# Contributions of Cancer Treatment, Comorbidities, and Obesity to Aging-related Disease Risks among Non-Hodgkin's Lymphoma Survivors

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# Abstract

*Purpose*. It is unknown whether cancer treatment or modifiable risk factors contribute more to the burden of long-term disease risks among B-cell non-Hodgkin's lymphoma (B-NHL) survivors.

*Methods*. B-NHL survivors were identified in the Utah Cancer Registry from 1997 to 2015. Population attributable fractions (PAF) were calculated to assess the role of clinical and lifestyle factors for 6 cardiovascular, pulmonary, and renal diseases.

*Results*. Cancer treatment contributed to 11% of heart and pulmonary conditions and 14.1% of chronic kidney disease. Charlson Comorbidity Index (CCI) at baseline contributed to all six diseases with a range of 9.9% of heart disease to 26.5% of chronic kidney disease. High BMI at baseline contributed to 18.4% of congestive heart failure and 7.9% of pneumonia, while smoking contributed to 4.8% of COPD risk.

*Conclusion*. Cancer treatment contributed more to heart disease, COPD, and chronic kidney disease among B-NHL survivors. High BMI at baseline contributed more to congestive heart failure and pneumonia than cancer treatment, whereas smoking at baseline was not a major contributor in this B-NHL survivor cohort. Baseline comorbidities consistently demonstrated high attributable risks for these diseases, demonstrating a strong association between preexisting comorbidities and aging-related disease risks.


# Introduction

There were more than 700,000 non-Hodgkin's lymphoma (NHL) survivors in the United States as of 2019 [1]. Although the 5-year survival rate for NHL patients is fairly high at 72% in recent years [2], prior studies have reported on elevated risks of heart failure [3, 4] as well as respiratory-related complications for NHL survivors [5]. A Danish population-based study reported a 42% elevated risk of heart failure among 2,508 NHL survivors compared to 7,399 individuals from the general population, with increased risks of preexisting cardiovascular-related comorbidities associated with chemotherapy [3]. Similarly, a Dutch population-based study of 974 patients with advanced aggressive NHL estimated a 5.4-fold risk of chronic heart failure after treatment [4]. We previously reported that cancer treatment, baseline hypercholesterolemia, and baseline hypertension increased the risk of heart disease among B-cell non-Hodgkin's lymphoma (B-NHL) survivors in a U.S. population-based cohort study [5]. A separate study of 123 NHL patients found that 24% of patients with preexisting congestive heart failure had a 2.7-fold risk of developing pulmonary complications after chemotherapy compared to those without preexisting congestive heart failure [6]. Various pulmonary and renal complications have also been associated with hematopoietic stem cell transplantation (HSCT), but few longitudinal studies investigated the association in NHL survivors [7–12].

Previous studies on risk factors for adverse health outcomes are lacking in NHL survivorship [13]. In order to improve targeted screening and primary prevention of aging-related diseases among B-NHL survivors, the contribution of specific risk factors such as cancer treatment, preexisting comorbidities, smoking, and

obesity would be important to understand [14]. Therefore, the purpose of this study is to calculate population attributable fractions (PAF) of clinical and lifestyle risk factors for cardiovascular, pulmonary, and renal disease risks among B-NHL survivors.

## Methods

# Data collection

Eligibility criteria included individuals who were diagnosed with NHL at 18 years of age (SEER ICD-O-3 codes: 33041–33042) from 1997 to 2015 in the Utah Cancer Registry (UCR). We restricted the histology subtypes to B-cell lymphoma since it is the predominant type of NHL and treatment differs across histology subtypes (ICD-O-3 codes: 9670, 9671, 9673, 9675, 9679, 9680, 9684, 9687, 9689, 9691, 9695, 9698, 9699, and 9823). Histology subtypes of B-cell lymphomas were further classified into aggressive [15–18] and indolent types [19–23]. A general population cohort of up to 5 cancer-free individuals were matched to each B-NHL patient at the time of NHL diagnosis by sex, birth year, and birth state (Utah/not Utah) using the Utah Population Database (UPDB). The last follow-up date was determined through the last contact with a number of data sources, including driver's license division, Utah birth certificate, death certificate, voter registration, and the Utah Department of Health (UDOH). Death dates were also captured nationwide using the Social Security Death Index and UCR records.

From the initial cohort of 5,326 NHL patients that were identified, exclusion criteria included: Missing cancer stage (n = 134), non B-cell histology subtypes (n = 1,124), < 5 years follow-up to examine long-term aging-related disease outcomes (n = 1,918), resulting in 2,146 B-cell non-Hodgkin's lymphoma (B-NHL) survivors and 8,969 individuals from the general population. Studies using the UPDB data have been approved by the University of Utah's Resource for Genetic and Epidemiologic Research (oversight committee) and the University of Utah Institutional Review Board.

