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Circulating Levels of Insulin-like Growth Factor 1 and Insulin-like Growth Factor Binding Protein 3 Associate With Risk of Colorectal Cancer Based on Serologic and Mendelian Randomization Analyses

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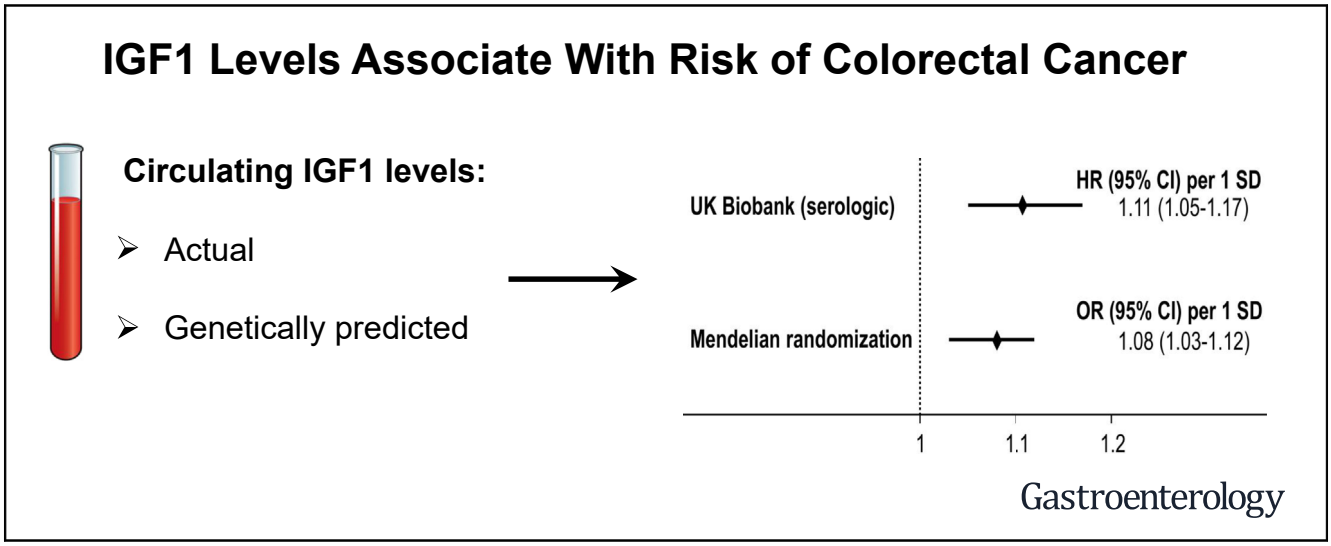

BACKGROUND & AIMS: Human studies examining associations between circulating levels of insulin-like growth factor 1 (IGF1) and insulin-like growth factor binding protein 3 (IGFBP3) and colorectal cancer risk have reported inconsistent results. We conducted complementary serologic and Mendelian randomization (MR) analyses to determine whether alterations in circulating levels of IGF1 or IGFBP3 are associated with colorectal cancer development.
METHODS: Serum levels of IGF1 were measured in blood samples collected from 397,380 participants from the UK Biobank, from 2006 through 2010. Incident cancer cases and cancer cases recorded first in death certificates were identified through linkage to national cancer and death registries. Complete follow-up was available through March 31, 2016. For the MR analyses, we identified genetic variants associated with circulating levels of IGF1 and IGFBP3. The association of these genetic variants with colorectal cancer was examined with 2-sample MR methods using genome-wide association study consortia data (52,865 cases with colorectal cancer and 46,287 individuals without [controls])
RESULTS: After a median follow-up period of 7.1 years, 2665 cases of colorectal cancer were recorded. In a multivariable-adjusted model, circulating level of IGF1 associated with colorectal cancer risk (hazard ratio per 1 standard deviation increment of IGF1, 1.11; 95% confidence interval [CI] 1.05–1.17). Similar associations were found by sex, follow-up time, and tumor subsite. In the MR analyses, a 1 standard deviation increment in IGF1 level, predicted based on genetic factors, was associated with a higher risk of colorectal cancer risk (odds ratio 1.08; 95% CI 1.03–1.12; $P = 3.3 \times 10^{-4}$). Level of IGFBP3, predicted based on genetic factors, was associated with colorectal cancer risk (odds ratio per 1 standard deviation increment, 1.12; 95% CI 1.06–1.18; $P = 4.2 \times 10^{-5}$). Colorectal cancer risk was associated with only 1 variant in the *IGFBP3* gene region (rs11977526), which also associated with anthropometric traits and circulating level of IGF2.
CONCLUSIONS: In an analysis of blood samples from almost 400,000 participants in the UK Biobank, we found an association between circulating level of IGF1 and colorectal cancer. Using genetic data from 52,865 cases with colorectal cancer and 46,287 controls, a higher level of IGF1, determined by genetic factors, was associated with colorectal cancer. Further studies are needed to determine how this signaling pathway might contribute to colorectal carcinogenesis.

Keywords: CRC; Risk Factors; Signal Transduction; GWAS.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Human studies examining associations between circulating levels of insulin-like growth factor 1 (IGF1) and insulin-like growth factor binding protein 3 (IGFBP3) and colorectal cancer risk have reported inconsistent results

NEW FINDINGS

In an analysis of blood samples from almost 400,000 participants in the UK Biobank, we found an association between circulating level of IGF1 and colorectal cancer. Using genetic data on 52,865 persons with colorectal cancer and 46,287 persons without, a higher level of IGF1, determined by genetic factors, was also associated with colorectal cancer. Further studies are needed to determine how this signaling pathway might contribute to colorectal carcinogenesis.

LIMITATIONS

This is an association study between measured and genetically determined blood levels of proteins and cancer incidence.

IMPACT

Changes in IGF signaling might contribute to colorectal carcinogenesis, but further studies are needed to determine the mechanisms of this process.

Insulin-like growth factor-1 (IGF1) has mitogenic and anti-apoptotic effects and has been implicated in the development and progression of several cancers.[1,2] The bioactivity of IGF1 is partially regulated through insulin-like growth factor binding proteins (IGFBPs-), with approximately 80% bound to IGFBP3.[3] In addition to its IGF-binding properties, IGFBP3 also has been shown to exhibit direct antiproliferative and pro-apoptotic effects.[4,5] Multiple epidemiological studies have investigated the associations of circulating IGF1 and IGFBP3 levels with colorectal cancer risk.[6–14] However, most of these studies were of relatively small size (<500 colorectal cancer cases) and reported inconsistent results. As such, there is currently a lack of consensus as to whether higher circulating levels of IGF1 and lower levels of IGFBP3 are risk factors for colorectal cancer.

To address this, we conducted complementary serologic and Mendelian randomization (MR) analyses to examine the role of circulating IGF1 and IGFBP3 in colorectal cancer development. We investigated how prediagnostic circulating levels of IGF1 are related to colorectal cancer risk in the UK Biobank study, a large prospective cohort. We then used a 2-sample MR approach to obtain causal estimates of the associations by combining genetic variants associated with circulating IGF1 and IGFBP3 levels in genome-wide association studies (GWAS) and then assessing the association of these variants with colorectal cancer risk in a large consortium of 52,865 colorectal cancer cases and 46,287 controls.[15]

Abbreviations used in this paper: **BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; GWAS, genome-wide association studies; HbA1c, glycolated hemoglobin; HR, hazard ratio; ICC, intraclass correlation coefficient; IGF1, insulin-like growth factor 1; IGFBP3, insulin-like growth factor binding protein 3; MR, Mendelian randomization; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier; OR, odds ratio; SD, standard deviation; SHBG, sex hormone binding globulin; SNP, single nucleotide polymorphism.**

Most current article

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Methods

UK Biobank: Serologic Analysis

Study participants. The UK Biobank is a prospective cohort study that aims to investigate the genetic, lifestyle, and environmental causes of a range of diseases.[16,17] This research has been conducted using the UK Biobank Resource under application number 25897. Between 2006 and 2010, 502,656 adults aged between 40 and 69 years (229,182 men and 273,474 women) were recruited. All participants were registered with the UK National Health Service and lived within approximately 25 miles (40 km) of 1 of the 22 study assessment centers. The UK Biobank invited approximately 9.2 million people to participate through postal invitation with a telephone follow-up, with a response rate of 5.7%. The UK Biobank has approval from the North West Multi-centre Research Ethics Committee, the National Information Governance Board for Health and Social Care in England and Wales, and the Community Health Index Advisory Group in Scotland. In addition, an independent Ethics and Governance Council was formed in 2004 to oversee the UK Biobank's continuous adherence to the Ethics and Governance Framework that was developed for the study (http://www.ukbiobank.ac.uk/ethics/). All participants provided written informed consent. During the baseline recruitment visit, participants were asked to complete a self-administered touchscreen questionnaire, which included questions on sociodemographics (including age, sex, education, and Townsend deprivation score), health and medical history, lifestyle exposures (including smoking habits, dietary intakes, and alcohol consumption), early life exposures, and medication use. At the baseline visit, participants also underwent physical measurements, including body weight, height, and waist circumference. Blood samples were collected from all participants at recruitment and from a subset of approximately 20,000 participants who re-attended the assessment center between 2012 and 2013 for a repeat assessment visit. Blood samples were labeled, centrifuged, and stored at −80°C.

Exclusions before the onset of analyses were participants with prevalent cancer at recruitment (n = 27,264); missing data on body size measurements (n = 3032); prevalent type-2 diabetes or unknown diabetes status at recruitment (as diabetes medications can affect circulating levels of IGF proteins[18]; n = 26,698); those who reported oral contraceptive and menopausal hormone use at recruitment (as oral estrogens exert a strong first-pass effect on the liver that alters hepatic protein production and changes circulating levels of multiple hormones, including IGF-system markers[18]; n = 19,802); and participants without an IGF1 measurement (n = 28,480). Our analysis therefore included 397,380 participants.

Blood collection and laboratory methods. As part of the UK Biobank Biomarker Project,[19] serum levels of IGF1 (DiaSorin Liaison XL), testosterone, and sex hormone binding globulin (SHBG) (all Beckman Coulter DXI 800) were determined by a chemiluminescent immunoassay. The Immunoturbidimetric method (Beckman Coulter DXI 800) was used to assay serum high sensitivity C-reactive protein (CRP) levels. Glycated hemoglobin (HbA1c) levels were determined using the high-performance liquid chromatography Variant II Turbo 2.0 system (Bio-Rad, Hercules, CA). Full details on assay performance have been published.[19] In summary, average within-laboratory (total) coefficient of variation for low, medium, and high internal quality control level samples for each biomarker ranged from 1.7% to 15.3% (for IGF1, the coefficients of variation ranged from 5.3% to 6.2%).[19] A total of 16,357 participants had IGF1 levels measured in blood samples collected at both the recruitment and repeat assessment visit (median of 4 years apart).

Assessment of outcome. Incident cancer cases and cancer cases recorded first in death certificates within the UK Biobank cohort were identified through linkage to national cancer and death registries. Complete follow-up was available through March 31, 2016, for England and Wales and October 31, 2015, for Scotland. Cancer incidence data were coded using the 10th Revision of the International Classification of Diseases (ICD-10). Proximal colon cancers included those found within the cecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure (C18.0–18.5). Distal colon cancers included those found within the descending (C18.6) and sigmoid (C18.7) colon. Overlapping (C18.8) and unspecified (C18.9) lesions of the colon were included in colon cancers only. Cancer of the rectum included cancers occurring at the recto-sigmoid junction (C19) and rectum (C20).

