original reports abstract

Sex Differences in Risk of Severe Adverse Events in Patients Receiving Immunotherapy, Targeted Therapy, or Chemotherapy in Cancer Clinical Trials

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PURPOSE Women have more adverse events (AEs) from chemotherapy than men, but few studies have investigated sex differences in immune or targeted therapies. We examined AEs by sex across different treatment domains.

METHODS We analyzed treatment-related AEs by sex in SWOG phase II and III clinical trials conducted between 1980 and 2019, excluding sex-specific cancers. AE codes and grade were categorized using the Common Terminology Criteria for Adverse Events. Symptomatic AEs were defined as those aligned with the National Cancer Institute's Patient-Reported Outcome–Common Terminology Criteria for Adverse Events; laboratory-based or observable/measurable AEs were designated as objective (hematologic *v* nonhematologic). Multivariable logistic regression was used, adjusting for age, race, and disease prognosis. Thirteen symptomatic and 14 objective AE categories were examined.

RESULTS In total, N = 23,296 patients (women, 8,838 [37.9%]; men, 14,458 [62.1%]) from 202 trials experiencing 274,688 AEs were analyzed; 17,417 received chemotherapy, 2,319 received immunotherapy, and 3,560 received targeted therapy. Overall, 64.6% (n = 15,051) experienced one or more severe (grade ≥ 3) AEs. Women had a 34% increased risk of severe AEs compared with men (odds ratio [OR] = 1.34; 95% CI, 1.27 to 1.42; $P < .001$), including a 49% increased risk among those receiving immunotherapy (OR = 1.49; 95% CI, 1.24 to 1.78; $P < .001$). Women experienced an increased risk of severe symptomatic AEs among all treatments, especially immunotherapy (OR = 1.66; 95% CI, 1.37 to 2.01; $P < .001$). Women receiving chemotherapy or immunotherapy experienced increased severe hematologic AE. No statistically significant sex differences in risk of nonhematologic AEs were found.

CONCLUSION The greater severity of both symptomatic AEs and hematologic AEs in women across multiple treatment modalities indicates that broad-based sex differences exist. This could be due to differences in AE reported, pharmacogenomics of drug metabolism/disposition, total dose received, and/or adherence to therapy. Particularly large sex differences were observed for patients receiving immunotherapy, suggesting that studying AEs from these agents is a priority.

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INTRODUCTION

Sex differences in response to treatment have been observed in multiple disease settings.[1,2] Yet despite growing evidence identifying patient sex as a predictor of disease sequelae, sex is rarely included in the evaluation of risk.[2,3] This is surprising given the increased individualization of treatments in an era of precision medicine.

For patients with cancer, female sex has been associated with an increased risk of adverse events (AEs) from cytotoxic therapy.[4-6] However, almost no research has examined the experience of women and men receiving immune and targeted therapies. Differences in the toxic effects and outcomes from treatment may be due to multiple factors, such as subjective differences in reporting, or differences in pharmacokinetics, pharmacodynamics, and pharmacogenomics, or differences in drug therapy received.[7-10] Indeed, sex-based differences in the experience of disease have recently been highlighted by worse symptoms and mortality observed for men with COVID-19 infection.[11,12]

In this study, we systematically examined the role of patient sex in the experience of both symptomatic and objective AEs across multiple cancer treatment paradigms including cytotoxic, immune, and targeted therapies. To improve power to detect possible sex differences in AEs, we combined data from several decades of therapeutic clinical trials. Patients receiving care under study are uniformly followed for acute

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Women have more adverse events (AEs) from chemotherapy than men, but almost no research has examined the experience of women compared with men receiving immune or targeted therapies. We examined AEs by sex across different treatment domains using combined data from 23,296 patients enrolled in 202 clinical trials from 1989 to 2019.

Knowledge Generated

Women had a 34% increased risk of severe AEs compared with men (odds ratio = 1.34; 95% CI, 1.27 to 1.42; $P < .001$), including a 49% increased risk among those receiving immunotherapy (odds ratio = 1.49; 95% CI, 1.24 to 1.78; $P < .001$).

Relevance

The greater severity of AEs in women across multiple treatment modalities indicates that broad-based sex differences exist. Particularly large sex differences were observed for patients receiving immunotherapy. These findings support the idea that sex may independently modulate drug toxicity, including for novel treatments.

AEs while on treatment; thus, analyses from a large-scale, well-characterized clinical trials database provides a unique opportunity to explore this issue.

METHODS

Data

Data were obtained from the SWOG Cancer Research Network. We included data on eligible patients evaluable for AE assessment from phase II and III clinical treatment trials over 30 years from July 1, 1989 to June 30, 2019; data were collected through January 1, 2020, thereby allowing at least 6-months for data collection. More recent follow-up was not included to limit the potential for confounding of the patient treatment experience by the COVID-19 pandemic.[11,12] Trials in sex-specific or sex-dominant cancers (eg, prostate and breast) were excluded. The focus was on systemic therapies only. Study arms that included observation, autologous/allogeneic transplant, or surgery were excluded. Only the initial on-protocol treatment was evaluated. For patients enrolled in multiple studies, only data from the first study were included. Studies with fewer than 10 patients were excluded to limit study-level heterogeneity.

All study protocols included in this analysis were approved by local Institutional Review Boards, and all patients gave written informed consent.

AE Coding and Definitions

To establish a common reference, all AE codes and grades were mapped to Version 4 of the Common Terminology Criteria for Adverse Events (CTCAE).[13] Given evidence that clinician reports of subjective AEs may be less reliable and under-reported, the NCI developed a set of patient-reported toxicity criteria for symptomatic AEs, termed Patient-Reported Outcome (PRO)-CTCAE.[14] Symptomatic AEs were defined as those aligned with PRO-CTCAE using the PRO-CTCAE item library (Data Supplement, online only).[15] Each AE in this item library was matched with the corresponding CTCAE v4.0 terminology.[16] To ensure that the CTCAE codes and terms were used in a consistent manner over time, corresponding terms and grading from CTCAE v3.0 and v2.0 for each of the CTCAE v4.0 terms were identified.[13] Borrowing from prior conceptualizations, laboratory-based or objective/measurable AEs were termed objective AEs.[14,17] Some AE categories included both symptomatic and objective AEs (cardiovascular, skin, gastrointestinal, neurologic, respiratory, and visual); within these categories, individual AE types were categorized into symptomatic or objective domains on the basis of the NCI specifications.[15,16] On the basis of observed patterns, objective AEs were further categorized as hematologic (blood/bone marrow) versus nonhematologic.

The CTCAE are categorized according to grade, ranging from 0 to 5, where 0 indicates no toxicity; 1, mild; 2, moderate; 3, severe; 4, life-threatening; and 5, death.[13] Only the highest degree for each category of AE experienced during treatment was recorded. Unknown AEs and AEs with unknown grade were excluded. Also, AEs that were uniformly rare (< 5% incidence) for both women and men across all diseases (clotting, endocrine, lymphatics, musculoskeletal, and syndromes) were excluded, as were sex-specific AEs (gynecologic and male and female sexual and sex-specific urinary function).

Data Collection

Institutional reports of AEs were collected with study-specific case report forms. Historically, AE data were derived from study flow sheets. Beginning in 2002, toxicities were reported according to electronic case report forms. All data were reviewed and subject to confirmation by the study principal investigator.

Treatment Types

Patients were identified as having received cytotoxic therapy (with or without radiation therapy), immunotherapy, or targeted therapy (eg, kinase inhibitors) on the basis of

published definitions and therapy names (Data Supplement).[18-20] Specific categories within immunotherapy (immune checkpoint inhibitors and immune system modulators [cytokines and biologic response modifiers]) were examined separately. Vaccine-based interventions, a category of immunotherapy, were excluded. Also, patients receiving combinations of different domains of systemic therapies (eg, cytotoxic therapy plus targeted therapy) were excluded since attribution to a treatment domain could not be clearly ascertained.

Statistical Methods

The primary end point was the occurrence of one or more treatment-related severe or greater (grade ≥ 3) AEs. This level of AE severity was chosen because hospitalization is commonly required. We analyzed severe AEs by self-reported sex within treatment domains using multivariable logistic regression. The number of individual severe AE categories (≥ 5 *v* < 5, the cut point best approximating the overall median) was also analyzed by sex using a similar logistic regression approach. Thirteen symptomatic and 14 objective AE categories were examined. Regression models incorporated demographic factors such as age (< 65 *v* ≥ 65 years), race (Black *v* Others; White *v* Others), and prestudy obesity status (body mass index ≥ 30 [obese] *v* < 30). Each analysis was stratified by study-level prognosis (advanced, poor prognosis (2-year overall survival < 25%) versus advanced, intermediate (2-year overall survival 25%-75%) versus adjuvant; denoted as cancer stratum) to reflect disease severity and treatment intensity. Finally, we adjusted for decade of trial registration (< 2000 *v* 2000-2009 *v* 2010+ using indicator variables).

