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Differential Effects of Wine Consumption on Colorectal Cancer Outcomes Based on Family History of the Disease

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Abstract: *Potentially favorable effects of wine consumption on colorectal cancer (CRC) incidence have been reported, but effects on clinical outcomes are unknown. This case-only analysis was designed to investigate outcomes among familial (n = 141) and sporadic (n = 358) CRC patients enrolled in the University of California Irvine CRC gene-environment study during 1994–1996 based on their reported frequency of wine consumption in the year prior to diagnosis. Cases were categorized as either regular or infrequent wine consumers. Univariate survival rate analyses were estimated using the Kaplan and Meier method and log-rank test. Multivariate survival analyses were performed using Cox proportional hazards ratios (HRs). Earlier stage at presentation (P = 0.034) was noted for familial (but not sporadic) CRC cases reporting regular wine consumption. An overall survival (OS) benefit was observed for familial (but not sporadic) CRC cases that were regular (10-yr OS = 75%) versus infrequent wine consumers (10-yr OS = 47%; P = 0.002). This survival improvement for familial CRC cases remained after adjustment for age, stage, treatment, and other clinically relevant factors (HR = 0.50, 95% confidence interval = 0.25–0.99). Our findings implicate favorable effects of wine consumption on stage at presentation and survival in CRC, selectively among familial CRC cases.*

Introduction

Alcohol consumption has been associated with an increased risk of developing colorectal cancer (CRC). One large meta-analysis reported an increased relative risk of 1.1 for developing CRC when consuming more than 2 alcoholic beverages per day (1). Other studies, including a large pooled analysis (2) and meta-analysis (3), have shown a similar modest risk of developing CRC associated with alcohol consumption at approximately 2 drinks per day and higher risk associated with higher quantities of alcohol consumption. The specific type of alcoholic beverage consumed in the aforementioned studies was not associated with CRC risk. Total alcohol consumption has been shown to increase the risk of developing CRC in familial cases through an interaction with family history by several investigators, but the effects of wine have not been assessed (4–6). Controversy over this issue remains, as it has been reported that the risk of developing CRC may depend on the type of alcoholic beverage consumed. Beer intake has been shown to have a strong association with CRC in several studies (7–9). Interestingly, in a large population-based cohort study analyzing 28,000 individuals, alcohol intake was associated with an increased risk of rectal cancer; however, this risk was diminished in alcohol drinkers who consumed at least some wine versus those who did not drink any wine at all (10). In the same study, wine intake was associated with a nonsignificant trend toward decreased risk of developing colon cancer ($P = 0.07$) (10).

Moderate wine consumption has been associated with decreased risk of total mortality, an effect attributed to decreased risk of death from cardiovascular causes and protection from cancer and other causes (11). Light to moderate wine drinkers have been observed to have a lower risk for death from cancer than those who did not drink wine—an effect not observed for consumers of beer and spirits (12). In a large U.S. mortality study, alcohol was noted to have a trend toward decreased CRC-specific mortality among women ($P = 0.06$)—particularly at light consumption levels (i.e., daily use or less than 1 drink per day) (13).

Familial CRC is characterized by multifactorial inherited susceptibility to CRC and represents approximately 20% of CRC cases; another approximately 79% are considered to be sporadic cases. Based on evidence that there is a decreased

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risk of developing CRC for wine drinkers, that a decreased cancer-related mortality is associated with wine consumption, and that light to moderate alcohol use among female CRC cases results in a trend toward decreased mortality, we set out to determine if wine consumption was associated with favorable effects on tumor characteristics or survival among CRC cases.

Materials and Methods

Using data from the University of California (UC) Irvine CRC gene-environment study (14), incident cases of invasive colorectal carcinoma during the period 1994–1996 were analyzed. Family history of cancer was ascertained via telephone interview. Familial CRC cases were identified as those having at least 1 first-degree relative (parent, sibling, or offspring) with CRC. Amsterdam criteria were used to define hereditary nonpolyposis colon cancer (HNPCC) families (15). HNPCC cases and 1 case with clinically diagnosed Familial Adenomatous Polyposis were excluded from the analysis (14). The remaining sporadic and familial CRC cases were included for analysis by wine consumption frequency group. Food consumption was self-reported via a validated 100-item National Cancer Institute (NCI)-Block food-frequency questionnaire (FFQ) in which cases were asked to report their usual eating habits during the 1 yr prior to diagnosis of CRC (16,17). Frequency of wine (1 glass), beer (one 12-ounce can or bottle), and liquor (1 shot) consumption was recorded, and available responses ranged from "never" to "6+" servings a day. Total daily energy intake, total daily fiber intake, total daily dietary calcium intake, vegetable and fruit consumption, and body mass index (BMI) were analyzed from FFQ data using the NCI-Block Analysis Program (HHQ-DietSys, 1993), version 4.0, as previously reported (18). All cases were dichotomized as either *infrequent* wine consumers (i.e., "never" or consumption of less than 1 glass of wine per month) or *regular* wine consumers (i.e., consumption of at least 1–3 glasses of wine per month). In the same manner, cases were classified as regular or infrequent consumers of beer and liquor.

