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Genetic variation in sex-steroid receptors and synthesizing enzymes and colorectal cancer risk in women

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Abstract

Objectives—Several lines of evidence have suggested that female hormones may lower risk for developing colorectal cancer. However, the mechanisms by which sex hormones affect colorectal cancer development remain unknown. We sought to determine whether the association may be under genetic control by evaluating genetic variation in estrogen receptors (ESR1 and ESR2), progesterone receptor (PGR), aromatase cytochrome 450 enzyme (CYP19A1) and 17 beta-hydroxysteroid dehydrogenase type 2 gene (HSD17B2).

Methods—We included 158 incident cases of colorectal cancer and 563 randomly chosen control subjects from 28,345 women in the Women's Health Study aged 45 years or older who provided blood samples and had no history of cancer or cardiovascular disease at baseline in 1993. All cases and controls were Caucasians of European descent. A total of 63 tagging and putative functional SNPs in the 5 genes were included for analysis. Unconditional logistic regression was used to estimate odds ratio (ORs) and 95% confidence intervals (CIs).

Results—There was no association between variation in ESR1, ESR2, PGR, CYP19A1 and HSD17B2 and colorectal cancer risk after correction for multiple comparisons (p values after correction ≥0.25). There was also no association with any of the haplotypes examined (p ≥0.15) and no evidence of joint effects of variants in the 5 genes (p ≥0.51).

Conclusion—Our data offer insufficient support for an association between variation in ESR1, ESR2, PGR, CYP19A1 and HSD17B2 and risk for developing colorectal cancer.

INTRODUCTION

Men tend to have a higher incidence rate of colorectal cancer than women of similar age in the US (1). In families with hereditary nonpolyposis colorectal cancer (HNPCC), the lifetime risk of developing colon cancer is much lower in females (30%) than in males (74%) (2). Male rats experimentally exposed to the carcinogen dimethylhydrazine also have twice the risk of developing colon cancer and shorter survival time than their female counterparts (3-5). Epidemologic studies have further shown that an increase in female hormones as a result of pregnancy and use of exogenous hormones such as oral contraceptives (OC) and postmenopausal hormone therapy (HT) are associated with a lower risk for developing

colorectal cancer (6-9). It has been suggested that female hormones such as estrogen reduce synthesis or secretion of bile acids, which are believed to be carcinogenic and trophic to colonic epithelium (10-12).

In agreement with the observational findings, the Women's Health Initiative (WHI) estrogen plus progestin (E+P) clinical trial reported a 40% lower risk for colorectal cancer in the treatment group compared with the placebo group (13). However, the WHI estrogen-alone (E-alone) trial among hysterectomized women did not find a lower risk of colorectal cancer in the treatment group (14). Two recent observational studies also found no reduced risk for colorectal cancer incidence among postmenopausal women with higher circulating levels of estradiol and estrone (15,16). Findings from these studies seemingly suggest that progesterone, but not estrogen, may be the key candidate for risk reduction in colorectal cancer. Alternatively, estrogen effects on colorectal cancer prevention may be modified by other risk factors. In the WHI E-alone trial, different risk estimates were observed in specific age groups; a decrease in colorectal cancer incidence was seen in women aged <70 (p value for age interaction=0.048) (14). Excess body weight in women tends to be associated with increased estrogen levels and it has been suggested that the beneficial effects associated with elevated estrogen levels on colorectal cancer may be offset by the adverse effects of obesity (17). Likewise, the risk associated with estrogen or progesterone may be under genetic control, as these hormones bind to their respective receptors to exert biological actions in target tissues such as the colorectum. Genes responsible for sex-hormone synthesis also affect changes in sex hormone concentrations. Given that the transcriptional activity of genes in target tissues is determined by genetic variation, variation in these hormone-related genes may affect risk for disease development.

Two estrogen receptors, estrogen receptor α (ESR1) and estrogen receptor β (ESR2) have been identified for mediating estrogen action (18). Both ESR1 and ESR2 were found to be expressed, with a greater expression of ESR2, in the gastrointestinal tract, (19,20) and loss of both receptors have been detected in colon tumors (19-22). Progesterone receptor (PGR), activated mostly through binding to progesterone, has been detected at low to moderate levels in both normal and malignant colorectal tissues (23-27), and a lower expression of PGR has been reported in tumors than in normal colorectal mucosa (23). Two other estrogen-synthesizers, the aromatase cytochrome 450 enzyme (encoded by CYP19A1) and 17 beta-hydroxysteroid dehydrogenase type 2 gene (encoded by HSD17B2), have also been linked to growth development in colon cancer cells (28). The CYP19A1 gene is responsible for catalyzing the conversion of testosterone to estradiol and of androstenedione to estrone (29). The HSD17B2 gene plays a key role in the conversion of estradiol to estrone (30). To date, variation in these genes and colorectal cancer risk has been evaluated in three candidate-gene studies (31-33) and six genome-wide association studies (GWAS) (34-39), which have yielded different findings.

In this case-control study nested in a large female health professional cohort, we evaluated variation in ESR1, ESR2, PGR, CYP19A1, and HSD17B2 in relation to risk for colorectal cancer development. We undertook a comprehensive evaluation of common variants and putative functional variants in these 5 genes. We additionally evaluated effect modification by age, BMI, and hormone therapy (HT) use in relation to variation in these 5 genes and colorectal cancer risk.

