Gender Disparities in Metastatic Colorectal Cancer Survival

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Abstract

Purpose: Previous studies have shown that estrogen prevents colon cancer in postmenopausal women, indicating a role in colorectal cancer carcinogenesis and tumor progression. We investigated the interactions between sex, age, ethnicity, and year of diagnosis on overall survival (OS) in patients with metastatic colorectal cancer (MCRC).

Experimental Design: We screened 52,882 patients with MCRC from 1988 to 2004, using the Surveillance Epidemiology and End Results registry. Age at diagnosis, sex, ethnicity, tumor location, year of diagnosis, OS, and cancer-specific survival were evaluated using Cox proportional hazards model. The models were adjusted for marital status, tumor site, tumor differentiation, and treatment with radiation and/or surgery.

Results: We observed that younger women (18-44 years old) with MCRC lived longer than younger men (17 months versus 14; $P < 0.0001$, log-rank test). In contrast, older women (55 years and older) had significantly worse OS than older men (7 months versus 9; $P < 0.0001$, log-rank test). In multivariate analysis, we found that gender discrepancies have widened in recent years; young women diagnosed after 2000 have improved cancer-specific survival, compared to men (hazard ratio, 0.778; 95% confidence interval, 0.669-0.904), but those diagnosed before 2000 benefit less (hazard ratio, 0.931; 95% confidence interval, 0.821-1.056).

Conclusion: As one of the largest data sets analyzed to establish that younger women with MCRC survive longer than younger men, hormonal status not only seems to play an important role in the development and pathogenesis of colorectal cancer but also may be of prognostic significance. These data warrant further studies to determine the role of estrogen in colorectal cancer. (Clin Cancer Res 2009;15(20):6391–7)

The effect of gender on colorectal cancer (CRC) incidence is well established. At all ages, women are less likely to develop CRC than men (1, 2). Indeed, their risk is comparable to men 4 to 8 years younger in age (3). Variable environmental exposures and comorbidities may contribute to these findings; however, an alternate explanation is emerging.

In the Women's Health Initiative trial, postmenopausal hormone use was associated with a 40% decrease in colorectal cancer (4). This association between hormone replacement therapy and colon cancer prevention is consistent with previous reports (5, 6). Hormones also protect premenopausal women, as oral contraceptive use reduces the risk of developing CRC by ~20% (7, 8). The mechanism by which this occurs is unclear, but these findings parallel reports that menopause increases a woman's risk of developing colon cancer over premenopausal women of the same age (9).

Gender differences in CRC extend to environmental sequelae, tumor biology, and therapeutic response. For example, obesity (10) and a sedentary lifestyle (11) increase the risk of colon cancer mostly in men. There is also evidence that tumorigenesis may be gender specific as women are more likely to develop right-sided tumors with the microsatelllite instability phenotype (12, 13). In addition, polymorphisms in methylenetetrahydrofolate reductase (*MTHFR*) and epidermal growth factor receptor (*EGFR*) genes have gender-specific prognostic significance in MCRC (14, 15). Many reports suggest that women derive more benefit from adjuvant chemotherapy (13), whereas others suggest that women have a greater incidence of 5-fluorouracil toxicity when treated for colorectal cancer (16).

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Note: All of the authors have directly participated in the planning, execution, or analysis of the study. An abstract of this work was accepted at ASCO 2008 Annual Meeting and included in the poster discussion for Colorectal Cancer abstracts.

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Translational Relevance

This article shows the effect of gender on survival in metastatic colorectal cancer. Younger women have an increased overall survival when compared with their male counterparts. Conversely, older women have a comparatively decreased overall survival. We also report for the first time that the benefits among younger women have increased with newly available treatments. We postulate an interaction of hormonal status and chemotherapy options recently approved for colorectal cancer. These findings add to the burgeoning principle that hormones, specifically estrogen, may play an important role in colorectal cancer tumorigenesis. Additionally, these findings emphasize the importance of investigating menopausal status as a predictive and prognostic marker in colorectal cancer.

