

Most common health problems in general practice among adolescents, and young adults' survivors of lymphoma: A register-based cohort study in Norway.

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Abstract

Background: The aim was to investigate the distribution of health problems in general practice (GP) among adolescent and young adult (AYA) survivors of lymphoma and to compare problem rates with the general population.

Methods: All GP consultations between 2006 and 2020 were identified from the national GP claims register. Diseases and complaints presented 3-10 years after the cancer diagnosis were identified using the International Classification of Primary Care codes (ICPC-2) and compared applying logistic regression models, presented with odds ratio (OR) and 95%CI.

Results: A total of 2,500,557 AYAs, of whom 1105 were diagnosed with lymphoma, and over 50 million GP consultations were included. The most common causes of consultation among AYA survivors of lymphoma were related to Hodgkin's disease (13%), pregnancy (11%), respiratory diseases (9%), psychological problems (8%), musculoskeletal system (6%) and fatigue (4%). Almost all these problems were significantly higher among AYA lymphoma survivors compared to the general population (OR ranging from 1.1 to 1.5).

Conclusion: Compared to the general population, young lymphoma survivors have increased contact with the GP for a considerable number of health problems for up to 10 years post-diagnosis. This emphasizes the importance of robust follow-up and a good flow of information between hospital and primary care.

Key words: lymphoma, GP consultations, late effects of cancer, adolescents and young adults, register-based study.

1. Introduction

Cancer is the most common cause of disease-related death in adolescents and young adults (AYAs) in high-income countries. [1] The age range for AYAs is typically defined as persons aged 15-39 years. (1) In Norway the age-specific incidence of AYA Hodgkin lymphoma (HL) is 3.5/100,000 in males and 3.8/100,000 in females. [2] Corresponding rates for non-Hodgkin lymphoma (NHL) is 3.1/100,000 in males and 2.5/100,000 in females.

In Norway, survival among individuals diagnosed with lymphoma has improved significantly over the past 50 years. Among lymphoma patients aged 18-39 years at diagnosis, close to 100% are alive after 5 years after treatment for HL, while NHL 5-year survival is close to 80%. [3] Previous research shows that persons treated for cancer during the early adult stage of life is a highly vulnerable group, due to an age of establishing relationships, completing an education and being economically independent. [4,5]

AYA lymphoma survivors are at increased risk of treatment-related morbidity and mortality. [6] Most of these cancer survivors will have at least one chronic health condition by 50 years of age. [7] Side effects of cancer treatment such as fatigue is one of the most common problems among lymphoma survivors. [8,9] After completion of the cancer treatment at the hospital, the GP will be involved in the follow-up of the survivors with the objective to achieve the best possible recovery, and thereafter have the responsibility for long term follow-up of the survivors. [10] Still, some unanswered questions are related to healthcare access and delivery, as well as long-term effects of cancer treatment and survival. [11] A Norwegian study showed that lymphoma survivors perceived themselves, and their GPs, to lack necessary knowledge of late effects and recommended screening procedures. [12] Consequently, there is a strong call for more research for improved understanding of the long-term morbidity and use of the health care services associated with cancer treatments to contribute to early detection and intervention. Good evidence may help clarify which services that ought to be expanded or developed and how responsibilities should be distributed between the specialist and municipal health services.

The primary objective of the study was to analyse the frequency and distribution of health problems in GP consultations among AYAs lymphoma survivors by using data from the Norwegian Control and Payment of Health Reimbursement (KUHR) database. [13] We aimed to study GP diagnoses identified during 3-10 years of follow-up, and further to identify how these health problems differ from problems among sex-and age-matched AYAs without a history of cancer.

2. Materials and methods

2.1 Study population and data sources

The present study includes a cohort of Norwegian AYAs born between 1966 and 2001 and who were alive at least 10 years in the follow up period (2006-2020). We used the personal Norwegian ID number to link to the Norwegian Cancer Registry and the KUHR registry. [14,15] *Cancer cases* were all individuals with a primary diagnosis of HL and NHL diagnosed at the age of 15-39 years between 2006 and 2017 and reported to the Norwegian Cancer Registry (NCR). From NCR we obtained information on date and age of cancer diagnosis, and histology. From the Norwegian Cause of Death Registry, we obtained information on date of death. [16] From the Norwegian Cause of Death Registry, we obtained information on date of death. Lymphomas were coded using the 2008 ICD-O-3/WHO classification of lymphoid neoplasms (Appendix 1). [17,18] *Non-cases* were all AYAs in the cohort without lymphoma or any other type cancer diagnosis.