Statistical analysis. To assess reproducibility between the 2 measurements of IGF1 available in a subsample of participants, we calculated intraclass correlation coefficients (ICC) by dividing the between-person variance by the sum of the between-person and within-person variances.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models. Age was the primary time variable in all models. Time at entry was age at recruitment. Exit time was age at whichever of the following came first: colorectal cancer diagnosis, death, or the last date at which follow-up was considered complete. Models were stratified by age at recruitment in 5-year categories, Townsend deprivation index quintiles, and region of the recruitment assessment centre. Deviations from proportionality were assessed using an analysis of Schoenfeld residuals,[20] with no evidence of nonproportionality detected. IGF1 was modeled on the continuous scale (per 1-standard deviation [SD] increment of log-IGF1) and with participants grouped into sex-specific quintiles of circulating levels. Continuous scale models were additionally corrected for regression dilution using regression dilution ratios obtained from participants with repeated IGF1 measurement.[21,22] To obtain corrected HRs, the log HRs and their standard errors were divided by the regression dilution ratio for IGF1 (0.76) and then exponentiated.[23]

The multivariable model (model 1) was adjusted for a set of a priori–determined colorectal cancer risk factors, namely waist circumference, total physical activity, height, alcohol consumption frequency, smoking status and intensity, frequency of red and processed meat consumption, family history of colorectal cancer, educational level, regular aspirin/ibuprofen use, and ever use of hormone replacement therapy. We also additionally adjusted the multivariable models (model 2) for markers of inflammation, sex hormones, and glycemic pathways that are known to interrelate/cross talk with IGF-system markers,[18] and have been linked to colorectal cancer risk in some studies,[24–27] namely CRP, testosterone, SHBG, and HbA1c. Statistical tests for trend were calculated using the ordinal quintile IGF1 entered into the model as a continuous variable. Analyses were also conducted by sex and anatomic

subsite (colon, proximal colon, distal colon, and rectal cancer). Heterogeneity of associations by sex and across subsite was assessed by calculating χ^2 statistics. Possible nonlinear effects were modeled using restricted cubic spline models with 5 knots placed at Harrell's default percentiles of circulating IGF1 levels.[28]

The associations between circulating IGF1 and colorectal cancer were further assessed across subgroups of body mass index (BMI; <25, ≥25 kg/m^2), height (below or above median), age at recruitment (<60 years, ≥60 years), follow-up time (<5 years, ≥5 years), smoking status (never, former, current), and circulating levels (below or above median) of CRP, HbA1c, testosterone, and SHBG. Interaction terms (multiplicative scale) between these variables and circulating IGF1 levels were included in separate models and the statistical significance of the cross-product terms were evaluated using the likelihood ratio test. In a sensitivity analysis, we excluded those participants with circulating levels of HbA1c ≥48 mmol/mol (or 6.5%, the cutoff for type-2 diabetes).

Statistical tests were all 2-sided and $P < 0.05$ was considered statistically significant.

Mendelian Randomization

We conducted 2-sample MR analyses, in which 2 different independent study samples (GWAS) were used to estimate the single nucleotide polymorphism (SNP)-risk factor (circulating IGF1 and IGFBP3 levels) and SNP-outcome (colorectal cancer) associations to allow causal effect estimates of risk factor-outcome association to be obtained.

Genetic determinants of IGF1 and IGFBP3. Genetic markers for circulating IGF1 and IGFBP3 levels comprised SNPs that were identified ($P < 5 \times 10^{-8}$) from the largest GWAS to date.[29,30] For IGF1, this GWAS was of 358,072 participants from the UK Biobank.[29] The GWAS analyses of IGFBP3 combined data on 18,995 individuals from 13 studies.[30] All participants were of European ancestry. From the genome-wide significant variants identified in these GWAS, we excluded correlated SNPs based on a linkage disequilibrium level of $R^2 < 0.01$. Consequently, the instruments for IGF1 (413 SNPs spanning 22 autosomes) and IGFBP3 (4 SNPs spanning 3 autosomes) explained 9.4% (F-statistic 89.9) and 6.1% (F-statistic 308.4) of variability in circulating levels, respectively. Summary information on the genetic instruments and the effect estimates for each individual SNP regarding their association with IGF1 and IGFBP3 levels are presented in Supplementary Tables 1 and 2.

Data on colorectal cancer. Summary data for the associations of the IGF1- and IGFBP3-related genetic variants with colorectal cancer were obtained from a GWAS of 99,152 participants (52,865 colorectal cancer cases and 46,287 controls). The GWAS data were from a meta-analysis within the ColoRectal Transdisciplinary Study, the Colon Cancer Family Registry, and the Genetics and Epidemiology of Colorectal Cancer consortium.[15] Imputation was performed using the Haplotype Reference Consortium r1.0 reference panel and the regression models were further adjusted for age, sex, genotyping platform (whenever appropriate), and genomic principal components as detailed here.[31] Strength-of-association estimates for each individual SNP with colorectal cancer are presented in Supplementary Table 2.

Statistical power. The a priori statistical power was calculated using an online tool at http://cnsgenomics.com/shiny/mRnd/.[32] Given a type 1 error of 5%, we had sufficient power (>80%) to detect an odds ratio (OR) per 1 SD for colorectal cancer risk of ≤0.94/≥1.06 for IGF1 and ≤0.93/≥1.08 for IGFBP3.

Statistical analysis. A 2-sample MR approach using summary data and a likelihood-based approach was implemented. Likelihood-based MR analyses are considered the most accurate method to estimate causal effects when there is a continuous log-linear association between risk factor and disease risk. The causal estimate of X on Y (β), assumed to be the same for all genetic variants (k), is obtained from the likelihood function of the following model[33,34]:

$$X_k \sim \mathcal{N}(\xi_k,\ \sigma^2_{Xk})$$

$$Y_k \sim \mathcal{N}(\beta_L \xi_k, \sigma^2_{Yk}) \text{ for } k = 1,\ \ldots., K.$$

MR results correspond to an OR per 1-SD increment in genetically predicted circulating levels of IGF1 and IGFBP3. Heterogeneity of associations by sex and across colorectal anatomic subsites was assessed by calculating χ^2 statistics. Cochran's Q statistics quantified heterogeneity across the individual SNPs. Sensitivity analyses were used to check and correct for the presence of pleiotropy in the causal estimates. To evaluate the extent to which directional pleiotropy (nonbalanced horizontal pleiotropy in the MR risk estimates) may have affected the causal estimates for the IGF1 and colorectal cancer association, we used an MR-Egger regression approach.[35] We also computed OR estimates using the complementary weighted-median method that can give valid MR estimates under the presence of horizontal pleiotropy when up to 50% of the included instruments are invalid.[36] The MR-PRESSO (Mendelian Randomization Pleiotropy RESidual Sum and Outlier) distortion test was used to estimate if horizontal pleiotropy caused by any identified outlier SNPs biased the effect estimates ($P < .05$).[37] As a visual evaluation of pleiotropy, we also provided funnel plots depicting the weight exerted on the effect estimate along the y-axis and estimates of the effect on colorectal cancer along the x-axis for each SNP used in the corresponding instrumental variable. For the IGFBP3 instrument that had 4 SNPs, we conducted leave-one-out analyses to assess the influence of individual variants on the observed associations.

Results

UK Biobank: Serologic Analysis

After a median follow-up time of 7.1 years, 2665 cases of colorectal cancer (1539 in men and 1126 in women) were recorded. Compared with those in the lowest quintile, participants in the highest circulating IGF1 quintile were younger, taller, had lower BMI and waist circumference, were more likely to be never smokers, and less likely to be daily or almost daily consumers of alcohol and to be regular aspirin/ibuprofen users (Table 1). In addition, participants in the highest circulating IGF1 quintile had lower circulating CRP, testosterone, SHBG, and HbA1c levels.

The reproducibility (ICC) of IGF1 levels measured at both the recruitment and repeat assessment visit (n = 16,357 participants; median of 4 years apart) was 0.78 (95% CI 0.77–0.79).

Association between circulating IGF1 levels and colorectal cancer risk. For men and women combined, higher circulating IGF1 levels were associated with elevated colorectal cancer risk in the multivariable models (model 1, HR comparing quintile 5 vs 1 [q5 – q1] = 1.24, 95% CI 1.10–1.40; *P*-trend = .006) (Table 2). This positive association strengthened after additional adjustment for circulating levels of CRP, HbA1c, testosterone, and SHBG (model 2, HR [q5 – q1] = 1.34, 95% CI 1.18–1.52; *P*-trend < 0.0001). In the restricted cubic spline model, no deviation from linearity for the relationship between IGF1 and colorectal cancer was observed (*P*-nonlinear = 0.91). In the continuous multivariable model 2, adjusted for circulating levels of CRP, HbA1c, testosterone, and SHBG, a 1-SD increment of IGF1 was associated with an 8% higher colorectal cancer risk (HR 1.08; 95% CI 1.04–1.13). Correction for regression dilution resulted in a stronger positive association (HR per 1-SD increment of IGF1, HR 1.11; 95% CI 1.05–1.17) (Table 2; Figure 1). Similar magnitude positive associations were found for men and women (*P*-heterogeneity = .1), and across anatomic subsites (colon vs rectal, *P*-heterogeneity = 1; proximal colon vs distal colon, *P*-heterogeneity = 0.8) (Table 2).

The positive association observed between circulating IGF1 levels and colorectal cancer was evident across subgroups of BMI, height, age at recruitment/blood collection, follow-up time, smoking status, and circulating levels of CRP, HbA1c, testosterone, and SHBG (all *P*-interactions ≥ .1) (Figure 1). In a sensitivity analysis, similar relationships for circulating IGF1 levels and colorectal cancer were found when participants with HbA1c levels ≥48 mmol/mol (or 6.5%, cutoff for type-2 diabetes), were excluded from the analyses (Supplementary Table 3).

Mendelian Randomization

Association between genetically determined circulating IGF1 levels and colorectal cancer risk. We estimated that a 1-SD increment in genetically determined IGF1 levels was associated with an 8% higher colorectal cancer risk (OR 1.08; 95% CI 1.03–1.12; *P* value = 3.3×10^{-4}) (Table 3). Positive associations of similar magnitude were

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Table 1. Characteristics of UK Biobank Study Participants by Category of Circulating IGF1 levels (n = 397,380 participants

Baseline characteristic	IGF1 levels				
	Q1	Q2	Q3	Q4	Q5
IGF1, *nmol/L*[a]	14.3 (2.2)	18.6 (1.1)	21.4 (0.9)	24.1 (1.0)	29.5 (3.9)
Colorectal cancer (n cases)	595	586	528	475	481
Age at recruitment, *y*[a]	59.1 (7.2)	57.6 (7.6)	56.3 (7.9)	55.1 (8.2)	53.2 (8.3)
Women (%)	55.5	52.5	52.5	52.5	52.5
Body mass index (kg/m^2)[a]	28.3 (5.4)	27.4 (4.7)	27.1 (4.4)	26.8 (4.2)	26.6 (4.0)
Waist circumference (*cm*)[a]	92.7 (14.2)	90.4 (13.1)	89.5 (12.7)	88.9 (12.4)	88.2 (12.2)
Height (*cm*)[a]	167.7 (9.2)	168.4 (9.3)	168.9 (9.3)	169.2 (9.3)	169.8 (9.3)
Total physical activity (MET hours per wk) (%)					
<10	23.8	21.8	21.1	21.2	21.0
≥60	22.8	23.1	22.7	22.1	21.3
Smoking status (%)					
Never	50.3	53.3	55.5	57.2	59.5
Current	11.8	10.9	10.2	10	9.8
Alcohol consumption (%)					
Never	9.7	7.4	6.9	6.6	6.7
Daily or almost daily	24.2	22.7	21.4	19.4	16.2
Socioeconomic status (Townsend deprivation index) (%)					
Highest quintile	22.2	19.2	18	18	17.8
Family history (first degree relative) of colorectal cancer (%)					
Yes	11.5	11.2	10.7	10.5	10.1
Regular aspirin/ibuprofen use (%)					
Yes	26.8	25.6	24.8	24.8	24.8
Red and processed meat (%)					
<1 occasion per week	10.3	10	9.9	9.9	10.2
≥3 occasions per week	23.4	22.3	21.8	21.2	20.7
Ever menopausal hormone use (%)[b]					
Yes	43.8	38.1	33.8	30	24.9
CRP (*mg/L*)[a]	3.4 (5.1)	2.6 (4.1)	2.3 (3.8)	2.1 (3.7)	1.8 (3.8)
Testosterone (*nmol/L*)[a]	7.0 (6.3)	6.9 (6.2)	6.8 (6.1)	6.7 (6.1)	6.6 (6.0)
SHBG (*nmol/L*)[a]	55.4 (28.6)	52.2 (25.8)	50.5 (24.9)	49.1 (24.2)	46.5 (23.3)
HbA1c (*mmol/mol*)[a]	35.9 (5.3)	35.4 (4.5)	35.1 (4.4)	34.9 (4.2)	34.7 (4.5)

MET, metabolic equivalents.
[a]Mean and SD.
[b]Among women only.

