.5	0.6	0.4	64.6	64.1	65.3
Chronic lymphocytic	3.6	5.1	2.4	1.6	2.3	1.1	74.2	73.0	76.0
Other lymphocytic	0.4	0.7	0.2	0.1	0.2	0.1	78.7	82.5	68.8
Myeloid and Monocytic	5.8	7.3	4.7	3.5	4.6	2.8	25.6	25.1	26.2
Acute myeloid	3.8	4.7	3.1	2.6	3.4	2.1	19.8	18.8	20.9
Chronic myeloid	1.6	2.1	1.2	0.6	0.8	0.5	39.0	38.3	40.1
Acute monocytic	0.3	0.4	0.2	0.0	0.1	0.0	16.7	17.2	16.5
Other myeloid and monocytic	0.2	0.2	0.1	0.2	0.3	0.1	25.9	26.0	23.2

[a]SEER 13 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, and Rural Georgia).
[b]NCHS public use data file for the total United States.
[c]SEER nine areas.
Incidence and death rates are per 100 000 and are age-adjusted to the 2000 USA standard population (19 age groups—Census P25–1130).
From: http://seer.cancer.gov/csr/1975_2002/resuls_merged/topic_survival.pdf

<20, accounting for over 80% of all leukemia patients and for 30% of all cancers in children The incidence rate of ALL among 1- to 4-year-old children is >10 times greater than in the young adults aged 20–24. About 10 000 new cases are diagnosed in adults in Europe each year, with incidence rates between two and four per 100 000/year, roughly similar to the rates in other developed continents. ALL is slightly more common in men than in women.

chronic B-cell lymphocytic leukemia (CLL)

CLL is a disease of the elderly, with nearly no patients before age 30, ~90% of cases occurring after age 50 and a median age of presentation of 70 years.

CLL is the most common leukemia in adults in many Western countries, but it is rare in Asia and possibly also in Americans of Asian descent. In the United States, in the 1998–2002 time period, the age-adjusted incidence rate was 3.6 per 100 000/year and CLL was the most common leukemia type among white adult males The incidence of CLL in Japan is at least 4–5 times lower than that in Western countries. The basis for this ethnic and geographic variation is unknown. In a recent epidemiologic study, neither birthplace nor socioeconomic state accounted for this difference suggesting a role for genetic or other environmental factors

lymphomas

Malignant lymphomas constitute a heterogeneous group of neoplasms deriving from cells of the immune system [either B or T/natural killer (NK) lymphocytes] and primarily arising from lymphoid organs and tissues but also in organs normally devoid of lymphocytes. The term extranodal lymphoma usually refers to the latter group that comprises about one third of the patients.

Malignant lymphomas comprise Hodgkin's lymphoma (HL) and NHLs, which consist of >30 separate disease entities with different morphology, immunologic and genetic profile, and clinical behavior. This variety, as well as the repeated changes over time in lymphoma classification systems, have made it difficult to study their epidemiology.

About 120 000 Europeans were diagnosed with lymphoma in 2005, at least three of four of them with NLH, the rest with HL.

Hodgkin's lymphoma

The incidence of HL is about three per 100 000 in Western Europe and the United States, consistently lower than that of NHL and has remained stable over the last 25 years, with possibly a slight decrease of the incidence in males.

Lower incidence rates have been reported for Asia, especially Japan and China, suggesting genetic resistance to disease development, possibly associated with human leukocyte antigen type, as well as environmental influences in the etiology of HL. Indeed, recent population-based studies from the United States and several Asian countries, showed a quite low incidence in all Asian subgroups. HL incidence rates were approximately two times higher in the United States Asians than in native Asians and in both groups, rates were lower for Japanese and Chinese than for Filipinos and Asian Indians.

Hodgkin's disease can occur in both children and adults. It is more common, however, in two age groups: early adulthood (age 15–40, usually 25–30) and late adulthood (after age 55). About 10% of cases are diagnosed in young boys before 15 years of age but the disease is very rare before 5 years of age.

non-Hodgkin's lymphomas

The overall incidence of NHL has steadily risen in most developed areas of the World between the 1970s and the late-1990s. While other cancers have increased ~25% in the past 25 years, NHL has increased >80%; in the population over the age of 65, the rate of NHL has tripled. Some of the rise may be related to acquired immunodefiency syndrome (AIDS) and some may be the results of better diagnosis but the causes of this long-term increase are largely unknown, though, age-related immunodeficiency is likely involved.

