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Meat consumption, ornithine decarboxylase gene polymorphism, and outcomes after colorectal cancer diagnosis

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Abstract

Background:

Dietary arginine and meat consumption are implicated in colorectal cancer (CRC) progression via polyamine-dependent processes. Polymorphism in the polyamine-regulatory gene, ornithine decarboxylase 1 (*Odc1*, rs2302615) is prognostic for CRC-specific mortality. Here, we examined joint effects of meat consumption and *Odc1* polymorphism on CRC-specific mortality.

Materials and Methods:

The analytic cohort was comprised of 329 incident stage I-III CRC cases diagnosed 1994-1996 with follow-up through March 2008. *Odc1* genotyping was conducted using primers that amplify a 172-bp fragment containing the polymorphic base at +316. Dietary questionnaires were administered at cohort entry. Multivariate Cox proportional hazards regression analysis for CRC-specific mortality was stratified by tumor, node, metastasis (TNM) stage, and adjusted for clinically relevant variables, plus meat consumption (as a continuous variable, i.e., the number of medium-sized servings/week), *Odc1* genotype, and a term representing the meat consumption and *Odc1* genotype interaction. The primary outcome was the interaction of *Odc1* and meat intake on CRC-specific mortality, as assessed by departures from multiplicative joint effects.

Results:

Odc1 genotype distribution was 51% GG, 49% GA/AA. In the multivariate model, there was a significant interaction between meat consumption and *Odc1* genotype, $P\text{-int} = 0.01$. Among *Odc1* GA/AA CRC cases in meat consumption Quartiles 1-3, increased mortality risk was observed when compared to GG cases (adjusted hazards ratio (HR) = 7.06 [95% CI 2.34-21.28]) – a difference not found among cases in the highest dietary meat consumption Quartile 4.

Conclusions:

Effects of meat consumption on CRC-specific mortality risk differ based on genetic polymorphism at *Odc1*. These results provide further evidence that polyamine metabolism and its modulation by dietary factors such as meat may have relevance to CRC outcomes.

Keywords: Colorectal cancer, meat consumption, mortality, ornithine decarboxylase, ornithine decarboxylase 1, polyamines, single nucleotide polymorphism

BACKGROUND

Abnormalities in the control of polyamine metabolism and transport result in increased polyamine levels that can promote tumorigenesis in the colorectum and other tissues.[1] For instance, polyamine metabolism is upregulated in intestinal epithelial tissues of humans with familial adenomatous polyposis (FAP)[2] a syndrome associated with high risk of colon and other cancers. FAP is caused by mutations in the *adenomatous polyposis coli* (*APC*) tumor suppressor gene, and wild-type *APC* signaling downregulates ornithine decarboxylase 1 (*Odc1*, i.e., the gene encoding ornithine decarboxylase (ODC), which is the rate-limiting enzyme in polyamine biosynthesis) expression in both human cells[3] and in a FAP mouse model.[4] The relevance of polyamine inhibition as a target for therapeutic prevention of colorectal neoplasia in humans has been demonstrated with the selective ODC inhibitor D, L- α -Difluoromethylornithine (DFMO, eflornithine) in combination with sulindac (a nonsteroidal anti-inflammatory drug [NSAID] that promotes cellular polyamine export[5] via induction of spermidine spermine acetyltransferase [SSAT]). In a randomized controlled clinical trial of individuals with history of colorectal adenomas, the combination of eflornithine and sulindac compared to placebo markedly lowered the adenoma recurrence rate.[6] The observed clinical effects of this therapeutic prevention regimen appear to be mediated by polyamine-inhibitory mechanisms and not due to the cyclooxygenase-inhibitory mechanisms of sulindac.[7] The robust effects of these polyamine-inhibitory agents against colorectal adenomas, and in particular high-risk adenomas (multiple adenomas, advanced adenomas) were achieved at the cost of moderate subclinical ototoxicity[8] that may be related to genetic polymorphism in *Odc1*,[9] with no clear differences in gastrointestinal or cardiovascular toxicity.[6,10] These recent clinical findings, demonstrating efficacy against recurrent colorectal adenomas with a favorable safety profile, have spawned new interest in polyamine inhibition of colorectal carcinogenesis.

