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# Late Outcomes of Adult Survivors of Childhood Non-Hodgkin Lymphoma: A Report from the St. Jude Lifetime Cohort Study

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## Abstract

**Background—**Survivors of childhood non-Hodgkin lymphoma (NHL) are at increased risk for chronic health conditions. The objective of this study was to characterize health conditions,

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**AUTHOR CONTRIBUTIONS**

Study concepts: MJE, JTS, MMH, LLR, DAM
Study design: MJE, JTS, MMH, LLR, DAM
Data acquisition: MJE, DBC, NZ, NB, KS, TMB, KRK, KKN, WC, LLR, DAM
Quality control of data and algorithms: MMH, LLR, KKN, KS
Data analysis and interpretation: All authors
Statistical analysis: NZ, KS, MJE, DAM, WL
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**CONFLICT OF INTEREST STATMENT**

The author(s) indicated no potential conflicts of interest.

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neurocognitive function, and physical performance among a clinically evaluated cohort of 200 childhood NHL survivors.

**Methods—**Chronic health and neurocognitive conditions were graded per a modified version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) and impaired physical function defined as performance <10$^{th}$ percentile of normative data. Multivariable regression was used to investigate associations between sociodemographic characteristics, therapeutic exposures, and outcomes.

**Results—**Survivors were a median age of 10 years (range 1–19) at diagnosis and 34 years (20–58) at evaluation. Eighty-eight (44%) received radiation, 46 (23%) cranial radiation, and 69 (35%) high-dose methotrexate. Most prevalent CTCAE Grades 3–4 (severe-life-threatening) conditions were obesity (35%), hypertension (9%), and impairment of executive function (13%), attention (9%), and memory (4%). Many had impaired strength (48%), flexibility (39%), muscular endurance (36%), and mobility (36%). Demographic and treatment-related factors were associated with the development of individual chronic diseases and functional deficits.

**Conclusions—**Clinical evaluation identified a high prevalence of chronic health conditions, neurocognitive deficits, and performance limitations in childhood NHL survivors.

### Keywords

non-Hodgkin lymphoma; late-effects; chronic health conditions; neurocognitive; survivorship

## BACKGROUND

Treatment intensification has increased the 5-year overall survival rate for childhood non-Hodgkin lymphoma (NHL) from 45% in 1975 to now greater than 85%.[1] Improved survival has resulted in recognition of the long-term sequelae of cancer therapy [2] and motivated the use of risk-adapted therapies and the omission of radiation from most current frontline treatment regimens.[3]

Heterogeneity among the histologic classification systems and treatment regimens has resulted in limited access to uniform cohorts within which to assess the long-term health impacts of NHL therapy.[4, 5] Furthermore, late effects in NHL survivors have been investigated largely within the context of broader survivorship cohorts, potentially missing an opportunity to understand the unique impact of the combinations of therapy administered for childhood NHL.[2] Despite these limitations, existing data suggest that NHL survivors, compared to sibling controls, experience higher mortality, as well as performance limitations and health conditions that interfere with work or school attendance.[4, 6] The ability to discriminate late-occurring health conditions in NHL survivors will provide primary care and specialty clinicians tasked with managing long-term survivorship care with the knowledge necessary for early detection and attenuation of acquired risk factors. Therefore, our objective was to characterize late chronic health conditions, neurocognitive deficits, and physical performance limitations among a clinically evaluated cohort of adult survivors of childhood NHL.

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# PROCEDURE

## Study Population

Following informed consent, participants were enrolled in the St. Jude Lifetime cohort study (SJLIFE), an institutional review board-approved study designed to ascertain health outcomes in adult childhood cancer survivors. Detailed study methods have been described.[7] Briefly, eligible subjects for this analysis were ≥18 years old, treated for NHL at St. Jude Children's Research Hospital (SJCRH), and survived ≥10 years after diagnosis. Cumulative treatment exposures (including chemotherapy and radiation doses to individual anatomic sites), and medical events during and after therapy were abstracted from medical records. All survivors underwent a core assessment comprised of a history and physical examination, including measurement of resting heart rate and blood pressure, laboratory studies (complete blood cell count with differential, comprehensive metabolic panel, fasting lipid profile, insulin, glycosylated hemoglobin, thyroid stimulating hormone, free thyroxine, luteinizing hormone, follicle stimulating hormone, testosterone [male], estradiol [female], and urinalysis), and a comprehensive physical performance assessment (measurement of body composition and neuromuscular system integrity). Participants completed comprehensive questionnaires providing demographic and intervening medical history data. In addition, participants underwent comprehensive risk-based medical evaluations (echocardiography, pulmonary function testing, semen analysis, and cataract assessment) and neurocognitive testing on the SJCRH campus per guidelines endorsed by the Children's Oncology Group.[8, 9] As a result of early observation of cognitive impairment in SJLIFE, neurocognitive testing has evolved since the outset of the cohort such that it has now become part of the universal assessment.

## Outcomes

Primary outcomes were chronic health conditions whose severity was classified per a modified version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.[10] Graded conditions are defined in Supplemental Table S1. Chronic health conditions occurring prior to evaluation and subsequent neoplasms (SNs) were validated by medical record and pathology review.