In the early 2000s, NHL in Western countries has become in general the sixth most common cancer in males (after prostate, lung, colon and rectum, bladder and melanoma) and the fifth most common cancer in females (after breast, lung, colon and rectum, uterine corpus). It represents the third most common neoplasm group in children (after ALL and central nervous system tumors). The incidence of NHL is usually slightly higher in men than in women and this difference is more marked in younger than older individuals.

The most common histological subtype, diffuse large B-cell lymphoma, accounts for ~40% of NHL and occurs more frequently among males than females at middle age and among whites than blacks at older ages. Follicular lymphomas account for ~20% of NHL, are more common in whites and occur almost equally in men and women.

Distribution of the most common subtypes of NHL (diffuse large B cell and follicular) appears to differ by geographic region, suggesting differences in etiologic or host factors. The difference is particularly striking for follicular NHL, which is most common in North America and Western Europe, and for Burkitt's lymphoma, which is endemic in equatorial Africa, but constitutes only 1%–2% of lymphomas in the United States and Western Europe. In Western countries, NHL is more commonly of B-cell origin; a higher frequency of T-cell diseases is seen in the Far East.

In the majority of NHL patients the disease arises in lymph nodes, but primary extranodal disease accounts for ~30% of new lymphoma patients and often present as localized disease. The most frequent primary extranodal sites are the stomach, small intestine, skin, and brain. Incidence rates increased 3.0%–6.9% per year for extranodal cases, compared to 1.7%–2.5% per year for nodal cases.

plasma cell neoplasms

Multiple myeloma (MM) is a plasma cell malignancy that accounts for <1% of all cancers and for ~10% of the hematological malignancies. MM primarily affects older individuals with the median age of onset of ~65–70 years.

The incidence of MM has been increasing over the past several decades as the elderly population has increased. Incidence rates are similar in Europe and in the United States.

In the EU, the estimated incidence of MM is 5.7 per 100 000/year. In the United States, the age-adjusted incidence rate in the 1998–2002 SEER registries was 5.5 per 100 000 men and women per year. The incidence in African Americans is markedly higher than in whites. The disease is more common in men for all ethnic groups with a male/female ratio of ~1.5 : 1.

etiologic factors

The control and prevention of hematological malignancies will require a precise understanding of their etiology, which is at present largely unknown. Several risk factors, however, have been shown by epidemiological studies to be associated with the development of these diseases.

leukemia

The exact cause of most cases of leukemia is not known. Studies, however, have found a number of conditions that can be associated with a higher risk of leukemia.

ionizing radiation

Several studies of populations exposed to ionizing radiation as a result of military (either participants at nuclear weapons tests or atomic bomb survivors) or occupational circumstances (nuclear workers and people exposed to nuclear power plant accidents) have provided adequate evidence of the association between exposure to a certain level of radiation and development of acute leukemias and chronic myeloid leukemia. Nevertheless, different cell types may have different responses to radiation. The epidemiologic evidence of a link between ionizing radiation and CLL remains weak. Medical irradiation can be another source of exposure. If very high doses are given to a limited tissue volume, cell killing will, however,

predominate over cell transformation and secondary leukemia is a relatively rare event after radiotherapy for cancer. The doses associated with diagnostic radiation procedures are generally very small and not linked to an increased leukemia risk.

electromagnetic fields

In the recent past, a number of reports have indicated that strong electromagnetic fields may be a risk factor for leukemia, although other investigations have failed to confirm these findings. To date, most publications indicate that leukemia seems not related to the exposure to electromagnetic fields.

chemicals

Professional exposure to benzene, formaldehyde, and dioxins is associated with greater risk of leukemia. Organic solvents, agricultural pesticides, and herbicides have been also associated with higher risk. Cigarette smoking is a known lifestyle-related risk factor for leukemia. Potential leukemia-causing carcinogens in tobacco smoke include benzene, polonium-210, and polycyclic aromatic hydrocarbons. It is estimated that ~20% of AMLs can be associated with cigarette smoking.

medical therapy and medical conditions

A previous cancer treatment with both chemotherapy and radiation therapy increases the risk of 'secondary' leukemias. Among anticancer drugs, alkylating agents such as melphalan, busulphan, procarbazine, chlorambucil, and cyclophosphamide and topoisomerase II inhibitors such as mitoxantrone, etoposide, and teniposide have been most commonly associated with the risk of development of secondary myelodysplasia and AML. The risk is higher for combined modality therapy and is well documented for Hodgkin's disease, NHLs, breast, ovarian, and testicular cancers.

Leukemias and lymphomas have been observed in recipients of organ transplants.

