Variation by age in neutropenic complications among patients with cancer receiving chemotherapy

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Background Age is among the most important risk factors for neutropenia-related hospitalization, but evidence is limited regarding the relative contributions of age and other risk factors.

Objective To explore the associations among patient age, other risk factors, and neutropenic complications in patients with cancer receiving myelosuppressive chemotherapy.

Methods This retrospective cohort study, which used a US commercial insurance claims database, included patients aged 40 years or older with non-Hodgkin lymphoma (NHL), breast cancer, or lung cancer who initiated chemotherapy between January 1, 2006 and March 31, 2010. The primary endpoint was the risk of neutropenia-related hospitalization during the first chemotherapy course. We used cubic spline modeling to estimate the association between neutropenia-related hospitalization and age, adjusting for patient and treatment characteristics. Logistic regression analyses examined the effects of other risk factors.

Results A total of 15,638 patients were included (NHL, n = 2,506; breast cancer, n = 9,110; lung cancer, n = 4,022), mean age 56-66 years. Neutropenia-related hospitalization occurred in 8.7% of NHL patients, 4.2% of breast cancer patients, and 3.9% of lung cancer patients. The association between age and the risk of neutropenia-related hospitalization was stronger in NHL than in lung or breast cancer. Patient comorbidities and chemotherapy characteristics had considerable effects on risk of neutropenia-related hospitalization.

Limitations Disease stage and other clinical factors could not be identified from the claims data.

Conclusion In addition to age, oncologists should evaluate individual patient risk factors including patient comorbidities and type of chemotherapy regimen.

Neutropenia is a common dose-limiting toxicity of myelosuppressive chemotherapy.[1-3] Although neutropenia may not be associated with specific symptoms, severe neutropenia (absolute neutrophil count of $< 1.0 \times 10^9$/L [grade 3] or $< 0.5 \times 10^9$/L [grade 4]) is a major risk factor for infection. Neutropenia with fever (febrile neutropenia) is a medical emergency that usually results in hospitalization and the need for intravenous antibiotics. It also carries the risk of infection-related mortality if not treated promptly.[1,2,4-14] Severe neutropenia and febrile neutropenia may result in reductions in myelosuppressive chemotherapy doses, or delays or discontinuation of chemotherapy, potentially compromising outcomes.[3-5,15] US costs of inpatient hospitalization for each neutropenic event in all cancer types have been estimated at $13,000-$19,000.[16-20]

To reduce the risk of neutropenia, guidelines of the American Society of Clinical Oncology (ASCO),[21] National Comprehensive Cancer Net-

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TABLE 1 Patient selection criteria: terms and definitions

Criterion	Term or concept	Definition
Diagnosis with female breast cancer, lung cancer, or NHL	Lung cancer	ICD-9-CM codes 162.2-162.9 or 231.2[ad]
	Breast cancer	ICD-9-CM codes 174.x or 233.0[bd]
	NHL	ICD-9-CM codes 200.xx, 202.0x, 202.1x, 202.2x, 202.7x, 202.8x[cd]
	Determination of primary cancer type	≥ 2 diagnoses, at least 7 days apart, of the same 3-digit ICD-9 CM code within 30 days before and after the first chemotherapy administration date.
Initiation of treatment with a new chemotherapy course between January 1, 2006 and March 31, 2010	Course	Period beginning with the first cycle of chemotherapy and ending on whichever of the following came first: • N weeks after the date of the last recorded chemotherapy administration (defined by a gap of at least 60 days with no additional chemotherapy claims after the previous administration) where N is the number of weeks in the previous chemotherapy cycle, • Start of a different chemotherapy regimen, • Start of radiation therapy, • Death, • The end of insurance eligibility, or • The end of the study period (March 31, 2010)
	New chemotherapy course	A course that started after a period of at least 90 days without a claim or other evidence of chemotherapy
Receipt of at least 2 cycles of chemotherapy	Cycle	Period beginning on the first date of treatment and ending with the second administration of the same chemotherapy agent(s)

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NHL, non-Hodgkin lymphoma.
[a] ICD-9-CM diagnosis codes for lung cancer: 162.2-162.9 = malignant neoplasm of bronchus and lung, 231.2 = carcinoma in situ of respiratory system; [b] for breast cancer: 174.x = malignant neoplasm of female breast; 233.0 = carcinoma in situ of breast; [c] for NHL: 200.xx = lymphosarcoma and reticulosarcoma; 202.0x = nodular lymphoma; 202.1x = mycosis fungoides; 202.2x = Sézary's disease; 202.7x = peripheral T-cell lymphoma; 202.8x = other lymphomas; [d] Claims from laboratories, diagnostic testing centers, or any diagnostic tests were not considered when identifying cancer claims; claims with "rule-out" codes (CPT-4 codes 36400-36425, 70010-76999, 78000-78799, 80000-89999; HCPCS codes S9529, G0001) were also not considered when identifying cancer claims.