The interplay between hormones and carcinogenesis is complex. In the Women's Health Initiative, combined estrogen and progesterone hormone replacement was both chemopreventative and carcinogenic. Defining these interactions is important to understanding the gender predilection of certain malignancies and will lead to improved treatment and prevention.

Whether female gender is associated with improved survival in CRC is under investigation. Although epidemiologic studies suggest that women present at a more advanced stage of disease (17), female gender is a predictor for improved survival after resection in a number of studies (18, 19). Recent reports also suggest that women with CRC may have lower cancer-specific mortality than men (20, 21).

Gender differences affect CRC incidence and gene expression patterns, yet the significance of gender as a prognostic or predictive factor for overall survival (OS) in MCRC is unclear. We used the Surveillance Epidemiology and End Results (SEER) database to investigate the interactions between sex, age, and ethnicity on OS and to evaluate the progression of these associations by year of diagnosis in a large cohort of patients with MCRC.

Study Design

As data source, the SEER public use database 1973-2004 was used for the current analysis. SEER registry, sponsored by the National Cancer Institute, collects information on cancer incidence and survival from 17 population-based cancer registries covering ~26% of the United States population.

Study population. All patients with primary, histologically confirmed MCRC were eligible for the study. The disease was defined by International Classification of Diseases for Oncology codes C18.0-C18.9, C19.9, and C20.9. We identified patients with metastasic disease defined by SEER Extent of Disease code 85. We restricted eligibility to adults (18 y and older) who were diagnosed with MCRC between 1988 and 2004, as the extent of disease was unavailable for accurate staging before 1988. We excluded those diagnosed at death or autopsy, missing follow-up records, and lacking documentation on age at the diagnosis or race/ethnicity. A total of 52,882 MCRC patients were included in the final sample for the current analysis.

Variable definitions. The primary end point in this study was OS, defined as the period from diagnosis to death. For the patients still alive at the last follow-up, OS was censored at date of last follow-up or December 31, 2004, whichever came first. Colorectal cancer–specific survival was a secondary end point. Cancer-specific survival measures survival from diagnosis to death from colorectal cancer (SEER Cause of Death Recode: 21040 and 21050). Patients who died of causes other than colorectal cancer were considered to be censored (SEER website). Information on age at diagnosis, sex, race and ethnicity, marital status, treatment type, primary site, tumor grade and differentiation, and survival time was available in SEER database. We chose the range for age

