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Article

Sex and Adverse Events of Adjuvant Chemotherapy in Colon Cancer: An Analysis of 34 640 Patients in the ACCENT Database

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Abstract

Background: Adjuvant chemotherapy is a standard treatment option for patients with stage III and high-risk stage II colon cancer. Sex is one of several factors responsible for the wide inter-patient variability in drug responses. Amalgamated data on the effect of sex on the toxicity of current standard adjuvant treatment for colorectal cancer are missing. **Methods:** The objective of our study was to compare incidence and severity of major toxicities of fluoropyrimidine- (5FU or capecitabine) based adjuvant chemotherapy, with or without oxaliplatin, between male and female patients after curative surgery for colon cancer. Adult patients enrolled in 27 relevant randomized trials included in the ACCENT (Adjuvant Colon Cancer End Points) database, a large, multi-group, international data repository containing individual patient data, were included. Comparisons were conducted using logistic regression models (stratified by study and treatment arm) within each type of adjuvant chemotherapy (5FU, FOLFOX, capecitabine, CAPOX, and FOLFIRI). The following major toxicities were compared (grade III or IV and grade I-IV, according to National Cancer Institute Common Terminology Criteria [NCI-CTC] criteria, regardless of attribution): nausea, vomiting, nausea or vomiting, stomatitis, diarrhea, leukopenia, neutropenia, thrombocytopenia, anemia, and neuropathy (in patients treated with oxaliplatin). **Results:** Data from 34 640 patients were analyzed. Statistically significant and clinically relevant differences in the occurrence of grade III or IV nonhematological {especially nausea (5FU: odds ratio [OR] = 2.33, 95% confidence interval [CI] = 1.90 to 2.87, $P < .001$; FOLFOX: OR = 2.34, 95% CI = 1.76 to 3.11, $P < .001$), vomiting (5FU: OR = 2.38, 95% CI = 1.86 to 3.04, $P < .001$; FOLFOX: OR = 2.00, 95% CI = 1.50 to 2.66, $P < .001$; CAPOX: OR = 2.32, 95% CI = 1.55 to 3.46, $P < .001$), and diarrhea (5FU: OR = 1.35, 95% CI = 1.21 to 1.51, $P < .001$; FOLFOX: OR = 1.60, 95% CI = 1.35 to 1.90, $P < .001$; FOLFIRI: OR = 1.57, 95% CI = 1.25 to 1.97, $P < .001$)} as well as hematological toxicities (neutropenia [5FU: OR = 1.55, 95% CI = 1.37 to 1.76, $P < .001$; FOLFOX: OR = 1.96, 95% CI = 1.71 to 2.25, $P < .001$; FOLFIRI: OR = 2.01, 95% CI = 1.66 to 2.43, $P < .001$; capecitabine: OR = 4.07, 95% CI = 1.84 to 8.99, $P < .001$] and leukopenia [5FU: OR = 1.74, 95% CI = 1.40 to 2.17, $P < .001$; FOLFIRI: OR = 1.75, 95% CI = 1.28 to 2.40, $P < .001$]) were observed, with women being consistently at increased risk. **Conclusions:** Our analysis confirms that women with colon cancer receiving adjuvant fluoropyrimidine-based chemotherapy are at increased risk of toxicity. Given the known sex differences in fluoropyrimidine pharmacokinetics, sex-specific dosing of fluoropyrimidines warrants further investigation.

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Background

An individual's sex is one of the most important modulators of disease risk and response to treatment (1). The importance and potential for sex and gender analyses to foster scientific discovery has been highlighted recently (2). A growing number of peer-reviewed journals now require sex- or gender-specific reporting (3,4). In fact, the *JNCI* was the first journal to include instructions for addressing the effects of sex as part of its manuscript preparation policy (5). Although the European Society for Medical Oncology (ESMO) recently addressed the topic (6), oncology lags behind other disciplines, such as cardiology. A PubMed search for "sex," "toxicity," and "chemotherapy" conducted in 2016 before initiating this analysis, including all solid tumors, identified 11 studies including more than 100 participants. Available studies in patients with colorectal cancer did not include prospective data on currently used oxaliplatin- or capecitabine-based regimens.