All participants were linked to the available health care data in the UPDB. Outcome data used for this study included statewide ambulatory surgery and inpatient data from the Utah Department of Health (UDOH) and electronic medical record data from Intermountain Healthcare and the University of Utah. Utah is considered to have a minimal percentage of residents who seek health care out of the state, based on a report by the National Association of Health Data Organizations that reviewed interstate exchange of nonresident data for health research and public health purposes [24]. Additionally, according to the US Census Bureau's state-to-state migration flow data for 2016, approximately 2.9% of Utahns left the state; thus, the out-migration rate is fairly low [25].

Aging-related diseases were defined as a composite of physiological changes, diseases, and syndromes characterized by normal aging [26]. Otherwise common in adults over the age of 85, these diseases can be driven by accelerated-aging factors such as inflammation, oxidative stress, and the irradiation associated with cancer itself and its related treatments [27–29]. Therefore, outcome data included ICD-9 diagnosis codes and dates for heart disease, congestive heart failure, chronic obstructive pulmonary

disease (COPD), pneumonia, chronic kidney disease, and acute renal failure. We selected these outcomes due to prior papers demonstrating increased disease risks among B-NHL survivors compared to general population cohorts [5, 30]. The Clinical Classification Software (CCS) developed by the Health Cost and Utilization Project was used to categorize ICD-9 codes into four levels of specificity (levels 1–4). Disease outcomes diagnosed prior to the start of the analysis time period were considered prevalent cases, and individuals were excluded from the relevant models as they were not at risk for incidence of those outcomes which had already occurred.

Follow-up time for incident diagnoses of each outcome was calculated from the B-NHL survivor's initial cancer diagnosis to the date of disease outcome diagnosis, last date of follow-up, or date of death. Individuals who did not have any disease outcome identified were censored at the last follow-up or death if that date fell within the analysis time period.

# Statistical analysis

Cox Proportional Hazards models with 95% confidence intervals (CI) were used to investigate risk factors among B-NHL survivors such as treatment type, Charlson Comorbidity Index (CCI) at baseline, body mass index (BMI) at baseline, and tobacco smoking at baseline. We selected potential confounders to adjust for, based on an assessment of the three properties of a confounder [31]. These included matching factors, baseline BMI, baseline CCI, race, ethnicity, and smoking. The formulas were used to calculate PAF [31, 32] and the corresponding 95% CIs [33]:

PAF = P * ([RR − 1] / RR)

95% CI = PAF +/- 1.96*SE

where,

- P = proportion of B-NHL with the outcome of interest, exposed to the risk factors
- RR = adjusted relative risks of risk factors among B-NHL survivors
- SE = standard error of each risk factor

Baseline BMI values at least one year prior to B-NHL diagnosis were calculated from the driver's license records. For individuals with missing BMI, values were imputed using a linear regression model that included cancer diagnosis, baseline CCI, and race as covariates. We compared Cox regression models including those with and without imputed BMI to assure that inferences did not change due to the imputed BMI. We identified tobacco smokers with the ICD-9 code for "tobacco use disorders" 305.1, ICD-10 codes for nicotine dependence, and with CPT codes for tobacco cessation counseling based on the American Academy of Family Physicians coding guidelines [34].

All statistical tests were two-sided, and a *P* value of less than 0.05 was considered statistically significant for all tables.

# Results

Approximately 7.5% of B-NHL survivors were Hispanic, 21.0% had at least one preexisting comorbidity, and 18.9% had multiple preexisting comorbidities (Table 1). At baseline, 42.6% were overweight and 21.5% were obese.

Table 1
Demographic characteristics of B-NHL patients diagnosed 1997–2015 who survived ≥ 5 years in Utah (n = 2,146)

| | n (%) |
|---|---|
| **Sex** | |
| Female | 977 (45.5) |
| Male | 1,169 (54.5) |
| **Race/Ethnicity** | |
| Non-Hispanic White | 1,929 (90.6) |
| Non-Hispanic Other | 35 (1.6) |
| Hispanic | 159 (7.5) |
| Unknown | -† (0.3) |
| **Vital status** | |
| Alive | 1,607 (74.9) |
| Dead | 539 (25.1) |
| **Charlson comorbidity Index (CCI) at baseline** | |
| 0 | 1,291 (60.2) |
| 1 | 450 (21.0) |
| 2+ | 405 (18.9) |
| **Body mass index (BMI) at baseline** | |
| <18.5 kg/$m^2$ | 22 (1.0) |
| 18-24.9 kg/$m^2$ | 748 (34.9) |
| 25-29.9 kg/$m^2$ | 915 (42.6) |
| 30+ kg/$m^2$ | 461 (21.5) |
| **Smoking at baseline** | |
| No | 1,904 (88.7) |
| Yes | 242 (11.3) |
| **Family history of lymphoma‡** | |
| No | 2,037 (94.9) |
| Yes | 109 (5.1) |

*Includes Black, Asian, American Indian/Alaskan Native, and Pacific Islander

†Counts ≤11 are not shown per Utah Department of Health data suppression guidelines

‡Family history includes first, second, and third-degree relatives

In terms of clinical factors, 43.9% of B-NHL survivors had distant-stage B-NHL at the time of diagnosis (Table 2). Chemotherapy was the predominant mode of cancer treatment (40.4%), whereas 7.6% of B-NHL survivors underwent for hematopoietic cell transplantation (HCT). Diffuse large B-cell lymphoma was the most common aggressive subtype that was diagnosed (80.6%).