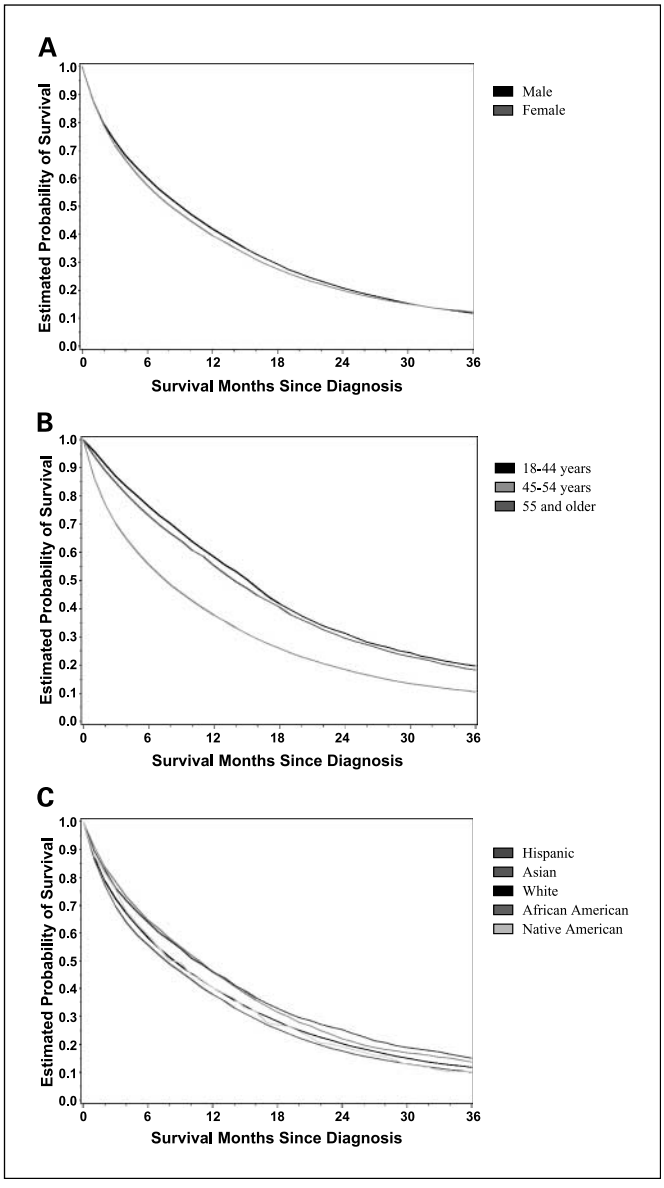

Fig. 1. Kaplan-Meier curves of OS in MCRC, stratified by sex (*A*), age (*B*), and ethnicity (*C*). Log-rank tests were used to calculate significance.

Table 1. Overall survival of men and women with MCRC by demographic characteristics, SEER data 1988-2004

Characteristics	Male (*n* = 27,427)		Female (*n* = 25,455)	
	n, (%)	Median OS (95% CI)	*n*, (%)	Median OS (95% CI)
Age, y				
18-44	1,458 (5)	14 (13-15)	1,501 (6)	17 (16-17)
45-54	3,291 (12)	14 (13-14)	2,761 (11)	15 (14-16)
>55	22,678 (83)	9 (8-9)	21,193 (83)	7 (7-8)
Race				
White	20,551 (75)	9 (9-10)	19,050 (75)	8 (8-9)
African American	3,034 (11)	8 (8-9)	3,193 (13)	8 (8-9)
Asian	1,852 (7)	11 (10-11)	1,498 (6)	12 (11-13)
Hispanic	1,862 (7)	11 (10-12)	1,587 (6)	11 (10-12)
Native American	128 (0.5)	10 (8-15)	127 (0.5)	8 (6-10)
Primary site				
Proximal	10,859 (40)	8 (8-8)	12,177 (48)	8 (7-8)
Distal	7,324 (27)	11 (11-12)	6,323 (25)	12 (11-12)
Rectosigmoid	2,779 (10)	13 (12-13)	2,111 (8)	11 (11-13)
Rectal	4,770 (17)	11 (11-11)	3,163 (12)	10 (9-10)
Overlapping or NOS	1,695 (6)	3 (3-3)	1,681 (7)	3 (3-3)
Year of diagnosis				
1988-1999	15,751 (57)	9 (9-9)	14,547 (57)	8 (8-8)
2000-2003	11,676 (43)	10 (10-11)	10,908 (43)	9 (9-10)

NOTE: Based on log-rank test; survival time was censored at 3 y.

groups based on previous studies (18-44, 45-54, 55, and older). Patients were divided into five race/ethnicity groups: non-Hispanic white, non-Hispanic Blacks, non-Hispanic Asians/Pacific Islanders, Hispanics (identified to have Spanish/Hispanic surname or of Spanish), and Native Americans. Subjects were categorized into "not married" (including never married, separated, divorced, widowed, and unknowns) and "married" (including common law). Treatment type was coded using surgery and radiation records and classified as colectomy or proctectomy, local surgery, radiation therapy only, untreated (for patients who did not have surgery nor radiation therapy), and unknown (for missing information on surgery and radiation). Records on chemotherapy were not available in the SEER public use data. Primary site was coded as proximal colon, distal colon, rectosigmoid, rectum, and overlapping or unspecified. Tumor grade and differentiation was coded as well/moderately differentiated, poorly differentiated, undifferentiated, and unknown.