Adjuvant chemotherapy is standard for patients with stage III and high-risk stage II colon cancer. The impact of a patient's sex on the incidence and severity of adverse events has not, however, been well documented. Of note, although self-reported gender is that what is being reported, given the low frequency of transgender persons (0.3%-0.5%) (7), we can assume biological sex and gender to be identical in 99.5%-99.7% of patients. Therefore, as we consider biological differences between men and women as primarily responsible for potential differences in treatment effects, throughout this manuscript, we will use the term sex differences and refer to males and females.

This study aimed to compare between the sexes the incidence and severity of major adverse events of clinically relevant fluoropyrimidine (5FU or capecitabine)-based adjuvant chemotherapy, with or without oxaliplatin or irinotecan, after curative surgery for colon cancer in a large population of clinical trial participants who are part of the Adjuvant Colon Cancer End Points (ACCENT) database.

Methods

Trial Selection

This is a secondary analysis of previously conducted trials and was approved by the Mayo Clinic Institutional Review Board. Patients provided informed consent for participating in the original trials, which were obtained by local enrolling centers.

All adult patients with colorectal cancer who participated in any of the 27 relevant randomized clinical trials of adjuvant chemotherapy that comprise the ACCENT database were included. A list of all trials and treatment arms included in this analysis is provided as Supplementary Table 1 (available online). ACCENT (8,9) is a large, multi-group, international data repository containing individual patient–level information from clinical trials. Categories of chemotherapy regimens were 5FU single agent (plus folinic acid), with or without oxaliplatin (eg, FOLFOX, FLOX), capecitabine as a single agent or in combination with oxaliplatin (CAPOX), and 5FU (plus folinic acid) plus irinotecan (FOLFIRI and other regimens).

FOLFIRI is not a standard adjuvant treatment, but given its frequent use in patients with metastatic disease, trials including this chemotherapy combination were also analyzed. Patients assigned to combinations of chemotherapy plus targeted treatments no longer used as adjuvant treatment, such as FOLFOX plus bevacizumab, FOLFOX plus cetuximab, or CAPOX plus bevacizumab (representing 14 treatment arms from 13 trials) were excluded.

Statistical Analysis

We analyzed patient characteristics and adverse events separately for each regimen category. The χ^2 test was used to detect differences in baseline characteristics between male and female patients. The following major adverse events were compared (grade III or IV and grade I-IV, according to National Cancer Institute Common Terminology Criteria (NCI-CTC) regardless of attribution) between males and females: nausea, vomiting, nausea or vomiting, stomatitis, diarrhea, leukopenia, neutropenia, thrombocytopenia, anemia, and neuropathy in patients treated with oxaliplatin. Results for comparisons between grade I-IV adverse events are included in the Supplementary Materials (available online). Total patients included in logistic models for each adverse event differed due to data availability, including specific adverse event data missing per patient and specific adverse event data missing per study. To assess the association between adverse events and sex, odds ratios (OR) were calculated using multivariable logistic models adjusting for age, grade, stage, performance score (PS), and body mass index (BMI) and compared using the stratified Wald test. The interaction effects between sex and adjusting variables were tested using the stratified Wald test, and none of them were found to be statistically significant. To account for study and treatment-specific differences, logistic models were stratified by study and treatment arm. Two-sided *P* values are reported. We designated comparisons in which the *P* value was less than .001 as statistically significant to adjust for multiple comparisons.

Results

This analysis included 34 640 patients with a median age for both males and females of 61.0 years. Clinical characteristics with statistically significant ($P < .001$) differences are displayed in Table 1 according to chemotherapy regimen. Across chemotherapy regimens, we noted statistically significant differences in patients' characteristics between the sexes.

Specifically, females more often had a BMI of less than 18.5 (4.5% females vs 1.2% males) or 18.5-25 kg/m^2 (46.3% females vs 39.4% males), whereas males more often had a BMI of 25 kg/m^2 or greater (59.3% males vs 49.2% females); females were more often younger than 50 years of age (18.9% females vs 16.8% males), whereas males more often were 65 years and older (37.5% males vs 36.3% females); and females more often had a PS of 1 (20.8% females vs 18.6% males), whereas males more often had a PS of 0 (80.5% males vs 78.5% females).