work (NCCN),[3] and European Organisation for Research and Treatment of Cancer (EORTC)[4] recommend routine use of granulocyte colony-stimulating factors (G-CSFs) as primary prophylaxis in patients considered to be at high risk of febrile neutropenia (≥ 20%). Oncologists must consider individual patients' risk factors in their risk assessment. Known risk factors for the development of neutropenia include older age; poor performance or nutritional status; poor renal or hepatic function; low white blood cell or neutrophil counts; low hemoglobin levels at the time of chemotherapy administration; and a myelosuppressive chemotherapy regimen.[3,7,22,23]

In particular, older age has been identified as an independent risk factor for severe neutropenia, febrile neutropenia, and related complications that include death.[5,6,10,11,13,14,24-33] The risk of neutropenia-related hospitalization has been reported to be higher in patients who are older than 65 years than it is in younger patients with breast cancer or non-Hodgkin lymphoma (NHL).[30,34] Patients with small-cell lung cancer who are 60 or older experience more febrile neutropenia than do those who are younger than 60 years.[35] Eight percent of patients aged ≥ 75 years with non−small-cell lung cancer (NSCLC) experienced febrile neutropenia, compared with 2% of those over age 55 years.[36] Older cancer patients may also have longer hospital stays and higher mortality rates than do younger patients when they experience neutropenic complications.[5,6,10,12,25,26,28-31,33]

The effect of age on neutropenia risk is an important issue. In the US, more than half of all cancers and about 70% of cancer deaths occur in patients aged 65 or older.[37] Increasing life expectancy suggests that the number of

TABLE 2 Patient demographic and disease characteristics

Characteristic	Type of cancer or tumor		
	NHL (n = 2,506)	Breast (n = 9,110)	Lung (n = 4,022)
Men, n (%)	1,361 (54.3)	0 (0.0)	2,169 (53.9)
Age, mean (SD), y	63.0 (11.7)	55.7 (9.5)	65.6 (10.0)
Age categories, n (%)			
40-49	351 (14.0)	2,772 (30.4)	255 (6.3)
50-59	676 (27.0)	3,325 (36.5)	859 (21.4)
60-64	383 (15.3)	1,332 (14.6)	710 (17.6)
65-69	335 (13.4)	887 (9.7)	720 (17.9)
70-74	262 (10.4)	436 (4.8)	658 (16.4)
75-79	260 (10.4)	233 (2.6)	480 (11.9)
80-84	152 (6.1)	104 (1.1)	276 (6.9)
85 or older	87 (3.5)	21 (0.2)	64 (1.6)
Comorbidities, n (%)			
Myocardial infarction	73 (2.9)	101 (1.1)	216 (5.4)
Congestive heart failure	186 (7.4)	330 (3.6)	377 (9.4)
Peripheral vascular disease	198 (7.9)	211 (2.3)	511 (12.7)
Cerebrovascular disease	106 (4.2)	173 (1.9)	521 (12.9)
Hemiplegia or paraplegia	7 (0.3)	6 (0.1)	19 (0.5)
Dementia	8 (0.3)	7 (0.1)	29 (0.7)
Chronic pulmonary disease	392 (15.6)	1,004 (11.0)	2,567 (64.8)
Rheumatologic disease	101 (4.0)	162 (1.8)	99 (2.5)
Peptic ulcer disease	78 (3.1)	27 (0.3)	42 (1.0)
Mild or moderate diabetes	393 (15.7)	954 (10.5)	664 (16.5)
Diabetes with chronic complications	57 (2.3)	111 (1.2)	105 (2.6)
Renal disease	137 (5.5)	107 (1.2)	178 (4.4)
Mild liver disease	258 (10.3)	658 (7.2)	402 (10.0)
Moderate or severe liver disease	8 (0.3)	7 (0.1)	7 (0.2)
AIDS	41 (1.6)	11 (0.1)	10 (0.2)
Evidence of metastatic disease, n (%)[a]	n/a	1,343 (14.7)	692 (17.2)

Abbreviation: NHL, non-Hodgkin lymphoma.
[a] Evidence of metastatic disease was not assessed in patients with NHL because lymph node involvement is an essential element of NHL for all patients.

elderly people with cancer will increase.[3] NCCN and EORTC guidelines state that advanced age should not preclude the use of effective cancer treatment and that older patients with good performance status can tolerate commonly used chemotherapy regimens with appropriate supportive care.[3,29] Nonetheless, the increased risk of myelosuppression in elderly patients may make oncologists hesitant to administer full doses of standard chemotherapy regimens to elderly patients, particularly those with inadequate performance status.[29] Although several studies have evaluated the risk of neutropenia in older patients, the available evidence has limitations. Many previous studies analyzed age as a dichotomous rather than a continuous variable, examining the incidence of neutropenia, for example, in patients who were younger than 65 years or 65 or older[6,10,12,30,33,34] or in patients who were 60 or younger or older than 60.[5,14,35] The effect of age as a continuous variable on the risk of neutropenia, while controlling for age-related risk factors, has not been analyzed in a large population in the community treatment setting.