Gene–environment interactions clearly play a role in colorectal cancer (CRC) risk, and it is believed that such interactions influence CRC progression. However, relatively little is known about gene–environment effects on outcomes after CRC diagnosis. Our group has previously demonstrated that the *Odc1* A-allele is an adverse prognostic factor after diagnosis of stage I-III (i.e., nonmetastatic) CRC.[11] Meat consumption is a major polyamine-related exposure commonly encountered in the CRC survivorship population, as meat is high in arginine content – the direct precursor to ornithine which itself undergoes conversion by ODC to form the various polyamines: Putrescine, spermidine, and spermine.[12] In *Apc*^{Min/+} mice, dietary arginine is associated with increased tissue polyamine levels and increased incidence of high-grade intestinal adenomas.[13] Among human CRC cases, total daily arginine content is dependent on meat consumption, and familial CRC cases consuming the highest quartile of meat intake experience adverse survival outcomes compared to those in lower meat intake quartiles.[13]

Supporting evidence for the adverse effects of diet on outcomes after CRC diagnosis comes from a separate report of stage III (lymph node positive) colon cancer patients, where high consumption of a Western dietary pattern (i.e., a diet high in meat, fat, refined grains, and dessert) was associated with decreased time to recurrence and decreased overall survival.[14] Additionally, an observed CRC-specific mortality risk reduction ascribed to NSAID use prior to diagnosis[15] was found to be restricted to CRC cases reporting low levels of meat consumption prior to diagnosis, consistent with a polyamine-inhibitory process.[16] Taken together, these results suggest potential roles for polyamine-related genetic alterations (*Odc1* polymorphism) and environmental exposures (dietary meat consumption) on clinical outcomes after CRC diagnosis. A large body of literature associates meat consumption (and particularly processed meat consumption) with increased risk of CRC in humans.[17] However, despite the possible relationship of meat consumption to polyamine regulation, no prior studies have investigated the joint effects of polyamine-related dietary and genetic factors among CRC cases. We have designed the present study to evaluate the joint effects of dietary meat consumption and genetic polymorphism at *Odc1* with CRC-specific mortality among nonmetastatic CRC cases.

METHODS

Study population

We studied incident cases of invasive CRC with stage I-III disease at presentation enrolled in the University of California, Irvine Gene-Environment Study of Familial CRC[13,18] during 1994-1996 with follow-up through March 2008. Patients with advanced (stage IV) CRC at presentation were excluded as they have a much higher event rate (rate of death), and the majority of such patients are treated indefinitely with palliative chemotherapy. Participants were identified through the population-based cancer registries of the Cancer Surveillance Program of Orange County/San Diego Imperial Organization for Cancer Control as previously described.[18] At study entry, cases signed a consent form allowing for blood draws and medical record release. The study was approved by the University of California (UC) Irvine Institutional Review Board (#93-257). Clinical and demographic data including vital status and follow-up were obtained through linkage to the regional cancer registry databases as previously described.[13,18,19] Tumor grade and tumor, node, metastasis (TNM) staging determination were derived from existing American Joint Commission on Cancer (AJCC) codes where available. Otherwise stage was derived via conversion of extent of disease codes, as previously reported.[20] Family history of cancer in a first-degree relative was ascertained through telephone interview-based self-reporting at time of enrollment.[19,21] Twenty-two cases with hereditary nonpolyposis colon cancer (HNPCC), as defined by Amsterdam criteria, were identified and excluded from the analysis. The median time from CRC diagnosis until study entry (i.e., date of family history interview) was 18 months (95% CI 12-32 months).

DNA extraction and *Odc1* + 316 single nucleotide polymorphism (SNP) genotyping

DNA was extracted from 2.0 mL red blood cell clot samples using the QIAGEN QIAamp DNA Midi or Mini Kits (Qiagen), as previously described.[11] Genotyping of the *Odc1* + 316 single nucleotide polymorphism (SNP) (National Center for Biotechnology Information SNP database ID rs2302615) was conducted with oligonucleotide primers designed to amplify a 172-bp fragment containing the polymorphic base at position +316 (Applied Biosystems, Foster City, CA). Allele-specific TaqMan probes were synthesized with different 5' labels (6-carboxyfluorescein or VIC) and the same 3' quencher dye (6-carboxytetramethylrhodamine).[11,22] Each PCR reaction (5 μ L total) contained 10 ng of participant DNA, 30 pmol of each primer, 12.5 pmol of each TaqMan probe, and 1x TaqMan Universal PCR Master Mix (Applied Biosystems, Foster City, CA), as previously reported.[11,22,23] Out of 481, 440 DNA samples were successfully genotyped. Forty-one cases (8.5%) resulted in an undetermined *Odc1* + 316 genotype due to low DNA concentration and/or poor DNA quality; however, no significant clinicopathological differences were observed between the successfully genotyped and unsuccessfully

genotyped cases as previously reported.[11] Forty cases had stage IV CRC at diagnosis and were excluded. Of the remaining 400 stage I-III CRC cases, 335 completed the dietary questionnaire including 329 who completed questions related to meat consumption (representing 82% of 400 eligible stage I-III CRC cases). No significant differences were observed between the group completing the food frequency questions (FFQ) related to meat consumption ($n = 329$) and the group not completing the FFQ ($n = 71$) based on age, gender, race/ethnicity, TNM stage, tumor subsite location, histology, tumor grade, family history of CRC, treatment (surgery radiation, chemotherapy), or *Odc1* genotype. When analyzed by three genotypes (GG, GA, and AA), *Odc1* genotype distribution by ethnicity revealed no significant differences: Caucasian (290 cases: 52% GG, 41% GA, 7% AA, minor-A allele frequency = 27%), African-American (3 cases: 67% GG, 33% GA, 0% AA, minor-A allele frequency = 17%), Hispanics (16 cases: 50% GG, 50% GA, 0% AA, minor-A allele frequency = 25%), and Asians (20 cases: 30% GG, 50% GA, 20% AA, minor-A allele frequency = 45%) ($P = 0.18$). Within each race, *Odc1* genotype distribution was in Hardy–Weinberg equilibrium (Caucasians, $P = 0.45$; African-Americans, $P = 0.73$; Hispanics, $P = 0.18$; and Asians, $P = 0.96$).