Three neurocognitive domains were assessed in individuals at risk for neurocognitive impairment related to previous cancer treatment [8]: 1) attention (Trail Making Test Part A [11] and Conners Continuous Performance Test [12]); 2) executive function (Trail Making Test Part B and Verbal Fluency,[11] and Digit Span Backward [13]); and 3) memory (California Verbal Learning Test [14]). Impairment was defined as ≥1 and <2 standard deviations (SD) (Grade 1, mildly impaired), ≥2 and <3 SD (Grade 2, moderately impaired), and ≥3 SD (Grade 3, severely impaired) below the mean age-adjusted population normative score on any one measure. Moderate impairment, falling below the lowest 3$^{rd}$ percentile for population norms, would be expected to impact instrumental activities of daily living (reading, writing), while severe impairment, falling below the lowest 0.3 percentile for population norms, would be expected to impact self-care activities of daily living (e.g. bathing and taking medications). One individual developed subsequent neurologic injury

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associated with neurocognitive impairment unrelated to cancer therapy and was excluded from the analyses of neurocognitive function.

Six functional status outcomes were assessed: 1) aerobic function (six-minute walk test [15, 16]); 2) strength (maximal hand grip [17] and peak isokinetic torque of the quadriceps at 60 degrees per second [18]); 3) muscular endurance (peak isokinetic torque of the quadriceps at 300 degrees per second [18]); 4) flexibility (sit and reach test [19] and ankle dorsiflexion range of motion [20]); 5) balance (sensory organization test) [21]; and 6) mobility (Timed Up and Go test [22]). Body composition was measured using waist-to-height ratio and percent fat from dual-energy x-ray absorptiometry.[23] Functional impairments were not considered as chronic conditions and therefore not assigned a CTCAE grade. Assessments falling below the lowest $10^{th}$ percentile for population normative data were considered abnormal and would be expected to impact instrumental activities of daily living (e.g. shopping for groceries or clothes).

### Statistical Analysis

Two-sample *t* tests and $\chi^2$ statistics were used to compare demographic and treatment-related characteristics between participants and eligible nonparticipants. Data for which <10% of a given outcome was missing were considered missing at random unless otherwise stated. Grades 1 and higher chronic conditions were considered clinically significant and included in relevant statistical analyses. Exceptions included hypertension, hypothyroidism, glucose intolerance, stroke and motor and sensory neuropathies, for which ≥Grade 2 was considered clinically significant. Predictors of interest for clinically significant chronic conditions and abnormal physical performance scores were selected *a priori* based on evidence from existing literature. Multivariable models were constructed for prevalent outcomes, retaining variables with a p-value ≤0.1 on univariate analysis. For rare outcomes (decreased ejection fraction, abnormal pulmonary function, hypogonadism, neuropathy), univariate analyses were conducted. Poisson regression models with robust error variance were used to model all chronic and physical performance outcomes.

Increased incidence of each SN was determined by first dividing the cohort into sex-, age-, race-, and calendar-year specific categories consistent with those for which incidences are described by the Surveillance, Epidemiology, and End Results data to calculate the person-time. Person-time at risk for SNs was calculated from 1 year after the diagnosis of NHL until diagnosis of SN, death, or last follow-up. Standardized incidence ratios (SIRs) were calculated by dividing the number of observed SNs by the number of expected.

## RESULTS

### Participants

Of 362 eligible NHL survivors, 200 (55%) underwent clinical assessments as of October 30, 2013 (Supplemental Figure S1). Participants were more likely to be female, younger, and fewer years from childhood cancer diagnosis, than non-participants (Table 1).

Participants were a median age of 10.0 years (range 1.0–19.0) at diagnosis and 34.0 years (20.0–58.0) at evaluation. Histological lymphoma subtypes comprised mature B-cell in 125

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(63%), lymphoblastic in 64 (32%), anaplastic large cell in 4 (2%), and other in 7 (3%). Nine individuals had received a hematopoietic stem cell transplant. Survivors were treated between 1964 and 2002.

## Chronic Conditions

The frequencies and severity of chronic conditions are listed in Table 2. The most prevalent included overweight/obesity (65%), elevated fasting glucose (37%), high total cholesterol (35%), and hypertension (25%). An additional 37% had evidence of prehypertension (Grade 1 hypertension). Among 164 individuals with a history of cardiotoxic therapies who underwent cardiac screening, 19 (12%) had cardiomyopathy, of which 7 (4%) were Grades 3–4.

