**RESEARCH ARTICLE**

# Epidemiology of Hairy Cell Leukemia (HCL) and HCL-Like Disorders

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**Abstract**

Hairy cell leukemia (HCL) is a very rare and well-defined entity that is characterized by the presence of hairy cells expressing the characteristic markers CD11c, CD25, CD103 and CD123 and in most cases by the presence of the $BRAF^{V600E}$ mutation. The incidence rate, directly adjusted to the 2000 United States standard population is estimated at 0.62 per 100 000 person-years (PA) in white men, 0.21 in black men, 0.20 in Asian men and 0.06 American Indian or Alaska native men. Based on the estimated 2019 leukemia incidence, of 61,780 in the United States, approximately 1,240 new HCL cases are expected per year, with only 60–75 new patients having a variant form of HCL each year. In France, the median age of patients at diagnosis is 63 years in men and 59 years in women. There is a strong male predominance, with a sex ratio of 5:1. HCL is a malignant disorder with a good prognosis, with a standardized average survival at 1 year and 5 years of 95% (95% CI: 91-97 for both). The etiology of HCL remains unknown. The risk of secondary cancers is high, especially that of another malignant hematologic disorder. This high risk justifies the need for prolonged hematological monitoring.

HCL must be distinguished from other HCL-like disorders, including the variant form of HCL (HCL-v) or splenic diffuse red pulp lymphoma (SDRPL), warranting the development of international epidemiologic studies.

**Keywords:** Hairy cell leukemia, epidemiology, incidence, survival, second malignancies

## 1. Introduction

Hairy cell leukemia (HCL), initially reported in 1958 by Bouroncle and colleagues, is an indolent mature B-cell chronic neoplasm (MB-CN) and a well-defined entity in the 4th revised 2016 classification of the World Health Organization (WHO) of hematopoietic and lymphoid tumors and in the 3rd International Classification of Diseases for Oncology (ICD-O-3 code 9940).

The accurate diagnosis of classic HCL is based on the identification of hairy cells in the peripheral blood and/or bone marrow, with a characteristic immunophenotype including high expression of CD19, CD20, CD22 and CD200. The HCL immunologic score, based on CD11c, CD25, CD103 and CD123 expression, is 3 or 4 in HCL (1). The HCL genetic profile is characterized by the presence of the activating BRAF serine/threonine protein kinase mutation ($BRAF^{V600E}$) identified in 2011, which is detected in approximately 80% of HCL cases (2). The mutation, an early genetic event, is the molecular hallmark of the disease and represents a novel diagnostic possibility and option for therapeutic targeting of B-Raf proto-oncogene **(**BRAF) using BRAF inhibitors. Identification of the mutation can also be useful in complex and unclear situations: it is also increasingly frequently used to confirm HCL diagnosis and guide therapeutic strategy. However, the mutation is not specific for HCL and is also observed in 50% of patients with melanoma or Langerhans cell histiocytosis in adults, rarely in non-small cell lung cancers, ovarian cancer, cholangiocarcinoma, thyroid cancer, prostate cancer, bladder cancer, sarcoma/gastrointestinal stromal tumor (GIST) and more rarely in patients with hematological malignancies (HM) such as chronic lymphocytic leukemia (CLL) and multiple myeloma (MM).

We recently proposed an algorithm for HCL treatment (3). Patients with asymptomatic HCL-$_C$ must be managed with a watch-and-wait strategy. In symptomatic HCL patients, past and standard first-line treatments include splenectomy and interferon-alpha (IFNα). Purine nucleoside analogs (PNAs), either cladribine or pentostatin, were subsequently introduced in monotherapy circa the 2000s. PNAs improved overall survival (OS), achieving a 10-year OS of 90%. However, HCL cases treated first-line with PNAs continue to relapse, suggesting that PNAs are usually not curative. In our study including 208 patients treated with PNAs, either cladribine (159 pts) or pentostatin (49 pts) as first-line therapy, the median relapse-free survival (RFS) was 11 years and only 7 years after second-line therapy (4).

HCL must be distinguished from other HCL-like disorders, including the variant form of HCL (HCL-$_V$) (5,6), splenic diffuse red pulp lymphoma (SDRPL) (7,8) and splenic marginal zone lymphoma (SMZL). There are overlaps between all of these entities, and identifying these diseases is a challenge in real life because of the different clinical courses and the need for appropriate treatment.

