RESEARCH ARTICLE

SECOND PRIMARY CANCERS IN NON-HODGKIN LYMPHOMA: FAMILY HISTORY AND SURVIVAL

Subhayan Chattopadhyay, MS[1,2], Guoqiao Zheng, MD [1,2], Amit Sud, MD[1,3], Kristina Sundquist MD[4,5,6], Jan Sundquist MD[4,5,6] Asta Försti, PhD[1,4], Richard Houlston, MD[3,7] , Akseli Hemminki, MD[8,9] and Kari Hemminki, MD [1,4]

[1] Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 580, D-69120, Heidelberg, Germany
[2] Faculty of Medicine, University of Heidelberg, Heidelberg, Germany
[3] Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK
[4] Center for Primary Health Care Research, Lund University, 205 02 Malmö, Sweden
[5] Department of Family Medicine and Community Health, Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, USA
[6] Center for Community-based Healthcare Research and Education (CoHRE), Department of Functional Pathology, School of Medicine, Shimane University, Japan
[7] Division of Molecular Pathology, The Institute of Cancer Research, London, UK
[8] Cancer Gene Therapy Group, Faculty of Medicine, University of Helsinki, Finland
[9] Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland

Correspondence: Kari Hemminki, Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 580, Heidelberg 69120, Germany.
Telephone: +496221421800
Fax: +496221421810
Email: K.Hemminki@dkfz.de

Words: 230 (abstract), 2871 (text)

Keywords: second cancers, familial risk, survival, prognostic grouping, prevention.

Running title: Familial second cancers and NHL

Novelty and Impact: Familial risks of nine particular cancers were associated with risks of second primary cancers (SPCs), and, in addition, any family history was associated with the risk. The results showed that in NHL patients with an SPC, SPC was the most common cause of death and accounted for 40% of deaths. Consistently, SPCs negatively influenced survival rates. Survival in non-Hodgkin lymphoma was worsened by second primary cancer, particularly, if it was known to be fatal as first primary cancer.

LIST OF ABBREVIATIONS

CI	Confidence interval
CUP	Cancer of unknown primary
HR	Hazard ratio
ICD	International classification of disease
NHL	non-Hodgkin lymphoma
RR	Relative risk
SCC	Squamous cell carcinoma
SPC	Second primary cancer

CONFLICT OF INTEREST STATEMENT

A.H. is a shareholder in Targovax ASA. A.H. is an employee and shareholder in TILT Biotherapeutics Ltd. Other authors declare no conflict of interest.

ABSTRACT

Second primary cancers (SPCs) account for an increasing proportion of all cancer diagnoses and family history of cancer may be a risk factor for SPCs. Using the Swedish Family-Cancer Database on non-Hodgkin lymphoma (NHL), we assessed the influence of family history on risk of SPCs and of SPCs on survival. NHL patients were identified from the years 1958 to 2015 and generalized Poisson models were used to calculate relative risks (RRs) for SPCs and familial SPCs. Among 14,393 NHL patients, a total of 1,866 (13.0%) were diagnosed with SPC. Familial risk of nine particular cancers were associated with risks of these cancers as SPCs, with 2 to 5-fold increases in RRs. At the end of a 25-year follow-up period, the survival probability for persons with SPC was only 20% of that for patients without SPC; the hazard ratio for SPC was 1.59 (95% CI: 1.46 – 1.72). Survival could be predicted by the prognostic groups based on first cancers and HRs increase systematically with worse prognosis yielding a trend of $P = 4.6 \times 10^{-5}$. SPCs had deleterious consequences for survival in NHL patients. Family history was associated with increasing numbers of SPCs. Prevention of SPCs and their early detection is an important target in the overall strategy to improve survival in NHL patients. Counseling for avoidance of risk factors and targeted screening based on family history are feasible steps in risk reduction.

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is the most common hematological malignancy, for which risk factors include immunosuppression and other types of immunodeficiency and autoimmunity, chronic inflammation induced by viral or other microbial causes and family history of NHL [1, 2]. Survival of NHL depends on tumor subtypes, the most common of which include a relatively benign follicular lymphoma and aggressive diffuse large B-cell lymphoma [3]. The management of NHL has evolved over the years and this has contributed to the improved survival rate [1, 4-6]. In particular, with the advent of rituximab around 2002, survival has improved dramatically for many subtypes of NHL [7-9]. Consequently, an increasing number of second primary cancers (SPCs) are being observed in NHL survivors [10-16]. According to our recent study, around 1 in 12 NHL patients are diagnosed with an SPC [17].

In the present study, we focused on familial risk factors and consequences of SPC in terms of mortality. We report on 14,393 NHL patients, based on an analysis from the Swedish Family-Cancer Database. Our goal was to examine two novel aspects of SPCs in NHL patients. We hypothesize that family history of a particular cancer may increase the risk of that cancer to appear as SPC; thus, a family history of breast cancer may increase the frequency of breast cancer as SPC in NHL patients. There is previous evidence on increased risk of SPC associated with family history in survivors of Hodgkin lymphoma and multiple myeloma [18, 19]. We further hypothesized that mortality of patients with SPC may be influenced by the type of SPC, which is in-line with distinct mortality differences known for first primary cancers [20, 21]. While family history may increase the numbers of SPCs we wanted, in addition, to test whether it also interferes with survival in NHL patients.