MATERIALS AND METHODS

Study Population

We conducted a case-control study nested in the Women's Health Study (WHS), a completed randomized trial of aspirin and vitamin E in the primary prevention of cancer and

cardiovascular disease. Beginning in 1993, 39,876 US female health professionals aged ≥45 years and free of cancer or cardiovascular disease enrolled in the study and completed a baseline questionnaire about their medical history and potential risk factors for colorectal cancer. Blood samples were collected in both EDTA and citrate tubes from 28,345 women before randomization. Baseline characteristics of women who provided blood were largely similar to those who did not (40).

In the present analysis, we included 158 women who had a confirmed diagnosis of incident colorectal cancer as of December 2005. A total of 563 healthy controls were randomly selected from the cohort. All cases and controls were Caucasians of European descent.

Single nucleotide polymorphism (SNP) selection

We selected a set of tagging SNPs that capture common variation and linkage disequilibrium (LD) structure across the ESR1 and HSD17B2 genes using the Tagger program implemented in Haploview software (41). The data source for tagging SNP selection was from the CEPH Utah residents with European ancestry in the International Hapmap Project (Release number #18) on the National Center for Biotechnology Information Build 34 assembly available in September 2005 (http://www.hapmap.org). Selection of tagging SNPs was based on a pairwise correlation coefficient (r^2) of 0.8 or greater between tagging SNPs and untyped SNPs and a minor allele frequency (MAF) of 5% or greater in the CEPH population. A total of 15 and 3 tagging SNPs in the ESR1 and HSD17B2 genes, respectively, were selected for subsequent genotyping.

Selection of tagging SNPs in the ESR2, PGR and CYP19A1 genes was based on the studies from the Breast and Prostate Cohort Consortium project (BPC3), which has performed SNP discovery and dense genotyping to capture most common haplotype diversity among multi-ethnic groups including 70 American Caucasians (http://www.uscnorris.com/MECGenetics). The tagging SNPs, chosen from common SNPs with a MAF of 1% or greater among whites, predicted an R_h^2 of 0.70 or greater between observed haplotypes and those predicted based on tagging SNP genotypes (42-44). Altogether, we included 4, 20, and 11 tagging SNPs in ESR2, PGR, and CYP19A1, respectively.

We also undertook a literature search in identifying putative functional SNPs associated with risk of cancers including colorectal cancer. Most of these chosen SNPs were either at coding (synonymous or nonsynonymous) or promoter regions. As a result, an additional 10 SNPs were selected for the 5 genes. In the present analysis of 63 SNPs with a MAF of ≥12%, we had ≥60% power to detect a relative risk of 1.85 or greater using a 2-sided test with a p value of 0.001 (Supplementary Table 1).

Genotyping

Genomic DNA was extracted from the whole blood samples of all subjects by the MagNa Pure LC instrument with the MagNA Pure LC DNA isolation kit (Roche Applied Science, Penzberg, Germany). Genotyping determination was performed with either an ABI fluorescence-based allelic discrimination method (Applied Biosystems, Foster City, CA) on an ABI 7900HT Sequence Detection System or a Sequenom genotyping method (Sequenom, San Diego, CA) according to the respective manufacture's specifications. Lab personnel were blinded to case-control status. Overall, the average call rate for all SNPs was 96%, ranged from 90% to 98%.

Statistical Analysis

Hardy-Weinberg equilibrium was first confirmed for each SNP among control subjects using a chi-square test. Genotyping data were then analyzed with unconditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) as risk estimates for

colorectal cancer in subjects with a linear (log-odds additive) scoring for 0, 1, or 2 copies of the minor allele of each SNP. The analyzed models were first adjusted for age (continuous), fasting status (≥8 hours or fewer), year of blood return (1-year interval), trial randomization date (12-month difference), and random treatment assignment (aspirin vs. placebo, vitamin E vs. placebo). The multivariate models were additionally adjusted for risk factors for colorectal cancer assessed at baseline, including menopausal status (premenopause, postmenopause, uncertain), hormone therapy use (never, past, current), body mass index (BMI, kg/m^2, continuous), physical activity (energy expenditure in kcal/week, continuous), family history of colorectal cancer in a first-degree relative (yes, no), history of colorectal polyps (yes, no), smoking status (never, ever), alcohol consumption (g/day, continuous), and total energy intake (kcal/day, continuous). Because the crude models with adjustment for age, time and status of blood return, and treatment assignment yielded very similar results to the multivariate models (data not shown), we reported here only the results from the multivariate models.

Haplotype frequency and subject-specific expected haplotype indicators were calculated based on the unphased genotype data using the expectation-maximization (EM) algorithm as implemented in SAS procedure PROC HAPLOTYPE (45). We used unconditional logistic regression with additive scoring (ie, number of the copies of specific haplotypes) and the most common haplotype as the referent to estimate haplotype-specific ORs and 95% CIs (46,47). Haplotypes with estimated frequencies of <5% in all subjects were pooled together into a single category. We performed a likelihood ratio test to examine the association between common haplotypes and colorectal cancer risk with a comparison of the log likelihood of the two models with and without additive effects of each haplotype.