We also examined associations of sex with AE categories at each grade-specific cut point, with results depicted using heat maps. To test a global association within AE domains (symptomatic *v* objective) and overall, for each AE category (eg, sleep) for a given AE domain (eg, symptomatic), we calculated the mean of the *z*-scores from the individual, grade-specific logistic regression models. A one-sample *t*-test was used to determine whether this sample of *z*-scores statistically significantly differed from zero. Differences in clinical characteristics between groups were tested using chi-square tests for categorical data and *t*-statistics from quantile regression for medians.[21]

Analyses were conducted using SAS, version 9.4 (SAS Institute Inc) and R, version 4.0.2 (R Foundation for Statistical Computing). Two-sided *P* values are reported.

Sensitivity Analyses

Our base-case model adjusted for overall prognosis to account for disease severity and treatment intensity. Alternative modeling approaches were also used that accounted for potential trial effects, including adjusting for study as a conditioning variable in logistic regression and by treating study as a clustering variable using generalized estimating equations. Also, AE domains (eg, symptomatic) were examined within levels of adjuvant versus advanced disease for each treatment. Finally, we evaluated potential differences in the relationship between sex and AEs across treatment domains using interaction tests, rather than in subsets of treatments.

RESULTS

Cohort and Patient Characteristics

In total, N = 23,296 unique patients (women, 8,838 [37.9%]; men, 14,458 [62.1%]) from 202 trials experiencing 274,688 of the specified 27 AE categories were analyzed. Cohort sample sizes by treatment domain included 17,417 for chemotherapy, 2,319 for immunotherapy, and 3,560 for targeted therapy.

The most common cancers were gastrointestinal (26.1%), lung (20.5%), and leukemia (12.1%; Table 1). Overall, 34.7% of patients were 65 years or older, 9.0% were Black, and 25.6% were obese. Female patients were more likely to be < 65 years (66.6% *v* 64.4%, *P* < .001), Black (9.8% *v* 8.6%, *P* = .001), and obese (27.7% *v* 24.3%, *P* < .001). One quarter (24.4%) of patients received adjuvant treatment. Chemotherapy was particularly common in trials from 1989 to 1999 (68.4%), whereas immunotherapy (53.6%) and targeted therapies (50.3%) were more common from 2010 to 2019.

The median treatment time was 88 (interquartile range, 34-170) days for women and 84 (interquartile range, 37-167) days for men (*P* = .16).

Severe AEs

Among all patients, 64.6% (n = 15,051) experienced one or more severe AEs. Women had a 34% increased risk of severe toxicity compared with men (68.6% *v* 62.2%, odds ratio [OR] = 1.34; 95% CI, 1.27 to 1.42; *P* < .001; Fig 1). An increased risk of severe toxicity for women versus men was consistently observed for each treatment domain, with the greatest increased risk for immunotherapy (OR = 1.49; 95% CI, 1.24 to 1.78; *P* < .001).

Number of Toxicity Categories

Among all treatments, women had a 25% higher risk of experiencing ≥ 5 severe AEs (females, 57.4% *v* males, 52.2%, OR = 1.25; 95% CI, 1.18 to 1.32; *P* < .001; Table 2). The increased risk of ≥ 5 severe AEs was greater for symptomatic AEs versus objective AEs. This pattern was generally consistent across treatment domains. The association was strongest for women receiving immunotherapy (OR = 1.42; 95% CI, 1.14 to 1.77; *P* < .001) or targeted therapy (OR = 1.50; 95% CI, 1.27 to 1.78; *P* < .001).

Symptomatic and Objective AEs by Sex

Women were at 30% or higher risk of experiencing symptomatic (female, 33.3% *v* male, 27.9%; OR = 1.33; 95% CI, 1.26 to 1.41; *P* < .001) and hematologic (female,

TABLE 1. Patient Characteristics

Characteristic	Chemotherapy, No./%			Immunotherapy, No./%			Targeted Therapies, No./%			All Treatments, No./%		
	All (n = 17,417)	Female (n = 6,642; 38.1%)	Male (n = 10,775; 61.9%)	All (n = 2,319)	Female (n = 843; 36.4%)	Male (n = 1,476; 63.6%)	All (n = 3,560)	Female (n = 1,353; 38.0%)	Male (n = 2,207; 62.0%)	All (n = 23,296)	Female (n = 8,838; 37.9%)	Male (n = 14,458; 62.1%)
Age, years												
< 65	11,780	4,596	7,184	1,393	509	884	2,034	785	1,249	15,207	5,890	9,317
	67.6	69.2	66.7	60.1	60.4	59.9	57.1	58.0	56.6	65.3	66.6	64.4
≥ 65	5,637	2,046	3,591	926	334	592	1,526	568	958	8,089	2,948	5,141
	32.4	30.8	33.3	39.9	39.6	40.1	42.9	42.0	43.4	34.7	33.4	35.6
P		< .001			.82			.40			< .001	
Race												
Black	1,684	665	1,019	180	84	96	242	113	129	2,106	862	1,244
	9.7	10.0	9.5	7.8	10.0	6.5	6.8	8.4	5.8	9.0	9.8	8.6
White	15,066	5,698	9,368	2,025	713	1,312	3,033	1,130	1,903	20,124	7,541	12,583
	86.5	85.8	86.9	87.3	84.6	88.9	85.2	83.5	86.2	86.4	85.3	87.0
Others/ Unknown	667	279	388	114	46	68	285	110	175	1,066	435	631
	3.8	4.2	3.6	4.9	5.5	4.6	8.0	8.1	7.9	4.6	4.9	4.4
P		.06			.006			.01			.001	
Obesity status												
Obese	4,011	1,704	2,307	721	255	466	1,225	486	739	5,957	2,445	3,512
	23.0	25.7	21.4	31.1	30.2	31.6	34.4	35.9	33.5	25.6	27.7	24.3
Not obese	13,406	4,938	8,468	1,598	588	1,010	2,335	867	1,468	17,339	6,393	10,946
	77.0	74.3	78.6	68.9	69.8	68.4	65.6	64.1	66.5	74.4	72.3	75.7
P		< .001			.51			.14			< .001	
Cancer stratum												
Adjuvant	3,591	1,360	2,231	1,023	362	661	1,076	348	728	5,690	2,070	3,620
	20.6	20.5	20.7	44.1	42.9	44.8	30.2	25.7	33.0	24.4	23.4	25.0
Advanced, IR	7,481	2,965	4,516	568	244	324	1,267	558	709	9,316	3,767	5,549
	43.0	44.6	41.9	24.5	28.9	22.0	35.6	41.2	32.1	40.0	42.6	38.4
Advanced, PR	6,345	2,317	4,028	728	237	491	1,217	447	770	8,290	3,001	5,289
	36.4	34.9	37.4	31.4	28.1	33.3	34.2	33.0	34.9	35.6	34.0	36.6
P		< .001			< .001			< .001			< .001	
Accrual years												
1989-1999	11,909	4,490	7,419	438	143	295	0	0	0	12,347	4,633	7,714
	68.4	67.6	68.9	18.9	17.0	20.0				53.0	52.4	53.4
1999-2009	4,072	1,491	2,581	638	206	432	1,768	712	1,056	6,478	2,409	4,069
	23.4	22.4	24.0	27.5	24.4	29.3	49.7	52.6	47.8	27.8	27.3	28.1
2010-2019	1,436	661	775	1,243	494	749	1,792	641	1,151	4,471	1,796	2,675
	8.2	10.0	7.2	53.6	58.6	50.7	50.3	47.4	52.2	19.2	20.3	18.5
P		< .001			.001			.006			.003	

(continued on following page)

TABLE 1. Patient Characteristics (continued)