Adjusted models, retaining variables significant after univariate analyses, were used to identify associations with chronic conditions for which the number of events was sufficient (Supplemental Table S2). Of note, current age (RR 1.1, 95% CI: 1.1–1.1, $p<0.01$) and body mass index ≥ 30 (RR 2.9, 95% CI: 1.6–5.3, $p<0.01$) were associated with an increased risk for hypertension. Current age (RR 1.04, 95% CI: 1.0–1.1, $p<0.01$) and abdominal radiation (RR 1.6, 95% CI: 1.1–2.4, $p=0.01$) were associated with an increased risk for high total cholesterol, while individuals of non-white race were at decreased risk (RR 0.2, 95% CI: 0.1–0.9, $p=0.04$) for the same. Similarly, current age (RR 1.03, 95% CI: 1.0–1.1, $p<0.01$), body mass index ≥ 25 and <30 (RR 1.5, 95% CI: 0.9–2.4, $p=0.02$), body mass index ≥ 30 (RR 2.0, 95% CI: 1.2–3.1, $p=0.02$), and abdominal radiation (RR 1.9, CI: 1.3–2.8, $p<0.01$) were associated with having elevated fasting glucose. Lastly, those of non-white race (RR 1.4, 95% CI: 1.1–1.8, $p<0.01$) and who received cranial radiation (RR 1.2, 95% CI: 1.0–1.5, $p=0.04$) were at increased risk for overweight/obesity, while females were at decreased risk for the same (RR 0.7, 95% CI: 0.5–0.9, $p<0.01$) compared to males. After excluding those who received cranial or abdominal radiation, 62% were overweight/obese, 29% had elevated fasting glucose, 30% high total cholesterol, and 20% hypertension.

Eight percent (15/200) experienced symptomatic primary gonadal failure (≥ Grade 2), among whom 4/15 were related to surgical resection (1 at cancer diagnosis, 3 during long-term follow-up). Among the remaining 11 non-surgical cases, all received alkylating agents (median [range] cyclophosphamide equivalent dose (CED) [24] of 11,975 mg/m$^2$ [1,651–47,788]) and 9 (82%) received radiation impacting the reproductive system.[8] Primary gonadal failure was associated in univariate analysis with radiation affecting the reproductive system (RR 31.5, 95% CI: 7.3–136.0, $p<0.01$). Among 121 males who received gonadotoxic therapy, 80 (67%) completed a semen analysis, 3 (2%) did not produce an adequate sample, 1 (0.8%) cancelled due to illness, and 37 (30.5%) declined, largely due to prior successful conception. Among those who received gonadotoxic therapy and completed a semen analysis, 19 (24%) had oligospermia and 10 (13%) azoospermia. Following multivariable adjustment, males treated with ≥4,000 mg/m$^2$ CED (RR 3.3, 95% CI: 1.5–7.0, $p<0.01$) and who received gonadal radiation (RR 2.2, 95% CI: 1.4–3.6, $p<0.01$) were at risk for oligospermia/azoospermia compared to those treated with <4,000 mg/m$^2$ CED and without radiation, respectively (Supplemental Table S2).

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All participants were screened for thyroid dysfunction. Although 68 of 200 individuals had previously received neck or thyroid radiation [8], only 27 of 200 had Grade 2 hypothyroidism. Among these 27 individuals, 21 (78%) had previously received neck or thyroid radiation (median [range]: 3,350 Gy [500–10,800]). Following adjustment for current age, survivors who received neck or thyroid irradiation were at risk for primary hypothyroidism compared to those who did not (RR 5.0, 95% CI: 1.8–13.8, p<0.01) (Supplemental Table S2).

## Subsequent Neoplasms

Twenty-one individuals developed 48 SNs (median 2, range: 1–10), 12 (57%) ≥Grade 3. Cancers for which incidences are not described by the Surveillance, Epidemiology, and End Results data were excluded from SIR calculations (non-melanoma skin cancers [27 basal cell carcinomas and 3 squamous cell carcinomas]). Overall, NHL survivors developed SNs at six times the expected rate of corresponding *de novo* cancers in the general population (observed/expected 6.3, 95% CI: 3.7–9.9) (Table 3). All occurred in previously irradiated individuals. Following adjustment for variables significant in univariate analyses (relapsed disease), exposure to cranial radiation (CRT) (RR 2.4, 95% CI: 1.1–5.2, p=0.03) and older attained age (RR 1.1, 95% CI: 1.06–1.14, p<0.01) were associated with having a SN compared to those not exposed to CRT and younger survivors, respectively.

## Neurocognitive Impairment

Among participants who underwent comprehensive neurocognitive assessments (n=171), 68% experienced at least mildly impaired executive function (≥ Grade 1), attention, and/or memory (Table 2). Forty-nine percent (n=78/160) had Grades 1–3 impaired executive function, 30% (n=49/159) attention, and 35% (n=56/158) memory (Figure 1). Although a minority experienced moderately to severely impaired (Grades 2–3) executive function (18%), attention (15%), and memory (12%), frequencies were substantially higher than the 2% expected in the general population.

The results of univariate analyses for neurocognitive impairment can be found in Supplemental Table S3. Univariate analyses identified no significant predictors for impaired executive function. Univariate analyses identified no significant predictors for impaired executive function and only one factor, race, as a predictor for increased risk of impaired attention comparing risk in non-white with white participants (RR 1.8, 95% CI: 1.1–3.0, p=0.03). Regarding memory, adjustment for variables significant after univariate analyses (current age, CRT, and high-dose methotrexate [HD-MTX]) identified non-white participants, compared to white, to be at increased risk for memory impairment (RR 1.8, 95% CI: 1.1–2.8, p=0.02).

