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Risk Factors for Adverse Events in Patients with Breast, Colorectal, and Lung Cancer

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Abstract

Objectives—We sought to identify risk factors associated with medical errors and iatrogenic injuries during an initial course of cancer-directed treatment.

Methods—In this retrospective cohort study of 400 patients age ≥18 years undergoing an initial course of treatment for breast, colorectal, or lung cancer at a comprehensive cancer center, we abstracted patient, disease, and treatment-related variables from the electronic medical record. We examined adverse events (AEs) and preventable AEs by risk factor using the chi-square or Fisher exact tests. We estimated the association between risk factors and the relative risk of an additional AE or preventable AE in multivariable negative binomial regression models with backwards selection ($p < 0.1$).

Results—There were 304 AEs affecting 136 (34%) patients and 97 preventable AEs affecting 53 (13%) patients. In multivariable analyses, AEs were over-represented in those with lung cancer compared to patients with breast cancer (IRR 1.9, 95% CI 1.1–3.2). Non-white race (1.6, 1.0–2.6), Hispanic or Latino ethnicity (2.0, 0.9–4.1), advanced disease (1.7, 1.1–2.6), use of each additional class of high-risk non-chemotherapy medication (1.6, 1.3–1.9), and chemotherapy (2.1, 1.3–3.3) were all associated with risk of an additional AE. Preventable AEs were associated with lung cancer (7.4, 2.4–23.2), Hispanic or Latino ethnicity (5.5, 1.7–17.9), and high-risk non-chemotherapy medications (1.5, 1.2–2.0).

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Conclusions—Risk factors for AEs among cancer patients reflected patients' underlying disease, cancer-directed therapy, and high-risk non-cancer medications. The association of AEs with ethnicity merits further research. Risk factor models could be used prospectively to identify cancer patients at increased risk of harm.

Keywords

Adverse event; medical error; patient safety; oncology; risk factors; epidemiology

INTRODUCTION

Despite its practitioners' commitment to safe and effective oncology practice, relatively little is known about the epidemiology of medical error and iatrogenic injury in cancer care.¹²³⁴⁵⁶⁷ While rigorous clinical trials examine the effects of carefully chosen treatments in narrowly defined patient populations, that approach may overlook mishaps that result from poorly designed or executed clinical processes in everyday practice. Understanding the epidemiology of treatment-related errors and injuries in oncology care may characterize the extent of the problem, and identify patient, disease, and treatment-related factors that increase patients' risk of harm.⁸

The present report is part of a larger study of patient safety in oncology, in which we described the incidence of adverse events (AEs) among a cohort of newly-treated cancer patients.⁹ The purpose of this sub-study is to identify risk factors that are associated with medical errors and injuries over an initial course of cancer-directed treatment. We hypothesized that risk factors for AEs among cancer patients would mirror those found to affect hospitalized patients, such as acuity and severity of illness, the number and type of interventions received, and use of high-risk medications. We hypothesized that certain cancer-specific risk factors could also confer increased risk, such as cancer type, advanced-stage disease, and receipt of cancer-specific treatments.

METHODS

Study Cohort and Medical Record Review

We performed a retrospective cohort study of 400 patients age ≥18 years with breast (n=128), colorectal (n=136), or lung (n=136) cancer and treated at Memorial Sloan Kettering Cancer Center (MSK). Subjects started their first cancer treatment with either curative or palliative intent at MSK between January 1 and December 31, 2012, and were followed as in- and outpatients for up to one year or death, whichever came first. We selected patients using stratified random sampling based on cancer stage and treatment to ensure a diverse and representative cohort.