The KUHR database contains information on bills from health services, which have been reimbursed to patients by the state. All GPs are required to use at least one code from the International Classification of Primary Care (ICPC) [19] to report clinical signs, symptoms, and diagnoses; diagnoses are entered into the KUHR database. *GP consultations* which took place between 2006 and 2020 within the study population were identified from the national KUHR database. We include face-to-face consultations (including e-consultation and home visits). Diseases and complaints presented to the GP were based on the International Classification of Primary Care codes (ICPC-2). [20] The data in the present study contain only GP consultations. Consultations after the cancer treatment in hospitals and specialists are not included. Since we did not have information on cancer treatment for each patient, the results are given for all treatments included.

2.2 Treatment of lymphomas during 2006-2017

In the present study, data concerning treatment were not available for each individual patient, but treatment of lymphomas have followed national and international guidelines. [21] The number of courses, radiation doses and duration of treatment are adapted to the stage and extent of the disease.

For *HL* ABVD chemotherapy (*doxorubicin, bleomycin, vinblastine, dacarbazine*) followed by involved site radiotherapy is used. For advanced disease ABVD chemotherapy or the BEACOPP regimen (*bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone*) is used. During later years, response adapted treatment has been introduced including PET in the evaluation. [9,22,23,24] For *NHL* the CHOP regimen (*cyclophosphamide, doxorubicin, vincristine, prednisolone*) and radiotherapy is used in the treatment of aggressive *NHL*. The CHOP regimen and Rituximab is used for treatment of B-cell lymphomas. Very aggressive *NHL* entities are treated according to leukemia like protocols.

In Norway, all health trusts/hospitals that investigate and treat cancer patients have Cancer Patient Pathways to ensure a well-organized and integrated cancer care. [25] After lymphoma treatment the GP take over the follow up. [26] During these checks, the GP have the roll of monitoring with a view to the development of late effects and other sequelae of the disease or treatment, as well as monitoring of recurrence. Thereafter, there are normal checks every six months until the five-year check. (9) The first GP check-up after the end of lymphoma treatment is usually after 1-3 months and involves imaging diagnostics to assess the status of the cancer itself and side effects caused by the treatment. In addition, the primary healthcare service must assist with revaccination where this is recommended.

2.2 Statistical analysis

The primary outcome was GP consultations/visits presented among AYAs lymphoma survivors and non-cases during 3-10 years after the lymphoma diagnosis. Knowledge about GP consultations rates among AYAs lymphoma survivors in Norway are limited, therefore this study has an exploratory approach. We present average number of consultations per survivor per year at selected years after diagnosis (3, 6 and 10) and total consultations in whole the follow up period. Logistic regression models with odds ratios (OR) and 95% confidence intervals (CI) were used to compare diseases and complaints for which cases and non-cases contacted their GP. Consultation frequency for each symptom was the explanatory variable and it was analysed as a continuous variable. The models were adjusted for birth year, sex, and year/period of consultation. A P value of < 0.05 was considered statistically significant.

Results are presented for each ICPC-2 diagnosis/disease code including all lymphoma survivors and separately across sex and lymphoma subtype (HL and NHL). We present a figure for visualization of the results, where the ICPC2 codes with statistically significant odds ratios calculated with 3 or more cancer cases are included. We also conducted subanalysis among individuals with high consultations rates. Statistical analyses were conducted using SPSS (version 28).

2.3 Ethical considerations

The present project was approved by the Regional Committee for Medical and Health Research Ethics, (REK Southeast Norway: 2016/1305 and 2020/194961). As this is a register-based linked study, the approval also covers exemption from informed consent. The study was performed in accordance with the Declaration of Helsinki.

3. Results

A total of 2,500,557 AYAs who were alive in the study period were included in the study, of whom 1105 individuals were individuals with lymphoma (Table 1). We excluded 58 individuals with lymphoma and 22884 non-cases who died during the follow-up period. Among the cancer cases 698 (63.2%) were survivors of HL and 407 (36.8%) of NHL. The median age at diagnosis was 27 (SD=6.8) years among HL survivors and 31 (SD=7.0) years among NHL survivors. Men constituted 52.7% and 56.3% of the HL and NHL survivors, respectively, and 50.7% of the non-cases.