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Table 2. Risk (HRs) of Colorectal Cancer Associated With Circulating IGF1 Levels in the UK Biobank

	Q1	Q2	Q3	Q4	Q5	*P*-trend	HR per 1-SD increment	HR per 1-SD increment (adjusted)[a]
Quintile cutpoints (*nmol/L*)								
Men	<17.6	17.6-<20.6	20.6-<23.1	23.1-<26.1	≥26.1			
Women	<16.3	16.3-<19.5	19.5-<22.3	22.3-<25.5	≥25.5			
Colorectal cancer								
Both sexes								
n cases	595	586	528	475	481			
Model [1]	1	1.11 (0.99–1.24)	1.09 (0.97–1.23)	1.07 (0.95–1.21)	1.24 (1.10–1.40)	0.006	1.05 (1.01–1.10)	1.07 (1.02–1.13)
Model [2]	1	1.14 (1.01–1.28)	1.14 (1.01–1.28)	1.14 (1.00–1.29)	1.34 (1.18–1.52)	<0.0001	1.08 (1.04–1.13)	1.11 (1.05–1.17)
Men								
Model [2]	1	1.09 (0.94–1.27)	1.09 (0.93–1.27)	1.09 (0.93–1.28)	1.29 (1.09–1.51)	0.009	1.06 (1.01–1.12)	1.09 (1.01–1.17)
Women								
Model [2]	1	1.20 (1.01–1.44)	1.21 (1.00–1.45)	1.20 (0.99–1.46)	1.41 (1.15–1.72)	0.003	1.11 (1.04–1.18)	1.14 (1.05–1.24)
Colon cancer								
Both sexes								
n cases	411	378	342	306	322			
Model [1]	1	1.05 (0.91–1.21)	1.04 (0.90–1.20)	1.02 (0.88–1.19)	1.24 (1.06–1.44)	0.03	1.05 (1.00–1.10)	1.07 (1.00–1.14)
Model [2]	1	1.08 (0.94–1.25)	1.09 (0.94–1.26)	1.09 (0.94–1.27)	1.35 (1.16–1.57)	0.001	1.09 (1.03–1.14)	1.11 (1.04–1.19)
Men								
Model [2]	1	1.07 (0.88–1.29)	1.05 (0.86–1.28)	1.09 (0.88–1.34)	1.28 (1.04–1.57)	0.04	1.07 (1.00–1.14)	1.09 (0.99–1.19)
Women								
Model [2]	1	1.10 (0.89–1.35)	1.13 (0.91–1.40)	1.09 (0.87–1.37)	1.42 (1.13–1.78)	0.01	1.10 (1.02–1.18)	1.13 (1.03–1.24)
Proximal colon cancer								
Both sexes								
n cases	209	210	189	140	159			
Model [1]	1	1.15 (0.95–1.39)	1.13 (0.93–1.38)	0.93 (0.75–1.16)	1.23 (1.00–1.52)	0.37	1.04 (0.97–1.11)	1.05 (0.96–1.15)
Model [2]	1	1.19 (0.98–1.45)	1.20 (0.98–1.47)	1.01 (0.81–1.26)	1.36 (1.10–1.69)	0.07	1.08 (1.00–1.15)	1.10 (1.01–1.21)
Men								
Model [2]	1	1.18 (0.90–1.55)	1.05 (0.79–1.40)	0.99 (0.73–1.34)	1.27 (0.94–1.71)	0.4	1.06 (0.96–1.17)	1.07 (0.94–1.22)
Women								
Model [2]	1	1.19 (0.90–1.58)	1.35 (1.02–1.79)	1.00 (0.73–1.39)	1.45 (1.05–1.99)	0.11	1.09 (0.99–1.20)	1.12 (0.98–1.27)
Distal colon cancer								
Both sexes								
n cases	181	151	141	152	145			
Model [1]	1	0.95 (0.77–1.18)	0.98 (0.78–1.22)	1.15 (0.92–1.44)	1.24 (0.99–1.55)	0.03	1.06 (0.99–1.15)	1.09 (0.99–1.20)
Model [2]	1	0.97 (0.78–1.21)	1.01 (0.81–1.27)	1.21 (0.97–1.51)	1.32 (1.05–1.67)	0.005	1.09 (1.01–1.18)	1.12 (1.01–1.24)
Men								
Model [2]	1	0.99 (0.74–1.32)	1.06 (0.79–1.42)	1.21 (0.90–1.62)	1.21 (0.89–1.65)	0.1	1.05 (0.95–1.17)	1.07 (0.94–1.23)
Women								
Model [2]	1	0.95 (0.68–1.34)	0.97 (0.68–1.38)	1.21 (0.85–1.71)	1.47 (1.03–2.09)	0.02	1.13 (1.01–1.27)	1.18 (1.01–1.37)
Rectal cancer								
Both sexes								
n cases	184	208	186	169	159			
Model [1]	1	1.23 (1.01–1.51)	1.20 (0.98–1.48)	1.18 (0.95–1.46)	1.26 (1.01–1.56)	0.09	1.06 (0.99–1.14)	1.08 (0.99–1.18)

Table 2. Continued

	Q1	Q2	Q3	Q4	Q5	*P*-trend	HR per 1-SD increment	HR per 1-SD increment (adjusted)[a]
Model [2]	1	1.26 (1.03–1.54)	1.24 (1.01–1.53)	1.23 (0.99–1.53)	1.33 (1.06–1.66)	0.03	1.08 (1.01–1.16)	1.11 (1.01–1.22)
Men								
Model [2]	1	1.13 (0.89–1.44)	1.15 (0.90–1.48)	1.09 (0.84–1.42)	1.30 (1.00–1.69)	0.11	1.06 (0.97–1.16)	1.08 (0.96–1.21)
Women								
Model [2]	1	1.58 (1.11–2.26)	1.48 (1.02–2.15)	1.58 (1.08–2.32)	1.43 (0.94–2.16)	0.12	1.13 (1.00–1.28)	1.18 (1.00–1.38)

NOTE. Model [1]: Multivariable Cox regression model using age as the underlying time variable and stratified by sex, Townsend deprivation index (quintiles), region of the recruitment assessment center, and age at recruitment. Models adjusted for waist circumference (per 5 cm), total physical activity (<10, 10 to <20, 20 to <40, 40 to <60, ≥60 metabolic equivalent hours per week, unknown), height (per 10 cm), alcohol consumption frequency (never, special occasions only, 1–3 times per month, 1–2 times per week, 3–4 times per week, daily/almost daily, unknown), smoking status and intensity (never, former, current- <15 per day, current- ≥15 per day, current- intensity unknown, unknown), frequency of red and processed meat consumption (<2, 2 to <3, 3 to <4, ≥4 occasions per week, unknown), family history of colorectal cancer (no, yes, unknown), educational level (Certificates of secondary education [CSEs]/Ordinary [O]-levels/General Certificates of Secondary Education [GCSEs] or equivalent, National Vocational Qualification [NVQ]/Higher National Diploma [HND]/Higher National Certificate [HNC]/Advanced [A]-levels/Advanced Subsidiary [AS]-levels or equivalent, other professional qualifications, college/university degree, none of the above, unknown), regular aspirin/ibuprofen use (no, yes, unknown), ever use of hormone replacement therapy (no, yes, unknown).
Model [2]: Model [1] plus additional adjustment for circulating levels (sex-specific quintiles, missing/unknown) of CRP (mg/L), HbA1c (mmol/mol), testosterone (nmol/L), and SHBG (nmol/L).
[a]HRs per SD increment were additionally corrected for regression dilution using a regression dilution ratio (0.76) obtained from the subsample of participants with repeat IGF1 measurements.

found for men and women when analyzed separately (*P*-heterogeneity = .24), and by anatomic subsite (colon vs rectal, *P*-heterogeneity = 1; proximal colon versus distal colon, *P*-heterogeneity = .55) (Table 3). Evidence of effect heterogeneity Cochran's Q *P* values < .001) and horizontal pleiotropy (MR-PRESSO *P* values $<1 \times 10^{-4}$) were observed for each model (Supplementary Table 4), but there was little evidence of directional pleiotropy (MR-Egger intercept *P* values >.20) for all models, except for distal colon cancer (MR-Egger intercept *P* value = .02). However, the corrected estimates for distal colon cancer and all other models from the MR-Egger and the weighted-median approach analyses replicated the initial positive effect estimates (Table 3; Supplementary Table 4), and the MR-PRESSO test identified a few outlier SNPs that did not distort the effect estimates (MR-PRESSO *P* values >.8). Finally, the funnel plot for the IGF1 instruments indicated a symmetric distribution of effect estimates (Supplementary Figure 1).

Association between genetically determined circulating IGFBP3 levels and colorectal cancer risk. A 1-SD increment in genetically determined IGFBP3 levels was associated with a 12% higher colorectal cancer risk (OR 1.12; 95% CI 1.06–1.18; $P = 4.2 \times 10^{-5}$) (Table 3). Similar positive associations were found for men and women when analyzed separately (*P*-heterogeneity = 1), and by anatomic subsite (colon vs rectal, *P*-heterogeneity = .87; proximal colon vs distal colon, *P*-heterogeneity = .77) (Table 3). Evidence of effect heterogeneity was weak (*P* > .10) for all models except colon cancer and distal colon cancer models (*P* values .04 and .02, respectively). The MR-PRESSO test identified possible horizontal pleiotropy for colon cancer and distal colon cancer (*P* < .05). However, little evidence of directional pleiotropy was found for all models (MR-Egger intercept *P* > .15), and the estimates from the weighted-median approach and MR-Egger were consistent with those of likelihood-based approach (Table 3; Supplementary Table 4). The leave-one-out analysis revealed that the positive association between IGFBP3 and colorectal cancer was driven by 1 variant, rs11977526, located in the *IGFBP3* gene region (OR per SD increment in IGFBP3 with rs11977526 excluded = 1.02; 95% CI 0.92–1.13; *P* = .7) (Supplementary Table 5).

Discussion

In serologic analyses of UK Biobank data, we found that higher prediagnostic levels of circulating IGF1 were associated with greater colorectal cancer risk, with similar-strength positive associations found by sex and colorectal anatomical subsite. Concordant with this, the MR analyses revealed a positive effect of IGF1 on colorectal cancer risk, suggesting that higher circulating IGF1 levels may have a causal role in the development of this malignancy. Collectively, these findings provide strong support for a role of the IGF-pathway in colorectal tumorigenesis.

Despite extensive experimental evidence indicating a role for IGF1 in colorectal tumorigenesis, results from previous epidemiological studies (most including <500

colorectal cancer cases) have been inconsistent, with null or weak positive associations found that did not meet the statistical significance threshold.[6–11] Our study, using UK Biobank data, is unique in that rather than following a nested study design including a subset of the cohort, IGF1 levels were measured in all study participants. Further, we were able to control statistically for other serologic risk factors that are related to both circulating IGF1 levels and colorectal cancer risk (CRP, testosterone, SHBG, and HbA1c). Our study was the largest to date to examine the IGF1 and colorectal cancer relationship (including >2600 incident cases) which meant we were sufficiently powered to study the IGF1 and colorectal cancer relationship by sex, anatomic subsite of tumor, and across subgroups of other risk factors. We found no heterogeneity for the positive association by sex, anatomic subsite, follow-up time, and other colorectal cancer risk factors.

Despite the robustness of this positive IGF1 and colorectal cancer association, as with all observational studies, these analyses are vulnerable to the inherent biases of this