Although the differences in BMI are clearly considered clinically meaningful, differences in age groups and PS are less important. Overall, 17 treatment-related deaths were observed: 12 females and 5 males (χ^2 $P = .04$). Due to the rarity of these events, we excluded them from the logistic models, which were limited to grade I-IV and grade III or IV adverse events. The adjusted associations between grade III or IV hematologic adverse

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Table 1. Patient characteristics by chemotherapy regimen

Characteristic	Female	Male	Total	P[a]
All patients, No.	15 976	18 664	34 640	
Age, No. (%), y				<.001
<50	3022 (18.9)	3142 (16.8)	6164 (17.8)	
50-64	7153 (44.8)	8519 (45.6)	15 672 (45.2)	
≥65	5801 (36.3)	7002 (37.5)	12 803 (37.0)	
Missing	0	1	1	
BMI, No. (%), kg/m^2				<.001
<18.5	645 (4.5)	208 (1.2)	853 (2.8)	
18.5-25	6631 (46.3)	6573 (39.4)	13 204 (42.6)	
≥25	7056 (49.%)	9889 (59.3)	16 945 (54.7)	
Missing	1644	1994	3638	
Performance score, No. (%)				<.001
0	12 224 (78.5)	14 675 (80.5)	26 899 (79.6)	
1	3233 (20.8)	3383 (18.6)	6616 (19.6)	
2	116 (0.7)	158 (0.9)	274 (0.8)	
3	2 (0.0)	4 (0.0)	6 (0.0)	
Missing	401	444	845	
5FU patients	10 521	12 259	22 780	
Age, No. (%), y				<.001
<50	1958 (18.6)	1990 (16.2)	3948 (17.3)	
50-64	4613 (43.8)	5501 (44.9)	10 114 (44.4)	
≥65	3950 (37.5)	4768 (38.9)	8718 (38.3)	
BMI, No. (%), kg/m^2				<.001
<18.5	412 (4.6)	138 (1.3)	550 (2.9)	
18.5-25	4187 (47.1)	4100 (39.9)	8287 (43.2)	
≥25	4300 (48.3)	6043 (58.8)	10 343 (53.9)	
Missing	1622	1978	3600	
Performance score, No. (%)				<.001
0	7851 (77.2)	9408 (79.4)	17 259 (78.4)	
1	2203 (21.7)	2292 (19.3)	4495 (20.4)	
2	109 (1.1)	149 (1.3)	258 (1.2)	
3	1 (0.0)	4 (0.0)	5 (0.0)	
Missing	357	406	763	
FOLFOX patients	2720	3149	5869	
Age, No. (%), y				.08
<50	573 (21.1)	608 (19.3)	1181 (20.1)	
50-64	1315 (48.3)	1502 (47.7)	2817 (48.0)	
≥65	832 (30.6)	1039 (33.0)	1871 (31.9)	
BMI, No. (%), kg/m^2				<.001
<18.5	106 (3.9)	20 (0.6)	126 (2.1)	
18.5-25	1183 (43.5)	1134 (36.0)	2317 (39.5)	
≥25	1430 (52.6)	1995 (63.4)	3425 (58.4)	
Missing	1	0	1	
Performance score, No. (%)				.53
0	2247 (83.2)	2621 (83.9)	4868 (83.6)	
1	449 (16.6)	495 (15.9)	944 (16.2)	
2	4 (0.1)	7 (0.2)	11 (0.2)	
3	1 (0.0)	0 (0.0)	1 (0.0)	
Missing	19	26	45	
Capecitabine patients	888	1026	1914	
Age, No. (%), y				.17
<50	121 (13.6)	141 (13.8)	262 (13.7)	
50-64	387 (43.6)	487 (47.5)	874 (45.7)	
≥65	380 (42.8)	397 (38.7)	777 (40.6)	
Missing	0	1	1	
BMI, No. (%), kg/m^2				<.001
<18.5	42 (4.8)	13 (1.3)	55 (2.9)	
18.5-25	434 (49.2)	449 (44.2)	883 (46.5)	
≥25	406 (46.0)	554 (54.5)	960 (50.6)	
Missing	6	10	16	

(continued)

Table 1. (continued)