3.1 Average GP consultations rate 3-10 years after the cancer diagnosis among lymphoma survivors across ICPC-2 codes

The study included over 50 million GP consultations in the study period of which 23,182 were among individuals with lymphoma. Figure 1 shows the most common causes of consultations 3 to 10 years after the cancer diagnosis, with mean number of consultations per survivor according to time since treatment (overall, and third, sixth and tenth year after diagnosis) among individuals with lymphoma.

The most common cause of consultation was related to Hodgkin's disease (code B72) and constituted 13% of the total number of consultations with a mean consultation rate of 4.8 consultations per survivor in the whole follow up period. Mean consultation rate per survivor per year in the tree selected years were 2.4 in the 3rd year, 2.6 in the 6th year and 1.9 in the 10th year. Consultations due to respiratory diseases (codes R81, R99, R21, R83, R75, R78, R80, R05, R74) was 9% of the total of all consultations with a mean consultation rate between 1.4 and 2.2 per year per survivor in the whole study period. Weakness/general tiredness general (code A04) constituted 4% of the total number of consultations (mean consultation rate 3.7 per survivor in whole study period). Psychological problems were also common with about 8% of the total consultations (mean consultation rate between 2.3 and 5.2 per survivor in whole study period). Consultations related to the musculoskeletal system (codes L86, L18, L01, L84, L08, L17, L02, L87, L03, L15) were responsible for about 6% of all consultations (mean consultation rate between 1.4 and 2.6 per survivor).

Other common causes of consultation were related to pregnancy, urinary infection, headache, vitamin/nutritional deficiency, conjunctivitis infectious, gastroenteritis, vertigo/dizziness, allergy, complication of medical treatment and hypothyroidism.

3.2 Results from the logistic regression models comparing rates of GP consultations between individuals with lymphoma and non-cases.

3.2.1 Results including all individuals with lymphoma.

Compared to non-cases and including all consultations, individuals with lymphoma had a significantly higher risk for consulting their GP after the cancer diagnosis with an OR of 1.02 (95% CI 1.02-1.03) (Appendix 2). However, when we excluded consultations related to Hodgkin's disease (code B72) lymphoma survivors had a reduced risk of GP consultations compared to non-cases OR of 0.96 (95% CI 0.96-0.97), (data not shown). There were not significantly differences in risk when we compared lymphoma survivors and non-cases among individuals with high GP consultations (40 GP consultations or more) OR 0.98 (95% CI 0.95-1.01).

Analysing one-by-one health problem, individuals with lymphoma had a higher risk for contacting GP for several health problems compared to age-matched individuals (Figure 2). We present problems with significantly increased odds compared to non-cases calculated with minimum three individuals with lymphoma. In total 38 ICPC-2 codes were significantly increased compared with non-cases.

The highest risks for consultations were found for consultations related to the blood and immune system including consultations related to Hodgkin's disease, fear of cancer in the blood/immune system, and symptoms and complains in lymph glands had significantly higher risk compared with non-cases (1.4 to 5.0-fold, Figure 2).

The risk for consultations related to respiratory diseases and herpes zoster were also significantly increased by 10-20% among AYAs lymphoma survivors compared to non-cases.

General and unspecified symptoms including fever, weakness/tiredness general, swelling, sweating problem and complications of the medical treatment had an increase of 1.1-1.2-fold. Other health issues with elevated risks were teeth/gum symptoms (1.1-fold), deafness (1.2-fold), and problems in the nerve system including peripheral neuritis/neuropathy and neurasthenia (1.1 to 1.2-fold). Cardiovascular diseases including heart failure and stroke showed also elevated risks compared to non-cases (1.1 to 1.2-fold).

3.2.2 Results across sex.

Most of the health problems across both sexes found with significantly elevated odds ratios showed similar distribution between men and women (Appendix 2). Some health problems related to men organs and female organs showed increased risks. Men had an increased risk for consultations related to infertility (1.9-fold). Female survivors of lymphoma had increased risks of consultation due to high-risk pregnancy and puerperal mastitis (1.1-1.3-fold) and a higher risk of consultation due to malignant neoplasm of breast (1.4-fold).

3.2.3. Results across types of lymphoma.

Nearly all health problems that were significantly more common among all lymphoma survivors were also statistically significantly elevated when analysed according to lymphoma subgroups with some few exceptions (Table 2).