Table 2
Clinical characteristics of B-NHL patients diagnosed 1997–2015 who survived ≥ 5 years after cancer diagnosis in Utah (n = 2,146)

| | n (%) |
|---|---|
| **Diagnosis year** | |
| 1997–2000 | 385 (17.9) |
| 2001–2005 | 704 (32.8) |
| 2006–2010 | 856 (39.9) |
| 2011–2015 | 201 (9.4) |
| **Cancer stage at diagnosis** | |
| Localized | 817 (38.1) |
| Regional | 387 (18.0) |
| Distant | 942 (43.9) |
| **First-course treatment** | |
| No treatment | 621 (28.9) |
| Chemotherapy | 868 (40.4) |
| Radiation therapy | 175 (8.2) |
| Chemotherapy + Radiation therapy | 391 (18.2) |
| Unknown | 91 (4.2) |
| **Hematopoietic cell transplantation** | |
| No | 1,982 (92.4) |
| Yes | 164 (7.6) |
| **Aggressive B-NHL subtypes** | |
| Diffuse large B-cell, NOS | 851 (80.6) |
| Diffuse large B-cell, immunoblastic, NOS | 32 (3.0) |
| Burkitt lymphoma, NOS | 35 (3.3) |
| Follicular lymphoma, grade 3 | 114 (10.8) |
| Other* | 24 (2.3) |
| **Indolent B-NHL subtypes** | |

*Includes diffuse mixed lymphoma and mediastinal large B-cell lymphoma

| | n (%) |
|---|---|
| Small B lymphocytic, NOS | 129 (14.6) |
| Lymphoplasmacytic lymphoma | 20 (2.3) |
| Mantle cell lymphoma | 79 (9.0) |
| Splenic marginal zone B-cell lymphoma | 22 (2.5) |
| Marginal zone B-cell lymphoma, NOS | 246 (27.9) |
| Chronic lymphocytic leukemia/SLL | 30 (3.4) |
| Follicular lymphoma, grade 2 | 172 (19.5) |
| Follicular lymphoma, grade 1 | 184 (20.9) |
| **Cancer site** | |
| Nodal | 1,436 (66.9) |
| Extra nodal | 710 (33.1) |
| *Includes diffuse mixed lymphoma and mediastinal large B-cell lymphoma | |

Attributable fractions for acute and chronic cardiovascular, pulmonary, and renal diseases for each risk factor among B-NHL survivors ≥ 5 years after cancer diagnosis are shown in Fig. 1. Cancer treatment had higher attributable fractions for heart disease, COPD, and CKD but did not appear to be a major contributor to congestive heart failure, pneumonia, or acute renal failure. Comorbidities at baseline had high attributable fractions for all six diseases. In contrast, the attributable fraction for family history of lymphoma was low and was therefore not included in the risk factor analysis.

Approximately 11.3% of heart disease and 0.4% of congestive heart failure were attributable to cancer treatment, including HCT, among B-NHL survivors ≥ 5 years after cancer diagnosis (Table 3). Chemotherapy alone contributed to 10.5% of heart disease and 5.2% of congestive heart failure among B-NHL. Preexisting comorbidities contributed to 9.9% of heart disease and 12.9% of congestive heart failure among B-NHL survivors ≥ 5 years after cancer diagnosis. High BMI at baseline contributed to 4.2% of heart disease and 18.4% of congestive heart failure. Approximately 1.8% of heart disease was attributable to smoking among B-NHL survivors ≥ 5 years after cancer diagnosis.

Table 3
Population attributable fractions (PAF) of cardiovascular risk factors for B-NHL survivors diagnosed 1997–2015 in Utah ≥ 5 years after cancer diagnosis

| | Heart disease | | | Congestive heart failure | | |
|---|---|---|---|---|---|---|
| | P | HR (95% CI) | PAF (95% CI) | P | HR (95% CI) | PAF (95% CI) |
| **First-course treatment type†** | | | | | | |
| No treatment | 30.1% | 1.00 | | 29.5% | 1.00 | |
| Chemotherapy | 44.5% | 1.31 (0.96–1.80) | 10.5% (7.2%, 13.8%) | 48.1% | 1.12 (0.74–1.70) | 5.2% (2.9%, 7.4%) |
| Radiotherapy | 8.5% | 0.69 (0.41–1.19) | -3.8% (-11.1%, 3.5%) | 8.3% | 1.06 (0.58–1.93) | 0.5% (-4.3%, 5.2%) |
| Chemotherapy + Radiotherapy | 16.9% | 0.95 (0.65–1.38) | -0.9% (-5.7%, 3.9%) | 14.1% | 0.86 (0.52–1.42) | -2.3% (-5.1%, 0.5%) |
| **Hematopoietic cell transplantation†** | | | | | | |
| No | 90.7% | 1.00 | | 94.1% | 1.00 | |
| Yes | 9.3% | 2.42 (1.60–3.65) | 5.5% (-2.2%, 13.2%) | 5.9% | 0.67 (0.33–1.39) | -2.9% (-7.3%, 1.5%) |
| Total PAF of treatment | | | 11.3% | | | 0.4% |
| **Charlson comorbidity Index (CCI) at baseline‡** | | | | | | |
| 0 | 72.2% | 1.00 | | 67.1% | 1.00 | |
| 1 | 19.4% | 1.38 (0.93–2.03) | 5.3% (0.7%, 10.0%) | 22.3% | 1.56 (1.04–2.35) | 8.0% (4.9%, 11.1%) |