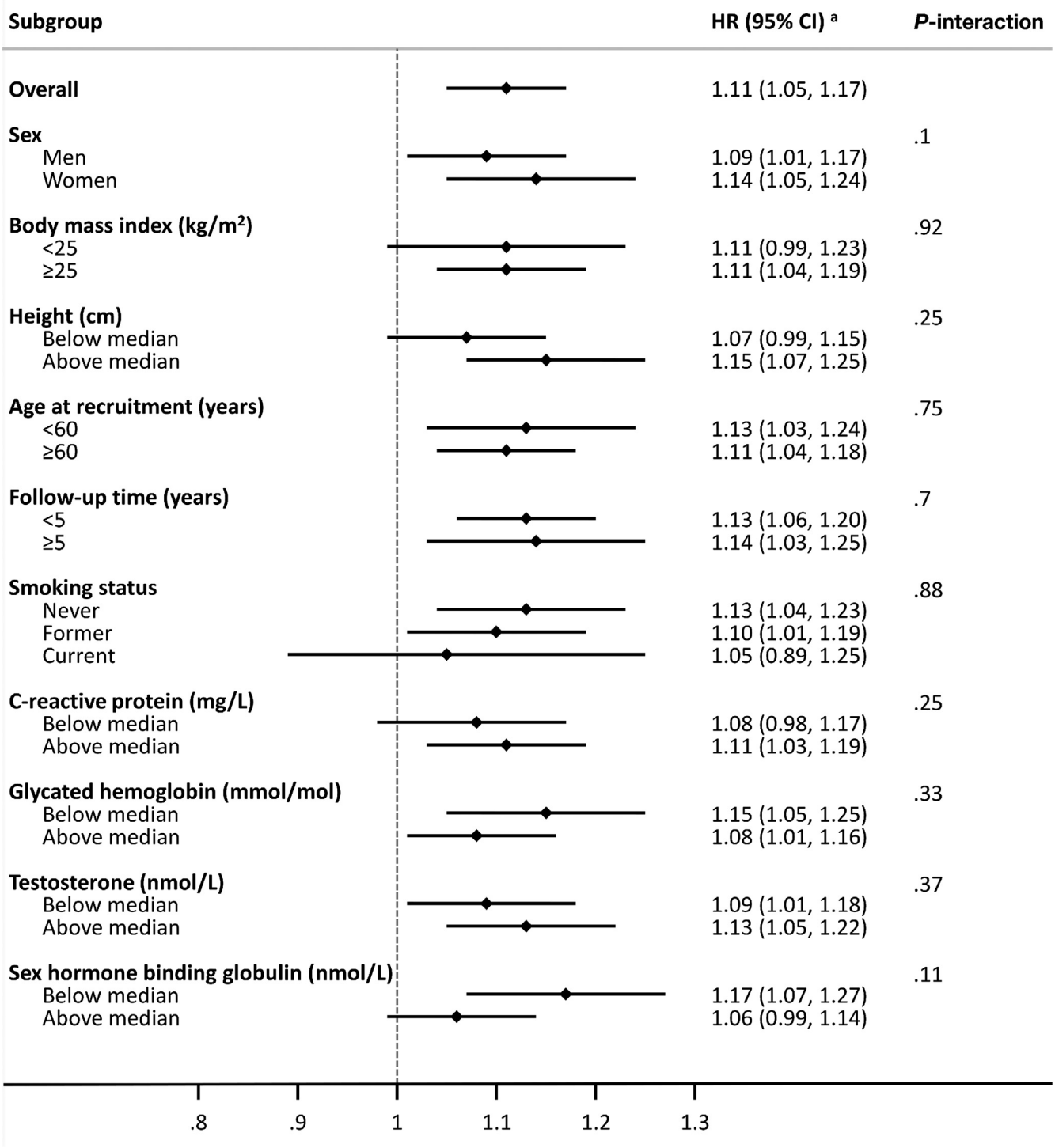

Table 3. MR Estimates Between Circulating Levels of IGF1 and IGFBP3 and Risk of Colorectal Cancer (n = 52,865 Colorectal Cancer Cases and n = 46,287 Controls)

	MR		
	Likelihood-based approach	Weighted median approach	MR-Egger test
	OR (95% CI) per 1-SD increment	OR (95% CI) per 1-SD increment	OR (95% CI) per 1-SD increment
IGF1			
Colorectal cancer			
Both sexes	1.08 (1.03–1.12)	1.12 (1.04–1.20)	1.11 (0.98–1.27)
Men	1.11 (1.05–1.17)	1.07 (0.97–1.18)	1.18 (1.00–1.38)
Women	1.05 (0.99–1.11)	1.07 (0.97–1.18)	1.06 (0.89–1.25)
Colon cancer			
Both sexes	1.06 (1.01–1.11)	1.12 (1.03–1.23)	1.14 (0.98–1.32)
Proximal colon cancer			
Both sexes	1.04 (0.97–1.11)	1.08 (0.97–1.21)	1.02 (0.84–1.23)
Distal colon cancer			
Both sexes	1.07 (1.00–1.14)	1.10 (0.98–1.23)	1.26 (1.05–1.50)
Rectal cancer			
Both sexes	1.06 (1.00–1.14)	1.01 (0.90–1.13)	1.09 (0.91–1.30)
IGFBP3			
Colorectal cancer			
Both sexes	1.12 (1.06–1.18)	1.14 (1.07–1.20)	1.18 (1.07–1.31)
Men	1.12 (1.04–1.21)	1.13 (1.04–1.22)	1.14 (0.98–1.34)
Women	1.12 (1.04–1.21)	1.13 (1.04–1.22)	1.25 (1.18–1.32)
Colon cancer			
Both sexes	1.11 (1.04–1.19)	1.13 (1.05–1.21)	1.27 (1.16–1.38)
Proximal colon cancer			
Both sexes	1.12 (1.03–1.22)	1.12 (1.02–1.23)	1.25 (1.21–1.29)
Distal colon cancer			
Both sexes	1.10 (1.01–1.20)	1.13 (1.03–1.24)	1.29 (1.01–1.65)
Rectal cancer			
Both sexes	1.12 (1.04–1.22)	1.14 (1.05–1.25)	1.18 (1.01–1.39)

study design, namely residual confounding and reverse causality. MR analyses are less susceptible to such biases because alleles are randomly assigned during meiosis and germline genetic variants are unaffected by disease process.[38] Our MR analyses yielded strikingly similar estimates of effect for IGF1 and colorectal cancer to our UK Biobank serologic analyses. Similar to the serologic analyses we found no heterogeneity by sex or anatomic subsite in our MR analyses. An important assumption of MR is that the genetic variants do not influence the outcome through a pathway independent of the main exposure of interest (horizontal pleiotropy). We conducted multiple sensitivity analyses to test for the influence of pleiotropy on our causal estimates, and our results for IGF1 were robust according to these various tests.

Experimental data support a role for IGF1 and its downstream signaling pathways in colorectal tumorigenesis. IGF1 can promote cellular proliferation through the

Figure 1. Subgroup analyses of the association between circulating IGF1 levels and colorectal cancer risk in the UK Biobank. HR per 1-SD increment in circulating IGF1 levels. Multivariable Cox regression model using age as the underlying time variable and stratified by sex, Townsend deprivation index (quintiles), region of the recruitment assessment center, and age at recruitment. Models adjusted for waist circumference (per 5 cm), total physical activity (<10, 10 to <20, 20 to <40, 40 to <60, ≥60 metabolic equivalent hours per week, unknown), height (per 10 cm), alcohol consumption frequency (never, special occasions only, 1–3 times per month, 1–2 times per week, 3–4 times per week, daily/almost daily, unknown), smoking status and intensity (never, former, current- <15 per day, current- ≥15 per day, current- intensity unknown, unknown), frequency of red and processed meat consumption (<2, 2 to <3, 3 to <4, ≥4 occasions per week, unknown), family history of colorectal cancer (no, yes, unknown), educational level (Certificates of secondary education [CSEs]/Ordinary [O]-levels/General Certificates of Secondary Education [GCSEs] or equivalent, National Vocational Qualification [NVQ]/Higher National Diploma [HND]/Higher National Certificate [HNC]/Advanced [A]-levels/Advanced Subsidiary [AS]-levels or equivalent, other professional qualifications, college/university degree, none of the above, unknown), regular aspirin/ibuprofen use (no, yes, unknown), ever use of hormone replacement therapy (no, yes, unknown), and circulating levels (sex-specific quintiles, missing/unknown) of CRP (mg/L), HbA1c (mmol/mol), testosterone (nmol/L), and SHBG (nmol/L). [a]HRs per SD increment were corrected for regression dilution using a regression dilution ratio (0.76) obtained from the subsample of participants with repeat IGF1 measurements. Median values: height = 176 cm for men and 162 cm for women; CRP = 1.3 mg/L; HbA1c = 35 mmol/mol; testosterone = 1 nmol/L for women and 11.8 nmol/L for men; SHBG = 56.3 nmol/L for men and 37.2 nmol/L for women.

activation of the mitogen activated protein kinase and the phosphoinositide 3-kinase pathways.[39] Colonocytes express IGF1-receptors and these are frequently overexpressed in neoplastic cells.[40] IGF1 has been shown to promote cellular proliferation in colorectal tissue, and the blockade of the IGF1-receptor by a monoclonal antibody inhibits cell proliferation.[41]

Potentially modifiable determinants of circulating IGF1 levels include dietary protein intake,[42–44] BMI,[43] and physical activity.[45] In addition, a number of pharmacologic agents targeting the IGF system have been developed, although, as of yet, they have not been successful in treating colorectal cancer patients in clinical trials.[46] Although circulating IGF1 levels are modifiable, it is currently unknown how long an intervention aimed at altering IGF1 concentrations would have to be applied to have measurable effects. Our result provides possible evidence for a causal role of circulating IGF1 levels in colorectal cancer development and will hopefully reinvigorate efforts to develop and introduce interventions targeting the IGF system for colorectal cancer prevention in susceptible individuals.

The bioactivity of IGF1 is partially regulated through IGFBPs, with most bound to IGFBP3. Higher levels of IGFBP3 both increase the serologic binding capacity for IGF1, but also lower circulating IGF1 bioavailability.[47] As well as IGF-binding properties, IGFBP3 has been shown to induce apoptosis and reduce proliferation in colon cancer cell lines.[4,5] The positive association we found in our MR analyses for IGFBP3 and colorectal cancer is inconsistent with its anticipated anti-tumorigenic effects. Epidemiologic studies examining the IGFBP3 and colorectal cancer association have reported mixed findings, with inverse, positive, and null results all previously reported.[6,7,10–14] The positive effect estimate in our MR analysis was driven solely by 1 variant, rs11977526, with a null result found when this variant was excluded. Although rs11977526 is located in close proximity to the *IGFBP3* gene, this variant has also been associated with several anthropometric traits[48] and circulating levels of IGF2,[49] for which there is evidence of a role in colorectal cancer development. The *IGF2* gene is imprinted and loss of imprinting has been detected in colorectal cancer tumor tissue.[50] Stroma-induced IGF2 has been shown to promote colon cancer progression in a paracrine and autocrine manner.[51] A meta-analysis of 3 prospective studies reported an almost 2-fold higher colorectal cancer risk when the highest and lowest groups of circulating IGF2 levels were compared.[52] MR analyses for IGF2 are currently limited as a GWAS for circulating IGF2 has not been conducted. Similarly, for IGFBP3 and other IGF system components (including bioavailable IGF1 levels), more precise genetic instruments are now required to help disentangle the possible biological effects of specific ligands and binding proteins on colorectal cancer development.

This was the largest and most comprehensive study that used 2 complementary study designs to examine the role of IGF1 on colorectal cancer development. A limitation of our analysis is that IGF1 levels were measured only once at baseline in all participants, and it is possible that these measurements may not reflect exposure levels across time. However, our reproducibility analysis in a subset of the cohort found an ICC value of 0.78 between IGF1 measurements collected 4 years apart, indicating that a single measurement provides a good estimate of medium to longer-term exposures. The availability of repeat IGF1 measurements also allowed us to correct for regression dilution bias, and thus limiting the effects of measurement error and within-person variability on our risk estimates[21]; the positive associations we found were stronger after regression dilution correction. A limitation of our MR analyses is that our use of summary-level data precluded the investigation of nonlinear effects and subgroup analyses by other risk factors (eg, age, BMI, smoking). However, our serologic analysis, which yielded a similar overall risk estimate to our MR result, found no evidence of a nonlinear association for IGF1 and colorectal cancer and little heterogeneity across subgroups of other risk factors.

In conclusion, our complementary serologic and MR analyses provide strong support for a positive association of circulating IGF1 levels on colorectal cancer risk. This result suggests that diet/lifestyle[42–44,53] or pharmacologic[1] interventions targeting the IGF system may offer a promising strategy in reducing the risk of colorectal cancer.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.12.020.

References

1. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. Nat Rev Cancer 2008;8:915.
2. Samani AA, Yakar S, LeRoith D, et al. The role of the IGF System in Cancer growth and metastasis: overview and recent insights. Endocr Rev 2007;28:20–47.
3. Kelley KM, Oh Y, Gargosky SE, et al. Insulin-like growth factor-binding proteins (IGFBPs) and their regulatory dynamics. Int J Biochem Cell Biol 1996;28:619–637.
4. Oh Y, Muller HL, Ng L, et al. Transforming growth factor-beta-induced cell growth inhibition in human breast cancer cells is mediated through insulin-like growth factor-binding protein-3 action. J Biol Chem 1995; 270:13589–13592.
5. Baxter RC. Signalling pathways involved in anti-proliferative effects of IGFBP-3: a review. Mol Pathol 2001;54:145–148.
6. Ma J, Pollak MN, Giovannucci E, et al. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. J Natl Cancer Inst 1999;91:620–625.
7. Kaaks R, Toniolo P, Akhmedkhanov A, et al. Serum C-Peptide, Insulin-Like Growth Factor (IGF)-I, IGF-Binding Proteins, and Colorectal Cancer Risk in Women. J Natl Cancer Inst 2000;92:1592–1600.