4. Discussion

To our knowledge, this is the first large-scale study on frequency of GP consultations among AYA survivors of lymphoma. Considering all causes of GP consultations together the risk of

consultation were similar between lymphoma survivors and non-cases. However, compared to the general population, AYA lymphoma survivors had elevated risks of consultation for several health problems. The most common problems presented 3 to 10 years after the cancer diagnosis were problems related to blood and immune system, respiratory diseases, weakness, or tiredness, musculoskeletal complaints and psychological problems.

Men had a greater risk for consultations related to infertility and females' survivors of lymphoma were more at risk of consultation due to pregnancy with high risk and puerperal mastitis. Analyses across lymphoma types showed similar risks, with some exceptions. Although the differences in risk of GP consultations between lymphoma survivors and non-cases were small, for some health problems these differences were more marked.

4.1 Comparison with existing literature

Direct comparison with other large studies is not possible because of lack of similar studies. However, there are several studies reporting late effects in lymphoma survivors. One study based on self-reported late effects including lymphoma survivors (NHL, n=79, HL, n=226) aged 15-24 years at diagnoses and similar years of follow up as our study, reports significant high risks of several of the same health problems as found in our study. [27]

A study by Mellblom and colleagues, including near 2000 Norwegian childhood and AYA cancer survivors report that 33% of NHL survivors (n=225) self-reported 5 or more late effects. [28] The most common health problems were psychological, memory and concentration problems, fatigue, reduced fertility, numbness in hands/feet, muscle cramps, hormonal changes, and dental problems, in line with results in our study.

A review published in 2018 by Shliakhtsitsava et al, showed that female survivors of leukemia and lymphoma are at high risk of preterm birth and delivering low birth weight babies. [29] Our finding confirm that women survivors of lymphoma have an elevated risk of GP consultations due to high-risk pregnancies.

4.2 Side effects of lymphoma treatment in view of our results

Our results show that in the period 3-10 years, most lymphoma survivors consulted their GP due to Hodgkin's disease on average 5 times each (Figure 1). Side effects from cancer treatment can range from mild to severe. They depend on treatment type and intensity, and the individual patient's susceptibility. [30] Several of the observed elevated risks of GP consultations were probably due to complications of the lymphoma treatment.

Health problems which might be related to chemotherapy and/or radiation therapy such as general weakness or tiredness, ie, fatigue, fever, swelling/inflammation, sweating problems, mouth problems, deafness, and cardiovascular diseases had elevated risks among lymphoma survivors vs. non-cancer cases. In our study, about 4% of lymphoma survivors consulted their GP around 5 times due to fatigue. The problem seemed to increase over time (Figure 1).

Fatigue is one of the most common late effects after cancer treatment and is reported among 25-50% of long-term cancer survivors, on the other hand it also differs significantly by age being more prominent among the elderly. [31] Of note, self-reported fatigue among long-term lymphoma survivors is reported to be higher than the prevalence of GP consultations found in our study.

A recent Norwegian study report a self-reported prevalence of chronic fatigue of 42% among HL survivors. [32] Despite the impact of fatigue on the patient's quality of life and

functioning, a review shows that cancer survivors might not discuss the health problem with their physician for a variety of reasons, consequently fatigue can be underdiagnosed and undertreated. [33] The impact of fatigue in daily activities might be more pronounced in survivors with other late effects, such as psychological problems and comorbidity. [34] Several studies show that fatigue or cognitive complaints are associated with lower work ability. [35]

Chemotherapy and radiation therapy can make patients more susceptible to infection. [36] In our study, several infections were overrepresented with elevated risk of consultations, such as respiratory diseases, especially upper respiratory infections, and pneumonia. Viral reactivation has been reported in some patients treated with chemotherapy, either with or without immunotherapy drugs. There are few data systematically analyzing the risk of herpes simplex and zoster virus reactivations in lymphoma patients. [37] Lee and colleagues report an incidence of 20% for 5 years follow up. [38] In our study, 41 lymphoma survivors consult their GP due to herpes zoster infection (Appendix 2). This corresponds to almost 4% of total population in the study.

We found significant elevated risk for consultations due to peripheral neuropathy. Chemotherapy-induced peripheral neuropathy is caused by damage to the peripheral nerves and is a common side effect of some chemotherapeutic agents, such as the drug vincristine or brentuximab vedotin. [39] Peripheral neuropathy might be under-reported by GP as compared with patients due to the clinical manifestation of peripheral neuropathy are subjective and predominantly manifest as pure sensory symptoms, such as numbness and tingling in the fingertips and toes.

