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Socioeconomic inequalities in prognostic markers of non-Hodgkin lymphoma: Analysis of a national clinical database

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ABSTRACT

The survival of non-Hodgkin lymphoma patients strongly depends on a range of prognostic factors. This registry-based clinical cohort study investigates the relation between socioeconomic position and prognostic markers in 6234 persons included in a national clinical database in 2000–2008, Denmark. Several measures of individual socioeconomic position were achieved from Statistics Denmark. The risk of being diagnosed with advanced disease, as expressed by the six prognostic markers (Ann Arbor stage III or IV, more than one extranodal lesion, elevated serum lactate dehydrogenase (LDH), performance status of two or more, presence of B symptoms and International Prognostic Index (IPI) of two or more), increased with decreasing level of education, in patients living alone, and in men. For instance, a significant decrease in the odds of being diagnosed with elevated LDH ($p = 0.02$), high performance status ($p = 0.004$), high IPI score ($p = 0.004$) and B symptoms ($p = 0.02$) was seen with higher level of education, whereas high stage of disease was significantly less likely in the higher educated (odds ratio [OR] = 0.85 (0.74–0.99)). The difference in risk seemed not to be mediated by differences in histological subgroups reflecting aggressiveness of disease among the social groups. One of the most likely mechanisms of the social difference is longer delay in those with low socioeconomic position. The findings of social inequality in prognostic markers in non-Hodgkin lymphoma (NHL) patients could already be implemented in the clinical practice if general practitioners (GP's) and physicians on hospitals paid special attention to patients with low educational level and unspecific symptoms.

1. Introduction

There seems to be social inequality in survival after most cancers, with less advantaged patients having the worst prognosis.[1,2] Few studies have documented such inequalities in survival in non-Hodgkin lymphoma (NHL) patients.[3–7] As the survival of NHL patients strongly depends on a range of prognostic factors like stage at diagnosis and performance status, the association between these prognostic factors and socioeconomic position (SEP) is of particular relevance in order to

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explain social differences in prognosis. However, to our knowledge previous investigations of the association between SEP and advanced stage have only included other types of cancer, e.g. breast, lung and colorectal cancer, showing diverging results but mainly increased risk of late-stage disease in persons with low SEP.[8–12]

Symptoms of NHL are generally rather unspecific, in particular for indolent sub-types, and may include fatigue, weight loss, fever, night sweats and swollen lymph nodes. Symptoms of NHL may be mixed up with symptoms of other chronic diseases, especially in patients with several comorbid disorders. In addition, characteristics such as the patients' awareness of their symptoms, an appropriate health behaviour (e.g. visiting the general practitioner (GP) for relevant symptoms) and good communication with health staff may impact on the time passed from the initial symptoms of NHL until the diagnosis and thus on the likelihood of being diagnosed with advanced disease. These characteristics may be more predominant among persons with high SEP, while comorbid disorders are more frequent among persons with low SEP.[13] This leads us to hypothesise that NHL patients with low SEP are diagnosed with more advanced disease than are those with high SEP; and further that education may be of greater impact than income, since the above mentioned characteristics presumably are more closely associated to education than to income, even though these SEP indicators are correlated.

Thus, in this study we investigate the association between three individual socioeconomic factors as well as comorbidity and a range of prognostic markers. The prognostic factors analysed are three indicators with relation to the progression of the disease: the Ann Arbor stage, the presence of extranodal involvement of the lymphoma, and elevated levels of lactate dehydrogenase (LDH), two indicators more closely related to the general condition and the symptoms of the patient: the Eastern Cooperative Oncology Group (ECOG) performance status[14] and the presence of B symptoms (fever, night sweats, and weight loss), and one composite measure: The International Prognostic Index (IPI) originally developed for aggressive lymphomas and a powerful and widely used tool in describing prognostic factors of NHL, which is generated from data on Ann-Arbor stage, performance status, extranodal lesions, LDH level and age.[15,16] We also investigate if social differences are mediated by differences in histological subtypes, reflecting the aggressiveness of disease, among social groups. Further, analyses are performed within the subgroup of patients diagnosed with diffuse large cell b-cell lymphoma (DLBCL), which is the largest subgroup, and belonging to one of the most aggressive subtypes of NHL cancer.

2. Materials and methods

2.1. Study population

The study population was derived from the Danish national lymphoma database, LYFO, which includes more than 90% of patients diagnosed in Denmark with *de novo* NHL.[17] The data are collected from questionnaires filled in by the medical doctors in all 13 haematological departments in Denmark, who diagnose and treat NHL. It is obligatory for all lymphoma-treating departments to report cases of lymphoma to the LYFO database. The database included 6596 persons born between 1920 and 1982 and diagnosed with NHL between 2000 through 2008. About 63 patients below the age of 25 were censored, since education and income of these young age groups does not reflect their true SEP. Further, a total of 362 persons (5%) for whom there were no achievable information on either highest attained education, cohabiting status, or disposable income 1 year prior to the diagnosis of lymphoma was excluded, leaving 6234 persons for analysis. Of these 2570 (41%) were diagnosed with DLBCL.

2.2. Outcome variables

A number of dichotomous outcome variables were defined based on data from the database describing presence or absence of the following prognostic markers: (i) Ann Arbor stage III or IV – indicating involvement of lymph node regions on both sides of the diaphragm muscle, (ii) more than one extranodal lesion, (iii) elevated serum LDH – above the reference value which depends on age, (iv) ECOG performance status of 2, 3 or 4 – indicating how the disease affects the daily living abilities of the patient, ranging from 0 'fully active without restrictions' to 4 ' completely disabled', (v) presence of B symptoms, and finally (vi) IPI of two or more – range from 0 to 5.

2.3. Exposure variables

The socioeconomic data were derived by linkage to the Central Population Registry and the population-based Integrated Database for Labour Market Research (IDA) in Statistics Denmark, by means of a unique personal 10-digit identifier, which is given to all persons residing in Denmark for more than 3 months.[18] Thus information on age, sex, cohabitation status, education and income was obtained for each patient. Cohabitation status was categorised as single and living with partner. Education was categorised in three groups, as short education (i.e. mandatory education of up to 7 and 9 years for patients born before and after 1st January 1958, respectively), medium education (between 8/10 and 12 years – latest grades of primary school, secondary school, and vocational education) and higher education (over 12 years). Income was defined as household income after taxation and interest per person, adjusted for number of persons in the household and deflated according to the 2000 value of the Danish crown (DKK). Yearly variation in income was accounted for by calculating the average income in the 5 years before the diagnosis.

A Charlson Comorbidity Index (CCI) was generated by linking the personal identification number to the files of the Danish National Patient Register.[19] Hereby full histories of diseases leading to hospitalisations and outpatient visits from 1978 and 1995, respectively, accumulated up to the year preceding the lymphoma diagnosis were obtained for each individual. The information in the Register includes dates of admission and discharge and diagnoses coded according to Danish modified versions of the ICD-8 and, from 1994, ICD-10.[20]

2.4. Other variables

Information on histological subgroups of NHL was retracted from the LYFO database and subtypes were grouped according