PATIENTS AND METHODS

The Swedish Family-Cancer Database includes data on the Swedish population collated in family data and is linked to the Swedish Cancer Registry, which was founded in 1958 and covers the entire population with more than two million cancers included in the dataset [22]. The registry is based on compulsory cancer notifications made by clinicians and pathologists/cytologists [23]. Since the mid-1980's, there are six regional registries associated with the oncological centers in each medical region of Sweden where the registration, coding and major check-up and correction work is performed. The regionalization implies a high level of quality as a result of close contact between the

Swedish Cancer Registry at the regional level and the reporting clinician thus simplifying the task of checking and correcting the data. All registered NHL cases were histologically verified. While the cancer registry does not publish separate statistics on histological verification of SPCs, they are included with primary cancers for which histological verification has been approximately 98% from the 1970s onwards [24]. An *ad hoc* study on the diagnostic accuracy of second neoplasms found 98% to be correctly classified [25]. NHLs were identified through reference to the 7th revision of International Classification of Diseases (ICD). NHL patients were followed from diagnosis until death, detection of an SPC, emigration or December 31, 2015, whichever came first. NHL patients with second primary NHL were not considered. Person-years and SPCs were categorized according to age (5-year bands), sex, socioeconomic index (six groups), region (four groups) and calendar year. Category-specific incidence rates among NHL patients were multiplied by the corresponding person-years at risk to estimate the expected number of malignancies in respective strata.

Relative risks (RRs) were assessed for SPC by means of incidence rate ratios, regressed over a fixed-effects generalized Poisson model. RRs for SPCs were obtained by comparing incidence rates for each SPC in NHL patients with respective population background rates for primary cancer. In familial analyses, RRs were calculated for the offspring generation (born after 1931). Family history was recorded from the beginning of cancer registration in Sweden (1958 onwards). The family history was called when the SPC was the same, concordant cancer, which was diagnosed in the first-degree relative (parent or sibling). Sex, age group, calendar-period, socioeconomic status and residential areas were treated as potential confounders and were adjusted for in the multivariable regression model. We used waiting time distribution with Poisson assumption to estimate RRs and corresponding confidence intervals (CIs) were calculated for 5%, 1% and 0.1% levels of significance respectively, and p-values associated with RRs were obtained with two-tailed tests against Chi-square distribution with one degree of freedom [26]. Test of trend was performed to compare RRs of familial cases of SPCs to that of non-familial cases obtained from the Poisson regression.

Survival was modeled with multivariable Cox-regression model, meeting the proportional-hazards assumption, adjusted for sex, age group, residential area and socioeconomic status. In this model, the diagnosis of SPC was treated time-dependent variable in order to avoid the immortal time bias [27]. Deaths due to NHL or any other cause resulted in censoring. Considering the large changes in incidence and survival in NHL, we restricted survival analysis to the latter part of the total follow-up, starting follow-up from 1991 and thus rendering 25 years of maximal follow-up time. We assessed survival probabilities and hazard ratios (HRs) of NHL patients with SPC against the baseline hazard

for patients without SPC. We grouped SPCs into three 'prognostic groups' based on 5-year relative survival of these cancers as first primary cancer [28, 29]: 'good survival' (relative survival >60%) included cancers in lip, larynx, anus, breast, cervix, endometrium, prostate, testis, male genitals, kidney, bladder, melanoma, skin (squamous cell, SCC), eye, thyroid gland and endocrine and Hodgkin lymphoma; 'moderate survival' (40-60%) included cancers in upper aerodigestive tract (except lip and larynx), salivary glands, small intestine, colorectum, female genitals, bone and connective tissue and non-Hodgkin lymphoma; 'poor survival' (<40%) included cancers in stomach, esophagus, liver, pancreas, lung, ovary and nervous system and myeloma. We analyzed the effect of family history of cancer on survival with further stratification. To obtain a deeper understanding of this impact of specific family histories, we also analyzed cancer type specific survival.

Causes of death were available in the database as obtained from the national causes of death register. The underlying cause of death is ascertained by merging the cancer registry and the death certificate notification [30]. Causes of deaths were annotated with the following ICD codes, ICD-7 (1958 –1968), ICD-8 (1969 – 1986), ICD-9 (1987 - 1996) and with ICD-10 (1997 onwards). All cancer-related deaths were stratified into NHL, SPC, 'higher order primaries', 'other cancer' and non-neoplastic cause of death 'other causes'. 'Other cancer' includes cases diagnosed at the issue of death certificates, referred to 'death certificate notifications' [23, 30, 31]. These notifications are not used by the Swedish Cancer Registry to complement cancer data in contrast to the other Nordic Cancer Registries [23, 30, 31]. We have found that the notifications often included multiple cancers and cancer of unknown primary (CUP). In our previous studies, we have earlier used these notifications as information on metastases [32, 33]. If the death certificate notification matched the organ site of the reported primary cancer it was classified to that site but in some cases, when such an assignment could not be made, the classification was put to 'other cancer'. A small number (N=63) of NHL patients were reported to have NHL as SPC; these were not considered.

All statistical analyses were done with R version 3.5 and SAS version 9.4.

The study was approved by the Ethical Committee of Lund University, without requirement for informed consent. People could choose to opt out before the research database was constructed, which was advertised in major newspapers. The project database is located at the Center for Primary Health Care Research in Malmö, Sweden.