## Psychiatric Symptoms

Participants were universally evaluated (n=200) for anxiety, depression, and suicide ideation/attempt (Table 2). No significant predictors were identified for anxiety. Following multivariable adjustment, female sex (RR 2.2, 95% CI: 1.0–4.8, p=0.04), exposure to CRT (RR 3.3, 95% CI: 1.4–7.8, p<0.01), and cumulative corticosteroid exposure (RR 1.1, 95% CI: 1.0–1.2, p=0.02) were significantly associated with depression. Those of older attained

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age (RR 0.9, 95% CI: 0.9–1.0, p=0.04) were less likely to have experienced suicide ideation/attempt than those of younger age, and females were three times more likely than males to experience suicide ideation/attempt (RR 3.0, 95% CI: 1.0–8.9, p=0.04).

### Physical Function

Survivors exhibited physical performance deficits across all domains (Figure 2). Following multivariable adjustment, obesity (RR 2.4, 95% CI: 1.2–4.8, p=0.03) and cardiac radiation (RR 2.5, 95% CI: 1.1–5.4, p=0.02) were associated with risk for decreased aerobic function, and obesity was associated with decreased mobility (RR 2.1, 95% CI: 1.3–3.5, p<0.01) (Table 4). Twenty-three survivors (11.5%) were unable to complete the muscular endurance segment of the physical function testing due to medical restrictions (n=21) or scheduling error (n=2).

## DISCUSSION

Comprehensive, risk-based clinical assessments and validation of medical events provide detailed heath status characterization of adult survivors of pediatric NHL. Study results indicate a high prevalence of chronic health conditions, neurocognitive impairment, and physical performance limitations more than 20 years after treatment for NHL.

Similar to previous studies evaluating the burden of chronic conditions in cancer survivors, [9] we identified a high prevalence of specific conditions in aging NHL survivors, especially those cardiovascular risk factors well-described within the context of the metabolic syndrome (hypertension, dyslipidemia, obesity, and elevated blood glucose).[25] A number of studies have reported a high prevalence of the metabolic syndrome in childhood cancer survivors.[26] Among survivors of other hematologic malignancies, the prevalence ranges from 6% to 34%, strongly associated with cranial and abdominal radiation.[27–29] Meacham and colleagues previously observed no difference in the prevalence of obesity between survivors and siblings (20.6% vs. 20.8% reported a BMI ≥ 30 kg/$m^2$, respectively); however, survivors, including those of NHL, were more likely than siblings to self-report taking medication for hypertension and dyslipidemia.[29] In contrast, 35% of our NHL survivors were identified as obese. Additionally, we identified a high prevalence of hypertension, high total cholesterol, and elevated blood glucose levels, even in individuals who were not exposed to cranial or abdominal radiation. Although the high prevalence of these individual components of the metabolic syndrome in our cohort does not establish the diagnosis, and the prevalence of some (e.g. obesity) components may not actually exceed that in the general population,[30] their occurrences remain particularly concerning given that 4 of 5 NHL survivors in our cohort received anthracycline chemotherapy, 1 of 5 received chest-directed radiotherapy, and two-thirds had prehypertension/hypertension. Hypertension alone, and in combination with 1 or more additional cardiovascular risk factors has been shown to potentiate the risk for heart failure in those treated with anthracyclines, as well as the risk for heart failure, coronary artery disease, and valvular disease in survivors treated with chest-directed radiotherapy [31], underscoring the additional risks associated with blood pressure and metabolic derangements in NHL survivors already at increased risk for cardiovascular diseases due to treatment-related exposures.

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In addition to the identification of well-established cardiovascular risk factors, we are the first to report directly-assessed physical performance outcomes for childhood NHL survivors. Many survivors experienced physical performance limitations (Figure 2). Hoffman and colleagues have suggested that survivors cannot overcome performance deficits through routine exercise alone, leading to speculation that they may benefit from tailored interventions targeting physiological deficits.[32] Despite the inability to resolve measurable deficits, regular exercise has been shown to reduce the risk for cardiovascular events in Hodgkin lymphoma survivors.[33] Similar advantages may be possible in NHL survivors. Therefore, early identification of performance limitations unrecognized by current screening practices may enhance the ability to optimally reduce modifiable cardiovascular risk factors in NHL survivors and represents an area for future investigation.

Reassuringly, our data demonstrate a low prevalence of hypothalamic-pituitary-, and thyroid dysfunction, likely reflecting elimination of CRT from frontline NHL protocols. However, survivors treated with alkylating agents and/or gonadal radiation were at risk for gonadal (ovarian and testicular Leydig cell) failure, as well as oligospermia/azoospermia among male survivors. Despite the elimination of radiation, alkylating agent exposure (CED) exceeding 4,000 mg/m$^2$ remains common in current frontline NHL protocols,[3] and newly diagnosed children will likely continue to incur a risk to future fertility.