Characteristic	Chemotherapy, No./%			Immunotherapy, No./%			Targeted Therapies, No./%			All Treatments, No./%		
	All (n = 17,417)	Female (n = 6,642; 38.1%)	Male (n = 10,775; 61.9%)	All (n = 2,319)	Female (n = 843; 36.4%)	Male (n = 1,476; 63.6%)	All (n = 3,560)	Female (n = 1,353; 38.0%)	Male (n = 2,207; 62.0%)	All (n = 23,296)	Female (n = 8,838; 37.9%)	Male (n = 14,458; 62.1%)
Cancer type												
Brain	488	186	302	0	0	0	0	0	0	488	186	302
	2.8	2.8	2.8							2.1	2.1	2.1
GI	5,545	2,175	3,370	105	26	79	425	175	250	6,075	2,376	3,699
	31.8	32.7	31.3	4.5	3.1	5.4	11.9	12.9	11.3	26.1	26.9	25.6
Genitourinary	616	151	465	444	120	324	953	288	665	2,013	559	1,454
	3.5	2.3	4.3	19.1	14.2	22.0	26.8	21.3	30.1	8.6	6.3	10.1
Head and neck	524	102	422	113	60	53	39	7	32	676	169	507
	3.0	1.5	3.9	4.9	7.1	3.6	1.1	0.5	1.4	2.9	1.9	3.5
Leukemia	2,461	1,082	1,379	15	4	11	337	122	215	2,813	1,208	1,605
	14.1	16.3	12.8	0.6	0.5	0.7	9.5	9.0	9.7	12.1	13.7	11.1
Lung	3,731	1,323	2,408	426	149	277	630	267	363	4,787	1,739	3,048
	21.4	19.9	22.3	18.4	17.7	18.8	17.7	19.7	16.4	20.5	19.7	21.1
Lymphoma	2,002	799	1,203	53	23	30	39	15	24	2,094	837	1,257
	11.5	12.0	11.2	2.3	2.7	2.0	1.1	1.1	1.1	9.0	9.5	8.7
Melanoma	165	59	106	551	176	375	459	167	292	1,175	402	773
	0.9	0.9	1.0	23.8	20.9	25.4	12.9	12.3	13.2	5.0	4.5	5.3
Myeloma	1,639	673	966	521	237	284	150	67	83	2,310	977	1,333
	9.4	10.1	9.0	22.5	28.1	19.2	4.2	5.0	3.8	9.9	11.1	9.2
Sarcoma	246	92	154	19	10	9	528	245	283	793	347	446
	1.4	1.4	1.4	0.8	1.2	0.6	14.8	18.1	12.8	3.4	3.9	3.1
Others	0	0	0	72	38	34	0	0	0	72	38	34
				3.1	4.5	2.3				0.3	0.4	0.2
P		< .001			< .001			< .001			< .001	

Abbreviations: IR, intermediate risk; PR, poor risk.

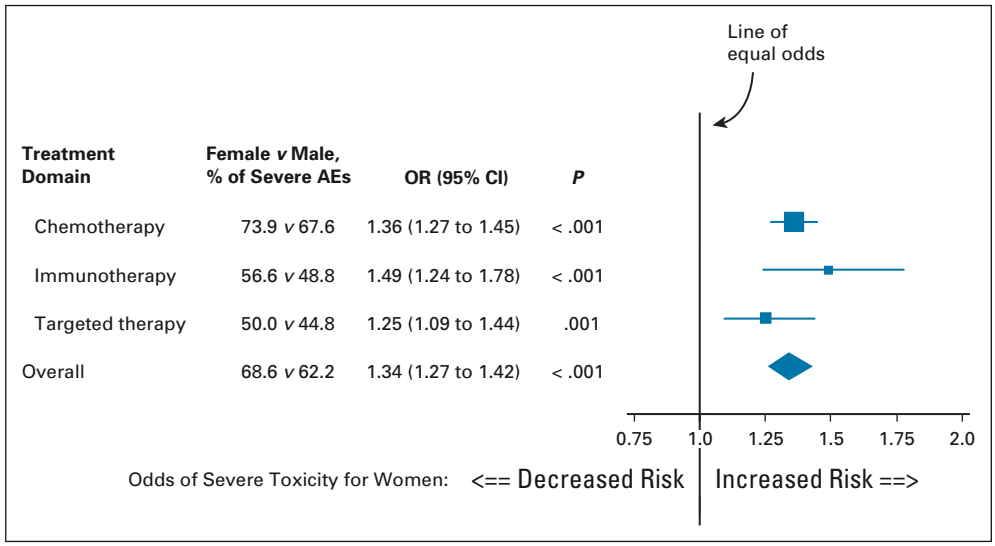

FIG 1. Forest plot of the association of patient sex with the risk of severe AEs. The boxes indicate the OR, and the horizontal lines indicate the 95% CIs. Boxes to the right of the vertical line (the line of equal odds) indicate increased risk of severe AEs for females, and to the left, for males. For each treatment domain, women had an increased risk of severe AEs of any kind. AE, adverse event; OR, odds ratio.

45.2% *v* male, 39.1%; OR = 1.30; 95% CI, 1.23 to 1.37; $P < .001$) AEs (Fig 2). The risk of objective, nonhematologic AEs was also statistically significantly greater in women (female, 30.9% *v* male, 29.0%; OR = 1.08; 95% CI, 1.02 to 1.14; $P = .01$). Similar patterns of notably higher increased risk of symptomatic and hematologic AEs for females versus males were greatest among patients treated with immunotherapy (female, 33.7% *v* male, 25.4%; OR = 1.66; 95% CI, 1.37 to 2.01; $P < .001$). The risk of objective, nonhematologic AEs was similar for females compared with males across the treatment domains.

Association of Sex and AE Outcomes in Subgroups of Immunotherapy Treatment

Within subsets of patients receiving immunotherapy, the risk of symptomatic AEs was greater for females receiving immune checkpoint inhibitors (n = 877; female, 19.6% *v* male, 13.0%; OR = 1.54; 95% CI, 1.05 to 2.26; $P = .03$) and immune system modulators (n = 1,243; female, 44.1% *v* male, 33.6%; OR = 1.62; 95% CI, 1.27 to 2.06; $P < .001$; Fig 3). This association was not observed for nonsymptomatic AEs.

Individual Categories of Symptomatic and Objective AEs by Sex

Figures 4A and 4B provide a heat map representation of the individual categories of symptomatic and objective AEs by sex, for different cut point levels (grades 1-4) of severity. Among symptomatic AEs, women receiving chemotherapy had statistically significantly increased risk of symptomatic skin AEs (grades ≥ 1, ≥ 2, and ≥ 3) and oral AEs (grades ≥ 1 through ≥ 4; Fig 4A). For each treatment domain, women were also at statistically significantly increased risk of symptomatic gastrointestinal AEs at grades ≥ 1 through ≥ 3. Among those receiving chemotherapy and immunotherapy, women were at increased risk of sleep-related AEs. Among 141 evaluable comparisons, females had a statistically significantly increased risk of a specific AE category at a given grade cut point 43 times, compared with 0 for males (30.5% *v* 0.0%, $P < .001$).

Among objective AEs, women were at increased risk of hematologic AEs among those receiving chemotherapy (grades ≥ 1 through ≥ 4), immunotherapy (grades ≥ 2 and ≥ 3), and targeted therapy (grade ≥ 2). Among those receiving chemotherapy or immunotherapy, women had statistically significantly increased risk of objective cardiovascular AEs (grades ≥ 1 and ≥ 2). Among 154 evaluable comparisons, females had a statistically significantly increased risk of a specific AE category at a given grade cut point 25 times, compared with five for males (16.2% *v* 3.2%, $P = .009$).

Among all 27 symptomatic and objective AE categories, among 295 evaluable comparisons, there were 68 instances where females had a statistically significantly increased risk of a specific AE category at a given grade cut point and five instances for males (23.1% *v* 1.7%, $P < .001$).

Sensitivity Analyses

Nearly all estimates using alternative analytic approaches corresponded closely to the base-case analysis, suggesting that the primary analysis results are robust to the modeling approach (Data Supplement).

When results were stratified by adjuvant versus advanced disease, the increased risk of severe symptomatic and hematologic AEs for women was greater among patients on

TABLE 2. No. of Serious AEs

Therapy	Outcome, No. or Mean	Female v Male, % or Mean	OR or Mean Difference[a]	95% CI[a]	*P*
Cytotoxic therapies					
All toxicities	≥ 5	57.6% *v* 53.3%	OR: 1.20	1.13 to 1.28	< .001
	Mean	5.71 *v* 5.40	Diff: 0.30	0.21 to 0.40	< .001
Symptomatic	≥ 5	24.1% *v* 20.3%	OR: 1.26	1.17 to 1.36	< .001
	Mean	3.46 *v* 3.22	Diff: 0.25	0.19 to 0.30	< .001
Objective	≥ 5	12.2% *v* 11.3%	OR: 1.07	0.97 to 1.18	.18
	Mean	2.63 *v* 2.58	Diff: 0.04	−0.01 to 0.09	.15
Immunotherapy					
All toxicities	≥ 5	51.0% *v* 41.7%	OR: 1.57	1.31 to 1.87	< .001
	Mean	5.87 *v* 5.05	Diff: 0.81	0.47 to 1.14	< .001
Symptomatic	≥ 5	21.2% *v* 16.9%	OR: 1.42	1.14 to 1.77	< .001
	Mean	3.41 *v* 3.10	Diff: 0.33	0.13 to 0.52	< .001
Objective	≥ 5	15.5% *v* 12.4%	OR: 1.28	1.00 to 1.64	.05
	Mean	3.14 *v* 2.77	Diff: 0.31	0.13 to 0.49	< .001
Targeted therapies					
All toxicities	≥ 5	60.3% *v* 53.9%	OR: 1.37	1.19 to 1.58	< .001
	Mean	5.84 *v* 5.44	Diff: 0.47	0.26 to 0.68	< .001
Symptomatic	≥ 5	25.2% *v* 18.9%	OR: 1.50	1.27 to 1.78	< .001
	Mean	3.52 *v* 3.22	Diff: 0.33	0.21 to 0.45	< .001
Objective	≥ 5	13.2% *v* 12.1%	OR: 1.18	0.96 to 1.45	.13
	Mean	2.79 *v* 2.74	Diff: 0.09	−0.03 to 0.21	.14
Any systemic therapy					
All toxicities	≥ 5	57.4% *v* 52.2%	OR: 1.25	1.18 to 1.32	< .001
	Mean	5.74 *v* 5.37	Diff: 0.37	0.29 to 0.46	< .001
Symptomatic	≥ 5	24.0% *v* 19.8%	OR: 1.30	1.22 to 1.39	< .001
	Mean	3.47 *v* 3.21	Diff: 0.26	0.21 to 0.31	< .001
Objective	≥ 5	12.7% *v* 11.6%	OR: 1.10	1.01 to 1.19	.03
	Mean	2.70 *v* 2.62	Diff: 0.07	0.02 to 0.11	.004

Abbreviations: AE, adverse event; OR, odds ratio.
[a]Model-adjusted estimates with corresponding 95% CIs.

adjuvant trials, particularly those using chemotherapy (interaction *P* value ≤ .01). These patterns were consistent but less extreme in patients receiving immune or targeted agents (Data Supplement). Importantly, there remained a strong, statistically significantly increased risk of severe symptomatic and hematologic toxicities in women versus men in advanced disease trials.

