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The Association Between a Functional CYP1A1 Polymorphism and Colorectal Neoplasia Risk in Post Menopausal Women

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Abstract

Background—The impact of estrogen on risk of colorectal neoplasia is uncertain. Carriers of the *AA* and *CA* genotype allele of the C4887A polymorphism of the CYP1A1 gene have enhanced estrogen metabolism relative to carriers of the *CC* genotype.

Aims—This study examined whether this genetic marker of enhanced estrogen catabolism segregated with colorectal neoplasia (CRN) in postmenopausal women.

Methods—We enrolled hormone negative postmenopausal women having screening or surveillance colonoscopy. Demographic and medical data were gathered. Blood was collected and analyzed for CYP1A1 polymorphisms of the C4887A allele by PCR–RFLP. Colonoscopy and pathology data were gathered from hospital databases.

Results—One hundred sixty-eight women were enrolled in the study. Twenty-one subjects (12.5%) carried at least one *A* allele, and 147 subjects (87.5%) carried the *CC* alleles for the C4887A polymorphism of the CYP1A1 gene. Seventy subjects (41.7%) had CRN and 98 subjects (58.3%) did not have CRN. Of the subjects who carried the *A* allele, 57% had CRN as compared

to 39% of those who carried the *CC* allele; the association was not statistically significant ($P=0.16$). In a multivariate logistic regression analysis, age, BMI, current tobacco use, and first degree relative with CRN were independent risk factors for CRN but the C4887A polymorphisms remained not statistically significant ($P=0.35$).

Conclusions—Carriers of the *A* allele of the C4887A polymorphism have enhanced estrogen catabolism and lower free estradiol. Our results suggest, however, that inherent estrogen metabolism as determined by C4887A polymorphisms is not associated with CRN risk.

Keywords

Colorectal neoplasia; Postmenopausal; Estrogen; Screening; CYP polymorphisms

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer related deaths, yet understanding of the genetic and environmental risk factors remains incomplete. Premenopausal women have an age-adjusted reduced incidence of CRC [1], suggesting the possibility that estrogen status may be an important component of the gender-related prevalence rate. The Women's Health Initiative (WHI) showed a 20% decreased risk for colon cancer with the use of combined (estrogen plus progestin) hormone therapy (HRT) [2], while the estrogen only arm did not show a protective effect against colorectal cancer (CRC) [3]. Two other large meta-analyses concluded that a reduction in CRC incidence was associated with postmenopausal HT [4, 5]. The impact of estrogen alone on risk of colorectal neoplasia (CRN) is uncertain. Estrogen receptors are found in colorectal tissue [6, 7], and estrogen has been shown to induce p53-associated apoptosis of colorectal cells in animal models [8]. Multiple epidemiologic studies have examined the impact of estrogen supplementation on risk of colorectal neoplasia [9–23]. These studies have generally determined that HT is protective, but the mechanisms remain unknown.

There are four major enzymes involved in estrogen metabolism, each encoded by a different gene: *CYP1A1*, *CYP1B1*, *CYP1A2* and *CYP3A4*. Although all of these enzymes can be found in the liver; *CYP1A1* and *CYP1B1* are predominantly extrahepatic in location [24, 25]. Each enzyme has a different hydroxylation activity, thus implying that the overall estrogen metabolic profile in each individual is imparted by the relative activity of each of these enzymes. Villareal et al. have demonstrated that subjects carrying the *A* allele (*CA* or *AA*) for the C4887A polymorphism of the *CYP1A1* gene have significantly lower free estradiol index and higher levels of total urinary estrogen metabolites than subjects with the *CC* genotype, suggesting accelerated estrogen catabolism in these (*CA* + *AA*) individuals [26]. They also demonstrated that subjects with the *A* allele had lower bone mineral density of the femur, implying that this gene polymorphism has functional significance.

To further examine the association between estrogen and CRN, we examined the relationship of the *A* allele of the C4887A polymorphism, which is associated with accelerated estrogen metabolism, with rates of CRN in postmenopausal women. To our knowledge, this is the first study to examine the relationship between this particular polymorphism and colorectal neoplasia. We hypothesized that carriers of the *A* allele would have higher rates of CRN than carriers of the *CC* genotype.