RESULTS

A total of 14,393 NHL patients (median age at diagnosis 59 years) belonged to the offspring generation for which RRs were calculated. A total of 1,866 (13.0%) of these patients were diagnosed with SPC; of these 1,250 (67.0%) had a first-degree family history of any cancer (median follow-up to SPC six years) while 616 had no family history but the median follow-up to SPC was also six years. The total number of deaths numbered 5,271 (36.6% of all NHL patients), of which 4,267 had no SPC (34.1% of all NHL patients without SPC) while 1,004 had an SPC (53.8% of all with SPC).

Familial risks for SPC are shown in **Table 1** for 12 cancers with two or more concordant familial patients (i.e. SPC was the same cancer that was diagnosed in the family member) and, in the bottom line, for any familial patients, including concordant and discordant family histories. The risk for SPC without family history was increased for many SPCs but we used trend test to assess the influence of family history on risk. For nine cancers the trend test was significant. The test was highly significant for breast (RR, 2.55 [95% CI, 1.79 – 3.63] with family history against an RR of 0.92 [0.75 – 1.13] without family history) and prostate cancers (1.88 [1.49 – 2.37] vs. 0.84 [0.74 – 0.97]). The differences between these RRs were much higher for stomach cancer (10.92 [4.90 – 24.33] vs. 2.26 [1.61 – 3.19]), bladder cancer (4.56 [2.17 – 9.56] vs. 1.90 [1.52 – 2.38]), melanoma (4.03 [1.81 – 8.98] vs. 1.66 [1.33 – 2.06]) and cancer of unknown primary (CUP, 7.02 [2.92 – 16.87] vs. 2.08 [1.59 – 2.73]). For NHL with SPSs of 'any', concordant and discordant family history, the RRs were 1.86 [1.76 – 1.96] vs. 1.58 [1.46 – 1.71].

We analyzed familial risks separately in two periods 1958-2003 and 2004-2015 in order to test if new therapies, such as rituximab, might have influenced familial risk [7]. For family history of any concordant SPC the case numbers were too few (51 in the latter and 141 in the former period) to provide conclusive results. We analyzed also family histories after specific histological subtypes of NHL (which were available from 1993 onwards). For diffuse large B-cell lymphoma, 31 SPCs with a concordant family history were recorded; for follicular lymphoma the number was 40. As the family histories covered approximately 10 different cancers the small case numbers did not allow conclusions about the possible histological differences.

Follow-up for survival studies started from 1991 and covered 11,586 NHL patients in the offspring generation of whom 3,661 (31.6%) had died by the end of 2015. SPC had deleterious consequences for survival in NHL (**Fig. 1**). Kaplan-Meier survival curves started to diverge from year six onwards, and by the end of 25-year follow-up in 2015, the survival probability for persons with SPC was only

20% of patients without SPC. The HR for patients with SPC was 1.59 (1355 cases, 688 deaths, 95% CI 1.46-1.72) compared to the baseline hazard (HR 1.00) of those without SPC (10,231 cases, 2973 deaths). Survival in NHL patients with SPC and family history was marginally worse (HR 1.07 [0.91 – 1.25]) than in those with SPC lacking a family history. We explored also the influence of some of the most common family histories and a concordant family history of breast cancer was particularly unfavorable (HR 2.64 [1.13 – 9.01] among 17 cases and 9 deaths) while concordant family histories of colorectal and prostate cancers did not influence survival (data not shown).

For the NHL patients with SPC, causes of death are shown in **Table 2**. As of the end of 2015, a total of 1,004 (53.8%) patients had died. SPCs accounted for 40.0% of all causes of death, followed by non-neoplastic 'other causes' (23.8%) and first primary cancer (20.9%), i.e. NHL. Fatal SPCs included esophageal, liver, lung and stomach cancers for which 70% or more of patients died of SPC. 'Other causes' were the most common cause of death for endocrine, skin (SCC) and a few other SPC patients. 'Other neoplasia' accounted for more than half of deaths for CUP.

Survival analysis among patients with SPC and stratified in prognostic groups (see methods) is shown in **Fig. 2.** We observed monotonically differentiated survival probabilities in-line with the prognostic stratification: cancers with good prognosis (HR of 1.05 [1.00 – 1.12] among 759 cases and 276 deaths), moderate prognosis (1.42 [1.14 – 1.79] among 349 cases and 204 deaths) and poor prognosis (2.27 [1.73 – 2.82] among 210 cases and 171 deaths). A trend test over the three prognostic groups (good, moderate and poor) yielded a $P = 4.6 \times 10^{-5}$.

DISCUSSION

The four novel findings of the present study on SPCs after NHL included demonstration of an increased risk of SPCs depending on family history. Furthermore, there was unfavorable overall survival in patients with SPC and high mortality related to defined SPCs. In addition, as a related finding, there was unfavorable survival depending on the prognostic group of SPCs. We showed that for nine concordant cancers, family history was associated with a significant risk of SPCs including cancers such as breast, prostate and bladder cancers and melanoma for with the RRs were increased from 2 to 5-fold. Even for any family history (concordant and discordant) the RR was highly significant, 1.86 vs. 1.58 compared to those without family history. Previous evidence along the same lines was reported for rarer cancers, Hodgkin lymphoma and multiple myeloma [18, 19]. Family

history and testing for genetic susceptibility offers a strategy for prevention of fatal SPC when taken at NHL diagnosis, and relevant advice could be given, for example, regarding lung cancer (smoking cessation), colorectal, prostate and skin cancers (screening) and stomach and bladder cancer (early signs).