Statistical analysis. We compared men and women using descriptive statistics. Survival time was censored at 3 y for all analyses. Univariate survival analysis was done using Kaplan-Meier curves and log-rank tests. We constructed Cox proportional hazards models to evaluate associations between patient characteristics and survival in men and female separately. All multivariable models included year of diagnosis and registry as stratification variables and marital status, treatment, primary site, and tumor grade and differentiation as covariates. Hazard ratios (HR) and 95% confidence intervals (95% CI) were generated, with HRs <1.0 indicating survival benefit. Pairwise interactions (i.e., age and sex, age and race, and sex and race) were examined using stratified models and were tested by comparing corresponding likelihood ratio statistics between the baseline and nested Cox proportional hazards models that included the multiplicative product terms (22). Departure of the proportional hazard assumption of Cox models will be examined graphically such as log-log survival curves or smoothed plots of weighted Schoenfeld residuals (23) and by including a time-dependent component individually for each predictor. All analyses were conducted using $P < 0.05$ as the significance level; statistical analyses were done with the use of SAS software (version 9.1, SAS Institute).

Results

Patient characteristics. We studied 52,882 patients with metastatic colorectal cancer (MCRC) diagnosed from 1998 to 2003. The number of male MCRC patients was 27,427 (52%), with a median OS of 10 months; 25,455 (48%) were women and their survival was 9 months (Fig. 1A). In our cohort, the average age of MCRC patients was 68 years; 5.6% of the patients were <45 years old, 11.4% were between 45 and 54 years old, and 83% were >55 years old. Across all age groups, the OS significantly decreased as patients aged (Fig. 1B).

For the ethnicities of our CRC patients, 74.9% were White, 11.8% African American, 6.3% Asian, 6.5% Hispanic, and 0.5% Native American. Asians and Hispanics had the longest median OS (11 months) followed by Whites (9 months), Native Americans (9 months), and African Americans (8 months; $P < 0.0001$; Table 1; Fig. 1C).

Gender and MCRC. The characteristics of men and women with MCRC are shown in Table 1. The distribution of MCRC across age groups is fairly consistent between genders. The average age of diagnosis for men and women was 67 and 69 years, respectively. However, 40% of the women with MCRC were diagnosed at >75 years of age as compared with 30% of the men.

There were no gender differences in MCRC prevalence across ethnicities. White, African American, and Native American men survived longer than women. However, Asians women were the sole ethnicity that had better survival than men (Table 1).