Finally, estimates of the increased risk of AEs for women versus men were similar in an aggregate model (Data Supplement).

DISCUSSION

Our study showed that women are at substantially greater risk of severe symptomatic AEs across multiple treatment domains, including patients receiving immune checkpoint inhibitor therapy and targeted therapies with kinase inhibitors. In fact, women receiving immunotherapy had a 66% increased risk of symptomatic AEs compared with men. Moreover, women were more likely to experience severe hematologic AEs among those receiving chemotherapy and immunotherapy. These results are robust because of the breadth of the data, the large sample size, and the quality of the prospective, clinical trial–based data.

Major research advisory and regulatory agencies of the federal government, including the National Institutes of Health and US Food and Drug Administration, have issued mandates and guidelines to better understand the possible disease outcome differences between men and women.[22-25] Identification of possible sex-related differences might lead

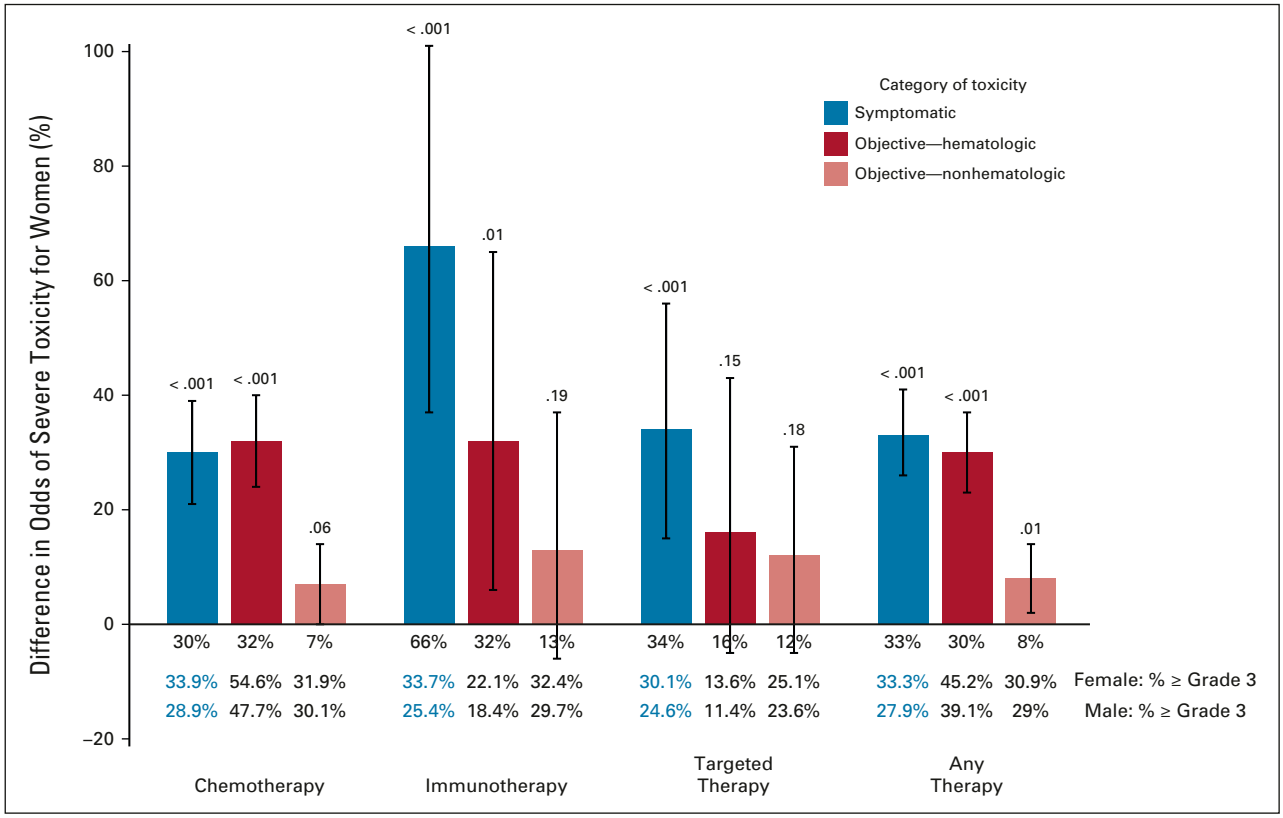

FIG 2. Difference in the odds of severe AEs by category of adverse events. AEs were categorized as symptomatic versus objective and hematologic versus objective and nonhematologic. The vertical bars indicate the percentage increased odds, and the vertical lines show the 95% CIs. The observed percentage of patients experiencing severe (grade ≥ 3) AEs for a given category are also shown. AE, adverse event.

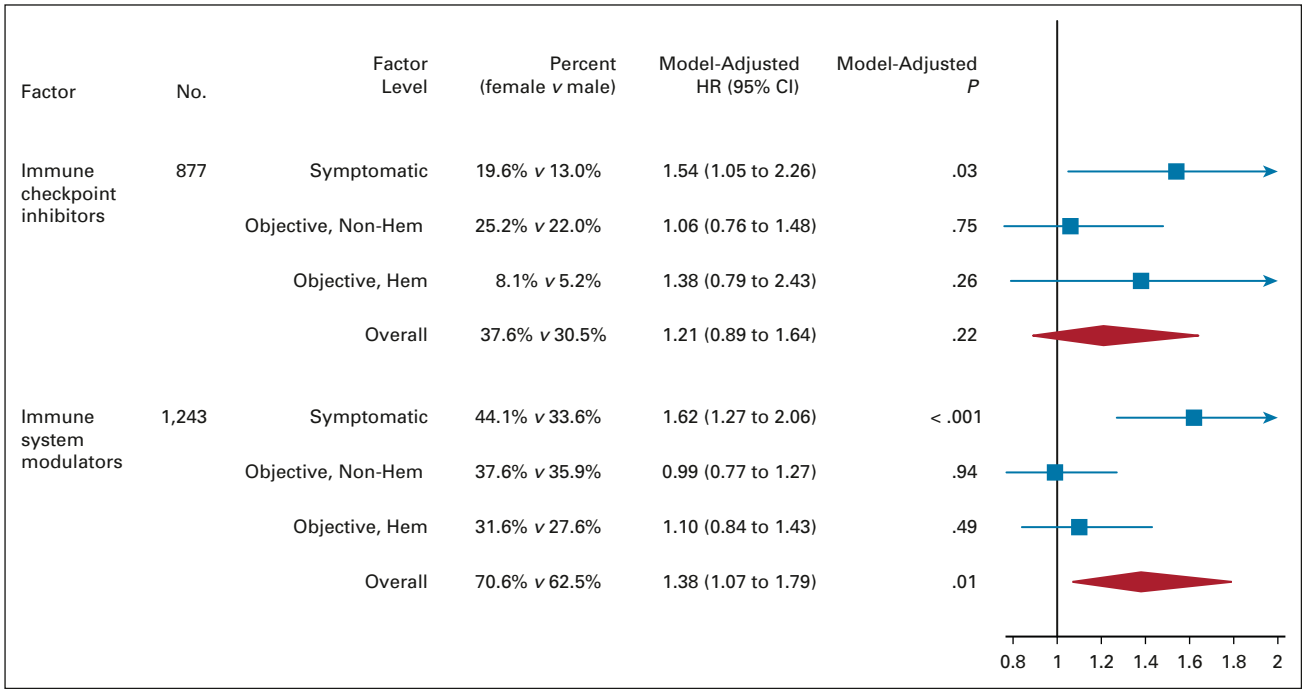

FIG 3. Forest plot of the association of patient sex with the risk of severe AEs in subgroups of immunotherapy treatment. The boxes indicate the OR, and the horizontal lines indicate the 95% CIs. Boxes to the right of the vertical line (the line of equal odds) indicate increased risk of severe AEs for females, and to the left, for males. AE, adverse event; HR, hazard ratio.