Previous neurocognitive studies in survivors of childhood NHL are limited to self-reported outcomes. For example, Kadan-Lottick and colleagues observed that, despite the omission of CRT from treatment strategies, 13–20% of NHL survivors reported impaired task efficiency, memory, and emotional regulation compared to siblings.[34] Through direct neurocognitive assessment, we identified at least mild neurocognitive impairment in more than two-thirds of at-risk survivors. Although radiation was associated with impaired memory, it was not associated with impaired attention or executive function, suggesting that survivors may remain at risk for neurocognitive impairment from systemic central nervous system-directed therapies (HD-MTX and high-dose cytarabine) despite the elimination of CRT from frontline treatment regimens.

Our results should be interpreted within the context of study limitations. First, grading of chronic conditions required determination of diagnoses at a single point in time. Longitudinal assessment of these conditions has not yet been undertaken in SJLIFE, therefore conditions such as hypertension may be overestimated due to variation in point measurements. Second, the study sample size precludes more detailed risk factor modeling. This is particularly relevant for risk-based conditions, where the sample size is further reduced. In addition, outcomes such as oligo/azoospermia must be interpreted within the context of potential participation biases for subjects at risk.

Participants and non-participants were similar in treatment exposures and age at diagnosis, while participants were slightly younger and closer to diagnosis than non-participants, suggesting a potential underestimate of our outcomes. Similarities between participants and the SJLIFE source population have been previously demonstrated, alleviating concerns regarding selective non-participation within the cohort.[35] Lastly, contemporary childhood NHL therapy differs from that used decades ago in both intensity and omission of

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irradiation, thus potentially limiting generalization of our findings beyond agent-specific risks for late-occurring complications. Moreover, differences in treatment between histologic NHL subtypes (e.g. lymphoblastic lymphoma vs. mature B-cell lymphoma) have resulted in heterogeneous exposures in survivors, limiting generalization of findings across the cohort of NHL survivors as a whole. However, despite these variations in combination and cumulative exposure, the same chemotherapeutic agents continue to form the backbone of current treatment regimens.[3] Survivors treated with contemporary protocols are only now beginning to emerge, but may be at risk for similar adverse late-health outcomes as a result of these exposures. Follow-up of contemporary cohorts will be needed.

Survivors of childhood NHL experience a significant burden of chronic health conditions. Most notable are the high prevalence of cardiovascular risk factors common to the metabolic syndrome, impaired neurocognitive performance, and decreased physical function. Our direct systematic assessments likely represent a more accurate representation of the true long-term health burden on adult survivors of NHL. Early recognition of subclinical chronic conditions offers a unique opportunity for secondary prevention strategies that may otherwise be ineffective at the time of symptom onset. The results of such investigations will inform the development of future treatment protocols and therapeutic interventions designed to ameliorate late complications among cancer survivors, seeking to extend quality and quantity of life-years for children with NHL.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

| | |
|---|---|
| **CED** | cyclophosphamide equivalent dose |
| **CTCAE** | Common Terminology Criteria for Adverse Events |
| **CI** | confidence interval |
| **CRT** | cranial radiation |
| **Gy** | gray |
| **HD-MTX** | high-dose methotrexate |
| **NHL** | non-Hodgkin lymphoma |

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|---|---|
| **RR** | relative risk |
| **SD** | standard deviations |
| **SIR(s)** | standardized incidence ratio(s) |
| **SJCRH** | St. Jude Children's Research Hospital |
| **SJLIFE** | St. Jude Lifetime Cohort study |
| **SN(s)** | subsequent neoplasm(s) |

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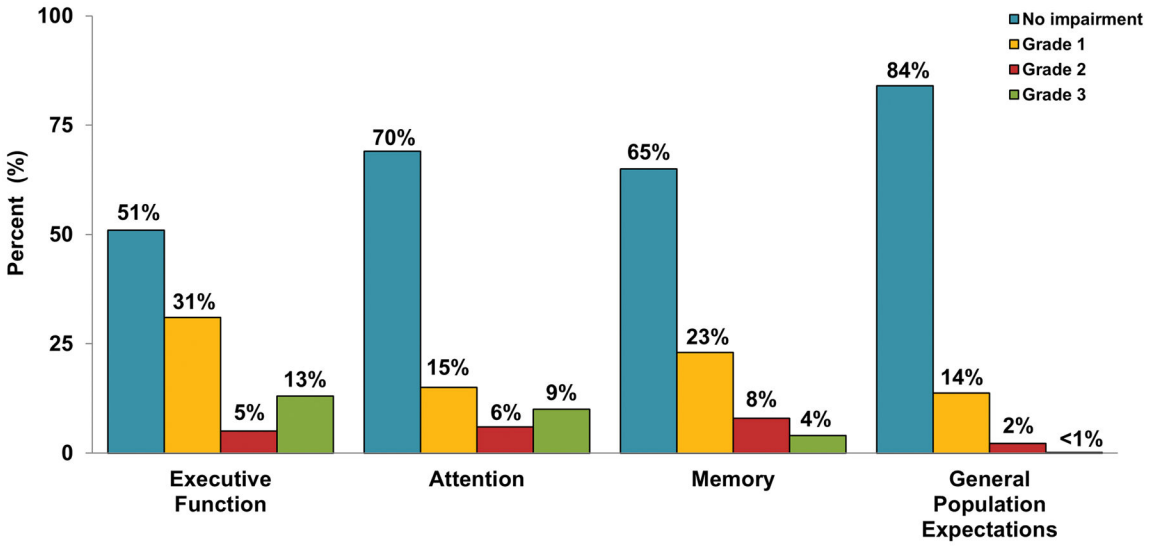