Characteristic	Female	Male	Total	P[a]
Performance score, No. (%)				.84
0	750 (84.8)	867 (84.5)	1617 (84.7)	
1	134 (15.2)	159 (15.5)	293 (15.3)	
Missing	4	0	4	
CAPOX patients	850	1014	1864	
Age, No. (%), y				.10
<50	146 (17.2)	176 (17.4)	322 (17.3)	
50-64	361 (42.5)	475 (46.8)	836 (44.8)	
≥65	343 (40.4)	363 (35.8)	706 (37.9)	
BMI, No. (%), kg/m^2				<.001
<18.5	43 (5.1)	20 (2.0)	63 (3.4)	
18.5-25	376 (44.2)	415 (40.9)	791 (42.4)	
≥25	431 (50.7)	579 (57.1)	1010 (54.2)	
Performance score, No. (%)				.03
0	607 (72.3)	774 (76.8)	1381 (74.7)	
1	233 (27.7)	234 (23.2)	467 (25.3)	
Missing	10	6	16	
FOLFIRI patients	997	1216	2213	
Age, No. (%), y				.005
<50	224 (22.5)	227 (18.7)	451 (20.4)	
50-64	477 (47.8)	554 (45.6)	1031 (46.6)	
≥65	296 (29.7)	435 (35.8)	731 (33.0)	
BMI, No. (%), kg/m^2				<.001
<18.5	42 (4.3)	17 (1.4)	59 (2.7)	
18.5-25	451 (45.9)	475 (39.3)	926 (42.2)	
≥25	489 (49.8)	718 (59.3)	1207 (55.1)	
Missing	15	6	21	
Performance score, No. (%)				.01
0	769 (78.0)	1005 (83.1)	1774 (80.8)	
1	214 (21.7)	203 (16.8)	417 (19.0)	
2	3 (0.3)	2 (0.2)	5 (0.2)	
Missing	11	6	17	

[a]The χ^2 *P* value for differences between male and female patients, statistical significance level less than .001.

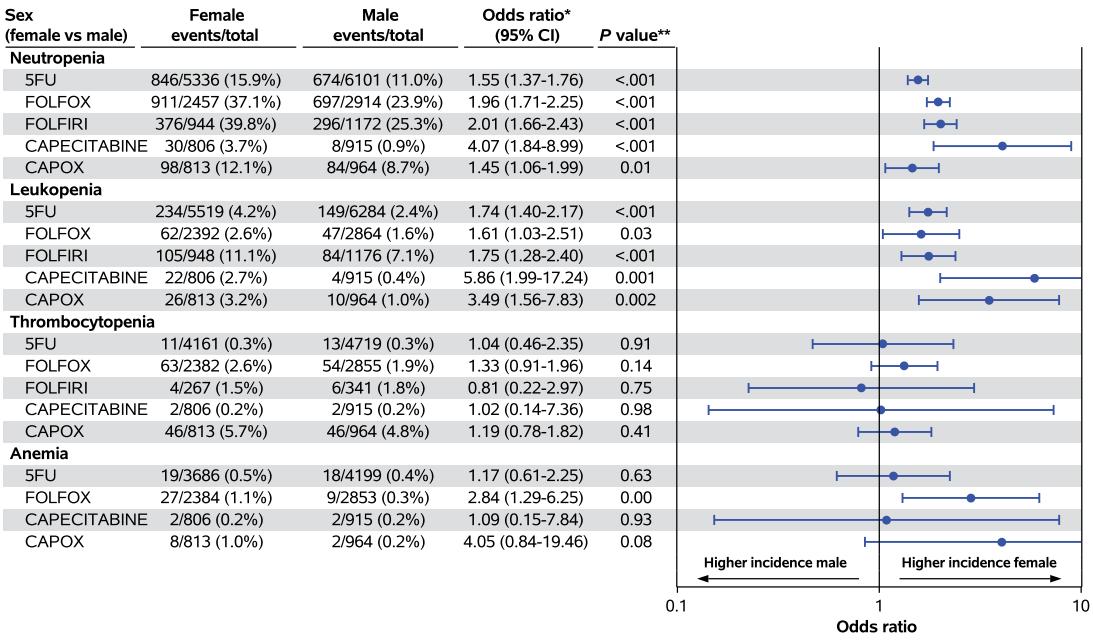

Figure 1. Adjusted odds ratios (95% confidence intervals) for grade III or IV hematological toxicities (log base 10 scale). *Stratified by study and treatment arm, adjusted for age, stage grade, performance status, and body mass index. **Stratified Wald *P* value. 5FU = fluorouracil therapy; CAPOX = capecitabine + oxaliplatin therapy; CI = confidence interval; FOLFOX = leucovorin + fluorouracil + oxaliplatin therapy.