Methods

Study Subjects

Postmenopausal women not on hormone therapy who were presenting for routine screening or surveillance colonoscopy to the outpatient Endoscopy Center at Washington University/Barnes Jewish Hospital were eligible for this study. Postmenopausal status was defined as complete cessation of menstrual cycles for at least 6 months or bilateral oophorectomy. A questionnaire and chart review were used to confirm postmenopausal status and to elicit information about prescription and non prescription hormone use. Women who reported prescription or non prescription hormone use in the past 6 months were excluded from the study. In addition, dietary information was collected regarding foods containing phytoestrogens (broccoli, kale, mustard greens, cabbage, turnips, brussel sprouts, cauliflower), and subjects were excluded from participation if they consumed foods containing phytoestrogens on a daily basis. Data was also collected about smoking status (current smoker, previous smoker, never smoker), height and weight, diabetes, personal history of colorectal adenoma or cancer and family history of colorectal adenoma or cancer. Information about use of calcium supplements, non-steroidal anti-inflammatory drugs (NSAIDs), aspirin and multivitamins was collected. Use of these drugs was further categorized as daily, weekly or monthly. Colonoscopy was subsequently performed per usual care, using conscious sedation after an adequate bowel preparation. Presence or absence of adenomas was determined by review of colonoscopy reports and histology of polyps was determined by review of surgical pathology reports. For the purposes of this study, subjects with adenomatous polyps and colorectal cancer were compressed into a single category of “colorectal neoplasia (CRN)”, and patients with hyperplastic polyps were compressed into the same category with subjects having no CRN. Additionally, since carriage of the C4887A polymorphism is considered a lifelong event, subjects with a prior history of confirmed adenoma or cancer were grouped with subjects having an adenoma at the time of study enrollment. A history of prior adenoma was confirmed by collection of surgical pathology reports. Therefore, subjects were considered as “ever” or “never” had CRN. Patients with genetic syndromes associated with CRN and those with inflammatory bowel disease were excluded.

This study was approved by the Human Research Protection Office of Washington University in St. Louis and all subjects gave written informed consent to participate.

Genotyping for the C4887A Polymorphism of the CYP1A1 Gene

Blood specimens for genotyping were obtained during the colonoscopy encounter. Polymorphisms of CYP1A1 were identified by PCR–RFLP. Genomic DNA was extracted from peripheral leukocytes using the Puregene DNA Isolation Kit (Gentra Systems, Minneapolis, MN, USA) and used as a template for genotyping procedures. Genotype characterizations to identify the C4887A polymorphism were performed using PCR and restriction fragment length polymorphism (RFLP). DNA fragments were identified by gel electrophoresis.

The base change was identified by amplifying a 204-bp fragment using the forward primer 5'-CTGTCTCCCTCTGGTTACAGGAAGC-3' and the reverse primer 5'-TTCCACCCGTTGCAGCAGGATAGCC-3' as previously described [26]. PCR conditions were 35 cycles for 0.5 min at 94°C, 0.5 min at 63°C, and 0.5 min at 72°C. The PCR products were digested with *BsaI* (New England Biolabs). The digested products were separated on a 3.0% Nusieve GTG agarose gel (BMA, Rockland, ME, USA). When digested with *BsaI*, those with *CC* genotype for the C4887A polymorphism yielded two fragments of

sizes 139 and 65 bp, those with *AA* genotype remained uncut at 204 bp, whereas those with the *CA* genotype generated three bands (204, 139, and 65 bp).

Statistical Methods

The association of colorectal neoplasia with polymorphisms of the *CYP1A1* gene as well as other patient/clinical characteristics (including age, race, diabetes, BMI, tobacco use, daily NSAID or aspirin use, first degree relatives with CRC) was assessed using Fisher's exact test or Student *t*-test as appropriate. A multivariate logistic regression model was also fitted and a backward elimination procedure was used to see whether the polymorphisms of the *CYP1A1* gene were an independent predictor of CRN. A *P* value under 0.05 was taken to indicate significance and all statistical tests were two-sided.

Results

One hundred seventy-six women were identified who met the inclusion and exclusion criteria and were invited to participate. Three women refused participation and one woman was excluded after phlebotomy was unsuccessful. PCR was unsuccessful in four patients; therefore, complete data was available for 168 subjects. The mean age was 62 years (STD 8.6 years). Ninety-six subjects were white, 70 were black and two were Asian. Twenty-one subjects (12.5%) carried the *A* allele; two subjects were genotype *AA* and 19 subjects were genotype *CA*. One hundred forty-seven subjects (87.5%) carried the *CC* genotype for the C4887A polymorphism of the *CYP1A1* gene. Other descriptive data presented by genotype are displayed in Table 1.