Assessment of dietary intake

Food consumption was self-reported via a validated 100-item National Cancer Institute Block food frequency questionnaire (FFQ) administered at baseline (cohort entry), where patients were asked to report their usual eating habits for 1 year before CRC diagnosis.[23] Micronutrient data, total daily fiber intake, and total daily energy intake were calculated from the self-reported FFQ responses.[24] The types of meat queried for this analysis were beef roast or beef steaks or beef sandwiches, beef stew or pot pie, burrito or taco with meat, hamburger or cheeseburger, hot dogs, liver (including chicken livers), lunch meat (including ham, bologna, other lunch meats made with or without turkey), other meat soups, pork (including pork chops and pork roast), sausage, chicken or turkey, chicken stew or mixed chicken dish, fried chicken, fried fish, other types of fish, oysters, shellfish, and tuna. Consumption of each meat item was converted to the number of medium-sized servings per week by multiplying the frequency of servings per week (never, once a month, 2-3 times/month, once a week, 2 times/week, 3-4 times/ week, 5-6 times/week, everyday) by the estimated serving size (0.5 for small, 1.0 for medium, and 1.5 for large) as previously described.[13,16] CRC patients were divided into quartiles based on their meat consumption of medium-sized servings: Quartile 1, 0.00-4.72 servings/week; quartile 2, 4.73-7.26 servings/week; quartile 3, 7.27-11.00 servings/week; and quartile 4, ≥ 11.01 servings/week. Cases in the highest quartile of meat consumption (Q4) were compared to those in all of the other meat consumption quartiles (Q1-Q3). Manual chart review of the dietary FFQ was conducted on all cases reporting total daily energy intake of less than 500 kcal or greater than 5,000 kcal,[13] and after review all data were considered valid and included in the final analysis.

Statistical analysis

Comparisons of demographic, clinical, and pathological variables among CRC cases were done using Pearson Chi-square statistic or Fisher's exact test for nominal variables and Kruskal–Wallis tests were used for two-group comparisons of nonparametric data. An estimated 1:1 ratio of *Odc1* GG genotype to *Odc1* GA/AA genotype was expected based on previous literature.[22–25] CRC-specific mortality was defined as death due to CRC, and data were censored in the following instances: Alive at the end of follow-up, loss to follow-up, or death from any cause other than CRC. Cox proportional hazards modeling was performed for all CRC cases using time since diagnosis to profile the adjusted risk of CRC-specific death based on *Odc1* genotype. Multivariable analyses assessing the interaction between *Odc1* genotype and meat consumption on CRC-specific mortality were done with TNM stage at diagnosis fit as a stratum variable in the Cox proportional hazards model and adjustment for age, gender, ethnicity, family history of CRC, tumor site within the colon, histological subtype, treatment with surgery, radiation therapy, chemotherapy, and meat consumption (as a continuous variable, i.e., the number of medium-sized meat servings per

week), with or without the interaction term (as assessed by departures from multiplicative joint effects: Meat intake \times *Odc1* genotype). Similarly, Cox regression analyses assessing the effects of *Odc1* genotype on mortality were also performed separately for each case of meat consumption quartile, and then in collapsed categorical groups based on the similar estimates for Q1-Q3 versus Q4. For covariates with categorical data, dummy coding was assigned (0 or 1) and each category was included in the multivariate models in comparison to the referent group. *Odc1* genotype was analyzed using the dominant genetic model (GG vs. GA/AA) using dummy variables with GA/AA coded as 1 and GG as the referent group. The dominant genetic model was selected as risk estimates for individual genotypes in the full additive model (GG, GA, and AA) revealed that compared to *Odc1* GG as a referent group, GA and AA risk estimates were within 15% of each other. All analyses were conducted using SAS 9.2 statistical software (SAS Institute, Cary, NC).