8. Gunter MJ, Hoover DR, Yu H, et al. Insulin, insulin-like growth factor-i, endogenous estradiol, and risk of colorectal cancer in postmenopausal women. Cancer Res 2008;68:329–337.
9. Otani T, Iwasaki M, Sasazuki S, et al. Plasma C-peptide, insulin-like growth factor-I, insulin-like growth factor binding proteins and risk of colorectal cancer in a nested case-control study: the Japan public health center-based prospective study. Int J Cancer 2007;120:2007–2012.
10. Palmqvist R, Stattin P, Rinaldi S, et al. Plasma insulin, IGF-binding proteins-1 and -2 and risk of colorectal cancer: a prospective study in northern Sweden. Int J Cancer 2003;107:89–93.
11. Rinaldi S, Cleveland R, Norat T, et al. Serum levels of IGF-I, IGFBP-3 and colorectal cancer risk: results from the EPIC cohort, plus a meta-analysis of prospective studies. Int J Cancer 2010;126:1702–1715.
12. Probst-Hensch NM, Yuan JM, Stanczyk FZ, et al. IGF-1, IGF-2 and IGFBP-3 in prediagnostic serum: association with colorectal cancer in a cohort of Chinese men in Shanghai. Br J Cancer 2001;85:1695–1699.
13. Giovannucci E, Pollak MN, Platz EA, et al. A prospective study of plasma insulin-like growth factor-1 and binding protein-3 and risk of colorectal neoplasia in women. Cancer Epidemiol Biomarkers Prev 2000;9:345–349.
14. Wei EK, Ma J, Pollak MN, et al. A prospective study of C-peptide, insulin-like growth factor-I, insulin-like growth factor binding protein-1, and the risk of colorectal cancer in women. Cancer Epidemiol Biomarkers Prev 2005;14:850–855.
15. Fred Hutchinson Cancer Research Center. Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO). Available at: https://www.fredhutch.org/en/research/divisions/public-health-sciences-division/research/cancer-prevention/genetics-epidemiology-colorectal-cancer-consortium-gecco.html. Accessed August 23, 2019.
16. Allen N, Sudlow C, Downey P, et al. UK Biobank: current status and what it means for epidemiology. Health Policy and Technology 2012;1:123–126.
17. UK-Biobank. UK Biobank. Protocol for a large-scale prospective epidemiological resources. Available at: http://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf; 2010. Accessed April 1, 2018.
18. Hosgood HD, Gunter MJ, Murphy N, et al. The relation of obesity-related hormonal and cytokine levels with multiple myeloma and non-Hodgkin lymphoma. Front Oncol 2018;8:103.
19. UK-Biobank. UK Biobank Biomarker Project - Companion Document to Accompany Serum Biomarker Data. Prepared for: UK Biobank Showcase 2019;Volume 1. Available at: http://biobank.ctsu.ox.ac.uk/showcase/showcase/docs/serum_biochemistry.pdf. Accessed June 1, 2019.
20. Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika 1982;69:239–241.
21. Clarke R, Shipley M, Lewington S, et al. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. Am J Epidemiol 1999;150:341–353.
22. MacMahon S, Peto R, Collins R, et al. Blood pressure, stroke, and coronary heart disease: Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990;335:765–774.
23. Clarke R, Emberson JR, Breeze E, et al. Biomarkers of inflammation predict both vascular and non-vascular mortality in older men. Eur Heart J 2008;29:800–809.
24. Murphy N, Strickler HD, Stanczyk FZ, et al. A prospective evaluation of endogenous sex hormone levels and colorectal cancer risk in postmenopausal women. J Natl Cancer Inst 2015;107(10).
25. Aleksandrova K, Jenab M, Boeing H, et al. Circulating C-reactive protein concentrations and risks of colon and rectal cancer: a nested case-control study within the European prospective investigation into cancer and nutrition. Am J Epidemiol 2010;172:407–418.
26. Mori N, Sawada N, Iwasaki M, et al. Circulating sex hormone levels and colorectal cancer risk in Japanese postmenopausal women: the JPHC nested case–control study. Int J Cancer 2019;145:1238–1244.
27. Rinaldi S, Rohrmann S, Jenab M, et al. Glycosylated hemoglobin and risk of colorectal cancer in men and women, the European Prospective Investigation into Cancer and Nutrition. Cancer Epidemiol Biomarkers Prev 2008;17:3108–3115.
28. Harrell F. Regression Modeling Strategies: With applications to linear models, logistic regression, and survival analysis. New York: Springer, 2001.
29. Sinnott-Armstrong N, Tanigawa Y, Amar D, et al. Genetics of 38 blood and urine biomarkers in the UK Biobank. bioRxiv 2019:660506.
30. Teumer A, Qi Q, Nethander M, et al. Genomewide meta-analysis identifies loci associated with IGF-I and IGFBP-3 levels with impact on age-related traits. Aging Cell 2016;15:811–824.
31. Huyghe JR, Bien SA, Harrison TA, et al. Discovery of common and rare genetic risk variants for colorectal cancer. Nat Genet 2019;51:76–87.
32. Brion M-JA, Shakhbazov K, Visscher PM. Calculating statistical power in Mendelian randomization studies. Int J Epidemiol 2013;42:1497–1501.
33. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genetic Epidemiol 2013;37:658–665.
34. Burgess S, Scott RA, Timpson NJ, et al. Using published data in Mendelian randomization: a blueprint for efficient identification of causal risk factors. Eur J Epidemiol 2015;30:543–552.
35. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 2015;44:512–525.
36. Bowden J, Davey Smith G, Haycock PC, et al. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol 2016;40:304–314.
37. Verbanck M, Chen C-Y, Neale B, et al. Detection of widespread horizontal pleiotropy in causal relationships

inferred from Mendelian randomization between complex traits and diseases. Nat Genet 2018;50:693–698.
38. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. Hum Mol Genet 2014;23:R89–R98.
39. Valentinis B, Baserga R. IGF-I receptor signalling in transformation and differentiation. Mol Pathol 2001; 54:133–137.
40. Sekharam M, Zhao H, Sun M, et al. Insulin-like growth factor 1 receptor enhances invasion and induces resistance to apoptosis of colon cancer cells through the Akt/Bcl-x_L Pathway. Cancer Res 2003;63:7708–7716.
41. Lahm H, Amstad P, Wyniger J, et al. Blockade of the insulin-like growth-factor-I receptor inhibits growth of human colorectal cancer cells: evidence of a functional IGF-II-mediated autocrine loop. Int J Cancer 1994; 58:452–459.
42. Levine Morgan E, Suarez Jorge A, Brandhorst S, et al. Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. Cell Metab 2014;19:407–417.
43. Bradbury KE, Balkwill A, Tipper SJ, et al. The association of plasma IGF-I with dietary, lifestyle, anthropometric, and early life factors in postmenopausal women. Growth Horm IGF Res 2015;25:90–95.
44. Zhu K, Meng X, Kerr DA, et al. The effects of a two-year randomized, controlled trial of whey protein supplementation on bone structure, IGF-1, and urinary calcium excretion in older postmenopausal women. J Bone Miner Res 2011;26:2298–2306.
45. Nishida Y, Matsubara T, Tobina T, et al. Effect of low-intensity aerobic exercise on insulin-like growth factor-I and insulin-like growth factor-binding proteins in healthy men. Int J Endocrinol 2010; 2010:452820.
46. Vigneri PG, Tirrò E, Pennisi MS, et al. The insulin/IGF system in colorectal cancer development and resistance to therapy. Front Oncol 2015;5:230.
47. Deal C, Ma J, Wilkin Fo, et al. Novel promoter polymorphism in insulin-like growth factor-binding protein-3: correlation with serum levels and interaction with known regulators1. J Clin Endocrinol Metab 2001;86:1274–1280.
48. Kamat MA, Blackshaw JA, Young R, et al. PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. Bioinformatics 2019;35:4851–4853.
49. Cui H, Cruz-Correa M, Giardiello FM, et al. Loss of IGF2 imprinting: a potential marker of colorectal cancer risk. Science 2003;299:1753–1755.
50. Cruz-Correa M, Cui H, Giardiello FM, et al. Loss of imprinting of insulin growth factor II gene: a potential heritable biomarker for colon neoplasia predisposition. Gastroenterology 2004;126:964–970.
51. Unger C, Kramer N, Unterleuthner D, et al. Stromal-derived IGF2 promotes colon cancer progression via paracrine and autocrine mechanisms. Oncogene 2017; 36:5341.
52. Morris JK, George LM, Wu T, et al. Insulin-like growth factors and cancer: no role in screening. Evidence from the BUPA study and meta-analysis of prospective epidemiological studies. Br J Cancer 2006;95:112–117.
53. Young NJ, Metcalfe C, Gunnell D, et al. A cross-sectional analysis of the association between diet and insulin-like growth factor (IGF)-I, IGF-II, IGF-binding protein (IGFBP)-2, and IGFBP-3 in men in the United Kingdom. Cancer Causes Control 2012;23:907–917.

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References

1. Sinnott–Armstrong N, Tanigawa Y, Amar D, et al. Genetics of 38 blood and urine biomarkers in the UK Biobank. bioRxiv 2019:660506.
2. Teumer A, Qi Q, Nethander M, et al. Genomewide meta–analysis identifies loci associated with IGF–I and IGFBP3 levels with impact on age–related traits. Aging Cell 2016;15:811–824.

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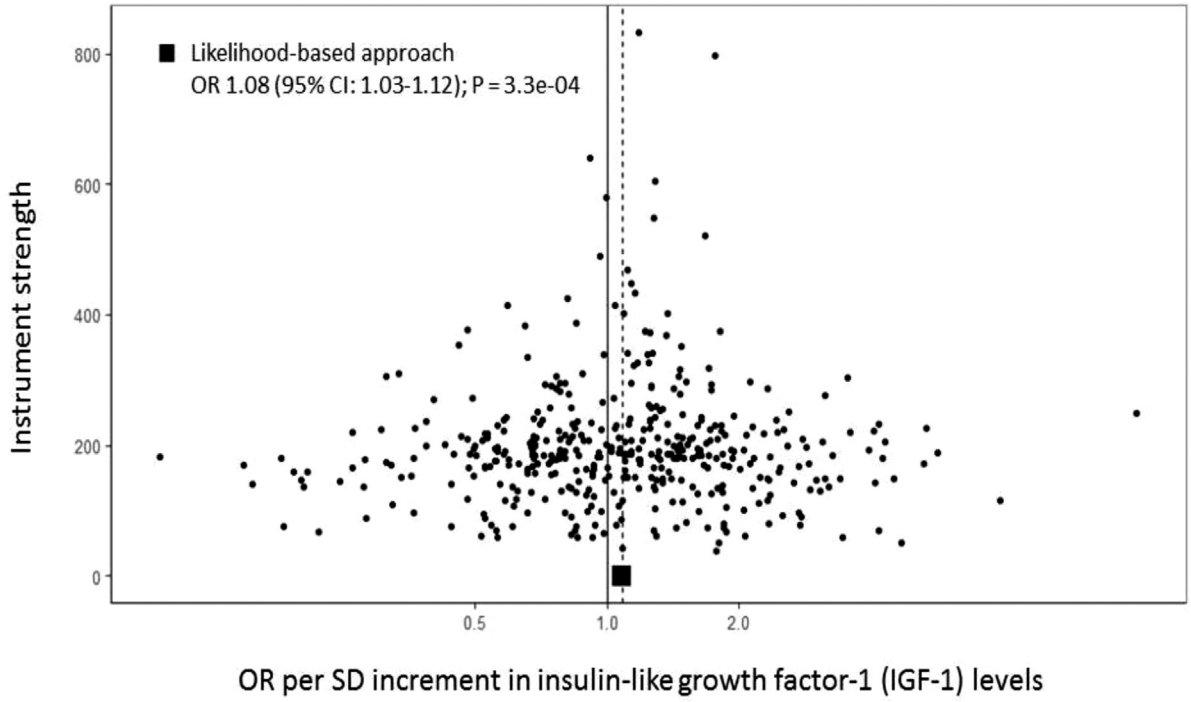