This analysis was designed to provide more comprehensive information about the variation by age on the incidence of neutropenic complications in cancer patients receiving myelosuppressive chemotherapy. We focused on common cancer types (breast, lung, and NHL) for which treatment-related neutropenia is relatively common. We also analyzed other factors that may affect the risk of neutropenia-related hospitalization.

TABLE 3 Cancer treatment characteristics

Characteristic	Type of cancer or tumor		
	NHL (n = 2,506)	Breast (n = 9,110)	Lung (n = 4,022)
Number of myelosuppressive[a] chemotherapy agents, mean (SD)	1.7 (0.6)	2.0 (0.6)	1.8 (0.5)
Number of patients on			
0 agents, n (%)	68 (2.7)	146 (1.6)	113 (2.8)
1 agent	736 (29.4)	817 (9.0)	809 (20.1)
2	1,631 (65.1)	6,818 (74.8)	3,086 (76.7)
3	69 (2.8)	1,327 (14.6)	14 (0.4)
4	2 (0.1)	2 (0.0)	0 (0.0)
Myelosuppressive chemotherapy agents used in ≥ 2% of patients of any tumor type, n (%)[b]			
Cyclophosphamide	2,163 (86.3)	7,301 (80.1)	6 (0.2)
Carboplatin	38 (1.5)	838 (9.2)	2,767 (68.8)
Cisplatin	10 (0.4)	12 (0.1)	863 (21.5)
Methotrexate	21 (0.8)	194 (2.1)	1 (0.0)
Pemetrexed	0 (0.0)	1 (0.0)	301 (7.5)
Fludarabine	226 (9.0)	1 (0.0)	1 (0.0)
Fluorouracil	2 (0.1)	532 (5.8)	5 (0.1)
Docetaxel	1 (0.0)	3,799 (41.7)	473 (11.8)
Paclitaxel	1 (0.0)	427 (4.7)	1,567 (39.0)
Doxorubicin	1,472 (58.7)	4,785 (52.5)	3 (0.1)
Epirubicin	3 (0.1)	327 (3.6)	0 (0.0)
Mitoxantrone	62 (2.5)	10 (0.1)	0 (0.0)
Etoposide	82 (3.3)	2 (0.0)	968 (24.1)
Time to second administration of same chemotherapy agent(s), n (%)			
Every week, QW	89 (3.6)	692 (7.6)	1,571 (39.1)
Every 2 weeks, Q2W	139 (5.6)	2,634 (28.9)	140 (3.5)
Every 3 weeks, Q3W	1,787 (71.3)	5,254 (57.7)	1,876 (46.6)
Every 4 weeks, Q4W	339 (13.5)	366 (4.0)	326 (8.1)
Longer than Q4W	152 (6.1)	164 (1.8)	109 (2.7)
Primary prophylaxis received, n (%)[c]			
None	1,236 (49.3)	3,499 (38.4)	3,125 (77.7)
Any primary prophylaxis	1,270 (50.7)	5,611 (61.6)	897 (22.3)
Filgrastim	62 (2.5)	163 (1.8)	57 (1.4)
Pegfilgrastim	1,192 (47.6)	5,413 (59.4)	828 (20.6)
Sargramostim	13 (0.5)	31 (0.3)	10 (0.2)
Multiple	3 (0.1)	4 (0.0)	2 (0.0)

Abbreviation: NHL, non-Hodgkin lymphoma.
[a] Chemotherapy agents classified as myelosuppressive:[3,4,21] bendamustine, busulfan, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clofarabine, cyclophosphamide, cytarabine, dacarbazine, daunorubicin, docetaxel, doxorubicin, doxorubicin – pegylated liposomal, epirubicin, etoposide, fludarabine, fluorouracil, hydroxyurea, idarubicin, ifosfamide, irinotecan, ixabepilone, lomustine, mechlorethamine, melphalan, mercaptopurine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, paclitaxel – albumin-bound, pemetrexed disodium, procarbazine, temozolomide, teniposide, thiotepa, topotecan; [b] Myelosuppressive chemotherapy agents used in < 2% of patients of any tumor type include bendamustine, albumin-bound paclitaxel, capecitabine, cladribine, cytarabine, dacarbazine, ifosfamide, irinotecan, ixabepilone, mechlorethamine, oxaliplatin, pegylated liposomal doxorubicin, temozolomide, thiotepa, and topotecan; [c] Defined as use of granulocyte colony or granulocyte-macrophage colony stimulating factors (G/GM-CSF, including filgrastim, pegfilgrastim, or sargramostim) within the first 5 days of the start of the first cycle.