RESULTS

Three hundred and twenty-nine stage I-III CRC cases with available meat consumption data identified from the UC Irvine CRC gene-environment study were used in the case-only analysis. Median follow-up duration was 11 years, 1 month. There were 209 (64%) colon cancer cases, 116 (35%) rectal cancer cases, and 4 (1%) CRC cases of unspecified location. Clinicopathological data for CRC cases are shown in [Table 1](#). Timing of radiation therapy was available for 51 cases (46 rectal and 5 colon cancer cases) receiving radiation therapy. Twelve (23.5%) received neoadjuvant (i.e., presurgery) radiation, 37 (72.6%) received adjuvant (i.e., postoperative) radiation, and 2 (3.9%) received combination of neoadjuvant and adjuvant radiation therapy. *Odc1* genotype distribution among all CRC cases was 167 (51%) GG, 139 (42%) GA, and 23 (7%) AA. There were no significant differences in *Odc1* genotype distribution (GG vs. GA/AA) by age, median meat consumption, gender, ethnicity, family history, stage, site within the colorectum, histology, tumor grade, surgical treatment, radiation therapy, or chemotherapy [[Table 1](#)]. There were no significant differences among the clinicopathological characteristics between *Odc1* GG versus GA/AA groups when separated by meat consumption score quartiles except for ethnicity in quartile 3 [[Table 2](#)]. Of the 329 stage I-III CRC cases, 92 (28%) were deceased at the time of analysis. Thirty-six (39%) deaths occurred in cases carrying the *Odc1* GG genotype, compared to 56 (61%) deaths in cases with the GA/AA genotypes. Cause of death was available for 63 of the 92 deceased CRC cases. Forty-eight (76%) CRC cases died as a result of CRC. A statistically significant decrease in CRC-specific mortality was observed among CRC cases homozygous for the *Odc1* G-allele (10-year mortality = 9%) compared to cases with at least one A-allele (*Odc1* GA/AA) (10-year mortality = 20%; $P = 0.0025$), as previously reported.[11]

CRC-specific mortality estimates based on *Odc1* genotype in the full regression model were as follows: Compared to the *Odc1* G-allele as a referent, the adjusted hazards ratio (HR) for the *Odc1* A-allele was 12.75, $P = 0.001$. In unadjusted analyses, the *Odc1* A-allele HR was 2.29, $P = 0.008$ [[Table 3](#)]. As a main effect, meat consumption was associated with increased CRC-specific mortality in the adjusted analyses (HR = 1.16, 95% CI 1.04-1.30, $P = 0.006$). The interaction between *Odc1* A-allele and meat consumption in the adjusted model was significant with a P value of 0.01. Multivariate overall mortality estimates showed a similar trend with *Odc1* G-allele conferring a prognostic advantage, *Odc1* G-allele HR = 1.00 (referent), *Odc1* A-allele adjusted HR = 2.55, $P = 0.033$ (unadjusted *Odc1* A-allele HR = 1.74, $P = 0.0098$).

Subset multivariate CRC-specific mortality analysis revealed that the *Odc1* A-allele (vs. *Odc1* GG as a referent group) confers a higher risk of CRC-specific mortality in the meat consumption quartiles 1-3, but not in the highest meat consumption quartile: Q1 HR = 11.3 ($P = 0.06$), Q2 HR = 9.2 ($P = 0.09$), Q3 HR = 8.8 ($P = 0.05$), and Q4 HR = 0.52 ($P = 0.29$). As risk estimates were similar in Q1-3, the risk estimates for the collapsed categorical group (Q1-Q3) versus Q4 are presented in [Table 4](#). In the collapsed categorical Q1-Q3 group, using *Odc1* GG as a referent, the *Odc1* A-allele HR is 7.06, $P = 0.0005$ (unadjusted *Odc1*

A-allele HR = 5.85, $P = 0.0003$) [Table 4]. In contrast, among cases in meat consumption Q4, no significant differences were detected for CRC-specific mortality risk based on *Odc1* genotype (compared with *Odc1* GG cases as a referent, the adjusted HR for GA/AA cases was 0.52, 95% CI 0.16-1.73, $P = 0.29$). On univariate analysis, lower CRC-specific mortality was observed among CRC cases homozygous for the *Odc1* G-allele in the group reporting meat consumption in first three quartiles (Q1-Q3), *Odc1* G-allele 10-year mortality = 4% versus A-allele 10-year mortality = 22%, $P = <0.0001$ [Figure 1]. In the highest meat consumption group (Q4), CRC-specific mortality differences for CRC cases based on *Odc1* genotype were not statistically different (*Odc1* A-allele 10-year mortality = 17% versus G-allele 10-year mortality = 27%; $P = 0.31$) [Figure 2].

DISCUSSION

In this population-based analysis of CRC cases, we observed a significant interaction between meat consumption and +316 *Odc1* genotype with regard to CRC-specific mortality. A statistically significant increased risk of CRC-specific mortality was observed for *Odc1* GA/AA CRC cases in meat consumption quartiles 1-3 compared to *Odc1* GG cases, a finding which was observed after stratification for stage and adjustment for age, gender, and clinically relevant factors. Of note, increased meat consumption itself was independently associated with increased CRC-specific mortality in this study ($P = 0.006$). The +316 *Odc1* SNP was chosen since it is the only SNP in the polyamine pathway that has been associated with differential survival outcomes in CRC cases.[11] The results presented here support the hypothesis that polyamine metabolism and its modulation by specific dietary factors have relevance on CRC outcomes.