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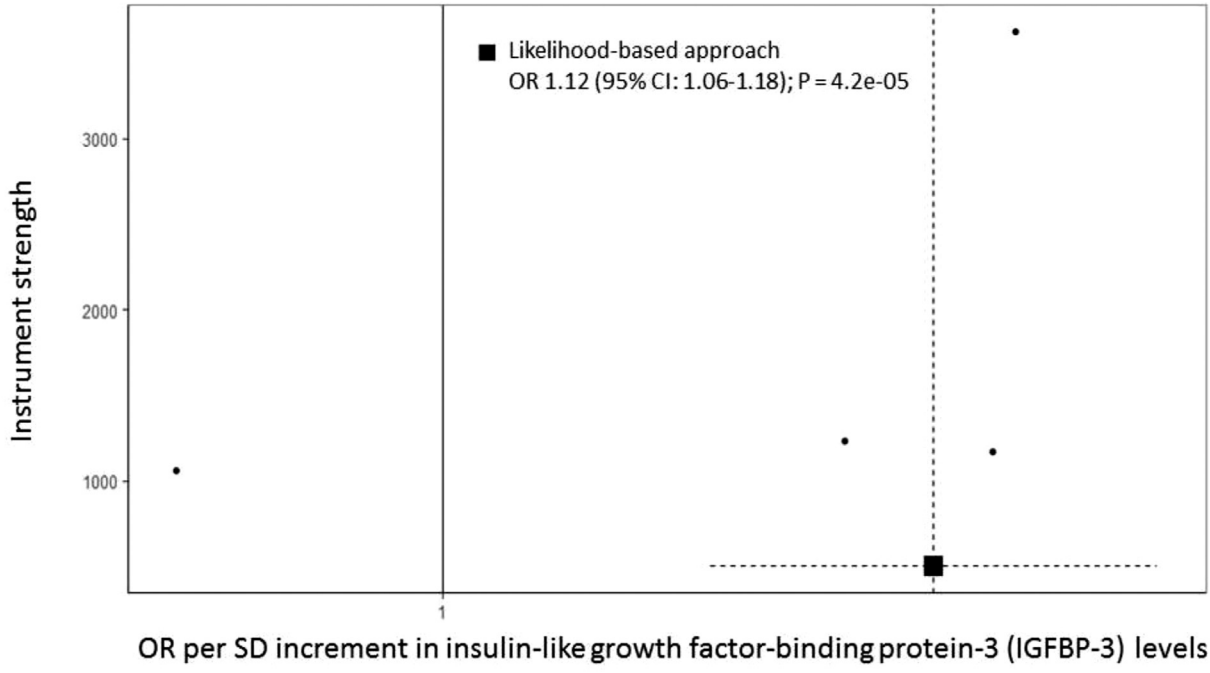

Supplementary Table 1. Summary Information on the IGF1 and IGFBP3 Genetic Instruments Used in the Mendelian Randomization Analyses

Exposure	Source/Publication	n SNPs	Variance explained (%)	Mean (SD)
IGF1	UK Biobank/Sinnott-Armstrong et al 2019[1]	413	9.4	21.6 (5.6) nmol/L
IGFBP3	Meta-analysis/Teumer et al 2016[2]	4	6.1	3340.4 (863.3) ng/mL

Supplementary Figure 1. Funnel plots of risk estimates of (*A*) IGF1 and (*B*) IGFBP3 with colorectal cancer against instrumental strength. Instrumental strength is SNP to colorectal cancer effect corrected by SNP to IGF1 or IGFBP3 standard error of the effect. X-axis is in logarithmic scale. *P* values are 2-sided, MR test.

Supplementary Table 2. Association Parameters of Instrumental SNPs Used in the IGF1 and IGFBP3 Genetic Instruments

SNP	Chr	Position	Gene[a]	Effect allele	Other allele	Association parameters for the exposure		Association parameters for colorectal cancer		Association parameters for colorectal cancer men		Association parameters for colorectal cancer women		Association parameters for colon cancer		Association parameters for proximal colon cancer		Association parameters for distal colon cancer		Association parameters for rectal cancer	
						Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE
IGF1 - n SNPs = 413																					
rs903908	1	2,202,967	SKI	T	C	−0.016	0.003	−0.006	0.009	−0.014	0.013	0.003	0.013	−0.016	0.011	−0.006	0.014	−0.023	0.014	0.016	0.014
rs17393144	1	9,210,262	MIR34A	G	A	−0.016	0.003	0.006	0.010	0.019	0.013	−0.007	0.014	0.005	0.011	0.012	0.015	−0.002	0.015	−0.005	0.015
rs112436634	1	10,637,709	PEX14	C	T	−0.016	0.003	0.001	0.009	−0.014	0.013	0.014	0.013	−0.002	0.011	−0.014	0.015	0.018	0.015	0.017	0.015
rs17037452	1	11,895,675	CLCN6	A	G	0.023	0.003	0.000	0.012	−0.011	0.017	0.011	0.018	0.000	0.015	0.029	0.019	−0.029	0.019	−0.003	0.019
rs36086195	1	16,510,894	ARHGEF19−AS1	T	C	−0.019	0.003	0.018	0.009	0.012	0.013	0.028	0.013	0.020	0.011	0.003	0.014	0.043	0.014	0.010	0.014
rs12723255	1	21,233,570	EIF4G3	T	C	−0.017	0.003	0.002	0.009	0.004	0.013	0.001	0.013	0.003	0.011	−0.002	0.014	0.008	0.014	0.010	0.014
rs6701954	1	22,022,176	USP48	T	G	0.014	0.003	0.005	0.009	0.007	0.012	−0.001	0.013	−0.008	0.011	0.007	0.014	−0.022	0.014	0.014	0.014
rs76914895	1	23,292,603	LACTBL1	T	C	−0.027	0.005	0.046	0.019	0.054	0.026	0.038	0.027	0.030	0.022	0.026	0.029	0.054	0.030	0.093	0.029
rs2075995	1	23,847,464	E2F2	A	C	−0.014	0.003	0.003	0.009	0.011	0.012	−0.003	0.013	0.008	0.011	−0.004	0.014	0.024	0.014	0.014	0.014
rs2802330	1	26,466,831	PDIK1L	A	G	−0.031	0.003	0.003	0.012	−0.001	0.016	0.004	0.016	0.011	0.014	0.025	0.018	−0.009	0.018	−0.004	0.018
rs17360994	1	27,278,573	KDF1	C	T	−0.042	0.005	−0.012	0.017	−0.003	0.023	−0.023	0.024	−0.006	0.020	−0.012	0.026	0.022	0.026	−0.005	0.026
rs569356	1	29,136,686	OPRD1	A	G	−0.027	0.004	0.007	0.013	−0.016	0.018	0.035	0.019	0.005	0.016	0.019	0.020	−0.001	0.021	0.012	0.020
rs3131646	1	40,383,552	MYCL	G	T	0.016	0.003	−0.006	0.010	−0.006	0.013	−0.008	0.014	−0.013	0.012	−0.029	0.015	0.002	0.015	0.002	0.015
rs61780439	1	41,490,177	SLFNL1−AS1	G	A	0.021	0.003	0.004	0.011	0.012	0.015	−0.001	0.015	−0.011	0.013	−0.013	0.017	−0.007	0.017	0.013	0.017
rs2819336	1	44,015,809	PTPRF	C	T	−0.027	0.003	−0.004	0.009	−0.003	0.013	−0.006	0.013	−0.007	0.011	−0.019	0.014	0.001	0.015	0.008	0.014
rs7539178	1	65,383,002	JAK1	A	C	−0.026	0.004	−0.024	0.013	−0.026	0.018	−0.023	0.018	−0.036	0.016	−0.047	0.020	−0.008	0.021	−0.015	0.020
rs1046011	1	65,898,996	LEPR / LEPROT	C	T	−0.021	0.003	0.011	0.010	0.006	0.014	0.017	0.014	0.005	0.012	−0.001	0.015	0.014	0.015	0.015	0.015
rs1430753	1	68,692,642	WLS	G	A	−0.021	0.003	−0.011	0.011	−0.012	0.016	−0.010	0.016	−0.007	0.013	0.000	0.017	−0.020	0.018	−0.041	0.017
rs165316	1	91,533,297	RPL5P6	A	G	−0.073	0.003	−0.018	0.011	−0.045	0.015	0.009	0.016	−0.037	0.013	−0.035	0.017	−0.033	0.017	0.006	0.017
rs1825813	1	92,708,973	C1orf146	G	A	−0.023	0.003	−0.027	0.011	−0.044	0.016	−0.009	0.016	−0.037	0.013	−0.034	0.017	−0.040	0.018	−0.019	0.017
rs599839	1	109,822,166	PSRC1/ CELSR2	A	G	−0.031	0.003	0.006	0.011	0.013	0.015	−0.002	0.015	0.009	0.013	−0.004	0.016	0.022	0.017	0.029	0.016
rs45505697	1	153,651,058	NPR1	C	A	0.030	0.005	0.011	0.020	−0.009	0.028	0.037	0.029	0.021	0.024	0.015	0.031	0.023	0.032	0.022	0.031
rs1127313	1	154,556,425	ADAR	G	A	0.024	0.003	0.009	0.009	0.007	0.012	0.013	0.013	0.007	0.011	−0.001	0.014	0.017	0.014	0.019	0.014
rs77369503	1	163,027,266	RGS4	G	A	0.045	0.007	−0.004	0.028	−0.002	0.038	−0.013	0.041	−0.027	0.033	−0.048	0.042	−0.051	0.043	0.012	0.042
rs75681856	1	174,916,323	RABGAP1L	C	T	−0.023	0.004	0.006	0.013	0.016	0.019	−0.007	0.019	−0.004	0.016	−0.010	0.021	−0.007	0.021	0.015	0.021
rs12749024	1	176,522,365	PAPPA2	C	T	−0.075	0.004	−0.008	0.013	−0.019	0.018	0.000	0.018	−0.011	0.015	−0.008	0.020	−0.009	0.020	−0.013	0.020
rs10913351	1	177,447,742	AL122019.1	G	A	−0.032	0.005	0.021	0.018	0.028	0.026	0.017	0.026	0.020	0.022	0.022	0.028	0.023	0.029	0.004	0.028
rs11577063	1	179,341,999	AXDND1	G	T	−0.020	0.003	−0.011	0.011	0.007	0.015	−0.031	0.015	−0.011	0.013	−0.025	0.016	−0.002	0.017	−0.020	0.016
rs143885630	1	183,482,785	SMG7	G	A	0.030	0.004	−0.013	0.014	−0.013	0.019	−0.008	0.020	−0.014	0.017	−0.045	0.022	0.016	0.022	0.019	0.022
rs940400	1	200,269,134	LINC00862	C	A	0.025	0.004	0.012	0.014	0.016	0.019	0.007	0.020	0.023	0.017	0.001	0.021	0.014	0.022	−0.016	0.021
rs7545345	1	205,690,941	NUCKS1	T	C	−0.026	0.004	0.000	0.013	0.007	0.019	−0.007	0.019	0.002	0.016	−0.017	0.021	0.016	0.021	−0.013	0.021
rs2724373	1	207,999,200	C1orf132	C	T	0.019	0.003	−0.014	0.009	−0.003	0.013	−0.030	0.013	−0.024	0.011	−0.024	0.014	−0.022	0.015	−0.011	0.014
rs10779509	1	209,728,370	AL023754.1	T	C	−0.014	0.003	−0.012	0.009	−0.024	0.013	0.000	0.013	−0.016	0.011	−0.013	0.014	−0.021	0.014	−0.017	0.014
rs340837	1	214,162,734	PROX1	T	G	−0.021	0.003	−0.025	0.009	−0.034	0.012	−0.011	0.013	−0.032	0.011	−0.029	0.014	−0.029	0.014	−0.019	0.014
rs12141189	1	221,053,545	HLX	C	T	−0.045	0.003	0.023	0.010	0.015	0.015	0.033	0.015	0.031	0.013	0.033	0.016	0.027	0.017	0.000	0.016
rs4306136	1	221,608,720	AL360013.2	A	G	0.017	0.003	0.014	0.009	0.001	0.013	0.029	0.013	0.010	0.011	0.026	0.014	0.001	0.014	0.022	0.014
rs708108	1	228,189,855	WNT3A	C	T	−0.015	0.003	−0.007	0.009	−0.009	0.013	−0.009	0.013	−0.007	0.011	−0.013	0.014	−0.001	0.014	−0.011	0.014
rs684818	1	234,854,779	AL160408.6	T	C	0.024	0.003	0.030	0.009	0.028	0.012	0.029	0.013	0.021	0.011	0.019	0.014	0.027	0.014	0.038	0.014