TABLE 4 Hospitalization: neutropenia-related and all-cause, unadjusted results by age group

Type of cancer or tumor	All age groups	Age group, y							
		40-49	50-59	60-64	65-69	70-74	75-79	80-84	85+
NHL, N then n	2,506	351	676	383	335	262	260	152	87
Patients who had neutropenia-related hospital stays, n (%)	217 (8.7)	22 (6.3)	48 (7.1)	35 (9.1)	31 (9.2)	24 (9.2)	29 (11.2)	21 (13.8)	7 (8.0)
Patients who had hospital stays, any cause, n (%)	566 (22.6)	63 (18.0)	131 (19.4)	78 (20.4)	74 (22.1)	70 (26.7)	67 (25.8)	50 (32.9)	33 (37.9)
Breast cancer, N then n	9,110	2,772	3,325	1,332	887	436	233	104	21
Patients who had neutropenia-related hospital stays, n (%)	381 (4.2)	71 (2.6)	142 (4.3)	82 (6.2)	51 (5.8)	24 (5.5)	8 (3.4)	2 (1.9)	1 (4.8)
Patients who had hospital stays, any cause, n (%)	1,044 (11.5)	246 (8.9)	357 (10.7)	182 (13.7)	126 (14.2)	65 (14.9)	46 (19.7)	19 (18.3)	3 (14.3)
Lung cancer, N then n	4,022	255	859	710	720	658	480	276	64
Patients who had neutropenia-related hospital stays, n (%)	156 (3.9)	7 (2.8)	25 (2.9)	29 (4.1)	31 (4.3)	34 (5.2)	16 (3.3)	10 (3.6)	4 (6.2)
Patients who had hospital stays, any cause, n (%)	880 (21.9)	46 (18.0)	166 (19.3)	157 (22.1)	162 (22.5)	182 (27.7)	93 (19.4)	65 (23.6)	9 (14.1)

Material and methods

Data sources

This retrospective, observational, cohort study examined records from a commercial insurance claims database (OptumInsight) that contained medical, pharmacy, and enrollment data for a geographically diverse US patient population. The International Classification of Diseases, Ninth Revision Clinical Modification (ICD-9-CM), Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS) codes are used for hospital care. National Drug Code (NDC) codes are used to track pharmacy claims.

Patient selection

The patients who were selected for analysis had been diagnosed with female breast cancer, lung cancer, or NHL. Patients with multiple primary cancers were excluded. Table 1 provides detailed definitions used in patient selection criteria. Patients had initiated treatment with a new chemotherapy course between January 1, 2006 and March 31, 2010 and received at least 2 cycles of that course. Patients who were receiving biologics or corticosteroids were included if they were also receiving systemic chemotherapy agents. Patients were excluded if they had received radiation therapy or bone marrow or stem cell transplantation during the 90 days before the start of chemotherapy. Participants were continuously enrolled in a commercial or Medicare Advantage health plan. They had received medical and pharmacy benefits for 90 days or more before the start of the first chemotherapy administration and through the end of the chemotherapy course.

Statistical analysis

The analysis sample included only the first eligible course of chemotherapy for each patient. Patients who were younger than 40 years were excluded because there were so few of them;[37] such age restriction has been used in cancer epidemiology literature.[38] Neutropenia was identified using ICD-9-CM code 288.0. The number of myelosuppressive agents (see footnote a in Table 3) received during the first chemotherapy course was analyzed as ≤ 1 or ≥ 2. Myelosuppressive agents were identified from ASCO, EORTC, and NCCN guidelines[3,4,21] and from discussions with clinical experts. Although chemotherapy regimens often contain both myelosuppressive and nonmyelosuppressive agents, this analysis includes only myelosuppressive agents because of their effects on the risk of neutropenic events. De-