Sex (female vs male)	Female events/total	Male events/total	Odds ratio* (95% CI)	*P* value**
Nausea				
5FU	290/5344 (5.4%)	151/6111 (2.5%)	2.33 (1.90-2.87)	<.001
FOLFOX	174/2407 (7.2%)	92/2862 (3.2%)	2.34 (1.76-3.11)	<.001
FOLFIRI	98/955 (10.3%)	84/1186 (7.1%)	1.53 (1.12-2.09)	0.007
CAPECITABINE	14/806 (1.7%)	18/915 (2.0%)	0.85 (0.42-1.73)	0.64
CAPOX	34/813 (4.2%)	60/964 (6.2%)	0.63 (0.40-0.97)	0.03
Vomiting				
5FU	208/5340 (3.9%)	105/6107 (1.7%)	2.38 (1.86-3.04)	<.001
FOLFOX	159/2405 (6.6%)	96/2865 (3.4%)	2.00 (1.50-2.66)	<.001
FOLFIRI	92/954 (9.6%)	71/1186 (6.0%)	1.69 (1.21-2.35)	0.001
CAPECITABINE	22/806 (2.7%)	6/915 (0.7%)	4.40 (1.77-10.92)	0.001
CAPOX	74/813 (9.1%)	40/964 (4.1%)	2.32 (1.55-3.46)	<.001
Nausea or vomiting				
5FU	341/5344 (6.4%)	189/6111 (3.1%)	2.20 (1.82-2.66)	<.001
FOLFOX	244/2415 (10.1%)	141/2871 (4.9%)	2.23 (1.76-2.83)	<.001
FOLFIRI	128/955 (13.4%)	114/1186 (9.6%)	1.48 (1.13-1.95)	0.005
CAPECITABINE	32/806 (4.0%)	18/915 (2.0%)	2.04 (1.13-3.68)	0.01
CAPOX	88/813 (10.8%)	70/964 (7.3%)	1.52 (1.09-2.11)	0.01
Stomatitis				
5FU	351/4829 (7.3%)	236/5403 (4.4%)	1.62 (1.36-1.94)	<.001
FOLFOX	53/2390 (2.2%)	40/2866 (1.4%)	2.00 (1.22-3.28)	0.005
FOLFIRI	4/266 (1.5%)	3/340 (0.9%)	1.81 (0.38-8.60)	0.45
CAPECITABINE	10/806 (1.2%)	2/915 (0.2%)	5.68 (1.23-26.27)	0.02
Diarrhea				
5FU	869/5514 (15.8%)	793/6275 (12.6%)	1.35 (1.21-1.51)	<.001
FOLFOX	430/2444 (17.6%)	365/2899 (12.6%)	1.60 (1.35-1.90)	<.001
FOLFIRI	209/955 (21.9%)	191/1186 (16.1%)	1.57 (1.25-1.97)	<.001
CAPECITABINE	118/806 (14.6%)	92/915 (10.1%)	1.45 (1.08-1.94)	0.01
CAPOX	170/813 (20.9%)	180/964 (18.7%)	1.13 (0.89-1.43)	0.30
Peripheral neuropathy				
FOLFOX	493/2483 (19.9%)	460/2948 (15.6%)	1.34 (1.15-1.57)	<.001
CAPOX	80/813 (9.8%)	90/964 (9.3%)	1.12 (0.81-1.55)	0.48
Rash				
5FU	25/3611 (0.7%)	21/4099 (0.5%)	1.16 (0.63-2.11)	0.63
FOLFOX	21/2381 (0.9%)	19/2855 (0.7%)	1.41 (0.72-2.76)	0.31
CAPOX	6/813 (0.7%)	4/964 (0.4%)	1.91 (0.53-6.83)	0.31
Handfoot syndrome				
5FU	21/3980 (0.5%)	16/4536 (0.4%)	1.55 (0.80-2.99)	0.19
FOLFOX	38/2390 (1.6%)	20/2858 (0.7%)	2.29 (1.21-4.36)	0.01
FOLFIRI	1/266 (0.4%)	1/341 (0.3%)	1.59 (0.10-26.02)	0.74
CAPECITABINE	150/806 (18.6%)	168/915 (18.4%)	0.99 (0.78-1.27)	0.96
CAPOX	40/813 (4.9%)	52/964 (5.4%)	1.02 (0.66-1.56)	0.94
Transaminitis				
5FU	13/3553 (0.4%)	12/4039 (0.3%)	1.07 (0.48-2.38)	0.86
FOLFOX	61/2389 (2.6%)	36/2863 (1.3%)	2.45 (1.51-3.96)	<.001
FOLFIRI	3/269 (1.1%)	3/344 (0.9%)	1.32 (0.26-6.80)	0.73
CAPECITABINE	4/806 (0.5%)	4/915 (0.4%)	1.11 (0.27-4.50)	0.88
CAPOX	6/813 (0.7%)	16/964 (1.7%)	0.36 (0.14-0.96)	0.04