To explore the possible joint effects of variation in the 5 genes on colorectal cancer risk, we evaluated multi-locus interaction by performing multifactor dimensionality reduction (MDR) analysis using the MDR software vesion1.0.Orc1. (48-50). The MDR methods perform exhaustive searches of all possible combinations of n loci with cross-validation procedures and reduce n-dimensional data to a single dimensional variable with 2 levels (high vs. low risk). In the present analysis, we allowed the MDR to choose up to 4 loci simultaneously and repeat 10-fold cross validation 10 times. P values were calculated by permutation testing with 1000 permutations.

We also assessed effect modifiers including age (<70, ≥70 years), BMI (<25, ≥25 kgm2), and HT use (current or never) on genetic association with colorectal cancer risk. We performed unconditional logistic regression analysis according to these factors with adjustment for the covariates described above. We performed a global likelihood ratio test with a comparison of the log likelihood of the two models with and without the interaction terms.

To account for the multiple comparison testing made in the study, we calculated the false discovery rate (FDR) for the analysis on each gene using SAS procedure PROC MULTTEST (51). All analyses except for the MDR were performed using SAS statistical package (version 9.1 for window; SAS Institute). All tests were two sided.

RESULTS

We first compared the baseline characteristics of colorectal cancer patients and control subjects (Table 1). Cancer patients were less likely than control subjects to be current users of hormone therapy. However, there was no difference in distribution between cases and controls with respect to several risk factors for colorectal cancer including smoking, history of colon polyps, family history of colorectal cancer, and screening exams. Both cases and controls were also similar in BMI, physical activity, and in total intakes of alcohol, total calories, and fiber.

There were Two (rs2982712 in ESR1 and rs723012 in HSD17B2) among the total 63 SNPs were not in agreement with Hardy-Weinberg equilibrium (HWE) among controls before the FDR correction ($p<0.05$). After the correction for multiple comparisions, however, these two SNPs did not significantly deviate from HWE (FDR p values ≥0.25) and were retained for further analysis (Supplementary Table 1).

For the 63 SNPs evaluated, three SNPs, rs10046 in CYP19A1 and rs2911422 and rs2042429 in HSD17B2 genes, were marginally associated with colorectal cancer risk ($p <0.05$) (Table 2). Women who carried two copies of the minor allele for each of the two SNPs were at a greater risk for developing colorectal cancer as compared with non-carriers of the minor allele (Table 2). However, none of these 3 SNPs remained significant after the FDR correction for multiple testing (FDR p values ≥0.25). For the SNPs residing in the ESR1, ESR2, and PGR genes, there was no evidence of an association with colorectal cancer risk (Table 2).

The MDR analysis also revealed no evidence of interaction among the SNPs for colorectal cancer risk. Four best models identified by the MDR procedure were one 1-factor (rs2982683 in ESR1), one 2-factor (rs12199722 in ESR1 and rs2042429 in HSD17B2), one 3-factor (rs2234693, and rs12199722 in ESR1, and rs2042429 in HSD17B2), and one 4-factor (rs1709183, rs2982712, and rs3798577 in ESR1, and rs2042429 in HSD17B2) models. However, these 4 models had only moderate prediction accuracy (~50%). The cross-validation consistency was low in most models (20 to 70%) and none of the models was significantly associated with the disease status (p values ≥0.51).

The tagging SNPs included in the present analysis represented a total of 16 regions of strong linkage disequilibrium (blocks) covering the 5 genes. Specifically, ESR2 and HSD17B2 each contained 1 haplotype block, and CYP19A1, ESR1, and PGR had 4, 6, and 4 blocks, respectively. There was no significant association between the 16 representative blocks and colorectal cancer risk (global p values ≥0.13). The risk estimates for specific haplotypes relative to the most common haplotypes are presented in Table 3.

When evaluating the association between the SNPs and colorectal cancer risk according to modifying factors, we observed effect modification by BMI for the associations between several SNPs and colorectal cancer risk (p values for interaction <0.05) (Table 4). Notably, the risk associated with the two HSD17B2 SNPs, rs2911242 and rs2042429, was altered by BMI; the reported elevated risk for colorectal cancer was more pronounced among minor-allele carriers with normal BMI. However, none of the interactions remained statistically significant after correction for multiple testing (FDR p values ≥0.25). Age and HT use also did not appear to modify the association (data not shown).

DISCUSSION

In this study of common and coding variation in 3 sex hormone receptors (ESR1, ESR2, PGR) and 2 hormone-synthesizing enzymes (CYP19A1, HSD17B2) in relation to colorectal cancer risk, we observed little evidence for an association of variation in these genes with colorectal cancer risk after correcting for multiple comparisons. There was also no evidence of joint effects among multiple loci residing in these sex-hormone genes on risk for developing colorectal cancer.

Very few candidate-gene studies have evaluated variation in sex-hormone genes in relation to colorectal cancer risk and findings have been mixed. Two studies reported a potential link of two variants, rs9340799 (or XbaI-351) in ESR1 and rs125593 in ESR2, to colorectal cancer development (31,32). However, we did not observe such an association. Variation in CYP19A1 was also not associated with colorectal cancer risk in both our study and the other case-control study of middle-aged men and women (33). To date, six phase-design GWAS of colorectal

cancer have undertaken a comprehensive scan which identified several novel susceptibility loci mapping to 8q24, 8q23.3, 10p14, 15q13, and 18q21 (34-39). However, none of these detected regions harbor the sex-hormone genes evaluated in our study.