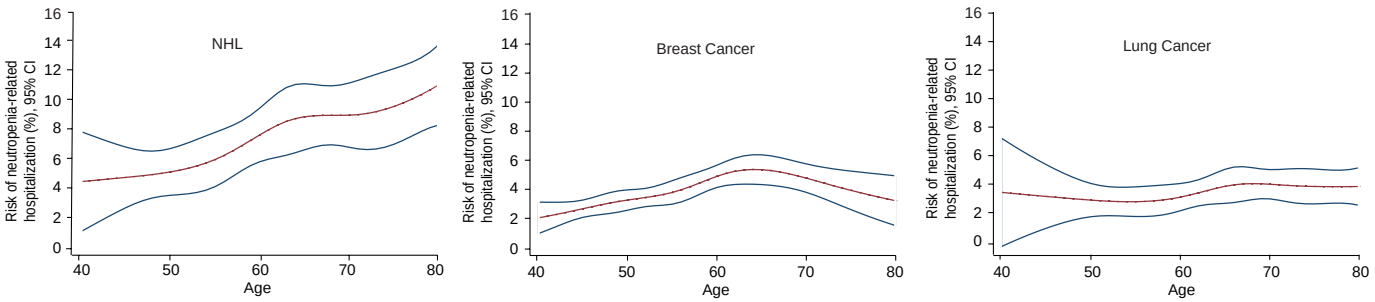

FIGURE 1 Neutropenia-related hospitalization by age, spline regression analysis for NHL, breast cancer, and lung cancer. Cubic spline regression curve (5 knots) fit using a logistic regression model relating age and risk of neutropenia-related hospitalization in the first chemotherapy course for each patient, adjusted for sex; use of ≤1 or ≥2 myelosuppressive chemotherapy agents; time to next administration of same chemotherapy agent(s); non-cancer comorbidities in the Deyo-Charlson index; evidence of metastases (breast and lung cancer only); and primary prophylaxis, defined as use of granulocyte colony or granulocyte-macrophage colony stimulating factors (G/GM-CSF, including filgrastim, pegfilgrastim, or sargramostim) within the first 5 days of the start of the first chemotherapy cycle. Upper and lower lines represent 95% confidence intervals (CI). Abbreviation: NHL, non-Hodgkin lymphoma.

scriptive, unadjusted, unstratified analyses included mean values, medians, quartiles, and standard deviations (SD) of continuous measures of interest and frequency distributions for categorical measures.

The relationship between age and the risk of neutropenia-related and all-cause hospitalization was analyzed using a cubic spline curve, a nonlinear fitted function composed of polynomials and points (called knots) that join polynomial pieces. The Stata mkspline, logit, and adjustrcspline programs were used for calculations.[39,40] In the spline analysis, the effect of age was adjusted in a logistic regression model that included the following covariates: the sex of the patient; use of ≤1 or ≥2 myelosuppressive chemotherapy agents; the time to next administration of the same chemotherapy agent(s); all noncancer comorbidities in Deyo-Charlson comorbidity index;[41] evidence of metastases (ICD-9-CM codes for secondary malignancies 196.xx-199.xx); and primary prophylaxis (defined as use of G-CSF or granulocyte-macrophage colony stimulating factor [GM-CSF] within the first 5 days of the start of the first chemotherapy cycle). The use of primary prophylaxis, which should depend on the neutropenia risk assessment that an oncologist performs for individual patients, was included in the models together with the number of myelosuppressive agents to control for a patient's expected risk of myelosuppression in the chemotherapy course of interest.

To examine further potential confounding effects, we also used a logistic regression model to estimate risk ratios for neutropenia-related hospitalization and all-cause hospitalization during the first chemotherapy course in patients aged 79 or younger. Patients older than 79 years (a small fraction of patients in the study) were excluded from this analysis. Covariates were the same as those used in the cubic spline analysis. We report effect estimates as risk ratios, which were estimated from odds ratios, with 95% confidence intervals.

Results

Patients

A total of 15,638 patients met the criteria for this analysis. Table 2 summarizes the demographic and disease characteristics of the study population. Breast cancer was the most frequent diagnosis (n = 9,110), followed by lung cancer (n = 4,022), and NHL (n = 2,506). The mean (SD) age ranged from 56 (10) years for patients with breast cancer to 66 (10) years for lung cancer patients. The distribution of ages varied with cancer type. About 54% of the patients with NHL and lung cancer were men. The most common comorbidities included chronic pulmonary disease, diabetes, liver disease, and cardiovascular disease.

Disease and treatment characteristics

About 15% of breast cancer patients and 17% of lung cancer patients had evidence of metastatic disease. Most of the patients (89%) received regimens containing 1 or 2 myelosuppressive chemotherapy agents (Table 3). Most (57%) had a 3-week chemotherapy cycle length (defined as the time to second administration of same chemotherapy agent(s)). About 62% of breast cancer patients, half of NHL patients, and 22% of lung cancer patients received primary prophylaxis, most commonly with pegfilgrastim, for the prevention of neutropenic complications.

Mortality during the first course of chemotherapy was low. Death occurred in 88 patients (2%) with lung cancer, 26 patients (1%) with NHL, and 16 patients with breast cancer (0.2%).

TABLE 5 Effect of age and other factors on risk of hospitalization: results of logistic regression analysis