We observed a high risk of GP consultations for some health issues related to the endocrine and metabolic system (Figure 2), including hypothyroidism, infertility among men, anemia, and vitamin deficiency. Endocrine glands may be influenced by surgical and radiation interventions if the tumor is located next to endocrine organs. Chemotherapy may have systemic effects including effects on endocrine glands, often affecting the reproductive organs. [40] In our study a total of 51 (4,6%) lymphoma survivors had at least one consultation related to hypothyroidism. The majority were HL survivors. Early studies among survivors of childhood HL show an incidence of hypothyroidism of 14% among these survivors. [41]

Our study show that female survivors of lymphoma were more at risk of consultation due to high risk-pregnancy and complications in the postpartum such as puerperal mastitis. This indicates the potential of side effects from cancer treatment to extend years after a woman has completed cancer treatment. Reproductive-aged AYAs lymphoma survivors might be a risk group who need special follow up. Further, the review by Shliakhtsitsava highlights the considerable gaps existing regarding research on this population on adverse perinatal outcomes and interventions to modify these risks.

AYAs lymphoma survivors showed an elevated significant risk to consult their GP due to fear of cancer recurrence. This in accordance with earlier studies showing that this is a prevalent concern among young cancer survivors. [42] Fear of cancer recurrence among young survivors might be influenced by high levels of worry and distress making it difficult for survivors to make plans for the future or struggling to manage day-to-day tasks and activities. This in turn might increase the number of visits to the GP or other health services. It

highlights the role of the health care services and the importance of early recognition, support, and appropriate referrals to psychosocial services.

4.2 Strengths and limitations

The strengths of this study include a well-defined study population with a large sample size and a population-based cohort of individuals with minimal selection bias. Another major strength is that the consultation frequency used in this study reflects the true usual GP consultation pattern among cancer survivors and a cancer-free population in Norway. The use of nationwide data registries has several well-known strengths, the claims registry (KUHR) for Norwegian GP used is nearly complete for the studied years, as >99% of the population were included in the regular GP scheme and no selection bias was therefore present. [43] The long follow-up of the study period makes it possible to analyse health problems several years after the cancer diagnosis and to identify long-term effects. In the present study it was possible to have a control group, which can help to ensure the internal validity and strengthen the findings of the study.

The most important limitation of this study is that in the KUHR registry there is a potential variability and lack of specificity of the GPs' diagnoses, which were not formulated for research purposes. However, many diagnoses need to be verified by laboratory tests before they can be confirmed. We did not have information to distinguish GP regularly controls from other type GP consultations. Moreover, data on visits to hospital/specialists were not included in this study. The consultation rate for late effects of cancer among lymphoma survivors may be higher. Another limitation was that predictor variables available in the dataset are limited and the study could have been improved with more information on cancer treatment and possible confounders, especially regarding the social context and predictors of higher/lower GP utilisation such as rurality, education level, and socioeconomic status. We didn't have any information either. Few cancer cases in some of the calculations could have reduced the statistical power.

4.3 Contribution/implications for policy and research

The survival after lymphoma among AYAs in Norway is excellent implicating that most of the cancer survivors are expected to return to a normal life after the cancer treatment. [44] From the data presented in this paper and by previous reports, lymphoma survivors face unique medical, psychosocial, and supportive care needs. We show that the GP has an important role in the follow up of these survivors. However, from our results we do not know if GP consultations solve patients' problems. Previous research show that there is a need for development of resources for GPs and/or patients to address the common issues after the cancer treatment. Moreover, more research exploring survivors' perception of the quality of these consultations is needed. Our results can contribute to the development of interventions and rehabilitation programmes for this group of cancer survivors. High GP consultation rates found for some health problems can help to increase awareness among GPs on long-term treatment-related toxicities and their impact on the quality of life in survivors. Moreover, a better understanding of late effects of cancer can contribute to the GP role in the administration of social security agreements related with survivor's occupational situation.

5. Conclusion

Compared with AYAs without a history of cancer lymphoma survivors have an increased risk of consultations with the GP due to a great number of health problems for up to 10 years postdiagnosis. Our results indicate that the GP has an important role in the follow up of these survivors. However, from our results we do not know if GP consultations solve patients'

problems. More research exploring survivors' perception of the quality of these consultations is needed.

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