Higher circulating levels of sex hormones such as estrogens have been linked to an increased risk for developing breast cancer in postmenopausal women (52-54). However, variation in sex hormone synthesizers such as CYP19A1 which is predictive of estradiol levels has not been associated with breast cancer development (42,55,56). The observations raise the possibility that hormone synthesizers are related to hormonal levels instead of breast cancer susceptibility, although it remains possible that hormone synthesizers could be related to both and more studies are needed.

Evidence from the GWAS of breast cancer showing low odds ratios (<1.5) for the detected loci (57-62) suggests that the effects attributable to common genetic variants on disease susceptibility are likely small. It is, thus, plausible that variation in hormone synthesizers and other sex-hormone genes confers a small contribution to risk for breast cancer development and studies with larger sample sizes are needed for the detection of such small effects (55). A recent breast cancer consortium study of comprehensive analysis on ESR1 variants among >55000 women of European decent reported a weak association (OR=1.05) between an ESR1 variant tagging a conserved region of intron 4 and risk for developing estrogen receptor-positive breast cancer (63); the association with ESR1 variation was later replicated in a genome-wide scan of Chinese women (62). Current studies of other sex hormone-associated cancers such as colorectal cancer, however, are not well powered to detect the potential, possibly small, effects of variation in sex-hormone genes (64).

If genes respond to sex hormones such as estrogens in a similar fashion in colorectal tissue, combination of variants in these genes may have a more measureable effect on colorectal carcinogenesis. In addition to binding to their ligand receptors (ie, ESR1 and ESR2) to exert their biological function in target tissues, estrogens mediate the activity levels of other genes such as vitamin D receptor (VDR) that contain a response element of activation protein-1 (AP-1) (65,66). A recent pathology report has shown that the joint variation in both ESR1 (eg, XbaI variant) and VDR (eg, bsmI variant) may enhance the association with rectal cancer risk, possibly through the inhibitory effects of these 2 genes on the expression of a downstream growth factor, erbB2, in rectal tumors (31). Replication of this finding as well as evaluation of sex hormone genes and other estrogen-responsive genes in relation to colorectal cancer will be addressed in our future studies.

Limitations of this study include the fact that the genotyped SNPs may not sufficiently cover the entire gene regions. Although we have chosen a commonly used selection threshold (r^2 ≥70%) for tagging SNP selection and have also included several functional SNPs, we cannot rule out the possibility that other untyped variants may contribute to risk of developing colorectal cancer. In addition, our single-gene analyses have very limited statistical power after correction for multiple testing. Power is also limited in this study to allow for subgroup analysis according to menopausal status and tumor characteristics such as tumor location and tumor stage.

In summary, our findings offer little support for the association of variation in ESR1, ESR2, and PGR, CYP19A1 and HSD17B2 with colorectal cancer susceptibility in a female Caucasian population. The risks associated with these sex hormone genes are likely small and studies with larger sample sizes are required for such detection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics (mean ± standard deviation or %) among colorectal cancer cases and control subjects in the Women's Health Study.

Characteristics	Cases (N=158)	Controls (N=563)	P_{value}
Age, year (SD)	59.2 (8.5)	58.5 (8.4)	0.34
Body mass index, kg/m^2 (SD)	26.2 (5.4)	25.8 (5.0)	0.38
History of colorectal polyps, %	4.4	2.1	0.11
Family history of colorectal cancer, %	11.4	11.4	>0.9
Colonoscopy/sigmoidoscopy exam, %*	3.2	4.6	0.42
Current smoking, %	7.0	11.7	0.09
Postmenopause, %	73.4	67.1	0.52
Current use of hormone therapy, %	36.1	48.0	<0.01
Current use of multivitamins, %	31.4	30.8	>0.9
Physical activity, kcal/week (SD)	970 (1145)	1065 (1649)	0.41
Alcohol intake, g/day (SD)	4.4 (9.2)	4.4 (8.3)	>0.9
Total energy intake, kcal/day (SD)†	1,724 (523)	1,732 (524)	0.87
Total fiber intake, g/day (SD)†	19 (6)	20 (6)	0.43
Tumor location			
Proximal colon (right-sided), N	63	N/A	
Distal colon + rectum (left-sided), N	92	N/A	
Dukes' stage			
Dukes' A, N	52	N/A	
Dukes' B, N	41	N/A	
Dukes' C, N	60	N/A	

* Information was obtained at the 12-month follow-up questionnaire.

† Nutrient intakes were energy-adjusted.

Table 2

Variation in sex-steroid receptors and hormone-synthesizing enzymes with colorectal cancer risk in the Women's Health Study.