Clinical and demographic data from consented cases were obtained from the Cancer Surveillance Programs of Orange County, Imperial County, and San Diego County, California (CSPOC/SANDIOCC databases) as described previously (14). Recorded data included demographic information (age, gender, ethnicity), histology, tumor grade, stage at presentation, and survival status. Therapeutic information related to the first course of treatment was obtained including surgical treatment rendered at the primary site, treatment with radiation therapy, and use of chemotherapy. Data were abstracted from medical and laboratory records by trained tumor registrars according to *Cancer Reporting in California: Vol. 1. Abstracting and Coding Procedures for Hospitals* (19). Tumor site and histology were coded according to criteria specified by the World Health Organization in *International Classification of Diseases for Oncology* (20). Primary site code was searched as described previously (18) using the Surveillance, Epidemiology, and End Results (SEER) site code for colon (21041, 21043–21048) and rectum (21051–21052). Appendiceal cancers were excluded. Histology codes included adenocarcinoma (8140, 8144, 8210, 8260–8263, 8380, 8490), mucinous adenocarcinoma (8470, 8480, 8481), carcinoma (8010, 8020, 8070, 8071, 8124, 8240), and not otherwise specified (8000, 8041, 8042, 8120, 8130, 8243, 8246, 8560, 8570, 8722). Only invasive cases of cancer were included in the analysis. Staging was grouped into 3 broad categories that could be classified from clinical and pathologic records and defined according to SEER summary staging as localized disease, regional disease, and remote disease (localized or regional disease with distant metastases). Socioeconomic status (SES) quintiles were obtained from the SES variable available in the California Cancer Registry as described previously (21). This index variable utilized for SES includes a combination of 7 indicator variables for census block data including assessments of educational status, income, and housing information (21).

Follow-Up

Cause of death was recorded according to the *International Classification of Diseases* criteria in effect at the time of death (22). Hospital registrars contacted cases annually, and CSPOC/SANDIOCC staff annually reviewed state death certificates to identify deceased registry cases. Follow-up data through December 2003 were available for analysis. The last date of follow-up was either the date of death or the last date the patient was contacted.

Statistical Analysis

The sample was acquired based on reported family history of CRC; thus, all analyses were performed as stratified by family history. Comparisons of demographic, clinical, and pathologic variables between cases with various categories were performed using Pearson χ^2 statistic or Fisher's exact test for nominal variables and Student t-test for continuous variables. Univariate survival rate analyses were estimated using the Kaplan and Meier method, with comparisons made between groups by the log-rank test. Cox proportional hazards modeling using time since diagnosis were performed. Each variable in the model was coded using dummy variables. All statistical analyses were conducted using SAS version 9.1 statistical software (SAS Institute, Cary, NC). Statistical significance was assumed for a 2-tailed P value less than 0.05.

Ethical Considerations

Probands signed a consent form allowing for release of medical information including pathology reports, tissue blocks, and linkage to the aforementioned cancer surveillance programs. This study has been approved by the UC Irvine Institutional Review Board (No. 1993–257).

Table 1. Descriptive Comparisons for Colorectal Cancer (CRC) Cases in the University of California Irvine Colorectal Cancer Gene Environment Study, 1994–1996 ($n = 1{,}235$)[a]

	Familial CRC ($n = 228$)	Sporadic CRC ($n = 1{,}007$)
Median age, yr (95% CI)	65 (46–82)	63 (40–84)
Gender		
Male	119 (52%)	536 (53%)
Female	109 (48%)	471 (47%)
Ethnicity		
Caucasian	202 (89%)	845 (84%)
African-American	2 (1%)	15 (1%)
Hispanic	14 (6%)	82 (8%)
Asian	9 (4%)	60 (6%)
Other	1 (<1%)	5 (<1%)
Stage at diagnosis		
Local	112 (50%)	413 (42%)
Regional	76 (34%)	421 (43%)
Remote	36 (16%)	156 (16%)
Colon site		
Proximal and transverse	99 (43%)	363 (36%)
Descending	12 (5%)	37 (4%)
Sigmoid	54 (24%)	256 (25%)
Rectosigmoid	29 (13%)	116 (12%)
Rectum	33 (14%)	212 (21%)
Large intestine NOS	1 (<1%)	23 (2%)
Histologic subtype Adenocarcinoma	201 (88%)	887 (89%)
Mucinous adenocarcinoma	18 (8%)	78 (8%)
Carcinoma	8 (4%)	26 (3%)
NOS	1 (<1%)	10 (1%)
Tumor grade		
1	39 (18%)	136 (15%)
2	136 (64%)	629 (68%)
3	35 (17%)	163 (18%)
4	1 (<1%)	2 (<1%)
First course of treatment		
Surgery	218/228 (96%)	910/1,003 (91%)
Radiation therapy	26/228 (11%)	134/1,004 (13%)
Chemotherapy	79/215 (37%)	424/957 (44%)

a: Abbreviations are as follows: CI, confidence interval; NOS, not otherwise specified.