Risk factor, risk ratio (95% CI)	Type of tumor or cancer: NHL (n = 2,267)	
	Neutropenia-related hospitalization	All-cause hospitalization
Age, 40-79 y in 5-y increments	1.144 (1.054–1.242)	1.058 (1.002–1.118)
Male sex	0.681 (0.498–0.931)	0.897 (0.726–1.110)
Comorbidities		
Myocardial infarction	0.899 (0.340–2.374)	1.067 (0.579–1.967)
Congestive heart failure	0.869 (0.461–1.638)	1.633 (1.113–2.395)
Peripheral vascular disease	0.871 (0.473–1.601)	1.329 (0.904–1.954)
Cerebrovascular disease	0.862 (0.380–1.953)	1.481 (0.897–2.446)
Hemiplegia or paraplegia	[b]	0.359 (0.040–3.227)
Dementia	5.143 (0.496–53.286)	0.953 (0.087–10.451)
Rheumatologic disease	1.464 (0.752–2.847)	1.675 (1.050–2.674)
Chronic pulmonary disease	1.094 (0.726–1.651)	0.936 (0.703–1.245)
Peptic ulcer disease	0.616 (0.217–1.749)	1.210 (0.675–2.169)
Mild or moderate diabetes	1.589 (1.078–2.343)	1.320 (1.000–1.743)
Diabetes with chronic complications	2.321 (1.039–5.187)	1.520 (0.818–2.825)
Renal disease	1.390 (0.753–2.567)	2.097 (1.382–3.183)
Mild liver disease	0.899 (0.542–1.491)	0.943 (0.671–1.326)
Moderate or severe liver disease	14.209 (2.904–69.522)	8.749 (1.583–48.351)
AIDS	5.858 (2.317–14.815)	2.766 (1.356–5.644)
Evidence of metastases	[c]	[c]
Primary prophylaxis[d]	0.982 (0.702–1.374)	1.225 (0.974–1.542)
Time to second administration of same chemotherapy agent(s) (reference, 3 weeks)		
1 week	0.637 (0.213–1.905)	1.256 (0.700–2.251)
2 weeks	1.973 (1.121–3.471)	1.596 (1.044–2.442)
≥ 4 weeks	1.455 (0.993–2.132)	2.093 (1.627–2.693)
Two or more myelosuppressive chemotherapies[e]	2.650 (1.707–4.112)	1.253 (0.973–1.615)

Abbreviation: NHL, non-Hodgkin lymphoma.
[a] Men with breast cancer were excluded from the study; [b] This factor was not included in logistic regression analysis because it perfectly predicts either hospitalization or no hospitalization; [c] Evidence of metastatic disease was not assessed in patients with NHL because lymph node involvement is an essential element of NHL for all patients; [d] Primary prophylaxis is defined as use of granulocyte or granulocyte-macrophage colony-stimulating factor (G/GM-CSF), including filgrastim, pegfilgrastim, or sargramostim] within the first 5 days of the start of the first chemotherapy cycle; [e] Myelosuppressive chemotherapies are listed in notes for Table 3 on page XXX.

Neutropenia-related hospitalization

Neutropenia-related hospitalization occurred most often in patients with NHL, with an overall unadjusted frequency of about 9% (Table 4), compared with 4% each of breast and lung cancer patients. Adjusted spline analysis also showed that the risk of neutropenia was highest in patients with NHL, for whom the risk increased with advancing age (Figure 1A). The association between age and the risk of neutropenia-related hospitalization was stronger in NHL than in breast or lung cancer (Figure 1B and C).

Logistic regression analysis showed that several factors other than age had marked effects on the risk of neutropenia-related hospitalization (Table 5). Patient-related factors associated with increased risk in patients with NHL included female sex; diabetes with or without complications; moderate or severe liver disease; and AIDS. Evidence of metastases was an important risk factor in patients with breast or lung cancer. Treatment-related factors associated with increased risk of neutropenia-related hospitalization included administration of a regimen containing 2 or more myelosuppressive

TABLE 5 (*continued*)

Type of tumor or cancer			
Breast (n = 8,985)		Lung (n = 3,682)	
Neutropenia-related hospitalization	All-cause hospitalization	Neutropenia-related hospitalization	All-cause hospitalization
1.130 (1.065–1.198)	1.092 (1.051–1.134)	1.070 (0.965–1.186)	1.032 (0.983–1.082)
[a]	[a]	0.932 (0.661–1.315)	0.917 (0.779–1.080)
0.513 (0.159–1.655)	1.477 (0.881–2.475)	0.811 (0.368–1.788)	1.326 (0.951–1.851)
1.287 (0.790–2.094)	1.195 (0.866–1.649)	1.073 (0.608–1.894)	1.544 (1.189–2.005)
0.634 (0.291–1.383)	0.902 (0.585–1.391)	1.352 (0.843–2.168)	1.265 (0.994–1.610)
1.135 (0.567–2.274)	1.345 (0.879–2.057)	1.196 (0.746–1.918)	1.200 (0.950–1.518)
3.835 (0.430–34.203)	2.965 (0.524–16.779)	[b]	1.849 (0.617–5.543)
[b]	[b]	1.744 (0.397–7.663)	0.900 (0.344–2.356)
0.956 (0.442–2.066)	1.080 (0.667–1.748)	1.752 (0.741–4.140)	1.432 (0.894–2.295)
1.145 (0.840–1.561)	1.356 (1.119–1.644)	1.309 (0.894–1.915)	1.207 (1.013–1.439)
[b]	0.512 (0.119–2.195)	1.237 (0.290–5.276)	0.829 (0.370–1.855)
1.106 (0.803–1.523)	1.342 (1.100–1.637)	1.020 (0.652–1.595)	1.285 (1.043–1.585)
1.305 (0.586–2.907)	1.777 (1.090–2.899)	1.023 (0.361–2.896)	1.690 (1.068–2.675)
1.344 (0.600–3.011)	1.283 (0.762–2.161)	1.238 (0.580–2.640)	1.019 (0.691–1.504)
1.259 (0.868–1.825)	1.019 (0.793–1.310)	0.807 (0.447–1.454)	0.762 (0.576–1.007)
2.953 (0.340–25.636)	2.388 (0.438–13.026)	[b]	2.054 (0.361–11.697)
2.566 (0.315–20.915)	2.694 (0.671–10.814)	[b]	2.353 (0.606–9.134)
1.805 (1.397–2.332)	2.245 (1.913–2.635)	1.551 (1.041–2.310)	2.323 (1.920–2.812)
0.806 (0.640–1.015)	0.985 (0.846–1.147)	0.820 (0.531–1.266)	1.032 (0.838–1.271)
0.697 (0.355–1.366)	1.056 (0.753–1.482)	0.789 (0.510–1.219)	1.032 (0.843–1.264)
1.137 (0.887–1.458)	1.077 (0.918–1.264)	1.085 (0.419–2.806)	1.677 (1.103–2.551)
1.912 (1.340–2.727)	2.140 (1.693–2.706)	1.839 (1.159–2.918)	1.845 (1.440–2.365)
3.417 (1.874–6.233)	1.568 (1.170–2.102)	1.467 (0.890–2.420)	1.289 (1.036–1.603)