*Models adjusted for sex, race/ethnicity

†Additionally adjusted for sex, race/ethnicity, CCI at baseline, BMI at baseline, smoking, cancer stage at diagnosis, year of cancer diagnosis

‡Additionally adjusted for sex, race/ethnicity, smoking, BMI at baseline, year of cancer diagnosis

§Additionally adjusted for sex, race/ethnicity, smoking, family history of heart disease, year of cancer diagnosis, CCI at baseline

| | Heart disease | | | Congestive heart failure | | |
|---|---|---|---|---|---|---|
| 2+ | 8.4% | 2.18 (1.11–4.28) | 4.5% (-2.3%, 11.4%) | 10.6% | 1.87 (1.01–3.46) | 4.9% (-0.3%, 10.2%) |
| Total PAF of CCI at baseline | | | 9.9% | | | 12.9% |
| **Body mass index (BMI) at baseline§** | | | | | | |
| < 18.5 kg/m$^2$ | 0.9% | 2.30 (0.91–5.77) | 0.5% (-20.1%, 21.1%) | 0.8% | 1.36 (0.33–5.70) | 0.2% (-14.5%, 14.9%) |
| 18-24.9 kg/m$^2$ | 34.6% | 1.00 | | 30.5% | 1.00 | |
| 25-29.9 kg/m$^2$ | 43.5% | 1.08 (0.81–1.44) | 3.2% (0.0%, 6.4%) | 43.1% | 1.37 (0.94–2.01) | 11.6% (9.5%, 13.8%) |
| 30 + kg/m$^2$ | 21.0% | 1.05 (0.73–1.50) | 1.0% (-3.5%, 5.5%) | 25.6% | 1.36 (0.86–2.17) | 6.8% (3.7%, 9.9%) |
| Total PAF of overweight/obese at baseline | | | 4.2% | | | 18.4% |
| **Smoking*** | | | | | | |
| No | 89.9% | 1.00 | | 88.4% | 1.00 | |
| Yes | 10.1% | 1.21 (0.68–2.17) | 1.8% (-4.5%, 8.0%) | 11.6% | 0.85 (0.46–1.58) | -2.0% (-5.9%, 1.8%) |
| *Models adjusted for sex, race/ethnicity | | | | | | |
| †Additionally adjusted for sex, race/ethnicity, CCI at baseline, BMI at baseline, smoking, cancer stage at diagnosis, year of cancer diagnosis | | | | | | |
| ‡Additionally adjusted for sex, race/ethnicity, smoking, BMI at baseline, year of cancer diagnosis | | | | | | |
| §Additionally adjusted for sex, race/ethnicity, smoking, family history of heart disease, year of cancer diagnosis, CCI at baseline | | | | | | |

For pulmonary complications, 11.2% of COPD and 0.6% of pneumonia were attributable to cancer treatment among B-NHL survivors ≥ 5 years after cancer diagnosis (Table 4). Chemotherapy contributed to 10.5% of COPD and HCT contributed to 8.7% of pneumonia. Preexisting comorbidities contributed to 11.5% of COPD and 13.9% of pneumonia among B-NHL survivors ≥ 5 years after cancer diagnosis. High BMI at baseline contributed to 0.2% of COPD and 7.9% of pneumonia. Approximately 4.8% of COPD and 0.3% of pneumonia were attributable to smoking among B-NHL survivors ≥ 5 years after cancer diagnosis.