Results

CRC Gene-Environment Study Population Characteristics

Using available family history data, 228 familial CRC cases (18%) and 1,007 sporadic CRC cases (82%) were identified among the 1,235 cases in the parent study. Clinicopathologic comparisons for familial and sporadic CRC cases are presented in Table 1. The familial and sporadic CRC cases were similar in age, gender distribution, and ethnicity (predominantly White). A greater proportion of cases with local stage at presentation was noted for familial CRC cases compared to sporadic CRC cases. Adenocarcinoma was the major histologic type for both categories of CRC cases in this study. The proportion of cases treated during the first course of therapy with surgery, radiation therapy, or chemotherapy was similar for familial and sporadic CRC cases.

Univariate survival analysis for all CRC cases was performed (Fig. 1). Overall survival (OS) for familial CRC cases [median OS = 128 mo, 95% confidence interval (CI) 112-upper limit not reached; 10-yr OS = 54%] was not statistically different than OS for sporadic CRC cases (median OS = 113 mo, 95% CI = 95–130; 10-yr OS = 48%; $P = 0.18$).

Clinicopathologic Variables

Of the 1,235 CRC cases enrolled in the UC Irvine CRC gene-environment study, 518 completed a dietary FFQ. Recorded data related to wine consumption frequency were available for 499 of these 518 cases including 141 familial CRC cases and 358 sporadic CRC cases. Median time from diagnosis to interview/completion of the FFQ was similar for sporadic (24.0 mo) and familial CRC cases (23.6 mo; $P = 0.67$). Clinical comparisons for familial and sporadic

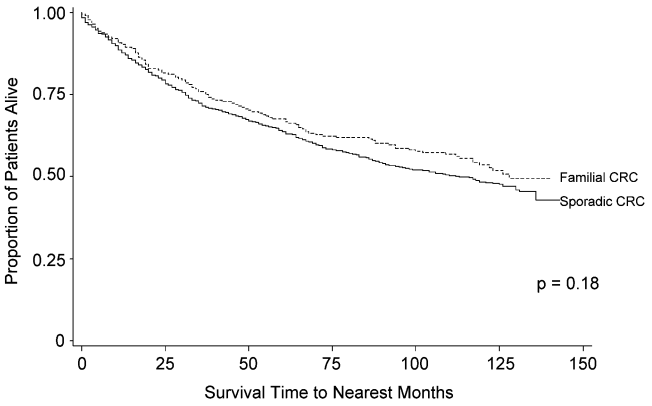

Figure 1. Overall survival among all colorectal cancer (CRC) cases in the University of California Irvine CRC gene-environment study: dashed line, familial CRC cases ($n = 228$); solid line, sporadic CRC cases ($n = 1{,}007$).

CRC cases are presented in Table 2. Sporadic CRC cases filling out the FFQ (Table 2) were younger than sporadic cases from the larger parent study (Table 1) and also had slightly advanced stage distribution and more frequent use of chemotherapy. Median age at diagnosis was significantly greater for familial CRC cases (64 yr, 95% CIs = 46–80) compared to sporadic CRC cases (57 yr, 95% CI = 36–69; $P < 0.0001$). Borderline significant differences in stage at presentation were noted for the 2 groups (favoring earlier stage at presentation for familial CRC cases; $P = 0.050$). Statistically significant baseline differences were detected in the proportion of cases within each SES quintile between familial and sporadic CRC cases. Differences were also noted for site of tumor location at diagnosis between familial and sporadic CRC cases ($P = 0.003$), favoring a greater proportion of proximal (i.e., right-sided) tumors among familial CRC cases. The 2 groups were similar by ethnic distribution, histologic distribution, grade of tumor at presentation, and the proportion receiving surgery or radiation therapy. Fewer familial CRC cases received chemotherapy than sporadic CRC cases; however, this was explained by the baseline differences in stage at presentation. As expected, treatment with chemotherapy was strongly associated with increased stage at presentation: Recorded use of chemotherapy was 16%, 69%, and 81% among local, regional, and remote stage cases, respectively ($P < 0.0001$). A similar proportion of cases were regular wine consumers or liquor consumers among familial and sporadic CRC cases. A greater proportion of sporadic CRC cases were beer consumers, which approached statistical significance ($P = 0.06$). Overall, 207 cases (41%) reported regular wine consumption in this study and 292 cases (59%) reported infrequent wine consumption. The majority of the 207 regular wine consumers reported consumption of 1 to 6 glasses of wine per week ($n = 105$, or 51%), 63 (30%) reported consumption of less than 1 glass of wine per week, and 39 (19%) reported consumption of at least 1 glass of wine daily.