Aplastic anemia and myelodysplastic syndrome are associated with an increased risk of leukemia.

genetic disorders

Certain immunological conditions and genetic disorders characterized by chromosomal alterations such as Bloom's syndrome and ataxia telangiectasia appear to predispose to leukemia. Klinefelter's syndrome and Down's syndrome are also associated with a greater risk of leukemia.

infections

The oncogenic retroviruses Human T-cell leukemia virus (HTLV) type-1 and type-2 have been identified as being related to the development of rare types of leukemia and lymphoma. HTLV-1 is endemic in certain areas of Japan, the Caribbean islands areas, Central and South America, and central Africa, and is associated with the development of adult T-cell leukemia or lymphoma (ATLL), which accounts for about half of the lymphoid malignancies in the endemic areas. The virus is transmitted mainly from mother to child, especially by breast-feeding. Sexual transmission and blood transfusion are minor routes of infection and cell-free blood products are not infectious. Over one million people in Japan are infected with the virus, and 10–20 million worldwide, but <1000 new patients with ATLL are diagnosed each year. The lifetime risk of developing ATLL is 0.5%–7%, with the highest risk associated with neonatal infection. Low incidence and long latency strongly indicate the accumulation of other genetic mutations is needed for induction of ATLL.

lymphoma

HL

HL is more common in men than in women and the main risk factors are a family history and a previous Epstein–Barr virus (EBV) infection.

Brothers and sisters of HL patients have a higher than average chance of developing this disease, nonfamilial clusters of HL have been observed too, but the evidence for common etiological factors behind such clusters is weak.

Various findings are suggestive of EBV being a factor contributing to oncogenesis in HL. Indeed, the risk of developing the disease is increased up to four-fold in patients with a previous history of infectious mononucleosis, a disease of adolescence caused by EBV. Moreover, HL patients have increased EBV antibody titers at the time of diagnosis and several years before the onset of lymphoma. More definitive evidence for a pathogenetic association is provided by the finding that EBV can be detected in ~50% of classic HL patients in developed countries.

The extent to which occupational factors can increase the risk for HL has not been established; organic solvents, phenoxy herbicides, and wood dust may be involved but the epidemiological evidence is limited and controversial.

NHL

The above-described increase in NHL incidence cannot be completely explained neither by changes in diagnosis nor by the AIDS epidemics and remain largely undefined. Nevertheless, there are a few well established and a number of postulated risk factors that can be implicated.

Immunodeficiency. Immunodeficiency, including both congenital and acquired conditions is the most powerful etiologic factors as summarized in Table 3. NHL is the most frequent malignancy associated with ataxia-telangiectasia or the Wiskott–Aldrich syndrome in young persons, as well as with X-linked lymphoproliferative syndrome or combined immunodeficiency in children. EBV seems to be a cofactor in the NHL development associated with congenital immunodeficiency. These disorders, however, are quite uncommon and their contribution to the NHL increase is limited.

Patients treated with immunosuppressive drugs are at much greater risk for NHL. Polyclonal B-cell proliferation is often seen in organ transplant recipients (either solid organ or allogeneic bone marrow/PBSC) and it can evolve into a monoclonal disease but can sometimes be reversible if immunosuppressive medication is discontinued. Loss of immune control of persistent EBV infection seems to be part of the process.

Table 3. Immunodeficiency associated with an increased risk of lymphoma

Congenital immunodeficiency diseases
Swiss-type agammaglobulinemia
Ataxia-telangiectasia syndrome
Wiskott–Aldrich syndrome
Chédiak-Higashi syndrome
Selective IgA or IgM deficiencies
Severe combined immunodeficiency
X-linked lymphoproliferative syndrome
Common variable immunodeficiency
Omenn's disease
Intestinal lymphangiectasia
Adenosine deaminase deficiency
Purine nucleoside phosphorylase deficiency
Iatrogenic immunosuppression
Organ transplantation
Treatment with cyclosporine or others immunosuppression (including low-dose methotrexate and alkylating agents)
Acquired Immunodeficiency syndrome
Collagenosis and related autoimmune diseases
Sjögren's syndrome
Rheumatoid arthritis
Systemic lupus erythematosus
Hashimoto's thyroiditis
Others
Treated Hodgkin's disease

An excess risk of developing NHL has also been reported among patients with a variety of autoimmune diseases, including rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, and celiac disease. Patients with rheumatoid arthritis or polymyositis treated with methotrexate (MTX) develop EBV-positive lymphomas more frequently than patients treated with other agents that should be equally or more immunosuppressive. It has been suggested that this predisposition may be due to the ability of MTX to induce EBV replication while at the same time producing immunosuppression. Transplant-related NHL as well as those associated with autoimmunity disorders are also relatively rare and cannot explain the rise of NHL in the general population.