Table 4
Population attributable fractions (PAF) of pulmonary risk factors for B-NHL survivors diagnosed 1997–2015 in Utah ≥ 5 years after cancer diagnosis

| | COPD | | | Pneumonia | | |
|---|---|---|---|---|---|---|
| | P | HR (95% CI) | PAF (95% CI) | P | HR (95% CI) | PAF (95% CI) |
| **First-course treatment type†** | | | | | | |
| No treatment | 28.4% | 1.00 | 1.00 | 32.0% | 1.00 | 1.00 |
| Chemotherapy | 47.8% | 1.28 (0.86–1.91) | 10.5% (8.1%, 12.9%) | 46.2% | 0.95 (0.67–1.35) | -2.4% (-4.9%, 0.1%) |
| Radiotherapy | 8.6% | 1.22 (0.66–2.23) | 1.6% (-3.6%, 6.7%) | 8.2% | 0.96 (0.55–1.66) | -0.3% (-5.6%, 4.9%) |
| Chemotherapy + Radiotherapy | 15.1% | 0.99 (0.61–1.61) | -0.2% (-3.2%, 2.9%) | 13.6% | 0.72 (0.46–1.13) | -5.3% (-8.4%, -2.2%) |
| **Hematopoietic cell transplantation†** | | | | | | |
| No | 94.0% | 1.00 | 1.00 | 85.6% | 1.00 | 1.00 |
| Yes | 6.0% | 0.90 (0.48–1.69) | -0.7% (-5.3%, 4.0%) | 14.4% | 2.52 (1.67–3.79) | 8.7% (1.7%, 15.6%) |
| Total PAF of treatment | | | 11.2% | | | 0.6% |
| **Charlson comorbidity Index (CCI) at baseline‡** | | | | | | |
| 0 | 65.8% | 1.00 | 1.00 | 57.6% | 1.00 | 1.00 |
| 1 | 17.0% | 1.14 (0.72–1.79) | 2.1% (0.8%, 3.4%) | 20.5% | 1.02 (0.68–1.52) | 0.4% (-0.7%, 1.5%) |

*Models adjusted for sex, race/ethnicity

†Additionally adjusted for sex, race/ethnicity, CCI at baseline, BMI at baseline, smoking, cancer stage at diagnosis, year of cancer diagnosis

‡Additionally adjusted for sex, race/ethnicity, smoking, BMI at baseline, year of cancer diagnosis

§Additionally adjusted for sex, race/ethnicity, smoking, family history of heart disease, year of cancer diagnosis, CCI at baseline

| | COPD | | | Pneumonia | | |
|---|---|---|---|---|---|---|
| 2+ | 17.2% | 2.22 (1.40–3.51) | 9.5% (7.7%, 11.2%) | 22.0% | 2.58 (1.74–3.84) | 13.5% (12.0%, 15.0%) |
| Total PAF of CCI at baseline | | | 11.5% | | | 13.9% |
| **Body mass index (BMI) at baseline§** | | | | | | |
| < 18.5 kg/m$^2$ | 1.2% | 2.85 (1.03–7.93) | 0.8% (-4.3%, 5.8%) | 1.3% | 1.14 (0.28–4.70) | 0.2% (-5.1%, 5.4%) |
| 18-24.9 kg/m$^2$ | 37.4% | 1.00 | 1.00 | 35.9% | 1.00 | |
| 25-29.9 kg/m$^2$ | 40.2% | 0.94 (0.65–1.36) | -2.6% (-3.3%, -1.9%) | 43.4% | 1.16 (0.83–1.62) | 6.0% (5.3%, 6.7%) |
| 30 + kg/m$^2$ | 21.1% | 1.15 (0.75–1.76) | 2.8% (1.6%, 3.9%) | 19.4% | 1.11 (0.74–1.67) | 1.9% (0.8%, 3.0%) |
| Total PAF of overweight/obese at baseline | | | 0.2% | | | 7.9% |
| **Smoking*** | | | | | | |
| No | 80.5% | 1.00 | 1.00 | 89.1% | 1.00 | |
| Yes | 19.5% | 1.33 (0.74–2.40) | 4.8% (2.6%, 7.0%) | 10.9% | 1.03 (0.59–1.78) | 0.3% (-1.4%, 2.1%) |
| *Models adjusted for sex, race/ethnicity | | | | | | |
| †Additionally adjusted for sex, race/ethnicity, CCI at baseline, BMI at baseline, smoking, cancer stage at diagnosis, year of cancer diagnosis | | | | | | |
| ‡Additionally adjusted for sex, race/ethnicity, smoking, BMI at baseline, year of cancer diagnosis | | | | | | |
| §Additionally adjusted for sex, race/ethnicity, smoking, family history of heart disease, year of cancer diagnosis, CCI at baseline | | | | | | |

For renal diseases, 14.1% of chronic kidney disease was attributable to cancer treatment (Table 5). Preexisting comorbidities contributed to 26.5% of chronic kidney disease and 21.9% of acute renal failure among B-NHL survivors ≥ 5 years after cancer diagnosis. High BMI at baseline contributed to 17.8% of chronic kidney disease and 12.8% of acute renal failure risks. Smoking contributed to 6.4% of acute renal failure among B-NHL survivors ≥ 5 years after cancer diagnosis.