The few available population-based studies in HCL are very limited. In this review, we present the epidemiological data of HCL and other HCL-like disorders, including data for HCL-$_V$ and SDRPL.

 

## 2. Incidence, geography, ethnicity and demographics

### Hairy cell leukemia

### HCL is a rare mature B-cell chronic neoplasm

In the United States**,** a total of 136,985 cases of hematopoietic neoplasms were diagnosed among residents of 12 Surveillance, Epidemiology, and End Results (SEER) registries, of which 114,548 cases (84%) were lymphoid neoplasms (9). MB-CN (86,896 pts) accounted for approximately three-quarters of all lymphoid neoplasms, Hodgkin lymphoma (9,948 pts) accounted for 8%, mature T/NK-cell neoplasms (6,078 pts) and lymphoblastic leukemia/lymphoma (6,098 pts) each accounted for 5%, and lymphoid neoplasms of unknown type (7,995 pts) accounted for 7%. Among the 86,896 patients with MB-CN, the top five hematologic malignancies were diffuse large B-cell lymphoma (DLBCL) (28%: 24,132 pts), plasma cell neoplasm (predominantly multiple myeloma) (22%: 18,484 pts), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (20%; 16,703 pts), follicular lymphoma (13%:10,606 pts) and various other known or unknown types (16%). A total of only 1,096 HCL patients, 835 men and 261 women, were identified, corresponding to 0.8% of all hematopoietic neoplasms, 0.95% of lymphoid neoplasms and 1.26% of all MB-CN.

### Incidence and ethnicity

**The United States**. Data were obtained between 1992-2001 from the National Cancer Institute's SEER program. The incidence rate after direct age adjustment to the 2000 United States standard population was 0.62 per 100,000 person-years (PA) in white men, 0.21 in black men, 0.20 in Asian men and 0.06 in American Indian or Alaska native men. Based on the estimated 2019 leukemia incidence, of 61,780 in the United States, approximately 1,240 new HCL cases are expected per year (10). The median age of HCL patients was 54 (41-80) years.

**European Union**. The Rarecare project (11) defined rare cancers as those with an annual incidence of less than six per 100,000 people in the European Union (EU). A total of 4,387 HCL cases were observed in 94 European registries, and the estimated number of new HCL cases was 1,417 cases in 2013, with a crude incidence rate per 100,000 people per year of 0.28.

**France.** Three hundred and four new cases of HCL were estimated in 2018, with HCL representing 1.3% (304/23,545) of the MB-CN analyzed. There was a clear male predominance in HCL, with 243 new cases in men (80%) and only 61 (20%) in women. The sex ratio was 5:1. The median age of patients at diagnosis was 63 years in men and 59 years in women. Unlike other hematologic malignancies (HMs), only 19.5% (59 pts) of patients were over the age of 75. The standardized incidence in the world population was 0.5/100,000 PA in men [95% CI: 0.4 - 0.6] and only 0.1 in women [95% CI: 0, 1 -0.1] (12). In men, the incidence increased with age, from 0.2 among those 30-34 years old to 2.2 in those aged 70-74 and 75-79 years, decreasing thereafter. In women, the increase remained less significant, with a rate of 0.1 in the 35-39 age group and 0.4/100,000 PA in the 80 and over age group. The incidence rate remained stable (0.1/100,000) in women between 1990 and 2018 and increased moderately in men, from 0.3/100,000 in 1990 to 0.5/100,000 in 2018 (increase + 1.2% per year) [95% CI: 0.2 - 2.3]. The increase in the number of cases over time could be explained by the aging of the population (life expectancy at birth in France in 2019: 79.8 years for men and 85.7 years for women) but also by easier access to diagnostic examinations, in particular immunophenotypic analysis by flow

 

cytometry and analysis of the $BRAF^{V600E}$ mutation.