Trained oncology nurses identified candidate AEs from patients' electronic medical records using an oncology trigger tool that flagged cases with potential complications. We combined this information with events reported to two MSK safety event reporting databases: Surgical Secondary Events for surgical complications and the RL6:RISQ (RL Solutions, Toronto, ON) confidential incident reporting system that is open to all staff. Candidate

AEs were reviewed and coded independently by two physician-investigators based on nurse case abstractions and review of the medical record, according to type, severity, and preventability.¹⁰¹¹ Physician-investigators calibrated their assessments based on practice cases, use of a coding guide (that distinguished events by type, severity, and preventability), and medical record review. Reviewers were cautious in their attribution of AEs to medical care given the prevalence of disease-related symptoms among patients with cancer. Interrater reliability was 98% for AEs, 79% for severity, and 78% for preventability.

Variables and Outcomes

We abstracted information from the electronic medical record and manually from patient intake forms, selecting potential AE risk factors based on prior studies, research team members' clinical judgments, and the availability of information in the record. Patient demographic and administrative variables included age, sex, race, ethnicity, non-English primary language, marital status, insurance type, and distance from home to the cancer center. Disease-related variables included cancer stage, drug allergies, prior cancer, and medical comorbidities. Treatment variables included enrollment in a therapeutic trial, surgery, chemotherapy, radiation therapy, and selected high-risk classes of non-chemotherapy medications. All variables were identified using information across the entire study period.

An AE was defined as unintended harm to a patient due to an act of commission or omission that was the direct or indirect result of medical treatment – such as medication management, surgery, radiation, or a diagnostic procedure – rather than by the underlying disease or condition of the patient. AEs included both preventable and non-preventable events based on the consensus judgment of a pair of physician-investigators with experience in clinical oncology or patient safety. An AE was classified as “preventable” if the event resulted from care that was inconsistent with sound clinical practice or a complication that could have been avoided had it been anticipated, and was not an expected manifestation of underlying disease. Reviewers were conservative in identifying AEs or attributing preventability, relying on documentation in the medical record, entries in the hospital-based safety reporting system, and their consensus judgments to make these determinations. Conflicts were infrequent and resolved by a third clinician.

Analyses

We examined the proportion of AEs and preventable AEs by patients' sociodemographic, disease, and treatment-related characteristics using chi-square or Fisher's exact tests. Since individual patients were susceptible to multiple events over the course of their treatment, we estimated the association between individual risk factors and a patient's risk of experiencing one or more AEs or preventable AEs using multivariable negative binomial regression models with backwards stepwise selection ($p < 0.1$) in order to account for outcome over-dispersion. The logarithm of patient days at risk was used as an offset. All tests were two-tailed with $p = 0.05$. Analyses were performed using SAS Software (SAS Institute, Cary, NC). This study was judged to be exempt research by the MSK Institutional Review Board.

RESULTS

Subject Characteristics

Of the 400 subjects, patients' mean age was 61 years, 32% were male, 19% were non-white, 6% were Hispanic or Latino, and 7% identified a language other than English as their primary language (Table 1). Most had commercial insurance or Medicare, and a minority of patients lived more than 50 miles from the cancer center. Although patients had few comorbid illnesses or prior cancer diagnoses, 43% presented with advanced-stage cancer. Many patients received cancer-directed treatments including surgery (74%), chemotherapy (63%), or radiation therapy (33%). Many patients received high-risk medications including anticoagulants, benzodiazepines, and opioid analgesics. Patients with colorectal and lung cancer were, on average, older than those with breast cancer and included a higher percent who received chemotherapy or other high-risk medications.

Risk Factors for Adverse Events and Preventable Adverse Events

We identified a total of 304 AEs affecting 136 (34%) patients and 97 preventable AEs affecting 53 (13%) patients. AEs were identified by medical record alone in 85% of cases, the internal reporting system alone in 5%, and by both methods in the remainder. AEs included a wide variety of event types including metabolic derangements, gastrointestinal findings and symptoms, hematologic disorders, infections, respiratory ailments, genitourinary, neurologic, vascular, and cardiac problems, as well as injuries affecting integumentary and lymphatic systems. Specific examples of non-preventable serious AEs included post-mastectomy and radiation lymphedema; sepsis after multi-agent chemotherapy following major abdominal surgery; and portal vein thrombosis attributed to heparin-induced thrombocytopenia. In comparison, examples of serious preventable AEs included a return to the operating room for an anastomotic leak; respiratory arrest for possible over-sedation; and delayed diagnosis and treatment of acute renal failure. Of the 53 patients with at least one preventable AE, about one in seven had either cancer-directed surgery, chemotherapy, or both.