Table 5
Population attributable fractions (PAF) of renal risk factors for B-NHL survivors diagnosed 1997–2015 in Utah ≥ 5 years after cancer diagnosis

| | Chronic kidney disease | | | Acute renal failure | | |
|---|---|---|---|---|---|---|
| | P | HR (95% CI) | PAF (95% CI) | P | HR (95% CI) | PAF (95% CI) |
| **First-course treatment type†** | | | | | | |
| No treatment | 27.0% | 1.00 | 1.00 | 31.1% | 1.00 | 1.00 |
| Chemotherapy | 47.3% | 1.46 (1.01–2.12) | 14.9% (12.7%, 17.1%) | 41.6% | 0.93 (0.64–1.37) | -3.1% (-5.0%, -1.2%) |
| Radiotherapy | 7.2% | 0.68 (0.35–1.31) | -3.4% (-7.7%, 0.9%) | 7.9% | 0.91 (0.49–1.69) | -0.8% (-4.9%, 3.4%) |
| Chemotherapy + Radiotherapy | 18.5% | 1.10 (0.70–1.74) | 1.7% (-1.4%, 4.7%) | 19.5% | 1.16 (0.75–1.81) | 2.7% (-0.2%, 5.6%) |
| **Hematopoietic cell transplantation†** | | | | | | |
| No | 89.4% | 1.00 | 1.00 | 90.2% | 1.00 | 1.00 |
| Yes | 10.6% | 1.09 (0.64–1.88) | 0.9% (-4.6%, 6.4%) | 9.9% | 1.06 (0.60–1.85) | 0.6% (-4.5%, 5.6%) |
| Total PAF of treatment± | | | 14.1% | | | -0.7% |
| **Charlson comorbidity Index (CCI) at baseline‡** | | | | | | |
| 0 | 49.1% | 1.00 | 1.00 | 52.5% | 1.00 | 1.00 |
| 1 | 22.5% | 1.57 (1.08–2.27) | 8.2% (7.1%, 9.3%) | 23.0% | 1.38 (0.93–2.03) | 6.3% (5.3%, 7.4%) |

*Models adjusted for sex, race/ethnicity

†Additionally adjusted for sex, race/ethnicity, CCI at baseline, BMI at baseline, smoking, cancer stage at diagnosis, year of cancer diagnosis

‡Additionally adjusted for sex, race/ethnicity, smoking, BMI at baseline, year of cancer diagnosis

§Additionally adjusted for sex, race/ethnicity, smoking, family history of heart disease, year of cancer diagnosis, CCI at baseline

| | Chronic kidney disease | | | Acute renal failure | | |
|---|---|---|---|---|---|---|
| 2+ | 28.4% | 2.82 (1.92–4.15) | 18.3% (16.7%, 20.0%) | 24.6% | 2.72 (1.84–4.03) | 15.5% (14.1%, 17.0%) |
| Total PAF of CCI at baseline | | | 26.5% | | | 21.9% |
| **Body mass index (BMI) at baseline§** | | | | | | |
| < 18.5 kg/m$^2$ | 0.6% | 0.65 (0.09–4.72) | -0.3% (-3.8%, 3.2%) | 0.8% | 0.82 (0.11–5.97) | -0.2% (-3.9%, 3.5%) |
| 18-24.9 kg/m$^2$ | 30.0% | 1.00 | 1.00 | 30.6% | 1.00 | 1.00 |
| 25-29.9 kg/m$^2$ | 44.7% | 1.37 (0.96–1.95) | 12.1% (11.4%, 12.8%) | 44.5% | 1.23 (0.86–1.77) | 8.3% (7.7%, 9.0%) |
| 30 + kg/m$^2$ | 24.7% | 1.30 (0.86–1.98) | 5.7% (4.6%, 6.8%) | 24.1% | 1.23 (0.80–1.90) | 4.5% (3.5%, 5.5%) |
| Total PAF of overweight/obese at baseline | | | 17.8% | | | 12.8% |
| **Smoking*** | | | | | | |
| No | 88.8% | 1.00 | 1.00 | 87.8% | 1.00 | 1.00 |
| Yes | 11.2% | 1.08 (0.64–1.80) | 0.8% (-0.8%, 2.5%) | 12.2% | 2.12 (1.40–3.21) | 6.4% (4.8%, 8.1%) |
| *Models adjusted for sex, race/ethnicity | | | | | | |
| †Additionally adjusted for sex, race/ethnicity, CCI at baseline, BMI at baseline, smoking, cancer stage at diagnosis, year of cancer diagnosis | | | | | | |
| ‡Additionally adjusted for sex, race/ethnicity, smoking, BMI at baseline, year of cancer diagnosis | | | | | | |
| §Additionally adjusted for sex, race/ethnicity, smoking, family history of heart disease, year of cancer diagnosis, CCI at baseline | | | | | | |

Comorbidities at baseline contributed largely to the attributable risk across the 6 diseases among B-NHL survivors. The most common comorbidities included chronic pulmonary disease (32.6%), diabetes without complications (12.5%), and myocardial infarction (9.2%) among B-NHL patients at cancer diagnosis (Supplemental Fig. 1). For each disease outcome, chronic pulmonary disease was consistently the most common preexisting comorbidity among B-NHL survivors (Supplemental Table 1).