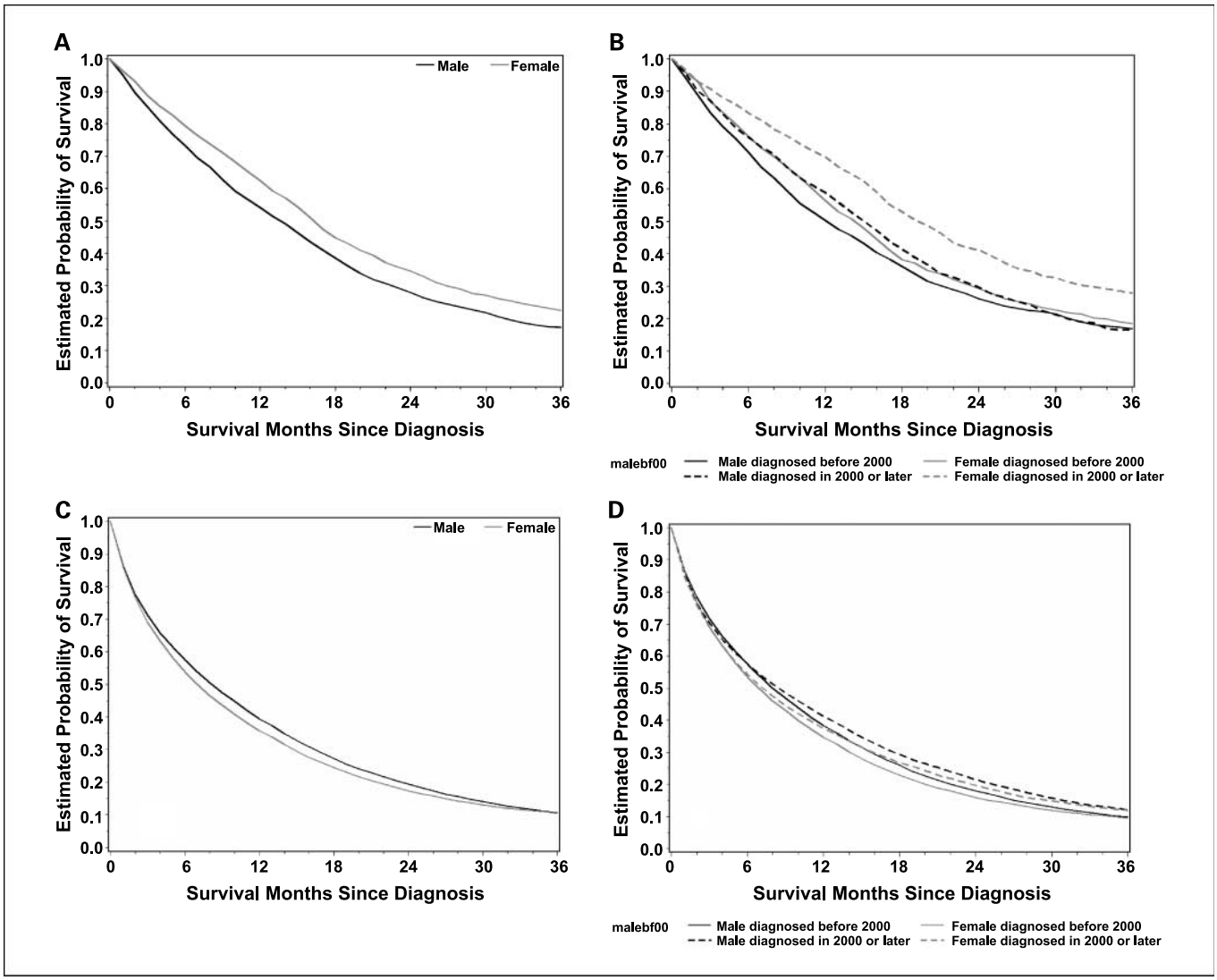

Fig. 2. Kaplan-Meier curves of OS by sex and year of diagnosis. *A,* young MCRC patients (≤44 y). *B,* young patients by year of diagnosis. *C,* old MCRC patients (>55 y). *D,* old patients by year of diagnosis.

Tumor location was also examined with respect to gender. We found significant differences in the frequency of right- and left-sided colon lesions among men and women. Women were more likely to have right-sided or proximal lesions. In women, 47.8% of MCRC lesions were located in the proximal or right colon. Only 39.6% of MCRC cancers from men were right sided. Among women, 45.6% presented with left-sided lesions, which include the descending colon, sigmoid, and rectal locations, whereas 54.2% of men presented with left-sided lesions (Table 1).

Gender, age, and MCRC. In the aggregate, there was little difference in OS between men and women. However, when age was accounted for, we found a significant divergence between the genders. OS for women <45 years old was 17 months, compared with 14 months for similarly aged men ($P < 0.0001$, log-rank test; Fig. 2). Conversely, OS for women >55 years old was 7 months, compared with 9 months for men ($P < 0.0001$, log-rank test; Fig. 2). These gender differences persisted when we evaluated for cancer-specific survival. Cancer-specific survival for women <45 years of age was greater than that for men (18 versus 16 months; $P < 0.0001$, log-rank test). Older men had poorer cancer-specific survival than women (11 versus 10 months; $P < 0.0001$, log-rank test). These findings were consistent across all ethnicities (data not shown).

Gender, age, and year of diagnosis. As expected, patients diagnosed with MCRC from 2000 to 2004 did significantly better than those diagnosed between 1988 and 1999 (Table 1). However, when we examined gender and age by year of diagnosis, the survival differences in the youngest age group became more pronounced. In those diagnosed from 2000 to 2004, women <45 years of age had an OS of 20 months, versus 15 months for men (Fig. 2). Among those diagnosed from 1988 to 1999, women <45 years of age had an OS of 15 months, versus 13 months for men. For patients above the age of 55 years, diagnosis did not affect survival in a clinically appreciable way.