Comparisons of familial and sporadic CRC cases by wine consumption frequency group are presented in Table 3. Familial CRC cases reporting regular wine consumption had earlier stage at presentation (63% local, 27% regional, 11% remote) compared to cases reporting infrequent wine consumption (41% local, 46% regional, 14% remote; $P = 0.034$). No differences in stage at presentation were noted for the sporadic CRC cases based on wine consumption group ($P = 0.90$). Among familial and sporadic CRC cases, regular wine consumers were similar to infrequent wine users according to age, gender, tumor grade, and proportion of cases treated with surgery or radiation therapy during the first course of treatment. Fewer familial CRC cases reporting regular wine use received chemotherapy, which was not observed for sporadic cases. This effect was believed to be stage related, as the use of chemotherapy was strongly associated with increased stage among familial CRC cases ($P < 0.0001$). Among familial CRC cases, a greater proportion of wine consumers were in the highest SES quintile; however, overall, the distribution of SES was not statistically different for regular versus infrequent wine consumers. Among sporadic CRC cases, the association between wine consumption and higher SES was statistically significant ($P = 0.0007$; Table 3). Stage at presentation was not associated with SES as a dichotomized variable (i.e., SES-hi vs. SES-low) among familial or sporadic CRC cases. Among familial CRC cases in the SES-hi category were $n = 37$ (51%) localized stage, $n = 25$ (34%) regional stage, and $n = 10$ (14%) remote stage cases compared with $n = 32$ (48%) localized, $n = 27$ (41%) regional, and $n = 7$ (11%) remote stage cases in the SES-low category ($P = 0.70$). Among sporadic CRC cases in the SES-hi category were $n = 68$ (39%) localized stage, $n = 86$ (49%) regional stage, and $n = 20$ (12%) remote stage cases compared with $n = 66$ (37%) localized, $n = 82$ (46%) regional, and $n = 31$ (17%) remote stage cases in the SES-low category ($P = 0.30$). Descriptive analysis of dietary data reveals that among familial and sporadic CRC cases, regular wine consumers were similar to infrequent wine consumers according to total energy intake, fiber intake, calcium intake, weekly fruit consumption, and weekly vegetable consumption. Borderline differences in BMI were noted for ($P = 0.055$) regular wine consumers [25.0 kg/m^2 $\pm$ 0.5 standard error (SE)] compared to infrequent wine consumers (26.5 kg/m^2 $\pm$ 0.6 SE) among familial CRC cases.

OS Analyses

The OS effects of wine consumption differed between familial and sporadic CRC cases. Among familial CRC cases, cases reporting regular wine consumption ($n = 59$) had improved survival (10-yr OS = 75%) compared to the infrequent wine consumption group ($n = 82$; 10-yr OS = 47%; $P = 0.002$). Because wine consumption was associated with stage at presentation among familial cases, further stratified analysis of OS by stage at presentation was performed to assess the stage-specific effects of wine consumption. Local staged familial CRC cases reporting regular wine consumption were noted to have improved OS ($n = 37$; 10-yr OS = 85%) compared to those reporting infrequent wine

Table 2. Descriptive Comparisons for Familial and Sporadic CRC Cases Included in the Wine Consumption Analysis, 1994–1996 ($N = 499$)[a]

	Familial CRC ($n = 141$)	Sporadic CRC ($n = 358$)	P
Median age, yr (95% CI)	64 (46–80)	57 (36–69)	<0.0001
Gender			
Male	72 (51%)	188 (53%)	0.77
Female	69 (49%)	170 (47%)	
Ethnicity			
White	128 (91%)	300 (84%)	0.13
African-American	0 (0%)	2 (<1%)	
Hispanic	9 (6%)	28 (8%)	
Asian	3 (2%)	27 (8%)	
Other	1 (1%)	1 (<1%)	
Stage at diagnosis			
Local	69 (50%)	134 (38%)	0.050
Regional	52 (38%)	168 (48%)	
Remote	17 (12%)	51 (14%)	
Colon site			
Proximal and transverse	61 (43%)	103 (29%)	0.003
Descending	8 (6%)	14 (4%)	
Sigmoid	29 (21%)	101 (28%)	
Rectosigmoid	22 (16%)	44 (12%)	
Rectum	21 (15%)	86 (24%)	
NOS	0 (0%)	10 (3%)	
Histologic subtype			
Adenocarcinoma	126 (89%)	327 (91%)	0.33
Mucinous adenocarcinoma	10 (7%)	18 (5%)	
Carcinoma	5 (4%)	8 (2%)	
NOS	0 (0%)	5 (1%)	
Tumor grade			
1	25 (19%)	41 (13%)	0.27
2	85 (66%)	230 (70%)	
3	19 (15%)	55 (17%)	
4	0 (0%)	1 (<1%)	
SES[b]			
Quintile 1 (lowest)	2 (1%)	16 (5%)	0.015
Quintile 2	20 (14 %)	24 (7%)	
Quintile 3	21 (15 %)	58 (16%)	
Quintile 4	26 (18 %)	95 (27%)	
Quintile 5 (highest)	72 (51 %)	165 (46%)	
First course of treatment			
Surgery	133/141 (94%)	330/357 (92%)	0.46
Radiation therapy	16/141 (11%)	59/357 (17%)	0.15
Chemotherapy	49/135 (36%)	179/341 (52%)	0.001
Beer consumption			
Infrequent[2]	103 (73%)	228 (64%)	0.06
Regular	38 (27%)	127 (36%)	
Liquor consumption			
Infrequent[2]	104 (74%)	253 (71%)	0.58
Regular	37 (26%)	102 (29%)	
Wine consumption			
Infrequent[c]	82 (58%)	210 (59%)	0.92
Regular	59 (42%)	148 (41%)	