chemotherapy agents and chemotherapy cycle length of 2 weeks or 4 or more weeks (compared with 3 weeks). The estimated risk ratio for primary prophylaxis compared with no primary prophylaxis was close to 1.

All-cause hospitalization

NHL and lung cancer patients had the highest overall probability of all-cause hospitalization in unadjusted analyses (NHL, 23%; lung cancer, 22%; breast cancer, 11%; Table 4). Spline regression curves showed that the probability of all-cause hospitalization increased with age in NHL and breast cancer (Figure 2). In lung cancer, all-cause hospitalization increased with age to about 73 years, but then flattened. In logistic regression analyses (Table 5), factors other than age that notably increased the risk of all-cause hospitalization included noncancer comorbidities and, in breast and lung cancer, metastatic disease.

Discussion

In this population of US patients with cancer receiving myelosuppressive chemotherapy, we examined the effect

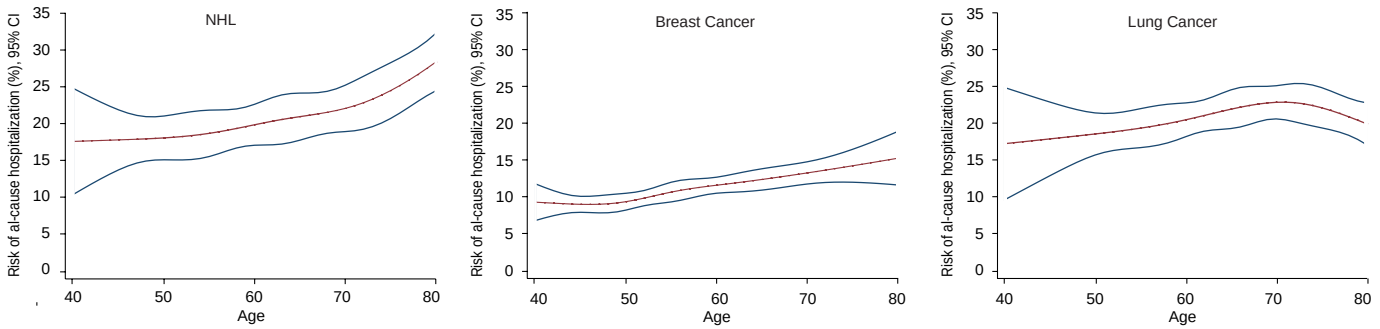

FIGURE 2 All-cause hospitalization by age, spline regression analysis for NHL, breast cancer, and lung cancer. Cubic spline regression curve (5 knots) fit using a logistic regression model relating age and risk of all-cause hospitalization in the first chemotherapy course for each patient, adjusted as described for Figure 1. Abbreviation: NHL, non-Hodgkin lymphoma.

of age as an independent risk factor for neutropenia-related hospitalization using spline regression analysis. This method smoothly represents the relationship between the continuous variable of age and the outcomes of neutropenia-related and all-cause hospitalization. The highest risk of neutropenia-related hospitalization was observed in NHL patients, whose risk increased with advancing age. Overall, these results show that age is an important component in the determination of risk. But the effect is gradual over a range rather than changing abruptly at a certain age (eg, 65 years). In addition, the association of age with the risk of neutropenia-related hospitalization is not linear and varies with the type of malignancy.