We tested also whether family history of SPC might have changed after introduction of novel therapies around 2003 or whether family histories of SPCs were distinct for histological types of NHL. However case numbers in both of these analyses were too few to allow conclusions. We have addressed the same questions in our recent study on SPCs in NHL irrespective of family history [17]. Even among all SPCs, no definite changes could be found in the period-specific analysis (Supplementary Tables 4 and 5 [17]). However histological types of NHL showed distinct patterns of SPCs which appeared to correlate with survival rates for the specific subtypes [17].

As for the second novel part, the dramatically worse survival in patients with SPC shown in Kaplan-Meier survival analysis where the curve for patients with SPC departed from NHL without SPC at six years of follow-up and reached by 25 years to only 20% of the survival probability for patients without SPCs. Although family history contributed to increased numbers of SPCs, as pointed out above, it did not influence overall survival. However, the HR for survival in patients with breast cancer with a concordant family history was unfavorable (2.64 [1.13 – 9.01]). However, case numbers were small.

According to the third novelty, we showed that mortality of SPCs was in line with known mortality of first primary cancers. Both the most fatal (esophageal, liver, lung and stomach) and least fatal (endocrine, skin) cancers were among those predicted from survival studies among first cancers [20, 21]. Unexpectedly, for CUP as SPC other neoplasia was given as the cause of death in over half of the patients. The reason for this is the Swedish practice of assigning death in CUP patients to the fatal metastatic cancer that the death registrar assumed to be the final cause [34]; CUP is the most fatal of all cancers with a median survival of two months and indeed we observed a mortality rate of 98% (57 of 58 NHL patients with CUP as SPC had died) [35].

As the related (fourth) novelty, we formally tested survival in three prognostic groups, which were constructed from the reported survival experience of first primary cancers [28, 29]. Survival could be predicted by the prognostic groups and HRs increase systematically from no SPC 1.00 to good

prognosis 1.05, moderate prognosis 1.42 and poor prognosis 2.27. A trend test over the three prognostic groups was convincing, $P = 4.6x10^{-5}$.

The strengths of this study include extensive nationwide coverage of cancers, high level of histological verification of the reported cancers and, for the family study, practically complete national family structures [22, 30]. Critical to the present study is the level of reporting of SPCs, which in Sweden is mandated by the overall obligation to report all cancers and certain other tumors to the cancer registry; consequently, some 20% of the reported cancers are multiple primaries [24]. The high level of reporting of SPC is also evident in international pooling studies where the Swedish rates of SPCs are among the highest of all cancer registries [10]. Limitations of the study are small case numbers when considering familial risk and SPC, rare events for any particular cancer, even in the present largest study published on the subject. We were lacking clinical data at presentation, any treatment data and some possible risk factors which may confound the observed associations. In the future, with accumulating case numbers, it will be possible to test the findings in the largest subtypes of NHL.

In conclusion, our results showed that SPCs have deleterious consequences for survival in NHL patients. The consequences were particularly devastating for cancers classified as fatal primary cancers. Family history augmented the deleterious consequences by contributing increasing numbers of SPCs. Hence prevention of SPC by considering individual risk factors (such as smoking) and by careful monitoring of family history would be important targets in the overall strategy to improve survival in NHL patients.

ACKNOWLEDGEMENT

G.Z. is a doctoral student supported by the China Scholarship Council (201606100057). A.S. is the recipient of a Guest Scientist Fellowship of DKFZ. We are grateful to Patrick Reilly for language editing. The study was supported by the Harald Huppert Foundation, Deutsche Krebshilfe, Jane and Aatos Erkko Foundation, Sigrid Juselius Foundation, Finnish Cancer Organizations, Swedish Research Council.

AUTHOR CONTRIBUTIONS

Design: KH, SC

Acquisition of data: JS, KS

Statistical analysis and interpretation: SC, GZ, KH, AH, AS, AF.

Table and figures: SC.

Manuscript writing: KH.

Manuscript editing: RSH, SC, AS, AH, AF, KS, JS.

Approval of the final text: All authors

REFERENCES

1. Shankland KR, Armitage JO, Hancock BW. Non-Hodgkin lymphoma. *Lancet* 2012;**380**: 848-57.

2. Fallah M, Kharazmi E, Pukkala E, Tretli S, Olsen JH, Tryggvadottir L, Sundquist K, Hemminki K. Familial risk of non-Hodgkin lymphoma by sex, relationship, age at diagnosis and histology: a joint study from five Nordic countries. *Leukemia* 2016;**30**: 373-8.

3. Evans LS, Hancock BW. Non-Hodgkin lymphoma. *Lancet* 2003;**362**: 139-46.

4. Pianko MJ, Moskowitz AJ, Lesokhin AM. Immunotherapy of Lymphoma and Myeloma: Facts and Hopes. *Clin Cancer Res* 2018;**24**: 1002-10.