A

AE category	Chemotherapy				Immunotherapy				Targeted Therapy			
	≥ Grade 1	≥ Grade 2	≥ Grade 3	≥ Grade 4	≥ Grade 1	≥ Grade 2	≥ Grade 3	≥ Grade 4	≥ Grade 1	≥ Grade 2	≥ Grade 3	≥ Grade 4
Cardiovascular, symptomatic	11.2 *v* 9 OR = 1.28 [1.15 to 1.42] *P* < .001	4.4 *v* 4.5 OR = 0.99 [0.86 to 1.15] *P* = .932	1.2 *v* 1.5 OR = 0.82 [0.62 to 1.08] *P* = .15	0.4 *v* 0.4 OR = 0.93 [0.56 to 1.53] *P* = .77	16.1 *v* 12.7 OR = 1.35 [1.05 to 1.73] *P* = .017	5.5 *v* 5.2 OR = 1.09 [0.74 to 1.6] *P* = .656	1.2 *v* 0.7 OR = 1.78 [0.74 to 4.26] *P* = .195		25 *v* 18.3 OR = 1.4 [1.17 to 1.67] *P* < .001	7.5 *v* 5.8 OR = 1.15 [0.87 to 1.52] *P* = .335	1.5 *v* 1.3 OR = 0.93 [0.52 to 1.68] *P* = .816	0.1 *v* 0.1 OR = 1.19 [0.17 to 8.56] *P* = .86
Skin, symptomatic	49.3 *v* 40.8 OR = 1.43 [1.34 to 1.52] *P* < .001	31.6 *v* 22.4 OR = 1.62 [1.51 to 1.74] *P* < .001	2.7 *v* 2 OR = 1.37 [1.12 to 1.68] *P* = .002	0 *v* 0.1 OR = 0.71 [0.18 to 2.75] *P* = .617	27.5 *v* 25.5 OR = 1.1 [0.91 to 1.34] *P* = .323	10.2 *v* 10 OR = 1.04 [0.78 to 1.38] *P* = .806	2.7 *v* 3 OR = 0.92 [0.55 to 1.53] *P* = .74	0.1 *v* 0.1 OR = 2.15 [0.13 to 35.21] *P* = .591	55.4 *v* 51.1 OR = 1.25 [1.09 to 1.44] *P* = .002	24.2 *v* 22.1 OR = 1.12 [0.95 to 1.32] *P* = .167	6.7 *v* 6.2 OR = 1.1 [0.83 to 1.46] *P* = .49	0.1 *v* 0.1 OR = 0.43 [0.04 to 4.28] *P* = .47
GI, symptomatic	76.7 *v* 72.8 OR = 1.24 [1.16 to 1.33] *P* < .001	46.7 *v* 40.6 OR = 1.3 [1.22 to 1.39] *P* < .001	17.8 *v* 14.4 OR = 1.33 [1.22 to 1.44] *P* < .001	2.1 *v* 2 OR = 1.12 [0.9 to 1.38] *P* = .323	58 *v* 48.2 OR = 1.55 [1.31 to 1.85] *P* < .001	34.3 *v* 23.2 OR = 1.77 [1.4 7 to 2.14] *P* < .001	10.9 *v* 8.2 OR = 1.49 [1.11 to 2] *P* = .007	0.4 *v* 0.4 OR = 1 [0.25 to 4.05] *P* = .998	72 *v* 64.9 OR = 1.33 [1.15 to 1.55] *P* < .001	38 *v* 27.8 OR = 1.55 [1.34 to 1.79] *P* < .001	11.6 *v* 7.2 OR = 1.59 [1.26 to 2.02] *P* < .001	0.6 *v* 0.2 OR = 2.2 [0.71 to 6.82] *P* = .172
Memory	1.1 *v* 1.2 OR = 0.93 [0.7 to 1.24] *P* = .632	0.5 *v* 0.4 OR = 1.29 [0.81 to 2.06] *P* = .279	0.1 *v* 0.2 OR = 0.56 [0.24 to 1.32] *P* = .186	0 *v* 0 OR = 0.8 [0.07 to 8.82] *P* = .854	2.1 *v* 1.4 OR = 1.51 [0.79 to 2.87] *P* = .208	0.6 *v* 0.6 OR = 0.97 [0.32 to 2.91] *P* = .952	0.4 *v* 0.3 OR = 0.93 [0.22 to 3.97] *P* = .921	0.1 *v* 0.1 OR = 0.61 [0.04 to 8.43] *P* = .709	1 *v* 1 OR = 1.05 [0.53 to 2.07] *P* = .885	0.5 *v* 0.2 OR = 2.82 [0.82 to 9.7] *P* = .1	0.1 *v* 0 OR = 3.2 [0.29 to 35.58] *P* = .343	
Miscellaneous, symptomatic	17.8 *v* 17.2 OR = 1.04 [0.96 to 1.13] *P* = .359	7 *v* 6.7 OR = 1.04 [0.92 to 1.18] *P* = .486	1.5 *v* 1.3 OR = 1.16 [0.9 to 1.5] *P* = .258	0.1 *v* 0.1 OR = 0.78 [0.24 to 2.54] *P* = .678	19.3 *v* 18.2 OR = 1.26 [0.99 to 1.61] *P* = .064	7 *v* 5.4 OR = 1.53 [1.06 to 2.21] *P* = .025	1.3 *v* 0.3 OR = 5.07 [1.73 to 14.85] *P* = .003	0.1 *v* 0.1 OR = 2.32 [0.13 to 40.38] *P* = .564	13.9 *v* 12.6 OR = 1.14 [0.93 to 1.39] *P* = .212	1.8 *v* 2.5 OR = 0.67 [0.41 to 1.09] *P* = .105	0.1 *v* 0.4 OR = 0.16 [0.02 to 1.27] *P* = .083	
Mood	5.8 *v* 4.7 OR = 1.26 [1.1 to 1.44] *P* = .001	2.5 *v* 2.1 OR = 1.17 [0.96 to 1.44] *P* = .125	0.7 *v* 0.5 OR = 1.27 [0.86 to 1.88] *P* = .235	0 *v* 0.1 OR = 0.17 [0.02 to 1.38] *P* = .098	11.4 *v* 6.8 OR = 2.02 [1.49 to 2.74] *P* < .001	6.8 *v* 3.4 OR = 2.41 [1.61 to 3.6] *P* < .001	2.1 *v* 1.6 OR = 1.59 [0.84 to 3.02] *P* = .153	0.1 *v* 0.1 OR = 1.88 [0.12 to 30.3] *P* = .655	4.5 *v* 2.6 OR = 1.67 [1.15 to 2.42] *P* = .007	1.3 *v* 1 OR = 1.35 [0.71 to 2.55] *P* = .363	0.2 *v* 0.2 OR = 0.94 [0.22 to 3.96] *P* = .932	0.1 *v* 0.1 OR = 0.8 [0.07 to 8.91] *P* = .859
Neurological, symptomatic	20.3 *v* 20.6 OR = 0.99 [0.92 to 1.07] *P* = .774	9.5 *v* 9 OR = 1.08 [0.97 to 1.2] *P* = .155	2.1 *v* 2.2 OR = 1.01 [0.82 to 1.25] *P* = .902	0.2 *v* 0.1 OR = 2.03 [0.94 to 4.4] *P* = .073	20.4 *v* 17.8 OR = 1.22 [0.97 to 1.52] *P* = .086	7 *v* 7.2 OR = 0.97 [0.69 to 1.36] *P* = .867	2 *v* 1.9 OR = 1.1 [0.59 to 2.03] *P* = .769	0.2 *v* 0.1 OR = 3.87 [0.35 to 43.01] *P* = .271	14.2 *v* 9.3 OR = 1.61 [1.31 to 2] *P* < .001	3 *v* 2.1 OR = 1.38 [0.9 to 2.13] *P* = .139	0.3 *v* 0.3 OR = 0.94 [0.27 to 3.26] *P* = .924	
Oral	36.4 *v* 33.1 OR = 1.18 [1.11 to 1.27] *P* < .001	20.7 *v* 17.4 OR = 1.26 [1.16 to 1.36] *P* < .001	7 *v* 5.7 OR = 1.27 [1.12 to 1.44] *P* < .001	1.2 *v* 0.8 OR = 1.49 [1.1 to 2.03] *P* = .011	8.5 *v* 7.9 OR = 1.13 [0.83 to 1.54] *P* = .441	1.9 *v* 2.5 OR = 0.81 [0.45 to 1.48] *P* = .5	0.2 *v* 0.8 OR = 0.33 [0.07 to 1.48] *P* = .147		23.9 *v* 24.5 OR = 1.23 [1.03 to 1.47] *P* = .023	10.2 *v* 11 OR = 1.22 [0.96 to 1.55] *P* = .105	3.3 *v* 3.8 OR = 1.2 [0.81 to 1.78] *P* = .359	0.1 *v* 0 OR = 1.67 [0.1 to 27.36] *P* = .72
Pain	1.4 *v* 0.9 OR = 1.21 [0.89 to 1.64] *P* = .219	0.7 *v* 0.4 OR = 1.5 [0.97 to 2.32] *P* = .066	0.1 *v* 0.1 OR = 1.59 [0.53 to 4.77] *P* = .406		10.4 *v* 7.9 OR = 1.2 [0.88 to 1.63] *P* = .256	4.5 *v* 3.1 OR = 1.27 [0.81 to 2] *P* = .3	1.1 *v* 0.5 OR = 1.57 [0.59 to 4.19] *P* = .365		10.5 *v* 9.6 OR = 1.35 [1.06 to 1.73] *P* = .017	2.3 *v* 2.4 OR = 1.08 [0.68 to 1.72] *P* = .736	0.4 *v* 0.4 OR = 0.91 [0.3 to 2.77] *P* = .871	
Respiratory, symptomatic	12.8 *v* 12.4 OR = 1.04 [0.95 to 1.15] *P* = .365	9.1 *v* 8.6 OR = 1.09 [0.98 to 1.21] *P* = .13	3 *v* 2.4 OR = 1.27 [1.05 to 1.53] *P* = .014	1 *v* 0.7 OR = 1.51 [1.09 to 2.11] *P* = .014	17.8 *v* 15.3 OR = 1.21 [0.96 to 1.53] *P* = .103	9.4 *v* 9.5 OR = 1.02 [0.76 to 1.37] *P* = .883	4.5 *v* 2.7 OR = 1.73 [1.1 to 2.74] *P* = .019	1.2 *v* 0.3 OR = 4.6 [1.42 to 14.86] *P* = .011	16.4 *v* 14.8 OR = 1.2 [0.99 to 1.45] *P* = .062	8 *v* 7.4 OR = 1.06 [0.82 to 1.38] *P* = .637	2.4 *v* 2.3 OR = 1.05 [0.67 to 1.65] *P* = .825	0.2 *v* 0.4 OR = 0.59 [0.16 to 2.24] *P* = .44
Sleep	46.1 *v* 44.2 OR = 1.09 [1.03 to 1.17] *P* = .006	24.2 *v* 22 OR = 1.16 [1.07 to 1.24] *P* < .001	7.1 *v* 6 OR = 1.24 [1.1 to 1.41] *P* = .001	0.3 *v* 0.3 OR = 1.23 [0.72 to 2.11] *P* = .454	54.3 *v* 49.7 OR = 1.29 [1.08 to 1.53] *P* = .004	35.2 *v* 28.8 OR = 1.44 [1.2 to 1.73] *P* < .001	14.5 *v* 11.1 OR = 1.48 [1.14 to 1.91] *P* = .003	0.2 *v* 0.4 OR = 0.63 [0.12 to 3.2] *P* = .576	55.1 *v* 53 OR = 1.12 [0.98 to 1.29] *P* = .103	26.2 *v* 23.6 OR = 1.18 [1 to 1.38] *P* = .045	6.5 *v* 5.5 OR = 1.22 [0.92 to 1.63] *P* = .174	0.3 *v* 0.3 OR = 1.09 [0.31 to 3.92] *P* = .889
Urinary	4.1 *v* 4.4 OR = 0.93 [0.8 to 1.09] *P* = .374	1.2 *v* 1.2 OR = 1.09 [0.82 to 1.45] p = 0.542	0.2 *v* 0.2 OR = 1.02 [0.54 to 1.9] *P* = .958		2.3 *v* 2 OR = 1.18 [0.65 to 2.12] *P* = .584	0.6 *v* 0.4 OR = 1.6 [0.48 to 5.3] *P* = .444	0.1 *v* 0.1 OR = 1.86 [0.11 to 30.26] *P* = .662		2.1 *v* 2 OR = 0.95 [0.58 to 1.54] *P* = .824	0.5 *v* 0.4 OR = 1.32 [0.47 to 3.69] *P* = .597	0.1 *v* 0 OR = 1.7 [0.1 to 27.77] *P* = .709	
Visual, symptomatic	3.2 *v* 2.9 OR = 1.11 [0.93 to 1.32] *P* = .266	1.6 *v* 1.5 OR = 1.1 [0.86 to 1.41] *P* = .425	0.3 *v* 0.4 OR = 0.78 [0.44 to 1.38] *P* = .387		6.5 *v* 4.2 OR = 1.62 [1.1 to 2.38] *P* = .015	2.4 *v* 1.7 OR = 1.46 [0.8 to 2.68] *P* = .217	0.6 *v* 0.1 OR = 4.59 [0.88 to 24.03] *P* = .071		6.5 *v* 4.3 OR = 1.49 [1.1 to 2.01] *P* = .01	2.5 *v* 1.1 OR = 2.17 [1.27 to 3.69] *P* = .004	0.3 *v* 0.3 OR = 0.96 [0.28 to 3.3] *P* = .944	