**Figure 1.**
Neurocognitive impairment among adult survivors of NHL

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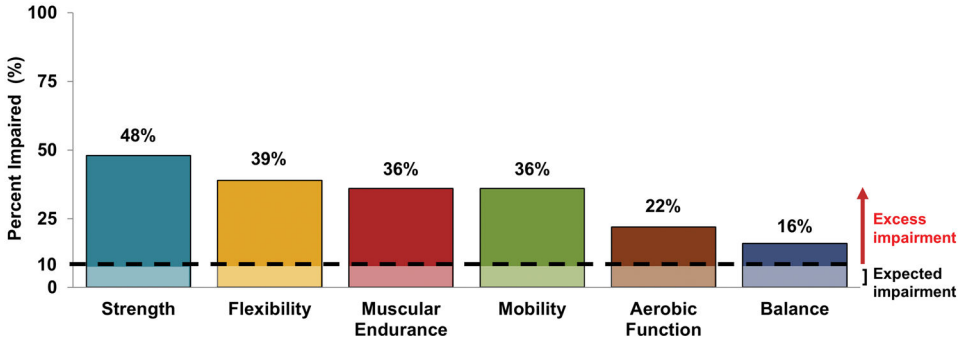


**Figure 2.**
Physical performance deficits among adult survivors of NHL

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**TABLE 1**

Participant and non-participant characteristics

| Characteristic | Participants | | Non-participants | | p-value |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Total | 200 | | 162 | | |
| Race | | | | | 0.51 |
| White | 174 | (87.0) | 137 | (84.6) | |
| Other | 26 | (13.0) | 25 | (15.4) | |
| Sex | | | | | 0.01 |
| Male | 131 | (65.5) | 126 | (77.8) | |
| Female | 69 | (34.5) | 36 | (22.2) | |
| Age at diagnosis (years) | | | | | 0.90 |
| 0–4 | 24 | (12.0) | 23 | (14.2) | |
| 5–9 | 69 | (34.5) | 53 | (32.7) | |
| 10–14 | 64 | (32.0) | 54 | (33.3) | |
| ≥15 | 43 | (21.5) | 32 | (19.8) | |
| Time since diagnosis (years) | | | | | 0.03 |
| 10–19 | 64 | (32.0) | 35 | (21.6) | |
| 20–29 | 88 | (44.0) | 68 | (42.0) | |
| 30–39 | 39 | (19.5) | 51 | (31.5) | |
| ≥ 40 | 9 | (4.5) | 8 | (4.9) | |
| Current age (years) | | | | | 0.01 |
| 20–29 | 63 | (31.5) | 28 | (17.3) | |
| 30–39 | 84 | (42.0) | 77 | (47.5) | |
| 40–49 | 45 | (22.5) | 41 | (25.3) | |
| 50–59 | 8 | (4.0) | 14 | (8.6) | |
| Irradiation | | | | | |
| Any | 88 | (44.0) | 69 | (42.6) | 0.79 |

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| Characteristic | Participants | | Non-participants | | p-value |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Brain/cranium | 46 | (23.0) | 41 | (25.3) | 0.61 |
| Chest/heart | 41 | (20.5) | 36 | (22.2) | 0.69 |
| Neck/thyroid | 68 | (34.0) | 54 | (33.3) | 0.89 |
| Abdomen/pelvis | 27 | (13.5) | 25 | (15.4) | 0.60 |
| Chemotherapy | | | | | |
| Anthracycline | 158 | (79.0) | 124 | (76.5) | 0.58 |
| Alkylating agent | 181 | (90.5) | 154 | (95.1) | 0.10 |
| Platinum agent | 19 | (9.5) | 18 | (11.1) | 0.61 |
| Corticosteroid | 161 | (80.5) | 133 | (82.1) | 0.66 |
| Epipodophyllotoxin | 61 | (30.5) | 37 | (22.8) | 0.10 |
| Antimetabolite | 183 | (91.5) | 148 | (91.4) | 0.96 |
| Intravenous methotrexate | 44 | (22.0) | 37 | (22.8) | 0.85 |
| High-dose methotrexate | 69 | (34.5) | 50 | (30.9) | 0.46 |
| Oral methotrexate | 66 | (33.0) | 56 | (34.6) | 0.75 |
| Intrathecal methotrexate | 147 | (73.5) | 115 | (71.0) | 0.60 |
| Intravenous cytarabine | 91 | (45.5) | 59 | (36.4) | 0.08 |
| Intrathecal cytarabine | 94 | (47.0) | 74 | (45.7) | 0.80 |
| Education | | | | | |
| < 12 years | 12 | (6.0) | - | - | |
| High school/GED | 38 | (19.0) | - | - | |
| Vocational training | 9 | (4.5) | - | - | |
| Some college | 42 | (21.0) | - | - | |
| College graduate | 56 | (28.0) | - | - | |
| Post-graduate college | 22 | (11.0) | - | - | |
| Employment | | | | | |
| Full time | 127 | (63.5) | - | - | |
| Part time | 21 | (10.5) | - | - | |
| Unemployed | 36 | (18.0) | - | - | |
| Student | 3 | (1.5) | - | - | |