a: Abbreviations are as follows: CRC, colorectal cancer; CI, confidence interval; NOS, not otherwise specified; SES, socioeconomic status.
b: By quintile rank among California residents.
c: Never or <1 small alcoholic beverage per month.

Table 3. Comparisons of Familial and Sporadic CRC Cases by Wine Consumption Frequency Group[a]

	Familial CRC Patients			Sporadic CRC Patients		
	Regular Wine Use ($n = 59$)	Infrequent Wine Use ($n = 82$)[c]	P	Regular Wine Use ($n = 148$)	Infrequent Wine Use ($n = 210$)[c]	P
Age, yr	63 ± 1.5	65 ± 1.3	0.32	55 ± 0.8	56 ± 0.7	0.34
Gender						
Male	28 (47%)	45 (55%)	0.38	77 (52%)	111 (53%)	0.88
Female	31 (53%)	37 (45%)		71 (48%)	99 (47%)	
Stage						
Local	37 (63%)	32 (41%)	0.034	54 (37%)	80 (38%)	0.90
Regional	16 (27%)	36 (46%)		71 (49%)	97 (47%)	
Remote	6 (11%)	11 (14%)		20 (14%)	31 (15%)	
Tumor grade						
1	12 (23%)	13 (17%)	0.54	14 (11%)	27 (14%)	0.66
2	32 (60%)	53 (70%)		96 (73%)	134 (68%)	
3	9 (17%)	10 (13%)		21 (16%)	34 (17%)	
4	0 (0%)	0 (0%)		0 (0%)	1 (1%)	
SES[b] quintile (Q)						
Q1 (lowest)	0 (0%)	2 (2%)	0.19	1 (1%)	15 (7%)	0.0007
Q2	7 (12%)	13 (16%)		4 (3%)	20 (10%)	
Q3	5 (9%)	16 (20%)		22 (15%)	36 (17%)	
Q4	12 (20%)	14 (17%)		39 (26%)	56 (27%)	
Q5 (highest)	35 (59%)	37 (45%)		82 (55%)	83 (40%)	
Surgical treatment	57/59 (97%)	76/82 (93%)	0.32	138/147 (94%)	192/210 (91%)	0.39
Radiation therapy	6/59 (10%)	10/82 (12%)	0.71	21/147 (14%)	38/210 (18%)	0.34
Chemotherapy	15/57 (26%)	34/78 (44%)	0.039	69/140 (49%)	110/201(55%)	0.32
Body mass index (kg/m^2)	25.0 ± 0.5	26.5 ± 0.6	0.055	26.0 ± 0.4	26.6 ± 0.4	0.28
Daily energy intake (kcal/day)	1503 ± 91	1495 ± 103	0.95	1750 ± 75	1681 ± 66	0.50
Daily fiber intake (g/day)	12.0 ± 0.7	11.7 ± 0.8	0.74	12.5 ± 0.5	12.2 ± 0.5	0.72
Dietary calcium intake (mg/day)	692 ± 48	734 ± 87	0.67	701 ± 34	720 ± 39	0.71
Weekly fruit consumption (servings/week)	18.5 ± 1.4	18.0 ± 1.5	0.80	16.4 ± 0.8	16.6 ± 0.9	0.87
Weekly vegetable consumption (servings/week)	23.0 ± 1.6	20.7 ± 1.3	0.27	21.5 ± 0.8	22.3 ± 0.9	0.49
Beer consumption						
Infrequent[c]	31 (53%)	72 (88%)	<0.0001	67 (45%)	161 (78%)	<0.0001
Regular	28 (47%)	10 (12%)		81 (55%)	46 (22%)	
Liquor consumption						
Infrequent[c]	33 (56%)	71 (87%)	<0.0001	77 (53%)	176 (84%)	<0.0001
Regular	26 (44%)	11 (13%)		69 (47%)	33 (16%)	

a: Abbreviations are as follows: CRC, colorectal cancer; SES, socioeconomic status.
b: By quintile rank among California residents.
c: Never or <1 small alcoholic beverage per month.

consumption($n = 32$; 10-yr OS = 61%; $P = 0.014$; Fig. 2). Differences in OS were not statistically significant for regional stage familial CRC cases reporting regular wine consumption ($n = 16$; 10-yr OS = 75%) compared to those reporting infrequent wine consumption ($n = 36$; 10-yr OS = 48%; $P = 0.26$) or for remote stage familial CRC cases reporting regular ($n = 6$; 10-yr OS = 17%) versus infrequent wine consumption ($n = 11$; 10-yr OS = 18%; $P = 0.71$); however, these exploratory analyses are limited by small sample size.