FIG 4. Risk of AEs by sex for individual AE categories by the treatment domain and grade cut point. For each AE, the proportion of patients with grade ≥ 1 through ≥ 4 AEs was analyzed in a logistic regression model, adjusted for covariates. (A) Symptomatic AEs and (B) objective AEs. Within each cell, the observed percentage of women versus men experiencing at least the indicated grade level of AE, with the corresponding multivariable logistic regression model ORs, 95% CIs, and *P*-values, are shown. OR > 1.0 indicates greater risk of a given AE at the cut point level within the specific treatment domain for females and < 1.0 for males. Instances where women had greater odds of AEs than men are coded red, with blue indicating the reverse and gray indicating no difference or missing because of lack of events. The color intensity corresponds to greater divergence by sex in a given direction; thus, the darker red or darker blue indicates statistically significant ($P < .05$) findings and lighter red and blue indicate nonstatistically significant trends in favor of greater risk for females and males, respectively. The depiction thus represents a heat map of toxicity outcomes. The predominance of red over blue coloring indicates a generalized pattern of worse AE outcomes for women than men. AE, adverse event; OR, odds ratio. (continued on following page)

to potential sex-specific interventions.[2] There are several possible explanations for sex differences in AEs. For instance, given average body type differences, women may receive greater relative dose, although importantly we included covariate adjustment for obesity status to account for body type.[26-28] It has been suggested that medication adherence for oral therapies may differ by sex[29,30] although this may not apply as much in the trial setting. Finally, biases may exist in the reporting or interpretation of AEs, or men and women may differentially report AEs because of potential sex-related differences in symptom perception.[31,32] However, in our study,