Dietary influences relevant to polyamine regulation in humans with colorectal neoplasia have been investigated in a secondary analysis of data from the randomized, placebo-controlled phase III trial of DFMO, eflornithine + sulindac versus placebo among colorectal adenoma patients.[6] In the parent trial, a 70% reduction in recurrent colorectal adenomas was observed in the combination of eflornithine and sulindac group compared with the placebo group. Using dietary information recorded in the trial, a polyamine database was developed.[26] Major contributors of dietary polyamines include meat (ground meat, lunch meat, lasagna/pasta with meat sauce) as well as other sources such as green peas, peanut butter, peanuts, other nuts, corn, grapefruit juice, orange juice, and beer.[26] Interestingly, a greater proportion of patients consuming the highest quartile of dietary polyamine had large adenomas at baseline compared to patients in the remaining three dietary polyamine quartiles.[27] Furthermore, the preventive effect of the pharmacological polyamine-inhibitory intervention was abrogated in patients consuming high quartiles of dietary polyamines at baseline. A statistically significant interaction was observed between dietary polyamine group and treatment with regard to colorectal adenoma recurrence – a finding that remained after adjustment for genetic polymorphism at *Odc1*. These findings, when considered together with the findings from the present manuscript, suggest key roles for polyamine-related dietary influences on CRC progression. Ultimately, confirmation of the findings presented in this manuscript may emerge from future studies, such as the phase III post-adjuvant randomized double-blind trial of eflornithine, sulindac, placebo alone, or in combination among stage 0, I, II, or III colon cancer patients (which has pharmacogenetic and dietary substudies embedded within the protocol).[28]

Other studies of genetic variation in *Odc1* on CRC progression must be considered in light of the results presented here. In colorectal adenoma patients, the *Odc1* + 316 SNP may be prognostic for colorectal adenoma recurrence,[23] especially in association with aspirin usage.[23–25] Recently, the relevance of the rs2302615 *Odc1* SNP to colorectal adenoma recurrence has been challenged, as associations were detected for other downstream SNPs in *Odc1*, but not in rs2302615.[29] Clearly, further research must be done to sort out the contributions of genetic polymorphism in *Odc1* on the tumorigenic process. Little is known about how genetic polymorphism at *Odc1* influences outcomes in CRC. One study demonstrated no association with *Odc1* polymorphism on CRC risk,[30] despite the aforementioned associations of *Odc1* with mortality outcomes after CRC diagnosis.[11]

This observational study shares limitations of other population-based analyses, including lack of data on comorbid conditions, performance status, or particular chemotherapeutic regimens utilized. There is also a potential for selection bias, favoring a relatively healthy group of CRC survivors, since there was a median 18-month delay from the time of CRC diagnosis until study enrollment. The sample size is relatively small and despite the observed statistically significant results, it is possible that our findings are due to chance alone. Other factors affecting polyamine metabolism which were not accounted for in the present study may explain our observations. For example, aspirin activates polyamine acetylation and export and in association with the *Odc1* A-allele to reduce cell and tissue polyamine contents.[12,23,31] NSAIDs have been shown associated with prolonged survival outcomes in nonmetastatic CRC cases,[15,32] particularly among those consuming low levels of meat consumption.[16] Thus, aspirin, NSAIDs, or other concomitant medications or exposures (which are not available in the present study) may contribute to the observed risk estimates. Another limitation is that meat consumption was used as a surrogate for dietary polyamines, as no polyamine dietary database exists for this study. Also, information on cooking methods was unavailable, which may have relevance to the study outcomes. Given these important limitations, we consider the results presented here to be hypothesis-generating.

CONCLUSIONS

In summary, we have observed a statistically significant interaction between meat intake and *Odc1* + 316 SNP with regard to CRC-specific mortality among CRC cases. Our findings suggest roles for meat consumption and genetic polymorphism at *Odc1* on CRC progression. Furthermore, they may contribute to our ability to assess risk of CRC progression, with the ultimate goal of directing patient-specific pharmacogenetic risk-stratification, surveillance monitoring, and informing novel-targeted approaches to secondary and tertiary CRC prevention.

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Footnotes

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Conflict of Interest: None declared.