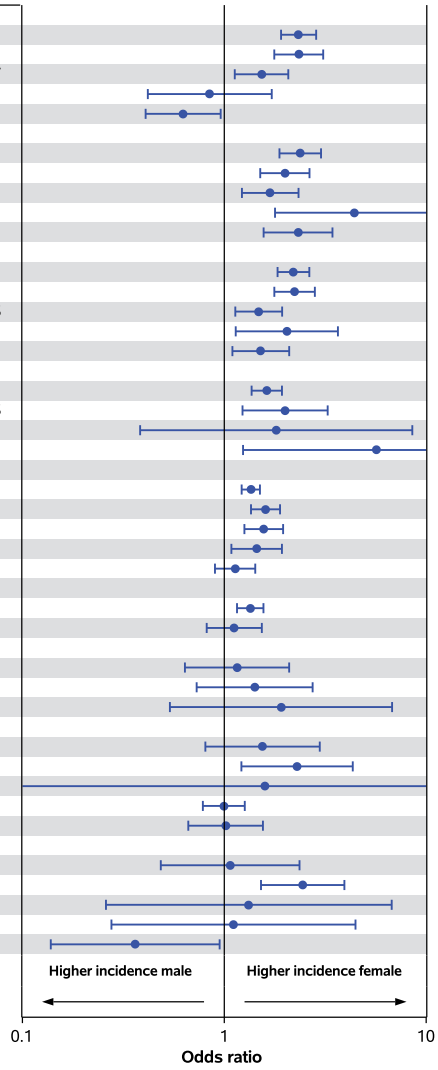

Figure 2. Adjusted odds ratios (95% confidence intervals) for grade III or IV nonhematological toxicities (log base 10 scale). *Stratified by study and treatment arm, adjusted for age, stage grade, performance status, and body mass index. **Stratified Wald *P* value; 5FU = fluorouracil therapy; CAPOX = capecitabine + oxaliplatin therapy; CI = confidence interval; FOLFOX = leucovorin + fluorouracil + oxaliplatin therapy.