The primary objective of this study was to describe the association between age and risk of neutropenic complications. However, other characteristics of patients and treatment regimens interact with age to affect the risk of neutropenic complications, including sex, tumor type, comorbid conditions, evidence of metastatic disease, use of primary prophylaxis, cycle length, and the number of myelosuppressive drugs used. A logistic regression model, which examined the interactions of these factors with age as they affect the risk of hospitalization, showed that numerous factors have a greater effect than age on the risk of both neutropenia-related and all-cause hospitalization.

The primary outcome measure in our study is risk of neutropenia-related hospitalization in the first chemotherapy course of each patient, whereas many published clinical studies reported the risk of febrile neutropenia during the first cycle or over a specific period of time. The neutropenia-related hospitalization events captured in claims databases are a good approximation of events of febrile neutropenia, which often requires hospitalization. As an operational definition of febrile neutropenia in claims data, neutropenia-related hospitalization has a sensitivity of 80%[42] when compared with the "gold standard" clinical definition (single temperature $\geq$ 38.3°C orally or $\geq$ 38.0° C for 1 hour; neutropenia defined as an ANC $< 0.5 \times 10^9$/L or $< 1.0 \times 10^9$/L and a predicted decline to $< 0.5 \times 10^9$/L over the next 48 hours).[3]

In our study, the claims-based estimates of the risk of febrile neutropenia (ie, neutropenia-related hospitalization) during the first course were 9% in NHL and 4% each in breast and lung cancer. With approximately 50% of patients receiving primary prophylaxis in our study, these risk estimates are generally within the range between first-course risk estimates for febrile neutropenia in the placebo (no primary prophylaxis) and primary prophylaxis arms of clinical trials and clinical practice.[43-45] Of note, Lyman reported febrile neutropenia during the first course in 17% of patients with NHL in a 2003 study.[6] One potential reason for this difference between results of that study and ours is the use of primary prophylaxis. In our study, 51% of NHL patients received primary prophylaxis to prevent neutropenic complications, compared with 8% of patients in the Lyman study. (The Lyman study had a stricter definition of primary prophylaxis than ours, including initiation of filgrastim [the only FDA-approved G-CSF at that time] within the first 5 days in cycles 1 and 2, and a duration of 7 or more days of filgrastim prophylaxis.) In addition, some NHL regimens used by patients in our study may have been less myelotoxic than the CHOP-like chemotherapy used in the Lyman study. As in previous studies,[6,13,34,36,46] the risk of neutropenic complications increased with age in this study, particularly in patients with NHL. Additional risk factors observed in our study were similar to those reported previously, including female sex and comorbid disease in patients with NHL, metastases in patients with breast or lung cancer,[5,6,10,12,15,17,32,42,47-49] and highly myelosuppressive chemotherapy.[4,7,22,23,46] The estimated risk ratio for primary prophylaxis compared with no primary prophylaxis (which is close to 1 in logistic regression models) should be

interpreted with caution because it is impossible to disentangle the real effect of primary prophylaxis from potential confounding by indication (confounding by anticipated severity of neutropenia) in our observational research design. Patients perceived by their oncologists as having a higher risk of febrile neutropenia are more likely to receive CSF primary prophylaxis.

Strengths of this study include the large population size; the specific, detailed information available about patient and treatment characteristics; and the analyses of age as a continuous variable. Although this study did not analyze cost, hospitalization for neutropenia and other complications is a driver of treatment cost for oncology patients. This study also provides additional insights that can be applied in analyzing the cost-related effects of treatment. Limitations of the study include those common to claims-based analyses in which clinical stage, planned chemotherapy regimen (dose and schedule) and other clinical factors cannot be determined from the available claims data. For this reason, it was impossible to comprehensively and accurately assess individual patients' neutropenia risk. Patient and treatment factors that were excluded from the logistic models may also have important effects on risk. The sample of patients analyzed also poses some limitations. It is probable that oncologists would have performed some risk assessment before recommending myelosuppressive chemotherapy for some patients. For example, very frail or very elderly patients might elect not to undergo chemotherapy, choosing hospice or palliative care instead. Chrischilles and colleagues reported that 47% of patients with NSCLC and aged 75 years or older received chemotherapy, compared with 72% of those aged 55 or younger.[36] Fewer myelosuppressive regimens might also be used for older patients who are considered to be at higher risk. Patients aged 80 or more years in our study might represent a selected sample of relatively healthy patients, potentially leading to underestimation of the relationship between age and neutropenia-related hospitalization. For this reason and because of their small numbers, they are not shown in the spline regression curves and excluded from the logistic models. Although the effect of age has been explored previously,[5,6,10,13,25-31] this study of a large population in a community oncology setting adds to the body of evidence to help oncologists evaluate risk for individual patients by analyzing age as a continuous variable rather than within broad categories as previous studies have done.[5,6,10,12,14,30,33-35] The effect of age should also be examined as a covariate with other patient, disease, and treatment characteristics (Table 5). In conclusion, age is one of several interrelated factors that oncologists should consider when evaluating the risk of neutropenic complications in patients with cancer receiving myelosuppressive chemotherapy.

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