Gene/Variant	0 copies		1 copy		2 copies		P_{trend}	*FDR P*
	case/control	OR	case/control	OR	case/control	OR		
ESR1								
rs2077647	37/155	1.00	82/255	1.36 (0.87-2.13)	29/121	1.02 (0.58-1.80)	0.81	0.95
rs6902771	40/164	1.00	79/270	1.22 (0.79-1.90)	33/106	1.25 (0.73-2.15)	0.39	0.90
rs2234693	37/167	1.00	83/269	1.39 (0.89-2.17)	31/104	1.34 (0.79-2.34)	0.25	0.88
rs9340799	52/229	1.00	78/239	1.41 (0.93-2.13)	18/58	1.45 (0.76-2.75)	0.11	0.88
rs712221	50/189	1.00	73/273	1.02 (0.67-1.56)	28/78	1.36 (0.78-2.38)	0.35	0.90
rs1709183	77/283	1.00	58/225	0.97 (0.65-1.45)	17/37	2.00 (1.04-3.86)	0.18	0.88
rs2347923	73/258	1.00	60/209	1.04 (0.69-1.56)	12/56	0.74 (0.37-1.50)	0.60	0.93
rs12199722	60/249	1.00	71/217	1.41 (0.94-2.12)	16/49	1.39 (0.72-2.70)	0.12	0.88
rs6912184	96/334	1.00	50/182	0.98 (0.65-1.47)	5/26	0.70 (0.25-1.91)	0.62	0.93
rs4583998	73/254	1.00	61/215	0.96 (0.64-1.44)	13/56	0.80 (0.41-1.57)	0.57	0.93
rs1801132	98/337	1.00	52/192	0.95 (0.64-1.41)	5/24	0.73 (0.27-2.03)	0.59	0.93
rs3020314	77/242	1.00	63/251	0.77 (0.52-1.15)	12/53	0.71 (0.35-1.42)	0.16	0.88
rs3020401	78/251	1.00	59/245	0.77 (0.51-1.15)	13/48	0.92 (0.46-1.81)	0.37	0.90
rs2982685	66/211	1.00	60/232	0.78 (0.51-1.18)	18/72	0.81 (0.44-1.48)	0.30	0.88
rs2982683	61/268	1.00	78/227	1.57 (1.06-2.33)	11/43	1.29 (0.61-2.71)	0.08	0.88
rs3020407	73/260	1.00	67/223	1.00 (0.67-1.48)	12/60	0.70 (0.35-1.40)	0.45	0.90
rs9340954	87/294	1.00	58/215	0.91 (0.62-1.35)	8/37	0.66 (0.29-1.51)	0.35	0.90
rs2982712	47/190	1.00	69/213	1.36 (0.88-2.10)	25/102	0.99 (0.56-1.75)	0.76	0.95
rs3020434	107/371	1.00	42/159	0.94 (0.62-1.42)	3/13	0.70 (0.19-2.62)	0.60	0.93
rs3020363	70/251	1.00	65/225	1.04 (0.70-1.55)	17/69	0.85 (0.46-1.57)	0.75	0.95
rs3020370	94/326	1.00	52/188	0.98 (0.65-1.45)	6/26	0.77 (0.30-1.98)	0.68	0.95
rs3798577	44/142	1.00	77/284	0.93 (0.60-1.45)	31/120	0.85 (0.49-1.47)	0.56	0.93
ESR2								
rs1255953	102/399	1.00	46/129	1.46 (0.96-2.21)	4/13	0.99 (0.31-3.18)	0.17	0.77
rs928554	48/176	1.00	68/254	1.01 (0.65-1.55)	35/109	1.12 (0.67-1.87)	0.70	0.77
rs1256031	42/163	1.00	70/256	1.12 (0.72-1.76)	40/120	1.28 (0.77-2.15)	0.34	0.77
rs3020450	72/258	1.00	60/230	1.05 (0.70-1.58)	20/57	1.29 (0.71-2.33)	0.46	0.77

Gene/Variant	0 copies		1 copy		2 copies		P_{trend}	FDR P
	case/control	OR	case/control	OR	case/control	OR		
PGR								
rs473409	82/320	1.00	66/193	1.32 (0.89-1.95)	7/28	0.94 (0.39-2.26)	0.39	0.91
rs484389	90/329	1.00	58/190	1.09 (0.73-1.610	7/24	1.00 (0.41-2.44)	0.77	0.91
rs500760	90/329	1.00	57/188	1.09 (0.74-1.62)	7/24	1.00 (0.41-2.45)	0.76	0.91
rs1042839	103/403	1.00	50/129	1.52 (1.00-2.29)	2/9	0.87 (0.18-4.24)	0.10	0.91
rs545835	38/145	1.00	84/265	1.18 (0.75-1.86)	31/132	0.89 (0.52-1.53)	0.70	0.91
rs1042838	104/402	1.00	49/129	1.47 (0.98-2.23)	2/9	0.86 (0.18-4.20)	0.13	0.91
rs1824128	98/393	1.00	51/133	1.54 (1.02-2.32)	4/15	1.15 (0.36-3.68)	0.08	0.91
rs477151	78/275	1.00	62/214	1.02 (0.69-1.50)	8/48	0.62 (0.28-1.40)	0.46	0.91
rs559700	103/401	1.00	48/132	1.42 (0.94-2.15)	2/10	0.76 (0.16-3.67)	0.21	0.91
rs516693	120/419	1.00	31/117	0.87 (0.55-1.38)	4/7	2.13 (0.50-9.02)	0.98	0.99
rs508533	58/211	1.00	77/252	1.11 (0.74-1.65)	19/79	0.94 (0.51-1.71)	0.98	0.99
rs572483	69/239	1.00	70/242	0.98 (0.66-1.45)	14/61	0.82 (0.42-1.61)	0.64	0.91
rs543215	102/376	1.00	44/152	1.04 (0.68-1.58)	7/14	1.95 (0.74-5.15)	0.38	0.91
rs613120	38/139	1.00	75/280	0.93 (0.58-1.47)	40/120	1.22 (0.72-2.06)	0.46	0.91
rs529359	55/211	1.00	73/246	1.15 (0.76-1.72)	20/78	0.99 (0.55-1.80)	0.82	0.91
rs481775	67/227	1.00	75/243	1.05 (0.7-1.55)	40/66	0.61 (0.30-1.22)	0.35	0.91
rs1379130	71/231	1.00	71/251	0.93 (0.63-1.37)	13/68	0.64 (0.33-1.26)	0.26	0.91
rs3740753	98/386	1.00	46/129	1.37 (0.90-2.09)	2/8	1.02 (0.21-5.02)	0.20	0.91
CYP19A1								
rs4646	84/283	1.00	57/220	0.82 (0.55-1.22)	10/37	0.82 (0.38-1.77)	0.34	0.93
rs10046	31/153	1.00	77/270	1.26 (0.78-2.03)	42/120	1.72 (1.01-2.95)	0.05	0.64
rs2414096	31/148	1.00	76/250	1.32 (0.82-2.13)	37/119	1.39 (0.80-2.42)	0.24	0.90
rs727479	61/226	1.00	68/252	1.03 (0.69-1.54)	24/63	1.59 (0.90-2.80)	0.20	0.88
rs1008805	43/179	1.00	77/262	1.32 (0.85-2.03)	32/99	1.29 (0.75-2.21)	0.29	0.91
rs749292	56/175	1.00	66/264	0.79 (0.52-1.28)	28/104	0.85 (0.50-1.44)	0.44	0.93
rs936306	109/378	1.00	34/136	0.82 (0.46-1.46)	4/12	1.33 (0.41-4.37)	0.64	0.95
rs3751591	103/380	1.00	42/150	1.05 (0.69-1.60)	6/15	1.39 (0.56-1.90)	0.59	0.93
rs1004984	62/224	1.00	70/258	0.96 (0.64-1.43)	19/60	1.03 (0.56-1.90)	0.99	0.99
rs2445762	84/296	1.00	59/214	0.91 (0.61-1.34)	9/34	0.84 (038-1.88)	0.55	0.93
rs2470144	44/156	1.00	81/274	1.02 (0.66-1.58)	27/115	0.79 (0.46-1.37)	0.46	0.93