Among sporadic CRC cases, no statistically significant OS differences were detected between regular wine consumers ($n = 148$; 10-yr OS = 65%) and infrequent wine consumers ($n = 210$; 10-yr OS = 59%; $P = 0.28$), and there were no OS differences for local ($P = 0.23$), regional ($P = 0.76$), or remote ($P = 0.35$) stage sporadic CRC cases based on wine consumption frequency.

Multivariate Survival Analyses

Variables known to predict survival in CRC were included into the multivariate survival model including age, gender, stage at presentation, surgical treatment rendered at the primary site, radiation therapy, and chemotherapy. Total daily energy intake, total daily fiber intake, total daily dietary calcium intake, weekly fruit consumption, and weekly vegetable consumption were initially added to the multivariate

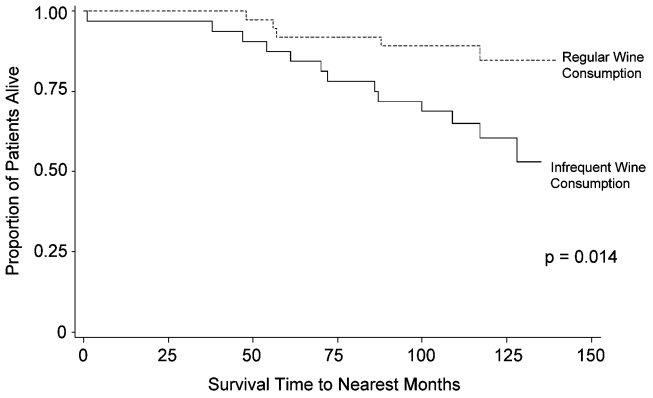

Figure 2. Familial colorectal cancer cases with local stage at presentation: overall survival by wine consumption group. Dashed line indicates regular wine consumers [$n = 37$; 10-yr overall survival (OS) = 85%]; solid line indicates infrequent wine consumers (n = 32; 10-yr OS = 61%).

model; however, none of these covariates were associated with survival (data not shown), and they were subsequently removed from the analysis. Because wine consumption was associated with SES in sporadic CRC cases and a similar, nonsignificant trend was noted for familial CRC cases (Table 3), SES was included into the multivariate model. BMI was included in the model because borderline differences in BMI were noted among familial CRC cases based on wine consumption frequency on univariate analysis (Table 3). Regular wine consumption was independently associated with improved survival among familial CRC cases after adjustment for age, gender, stage at presentation, SES, BMI, beer consumption, liquor consumption, surgical treatment, radiation therapy, and chemotherapy [hazards ratio (HR) for regular wine consumers compared to infrequent wine consumers = 0.50, 95% CI = 0.25–0.99; $P = 0.046$; Table 4). Regular beer consumption (HR = 1.07 vs. infrequent beer consumption; $P = 0.87$) and regular liquor consumption (HR = 1.13 vs. infrequent liquor consumption; $P = 0.73$) were not significantly associated with survival in this model.

In contrast, among sporadic CRC cases, there was no independent association with survival for regular wine consumers noted in the adjusted analysis (HR for regular wine consumers vs. infrequent wine consumers = 0.89, 95% CI = 0.59–1.33; $P = 0.56$; Table 4). Among the familial and sporadic CRC cases, young age (familial CRC: HR = 1.06, 95% CI = 1.03–1.09; sporadic CRC: HR = 1.02, 95% CI = 1.00–1.04), early stage at presentation (Table 4), and surgical treatment (familial CRC: HR = 0.20, 95% CI = 0.07–0.53; sporadic CRC: HR = 0.54, 95% CI = 0.30–0.97) were independently associated with improved OS. Male gender (familial CRC: HR = 1.16, 95% CI = 0.62–2.18; sporadic CRC: HR = 1.36, 95% CI = 0.92–2.01), SES (Table 4), and BMI (Table 4) were not associated with OS for familial or sporadic CRC cases. When wine consumption was added separately into the model for familial CRC cases (without beer or liquor consumption as covariates), a statistically significant improvement in OS was noted (HR = 0.53, 95% CI = 0.28–0.98, $P = 0.044$) after adjustment for age, gender, stage, SES, BMI, surgical treatment, radiation therapy, and chemotherapy. When beer and then liquor consumption were substituted into this model to replace wine consumption, neither regular beer consumption (HR = 0.83, 95% CI = 0.41–1.67, $P = 0.59$) nor regular liquor consumption (HR = 0.87, 95% CI = 0.46–1.65, $P = 0.67$) were associated with survival compared to infrequent consumption of the respective beverages.

