# Parental longevity and survival in elderly patients with Hodgkin's lymphoma

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*Background and Objectives.* In general, elderly patients with Hodgkin's lymphoma (HL) have a less favorable prognosis than younger patients. Factors such as inadequate therapy often due to decreased tolerance to treatment, presence of intercurrent diseases and accumulation of certain clinical and biological risk factors contribute to the poor outcome. Established predictors of prognosis in HL are less appropriate in the elderly population. Consequently, there is a need for additional markers to guide treatment decisions and to improve prediction of outcome. In the general population, the expected length of life of an individual is intimately associated with that of his/her parents. In a small cohort of elderly HL patients, we had previously observed high familial lifespan of two previous generations predicts superior survival. The aim of this study was to test the hypothesis that *parental* longevity alone — an easily accessible and non-disease associated variable — is also associated with improved outcome using an enlarged series of elderly HL patients.

*Design and Methods.* One hundred and twenty-one patients with HL >60 years at diagnosis were included. The median follow-up time was 67 (range 37-175) months. Data regarding age at death and reported cause of death were available through parish offices for 228 (94%) parents. The effect of parental lifespan on HL survival included the use of Kaplan-Meier curves and Cox' proportional hazards regression analysis.

*Results.* Maternal as well as paternal lifespan correlated poorly with HL survival, both with regard to overall and disease-specific survival. There was, however, a tendency towards a decreased risk of dying among patients with low maternal lifespan (all-cause mortality: RR=0.7, 95% CI 0.5-1.0).

*Interpretation and Conclusions.* Parental longevity does not predict superior survival in elderly patients with HL. ©2002, Ferrata Storti Foundation

Key words: Hodgkin's lymphoma, longevity, lifespan, prognosis, elderly.

The introduction of modern staging procedures, and developments in both radiotherapy and chemotherapy have significantly contributed to the improved survival of patients with Hodgkin's lymphoma (HL) over the last three decades.[1,2] However, these achievements are mainly confined to the young population and outcome of elderly patients still remains poor, including an inferior complete remission rate and overall survival.[1,3-6] Besides age, the discriminatory power of easily accessible prognostic factors, including the International Prognostic Score (IPS),[7] is reported to be of limited value in most series of elderly HL patients.[8] Thus, there is need for more appropriate markers of outcome in elderly HL patients.[1,3-5]

In the general population the length of life of an individual is significantly longer if she or he has had long-lived parents.[9] Similar findings have been reported in patients with specified diagnoses, e.g., coronary heart disease.[10,11] In order to look for mechanisms explaining the heterogeneity in outcome and also to improve prediction of prognosis in elderly patients with HL, we previously studied familial longevity and prognosis in a small cohort of HL patients.[12] Increased lifespan of the previous *two* generations was associated with a significantly superior survival in 30 elderly HL patients. In that study, the contribution of the grandparental generation was strong. However, no prognostic discriminatory capacity of familial longevity was seen in younger patients (<50 years). We also found that in families with a low lifespan, individuals showed an increased mortality from infectious diseases, mainly pneumonia and tuberculosis.

The primary aim of the present study was to assess the significance of *parental* longevity in a larger cohort of elderly patients with HL. A secondary objective was to identify and evaluate causes of death among the parents.

## Design and Methods

### Patients' characteristics

Between 1973 and 1994, 147 elderly (>60 years) patients with HL were diagnosed within the Stockholm HL Study Group. Twenty-six patients (18%) were excluded since information on both the mother and the father could not be obtained. The median age at diagnosis of the remaining 121 patients was 71 (range 60-95) years and the median observation time at follow-up for surviving patients was 67 (range 37-175) months. The year of birth of the patients ranged from 1885 to 1934. The patients' characteristics are given in Table 1.

### Diagnostic and staging procedures

Tissue biopsies were subclassified according to the Rye nomenclature (LP = lymphocyte predominance; NS = nodular sclerosis; MC = mixed cellularity; LD = lymphocyte depletion).[13] When necessary, complementary immunostainings for CD15, CD30, CD20, LN-1, CD79a, CD3, UCHL-1 and EMA (avidin-biotin-peroxidase complex technique) were performed to confirm the diagnosis. The histopathologic distribution was dominated by MC histology (Table 1). The Ann Arbor staging classification was used to describe the extent of disease (Table 1).[14] For further details see previous reports.[15-20]