5. van de Schans SA, Gondos A, van Spronsen DJ, Rachtan J, Holleczek B, Zanetti R, Coebergh JW, Janssen-Heijnen ML, Brenner H. Improving relative survival, but large remaining differences in survival for non-Hodgkin's lymphoma across Europe and the United States from 1990 to 2004. *J Clin Oncol* 2011;**29**: 192-9.

6. Howlader N, Mariotto AB, Besson C, Suneja G, Robien K, Younes N, Engels EA. Cancer-specific mortality, cure fraction, and noncancer causes of death among diffuse large B-cell lymphoma patients in the immunochemotherapy era. *Cancer* 2017;**123**: 3326-34.

7. Junlen HR, Peterson S, Kimby E, Lockmer S, Linden O, Nilsson-Ehle H, Erlanson M, Hagberg H, Radlund A, Hagberg O, Wahlin BE. Follicular lymphoma in Sweden: nationwide improved survival in the rituximab era, particularly in elderly women: a Swedish Lymphoma Registry study. *Leukemia* 2015;**29**: 668-76.

8. Sarkozy C, Maurer MJ, Link BK, Ghesquieres H, Nicolas E, Thompson CA, Traverse-Glehen A, Feldman AL, Allmer C, Slager SL, Ansell SM, Habermann TM, et al. Cause of Death in Follicular Lymphoma in the First Decade of the Rituximab Era: A Pooled Analysis of French and US Cohorts. *J Clin Oncol* 2019;**37**: 144-52.

9. Mohammed R, Milne A, Kayani K, Ojha U. How the discovery of rituximab impacted the treatment of B-cell non-Hodgkin's lymphomas. *Journal of blood medicine* 2019;**10**: 71-84.

10. Brennan P, Scelo G, Hemminki K, Mellemkjaer L, Tracey E, Andersen A, Brewster DH, Pukkala E, McBride ML, Kliewer EV, Tonita JM, Seow A, et al. Second primary cancers among 109 000 cases of non-Hodgkin's lymphoma. *Br J Cancer* 2005;**93**: 159-66.

11. Tward JD, Wendland MM, Shrieve DC, Szabo A, Gaffney DK. The risk of secondary malignancies over 30 years after the treatment of non-Hodgkin lymphoma. *Cancer* 2006;**107**: 108-15.

12. Mudie NY, Swerdlow AJ, Higgins CD, Smith P, Qiao Z, Hancock BW, Hoskin PJ, Linch DC. Risk of second malignancy after non-Hodgkin's lymphoma: a British Cohort Study. *J Clin Oncol* 2006;**24**: 1568-74.

13. Hemminki K, Lenner P, Sundquist J, Bermejo JL. Risk of subsequent solid tumors after non-Hodgkin's lymphoma: effect of diagnostic age and time since diagnosis. *J Clin Oncol* 2008;**26**: 1850-7.

14. Morton LM, Curtis RE, Linet MS, Bluhm EC, Tucker MA, Caporaso N, Ries LA, Fraumeni JF, Jr. Second malignancy risks after non-Hodgkin's lymphoma and chronic lymphocytic leukemia: differences by lymphoma subtype. *J Clin Oncol* 2010;**28**: 4935-44.

15. Lorenzo Bermejo J, Pukkala E, Johannesen TB, Sundquist J, Hemminki K. Age-time risk patterns of solid cancers in 60 901 non-Hodgkin lymphoma survivors from Finland, Norway and Sweden. *Br J Haematol* 2014;**164**: 675-83.

16. Tao L, Clarke CA, Rosenberg AS, Advani RH, Jonas BA, Flowers CR, Keegan THM. Subsequent primary malignancies after diffuse large B-cell lymphoma in the modern treatment era. *Br J Haematol* 2017;**178**: 72-80.

17. Chattopadhyay S, Sud A, Zheng G, Yu H, Sundquist K, Sundquist J, Försti A, Houlston R, Hemminki A, Hemminki K. Second primary cancers in non-Hodgkin lymphoma: Bi-directional analyses suggesting role for immune dysfunction *Int J Cancer* 2018;**143**: 2449-57.

18. Sud A, Thomsen H, Sundquist K, Houlston RS, Hemminki K. Risk of second cancer in Hodgkin lymphoma survivors and the influence of family history. *J Clin Oncol* 2017;**35**: 1584-90.

19. Chattopadhyay S, Yu H, Sud A, Sundquist J, Forsti A, Hemminki A, Hemminki K. Multiple myeloma: family history and mortality in second primary cancers. *Blood cancer journal* 2018;**8**: 75.

20. Baili P, Di Salvo F, Marcos-Gragera R, Siesling S, Mallone S, Santaquilani M, Micheli A, Lillini R, Francisci S. Age and case mix-standardised survival for all cancer patients in Europe 1999-2007: Results of EUROCARE-5, a population-based study. *Eur J Cancer* 2015;**51**: 2120-9.

21. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, Bannon F, Ahn JV, Johnson CJ, Bonaventure A, Marcos-Gragera R, Stiller C, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet* 2015;**385**: 977-1010.

22. Hemminki K, Ji J, Brandt A, Mousavi SM, Sundquist J. The Swedish Family-Cancer Database 2009: Prospects for histology-specific and immigrant studies. *Int J Cancer* 2010;**126**: 2259-67.