Supplementary Table 2. Continued

SNP	Chr	Position	Gene[a]	Effect allele	Other allele	Association parameters for the exposure		Association parameters for colorectal cancer		Association parameters for colorectal cancer men		Association parameters for colorectal cancer women		Association parameters for colon cancer		Association parameters for proximal colon cancer		Association parameters for distal colon cancer		Association parameters for rectal cancer	
						Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE
rs7517340	1	243,710,190	AKT3	C	T	0.035	0.003	−0.001	0.011	0.018	0.016	−0.020	0.016	−0.009	0.014	−0.011	0.018	0.003	0.018	0.013	0.018
rs35135518	2	16,120,506	RN7SL104P	T	C	0.029	0.004	−0.006	0.015	−0.006	0.020	−0.006	0.021	0.004	0.018	−0.002	0.024	0.001	0.024	−0.004	0.024
rs12710648	2	17,989,500	SMC6	A	G	0.017	0.003	−0.003	0.009	−0.003	0.013	0.000	0.013	−0.002	0.011	0.015	0.014	−0.015	0.014	0.004	0.014
rs6760135	2	26,088,769	ASXL2	C	T	−0.050	0.003	−0.002	0.011	0.001	0.016	−0.005	0.016	−0.010	0.013	−0.006	0.017	−0.015	0.017	0.004	0.017
rs1260326	2	27,730,940	GCKR	C	T	0.063	0.003	0.036	0.009	0.043	0.013	0.029	0.013	0.035	0.011	0.019	0.014	0.052	0.014	0.034	0.014
rs11677980	2	30,522,137	LBH	A	G	−0.015	0.003	−0.014	0.010	0.002	0.014	−0.031	0.014	−0.011	0.012	−0.006	0.015	−0.014	0.015	−0.017	0.015
rs7574340	2	40,621,239	SLC8A1	C	T	−0.017	0.003	0.012	0.009	0.025	0.013	0.000	0.014	0.019	0.012	0.021	0.015	0.016	0.015	0.005	0.015
rs6544549	2	42,693,056	KCNG3	T	C	0.024	0.004	0.026	0.013	0.022	0.018	0.027	0.018	0.025	0.016	0.041	0.020	0.007	0.020	0.039	0.020
rs62136965	2	44,347,953	snRNA	T	C	−0.037	0.006	0.022	0.022	0.001	0.030	0.051	0.032	0.031	0.026	0.025	0.034	0.035	0.034	−0.012	0.033
rs3791679	2	56,096,892	EFEMP1	A	G	−0.018	0.003	0.020	0.010	0.031	0.014	0.011	0.015	0.021	0.012	0.013	0.016	0.032	0.016	0.023	0.016
rs12471768	2	64,928,603	SERTAD2	C	T	0.022	0.003	−0.012	0.010	−0.004	0.014	−0.020	0.014	−0.021	0.012	−0.038	0.015	0.000	0.015	0.000	0.015
rs702878	2	65,702,609	AC007389.1	A	G	0.014	0.003	0.011	0.009	0.020	0.012	0.003	0.013	0.014	0.011	0.009	0.014	0.009	0.014	0.015	0.014
rs35641591	2	70,323,994	PCBP1−AS1	C	T	0.050	0.006	0.070	0.027	0.031	0.037	0.103	0.038	0.040	0.032	0.032	0.041	0.039	0.043	0.071	0.042
rs6749680	2	73,685,852	ALMS1	A	G	0.015	0.003	−0.001	0.009	−0.001	0.013	−0.003	0.013	−0.004	0.011	0.009	0.014	−0.016	0.014	−0.004	0.014
rs73954943	2	111,890,432	BCL2L11	G	A	−0.031	0.005	−0.032	0.018	−0.069	0.025	−0.003	0.025	−0.036	0.022	−0.044	0.028	−0.047	0.029	−0.041	0.029
rs7578633	2	113,978,650	PAX8	C	T	−0.018	0.003	−0.017	0.009	−0.013	0.013	−0.021	0.013	−0.014	0.011	−0.035	0.014	−0.003	0.014	−0.021	0.014
rs17050272	2	121,306,440	AC073257.2	G	A	0.024	0.003	0.010	0.009	0.012	0.013	0.007	0.013	0.003	0.011	−0.010	0.014	0.018	0.014	0.011	0.014
rs58387407	2	152,924,773	CACNB4	A	G	−0.018	0.003	−0.002	0.011	0.013	0.015	−0.017	0.016	−0.018	0.013	−0.022	0.017	−0.023	0.017	0.017	0.017
rs2674492	2	172,422,338	CYBRD1	G	A	−0.014	0.003	0.027	0.009	0.029	0.013	0.022	0.013	0.028	0.011	0.033	0.014	0.029	0.015	0.028	0.014
rs17400325	2	178,565,913	PDE11A	C	T	0.054	0.006	0.004	0.023	−0.004	0.031	0.011	0.033	0.016	0.027	0.003	0.035	0.052	0.035	0.011	0.034
rs6435156	2	203,425,475	BMPR2	C	T	0.024	0.003	0.015	0.010	0.013	0.014	0.017	0.015	0.013	0.012	0.015	0.016	0.020	0.016	0.025	0.016
rs1427676	2	204,741,166	CTLA4	T	C	0.015	0.003	0.025	0.009	0.026	0.013	0.022	0.013	0.025	0.011	0.008	0.015	0.035	0.015	0.030	0.015
rs13418037	2	218,314,141	DIRC3	C	T	−0.020	0.003	−0.006	0.011	−0.017	0.016	0.003	0.016	−0.002	0.014	0.002	0.018	−0.010	0.018	−0.036	0.018
rs62182127	2	219,279,588	VIL1	A	G	0.019	0.003	0.017	0.009	0.005	0.013	0.029	0.013	0.019	0.011	0.012	0.014	0.024	0.014	0.027	0.014
rs11678946	2	222,302,730	EPHA4	C	A	−0.014	0.003	0.003	0.009	0.003	0.012	0.003	0.013	−0.007	0.011	0.005	0.014	−0.024	0.014	0.012	0.014
rs4402747	2	225,457,173	CUL3	G	A	−0.016	0.003	0.003	0.009	0.002	0.012	0.002	0.013	−0.004	0.011	−0.006	0.014	0.007	0.014	0.013	0.014
rs17323117	2	230,162,971	PID1	A	G	−0.029	0.005	−0.014	0.017	−0.022	0.024	0.000	0.025	−0.029	0.020	−0.064	0.026	0.001	0.027	0.035	0.027
rs1465529	2	231,039,037	SP110	T	C	0.019	0.003	0.009	0.010	−0.003	0.014	0.018	0.014	0.017	0.012	0.017	0.015	0.020	0.015	0.007	0.015
rs6437249	2	242,175,331	HDLBP	C	T	0.019	0.003	−0.018	0.010	−0.014	0.014	−0.021	0.014	−0.010	0.012	−0.008	0.015	−0.016	0.015	−0.030	0.015
rs7625680	3	11,378,069	ATG7	A	G	0.015	0.003	0.005	0.009	0.004	0.013	0.007	0.013	0.007	0.011	0.012	0.014	−0.004	0.014	−0.002	0.014
rs1822825	3	12,449,963	PPARG	A	G	−0.014	0.003	0.005	0.009	0.014	0.012	−0.005	0.013	0.013	0.011	0.001	0.014	0.026	0.014	0.002	0.014
rs2607748	3	14,158,725	CHCHD4	T	C	−0.017	0.003	−0.007	0.009	0.002	0.012	−0.017	0.013	−0.005	0.011	0.000	0.014	−0.005	0.014	−0.020	0.014
rs11717397	3	23,368,583	UBE2E2	G	A	0.015	0.003	−0.001	0.009	−0.027	0.012	0.027	0.013	−0.008	0.011	−0.017	0.014	−0.002	0.014	0.018	0.014
rs2362755	3	24,716,668	THRB−AS1	G	T	−0.016	0.003	0.006	0.009	−0.001	0.012	0.012	0.013	0.004	0.011	−0.016	0.014	0.026	0.014	−0.009	0.014
rs11928797	3	33,457,493	UBP1	A	C	0.030	0.004	−0.003	0.015	0.003	0.021	−0.005	0.022	−0.017	0.018	−0.023	0.023	0.004	0.024	0.008	0.023
rs33969824	3	42,679,777	NKTR	G	T	0.020	0.004	0.002	0.013	0.014	0.018	−0.014	0.019	0.030	0.016	0.036	0.021	0.020	0.021	−0.011	0.021
rs12491473	3	46,989,904	CCDC12	G	A	0.020	0.003	0.019	0.009	0.025	0.012	0.009	0.013	0.019	0.011	0.024	0.014	0.011	0.014	0.021	0.014
rs2228561	3	48,628,014	COL7A1	A	G	0.020	0.004	0.005	0.014	0.007	0.019	0.004	0.020	0.007	0.017	−0.008	0.022	0.017	0.022	−0.003	0.022
rs4768	3	49,758,764	RNF123	A	G	−0.015	0.003	0.008	0.010	0.005	0.013	0.007	0.014	0.010	0.012	0.021	0.015	0.000	0.015	−0.006	0.015
rs9809209	3	51,281,664	DOCK3	G	A	−0.017	0.003	0.007	0.009	0.009	0.013	0.005	0.013	0.014	0.011	0.007	0.014	0.030	0.015	−0.026	0.014
rs112893170	3	57,211,863	IL17RD	T	C	0.020	0.003	0.012	0.012	0.013	0.017	0.012	0.017	0.019	0.014	−0.003	0.019	0.043	0.019	0.008	0.019
rs7628689	3	88,216,647	C3orf38	G	A	0.029	0.003	0.014	0.013	0.016	0.017	0.010	0.018	0.009	0.015	0.000	0.020	0.026	0.020	0.023	0.020
rs3772102	3	98,502,628	ST3GAL6	T	G	−0.020	0.003	0.006	0.009	0.007	0.013	0.004	0.013	0.008	0.011	0.004	0.014	0.023	0.014	0.018	0.014