### Treatment and response criteria

Details of treatment have been described previously.[15,18,19,21] In brief, patients with limited disease (stage I-IIA) were given radiotherapy. Patients diagnosed between 1974 and 1979 were included in a study regarding the value of early splenectomy. In this study, patients mainly with stage IIA-IIIA disease were given total nodal irradiation.[19]

During this period, patients with stage IIIB-IV disease were given MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) or CCNU-OPP (1-[2-chloroethyl]3-cyclohexyl-1-nitrosourea, vincristine, procarbazine, and prednisone) chemotherapy.[19] From 1979, most patients with stage IIB-IV disease received 2-4 cycles of MOPP/ABVD (mechlorethamine, vincristine, procarbazine, and prednisone/doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy with irradiation given to bulky disease.[15] Complete remission corresponded to complete regression of all palpable or histologically documented tumors and resolution of all radiographic and biochemical abnormalities due to HL for a minimum of three months.

Table 1. Characteristics of the patients and their parents.

| | n (%) |
|---|---|
| All patients | 121 (100) |
| **Sex** | |
| Male | 64 (53) |
| Female | 57 (47) |
| **Age** | |
| 60-69 years | 55 (45) |
| 70-79 years | 44 (36) |
| 80-89 years | 19 (17) |
| 90-years | 3 (2) |
| **Clinical stage** | |
| I | 41 (34) |
| II | 27 (22) |
| III | 32 (27) |
| IV | 21 (17) |
| **B-symptoms** | |
| Yes | 49 (40) |
| No | 72 (60) |
| **Bulky disease** | |
| Yes | 6 (5) |
| No | 115 (95) |
| **Histopathology** | |
| LP | 10 (8) |
| NS | 31 (26) |
| MC | 55 (45) |
| LD | 10 (8) |
| Unclassified | 15 (13) |
| **Parental information available** | |
| Yes | 228 (94) |
| No | 14 (6) |
| | range (median) |
| **Parental year at birth** | |
| Fathers | 1838-1907 (1876) |
| Mothers | 1848-1913 (1879) |
| **Parental age at death** | |
| Fathers | 31-94 (73) |
| Mothers | 27-100 (77) |

### Parental data

Through the Swedish civil registration system, the parents of each individual were identified and information regarding age and reported cause of death was retrieved at parish offices. In 14 patients data were missing for one of the parents, either due to emigration or due to incompleteness of registry files. Thus, complete information (Table 1) was available for 228 of 242 (94%) parents. No parents were alive at the end of the observation period.

### Statistical analyses

Disease-specific mortality was defined as death from HL or death judged to be related to treatment of the disease (infections, certain second malignancies and cardiovascular events). All-cause mortality was defined as crude death, irrespective of cause. Cause-specific survival was defined as the time from diagnosis to death from HL or death related to treatment of the disease (*see above*). Overall survival was defined as the time from diagnosis to death, irrespective of cause.

The association between parental lifespan and risk of death was evaluated using Kaplan-Meier curves and Cox' proportional hazards regression analysis.[22] We assessed the significance of maternal, paternal, and total parental lifespan on the risk of dying. The lifespan was analyzed both as quartiles and as below or above the median. The significance of parental longevity on survival following diagnosis of HL was assessed in crude analyses as well as after adjustment for non-laboratory factors of the International Prognostic Score i.e. age, clinical stage at diagnosis, sex, and calendar period (Table 2).[3,4] Models restricted to death from HL as well as models of deaths from all causes were used. We used time-varying co-variates to assess whether the effect of lifespan on the risk of dying varied with time of follow-up. The study was approved by the Ethics committee at Karolinska Institutet.

### Results

Seventy-nine (65%) of 121 patients achieved complete remission, 23 (29%) of whom relapsed during the observation period. The overall survival at five years was 0.44 (95% confidence interval 0.35-0.52), median: 1257 days (95% CI 757-2031 days). The cause-specific survival at five years was 0.54 (95% CI 0.44-0.62), median: 2475 days (95% CI 1154-not estimable).