As shown in Table 2, AEs were over-represented among patients with colorectal and lung cancer compared to those with breast cancer. Hispanic/Latino ethnicity was the only sociodemographic characteristic associated with a higher incidence of AEs (52% vs. 33%, $p=0.049$). Among patients' clinical characteristics, AEs were more likely among those with at least one drug allergy (43% vs. 28%, $p=0.003$), any high-risk medication (38% vs. 17%, $p<0.001$), advanced-stage disease (43% vs. 28%, $p=0.001$), patients enrolled in therapeutic protocols (49% vs. 32%, $p=0.011$), and those who received surgery (38% vs. 23%, $p=0.005$) or chemotherapy (41% vs. 22%, $p<0.001$).

For preventable AEs, colorectal or lung cancer, Hispanic/Latino ethnicity, antiarrhythmic, anticoagulant, and diabetes medications, advanced stage disease, and cancer surgery were associated with preventable AEs. Notably, there were no statistically significant bivariate associations between the presence of preventable AEs and drug allergies, enrollment in therapeutic protocols, or chemotherapy.

Multivariable Analyses

In multivariable regression analyses (Table 3), the risk of experiencing an additional AE was greater among patients with lung cancer compared to patients with breast cancer (incident rate ratio 1.8, 95% CI 1.1-3.2). Non-whites (1.6, 1.0-2.6) were at increased risk of AEs compared to whites. Patients with more high-risk medication classes were more likely to experience additional AEs (1.6, 1.3-1.9, for each additional medication class). Patients with advanced disease (1.7, 1.1-2.6) and patients receiving chemotherapy (2.1, 1.3-3.3) were at increased risk of AEs.

For preventable AEs, colorectal and lung cancer conferred increased risk of experiencing an additional preventable AE compared to patients with breast cancer – although the confidence intervals were wide and the significance of colorectal cancer was marginal. In contrast to the “all AE” analysis, non-white race, advanced disease, and chemotherapy were not associated with risk of preventable AEs. Hispanics and Latinos were at increased risk (5.5, 1.7-17.9), as were patients who received more high risk medications (1.5, 1.2-2.0, for each additional medication class).

DISCUSSION

We documented a significant burden of AEs and preventable AEs in this cohort of 400 patients with newly treated breast, colorectal, and lung cancer followed for up to a year. One in three patients experienced an AE and one in eight had an AE that was judged to be preventable. In multivariable analyses, AEs were over-represented in those with lung cancer, and among non-whites, Hispanics and Latinos (marginal), patients with advanced disease, and in those receiving high-risk medications or chemotherapy. Preventable AEs were over-represented among patients with many of the same risk factors, including cancer type, Hispanic/Latino ethnicity, and high-risk medications. The association of AEs and preventable AEs with race, disease stage, and chemotherapy was inconsistent.

Prevalent AEs are no surprise to oncology practitioners, who regularly advise patients about the risks of treatment-related toxicities in light of disease state, patient age and functional status, and patient preferences.¹²¹³ That said, a focus on known toxicities and expected complications may obscure our collective understanding of the broader risk of cancer treatment among unselected patient populations. There has been relatively little rigorous attention in the oncology literature to chemotherapy treatment errors or to AEs associated with the use of non-chemotherapy medications in cancer patients.²³¹⁴