events and sex according to treatment regimen are displayed in Figure 1. While the odds of experiencing grade III or IV thrombocytopenia and anemia were comparable, female patients had higher odds of experiencing grade III or IV neutropenia (5FU: OR = 1.55, 95% confidence interval [CI] = 1.37 to 1.76, $P < .001$; FOLFOX: OR = 1.96, 95% CI = 1.71 to 2.25, $P < .001$; FOLFIRI: OR = 2.01, 95% CI = 1.66 to 2.43, $P < .001$; capecitabine: OR = 4.07, 95% CI = 1.84 to 8.99, $P < .001$) and leukopenia (5FU: OR = 1.74, 95% CI = 1.40 to 2.17, $P < .001$; FOLFIRI: OR = 1.75, 95% CI = 1.28 to 2.40, $P < .001$), which reached statistical significance within at least 1 treatment subgroup. The adjusted associations between grade III or IV nonhematologic adverse events are shown in Figure 2. Again, female patients had higher odds of experiencing grade III or IV nausea (5FU: OR = 2.33, 95% CI = 1.90 to 2.87, $P < .001$; FOLFOX: OR = 2.34, 95% CI = 1.76 to 3.11, $P < .001$), vomiting (5FU: OR = 2.38, 95% CI = 1.86 to 3.04, $P < .001$; FOLFOX: OR = 2.00, 95% CI = 1.50 to 2.66, $P < .001$; CAPOX: OR = 2.32, 95% CI = 1.55 to 3.46, $P < .001$), stomatitis (5FU: OR = 2.20, 95% CI = 1.82 to 2.66, $P < .001$), diarrhea (5FU: OR = 1.35, 95% CI = 1.21 to 1.51, $P < .001$; FOLFOX: OR = 1.60, 95% CI = 1.35 to 1.90, $P < .001$; FOLFIRI: OR = 1.57, 95% CI = 1.25 to 1.97, $P < .001$), peripheral neuropathy (FOLFOX: OR = 1.34, 95% CI = 1.15 to 1.57, $P < .001$), and transaminitis (FOLFOX: OR = 2.45, 95% CI = 1.51 to 3.96, $P < .001$), which reached statistical significance within at least 1 treatment subgroup, and the odds of experiencing grade III or IV peripheral neuropathy (only CAPOX subgroup), rash, hand-foot syndrome, and transaminitis (with the exception of FOLFOX subgroup) were comparable. Adjusted associations between grade I and IV hematological and nonhematological adverse events according to sex and treatment regimen are available as Supplementary Figure 1 and 2 (available online).

Discussion

Including 34 640 patients, our analysis is the largest to date to address in a systematic manner the impact of a patient's sex on the toxicity of all currently used adjuvant chemotherapy regimens. Importantly, for the first time, to our knowledge, we

report prospectively collected data on oxaliplatin-based and capecitabine-based regimens. We confirm that female patients with colon cancer consistently experience clinically and statistically significant greater toxicity. This effect is seen across regimens and most adverse events but is greatest for severe neutropenia and leukopenia.

Variability in outcomes in either efficacy or toxicity can broadly be broken down into 2 categories. Pharmacokinetic variability reflects differences within populations with respect to the extent of drug exposure due, for example to differences in absorption or metabolism. By contrast, pharmacodynamic variability is the result of differences in the biological effects of a drug between patients with the same drug exposure. A patient's sex is known to affect both the pharmacokinetics of drug disposition and the pharmacodynamics of drug sensitivity (10) but is usually not taken into account for dosage individualization. In addition, current chemotherapy dosing according to body surface area takes into account neither the sex differences in fat-free body mass (6) nor the large individual differences in body composition among patients with a similar body surface area.

Our findings raise several important questions. The first is: how can we explain the observed differences in toxicity, and what are the roles of genetic and nongenetic factors? While patients' sex has no effect on the clearance of oxaliplatin (11), sex differences in the clearance of 5FU (12,13), which are independent of age (14), are likely to explain the differences in toxicity observed. As a consequence of their lower clearance of 5FU, dosing according to body surface area results in higher plasma fluoropyrimidine levels in females (12–14).

Although the precise reason for the lower clearance of 5FU in females is not certain, the major route of elimination of 5FU is hepatic metabolism by the enzyme dihydropyrimidine dehydrogenase (DPYD). DPYD activity is associated with fluoropyrimidine toxicity (15), but data on sex differences in DPYD activity are controversial (16–18). A strong interaction between DPYD genetics and sex has been observed by different authors (18–20), with a greater predictive impact of several DPYD variants in males. By contrast, the lower clearance of 5FU explains the higher toxicity in females. These observations provide a strong case for a sex-specific approach to personalized fluoropyrimidine dosing. Sex differences in body composition, including the higher percentage of metabolically active, fat-free body mass in men (6), may also be relevant, because 5FU pharmacokinetics are better predicted by fat-free mass and total body weight than standard anthropometric parameters (21).

The second major question raised by our analysis is whether the higher plasma levels and toxicity in females translate to a higher treatment efficacy. In this context, a recently presented, pooled analysis including 18 399 patients in first-line chemotherapy trials for metastatic colorectal cancer (22) confirmed the higher toxicity but demonstrated equal efficacy of chemotherapy in females and males in terms of both progression-free and overall survival. Thus, differences in pharmacodynamics must be postulated. Whether the tolerability of chemotherapies with greater toxicity in female patients could be improved by either dose reductions or intensification of supportive care measures only in female patients, and if dose reductions would decrease the efficacy are further important open questions.