The Kaplan-Meier curves revealed relatively modest differences in survival according to parental lifespan, true both for parental and for maternal lifespan dichotomized according to the median value in each category (Figures 1 and 2). Likewise, in unadjusted Cox' regression models, little effect of parental lifespan, defined according to the median, on cause-specific deaths (unadjusted RR of death from HL for patients with mothers' lifespan below median = 0.9 [95% CI 0.6-1.6], and unadjusted RR of death from HL for patients with fathers' lifespan below median = 0.8 [95% CI 0.5-1.4]) or overall survival (Table 2) was observed. No

Table 2. Relative risk of death among 121 elderly HL patients according to parental lifespan and other variables simultaneously adjusted for (95% confidence interval).

| Parameter | Relative risk of death | | | |
|---|---|---|---|---|
| | All-cause, unadjusted | All-cause, adjusted | Hodgkin's lymphoma, unadjusted | Hodgkin's lymphoma, adjusted |
| **Parental lifespan** | | | | |
| Mother <median (78 years) | 0.7 (0.5-1.0) | 0.7 (0.4-1.1) | 0.9 (0.6-1.6) | 1.1 (0.6-2.0) |
| Father <median (72 years) | 0.9 (0.6-1.3) | 0.8 (0.5-1.3) | 0.8 (0.5-1.4) | 0.6 (0.3-1.1) |
| **Age at HL (quartiles)** | | | | |
| 60-63 | | 1.0 (ref.) | | 1.0 (ref.) |
| 64-70 | | 1.7 (0.9-3.1) | | 1.7 (0.7-4.2) |
| 71-76 | | 2.3 (1.1-4.6) | | 2.5 (1.0-6.6) |
| 77-94 | | 3.8 (1.9-7.6) | | 3.6 (1.4-9.3) |
| **Clinical stage** | | | | |
| Stage I | | 1.0 (ref.) | | 1.0 (ref.) |
| Stage II | | 1.5 (0.7-2.9) | | 2.6 (1.0-6.6) |
| Stage III | | 2.1 (1.1-3.8) | | 3.0 (1.3-6.9) |
| Stage IV | | 2.9 (1.4-5.7) | | 4.2 (1.7-10) |
| **Sex** | | | | |
| Male | | 1.0 (ref.) | | 1.0 (ref.) |
| Female | | 1.1 (0.7-1.7) | | 1.1 (0.6-2.0) |
| **Year of HL (quartiles)** | | | | |
| 1973-1975 | | 1.0 (ref.) | | 1.0 (ref.) |
| 1976-1980 | | 1.3 (0.7-2.4) | | 1.8 (0.8-4.0) |
| 1981-1986 | | 0.4 (0.2-0.8) | | 0.5 (0.2-1.1) |
| 1987-1994 | | 0.6 (0.3-1.1) | | 0.5 (0.2-1.3) |

apparent effect was observed when each quartile of parental age was analyzed separately (*data not shown*). In a multivariate analysis in which parental lifespan was adjusted for several other variables, little confounding effect was observed and the risk estimates remained essentially similar to those of the crude analyses (Table 2). Also, when maternal and paternal lifespans were combined into one estimate, little difference in risk of death from HL was observed among patients with both parents below (compared to above) the median lifespan (RR=0.8, 95% CI 0.4-1.2).

Overall there was no significant difference in the distribution of causes of death with reference to parental lifespan. However, four of the five deaths from tuberculosis occurred in parents with lifespan below the median, in all four cases below 50 years of age.
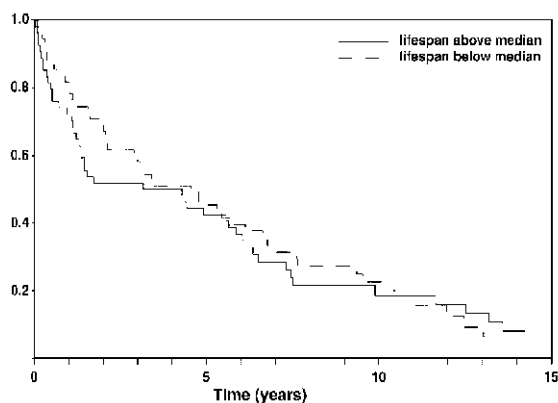
**Figure 1. Kaplan-Meier estimates of the overall survival following diagnosis of Hodgkin's lymphoma and according to father's lifespan.**
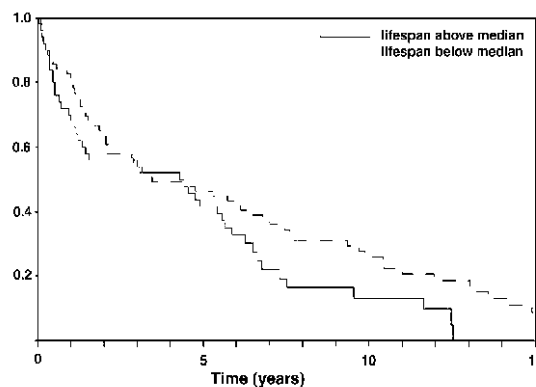


**Figure 2. Kaplan-Meier estimates of the overall survival following diagnosis of Hodgkin's lymphoma and according to mother's lifespan.**

## Discussion

Elderly patients (>60 years at diagnosis) with HL constitute a heterogeneous patient population reflected by decreased tolerance of treatment and inferior outcome.