23. Pukkala E, Engholm G, Hojsgaard Schmidt LK, Storm H, Khan S, Lambe M, Pettersson D, Olafsdottir E, Tryggvadottir L, Hakanen T, Malila N, Virtanen A, et al. Nordic Cancer Registries - an overview of their procedures and data comparability. *Acta Oncol* 2018;**57**: 440-55.

24. Centre for Epidemiology. *Cancer incidence in Sweden 2012*ed. Stockholm: The National Board of Health and Welfare, 2013.

25. Frödin J-E, Ericsson J, Barlow L. Multiple primary malignant tumors in a national cancer registry. Reliability of reporting. *Acta Oncol* 1997;**36**: 465-9.

26. Tibshirani R. Estimating Transformations for Regression via Additivity and Variance Stabilization. *J Am Stat Associat* 1988;**83**: 394-405.

27. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. *J Clin Oncol* 2013;**31**: 2963-9.

28. Talbäck M, Dickman PW. Predicting the survival of cancer patients recently diagnosed in Sweden and an evaluation of predictions published in 2004. *Acta Oncologica* 2012;**51**: 17-27.

29. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, Trama A, Visser O, Brenner H, Ardanaz E, Bielska-Lasota M, Engholm G, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. *The Lancet Oncology* 2014;**15**: 23-34.

30. Ji J, Sundquist K, Sundquist J, Hemminki K. Comparability of cancer identification among Death Registry, Cancer Registry and Hospital Discharge Registry. *Int J Cancer* 2012;**131**: 2085-93.

31. Brooke HL, Talback M, Hornblad J, Johansson LA, Ludvigsson JF, Druid H, Feychting M, Ljung R. The Swedish cause of death register. *Eur J Epidemiol* 2017;**32**: 765-73.

32. Riihimaki M, Hemminki A, Fallah M, Thomsen H, Sundquist K, Sundquist J, Hemminki K. Metastatic sites and survival in lung cancer. *Lung Cancer* 2014;**86**: 78-84.

33. Riihimaki M, Hemminki A, Sundquist J, Hemminki K. Patterns of metastasis in colon and rectal cancer. *Scientific reports* 2016;**6**: 29765.

34. Hemminki K, Bevier M, Sundquist J, Hemminki A. Cancer of unknown primary (CUP): does cause of death and family history implicate hidden phenotypically changed primaries? *Ann Oncol* 2012;**23**: 2720-24.

35. Hemminki K, Bevier M, Hemminki A, Sundquist J. Survival in cancer of unknown primary site: population-based analysis by site and histology. *Ann Oncol* 2012;**23**: 1854-63.

FIGURE LEGEND

Fig 1. Kaplan-Meier survival curves for non-Hodgkin lymphoma patients with and without second primary cancer since 1991 (SPC). The shading around the curves shows 95%CIs.

Fig 2. Kaplan-Meier survival curves for non-Hodgkin lymphoma patients (1991 onwards) with second primary cancer divided in three prognostic groups based on survival of these cancers as first primary cancers, as described in methods : 'good prognosis'. relative survival >60%, 'moderate prognosis', relative survival 40-60%, and 'poor prognosis', relative survival <40%. The shading around the curves shows 95%CIs.

Table 1 Relative risks of second primary cancers among non-Hodgkin lymphoma survivors stratified over family history of cancer

	With family history				No family history				Trend test *P* value
Second primary cancer	**N**	**RR**	**L_{CI}**	**U_{CI}**	**N**	**RR**	**L_{CI}**	**U_{CI}**	
Upper aerodigestive tract	2	**4.10**	1.03	16.40	45	***2.21***	1.65	2.96	0.092
Stomach	6	***10.92***	4.90	24.33	33	***2.26***	1.61	3.19	0.013
Colorectum	24	***2.09***	1.40	3.12	131	***1.35***	1.14	1.60	0.002
Lung	19	***3.44***	2.19	5.40	127	***1.64***	1.38	1.95	0.008
Breast	31	***2.55***	1.79	3.63	96	0.92	0.75	1.13	<0.001
Prostate	71	***1.88***	1.49	2.37	205	**0.84**	0.74	0.97	<0.001
Kidney	2	3.25	0.81	12.99	58	***2.59***	2.00	3.36	0.269
Urinary bladder	7	***4.56***	2.17	9.56	76	***1.90***	1.52	2.38	0.017
Melanoma	6	***4.03***	1.81	8.98	79	***1.66***	1.33	2.06	0.019
Skin (squamous cell carcinoma)	13	***7.43***	4.31	12.80	216	***5.11***	4.46	5.85	0.009
Leukemia	4	***4.85***	1.82	12.92	121	***4.55***	3.80	5.45	0.215
Cancer of unknown primary	5	***7.02***	2.92	16.87	53	***2.08***	1.59	2.73	0.037
Any	1250	***1.86***	1.76	1.96	616	***1.58***	1.46	1.71	<0.001

Abbreviations:
FDR, first degree relative; N, total number; RR, relative risk; **L_{CI}**, **U_{CI}**, lower and upper 95% confidence intervals;
*Cancer sites with at least two or more familial cases are shown; 'All' includes all cancer sites.
**Bold, italics and underline represent 5%, 1% and 0.01% level of significance.