# Discussion

To our knowledge, our study is the first to examine the contribution of risk factors for long-term disease outcomes among B-NHL survivors using PAF estimates within a large-scale population-based study. Cancer treatment contributed greatly to chronic disease risks such as heart disease, COPD, and chronic kidney disease. Being overweight or obese at baseline contributed more to congestive heart failure and pneumonia than cancer treatment, while smoking at baseline was not a major contributor to the aging-related disease risks in this cohort. Having baseline comorbidities was consistently a large component of attributable risk for these diseases.

Cancer treatment was a contributor to heart disease, COPD, and chronic kidney disease among B-NHL survivors in our study. Specifically, 10.5% of risks relating to heart disease and COPD were attributed to chemotherapy, while 14.9% of chronic kidney disease risk was attributed to chemotherapy. A strong association between chemotherapeutic agents and renal complications may be expected, considering the mechanisms involved in metabolizing and excreting toxic agents from the body. In addition to an established association between chemotherapy and cardiovascular disease risks, the use of chemotherapy can also result in acute or chronic lung complications, depending on dose rate, duration of treatment, preexisting lung disease, and concurrent use of steroids [35]. Few studies evaluated associations between specific NHL treatment regimens and aging-related disease risks. Our current finding supports the association between cancer treatment and chronic disease risks for B-NHL survivors in a population-based cohort.

In terms of lifestyle factors, smoking was not a large contributor to these aging-related disease risks in our cohort, possibly due to the low prevalence of smokers in Utah. Nevertheless, smoking contributed to varying levels of risk for heart disease, COPD, and acute renal failure. Being overweight or obese at baseline contributed more to congestive heart failure (18.4%) and pneumonia (7.9%) than cancer treatment in our cohort. Given that obesity is a risk factor of several aging-related diseases in the general population [36], the health-related implications are similar for B-NHL survivors, as a population-based study of 1,286 NHL survivors reported that obesity prior to cancer diagnosis was associated with poorer survival [37]. Few studies evaluated associations between lifestyle factors and aging-related disease risks, however, as prior studies focused more on survival outcomes and not on clinical implications after treatment.

Given the correlation between high CCI score and worse survival outcomes in prior studies involving DLBCL patients [38–40], we found that having preexisting comorbidities at cancer diagnosis was a consistent contributor to cardiovascular, pulmonary, and renal disease risks in our B-NHL survivor cohort. This suggests that the management of comorbidities may be integral in reducing the risks of aging-related diseases among individuals once diagnosed with B-NHL. This also warrants further research in investigating the risks pertaining to the potential interplay of concomitant prescriptions for preexisting comorbidities and cancer treatment regimens. Although our results may potentially underestimate the impact of preexisting comorbidities, considering that we excluded prevalence of the outcome of interest to investigate incidence of disease, it allows us to identify the extent to which multiple disease risks are associated with each risk factor and avoids double-counting of comorbidities.

The strengths of this study include the utilization of PAF, which was used to estimate the role of risk factors on disease incidence among B-NHL survivors. Another strength is the large sample size, which provided sufficient power to examine several outcomes for the B-NHL survivors. In addition, our follow-up period was ≥ 5 years after cancer diagnosis allows for a focus on long term health outcomes. This approach also helps to minimize the impact of surveillance bias in our study. The data used in the study incorporate medical records from the state's two largest healthcare providers as well as statewide ambulatory surgery and inpatient data, which provide comprehensive medical record data for a large number of individuals. In contrast to cancer survivor studies that rely on self-reports of the disease, which are susceptible to survival bias, our study is less susceptible to survival bias because we used long-term health records as the source for disease diagnoses.

This study also has a number of limitations. The attributable risks of lifestyle factors observed in this cohort such as smoking and obesity at baseline may not be generalizable to other populations because of the lower prevalence of exposure in Utah compared to other states. However, other risk factors such as cancer treatment and presence of preexisting comorbidities may be important to other B-NHL cohorts. While this study utilized comprehensive electronic medical record data from the two largest statewide healthcare systems, along with statewide ambulatory surgery and inpatient data, there is the possibility that study participants could have been diagnosed with disease outcomes in hospitals and clinics not covered by data sources. However, our data source also include statewide records; thus, the majority of the population was covered.

Another limitation of this study is that some subjects had missing baseline BMI data, which were addressed by imputation of BMI values. It was required that baseline BMI recorded at least one year prior to the NHL survivor's cancer diagnosis to minimize temporal issues. We assured that inferences for our results did not change whether we used only those with BMI included or those whose BMI was imputed. Smoking was identified using ICD codes, which may be a limitation because only heavy smokers who used cessation services may be captured. However, the proportion of smokers identified was fairly similar to the expected Utah population smoking prevalence. Treatment data were limited to broad categories and did not include type of drug, dosage, specific chemotherapy cycles, and duration of treatment. However, the treatment data that were available provided evidence that risks for aging-related disease outcomes vary by treatment type and by age at diagnosis.