Most large epidemiological studies have demonstrated an increased risk of AEs among vulnerable patient populations receiving “intensive” treatment, a finding attributed to the number of interventions and to patients’ poor physiologic reserve.¹⁵¹⁶¹⁷¹⁸¹⁹²⁰²¹²²²³²⁴ The current study extends this principle to oncology care.²⁵ While the reduced risk of AEs in older patients would seem to contradict the “vulnerability” hypothesis, this finding may be accounted for by oncologists’ decision to defer or adjust the intensity of therapies in older patients to reduce the risk of toxicity.²⁶²⁷ While chemotherapy and advanced disease conferred increased risk of AEs, the lack of association between surgery or radiation therapy and AEs may reflect patient selection, a narrow exposure interval, a limited toxicity profile,

and a high degree of reliability in radiation treatment planning and delivery. Chemotherapy and advanced disease were not associated with preventable AEs in multivariable models, perhaps reflecting reviewers' difficulty or reluctance attributing adverse outcomes to patients with advanced illness or complex chemotherapy. Our finding that race and ethnicity increased the risk of AEs has face validity, as Hispanics and Latinos may be reluctant to report symptoms or have difficulty escalating their concerns due to language or cultural barriers. This relationship was particularly notable for preventable AEs, suggesting that interventions to support cultural sensitivity awareness and navigation services may offer opportunities to prevent injurious errors. This result conflicts with previous studies showing little relationship between sociodemographic characteristics and AEs, although critics have argued that adequately powered studies are lacking.²⁸²⁹³⁰³¹³²³³³⁴³⁵³⁶

Future research offers the possibility of creating risk prediction algorithms for cancer patients – using variables such as disease, age, race and ethnicity, and treatment – to estimate the risk of AEs through a course of therapy. For example, an otherwise healthy 64 year-old woman with early-stage breast cancer treated with surgery alone would, based on our data, expect 1.1 AEs within three years of initiating treatment. In contrast, a 70 year-old man with advanced-stage lung cancer treated with chemotherapy and any high-risk non-chemotherapy medication would expect 5.6 AEs during the same interval, a five-fold difference. Providing information about patient-specific AE risks could inform patients' preference-sensitive decisions about therapy. In addition, automated risk prediction algorithms within electronic health record systems may allow for real-time use of AE risk prediction in clinical oncology care.

Our research is subject to several limitations. First, while we examined the association of AEs with a variety of proposed risk factors, these analyses cannot determine causality. Second, the study was not designed to detect differences between disease groups. Therefore, null findings may result from lack of statistical power, and significant results with wide confidence intervals may suggest spurious associations. Third, we identified AEs based on information available in medical records and from incident reporting databases. This likely underestimates the true incidence of AEs, particularly if events occurred in non-MSK locations and were not relayed to MSK providers. Fourth, our study was performed at a single referral center. Findings may not be generalizable to other oncology care settings. Finally, this longitudinal study captured AEs over a year's course of care. This method was designed to capture the risks and harms affecting patients over time, but the approach makes it difficult to identify and isolate periods or settings of increased risk.

CONCLUSION

In conclusion, cancer patients' risk of AEs and preventable AEs is associated with the type of cancer, Hispanic or Latino ethnicity, use of high-risk medications, as well as chemotherapy treatment. Additional research is needed to understand how to identify cancer patients at highest risk of AEs, and how to reduce errors and injuries affecting this vulnerable population.

