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Outcomes for lymphoid malignancies in the Nurses' Health Study (NHS) as compared to the Surveillance, Epidemiology, and End Results (SEER) program

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Abstract

INTRODUCTION—Vital statistics for the lymphoid malignancies obtained from the Surveillance, Epidemiology and End Results (SEER) Program have seldom been directly compared to data from alternative national databases; while SEER is recognized as the standard, some lymphoid malignancies—especially the chronic ones—may be underreported.

METHODS—We compared the incidence, all-cause, and cause-specific mortality for Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), multiple myeloma (MM) and chronic lymphocytic leukemia (CLL) in SEER to that in the Nurses' Health Study (NHS), a national cohort study of 121,700 female registered nurses, matching for age and race.

RESULTS—In over 2.5 million person-years, the incidence of HL was the same as in SEER (SIR= 1.01 [0.75, 1.26]), while the incidence of NHL, CLL and MM were slightly higher. All-cause mortality was lower for the lymphoid malignancies except for MM, which was the same; there were no differences in cause-specific mortality, except for MM (HR= 1.26 [1.07, 1.48]).

CONCLUSION—Our analysis suggests that, at least among white women, SEER is a reliable data source with respect to lymphoid malignancies.

Keywords

hematologic malignancy; health services research; lymphoma; leukemia; myeloma

Introduction

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 26% of the US population.(1) When SEER diagnostic and mortality information is linked with other sources of data such as Medicare claims, it is an invaluable tool for oncology-related health services research. Possible limitations of the SEER

database, however, include potential systematic errors in coding, discrepancies in patient composition compared with the general United States population, and missing or incomplete data from composite registries.(1-4)

The lymphoid malignancies, due to their rare and sometimes chronic nature, may be particularly susceptible to inaccurate or incomplete reporting.(5) For example, many cases of chronic lymphocytic leukemia (CLL) are diagnosed in physician's offices without bone marrow examination, and patients may have few symptoms for many years. These factors may make indolent cases of CLL elude even the most vigilant cancer registrars. A recent population-based Canadian study examined the incidence and outcomes of CLL in Manitoba by combining data from a centralized flow cytometry facility and the provincial cancer registry.(6) Of 616 cases identified during the period for the period 1998 to 2003, 27% of patients identified by flow cytometry were actually not in the provincial cancer registry. The age-adjusted incidence was thus substantially higher than the reported incidence in registry reports.

Other myeloid malignancies such as multiple myeloma (MM) and the indolent non-Hodgkin lymphomas (NHL) share similar diagnostic issues, and given their predilection for the elderly, patients may die of other conditions without ever being diagnosed. In addition, due to their many sub-classifications and ability to transform, reporting of malignancies such as NHL can be extremely complicated, (7) as can correct assignment of true cause of death.(8)

Although the quality and completeness of data is tested annually in the SEER registries,(2) with a few exceptions,(9,10) SEER incidence and mortality rates for hematologic malignancies have seldom been directly compared to that in other large databases. We aimed to determine if the incidence, all-cause and cause-specific mortality in SEER for lymphoid malignancies were reproducible using another American data source. We took advantage of the presumably excellent health literacy and awareness of health status among professional nurses, as well as the outstanding quality of follow-up in a long-standing and well-respected cohort research study.

Methods

The Nurses' Health Study (NHS), established in 1976, is an ongoing prospective cohort comprised of 121,700 female registered nurses aged 30-55 years at baseline. Follow-up questionnaires are mailed every two years to update information on risk factors and disease diagnoses with response rates above 90%.

In the NHS cohort, women who reported a diagnosis of hematologic malignancy on any biennial questionnaire from 1976 to 2004 gave permission to obtain related medical records and pathology reports. Vital status was ascertained through next of kin and regular searches of the National Death Index; if the primary cause of death listed on a participant's death certificate was an unreported hematologic malignancy, permission to retrieve medical records and confirm the diagnosis was obtained from a family member. Confirmation of Hodgkin's lymphoma (HL, International Classification of Disease, Revision 8, code 201), NHL (ICD-8 codes 200 and 202), MM (ICD-8 code 203), and CLL (ie, non-acute lymphocytic leukemia, ICD-8 code 204, except known acute leukemias) was based on physician review of available medical records and pathology reports. We excluded myeloid malignancies either due to their acute nature (eg, AML) or their failure to also appear in SEER for most of the study time period (eg, MDS). We also excluded ALL given its acute and exceedingly rare nature. The institutional review board of the Brigham and Women's Hospital in Boston, Massachusetts, approved this study.

We analyzed SEER cases of lymphoid malignancies diagnosed among white females 30-84 years old between 1976 and 2004 from the nine original registries.(11) Because the NHS is

predominantly white (98%), only whites were included in this analysis. The SEER Program classifies cancer sites based on the International Classification of Disease for Oncology, 3rd Edition (ICD-O-3). These site codes have been translated to ICD-9 for cause of death. For the SEER data, HL included ICD-9 code 201; NHL included ICD-9 codes 200, 202.0-202.2, 202.8-202.9; MM included ICD-9 codes 203.0 and 238.6; and CLL included ICD-9 codes 204.1, 204.2, 204.8-204.9, and 202. For both data sources, only first primary malignancies were included.