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GED, Graduate Educational Development

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**TABLE 2**

Prevalence and severity of chronic health conditions by CTCAE grade* among NHL survivors

| **Cardiopulmonary** | **Cardiomyopathy** | | **Hypertension** | | **High Cholesterol** | | **Abnormal VC** | | **Decreased FEV1** | |
|---|---|---|---|---|---|---|---|---|---|---|
| Screening | Risk-Based** | | Universal (n=200) | | Universal (n=200) | | Risk-Based** | | Risk-Based** | |
| Number at risk | n=170 | | NA | | NA | | n=37 | | n=37 | |
| Number screened | n=164 | | n=198 | | n=192 | | n=37 | | n=37 | |
| | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** |
| Grade 1 | - | - | 74 | (37.3) | 52 | (27.1) | 4 | (10.8) | 8 | (21.6) |
| Grade 2 | 12 | (7.3) | 32 | (16.2) | 13 | (6.8) | 12 | (32.4) | 5 | (13.5) |
| Grade 3 | 4 | (2.4) | 18 | (9.1) | 2 | (1.0) | 1 | (2.7) | 5 | (13.5) |
| Grade 4 | 3 | (1.8) | 0 | (0.0) | 0 | (0.0) | - | - | 1 | (2.7) |

| **Endocrine and Metabolism** | **Hypothyroidism** | | **Overweight / Obesity** | | **Elevated Fasting Glucose** | |
|---|---|---|---|---|---|---|
| Screening | Universal (n=200) | | Universal (n=200) | | Universal (n=200) | |
| Number at risk | NA | | NA | | NA | |
| Number screened | n=200 | | n=200 | | n=200 | |
| | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** |
| Grade 1 | 0 | (0.0) | - | - | 55 | (27.5) |
| Grade 2 | 27 | (13.5) | 60 | (30.0) | 13 | (6.5) |
| Grade 3 | 0 | (0.0) | 53 | (26.5) | 5 | (2.5) |
| Grade 4 | 0 | (0.0) | 17 | (8.5) | 0 | (0.0) |

| **Musculoskeletal, Eye, and SN** | **Osteopenia / Osteoporosis** | | **Cataract** | | **SN** † | |
|---|---|---|---|---|---|---|
| Screening | Universal (n=200) | | Risk-Based** | | Universal (n=200) | |
| Number at risk | NA | | N=170 | | NA | |
| Number screened | n=194 | | n=155 | | n=200 | |
| | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** |
| Grade 1 | 29 | (14.9) | 28 | (18.0) | 0 | (0.0) |
| Grade 2 | 3 | (1.5) | 0 | (0.0) | 9 | (4.5) |
| Grade 3 | - | - | 1 | (0.1) | 4 | (2.0) |

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| **Cardiopulmonary** | **Cardiomyopathy** | | **Hypertension** | | **High Cholesterol** | | **Abnormal VC** | | **Decreased FEV1** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Grade 4 | - | - | 0 | (0.0) | 8 | (4.0) | | | | | | |
| **Neurologic** | **Sensory Neuropathy** | | **Motor Neuropathy** | | **Stroke** | | **Executive Function** | | **Attention** | | **Memory** | |
| Screening | Universal (n=200) | | Universal (n=200) | | Universal (n=200) | | Universal (n=200)[#] | | Universal (n=200)[#] | | Universal (n=200)[#] | |
| Number at risk | NA | | NA | | NA | | NA | | NA | | NA | |
| Number screened | n=200 | | n=200 | | n=200 | | n=160 | | n=159 | | n=158 | |
| | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** |
| Grade 1 | 52 | (26.0) | 2 | (1.0) | 3 | (1.5) | 49 | (30.6) | 24 | (15.1) | 37 | (23.4) |
| Grade 2 | 10 | (5.0) | 9 | (4.5) | 1 | (0.5) | 8 | (5.0) | 10 | (6.3) | 13 | (8.2) |
| Grade 3 | 1 | (0.5) | 5 | (2.5) | 2 | (1.0) | 21 | (13.1) | 15 | (9.4) | 6 | (3.8) |
| Grade 4 | - | - | 0 | (0.0) | 0 | (0.0) | - | - | - | - | - | - |
| **Psychiatric** | **Depression** | | **Anxiety** | | **Suicide Ideation/Attempt** | | | | | | | |
| Screening | Universal (n=200) | | Universal (n=200) | | Universal (n=200) | | | | | | | |
| Number at risk | NA | | NA | | NA | | | | | | | |
| Number screened | n=200 | | n=200 | | n=200 | | | | | | | |
| | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | | | | | | |
| Grade 1 | 7 | (3.5) | 18 | (9.0) | 1 | (0.5) | | | | | | |
| Grade 2 | 16 | (8.0) | 32 | (16.0) | 0 | (0.0) | | | | | | |
| Grade 3 | 0 | (0.0) | 0 | (0.0) | 9 | (4.5) | | | | | | |
| Grade 4 | 1 | (0.5) | 1 | (0.5) | 3 | (1.5) | | | | | | |
| **Reproductive** | **Central Hypogonadism** | | **Male Primary Hypogonadism** | | **Female Primary Hypogonadism / Ovarian Failure**[^] | | **Oligospermia / Azoospermia** | | | | | |
| Screening | Universal (n=200) | | Universal (n=131) | | Universal (n=69) | | Risk-Based[**] | | | | | |
| Number at risk | NA | | NA | | NA | | n=121 | | | | | |
| Number screened | n=200 | | n=131 | | n=68 | | n=80 | | | | | |
| | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | | | | |
| Grade 1 | 15 | (7.5) | 3 | (2.3) | - | - | - | - | | | | |
| Grade 2 | 3 | (1.5) | 7 | (5.3) | - | - | 19 | (23.8) | | | | |
| Grade 3 | 0 | (0.0) | 0 | (0.0) | 8 | (11.6) | 10 | (12.5) | | | | |