Gene/Variant	0 copies		1 copy		2 copies		P_{trend}	*FDR P*
	case/control	OR	case/control	OR	case/control	OR		
rs2445765	106/381	1.00	44/137	1.10 (0.72-1.66)	1/19	0.17 (0.02-1.28)	0.48	0.93
rs2446405	108/383	1.00	44/141	1.02 (0.68-1.55)	0/20	--	0.19	0.88
HSD17B2								
rs4445895	60/226	1.00	70/248	1.01 (0.68-1.52)	22/66	1.30 (0.73-2.32)	0.47	0.77
rs6564961	50/202	1.00	69/243	1.13 (0.74-1.74)	23/71	1.43 (0.79-2.56)	0.25	0.59
rs2911422	38/173	1.00	76/278	1.28 (0.82-2.00)	33/88	1.76 (1.01-3.06)	0.05	0.25
rs2042429	39/162	1.00	68/269	1.08 (0.69-1.71)	39/94	1.83 (1.07-3.10)	0.04	0.25
rs723012	63/203	1.00	74/272	0.91 (0.61-1.36)	13/62	0.70 (0.35-1.41)	0.34	0.62
rs9939740	62/178	1.00	68/273	0.71 (0.47-1.07)	19/84	0.69 (0.38-1.24)	0.11	0.39

*. OR=odds ratio; 95% CI= 95% confidence interval.

†. Multivariate models were adjusted for age (continuous), fasting status (≥8 hours or fewer), year of blood return (1-year interval), trial randomization date (12-month difference), random treatment assignment (aspirin vs. placebo, vitamin E vs. placebo), and additionally for risk factors for colorectal cancer assessed at baseline, including menopausal status (premenopause, postmenopause, uncertain), hormone therapy use (never, past, current), body mass index (kg/m^2, continuous), physical activity (energy expenditure in kcal/week, continuous), family history of colorectal cancer in a first-degree relative (yes, no), history of colorectal polyps (yes, no), smoking status (never, ever), alcohol consumption (g/day, continuous), and total energy intake (kcal/day, continuous).

Table 3

Haplotype-based association of sex-steroid receptors (ESR1, ESR2, and PGR) and hormone synthesizing enzymes (CYP19A1 and HSD17B2) with colorectal cancer risk in the Women's Health Study*.

Gene/Block #	N case (%)	N control (%)	OR (95% CI)	P_{trend}	*FDR P*
ESR1					
Block 1					
C-T-A	143 (50)	558 (55)	1.00	0.37	0.90
T-C-G	111 (39)	343 (34)	1.29 (0.96-1.75)		
T-C-A	26 (9)	106 (10)	0.97 (0.60-1.57)		
Freq <5%	4 (1)	13 (1)	0.86 (0.26-2.91)		
Block 2					
A-A	99 (36)	385 (40)	1.00	0.24	0.88
A-G	96 (35)	293 (30)	1.34 (0.95-1.88)		
C-A	79 (29)	294 (30)	1.00 (0.78-1.55)		
Block 3					
A-G-C	199 (71)	706 (69)	1.00	0.96	0.97
G-A-G	55 (19)	214 (21)	0.92 (0.64-1.30)		
A-A-C	27 (10)	101 (10)	0.94 (0.59-1.50)		
Freq <5%	1 (0.4)	3 (0.3)	1.21 (0.08-18.7)		
Block 4					
T-A	212 (71)	729 (67)	1.00	0.50	0.93
C-G	82 (27)	336 (31)	0.84 (0.62-1.13)		
Freq<5%	6 (2)	21 (2)	0.92 (0.35-2.39)		
Block 5					
G-C	95 (34)	363 (36)	1.00	0.21	0.88
A-C	88 (32)	344 (34)	0.96 (0.68-1.34)		
A-T	93 (34)	291 (29)	1.29 (0.92-1.82)		
Block 6					
T-C-T	155 (58)	574 (58)	1.00	0.22	0.88
C-T-C	43 (16)	167 (17)	0.91 (0.61-1.36)		
C-C-C	41 (15)	161 (16)	0.91 (0.61-1.35)		
C-C-T	29 (11)	74 (8)	1.62 (1.00-2.63)		