Table 2 Distribution of causes of death in non-Hodgkin lymphoma patients with second primary cancer diagnosis

	Causes of death									
	Second primary cancer		First primary cancer		Higher order primaries		Other neoplasia		Other causes	
Second primary cancer	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Upper aerodigestive tract	8	24.2	7	21.2	3	9.1	1	3.0	14	42.4
Esophagus	13	86.7	2	13.3	-	-	-	-	-	-
Stomach	21	70.0	2	6.7	-	-	6	20.0	1	3.3
Colorectum	40	49.4	10	12.3	1	1.2	5	6.2	25	30.9
Liver	23	74.2	3	9.7	-	-	2	6.5	3	9.7
Pancreas	23	65.7	3	8.6	-	-	3	8.6	6	17.1
Lung	88	72.7	12	9.9	1	0.8	4	3.3	16	13.2
Breast	10	28.6	10	28.6	6	17.1	2	5.7	7	20.0
Endometrium	3	33.3	2	22.2	2	22.2	-	-	2	22.2
Ovary	6	60.0	-	-	1	10.0	1	10.0	2	20.0
Prostate	18	20.5	26	29.5	5	5.7	7	8.0	32	36.4
Kidney	11	36.7	5	16.7	3	10.0	3	10.0	8	26.7
Urinary bladder	12	29.3	12	29.3	3	7.3	-	-	14	34.1
Melanoma	9	36.0	5	20.0	3	12.0	1	4.0	7	28.0
Skin (squamous cell carcinoma)	2	2.1	31	32.3	7	7.3	18	18.8	38	39.6
Nervous system	12	40.0	9	30.0	1	3.3	2	6.7	6	20.0
Endocrine glands	-	-	3	27.3	-	-	1	9.1	7	63.6
Hodgkin lymphoma	7	41.2	5	29.4	2	11.8	-	-	3	17.6
Multiple myeloma	9	60.0	2	13.3	-	-	1	6.7	3	20.0
Leukemia	45	45.0	33	33.0	3	3.0	4	4.0	15	15.0
Cancer of unknown primary	8	14.0	10	17.5	-	-	33	57.9	6	10.5
Total	377	40.0	197	20.9	42	4.5	101	10.7	224	23.8

Abbreviations:
N, Total number; %, percentage;

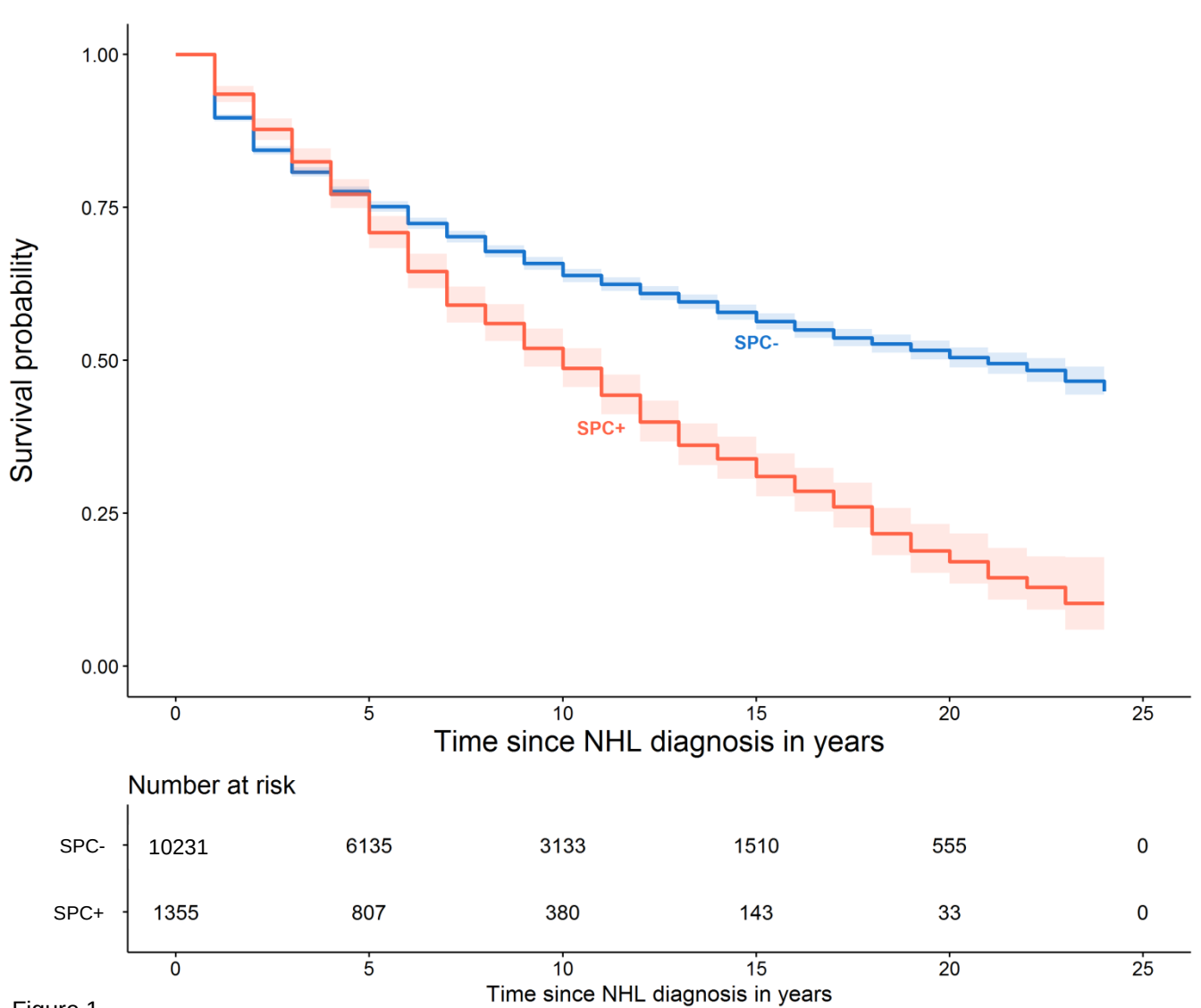
Survival probability
1.00
0.75
0.50
0.25
0.00
SPC-
SPC+
0
5
10
15
20
25
Time since NHL diagnosis in years
Number at risk
SPC-
10231
6135
3133
1510
555
0
SPC+
1355
807
380
143
33
0
0
5
10
15
20
25
Time since NHL diagnosis in years