A number of contributing factors have been suggested, such as: a) inadequate diagnostic procedure/therapy; b) decreased tolerance to conventional treatment; c) co-morbid diseases/organ dysfunction; d) accumulation of certain clinical, biological and other risk factors.[1, 2,18,23,24]

The distribution of clinical characteristics, complete remission rate and cause-specific and overall survivals in the present study are in good accordance with previously published series of elderly HL patients.[1] Thus, we believe the current series to be representative of HL in the elderly.

As an attempt to predict prognosis in HL with a non-disease associated factor, we previously assessed the potential prognostic discriminatory capacity of familial longevity. We observed that there was an association between longevity in the previous two generations and improved outcome in HL in the elderly, with an absence of effect in the younger patients.[12] Thus, we found familial longevity to be a powerful predictor of prognosis in a cohort of 30 elderly HL patients. Also, ancestors of elderly HL patients with a fatal outcome showed an excess mortality rate between 30 to 70 years, mainly due to tuberculosis, which led to a hypothesis on an association with a defect in cell-mediated immunity.[12] These results may possibly point to a familial immunological impairment that may both

predispose to tuberculosis and HL, and also modulate the course of the latter in the elderly. Previous studies in healthy elderly people have shown a progressive impairment of the immune system with increasing age,[25-29] suggesting that the immune system does not escape the aging process. In other studies blood lymphocyte abnormalities and T-cell immunodeficiency have been reported to be closely related to a poor prognosis in lymphoid neoplasms.[30-32] Since HL is a lymphoid malignancy a premature immunological aging has been hypothesized to influence the course of disease.[33]

The present study was undertaken to assess the discriminatory power of parental lifespan alone in all reported elderly HL patients diagnosed within the Stockholm region between 1973-1994. Our results indicate that parental longevity does not predict superior outcome in elderly patients with HL. Rather, there was a tendency for low maternal lifespan to be associated with an improved overall survival. Interestingly, this finding is in sharp contrast to preliminary results in a population of elderly patients with aggressive NHL (n=220)[34] in whom maternal longevity was significantly associated with improved survival. Neither could we confirm the results of our previous study showing that relatives who died from tuberculosis belonged to the group with elderly HL patients with a fatal outcome.[12] When the reported parental cause of death was assessed, four of the five deaths from tuberculosis occurred in mothers and fathers with a lifespan below the median which, however, did not relate to the survival of their progeny.

There may be several explanations for the discrepancy between the present findings and our previously reported results. While the previous study, which encompassed 30 patients, included assessment of grandparental and parental lifespan, the present study was limited to parental lifespan only, and included patients diagnosed with HL during more recent years.

Changes in the occurrence and survival from, e.g., infectious disease among the parental (versus grandparental) generation, as well as potential improvements in survival among HL patients over the last decades may therefore have concealed a true effect of parental lifespan on the prognosis in HL. Also, the possibility of a spurious finding in the previous report cannot be neglected.

As expected, an increased frequency (45%) of MC histopathology was recorded in this elderly population.[1,35] In a subgroup analysis of parental longevity and prognosis in MC patients, no findings deviated from those recorded in the whole patient series (*data not presented*).

Another feature of HL in the elderly is the increased occurrence of Epstein-Barr virus (EBV) genome positive tumors (also associated with MC histopathology).[21,35,36] Unfortunately, the potential association between parental longevity and prognosis according to EBV tumor status could not be evaluated in the present study since this information was only available in a small percentage (10%) of the patients.[37]

We conclude that parental longevity was not associated with improved outcome in the studied elderly HL population. Neither was there a significant difference in the distribution of causes of death with reference to parental lifespan.

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*All the authors´ contributions in the present study are in good accordance with the "Vancouver definition of authorship ". The authorship credit is based only on substantial contributions to: (a) conception and design, or analysis and interpretation of data (b) drafting the article or revising it critically for important intellectual content (c) final approval of the version to be published.*

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### Disclosures

*Conflict of interest: none.*

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