Gene/Block #	N case (%)	N control (%)	OR (95% CI)	P_{trend}	*FDR P*
Freq <5%	0	2 (0.2)	--		
ESR2					
Block 1					
C-C-G	127 (43)	452 (43)	1.00	0.13	0.77
T-T-A	92 (31)	331 (31)	1.03 (0.76-1.40)		
T-T-G	56 (19)	231 (22)	0.85 (0.59-1.22)		
Freq <5%	19 (7)	42 (4)	1.92 (1.03-3.59)		
PGR					
Block 1					
A-C-G-C	99 (33)	387 (36)	1.00	0.15	0.91
A-T-G-C	73 (24)	285 (27)	0.99 (0.09-1.42)		
A-C-G-A	53 (17)	153 (14)	1.33 (0.88-2.01)		
C-T-T-C	52 (17)	146 (14)	1.42 (0.95-2.14)		
C-T-G-C	21 (7)	90 (8)	0.78 (0.43-1.41)		
Freq<5%	6 (2)	11 (1)	2.42 (0.79-7.38)		
Block 2					
T-A-G-A	94 (33)	377 (36)	1.00	0.32	0.91
C-A-G-C	76 (27)	298 (28)	1.03 (0.73-1.47)		
T-G-G-A	50 (17)	145 (14)	1.41 (0.93-2.14)		
T-A-A-A	34 (12)	128 (12)	1.02 (0.64-1.63)		
T-A-G-C	32 (11)	99 (9)	1.29 (0.80-2.08)		
Freq <5%	0	5 (0.5)	--		
Block 3					
A-T-T	94 (31)	377 (35)	1.00	0.16	0.91
G-T-C	96 (31)	357 (33)	1.07 (0.76-1.50)		
A-C-T	56 (18)	178 (17)	1.26 (0.85-1.87)		
A-T-C	58 (19)	162 (15)	1.47 (0.98-2.20)		
Freq<5%	2 (1)	2 (0.2)	6.99 (0.89-54.8)		
Block 4					
G-C-C	103 (38)	373 (38)	1.00	0.51	0.91
A-T-C	85 (31)	349 (35)	0.87 (0.62-1.22)		
A-C-G	48 (18)	134 (14)	1.26 (0.82-1.94)		

Gene/Block #	N case (%)	N control (%)	OR (95% CI)	P_{trend}	*FDR P*
A-C-C	33 (12)	130 (13)	0.88 (0.56-1.39)		
Freq<5%	1 (0.4)	2 (0.2)	1.67 (0.12-22.5)		
CYP19A1					
Block 1					
G-T-A-T	125 (47)	497 (51)	1.00	0.23	0.90
G-C-G-G	58 (22)	162 (17)	1.49 (1.01-2.19)		
T-C-G-G	37 (14)	154 (16)	0.95 (0.62-1.46)		
T-C-G-T	31 (12)	97 (10)	1.14 (0.67-1.95)		
Freq < 5%	15 (6)	68 (6)	0.82 (0.43-1.57)		
Block 2					
C-C	135 (46)	452 (43)	1.00	0.74	0.98
T-T	118 (41)	461 (43)	0.87 (0.66-1.16)		
T-C	39 (13)	148 (14)	0.89 (0.59-1.35)		
Freq <5%	0	1 (0.1)	--		
Block 3					
G-T	217 (75)	801 (77)	1.00	0.48	0.93
G-C	30 (10)	79 (8)	1.39 (0.88-2.22)		
A-C	24 (8)	93 (9)	0.93 (0.55-1.58)		
A-T	15 (5)	63 (6)	0.88 (0.48-1.59)		
Block 4					
C-A-A-C-A	159 (54)	562 (54)	1.00	0.69	0.95
T-G-G-C-A	63 (21)	208 (20)	1.03 (0.72-1.46)		
T-A-G-G-T	31 (10)	111 (11)	0.92 (0.59-1.45)		
C-A-G-C-A	15 (5)	54 (5)	1.10 (0.59-2.06)		
Freq <5%	24 (10)	113 (10)	0.71 (0.43-1.17)		
HSD17B2					
Block 1					
C-A-G-T-T	79 (32)	326 (35)	1.00	0.55	0.79
T-G-C-C-C	88 (35)	289 (31)	1.25 (0.87-1.78)		
C-A-G-T-C	42 (17)	170 (18)	1.01 (0.66-1.56)		
C-A-G-T-C	14 (6)	0	--		