## Demographics

**France.** We recently analyzed the demographics of 123 HCL patients included in the Regional Register of Malignant Hemopathies of Western Normandy (RRHMBN) over a period of 20 years (1996-2016). The median age of the patients was 62.0 years (33-97 years) at diagnosis. Lymph node involvement was present in only 3.3% of patients, splenomegaly in one third (33.3%), hemorrhagic manifestations in 6.5% and infections in 19.5%. HCL patients presented with pancytopenia in 20.3% of cases, neutropenia (polymorphonuclear neutrophils $<1x10^9$/L) in slightly more than half of cases (53.7%), anemia (hemoglobin <11 g/dL) in 38.2% of cases and thrombocytopenia in 61.8% of cases. Bone marrow cellularity was reduced in 79.3% of cases, and median hairy cell infiltration was 18% (1-80%). Bone marrow biopsy was performed in 18.7% of cases and FCM cytometry in 68.3%. The immunologic score was assessed in 34% of the cases: 4 in 95% of cases and 3 in 5%. Analysis of the V600E mutation of the BRAF gene was available for only 32.5% of the cohort, and it was identified in all cases in which it was examined.

## HCL-like disorders

## Variant form of HCL

HCL-v, first recognized by Cawley et al in 1980, is a provisional entity in the latest WHO classification. It is an uncommon MB-CN accounting for 10–20% of patients with HCL and 0.4% of chronic lymphoid malignancies, representing approximately 60–75 of new patients with HCL-v each year in the United States (13,14). The disease affects the elderly population without predominance based on sex. The median age of the patients was higher than that observed in HCL, as 71 years (48-92) (18). HCL-v cases are typically characterized by splenomegaly and a high lymphocyte count without neutropenia or monocytopenia. HCL-v cells have an intermediate morphology between prolymphocytes and hairy cells, do not express CD25 and have weak CD123 expression. HCL-v patients lack the BRAF mutation but present activating *MAP2K1* (MEK) mutations in 40% of cases, irrespective of the *IGHV* profile (9), and *CCND3* mutations in 13% (15), with a frequency identical to that of SMZL patients and lower than that of SDRPL patients (16). Recurrent hotspot mutations in *U2AF1*, which encodes a protein belonging to the spliceosome, were also detected in 15% of HCL-v cases (16,17).

## Splenic Diffuse Red Pulp Lymphoma

The provisional entity is characterized by homogeneous infiltration of a large proportion (median 60%) of small- to medium-sized villous lymphoid cells in the peripheral blood (7,8). Monoclonal B cells express CD11c (97%) and CD103 (38%) and rarely express CD123 (16%) or CD25 (3%) in SDRPL. A scoring system based on CD11c, CD22, CD76, CD38, and CD27 was designed to differentiate SDRPL from SMZL. In addition, the CD200/CD180 median fluorescence intensity (MFI) ratio may be helpful to distinguish HCL from SDRPL, with a ratio of 0.5 or less suggestive of SDRPL (18,19). Most cases displayed a mutated IGHV status, with selective IGHV gene usage and overrepresentation of *IGHV4-34*. The *BRAF* V600E in exponent mutation was never detected. Mutations in *CCND3* and *BCOR* genes were identified in approximately a quarter of SDRPL cases (16).

 

## 3. Survival

### Hairy cell leukemia

Before the introduction of PNAs, that is, the gold standard in first-line treatment, the median duration of survival after diagnosis was only 4 years, with patients dying of complications related to cytopenia, particularly hemorrhage and infection. HCL is currently a hematological malignancy with a relatively good prognosis.

**The United States**. Data from Surveillance Epidemiology and End Results (SEER) showed a net 5-year survival of 92.4% (95% CI: 90.6 - 94.2) (1,840 patients), whereas it was only 88% for the same period in Germany (1,247 patients) (20, 21). SEER-17 data including 3,776 HCL patients between 1978 and 2008 showed improved survival over the last calendar period studied (2000-2008), reflecting the impact of important therapeutic development. Increasing age and African American (AA) ethnicity are associated with reduced survival (21). Another study population including SEER-18 data, with 3,033 HCL patients registered between 1973 and 2011, also demonstrated a significantly lower 10-year overall survival among AA individuals compared with other ethnic groups (54% in AA compared to 72% in whites) (22). Further evaluation of the contributory biological, socioeconomic, health system or other factors is needed to investigate such racial differences regarding OS. In a study of the Cleveland Clinic Taussig Cancer Institute including 61 consecutive HCL patients diagnosed between 1995 and 2013, the authors showed that the overall survival of all HCL patients was superior to that of age-, sex- and race-matched US populations (23).