NHL represents one of the most common malignancies associated with AIDS. The risk of NHL in persons infected with human immunodeficiency virus (HIV) is >100 times higher than that in the general population. These lymphomas are typically of B-cell origin with high-grade histology (diffuse large cell or Burkitt's lymphoma) and frequently occur in extranodal sites, such as the brain. HIV-related NHL accounts only for a relatively small fraction of NHL. Moreover, with the advent of HAART, after the mid-1990s, the incidence of HIV-associated NHL decreased among HAART users and their survival improved. In a Swiss cohort study, incidence rates and risk of HL, however, have apparently slightly increased in recent years both in men and women with HIV. Since random variation cannot be ruled out, the increase in HL risk among HAART users requires confirmation in other studies with longer post-HAART follow-up.

viruses other than HIV. Some viruses are implicated in the pathogenesis of NHL, probably because of their ability to induce B- or T-cell stimulation and proliferation.

The etiologic role of HTLV-1 in the development of adult T-cell leukemia or lymphoma has been discussed above.

EBV infection unlike HTLV-I, is a highly prevalent infection in the adult population, has been associated with a heterogeneous group of lymphomas, including Burkitt's lymphoma (especially the endemic form in Africa), Hodgkin's disease, NK, and T malignancies with cytotoxic phenotypes, and lymphomas in the immunocompromised patient (congenital immunodeficiency, organ transplantation, AIDS). The role of EBV in contributing to lymphomagenesis is well established in the EBV lymphoproliferative diseases that arise in immunosuppressed individuals. It is, however, less well defined in other EBV-associated lymphomas. Usually, these malignancies respond poorly to standard chemoradiotherapy and immunotherapeutic or pharmacologic strategies targeting EBV are being explored.

Hepatitis C virus (HCV) has been associated with mixed cryoglobulinemia type II and with B-cell lymphomas, especially the splenic B-cell marginal zone lymphoma and the lymphoplasmacytic lymphoma, but also with diffuse large cell lymphomas. The significance of the epidemiologic association between HCV and NHL shows a clear geographic variability, being the association with NHL more evident in the areas (e.g. Italy) with elevated endemic rate of HCV infection. A strong support for the etiological role of HCV in splenic marginal zone lymphoma came from the demonstration of lymphoma regression after HCV treatment.

Human herpes virus 8 (HHV 8) is associated with primary effusion lymphoma in patients with HIV infection and in patients with multicentric Castleman disease. Other viruses (including HHV 6, simian virus 40, HTLV-II and CMV) have been inconsistently reported as associated with lymphomas.

bacterial agents. A significant association has been reported in epidemiological studies between *Helicobacter pylori* infection and gastric lymphomas with either extranodal marginal zone B-cell lymphomas or diffuse large B-cell lymphomas; low grade or high grade. Moreover, the presence of the B-cell clone that will become predominant in the transformation to MALT lymphoma has been demonstrated in the chronic *H. pylori* gastritis that preceded the lymphoma and several clinical studies have reported regressions of gastric MALT lymphoma in more than half of the treated patients after antibiotic eradication of *H. pylori*. The association of *H. pylori* with gastric MALT lymphoma has led to the hypothesis that the microorganism may provide the antigenic stimulus for sustaining the growth of the lymphoma in the stomach. Besides *H. pylori*, other infectious agents are being associated to particular extranodal marginal zone B-cell lymphomas. *Borrelia burgdorferi* may be implicated in the pathogenesis of at least a subset of cutaneous marginal zone B-cell lymphomas. The microorganism can be found in skin lymphomas and a lymphoma complete remission can be achieved with adequate antibiotics therapy. Recently, the presence of *Chlamydia psittaci* has been associated with lymphomas of the ocular adnexa and it has been showed that antibiotic therapy aimed at *C. psittaci* can be followed by

histological regression of these NHL. A wide geographical variability, however, has been found for the epidemiologic association between NHL *C. psittaci* and *B. burgdorferi*. Since the 1970s it was already known that early-stage immunoproliferative small intestine disease, also known as alpha chain disease or Mediterranean lymphoma, may regress after antibiotic therapies eliminating unknown organisms, but only in 2004 this lymphoma has been linked to a specific pathogen, namely *Campylobacter jejuni*. All these data, together with the pattern of somatic hypermutation and ongoing mutations of the immunoglobulin genes, strongly associate the origin of extranodal marginal zone lymphomas from a background of chronic antigenic stimulation associated with infectious conditions (and/or autoimmune conditions).