B

AE category	Chemotherapy				Immunotherapy				Targeted Therapy			
	≥ Grade 1	≥ Grade 2	≥ Grade 3	≥ Grade 4	≥ Grade 1	≥ Grade 2	≥ Grade 3	≥ Grade 4	≥ Grade 1	≥ Grade 2	≥ Grade 3	≥ Grade 4
Blood/bone marrow	84 *v* 79.7 OR = 1.36 [1.25 to 1.47] *P* < .001	72.3 *v* 65.5 OR = 1.39 [1.3 to 1.49] *P* < .001	54.6 *v* 47.7 OR = 1.32 [1.24 to 1.4] *P* < .001	34 *v* 28.2 OR = 1.29 [1.21 to 1.38] *P* < .001	47.2 *v* 44.8 OR = 1.16 [0.98 to 1.39] *P* = .088	37.2 *v* 31 OR = 1.41 [1.17 to 1.7] *P* < .001	22.1 *v* 18.4 OR = 1.32 [1.06 to 1.65] *P* = .013	8.1 *v* 6.4 OR = 1.39 [0.99 to 1.94] *P* = .059	53.9 *v* 52.4 OR = 1.07 [0.93 to 1.23] *P* = .359	31.9 *v* 24.2 OR = 1.43 [1.23 to 1.67] *P* < .001	13.6 *v* 11.4 OR = 1.16 [0.95 to 1.43] *P* = .153	3.5 *v* 3.4 OR = 1 [0.69 to 1.44] *P* = .98
Cardiovascular, objective	14.6 *v* 13.2 OR = 1.12 [1.03 to 1.23] *P* = .01	11.3 *v* 10.2 OR = 1.11 [1.01 to 1.23] *P* = .031	6.2 *v* 5.5 OR = 1.13 [0.99 to 1.28] *P* = .072	1.7 *v* 1.6 OR = 1.06 [0.84 to 1.35] *P* = .621	17.3 *v* 13.8 OR = 1.34 [1.06 to 1.69] *P* = .016	13.4 *v* 10.6 OR = 1.32 [1.01 to 1.72] *P* = .039	7.8 *v* 6.4 OR = 1.28 [0.92 to 1.78] *P* = .148	1.3 *v* 1.9 OR = 0.69 [0.34 to 1.4] *P* = .301	14.4 *v* 16.4 OR = 0.89 [0.74 to 1.08] *P* = .251	9.6 *v* 12.1 OR = 0.81 [0.65 to 1.02] *P* = .068	5.6 *v* 5.4 OR = 1.06 [0.79 to 1.43] *P* = .705	0.9 *v* 1.2 OR = 0.73 [0.36 to 1.46] *P* = .372
Skin, objective	5.7 *v* 6.2 OR = 0.91 [0.8 to 1.04] *P* = .179	3.1 *v* 3.4 OR = 0.92 [0.77 to 1.1] *P* = .377	0.6 *v* 0.7 OR = 0.83 [0.56 to 1.24] *P* = .358	0 *v* 0.1 OR = 0.62 [0.16 to 2.34] *P* = .48	5.7 *v* 2.9 OR = 1.96 [1.28 to 3.02] *P* = .002	1.3 *v* 0.9 OR = 1.42 [0.63 to 3.21] *P* = .398	0.2 *v* 0.3 OR = 0.92 [0.17 to 5.05] *P* = .92		5.5 *v* 4.2 OR = 1.51 [1.1 to 2.08] *P* = .011	2.1 *v* 1.5 OR = 1.58 [0.95 to 2.63] *P* = .077	0.7 *v* 0.1 OR = 5.1 [1.37 to 19.03] *P* = .015	0.1 *v* 0 OR = 1.47 [0.09 to 23.61] *P* = .787
Endocrine	0.8 *v* 0.5 OR = 1.55 [1.06 to 2.27] *P* = .025	0.6 *v* 0.4 OR = 1.7 [1.1 to 2.64] *P* = .017	0.1 *v* 0.1 OR = 1.39 [0.42 to 4.57] *P* = .591		10.7 *v* 7.1 OR = 1.39 [1.01 to 1.91] *P* = .042	5.5 *v* 3.2 OR = 1.5 [0.97 to 2.32] *P* = .068	0.7 *v* 0.4 OR = 1.28 [0.4 to 4.09] *P* = .676	0.1 *v* 0.1 OR = 0.63 [0.04 to 11.17] *P* = .754	0.8 *v* 0.6 OR = 1.29 [0.58 to 2.85] *P* = .537	0.2 *v* 0.2 OR = 1.03 [0.24 to 4.34] *P* = .968		
Flu-like symptoms	24 *v* 24.4 OR = 0.99 [0.92 to 1.06] *P* = .764	11.9 *v* 12 OR = 1 [0.91 to 1.1] *P* = .961	1.7 *v* 1.6 OR = 1.07 [0.84 to 1.36] *P* = .592	0.1 *v* 0.1 OR = 0.75 [0.26 to 2.22] *P* = .608	25.5 *v* 24.1 OR = 1.18 [0.96 to 1.46] *P* = .108	10.6 *v* 11.5 OR = 0.98 [0.74 to 1.31] *P* = .903	1.2 *v* 1.6 OR = 0.82 [0.39 to 1.74] *P* = .612		23.5 *v* 21.9 OR = 1.04 [0.88 to 1.22] *P* = .663	8.7 *v* 7.7 OR = 1.04 [0.81 to 1.34] *P* = .751	1 *v* 0.8 OR = 1.28 [0.63 to 2.62] *P* = .497	
GI, objective	13.5 *v* 13.1 OR = 1.04 [0.95 to 1.15] *P* = .387	9 *v* 8.8 OR = 1.06 [0.94 to 1.18] *P* = .335	3.9 *v* 4 OR = 1 [0.85 to 1.17] *P* = .97	0.5 *v* 0.8 OR = 0.65 [0.43 to 0.97] *P* = .034	10.9 *v* 6.8 OR = 1.68 [1.25 to 2.27] *P* = .001	7.2 *v* 4.1 OR = 1.8 [1.24 to 2.62] *P* = .002	2.8 *v* 1.6 OR = 1.75 [0.98 to 3.13] *P* = .058	0.2 *v* 0.2 OR = 0.92 [0.15 to 5.65] *P* = .925	12.2 *v* 10.5 OR = 1.24 [1 to 1.54] *P* = .049	6.5 *v* 5.9 OR = 1.13 [0.85 to 1.5] *P* = .389	2.5 *v* 2.4 OR = 1.01 [0.65 to 1.57] *P* = .959	0.1 *v* 0.2 OR = 0.39 [0.04 to 3.55] *P* = .406
Hemorrhage/ bleeding	3.8 *v* 4.3 OR = 0.88 [0.76 to 1.03] *P* = .122	1.5 *v* 1.9 OR = 0.83 [0.65 to 1.06] *P* = .131	0.6 *v* 0.9 OR = 0.76 [0.53 to 1.09] *P* = .135	0.2 *v* 0.3 OR = 0.85 [0.46 to 1.55] *P* = .592	1.5 *v* 1.3 OR = 1.35 [0.66 to 2.78] *P* = .412	0.8 *v* 0.7 OR = 1.41 [0.53 to 3.77] *P* = .493	0.4 *v* 0.5 OR = 0.89 [0.23 to 3.52] *P* = .868		4.1 *v* 3.7 OR = 0.94 [0.66 to 1.35] *P* = .744	1.5 *v* 1.7 OR = 0.67 [0.38 to 1.16] *P* = .154	1.2 *v* 1.3 OR = 0.69 [0.37 to 1.29] *P* = .241	0.1 *v* 0.3 OR = 0.35 [0.07 to 1.7] *P* = .193
Hepatobiliary/ pancreas	15 *v* 14 OR = 1.09 [1 to 1.18] *P* = .063	5.3 *v* 5.4 OR = 0.96 [0.84 to 1.1] *P* = .582	1.9 *v* 2.3 OR = 0.82 [0.66 to 1.02] *P* = .077	0.6 *v* 0.6 OR = 1.02 [0.7 to 1.5] *P* = .911	16.5 *v* 16.7 OR = 1.07 [0.85 to 1.36] *P* = .565	8.4 *v* 8.6 OR = 1.07 [0.78 to 1.46] *P* = .0672	5.1 *v* 4.6 OR = 1.22 [0.82 to 1.82] *P* = .335	0.4 *v* 0.4 OR = 0.85 [0.21 to 3.54] *P* = .827	16.3 *v* 14.4 OR = 1.07 [0.88 to 1.29] *P* = .517	4.7 *v* 4.4 OR = 0.95 [0.68 to 1.32] *P* = .767	2.3 *v* 1.8 OR = 1.18 [0.73 to 1.91] *P* = .5	0.7 *v* 0.2 OR = 2.85 [0.95 to 8.6] *P* = .062
Metabolic/ laboratory	20.2 *v* 19.3 OR = 1.01 [0.93 to 1.1] *P* = .809	12.1 *v* 11.4 OR = 1.02 [0.93 to 1.13] *P* = 0.641	7.2 *v* 6.7 OR = 1.03 [0.91 to 1.16] *P* = .677	1.5 *v* 1.3 OR = 1.1 [0.85 to 1.44] *P* = .463	37.6 *v* 31.6 OR = 1.27 [1.05 to 1.54] *P* = .014	23.1 *v* 19 OR = 1.23 [0.99 to 1.53] *P* = .062	12.6 *v* 10.7 OR = 1.12 [0.86 to 1.47] *P* = .407	2.5 *v* 2.4 OR = 0.86 [0.49 to 1.51] *P* = 0.608	42.7 *v* 43.9 OR = 1.14 [0.98 to 1.32] *P* = 0.094	20.5 *v* 22.6 OR = 1.01 [0.85 to 1.2] *P* = .894	9.9 *v* 9.8 OR = 1.12 [0.89 to 1.41] *P* = .335	1.4 *v* 1.2 OR =1.3 [0.71 to 2.36] *P* = .396
Musculoskeletal	2.7 *v* 2.3 OR = 1.14 [0.94 to 1.4] *P* = .19	1.6 *v* 1.3 OR=1.13 [0.87 to 1.47] *P* = .349	0.5 *v* 0.6 OR = 0.81 [0.53 to 1.25] *P* = .344	0.1 *v* 0.1 OR = 1.03 [0.29 to 3.66] *P* = .969	13.4 *v* 11.6 OR = 1.1 [0.84 to 1.44] *P* = .499	8.1 *v* 6.7 OR=1.16 [0.83 to 1.63] *P* = .371	2.4 *v* 2.3 OR=1.02 [0.57 to 1.8] *P* = .953		8.5 *v* 8.1 OR = 1.11 [0.87 to 1.42] *P* = .411	3.8 *v* 3.8 OR = 0.97 [0.68 to 1.38] *P* = .855	1 *v* 1 OR = 0.93 [0.48 to 1.83] *P* = .843	0.1 *v* 0.1 OR = 0.53 [0.06 to 5.16] *P* = .587
Neurological, objective	13.7 *v* 12.5 OR = 1.15 [1.05 to 1.26] *P* = .003	7.8 *v* 6.9 OR = 1.19 [1.06 to 1.34] *P* = .004	3.7 *v* 2.8 OR = 1.4 [1.18 to 1.66] *P* < .001	0.4 *v* 0.3 OR = 1.16 [0.7 to 1.92] *P* = .567	15.7 *v* 13.2 OR = 1.3 [1.01 to 1.66] *P* = .039	9.4 *v* 7.7 OR = 1.31 [0.96 to 1.77] *P* = .087	4.7 *v* 4.4 OR = 1.11 [0.74 to 1.67] *P* = .619	0.4 *v* 0.5 OR = 0.61 [0.16 to 2.33] *P* = .467	5.6 *v* 5.2 OR = 1.1 [0.82 to 1.49] *P* = .521	2.9 *v* 2.4 OR = 1.18 [0.77 to 1.79] *P* = .447	1.4 *v* 1.3 OR = 1.11 [0.61 to 2.01] *P* = .727	0.3 *v* 0.4 OR = 0.75 [0.22 to 2.5] *P* = .635
Visual, objective	3 *v* 2.9 OR = 1.04 [0.87 to 1.24] *P* = .685	1.7 *v* 1.5 OR = 1.12 [0.88 to 1.43] *P* = .341	0.5 *v* 0.5 OR = 1.09 [0.69 to 1.7] *P* = .713	0 *v* 0 OR = 1.61 [0.22 to 11.68] *P* = .635	4.9 *v* 3.2 OR = 1.46 [0.95 to 2.26] *P* = .088	2.7 *v* 1.7 OR = 1.62 [0.91 to 2.88] *P* = .104	1.3 *v* 0.7 OR = 2.04 [0.86 to 4.85] *P* = .108		6.6 *v* 5.1 OR = 1.23 [0.92 to 1.64] *P* = .161	2.4 *v* 1.4 OR = 1.65 [1 to 2.72] *P* = .05	0.4 *v* 0.2 OR = 1.51 [0.43 to 5.27] *P* = .515	
Respiratory, objective	4.2 *v* 4.5 OR = 0.92 [0.79 to 1.07] *P* = .274	3 *v* 2.8 OR = 1.02 [0.85 to 1.23] *P* = .807	2 *v* 1.9 OR = 1.08 [0.87 to 1.35] *P* = .491	0.7 *v* 0.7 OR = 0.99 [0.69 to 1.42] *P* = .954	7.7 *v* 7.2 OR = 1.05 [0.75 to 1.46] *P* = .777	5.6 *v* 5.3 OR = 1.04 [0.71 to 1.53] *P* = .827	4.3 *v* 3 OR = 1.47 [0.94 to 2.32] *P* = .094	0.9 *v* 1.2 OR = 0.71 [0.31 to 1.67] *P* = .436	8.6 *v* 9.2 OR = 1.14 [0.89 to 1.46] *P* = .308	5.1 *v* 5.2 OR = 1.14 [0.83 to 1.56] *P* = .416	1.8 *v* 2 OR = 0.88 [0.53 to 1.45] *P* = .604	0.8 *v* 0.4 OR = 2.05 [0.82 to 5.14] *P* = .126
Renal/ genitourinary	8.7 *v* 11.5 OR = 0.74 [0.66 to 0.82] *P* < .001	4 *v* 5.2 OR = 0.76 [0.65 to 0.88] *P* < .001	1.3 *v* 1.8 OR = 0.69 [0.53 to 0.89] *P* = .004	0.5 *v* 0.7 OR = 0.7 [0.47 to 1.07] *P* = .098	8.7 *v* 10.2 OR = 0.81 [0.6 to 1.09] *P* = .169	3.8 *v* 4.5 OR = 0.82 [0.53 to 1.26] *P* = .362	1.5 *v* 1.6 OR = 0.89 [0.45 to 1.78] *P* = .751		12.7 *v* 17.1 OR = 0.71 [0.58 to 0.87] *P* = .001	4.1 *v* 5.3 OR = 0.78 [0.56 to 1.09] *P* = .148	1.4 *v* 0.9 OR = 1.62 [0.85 to 3.09] *P* = .143	0.6 *v* 0.3 OR = 1.99 [0.68 to 5.79] *P* = .207