Gene/Block #	N case (%)	N control (%)	OR (95% CI)	P_{trend}	*FDR P*
Freq <5%	27 (10)	223 (20)	1.04 (0.65-1.65)		

*Multivariate models were adjusted for age (continuous), fasting status (≥8 hours or fewer), year of blood return (1-year interval), trial randomization date (12-month difference), random treatment assignment (aspirin vs. placebo, vitamin E vs. placebo), and additionally for risk factors for colorectal cancer assessed at baseline, including menopausal status (premenopause, postmenopause, uncertain), hormone therapy use (never, past, current), body mass index (kg/m^2, continuous), physical activity (energy expenditure in kcal/week, continuous), family history of colorectal cancer in a first-degree relative (yes, no), history of colorectal polyps (yes, no), smoking status (never, ever), alcohol consumption (g/day, continuous), and total energy intake (kcal/day, continuous).

Table 4

Associated SNPs with colorectal cancer risk according to risk modifiers for colorectal cancer in the Women's Health Study*.

Gene/Variant	# copies	N cases (%)	N controls (%)	OR (95% CI)†‡	N cases (%)	N controls (%)	OR (95% CI)†‡	$P_{interaction}$	*FDR P*
		BMI <25 kg/m^2			BMI ≥25 kg/m^2				
HSD17B2									
rs6564961	0	19 (27)	115 (42)	1.00	30 (42)	83 (35)	1.00	0.05	0.25
	1	41 (59)	128 (47)	2.19 (1.14-4.22)	28 (39)	110 (47)	0.65 (0.35-1.22)		
	2	10 (14)	29 (11)	3.33 (1.27-8.74)	13 (18)	41 (18)	0.88 (0.40-1.93)		
rs2911422	0	12 (16)	100 (35)	1.00	25 (34)	71 (29)	1.00	0.02	0.25
	1	45 (62)	147 (51)	3.02 (1.46-6.26)	31 (23)	125 (52)	0.62 (0.32-1.18)		
	2	16 (22)	41 (14)	3.86 (1.58-9.43)	17 (23)	45 (19)	0.98 (0.45-2.10)		
rs2042429	0	12 (16)	91 (33)	1.00	26 (37)	71 (30)	1.00	0.01	0.25
	1	41 (55)	143 (51)	2.44 (1.15-5.13)	27 (38)	119 (50)	0.59 (0.31-1.12)		
	2	21 (28)	46 (16)	3.88 (1.65-9.12)	18 (25)	46 (19)	1.05 (0.50-2.21)		
ESR1									
rs2077647	0	24 (32)	81 (29)	1.00	13 (18)	71 (30)	1.00	0.04	0.88
	1	36 (47)	136 (48)	0.84 (0.45-1.56)	46 (65)	115 (48)	2.34 (1.15-4.75)		
	2	16 (21)	66 (23)	0.86 (0.40-1.85)	12 (17)	52 (22)	1.35 (0.55-3.32)		
rs2982685	0	25 (34)	115 (42)	1.00	41 (59)	92 (40)	1.00	0.04	0.88
	1	37 (50)	120 (44)	1.38 (0.75-2.53)	22 (32)	109 (47)	0.40 (0.21-0.76)		
	2	12 (16)	38 (14)	1.19 (0.51-2.76)	6 (9)	31 (13)	0.38 (0.14-1.03)		
PGR									
rs545835	0	27 (35)	77 (27)	1.00	11 (15)	65 (26)	1.00	0.03	0.91
	1	37 (48)	143 (50)	0.67 (0.36-1.25)	46 (61)	117 (48)	2.20 (1.03-4.70)		
	2	13 (17)	67 (23)	0.46 (0.21-1.02)	18 (24)	63 (26)	1.78 (0.75-4.24)		
rs477151	0	46 (62)	142 (50)	1.00	32 (43)	128 (53)	1.00	0.05	0.91
	1	24 (32)	118 (42)	0.57 (0.32-1.03)	38 (51)	92 (38)	1.79 (1.00-3.21)		
	2	4 (5)	24 (8)	0.42 (0.13-1.39)	4 (5)	23 (9)	0.82 (0.25-2.69)		
rs508533	0	35 (45)	105 (37)	1.00	23 (31)	102 (42)	1.00	0.02	0.91
	1	32 (41)	146 (51)	0.60 (0.34-1.07)	44 (59)	101 (41)	2.10 (1.12-3.91)		
	2	11 (14)	36 (12)	0.79 (0.34-1.85)	8 (11)	42 (17)	1.05 (0.41-2.66)		

[*] Included analysis with cell frequency ≥5%.

[†] OR=odds ratio; 95% CI= 95% confidence interval.

[‡] Multivariate models were adjusted for age (continuous), fasting status (≥8 hours or fewer), year of blood return (1-year interval), trial randomization date (12-month difference), random treatment assignment (aspirin vs. placebo, vitamin E vs. placebo), and additionally for risk factors for colorectal cancer assessed at baseline, including menopausal status (premenopause, postmenopause, uncertain), hormone therapy use (never, past, current), body mass index (kg/m^2, continuous), physical activity (energy expenditure in kcal/week, continuous), family history of colorectal cancer in a first-degree relative (yes, no), history of colorectal polyps (yes, no), smoking status (never, ever), alcohol consumption (g/day, continuous), and total energy intake (kcal/day, continuous).