Tumor location and MCRC. We also examined the relationships between tumor location, gender, ethnicity, and age. When age was considered, we found that older patients with MCRC,

both men and women, were more likely to have proximal cancers. Among those with MCRC at age <45 years, women had 39.6% proximal tumors and men 34.8%. Of those with MCRC at age 55 years and older, women had 49.1% proximal tumors and men 40.4%. As men and women aged, this "rightward shift" was consistent across all age groups (Table 2).

There are significant ethnic variations in tumor location as well. African Americans had the highest rate of proximal tumors (48.1%), followed by Whites (44.3%), Hispanics (37.7%), Native Americans (36.9%), and Asians (33.4%). Cancers of the rectum were most common in Native Americans (23.5%), then Hispanics (19.0%), Asians (18.1%), Whites (14.9%), and African Americans (11.5%).

Multivariate model. In multivariate analysis of cancer-specific survival, we adjusted for marital status, tumor site, treatment with radiation and/or surgery, and tumor differentiation, stratified by SEER registry site and year of diagnosis. We found that young (<45 years old) women have a lower risk of dying from MCRC than men (HR, 0.868; 95% CI, 0.789-0.955; Fig. 3, *top*). As women age, this risk reduction becomes more diminutive until the risk between men and women becomes equivalent (>55 years old; HR, 0.983; 95% CI, 0.96-1.01; *P* value for interaction = 0.011). When we accounted for year of diagnosis, we found that these differences have become more pronounced in recent years. For example, the HR of women ages <45 years has gone from 0.931 (95% CI, 0.821-1.056) for those diagnosed between 1988 and 1989 to 0.778 (95% CI, 0.669-0.904) for those diagnosed between 2000 and 2004 (Fig. 3, *bottom*). We also examined the HRs of men and women across all ethnicities and found no association between gender-specific survival and ethnicity (*P* value for interaction = 0.29).

Discussion

Our data suggests that sex, age, and ethnicity have a significant effect on OS in MCRC patients. This supports previous findings that as patients age, they have poorer survival, and that ethnicity significantly affects prognosis. We found in one of the largest cohorts of CRC patients analyzed that gender in combination with age has an important influence on OS and cancer-specific survival in patients with MCRC. We also note for the first time that the benefits among younger women are more pronounced in recent years, which may result from the interaction of hormonal status and treatment options recently available.

Menopause is commonly defined as 12 months of amenorrhea in women over the age of 45. Women typically reach menopause between 45 and 55 years of age, with an average age of 50.5 years (24). Only 5% of women become menopausal between 40 and 45 years of age, and another 5% occur after 55 years of age (25). Based on these data, we used the age of 45 as our proxy for a cohort of premenopausal women. This is consistent with reports and studies that have used age as a surrogate for menopause.

In our study, younger women (<45 years of age) have better OS than younger men. At 17 months, their OS was 20% higher than the male cohort and corresponded with a HR of 0.865 in our multivariate model. Yet this benefit did not extend to older women. Indeed, as women aged, their prognosis declined with respect to similarly aged men, and we found that women >55 years of age do even worse than older men (Fig. 2). These findings suggest that premenopausal women with MCRC may have an improved prognosis. As they age through menopause, they lose this advantage and their risk eventually becomes equivalent to men. Our findings are similar to those reported recently by Koo et al. (20), which described similar gender discrepancies in a prospective cohort of CRC patients of all stages.

These results are consistent across all ethnicities and not confounded by treatment with radiation and/or surgery or the site of disease. Access to care (26), treatment disparities (27), and sex-specific comorbidites (28) have often been associated with gender disparities in colorectal cancer survival, but are unlikely explanations for our findings. MCRC is uniformly treated with chemotherapy and perhaps less prone to treatment disparities that have been described in the adjuvant setting. In addition, we analyzed cancer-specific mortality to limit the effects of comorbidities that are not reported on the SEER database. Our analysis, after censoring patients whose cause of death was not attributed to their colorectal cancer, did not alter our findings. Cardiovascular disease was the cause of death in 2.92% of our patients and was not associated with the gender differences found (data not shown).