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Figures and Tables

Table 1Descriptive analysis for colorectal cancer cases overall and based on *Odc1* genotype

	All CRC cases n=329 (%)	<i>Odc1</i> GG n=167 (%)	<i>Odc1</i> GA/ AA n=162 (%)	P value
Median age (with age range)	58.0 (29-89)	59.0 (29-89)	57.0 (29-81)	0.30 ¹
Median meat consumption ² (with meat consumption range)	7.26 (0.00-37.50)	6.95 (0.00-33.02)	7.40 (0.00-37.50)	0.31 ¹
Gender				
Male	185 (56)	92 (55)	93 (57)	0.67
Female	144 (44)	75 (45)	69 (43)	
Ethnicity				
Non-hispanic white	290 (88)	151 (90)	139 (86.0)	0.27
African-American	3 (1)	2 (1)	1 (<1)	
Hispanic	16 (5)	8 (5)	8 (5)	
Asian	20 (6)	6 (4)	14 (9)	
Family history of CRC				
Yes	88 (27)	48 (29)	40 (25)	0.41
No	241 (73)	119 (71)	122 (75)	
Stage at diagnosis				
I	118 (36)	60 (36)	58 (36)	0.23
II	110 (33)	62 (37)	48 (30)	
III	101 (31)	45 (27)	56 (35)	
Colon/rectum site				
Proximal and transverse	96 (29)	49 (29)	47 (29%)	0.94
Descending	19 (6)	9 (5)	10 (6)	
Sigmoid	94 (29)	49 (29)	45 (28)	
Rectosigmoid	40 (12)	19 (11)	21 (13)	
Mid-low rectum	76 (23)	38 (23)	38 (23)	
Colorectum, unspecified	4 (1)	3 (2)	1 (1)	

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Table 2

Descriptive analysis for colorectal cancer cases overall and based on *Odc1* genotype and meat consumption score quartiles

Meat consumption score ¹ quartiles	1 (0.0-4.72)			2 (4.73-7.26)			3 (7.27-11.00)			4 (≥11.01)		
	GG (n=46) (%)	GA/AA (n=36) (%)	P value	GG (n=40) (%)	GA/AA (n=44) (%)	P value	GG (n=42) (%)	GA/AA (n=39) (%)	P value	GG (n=39) (%)	GA/AA (n=43) (%)	P value
Median age (with age range)	61.0 (30-77)	62.0 (32-75)	0.98 ²	59.0 (33-80)	57.0 (30-81)	0.33 ²	60.0 (35-78)	56.0 (38-79)	0.11 ²	52.0 (29-89)	55.0 (29-80)	0.43 ²
Gender												
Male	23 (50)	15 (42)	0.45	14 (35)	23 (52)	0.11	26 (62)	25 (64)	0.84	29 (74)	30 (70)	0.64
Female	23 (50)	21 (58)		26 (65)	21 (48)		16 (38)	14 (36)		10 (26)	13 (30)	
Ethnicity												
Non-hispanic white	38 (83)	32 (89)	0.55	38 (95)	42 (95)	1.00	42 (100)	32 (82)	0.04	33 (85)	33 (77)	0.31
African-American	1 (2)	0 (0)		0 (0)	0 (0)		0 (0)	1 (3)		1 (3)	0 (0)	
Hispanic	4 (9)	1 (3)		1 (3)	1 (2)		0 (0)	3 (8)		3 (8)	3 (7)	
Asian	3 (7)	3 (8)		1 (3)	1 (2%)		0 (0)	3 (8)		2 (5)	7 (16)	
Family history of CRC												
Yes	16 (35)	12 (33)	0.89	11 (28)	11 (25)	0.79	13 (31)	9 (23)	0.43	8 (21)	8 (19)	0.83
No	30 (65)	24 (67)		29 (73)	33 (75)		29 (69)	30 (77)		31 (79)	35 (81)	
Stage at diagnosis												
I	21 (46)	17 (47)	0.78	16 (40)	19 (43)	0.42	14 (33)	13 (33)	0.39	9 (23)	9 (21)	0.97
II	17 (37)	11 (31)		14 (35)	10 (23)		16 (38)	10 (26)		15 (38)	17 (40)	
III	8 (17)	8 (22)		10 (25)	15 (34)		12 (29)	16 (41)		15 (38)	17 (40)	
Colon/rectum site												
Proximal and transverse	13 (28)	12 (33)	0.93	10 (25)	13 (30)	0.56	15 (36)	9 (23)	0.54	11 (28)	13 (30)	0.61
Descending	4 (9)	2 (6)		2 (5)	1 (2)		2 (5)	3 (8)		1 (3)	4 (9)	
Sigmoid	12 (26)	9 (25)		14 (35)	15 (34)		12 (29)	10 (26)		11 (28)	11 (26)	
Rectosigmoid	6 (13)	4 (11)		6 (15)	3 (7)		4 (10)	8 (21)		3 (8)	6 (14)	
Mid-low rectum	10 (22)	9 (25)		7 (18)	12 (27)		9 (21)	9 (23)		12 (31)	8 (19)	
Colorectum, unspecified	1 (2)	0 (0)		1 (3)	0 (0)		0 (0)	0 (0)		1 (3)	1 (2)	
Histological subtype												
Adenocarcinoma	41 (89)	36 (100)	0.12	37 (93)	42 (95)	0.48	34 (81)	36 (92)	0.23	34 (87)	38 (88)	0.57
Mucinous adeno CA	2 (4)	0 (0)		2 (5)	1 (2)		6 (14)	3 (8)		5 (13)	4 (9)	
Carcinoma	3 (7)	0 (0)		0 (0)	1 (2)		2 (5)	0 (0)		0 (0)	1 (2)	
NOS	0 (0)	0 (0)		1 (3)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Tumor grade												
I	8 (20)	10 (29)	0.36	3 (9)	9 (22)	0.14	7 (18)	6 (18)	0.84	3 (8)	5 (13)	0.76
II	29 (73)	20 (57)		30 (86)	27 (66)		28 (72)	23 (68)		28 (78)	31 (78)	
III	3 (8)	5 (14)		2 (6)	5 (12)		4 (10)	5 (15)		5 (14)	4 (10)	
No. missing	6	1		5	3		3	5		3	3	
Surgical treatment												
Yes	42 (91)	36 (100)	0.07	40 (100)	44 (100)	1.00	42 (100)	39 (100)	1.00	38 (97)	42 (98)	0.94
No	4 (9)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)		1 (3)	1 (2)	
Radiation therapy												
Yes	3 (7)	4 (11)	0.46	6 (15)	7 (16)	0.91	8 (19)	10 (26)	0.48	6 (15)	10 (23)	0.37
No	43 (93)	32 (89)		34 (85)	37 (84)		34 (81)	29 (74)		33 (85)	33 (77)	
Chemotherapy												
Yes	12 (28)	13 (38)	0.34	13 (33)	17 (39)	0.62	20 (51)	22 (58)	0.56	20 (56)	24 (59)	0.79
No	31 (72)	21 (62)		26 (67)	27 (61)		19 (49)	16 (42)		16 (44)	17 (41)	
No. missing	3	2		1	0		3	1		3	2	