Seventy subjects (41.7%) were categorized as having past or present ("ever") CRN and 98 subjects (58.3%) were categorized as never having CRN. Although subjects who carried the *A* allele were more likely to "ever" have CRN than those who carried the *CC* allele (60% vs. 39%), the association was not statistically significant ($P = 0.16$; Table 2). We evaluated individual risk factors for CRN and found that age, BMI, current tobacco use, and first degree relative with CRN were independent risk factors for CRN. In a multivariate logistic regression analysis, these four factors were independently associated with CRN, and the C4887A polymorphism of the *CYP1A1* gene remained not statistically significant ($P = 0.35$; Table 3).

There was no racial difference with respect to carriage of either C4887A polymorphism; 11% of blacks and 14% of whites carried the *A* allele. We also compared the C4887A genotype with subjects who had a current adenoma only, and there was no statistical association between genotype and CRN ($P = 1.0$).

Of the 70 subjects with "ever" CRN, seven had a history of colorectal cancer and 24 had past or present advanced adenoma (>1 cm, villous, or high grade dysplasia). Due to small numbers, a subgroup analysis of those with cancer and advanced adenoma was not performed.

Discussion

Estrogen may be protective against CRN but the exact role of estrogen in colorectal health and tumorigenesis is unknown. Human data demonstrating a protective effect of estrogen on CRC risk has largely been in the form of case control and cohort studies of combined hormone therapy (HT). There is biologic data showing that estrogen not only induces proliferation of colorectal neoplasia, but also induces apoptosis and suppression of colorectal neoplasia. In order to study the impact of estrogen exposure in humans with

respect to CRN risk, we sought to evaluate the impact of the CYP1A1 C4887A allele, previously shown to be a marker of lifelong free estradiol exposure.

As mentioned, there is biologic data regarding estrogen effects on colorectal tissue and colorectal cancer cell lines. Estrogen metabolites such as 2-methoxyestradiol (2-MeOE₂) have been shown to induce apoptosis in CRC cell lines [8, 27–29]. 2-MeOE₂ binds weakly to estrogen receptors (ER), suggesting that induction of apoptosis is an ER independent mechanism. Estradiol (E₂) has been shown to inhibit vascular endothelial growth factor (VEGF), suggesting inhibition of angiogenesis [29] and to increase tumor necrosis factor (TNF)- gene expression, thus providing a possible mechanistic link between E₂ and CRC prevention [30, 31].

In addition to the ER-independent actions of estrogen metabolites discussed above, estrogen may impact colorectal tumorigenesis by ER-related mechanisms. Estrogen receptor (ER) expression declines in colon cancer tissue in parallel with loss of differentiation of the colon cancer tissues [6], suggesting a link between ER receptor expression and malignant progression of colorectal tumors.

In contrast to the above data, there is biologic evidence that estrogen and estrogen receptors play a role in stimulation of colorectal cancer growth [32, 33]. Despite the contradictory biological data presented above, and lack of human data that estrogen alone reduces CRN risk, there is a general perception that estrogen is protective against CRC in humans. We explored the hypothesis that this protection might be linked to a marker of estrogen metabolism. Cytochrome P450 (CYP450) enzymes have been shown to regulate estrogen metabolism, and polymorphisms in the CYP450 enzymes that metabolize estrogen (*CYP1A1* and *CYP1B1*) appear to result in variants with altered functional activity, resulting in variable estrogen catabolism [34, 35] and estrogenic activity in the body. These same polymorphisms have been shown to influence the risk of endometrial and breast cancer, which are traditionally viewed as hormone related cancers. The C4887A polymorphism, which was evaluated in our study, has been associated with a four-fold increased risk of breast cancer in postmenopausal women [36], which was the population we studied, and has also been associated with a greater than six-fold increased risk of endometrial cancer in a cohort that was predominantly postmenopausal [35]. Napoli et al. have previously demonstrated that individuals carrying the A allele (CA + AA) for the C4887A polymorphism of the *CYP1A1* gene have significantly lower free estradiol index and higher levels of total urinary estrogen metabolites than CC subjects, suggestive of an accelerated estrogen catabolism in these (CA + AA) individuals. This polymorphism was also shown to have physiologic consequences; those with the A allele demonstrated significantly lower BMD in all regions of the femur than subjects with the CC allele.

We therefore tested the hypothesis that estrogen is protective against CRN; that is, subjects carrying the A allele of the C4887A, thus having lower circulating free estrogen, would be at greater risk for CRN than subjects carrying the CC allele. We found that carrying the A allele, in our study population, was not significantly associated with CRN as compared to those carrying the CC allele. These results suggest that inherent estrogen metabolism may not be associated with CRN risk or that a larger sample size may be necessary for a definitive conclusion.