Subset analysis among familial CRC cases revealed that among the 98 colon cancer cases, regular wine consumption was not associated with a statistically significant improvement in OS after adjustment for age, gender, stage at presentation, SES, BMI, beer consumption, liquor consumption, and treatment variables (HR = 0.50, 95% CI = 0.22–1.12 vs. infrequent wine consumers; $P = 0.09$). No statistically significant differences were noted for the 42 familial rectal cancer cases based on wine consumption group (HR = 0.67, 95% CI = 0.07–6.17 vs. infrequent wine consumers; $P = 0.72$). However, it should be noted that interpretation of these subset analyses are limited due to small sample size.

Cause of Death

Out of the 199 total deaths occurring in the wine consumption study, the specific cause of death was confirmed in 106 cases including 29 familial CRC cases and 77 sporadic CRC cases. Overall, 95 of the recorded deaths (90%) were due to CRC; 3 deaths due to cardiovascular disease occurred. Among familial CRC cases, 25 out of 29 (i.e., 86%) deaths were due to CRC compared to 70 out of 77 deaths (i.e., 91%) observed for sporadic cases ($P = 0.48$).

Discussion

In this observational study, earlier stage at presentation and improved OS were noted for familial CRC cases who were regular wine consumers prior to the time of diagnosis compared to those that were infrequent wine users. The observed survival benefit persisted after adjustment for age, gender, stage at presentation, SES, BMI, treatment status, and consumption of beer and liquor. In contrast, among sporadic CRC cases, no differences in stage at presentation or survival were noted for regular versus infrequent wine consumers. The observed survival differences based on reported wine consumption were not detected for beer or liquor consumption. Greater than $\frac{1}{2}$ of the regular wine consumers in this study were moderate wine consumers (i.e., consuming the equivalent of 1 glass of wine, 1 to 6 times per week).

Familial CRC cases reporting regular wine consumption were noted to have earlier stage at presentation, and the major OS benefit from regular wine consumption was observed for local stage cases (Fig. 2). However, this survival

Table 4. Adjusted Survival Analysis Using Cox Proportional Hazards Model[a]

	Familial CRC (n = 141, Deaths = 59)			Sporadic CRC Patients (n = 358, Deaths = 134)		
	HR	95% HR Confidence Limits	*P*	HR	95% HR Confidence Limits	*P*
Stage						
Local	1.00	—	—	1.00	—	—
Regional	1.38	(0.70–2.70)	0.65	1.88	(1.13–3.13)	0.015
Remote	7.89	(3.43–18.12)	<0.0001	13.60	(7.4–25.17)	<0.0001
SES Quintile (Q1–Q5)						
	1.01	(0.79–1.30)	0.91	0.95	(0.81–1.12)	0.53
Body mass index (kg/m2)	1.01	(0.94–1.08)	0.83	0.96	(0.93–0.99)	0.035
Beer consumption						
Infrequent	1.00	—	—	1.00	—	—
Regular	1.07	(0.50–2.29)	0.87	1.01	(0.65–1.57)	0.97
Liquor consumption						
Infrequent	1.00	—	—	1.00	—	—
Regular	1.13	(0.56–2.29)	0.73	0.79	(0.51–1.24)	0.31
Wine consumption						
Infrequent	1.00	—	—	1.00	—	—
Regular	0.50	(0.25–0.99)	0.046	0.89	(0.59–1.33)	0.56

a: Model includes adjustment for age, gender, treatment with surgery, radiation, and chemotherapy. Abbreviations are as follows: CRC, colorectal cancer; HR, hazards ratio; SES, socioeconomic status.

improvement for regular wine consumption among familial CRC cases was independent of stage, age, and other clinical variables in an adjusted analysis as shown in Table 4. Local and regional stage CRC patients represent those with potentially curable disease after surgical resection and (in specific cases with high-risk features or regional disease) adjuvant chemotherapy. The cause of death analysis reveals that most CRC cases died from their cancer among familial (86%) and sporadic (91%) CRC cases. Thus, any protective benefit of wine consumption among familial CRC cases is not likely to be due to a specific decreased mortality risk from death by other causes when compared to sporadic CRC cases. It is not known whether the cases in our study continued with the same wine consumption habits after their diagnosis compared to before diagnosis, which remains a limitation of this study. Nonetheless, potentially operative gene-environment survival effects among wine-consuming early stage, familial CRC cases could be investigated further.