¹Servings per week. ²Kruskal-Wallis test. CRC=Colorectal cancer

Table 3

Multivariate colorectal cancer-specific mortality analysis for colorectal cancer cases based on ornithine decarboxylase 1 genotype

	<i>Odc1</i> Genotype		<i>P</i> value
	GG	GA/AA	
CRC-specific mortality			
Number of events	15	33	0.008
Number at risk	167	162	0.001
Unadjusted HR (95% CI)	1 (Reference)	2.29 (1.24-4.23)	
Adjusted HR (95% CI)*	1 (Reference)	12.75 (2.71-60.12)	

*Includes stratification for stage (I, II, III) and adjustment for age (years), gender, ethnicity, family history of CRC, TNM stage at diagnosis, tumor site within the colorectum, histological subtype, treatment with surgery, radiation therapy, chemotherapy, and meat consumption (as a continuous variable, i.e., the number of medium-sized servings per week), and the interaction between the *Odc1* SNP and meat consumption. *P* value of 0.01 for the interaction between the *Odc1* SNP and meat consumption on CRC-specific mortality. CRC=Colorectal cancer

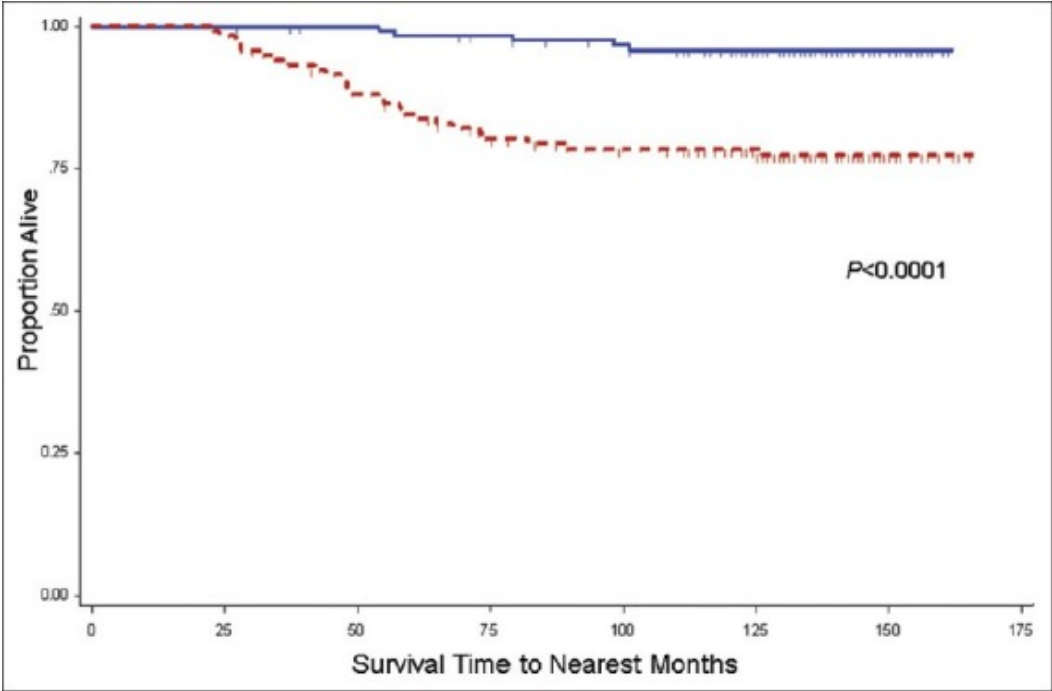
Table 4

Multivariate colorectal cancer-specific mortality analysis for CRC cases based on ornithine decarboxylase 1 genotype and meat consumption group