We compared the observed number of new diagnoses of lymphoid malignancies in the NHS from June 1976 to June 2004 to the expected number of cases based on SEER age-specific incidence rates for January 1976 to December 2003 using standardized incidence ratios (SIRs) and 95% confidence intervals (CIs).⁽¹²⁾ In addition, we performed a Cox proportional hazards analysis, stratified by calendar year of diagnosis and age in years, to estimate hazard ratios (HRs) and 95% CIs comparing survival among NHS members diagnosed with HL, NHL, MM and CLL between June 1976 and June 2004 with that among SEER cases during the same time period. The outcome variables were time in months from diagnosis until death from any cause or from lymphoid malignancy. Follow-up ended at death, June 2004, or the date last known to be alive (SEER only), whichever was earlier. Deaths from other causes were censored in the cause-specific analyses. All analyses were performed using SAS version 9 for UNIX (SAS Institute Inc., Cary, NC).

Results

In over 2.5 million person-years of follow-up, the incidence of HL in the NHS was the same as in SEER, but slightly increased for NHL, MM and CLL. (Table 1) All-cause mortality rates were lower in the NHS for HL, NHL, and CLL, but cause-specific mortality only differed for MM (HR= 1.26, 95% CI: 1.07, 1.48; Table 2).

Discussion

Given the prevalent use of SEER data in oncology-related health services research, it is reassuring that incidence rates and cause-specific mortality rates for the lymphoid malignancies were similar in the two cohorts we studied. Gatta and colleagues compared cancer incidence and survival rates between the European EURO CARE cancer registry and SEER for 1985 to 1989 (9), finding an incidence of 2.2 per 100,000 for HL versus 2.8 in SEER; and 7.6 per 100,000 for NHL versus 12.4 in SEER. In contrast, our analysis comparing SEER with another American cohort (rather than an international one possibly confounded by environmental and genetic differences), suggests that SEER data for lymphoid malignancies is highly reproducible.

Another way to interpret our analysis is as a comparison of nurses (NHS)—a group assumed to be well connected to health care—to a race, age and gender-matched sample of the general US population (SEER). Interestingly, the incidence of hematologic malignancy was not reduced in nurses, possibly because preventable risk factors for these cancers have yet to be elucidated. To the contrary, the slight increase in incidence for NHL, MM and CLL may be due to higher levels of overall health vigilance, and lower all-cause mortality rates among NHS participants may reflect a healthy worker effect. Finally, the fact that cause-specific mortality was largely similar for nurses as compared to the SEER population casts doubt on the roles of health literacy and access to care in improving survival for these disorders, although such a conclusion would be premature outside of a detailed socioeconomic analysis of white female participants in NHS and SEER.

Our analysis has limitations. First, it may be argued that an occupational cohort is inherently biased and therefore not an appropriate comparison for national registry data; on the other hand, we specifically chose the NHS because we figured that nurses would be more likely to have adequate levels of access to care and knowledge about health, and also because there are currently no known nursing occupational risk factors for lymphoid malignancies.(13) In addition, as most of the NHS cohort were white women, our need to restrict our analyses to this group makes our conclusions somewhat less generalizable. Next, the small numbers of cases of HL in the NHS compared to the number in the SEER registry makes that part of our analysis somewhat unstable, and therefore only suggestive. Finally, unfortunately, the NHS uses ICD-8 rather than the ICD-O codes used by SEER (the later being easily translated into ICD-9). We were thus forced to compare ICD-8 (NHS) to ICD-9 (SEER) codes, which may have resulted in some coding error.

In summary, SEER outcomes data for white women with lymphoid malignancies is highly reproducible in an independent age, race and gender-matched prospective cohort with excellent follow-up. This bodes well for the reliability of analyses of hematologic malignancies using SEER and the linked SEER-Medicare databases, especially now that other rare hematologic disease such as the myelodysplastic and the myeloproliferative syndromes are being reported therein.(10) It also suggests that SEER likely does an adequate job of collecting incidence and mortality data for other relatively rare and indolent cancers.

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Table 1
Incidence of lymphoid malignancies in the NHS standardized to SEER, 1976-2004

Subtype	Total person-years	Observed cases	Expected cases [*]	SIR ^{**}	95% confidence interval
Hodgkin lymphoma	2,895,481	62	61.7	1.01	0.75, 1.26
NHL	2,893,289	762	649.6	1.17	1.09, 1.26
Multiple myeloma	2,895,309	218	186.7	1.17	1.01, 1.32
CLL	2,894,854	202	149.3	1.35	1.17, 1.54

^{*} Expected # of cases based on SEER incidence rates

^{**} SIR: standardized incidence ratio.

Table 2

Mortality for lymphoid malignancies in the NHS compared to SEER

Outcome	Source	# deaths	total PY	Adjusted HR* (95% CI)
Hodgkin lymphoma (n=3,895)	SEER	1,545	33,910	ref
	NHS	22	706	0.63 (0.41, 0.97)
	SEER	690	33,910	ref
	NHS	14	706	1.02 (0.59, 1.78)
NHL (n=33,283)	SEER	20,130	205,872	ref
	NHS	337	5,565	0.80 (0.72, 0.89)
	SEER	13,064	205,872	ref
	NHS	296	5,565	1.01 (0.89, 1.13)
Multiple myeloma (n=9,772)	SEER	8,088	39,189	ref
	NHS	167	920	1.02 (0.88, 1.20)
	SEER	6,075	39,189	ref
	NHS	162	920	1.26 (1.07, 1.48)
CLL (n=8,020)	SEER	4,919	60,712	ref
	NHS	50	1,523	0.70 (0.53, 0.93)
	SEER	2,395	60,712	ref
	NHS	39	1,523	0.96 (0.70, 1.33)

* Stratified by calendar year, age (in years)