A possible explanation of these gender disparities in younger patients is forthcoming when we attempt to reconcile the more pronounced disparity among those diagnosed after 1999. Women <45 years of age, diagnosed from 2000 to 2004, had a 33% increase in OS when compared with those diagnosed

Table 2. Tumor location, gender, and age in MCRC, SEER data 1988-2004

Age, y	Male, *n* (%)						Female, *n* (%)					
	n	Proximal	Distal	Recto-Sigmoid	Rectum	NOS	*n*	Proximal	Distal	Recto-Sigmoid	Rectum	NOS
18-44	1,458	507 (34.8)	364 (25.0)	161 (11.0)	343 (23.5)	83 (5.7)	1,501	595 (39.6)	494 (32.9)	144 (9.6)	216 (14.4)	52 (3.5)
45-54	3,291	1,190 (39.2)	832 (25.3)	381 (11.6)	703 (21.4)	185 (5.6)	2,761	1,171 (42.4)	837 (30.3)	248 (9.0)	382 (13.8)	123 (4.5)
≥55	22,678	9,162 (40.4)	6,128 (27.0)	2,237 (9.9)	3,724 (16.4)	1,427 (6.3)	25,455	10,411 (49.1)	4,992 (23.6)	1,719 (8.1)	2,565 (12.1)	1,506 (7.1)
Total	27,427	10,859 (39.6)	7,324 (26.7)	2,779 (10.1)	4,770 (17.4)	1,695 (6.2)	25,455	12,177 (47.8)	6,323 (24.8)	2,111 (8.3)	3,163 (12.4)	1,681 (6.6)

Abbreviation: NOS, not otherwise specified; includes overlapping tumors.

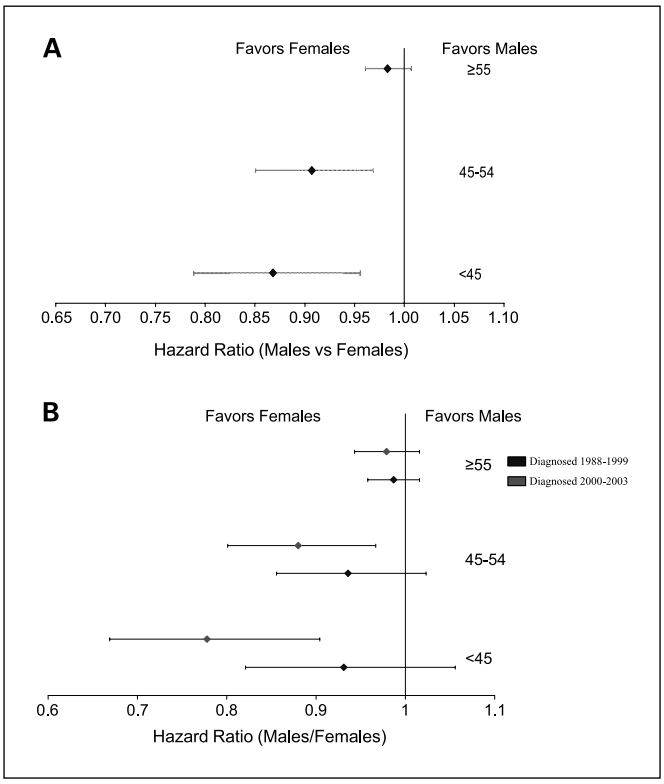

Fig. 3. Hazard ratio (females/males) of cancer-specific survival comparing females with males across age all groupings (*A*). *B*, a subgroup analysis by year of diagnosis. Cox proportional hazards models were developed to evaluate association between patient characteristics and survival in men and female separately. All multivariable models included year of diagnosis and registry as stratification variables and marital status, treatment, primary site, and tumor grade and differentiation as covariates.

from 1988 to 1999. Comparably aged men only had an increase in survival of 15%. Similar improvements based on year of diagnosis were absent from the older group, supporting recent reports of the underutilization of combination chemotherapy in elderly patients (29).