The third major question is whether conventional dosing of 5FU results in suboptimal therapeutic plasma levels in males. The overall lower frequency of toxicities in men could be interpreted as a sign of relative underdosing. Body surface area–based dosing was applied to individualizing chemotherapy doses in the 1950s and has remained the default approach, although its inaccuracy, including the risk of underdosing, has been recognized for more than 15 years (23). Accordingly, pharmacologists have proposed adjusting doses up or down based on a biologically relevant endpoint, such as myelosuppression (23,24). Moreover, in patients with metastatic colorectal cancer, an association between treatment with FOLFOX or trifluridine/tiperacil and improved median survival in patients with neutropenia (median survival in patients with grade III or IV neutropenia vs without neutropenia for FOLFOX 20.7 vs 12.5 months, $P < .001$; for trifluridine and tiperacil 9.8 vs 4.4 months) (25,26) has been reported. A relatively small study of 32 participants confirmed that conventional dosing of 5FU results in "subtherapeutic" plasma levels in the majority of males (13). In a separate study of 152 patients, 124 were considered to have "subtherapeutic" 5FU levels (27). To achieve "therapeutic" 5FU levels, the mean 5FU dose was higher in males (1837 vs 1763 mg/m^2/wk), respectively (27).

Arguably, a question of major importance is whether conventional dosing results in suboptimal treatment outcomes in males. A close relationship between plasma levels of 5FU and toxicity and efficacy has been observed in patients with several tumor types [for review see (28)]. A previous analysis of the ACCENT database showed that males had inferior time to recurrence (hazard ratio = 1.05, 95% CI = 1.01 to 1.09) and other efficacy endpoints after adjusting for age, stage, and treatment (8). Interestingly, the stage of disease and type of adjuvant regimen did not influence the prognostic value of sex (8). Another earlier ACCENT database analysis also showed that male sex, along with other patient and disease characteristics, was associated with increased early (<6 months) mortality (9).

A key strength of our analysis is the large number of patients included, which allows the identification of sex differences with clinical relevance and statistical significance. Furthermore, it enables to understand their magnitude while avoiding the risk of errors due to multiple testing observed in smaller datasets. Additional strong points are the inclusion of all currently relevant chemotherapy regimens, in which patients do not have confounding factors such as prior chemotherapy, which might complicate the interpretation of apparent differences in toxicity. Our analysis is, however, limited by the fact that not all types of toxicity were included in the ACCENT database. For example, data on neutropenic fever, lethargy, or fatigue are absent. Interestingly, a recently published analysis of the phase III PETACC-3 trial of FOLFIRI observed all-grade lethargy in 48.9% of females compared with 38.2% of males ($P < .001$) (29). Furthermore, trials usually report the worst grade of toxicity and not how many times it occurred in an individual patient. By necessity, therefore, we focus on differences in incidence rather than frequency of a given toxicity; likewise, the durations of these toxicities are also unavailable. Finally, data on dose reductions and delays, serious adverse events, and hospitalizations due to toxicity are not captured in the ACCENT database.

In conclusion, the current analysis raises several important questions, including whether males should receive higher doses of 5FU and if this may increase the effectiveness of adjuvant chemotherapy in males with colon cancer, and whether females should receive either reduced doses of 5FU or different and more intensive supportive treatments. Previous trials including pharmacokinetically adjusted dosing (27,30) confirmed that the balance between efficacy and toxicity of fluoropyrimidines may be improved statistically significantly and clinically relevantly but did not change clinical practice. Therefore,

further rationally designed, prospective clinical trials investigating alternatives to body surface area–based dosing of fluoropyrimidines are required to optimize dosing. Such trials need to take into account the well-known sex differences in their effects as well as other parameters, such as individual body composition determined by computed tomography scan, DPD phenotype and/or mutations, and pharmacokinetics.

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Data availability

The data sharing of individual patient data from each participating trial will be subject to the policy and procedures of the institutions and groups who conducted the original study.

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