**European Union**. In Europe and particularly the Netherlands, the net 10-year survival also improved over time, increasing in the 60-69 age group from 82% (1989-1993) to 95% over the 2001-2015 period. Moreover, it was 97% over the last period for 18-59-year-olds, 95% for 60-69-year-olds and 83% for those over 70 years old (24).

**France**. In France, survival data for patients diagnosed between 2003 and 2018 show a standardized 1-year net survival of 95% (95% CI: 91-97) and 5-year of 95% (95% CI: 91-97). The small number of women does not allow us to analyze differences in survival based on sex. Standardized net survival decreases with age from 97% (95% CI: 92-99) at 40 years to 92% (95% CI: 85-96) at 80 years.

### Hairy cell –like disorders

### Variant form of HCL and splenic diffuse red pulp lymphoma

The clinical course of $HCL_V$ is variable but usually more aggressive than that of HCL: in a large cohort including 52 $HCL_V$ patients, the median survival was 9 years, and 15% survived beyond 17 years (14). We lack epidemiological data on SDRPL.

## 4. Familial HCL

Data concerning genetic risk factors in HCL are scarce, and only anecdotal rare case reports of familial HCL have been reported in the literature. HCL may be an HLA-linked disorder. In the four familial forms extensively studied, and unlike chronic lymphocytic leukemia (CLL), no allelic variants capable of explaining a genetic predisposition have been identified (25). Note also that first-degree relatives of patients with CLL have a high risk of HCL, with a relative risk (RR) of 3.3 (95% CI: 1.0-10.9) (26). The Swedish Family-Cancer Registry recorded 153,115 malignant hematologic disorders between 1958 and 2015, including 847 patients with HCL. Familial hematologic malignancies represent 4.1% of all malignant hematologic disorders. The relative family

 

risk (FFR) was quantified by calculating the standardized incidence ratio (SIR) among 3,279 relatives. The risk of having CLL in relatives was 8.33 times higher (95% CI 1.01-30.10) in relatives whose ancestors have HCL compared to what is expected in relatives whose ascendants did not have HCL (27).

**Environmental factors and occupational exposure**

Issues related to environmental and exposure risk factors in HCL are unclear. The role of different environmental factors has been evaluated in several studies, including case-control studies (28,29,30,31). The protective role of cigarette smoking was demonstrated in a pooled analysis study of five case-control studies in Europe and Australia, with 154 HCL-C patients and 8,834 control cases (31). Indeed, cigarette smoking was inversely associated with HCL, with an odds ratio (OR=0.52, 95%CI=0.37 to 0.71). HCL risk was more marked in current smokers compared to ex-smokers. The risk was also reduced when the duration of smoking in years increased and the number of cigarettes consumed per day was high as was the number of pack-years. In contrast, the risk increased in people who have lived or worked on a farm, with an OR=1.68, 95%CI=1.04 to 2.71), and in farmers, with an OR=1.55, 95%CI=0.95 to 2.53. No relationship between atopic or autoimmune conditions and HCL risk was observed, though a significant positive association was identified between asthma and HCL risk in females (0R=3.31, 95%CI=1.37 to 8.03). A positive association was also observed between farming and HCL risk and a dose-response relationship with increasing duration of occupation as a farmer. Despite a marked male predominance in HCL, pooled analysis showed no sex specificity, with similar tendencies in direction and of comparable magnitude in men and women with regard to cigarette smoking and farming occupation exposure.