After decades of using 5-flurouracil alone in the metastatic setting, in 2000, irinotecan-based combination chemotherapy became the new first-line treatment for patients with MCRC (30). Over the next few years, oxaliplatin (31), bevacizumab (32), and cetuximab (33) were approved, and the OS of patients with MCRC improved considerably. Our findings suggest that younger women may benefit more from these current therapies than younger men. Whether this reflects a differential response or toxicity to modern chemotherapy or represents an emerging pattern is unclear. Regardless, these data support the growing notion that estrogen is an impediment to CRC development and progression.

Although the exact role of estrogen in CRC tumorigenesis is unclear, current investigations point to estrogen receptor β (ERβ) as the most likely mediator. As women age and their nascent levels of estrogen decline, the expression of ERβ is downregulated (34). Loss of ERβ is emerging as a common step in hormone-dependent tumor progression in several cancer models (35). In colon cancer, it has been shown that ERβ is selectively lost in malignant tissue (36), and ERβ knockout mice show increased proliferation and decreased differentiation and apoptosis of the colonic mucosa (37). Recent data have shown that functional polymorphisms in ERβ are associated with sex-specific survival in MCRC (38).

Estrogen may affect tumor biology and alter the effectiveness of screening and treatment. For example, one report has shown that loss of ERβ expression is associated with left-sided colon cancers and a more advanced presentation (39). Hormone status may also affect the underlying genetic underpinning of CRC cancer, predisposing one to chromosomal instability, microsatelllite instability (13, 40), or CpG island methylator phenotype (41).

Estrogen has also been shown to prevent carcinogenesis by down-regulating inflammation. In a mouse model of hepatocellular cancer, estrogen-mediated inhibition of interleukin-6 was shown to be protective for the development of hepatocellular carcinoma (42), perhaps explaining in part the gender disparities in hepatocellular carcinoma. The link between chronic inflammation and colon cancer has been shown by the increased rates of CRC in patients with chronic inflammatory bowel disease (43) and the risk reduction in those taking acetylsalicylic acid (44). Estrogen regulation of inflammatory cytokines may be a promising area of investigation in CRC.

Our study also confirmed reports that women (45) and the elderly (46) are more likely to have right-sided tumors. Gender differences in sidedness were not age dependent, and both men and women were more likely to develop proximal tumors as they aged. Furthermore, in our cohort, proximal tumors were a poorer prognostic marker than distal or rectal tumors across all ages and ethnicities. As such, sidedness does not explain the differences in survival between younger men and women.

We found that ethnicity significantly affects CRC survival. As previously reported (47, 48), African Americans and Native Americans had the worse survival among all ethnic groups. Notably, Whites had worse OS than Hispanics and Asian Americans. This may reflect differences in "western" and "eastern" diets (49), red-meat consumption (50), nonsteroidal anti-inflammatory drug use, amount of exercise (11), and other behaviors that have been shown to be associated with CRC incidence and recurrence. Additionally, environmental variations in estrogen exposure, either endogenous or exogenous, may contribute to these ethnic differences.

Our data were retrospective, and therefore this report is subject to errors that commonly arise from such analyses. Specifically, our proxy for hormone status was age, as the databases did not query menopausal status, history of hormone replacement therapy, or contraceptive use. The SEER database does not record chemotherapy use, and therefore this limited our ability to investigate its interaction with our findings.

As one of the largest data sets analyzed to establish that younger women with MCRC survive longer than younger men, hormonal status seems not only to play an important role in the development and pathogenesis of colorectal cancer but also to have prognostic significance. In CRC, estrogens have been shown to consistently improve clinical outcomes in women who take oral contraceptives or hormone replacement. Our report adds this body of evidence and warrants further studies to determine the role of age and estrogen in colorectal cancer development, growth, and progression.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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