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Table 1

Subjects' sociodemographic and clinical characteristics

Characteristic	Total N=400	Breast Cancer N=128	Colorectal Cancer N=136	Lung Cancer N=136
Mean age in years (SD) at start of study	61 (13)	55 (13)	60 (13)	67 (11)
Male	32%	0%	51%	42%
Non-white race	19%	23%	20%	15%
Hispanic/Latino	6%	5%	8%	6%
Non-English primary language	7%	6%	8%	7%
Married	66%	62%	68%	68%
Insurance status				
Commercial	55%	70%	56%	40%
Medicare	43%	27%	42%	57%
Medicaid	2%	2%	2%	2%
Self-pay	1%	1%	0%	1%
>50 miles to cancer center	18%	16%	23%	16%
Mean no. (SD) of comorbidities ^a	1.2 (1.3)	0.9 (1.0)	1.1 (1.3)	1.6 (1.4)
Drug allergy	14%	13%	14%	14%
Prior cancer diagnosis	15%	11%	12%	21%
Early stage of disease [In-situ – stage III]	57%	74%	48%	50%
Enrollment in therapeutic protocol	14%	13%	14%	14%
High-risk medication class				
Antiarrhythmia	24%	2%	32%	35%
Anticoagulant	52%	15%	80%	57%
Diabetes medication	10%	5%	9%	15%
Benzodiazepine	53%	28%	71%	57%
Opioid	75%	67%	90%	68%
Any	81%	72%	94%	76%
Mean no. (SD) of high risk medication classes ^b	2.1 (1.4)	1.2 (1.0)	2.8 (1.1)	2.3 (1.6)
Cancer-directed treatment				
Surgery	74%	78%	82%	62%
Chemotherapy	63%	59%	64%	66%
Radiation therapy	33%	42%	15%	42%

SD, standard deviation

^a Comorbid conditions include myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes, hemiplegia, moderate or severe renal disease, diabetes with end organ damage, moderate or severe liver disease, AIDS, hyperlipidemia, hypertension, and coronary artery disease.

^b High-risk medications classes include antiarrhythmia, anticoagulant, diabetes medication, benzodiazepine, opioid.

Table 2

Subjects' sociodemographic and clinical characteristics, by adverse event number and type

Characteristic	Adverse Events ^a (N=136 patients)			Preventable Adverse Events ^d (N=53 patients)			P-Value ^b
	None	1	2	None	1	2	
Cancer type							0.006
Breast	79%	13%	8%	96%	4%	0%	
Colorectal	59%	18%	24%	84%	10%	7%	
Lung	61%	17%	22%	81%	10%	10%	
Age at start of study							0.786
<50	69%	6%	25%	86%	10%	5%	
50–64	66%	18%	16%	88%	6%	5%	
65–74	60%	22%	19%	84%	11%	5%	
75	72%	17%	12%	88%	3%	8%	
Sex							0.101
Male	61%	17%	23%	83%	9%	9%	
Female	69%	16%	16%	89%	7%	4%	
Race							0.653
Non-white	60%	18%	22%	88%	10%	1%	
White	67%	15%	17%	86%	7%	7%	
Ethnicity							0.010
Hispanic/Latino	48%	16%	36%	68%	8%	24%	
Not Hispanic/Latino	67%	16%	17%	88%	8%	4%	
Primary language							0.449
Non-English	72%	17%	10%	83%	10%	7%	0.566
English	66%	16%	19%	87%	8%	5%	
Marital status							0.760
Unmarried	65%	16%	19%	86%	7%	7%	
Married	67%	16%	17%	87%	8%	5%	
Insurance type							0.931
Commercial	66%	15%	20%	87%	8%	5%	

	Adverse Events ^a (N=136 patients)			Preventable Adverse Events ^a (N=53 patients)		
	None	1	2	None	1	2
Medicaid or self-pay	73%	0%	27%	91%	0%	9%
Medicare	66%	19%	15%	86%	8%	6%
Distance to cancer center						
50 miles	67%	15%	18%	87%	7%	6%
>50 miles	63%	21%	16%	85%	10%	5%
Comorbidities ^c						
None	69%	14%	17%	89%	7%	5%
1	68%	16%	16%	89%	9%	2%
2	60%	18%	21%	83%	8%	10%
Drug allergy						
None	72%	14%	14%	87%	7%	6%
At least one	57%	19%	24%	86%	10%	4%
Prior cancer diagnosis						
Yes	72%	14%	14%	93%	3%	3%
No	65%	16%	19%	86%	8%	6%
Stage of disease						
Early [In-situ–stage III]	73%	14%	14%	90%	7%	4%
Late	57%	19%	24%	83%	9%	8%
Enrollment in therapeutic protocol						
Enrolled	51%	25%	24%	80%	13%	7%
Not enrolled	68%	14%	17%	88%	7%	5%
High-risk medication class						
Antiarrhythmic						
Yes	53%	16%	32%	76%	13%	12%
No	70%	16%	14%	90%	6%	4%
Anticoagulant						
Yes	53%	18%	28%	81%	12%	7%
No	79%	13%	7%	93%	3%	4%
Diabetes medication						