Among the numerous compounds found in wine, resveratrol and anthocyanin have been reported to have anticancer activity in vitro. Experimental studies suggest that resveratrol, a naturally occurring compound found in grape skin and wine (also found in peanuts and berries), has been shown to inhibit tumor initiation, promotion, and progression (23) and is reported to have antiproliferative effects in colon cancer cells (24,25) and in experimental murine models (26). Several mechanisms of action have been proposed for the antitumorigenic effects of resveratrol including inhibition of polyamine synthesis, cyclooxegenase inhibition, and inhibition of NF-kappa-B signaling, among others. Abnormalities in the control of polyamine metabolism result in increased polyamine levels that can promote tumorigenesis (27). Resveratrol has been shown to inhibit ornithine decarboxylase (ODC) (24), which is the rate-limiting step in polyamine biosynthesis (28). The polyamine catabolic enzyme spermine spermidine acetyltranferase (SSAT) is upregulated by resveratrol in colon cancer cell lines (29), promoting polyamine efflux. Thus, resveratrol, through its interactions with ODC and SSAT, affects both the biosynthetic and catabolic pathways involved in polyamine regulation to decrease polyamine levels. Resveratrol was reported to inhibit cyclooxegenase-1 and tumor initiation (23). Additionally, resveratrol has been shown to inhibit cyclooxygenase-2 (30) and I-kappa-B, thereby inhibiting NF-kappa-B dependent signaling (31,32). Preliminary data from our laboratory indicate that resveratrol downregulates signaling through the Wnt pathway (33), a pathway that is activated in over 85% of CRC cases (34). Recently, it was demonstrated that resveratrol improves health and survival in obese mice that had been fed a high-caloric diet—although the amounts of resveratrol used in that study were far beyond what could be obtained through wine consumption in humans (35). The flavonoid extract anthocyanin from red wine showed a suppressive effect on human colon and gastric cancer cells in vitro (36). White wine was not found to have anthocyanins, and yet the nonanthocyanic extractions from red wine and white wine still suppressed cell growth in the aforementioned study but at a reduced rate compared to anthocyanin (36). Phenolic acid and anthocyanin extracts from certain blueberries (37) and grapes (38) have been shown to inhibit viability of colon cancer cells, with increased apoptosis noted after anthocyanin treatment. Thus, a variety of compounds in wine may contribute to the observed survival benefit noted in our study through effects on multiple signaling pathways.

The observed survival differences for familial CRC cases in our study may reflect other unique differences between

regular wine consumers and infrequent wine users. Many of these factors are not accounted for via statistical modeling or adjustment. For example, Johansen et al. (39) conducted a cross-sectional study of dietary habits among wine drinkers and beer drinkers and found that people who purchase wine at grocery stores in Denmark also have a healthier selection of other foods. Wine buyers purchased more olives, chicken, fruits, vegetables, milk, and meat than beer buyers in that study. People buying beer purchased more ready-cooked dishes, sugar, chips, and sausages than wine buyers. Although dietary fiber, total daily energy intake, fruit and vegetable consumption, and BMI were not associated with survival in this study, it should be recognized that other dietary factors, lifestyle factors, or habits may contribute to the observed survival effects of wine consumption among familial CRC cases. Importantly, wine consumption has been associated with higher SES compared to beer drinkers (40), but SES was not a major determinant of survival in our epidemiologic study. This is consistent with other studies on CRC cases that have shown no effect of SES on survival (41). In contrast, higher SES has been associated with a higher incidence of breast cancer (21), among others, and has been associated with improved survival in aggregate data for all U.S. cancer patients (42). High SES is generally associated with improved access to care and insurance coverage—factors that affect screening practices and thus stage at presentation. In our study, there was an association with wine consumption and SES; however, there was not a statistically significant association with SES and stage at presentation among familial or sporadic CRC cases. Larger epidemiologic studies are needed to investigate SES as a potential confounder of the effects of wine consumption on stage at diagnosis among familial CRC cases.

It is important to note that the proportion of cases reporting regular wine consumption in this study is low compared to what has been reported in other major studies on alcohol consumption and mortality (11,43,44) or risk of CRC (10). Even among the regular wine consumers in this study, reported consumption appeared quite moderate (only 19% of the regular wine consumers reported drinking wine daily or more). This may reflect population differences between otherwise "healthy" cohort study subjects and our population, which was comprised purely of CRC cases.

This epidemiologic study provides important hypothesis-generating results related to wine consumption among familial CRC cases. Some of the genes and gene variants involved in multifactorial inherited susceptibility to colorectal adenomas have now been described (45). However, currently, there is an incomplete understanding of the genes involved, and even less is known about how these genes interact with environmental exposures to affect survival. Notwithstanding available investigations of wine consumption on CRC incidence, this study represents the first large, population-based study addressing outcomes for CRC patients based on reported wine consumption. Further investigations aimed at elucidating the mechanisms for the observed benefits of wine consumption in familial CRC patients are needed.

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