There are several limitations to our study. First, we did not gather data about supplemental hormone therapy prior to 6 months before study entry. However, what role, if any, prior HT has in CRC risk reduction seems minimal. Multiple epidemiologic studies have shown reduced risk with combined HT, but the greatest risk reduction has been shown with current users, suggesting that any effect of HT on CRN risk is transient. It is also recognized that the

doses of standard HT for menopausal women are much lower than the physiologic endogenous hormones of reproductive age women, suggesting that inherent estrogen metabolism, such as conferred by the C4887A polymorphism, has an overall greater impact on estrogen exposure over a woman's lifetime than finite periods of HT. Secondly, we did not measure markers of estrogen metabolism to confirm that the C4887A polymorphisms segregated with urinary estrogen metabolites and free estradiol index in our study subjects. However, the association between the *A* allele and higher estrogen metabolism has been previously established by Napoli et al. and further confirmed by ongoing study in that lab [37]. Third, the percent of subjects in our study who carried the *A* allele (11%) was lower than anticipated based on a previous study performed in this same general population (19% carried the *A* allele) [26]. There are recognized ethnic and regional variations in carriage of the *A* allele which may account for this difference [34], given the fact that a significant percentage of our participants are African-Americans and a few Asians compared to the participants in the study of Napoli et al. who were purely non-Hispanic Caucasians. We extended the study beyond the original planned enrollment and the genotype variations did not change, suggesting that this represents the true expression of this genotype in our population. Finally, as outlined in our discussion, estrogen may impact colorectal tissue growth and apoptosis in myriad ways. Our study was focused on a single marker of endogenous estrogen exposure and we recognize that estrogen may impact CRN risk in ways not examined by the aim and scope of this study.

In summary, our data suggest that carriers of the *CA* + *AA* genotype of the C4887A polymorphism of the *CYP1A1* gene have a trend toward a higher risk of CRN than those carrying the *CC* genotype in a cohort of postmenopausal, hormone negative women. Further study in a significantly larger population would be needed to confirm whether a true association exists between C4887A polymorphism of the *CYP1A1* gene and CRN.

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Table 1

Patient characteristics and medication usage

Descriptive data	Subjects with AA/CA genotype <i>N</i> = 21	Subjects with CC genotype <i>N</i> = 147
Age in years (mean ± STD)	63.2 ± 9.9	62.1 ± 8.5
Race (White/Black/Asian)	14/7/0	82/63/2
BMI (mean ± STD)	30.3 ± 4.6	29.6 ± 7.6
Diabetic	3 (15.8%)	42 (28.6%)
Smoker (current/never/former)	4/13/4	31/95/21
Daily NSAID or aspirin use	5 (23.8%)	54 (36.7%)
Daily calcium supplementation	10 (47.6%)	61 (41.5%)
Daily multivitamin use	10 (47.6%)	65 (43.6%)
First degree relative with CRC	6 (28.6%)	32 (21.8%)

STD standard deviation, *NSAID* non-steroidal anti-inflammatory drug, *BMI* body mass index, *CRC* colorectal cancer

Table 2

C4887A polymorphisms and colorectal neoplasia (CRN)

Category	Subjects with AA genotype <i>N</i> = 2	Subjects with CA genotype <i>N</i> = 19	Subjects with CC genotype <i>N</i> = 147
“Ever” CRN	1 (50%)	11 (57.9%)	58 (39.5%)
“Never” CRN	1 (50%)	8 (42.1%)	89(60.5%)

Table 3

Multivariate logistic regression of colorectal neoplasia (CRN) risk factors

Features	Odds ratios (95% CIs)	P-values
C4887A polymorphism		
CC	1.0 (–, –)	
CA/AA	1.654 (0.581, 4.707)	0.346
Age (per 1-year increase)	1.065 (1.019, 1.113)	0.005
Non-steroidal anti-inflammatory drugs (NSAID)		
None	1.0 (–, –)	
Daily	1.025 (0.470, 2.235)	0.950
Weekly/monthly	1.435 (0.394, 5.231)	0.584
Body mass index (BMI) (per 1-unit increase)	1.086 (1.026, 1.149)	0.004
Diabetes		
No	1.0 (–, –)	0.342
Yes	1.537 (0.634, 3.724)	
First degree relative with CRN		
No	1.0 (–, –)	
Yes	3.993 (1.699, 9.381)	0.002
Race		
Others	1.0 (–, –)	
White	1.359 (0.635, 2.910)	0.430
Tobacco use		
Never	1.0 (–, –)	
Quit	2.175 (0.833, 5.678)	0.113
Current use	4.767 (1.796, 12.653)	0.002