	Adverse Events ^a (N=136 patients)			Preventable Adverse Events ^a (N=53 patients)			P-Value ^b
	None	1	2	None	1	2	
Yes	38%	15%	48%	63%	20%	18%	
No	69%	16%	15%	89%	6%	4%	
Benzodiazepine							0.232
Yes	59%	17%	24%	85%	9%	7%	
No	74%	15%	11%	89%	7%	4%	
Opioid							0.080
Yes	62%	17%	22%	85%	9%	6%	
No	78%	14%	8%	92%	4%	4%	
No. of high risk medication classes ^d							0.003
0	83%	12%	5%	95%	3%	3%	
1	84%	11%	5%	95%	3%	2%	
2	65%	23%	11%	93%	4%	4%	
3	55%	19%	27%	77%	15%	7%	
4	51%	12%	37%	78%	11%	11%	
5	44%	22%	33%	78%	11%	11%	
Cancer-directed treat-ment							0.048
Surgery							
Yes	62%	16%	22%	85%	9%	6%	
No	77%	15%	8%	92%	5%	3%	
Chemotherapy							0.087
Yes	59%	18%	23%	85%	8%	7%	
No	78%	12%	9%	90%	7%	3%	
Radiation therapy							0.459
Yes	65%	16%	19%	89%	7%	5%	
No	67%	16%	17%	86%	8%	6%	

^aPercents may not equal 100% due to rounding

^bChi-square or Fisher's exact test comparing none vs. any adverse event (or preventable event) by characteristic

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Comorbid conditions include myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes, hemiplegia, moderate or severe renal disease, diabetes with end organ damage, moderate or severe liver disease, AIDS, hyperlipidemia, hypertension, and coronary artery disease.

High-risk medications classes include antiarrhythmia, anticoagulant, diabetes medication, benzodiazepine, opioid.

Table 3

Subjects' characteristics associated with adverse events, negative binomial regression models

Characteristic	Adverse Events (N=136 patients) Adjusted IRR (95% CI)	Preventable Adverse Events (N=53 patients) Adjusted IRR (95% CI)
Cancer type		
Breast	Ref	Ref
Colorectal	1.21 (0.68–2.15)	3.19 (0.96–10.59)
Lung	1.83 (1.06–3.18)	7.38 (2.35–23.19)
Age at start of study	NA	NA
Male	NA	NA
Non-white race	1.63 (1.01–2.64)	NA
Hispanic/Latino	1.95 (0.92–4.12)	5.47 (1.67–17.90)
Non-English primary language	NA	NA
Unmarried	NA	NA
Non-commercial insurance	NA	NA
>50 miles to cancer center	NA	NA
Comorbidities		
None	Ref	Ref
1	NA	NA
2	NA	NA
Drug allergy	NA	NA
Prior cancer diagnosis	NA	NA
Advanced stage disease	1.66 (1.07–2.56)	NA
Enrollment in therapeutic protocol	NA	NA
No. of high-risk medication classes	1.58 (1.30–1.86)	1.52 (1.15–2.02)
Cancer-directed treatment		
Surgery	NA	NA
Chemotherapy	2.07 (1.30–3.30)	NA
Radiation therapy	NA	NA

IRR, incident rate ratio; CI, confidence interval; NA, not applicable (variable dropped from final model)