FIG 4. (Continued)

objectively assessed hematologic AEs were also more commonly experienced in women.

Pharmacokinetics and pharmacodynamics could play a role. For the systemic therapies examined in this study, the literature is mixed. For instance, studies have found that women have lower capacity to clear fluorouracil than men.[33,34] By contrast, no differences between men and women in drug clearance were found in a study of patients receiving imatinib.[35] Evidence is conflicting regarding differential clearance rates of doxorubicin by sex.[36,37] Pharmacogenetics (ie, how drug metabolism and elimination of genetic polymorphisms modulate drug responses) may also vary by sex. For instance, survival in female patients with metastatic colon cancer treated with fluorouracil has been found to differ according to methylenetetrahydrofolate reductase gene polymorphism, but not in male patients.[38] The protein ABCG2/BCRP/MXR/ABCP, an ATP-binding cassette transporter, influences the absorption, distribution, and excretion of drugs and may be regulated by sex hormones, with potential differential effects on drug toxicity for agents that interact with high affinity with ABCG2.[39-41] In 2016, Yuan et al[42] conducted a comprehensive analysis

of sex differences in molecular profiles for 13 cancers, identifying two distinct groups of genes that predicted distinct incidence and mortality profiles. The gut microbiome may also be implicated given its role in regulating metabolic and immune inflammatory pathways.[43]

Findings regarding individual AE categories may serve as hypotheses for future research. The occurrence of sleep-related AEs among women receiving chemotherapy and immunotherapy is intriguing and could be a function of hormonal effects interacting with cancer treatment.[44] Disrupted sleep could contribute to an increased risk of poor cardiovascular outcomes.[45,46] The more common experience of severe hematologic AEs in female patients has been observed in patients receiving adjuvant treatment for colon cancer.[4,47] Female sex has been routinely identified as a risk factor for anthracycline-induced cardiotoxicity for patients with pediatric cancer.[48] Our findings indicate that among nonsex-specific cancers, the risk of cardiotoxicity may be higher for women than men, especially among those treated with chemotherapy or immunotherapy. Although the observation of increased risk of severe symptomatic gastrointestinal AEs is consistent with previous findings among those receiving chemotherapy, we have now shown that sex-based differences in gastrointestinal AEs in immunotherapy and targeted therapy exist as well.[49-51]

Our study has limitations. First, clinical trial patients tend to be younger and healthier than nontrial patients on average, and therefore, toxicities may be greater in nontrial patients.[52,53] Also, because only the worst toxicity grade in each category was recorded, our data do not allow for observation of toxicity patterns over time. Furthermore, toxicity must be considered in the context of survival; indeed, increased toxicity for women compared with men has been shown to occur in conjunction with improved survival.[49,54] However, the causal relationship between AEs and survival may be challenging to interpret since improved survival may allow more time/exposure to develop AEs or alternatively, increased AEs may represent, on average, increased delivery/efficacy of the anticancer agents, which could result in improved survival. In addition, reporting of AE data may be subject to misclassification, especially when CTCAE criteria are unable to depict subtle symptoms. For this reason, our primary analysis was based on severe AEs that are more clearly recognizable and commonly require hospitalization. Some conditions might have existed before study although all toxicities that we analyzed were deemed possibly, probably, or definitely related to treatment. For instance, some patients might have had existing sarcopenia, which might influence toxicity patterns and could not be fully accounted for by adjusting for obesity status. Also, although we were able to define symptomatic AEs, these symptomatic AEs were not actually reported by patients themselves. In this context, the incorporation of patient-reported symptomatic AEs into routine monitoring could shed further light on potential sex-related differences. Finally, although pooling across clinical trial databases is necessary to enhance statistical power to identify trends in AEs by sex,[2] pooling may also mask potentially meaningful associations.

Ideally, the goal in cancer therapy is to maximize treatment efficacy while limiting toxicity. Increasingly, treatment will be individualized on the basis of patient and tumor characteristics to optimize this relationship. In this context, our findings are supportive of the argument advanced by Özdemir et al, who stated that "sex as an independent modulator of drug efficacy and toxicity merits consideration for further individualization of treatments."[2] Indeed, if confirmed, our findings suggest that underlying mechanisms may result in generalized worse toxicity outcomes for women, with or without corresponding survival improvements or detriments. Therefore, more awareness of symptom differences or reporting differences in women versus men is needed. A better understanding of the nature of the underlying mechanisms could potentially lead to interventions or delivery modifications to reduce toxicity in women (in particular). In such cases, cancer treatment may then be able to be simultaneously modified or augmented, with the ultimate goal of extending therapeutic benefits.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Sex Differences in Risk of Severe Adverse Events in Patients Receiving Immunotherapy, Targeted Therapy, or Chemotherapy in Cancer Clinical Trials

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