		<i>Odc1</i> Genotype		<i>P</i> value
		GG	GA/AA	
Meat consumption quartiles 1-3 (0.0-11.0049 servings per week)	Number of events	5	26	0.0003
	Number at risk	128	119	0.0005
	Unadjusted HR (95% CI)	1 (Reference)	5.85 (2.24-15.29)	
	Adjusted HR (95% CI)*	1 (Reference)	7.06 (2.34-21.28)	
Meat consumption quartile 4 (≥11.0050 servings per week)	Number of events	10	7	0.28
	Number at risk	39	43	0.29
	Unadjusted HR (95% CI)	1 (Reference)	0.59 (0.22-1.54)	
	Adjusted HR (95% CI)*	1 (Reference)	0.52 (0.16-1.73)	

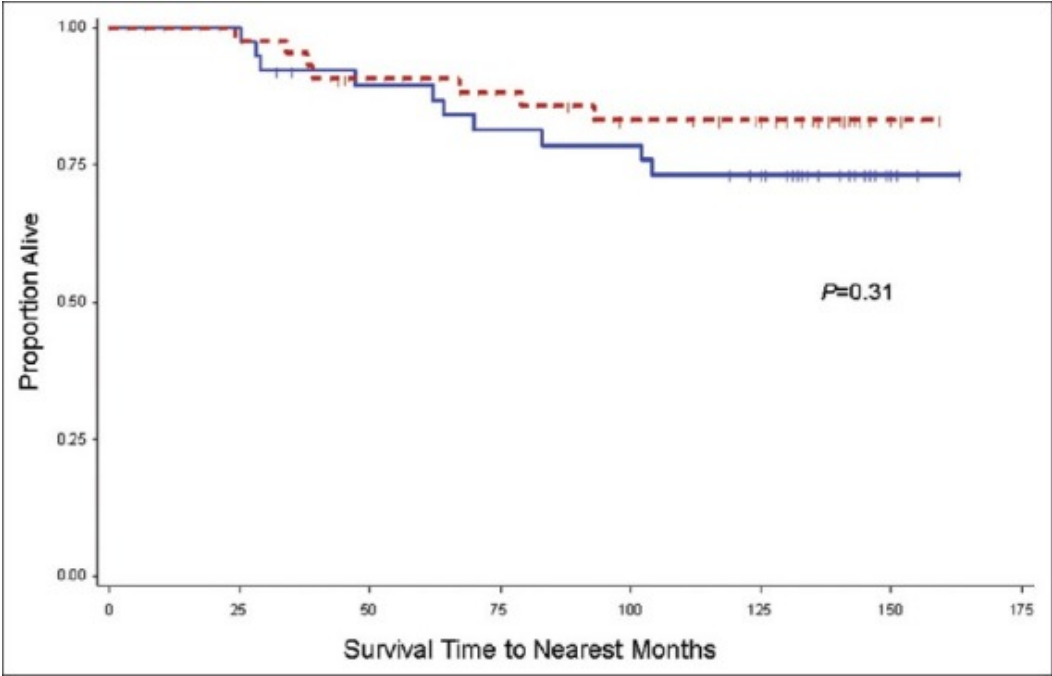
*Includes stratification for stage (I, II, III) and adjustment for age (years), gender, ethnicity, family history of CRC, TNM stage at diagnosis, tumor site within the colorectum, histological subtype, treatment with surgery, radiation therapy, and chemotherapy *Odc1*=Ornithine decarboxylase I

Figure 1



Kaplan-Meier colorectal cancer (CRC)-specific mortality rate estimates for stage I-III CRC cases in meat consumption quartiles 1-3, stratified by *ornithine decarboxylase 1* (*Odc1*) +316 genotype. Includes cases from the University of California Irvine Gene-Environment Study of Familial CRC diagnosed during 1994-1996 with follow-up through March 2008; Solid line, *Odc1* GG (128 cases, 5 CRC-specific deaths); Dashed line, *Odc1* GA/AA (119 cases, 26 CRC-specific deaths). Vertical tic marks represent censored observations

Figure 2



Kaplan-Meier colorectal cancer (CRC)-specific mortality rate estimates for stage I-III CRC cases in meat consumption quartile 4, stratified by *ornithine decarboxylase 1 (Odc1)* +316 genotype. Includes cases from the University of California Irvine Gene-Environment Study of Familial CRC diagnosed during 1994-1996 with follow-up through March 2008; Solid line, *Odc1* GG (39 cases, 10 CRC-specific deaths); Dashed line, *Odc1* GA/AA (43 cases, 7 CRC-specific deaths). Vertical tick marks represent censored observations