**5. Second malignancies (SMs)**

HCL patients also appear to be inherently prone to SMs: this appears to be more related to HCL tumor burden than to genetic predisposition or treatment effect. The long-term OS of patients with HCL must be considered, and the drugs administered must be safe and nontoxic. The occurrence of SMs in HCL patients is a subject of debate (32). Nevertheless, SMs are becoming more common, as survival in cancer is improving, and they are of main concern in cancers because they may cause early mortality. Data from worldwide cancer registries and studies tend to demonstrate an increased incidence of SMs, mainly hematological malignancies with a cumulative incidence ranging from 5 to 32% and probably depending on the time of follow-up. The observed-to-expected ratio (OER) of SMs is usually increased: 1.01, I95% CI=0.74 to 1.33) (33), 1.2 (95% CI= 1.1 to 1.4) (34), 1.65 (95% CI=1.40 to 1.93) (35), 1.86 (95% CI= 1.34 to 2.51) (36), 1.88 (95%CI=1.24 to 2.74) or 2.6 (90% CI=1.82-3.61) (37). Such high incidence mainly concerns hematological malignancies, at 5.32 (95% CI=2.90 to 8.92), particularly non-Hodgkin lymphomas, at 5.03, with 95% CI from 3.77 to 6.58, and 5.3, with 95% CI from 1.9 to 11.5 (34), and Hodgkin lymphomas, at 6.61 (95%CI=2.13 to 15.42) (35). In our study including 487 HCL patients, the standardized incidence rate (SIR) was 1.86 (95% CI=1.34 to 2.51), with an absence of a difference depending on the treatment used as

 

the first line and the type of PNAs. The SIR was 5.32 (95% CI=2.90 to 8.92) for the risk of hematologic malignancies (36). In the study we conducted with a longer follow-up, we identified 68 second malignancies in 59 patients: 49 solid cancers and 19 hematological malignancies, with a 10-year cumulative incidence of cancers, solid tumors and hematological malignancies of 15%, 11%, and 5.0%, respectively (4). Twenty-one percent of patients (59/279) experienced at least one second cancer, 17% (46/279) experienced one solid cancer, and 6.8% (19/279) experienced hematological malignancy. The most prevalent solid tumors were prostate and nonmelanoma skin cancers, and the most prevalent hematological malignancy was MGUS/multiple myeloma. The median times between HCL diagnosis and all second cancers, solid cancers and hematological malignancies were 81 months (range 0–374), 99 months (range 0–374), and 78 months (range 2–262), respectively. The median age at diagnosis of all second cancers, solid cancers or hematological malignancies was 70, 69, and 77 years, respectively. Considering death as a competing risk, the 10-year cumulative incidences of all SMs, solid cancers and hematological malignancies were 15% (95% CI: 11; 19), 11% (95% CI: 7.2; 15), and 5.0% (95% CI: 2.8; 8.2), respectively. In multivariate analysis, IFNα was a protective factor against SM ($p = 0.038$, HR 0.529, 95% CI: 0.290; 0.966), a familial history of cancer was a risk factor for solid cancers ($p = 0.017$, HR 2.117, 95% CI: 1.146; 3.910), and a personal history of cancer was a risk factor for hematological malignancies ($p = 0.028$). The Swedish Family-Cancer Registry was used to assess survival in CLL and HCL with and without SMs. SMs were grouped into three prognostic groups based on the 5-year relative survival of these cancers as the first primary cancer: good survival (relative survival > 60%), moderate survival (40–60%) and poor survival (<40%). Among 718 HCL patients, a total of 119 were diagnosed with SMs (16.6%) after a median (interquartile, 2–11) follow-up time of 7 years; of 234 HCL deaths, 57 (24.4%) were recorded in patients with SMs. For HCL, the data between patients with and without SMs were essentially similar: in year 1, patients with SMs had significantly better survival than did those without SMs, but survival trends were reversed at subsequent periods, though the differences were not significant. For HCL, the HRs for patients with SMs of good, moderate, and poor prognosis were 1.69 (1.11–2.57), 2.15 (0.92, 5.02), and 13.34 (4.92–36.33), respectively, and the trends were also significant (38). However, it is difficult to assess outcomes due to the disease and those due to different treatments including PNAs.

## 6. Conclusion

Efforts are needed to undertake more extensive studies involving larger patient cohorts aiming to determine the role of occupational and environmental risk factors in the development of HCL and HCL-like disorders. The outlook of HCL treatment changed dramatically with the introduction of PNAs, allowing patients to achieve durable complete remission and a long overall survival. The improvement is linked to therapeutic progress and improvement in the treatment of relapsed/refractory HCL cases, e.g., a combination of PNAs and various anti-CD20 monoclonal antibodies, recombinant immunotoxins targeting CD22 (moxetumomab pasudotox), BRAF inhibitors (vemurafenib, dabrafenib) or B-cell receptor

 

signaling inhibitors (ibrutinib). New effective drugs should be developed for the management of patients with relapsed/ refractory HCL, and there is still a need for further improvements using nonchemotherapy approaches.

 

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