exposure to agricultural pesticides and other chemicals. The association with the professional use of herbicide, insecticides, and fertilizers has been reported by several studies with high variability of risk estimates among different studies. Occupational exposure to solvents has also been associated with an increased risk. Epidemiological evidence indicates that exposure to the class of chemicals called organochlorines, which includes DDT and other pesticides, polychlorinated biphenols, and dioxins, may result in increased risk of NHL. The association between NHL and pesticide exposures is perhaps the best studied. An increased risk of NHL has been observed repeatedly, but not consistently. Results from a number of epidemiologic studies indicate that the excess risk of NHL is related to the use of phenoxyacetic acid herbicides, organophosphate insecticides, triazine herbicides, and fertilizers. Risk estimates, however, vary widely among studies, and in some studies no risk excess was detected; therefore, the role of agricultural and residential pesticides in the etiology of NHL needs further evaluation.

Other environmental exposures that have been linked with NHL are generally rare, only weakly associated, or on the basis of inconsistent reports. Radiation exposure probably has little effect.

Ultra violet (UV) exposure. Higher risk for developing squamous cell skin cancer and melanoma was reported among patients with NHL and CLL and conversely, patients with squamous cell skin cancer showed an excess risk for NHL and CLL. Therefore, it has been hypothesized that increased exposure to solar UV may have contributed to the incidence rise of NHL in many countries. Most recent studies, however, showed that sun exposure is associated with a decreased risk of NHL, therefore, the association between skin cancer and malignant lymphomas is unlikely to be mediated by UV exposure.

dietary and lifestyle risk factors. The risk of NHL has been linked to increased consumption of animal protein, fat, and meat but the data on diet are not conclusive. Some epidemiologic studies have evaluated the role of alcohol consumption in the etiology of NHL, but the findings have been inconsistent. A meta-analysis of nine case–control studies from the United States, United Kingdom, Sweden, and Italy with a pooled study population of >15 000 individuals, however, found decreased odds ratios among consumers of alcohol. Further studies are needed to determine whether confounding lifestyle factors or immunomodulatory effects of alcohol explain this finding.

Cigarette smoking appears to have no or only a weak association with increased risk of NHL.

Hair coloring products are widely used and contain compounds that are mutagenic and carcinogenic in animals. Several studies have indicated that exposure to hair dyes, particularly long-term use of dark permanent dyes produced before the 1980s, is associated to a moderately increased risk of lymphoma and chronic lymphocytic leukemia.

blood transfusions. Allogeneic blood transfusion has been indicated as a risk factor for NHL, possibly because they can expose the recipients to viruses or other immunomodulating antigens, but the results from epidemiologic studies have been inconsistent. While cohort studies supported the hypothesis, several case–control studies subsequently carried out failed to confirm the findings.

genetic susceptibility. Familial clustering of NHL has been described; it accounts only for a small proportion of NHL and may be due to inherited immune function abnormalities but also to shared exposure to environmental factors. Polymorphisms in genes regulating the inflammatory and the immune response or regulating the antioxidative mechanisms may influence the risk of lymphoma, but there are no conclusive data.

plasma cell neoplasms

Increasing age and a previous monoclonal gammopathy of undetermined significance (MGUS) are the main factors associated with MM. In most cases patients with MM have no known risk factors. Several studies have indicated an association between MM and environmental exposure to chemicals. Slightly higher rates of MM are found among agricultural workers (who are exposed to pesticides and fertilizers), petrochemical and sheet-metal workers, and those professionally exposed to wood dust. The role of viral infections is controversial. In rare cases, MM and MGUS can affect more than one person in a family.

prevention

The control and prevention of hematological malignancies will require a better understanding of the origins of the diseases. Avoiding exposure to risk determinants would result in a reduction in cancer risk. The little we know about the risk factors has not yet been translated into consistent attempts to prevent hematological malignancies. Some general consideration, however, can be done. Avoidance of exposure to radiation and benzene will reduce the risk of leukemias. Banning or restricting the use of organochlorines might on a long term result in reduction of the NHL incidence. About 20% of adult acute myeloid leukemia cases are linked to smoking and here prevention is therefore possible. HIV infection is clearly preventable and also other infectious agents associated with NHL might be the target of preventive measures. Finally, more modern and improved cancer therapies will likely result in a lower incidence of second tumors.