In conclusion, we observed that cancer treatment contributed greatly to heart disease, COPD, and chronic kidney disease. Being overweight or obese at baseline contributed more to congestive heart failure and pneumonia than cancer treatment, whereas smoking was not a major contributor to these aging-related disease risks in this cohort. Preexisting comorbidities significantly contributed to all these disease risks. This suggests the significant impact of baseline comorbidities on long-term, aging-related disease risks and demonstrates a need for lifestyle interventions aimed at mitigating these risk factors to achieve better outcomes for B-NHL patients and survivors after cancer diagnosis and treatment.

# Declarations

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### Disclosure of Potential Conflicts of Interest.

No potential conflicts of interest were disclosed.

### Authorship

Authors A and N conceived and designed the study. Authors A, J, K, L, M, and N developed the methodology. Authors D, E, F, G, H, I, and N acquired the data. Authors A, B, C, and N conducted data analysis and interpretation. Authors A, J, K, L, M, and N drafted, reviewed, and revised the article. Authors G, H, and N constructed and organized the databases. Author N supervised the entire study.

### Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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# Figures

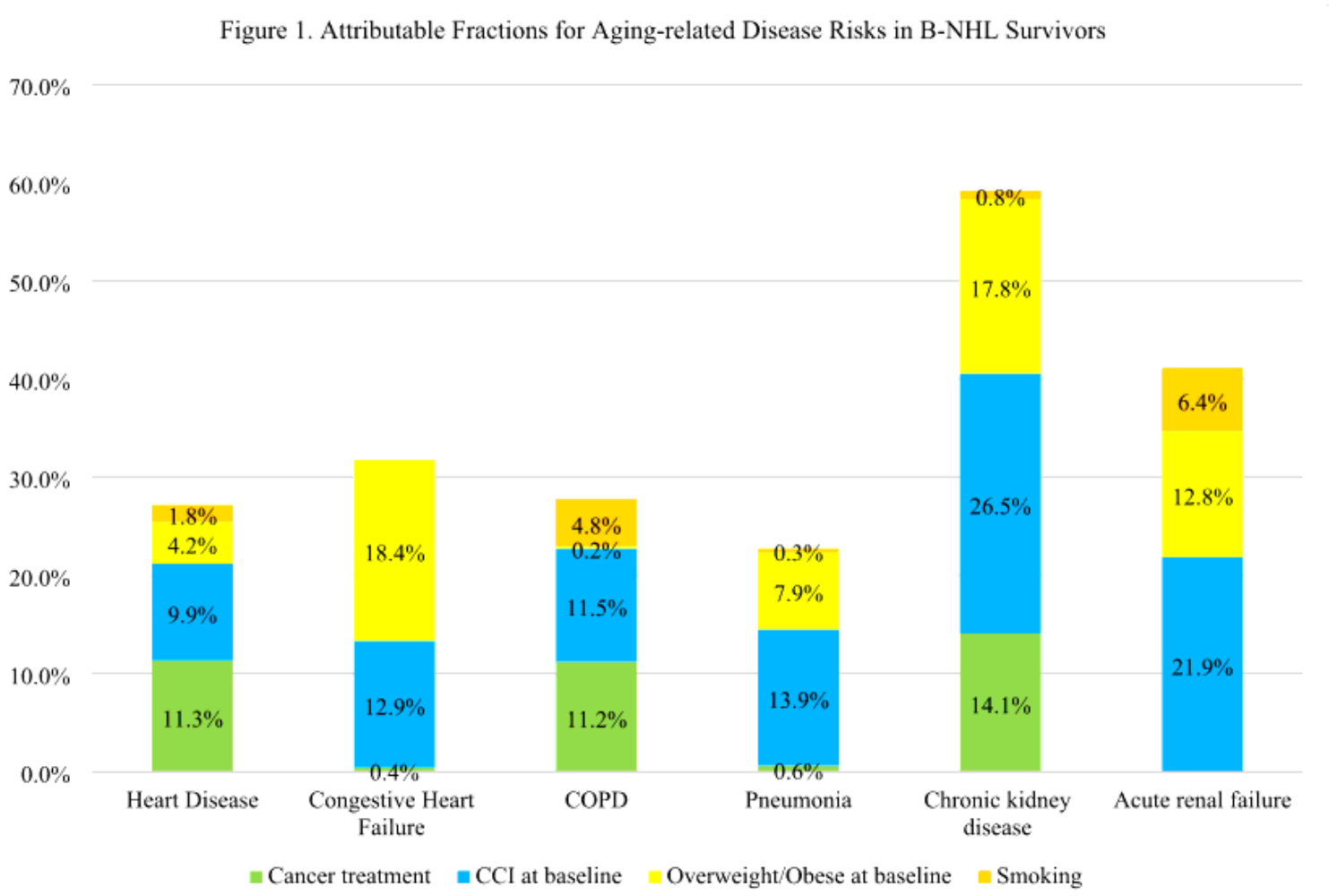


**Figure 1**

Attributable Fractions for Aging-related Disease Risks in B-NHL Survivors

# Supplementary Files

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- PAFofBNHLCancerCausesSupplemental2022.03.14.docx