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| Cardiopulmonary | Cardiomyopathy | | Hypertension | | High Cholesterol | | Abnormal VC | | Decreased FEV1 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Grade 4 | - | - | - | - | - | - | - | - | | |

VC indicates vital capacity; FEV1, forced expiratory volume in 1 second; SN, subsequent neoplasm;

*There were no grade 5 chronic health conditions identified in the cohort;

**risk-based screening performed in accordance with recommendations from the Children's Oncology Group Long-term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers [8];

†Reflects the maximally graded SN for any given individual;

#neurocognitive screening has evolved within SJLIFE, initially as a risk-based to now a universal screening approach, therefore not all participants have completed screening;

^4 out of 8 surgical (1 at diagnosis, 3 during long-term follow-up).

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## TABLE 3

Standardized incidence ratios (SIRs) of subsequent neoplasms (SNs)*

| SNs** | Observed | Expected | SIR | 95% Confidence Interval |
|---|---|---|---|---|
| **Overall** | 18 | 2.870 | 6.3 | 3.7–9.9 |
| **Site specific** | | | | |
| Colon | 2 | 0.03 | 67.3 | 7.6–242.8 |
| Bone and soft tissue | 3 | 0.05 | 64.7 | 13.0–199.9 |
| Central nervous system | 4 | 0.15 | 26.6 | 7.2–68.2 |
| Bladder | 1 | 0.05 | 21.7 | 0.3–120.6 |
| Breast | 4 | 0.28 | 14.5 | 3.9–37.2 |
| Cervix | 1 | 0.07 | 14.4 | 0.2–80.4 |
| Lymphoma | 1 | 0.07 | 14.1 | 0.2–78.7 |
| Thyroid | 2 | 0.24 | 8.5 | 1.0–30.6 |

*Only neoplasms whose incidences are described by the Surveillance, Epidemiology, and End Results data are included;

**Median (range) time to onset = 20.7 (3–35) years; 43 SNs were diagnosed prior to (31 [2–280] months) and 5 diagnosed after SJLIFE evaluation (20 [3–141] days)

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**TABLE 4**

Relative risk (RR) and 95% confidence interval (CI) for physical performance deficits among NHL survivors [†]

| | | Flexibility | Mobility | Aerobic function | Strength |
|---|---|---|---|---|---|
| **Predictor** [*] | | **RR (95% CI)** | **RR (95% CI)** | **RR (95% CI)** | **RR (95% CI)** |
| **Current age** | | 1.0 (1.0–1.0) | - | - | - |
| **Race** | White | 1.0 | 1.0 | 1.0 | - |
| | Other | 1.4 (1.0–2.1) | 1.4 (0.9–2.1) | 1.7 (0.9–3.3) | - |
| **Body mass index** | <25 | 1.0 | 1.0 | 1.0 | 1.0 |
| | 25–29.9 | 1.1 (0.7–1.7) | 1.4 (0.8–2.5) | 1.2 (0.6–2.5) | 0.9 (0.6–1.2) |
| | ≥ 30 | 1.6 (1.0–2.4) | **2.1 (1.3–3.5)** [**] | **2.4 (1.2–4.8)** [**] | **0.6 (0.4–0.9)** [**] |
| **Cranial radiation** | No | 1.0 | - | - | - |
| | Yes | 1.4 (1.0–2.0) | - | - | - |
| **Cardiac radiation** | No | 1.0 | - | 1.0 | - |
| | Yes | 1.1 (0.6–2.2) | - | **2.5 (1.1–5.4)** [**] | - |
| **Abdominal radiation** | No | 1.0 | - | 1.0 | 1.0 |
| | Yes | 1.4 (0.7–3.0) | - | 1.1 (0.4–2.6) | 1.4 (1.0–1.9) |

[†] No significant associations identified for muscular endurance. Balance abnormality was only associated with non-white race (RR 3.6, 95% CI: 1.9–6.7) after univariate analyses;

[*] Variables with a p-value ≤0.1 on univariate analysis were retained in multivariable analyses;

[**] p-value < 0.05.