Figure 1

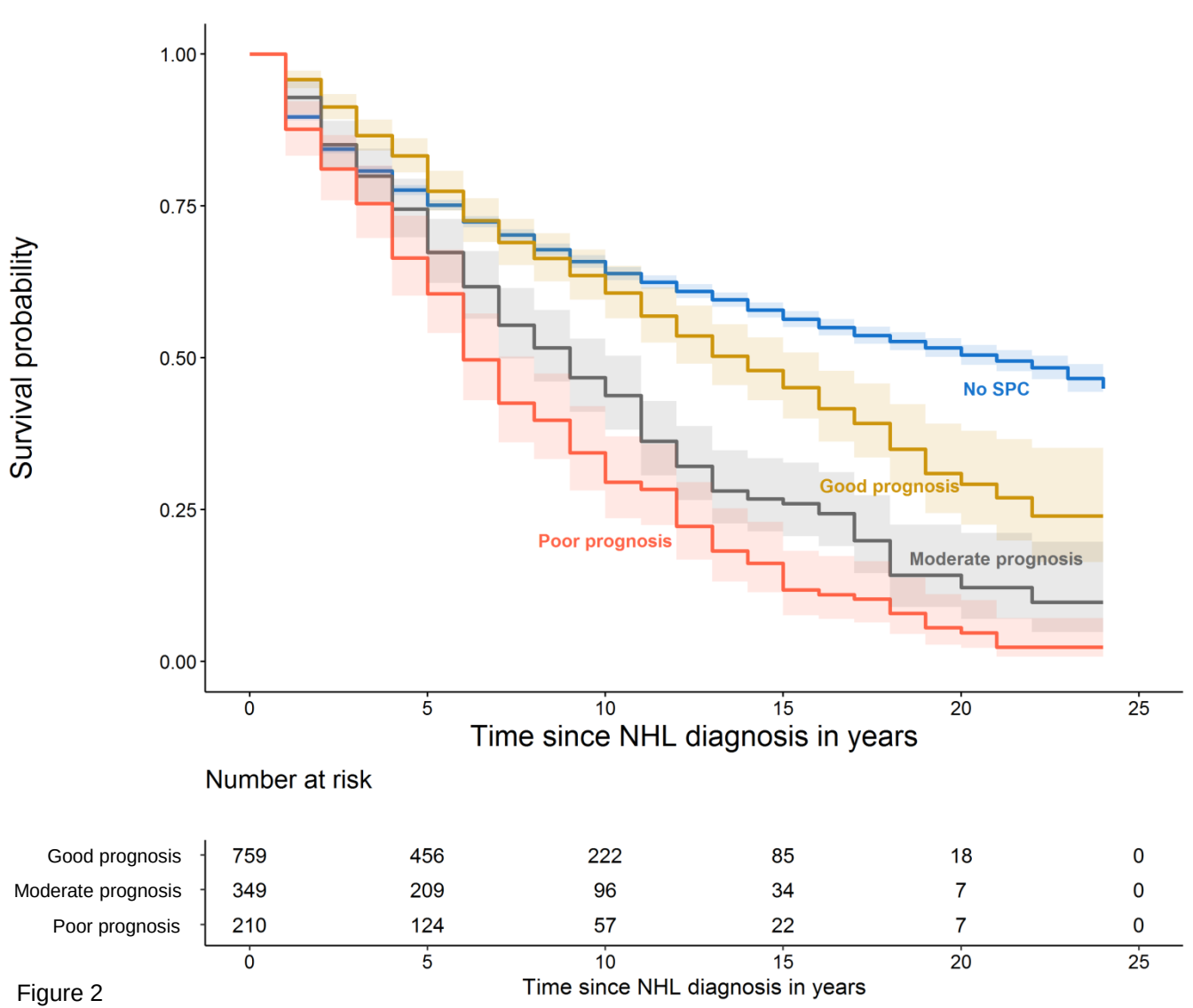
Survival probability
1.00
0.75
0.50
0.25
0.00
No SPC
Good prognosis
Moderate prognosis
Poor prognosis
0
5
10
15
20
25
Time since NHL diagnosis in years
Number at risk
Good prognosis 759 456 222 85 18 0
Moderate prognosis 349 209 96 34 7 0
Poor prognosis 210 124 57 22 7 0
0
5
10
15
20
25
Time since NHL diagnosis in years

Figure 2