Supplementary Table 2. Continued

SNP	Chr	Position	Gene[a]	Effect allele	Other allele	Association parameters for the exposure		Association parameters for colorectal cancer		Association parameters for colorectal cancer men		Association parameters for colorectal cancer women		Association parameters for colon cancer		Association parameters for proximal colon cancer		Association parameters for distal colon cancer		Association parameters for rectal cancer	
						Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE
rs62280667	3	101,084,604	SENP7	T	C	−0.028	0.003	−0.006	0.009	−0.005	0.013	−0.008	0.013	−0.006	0.011	0.001	0.015	0.000	0.015	0.011	0.015
rs62263345	3	107,252,190	BBX	A	G	0.028	0.004	−0.002	0.014	−0.012	0.019	0.006	0.019	0.008	0.016	0.007	0.021	0.013	0.021	−0.011	0.021
rs13069961	3	124,358,715	KALRN	A	G	−0.018	0.003	0.001	0.011	0.004	0.015	−0.002	0.015	−0.003	0.013	0.002	0.017	−0.008	0.017	0.002	0.017
rs687339	3	135,932,359	AC092991.1	T	C	0.040	0.003	0.012	0.010	−0.003	0.015	0.027	0.015	0.014	0.013	−0.001	0.016	0.011	0.017	0.004	0.016
rs811332	3	138,078,348	MRAS	C	T	0.019	0.003	−0.021	0.011	−0.009	0.016	−0.035	0.016	−0.035	0.013	−0.039	0.017	−0.026	0.018	0.015	0.018
rs55717031	3	138,848,505	MRPS22	G	T	0.032	0.003	−0.001	0.010	0.006	0.014	−0.003	0.014	0.012	0.012	0.019	0.015	0.005	0.015	−0.007	0.015
rs6440008	3	141,154,542	ZBTB38	T	C	0.035	0.003	−0.007	0.009	−0.015	0.013	−0.002	0.013	−0.017	0.011	−0.026	0.014	−0.004	0.015	0.000	0.014
rs73238159	3	142,078,759	XRN1	T	C	−0.025	0.004	−0.010	0.013	−0.019	0.018	−0.003	0.019	−0.003	0.016	0.010	0.021	−0.003	0.021	−0.002	0.021
rs13073970	3	170,630,520	EIF5A2	G	T	−0.025	0.003	0.009	0.011	0.001	0.015	0.017	0.015	0.008	0.013	0.000	0.017	0.013	0.017	0.004	0.017
rs56062334	3	172,299,226	LINC02068	T	C	0.017	0.003	−0.007	0.009	−0.017	0.013	0.004	0.013	−0.006	0.011	−0.007	0.015	−0.004	0.015	−0.021	0.015
rs9819762	3	178,914,879	PIK3CA	T	C	0.019	0.003	−0.030	0.011	−0.023	0.016	−0.038	0.016	−0.040	0.013	−0.053	0.017	−0.011	0.018	−0.031	0.017
rs66707192	3	186,382,065	HRG	G	A	0.018	0.003	0.012	0.010	0.025	0.014	0.000	0.014	0.007	0.012	0.003	0.016	0.005	0.016	0.001	0.016
rs13108218	4	3,443,931	HGFAC	G	A	0.017	0.003	0.002	0.009	−0.005	0.013	0.008	0.013	−0.009	0.011	−0.002	0.014	−0.002	0.015	0.011	0.014
rs1055582	4	39,700,173	UBE2K	C	T	0.027	0.003	−0.021	0.009	−0.016	0.012	−0.027	0.013	−0.027	0.011	−0.027	0.014	−0.020	0.014	−0.010	0.014
rs62302688	4	46,448,465	GABRA2	G	A	0.039	0.004	−0.006	0.017	0.022	0.023	−0.033	0.024	0.017	0.020	−0.007	0.026	0.025	0.026	−0.035	0.025
rs115805235	4	69,764,890	AC021146.3	C	T	0.039	0.006	−0.032	0.023	−0.080	0.032	0.022	0.033	−0.025	0.027	−0.032	0.035	−0.008	0.036	−0.037	0.035
rs16845929	4	72,017,058	SLC4A4	C	T	0.032	0.005	0.003	0.019	0.018	0.027	−0.016	0.028	0.004	0.023	0.027	0.030	−0.019	0.030	0.012	0.030
rs2280099	4	90,035,549	TIGD2	G	A	0.025	0.003	−0.006	0.011	−0.011	0.016	−0.004	0.016	0.012	0.014	0.037	0.018	−0.003	0.018	−0.017	0.018
rs35036084	4	97,552,791	LINC02267	T	C	0.017	0.003	0.007	0.009	0.009	0.013	0.006	0.013	0.003	0.011	0.002	0.014	−0.004	0.014	0.017	0.014
rs6532798	4	100,054,827	ADH4	T	C	0.037	0.003	0.003	0.010	−0.009	0.013	0.018	0.014	0.009	0.011	0.005	0.015	0.005	0.015	0.006	0.015
rs62342064	4	104,665,972	TACR3	C	T	0.022	0.004	−0.011	0.014	−0.002	0.020	−0.021	0.021	0.002	0.017	0.017	0.022	−0.017	0.023	−0.009	0.022
rs17429745	4	106,038,169	AC096577.1	G	T	0.026	0.003	0.022	0.010	0.043	0.013	−0.002	0.014	0.019	0.011	0.005	0.015	0.032	0.015	0.027	0.015
rs3804173	4	121,719,923	PRDM5	A	G	−0.020	0.003	−0.004	0.009	0.007	0.013	−0.020	0.013	−0.005	0.011	−0.023	0.015	0.007	0.015	−0.019	0.015
rs111443396	4	124,773,202	LINC01091	T	C	−0.026	0.004	0.014	0.014	0.020	0.019	0.008	0.020	−0.006	0.016	−0.011	0.021	0.004	0.021	0.048	0.021
rs7667562	4	129,133,826	LARP1B	C	A	0.016	0.003	0.017	0.010	0.007	0.014	0.032	0.014	0.029	0.012	0.036	0.016	0.020	0.016	0.006	0.016
rs6827641	4	145,653,694	GYPA/HHIP	C	T	−0.014	0.003	−0.020	0.009	−0.032	0.012	−0.008	0.013	−0.023	0.011	−0.007	0.014	−0.037	0.014	−0.017	0.014
rs6853741	4	148,982,559	ARHGAP10	A	G	0.024	0.003	−0.004	0.010	−0.014	0.014	0.008	0.015	−0.019	0.012	−0.023	0.016	−0.016	0.016	0.013	0.016
rs62334147	4	169,345,005	DDX60L	T	C	−0.019	0.003	−0.006	0.012	0.003	0.016	−0.012	0.017	0.003	0.014	0.012	0.018	−0.009	0.018	−0.004	0.018
rs4394044	4	186,607,420	SORBS2	T	C	0.014	0.003	−0.008	0.009	0.007	0.012	−0.024	0.013	−0.007	0.011	−0.010	0.014	−0.007	0.014	−0.007	0.014
rs9292578	5	35,230,075	PRLR	C	A	0.040	0.006	0.024	0.022	0.049	0.031	−0.002	0.032	0.022	0.027	−0.016	0.035	0.050	0.036	0.019	0.035
rs6895953	5	39,084,471	RICTOR	G	A	0.024	0.003	−0.026	0.009	−0.012	0.012	−0.041	0.013	−0.029	0.011	−0.042	0.014	−0.017	0.014	−0.009	0.014
rs72758321	5	41,464,841	PLCXD3	A	G	−0.047	0.006	0.003	0.025	0.002	0.035	−0.006	0.035	−0.037	0.029	−0.059	0.038	−0.004	0.039	0.037	0.039
rs6180	5	42,719,239	GHR	C	A	−0.035	0.003	−0.005	0.009	−0.001	0.012	−0.007	0.013	−0.005	0.011	-0.019	0.014	0.010	0.014	0.003	0.014
rs12520263	5	44,122,508	RNU6−381P	G	T	−0.017	0.003	0.010	0.010	0.004	0.014	0.015	0.014	0.016	0.012	0.035	0.016	−0.001	0.016	0.018	0.016
rs7719168	5	53,292,390	ARL15	A	C	−0.030	0.004	−0.024	0.014	−0.038	0.020	−0.008	0.021	−0.025	0.017	−0.023	0.022	−0.027	0.022	−0.023	0.022
rs28650790	5	55,861,464	C5orf67	C	T	−0.018	0.003	−0.008	0.011	0.016	0.016	−0.032	0.016	−0.019	0.014	−0.031	0.017	−0.009	0.018	0.014	0.018
rs1498603	5	58,333,125	PDE4D	T	G	0.031	0.005	0.032	0.019	0.055	0.026	0.009	0.026	0.035	0.023	0.056	0.030	0.009	0.030	0.010	0.029
rs11954036	5	59,028,853	PDE4D	T	C	0.037	0.003	0.006	0.009	−0.001	0.013	0.011	0.013	0.001	0.011	−0.004	0.015	0.011	0.015	−0.001	0.014
rs80170948	5	64,020,316	SREK1IP1	T	G	−0.039	0.006	0.007	0.025	0.034	0.034	−0.023	0.035	0.018	0.029	0.002	0.038	0.009	0.039	0.011	0.038
rs2227819	5	76,012,745	F2R	C	T	−0.022	0.004	0.022	0.015	0.008	0.021	0.036	0.021	0.020	0.018	0.037	0.023	0.004	0.023	0.039	0.023
rs12108803	5	77,158,507	TBCA	T	G	−0.033	0.006	−0.008	0.022	−0.021	0.031	0.008	0.031	−0.006	0.026	−0.020	0.034	0.009	0.035	−0.011	0.034
rs840809	5	87,173,927	TMEM161B	A	C	0.016	0.003	−0.022	0.010	−0.003	0.014	−0.044	0.014	−0.034	0.012	−0.029	0.015	−0.040	0.015	−0.002	0.015
rs13178887	5	88,355,993	MEF2C−AS1	T	C	0.023	0.003	0.013	0.009	0.002	0.013	0.023	0.013	0.016	0.011	0.015	0.014	0.015	0.014	−0.002	0.014

Supplementary Table 2. Continued

SNP	Chr	Position	Gene[a]	Effect allele	Other allele	Association parameters for the exposure		Association parameters for colorectal cancer		Association parameters for colorectal cancer men		Association parameters for colorectal cancer women		Association parameters for colon cancer		Association parameters for proximal colon cancer		Association parameters for distal colon cancer		Association parameters for rectal cancer	
						Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE
rs2366398	5	89,437,963	LINC01339	G	T	−0.018	0.003	0.012	0.011	0.010	0.015	0.015	0.015	0.009	0.013	−0.006	0.016	0.032	0.017	0.013	0.016
rs26822	5	102,518,795	PPIP5K2	A	G	−0.017	0.003	−0.009	0.010	−0.007	0.013	−0.012	0.014	−0.014	0.012	−0.024	0.015	−0.002	0.015	−0.017	0.015
rs73271090	5	132,313,550	AC010240.1	G	A	0.044	0.003	0.010	0.012	0.019	0.017	0.002	0.018	0.003	0.015	−0.008	0.019	0.003	0.020	−0.005	0.019
rs329122	5	133,864,599	JADE2	G	A	−0.018	0.003	0.003	0.009	0.003	0.012	0.002	0.013	0.006	0.011	0.018	0.014	−0.003	0.014	0.018	0.014
rs11242236	5	134,586,980	C5orf66	G	A	0.025	0.003	0.013	0.009	0.021	0.012	0.006	0.013	0.018	0.011	0.025	0.014	0.018	0.014	0.005	0.014
rs2348604	5	136,809,831	SPOCK1	T	C	−0.016	0.003	−0.004	0.010	−0.008	0.014	−0.001	0.014	−0.011	0.012	−0.005	0.015	−0.020	0.016	0.004	0.015
rs3734166	5	137,665,323	CDC25C	A	G	0.028	0.003	0.004	0.010	0.014	0.014	−0.005	0.014	0.008	0.012	0.005	0.015	0.011	0.016	−0.008	0.015
rs2042253	5	143,059,433	MIR5197	T	C	0.023	0.003	−0.023	0.010	−0.045	0.014	−0.001	0.014	−0.017	0.012	−0.027	0.016	−0.004	0.016	−0.021	0.016
rs35668185	5	168,256,455	SLIT3	T	C	0.056	0.003	−0.002	0.011	−0.001	0.015	−0.001	0.015	0.003	0.013	0.012	0.017	−0.009	0.017	−0.008	0.017
rs13168379	5	173,382,761	CPEB4	G	A	−0.031	0.005	0.003	0.017	−0.003	0.024	0.011	0.024	0.022	0.021	0.024	0.028	0.018	0.028	−0.006	0.027
rs17714046	5	180,661,980	TRIM41	C	T	0.042	0.006	0.026	0.024	−0.002	0.033	0.051	0.034	0.032	0.028	0.022	0.037	0.045	0.037	−0.009	0.037
rs584955	6	7,097,141	RREB1	A	G	0.036	0.006	0.037	0.021	0.018	0.030	0.053	0.031	0.035	0.026	0.034	0.034	0.039	0.034	0.022	0.034
rs2296198	6	18,399,750	RNF144B	C	T	0.016	0.003	−0.001	0.010	−0.004	0.014	0.002	0.015	−0.021	0.012	−0.024	0.016	−0.017	0.016	−0.005	0.016
rs72828596	6	19,183,591	AL589647.1	G	A	−0.019	0.004	−0.012	0.014	−0.019	0.019	−0.006	0.019	−0.040	0.016	−0.038	0.021	−0.059	0.021	0.028	0.021
rs73382439	6	20,404,420	E2F3	C	T	0.019	0.003	0.005	0.011	0.000	0.016	0.009	0.016	0.010	0.014	0.015	0.018	0.000	0.018	−0.003	0.018
rs17258904	6	21,928,131	CASC15	A	G	−0.017	0.003	−0.005	0.010	−0.011	0.014	0.004	0.014	0.002	0.012	−0.007	0.015	0.011	0.016	−0.008	0.015
rs1165196	6	25,813,150	SLC17A1	A	G	−0.029	0.003	−0.007	0.009	−0.022	0.012	0.010	0.013	0.002	0.011	0.010	0.014	0.005	0.014	−0.014	0.014
rs13195402	6	26,463,575	BTN2A1	T	G	−0.038	0.004	0.042	0.019	0.026	0.026	0.058	0.027	0.037	0.022	0.066	0.028	0.014	0.029	0.058	0.028
rs16897515	6	27,278,020	POM121L2	A	C	−0.023	0.003	0.036	0.012	0.022	0.017	0.051	0.017	0.038	0.014	0.051	0.018	0.036	0.019	0.058	0.018
rs33932084	6	28,268,824	PGBD1	G	A	−0.034	0.004	0.054	0.016	0.041	0.022	0.066	0.023	0.051	0.019	0.096	0.024	0.020	0.025	0.087	0.024
rs9267488	6	31,514,247	ATP6V1G2−DDX39B/ATP6V1G2	G	A	−0.031	0.004	0.051	0.014	0.059	0.020	0.044	0.020	0.048	0.017	0.057	0.022	0.037	0.022	0.092	0.022
rs1150752	6	32,064,726	TNXB	C	T	−0.031	0.004	0.058	0.015	0.066	0.021	0.047	0.021	0.054	0.018	0.066	0.023	0.041	0.023	0.096	0.022
rs12194618	6	38,091,030	ZFAND3	G	A	−0.017	0.003	0.007	0.009	0.011	0.013	0.002	0.013	0.009	0.011	−0.003	0.014	0.016	0.015	−0.002	0.014
rs7740433	6	42,908,013	CNPY3	A	G	0.017	0.003	0.003	0.011	−0.001	0.015	0.004	0.015	0.018	0.013	0.012	0.016	0.018	0.017	−0.021	0.016
rs998584	6	43,757,896	VEGFA	A	C	0.020	0.003	0.005	0.009	−0.020	0.012	0.033	0.013	0.009	0.011	0.012	0.014	0.008	0.014	0.007	0.014
rs6924225	6	45,584,732	RUNX2	G	A	0.019	0.003	0.005	0.012	0.020	0.017	−0.011	0.017	−0.006	0.014	−0.019	0.019	−0.004	0.019	0.006	0.019
rs2397112	6	52,684,333	GSTA6P	A	G	0.019	0.003	0.002	0.009	0.008	0.013	−0.004	0.013	−0.003	0.011	−0.001	0.014	0.005	0.014	0.005	0.014
rs9361489	6	79,816,785	PHIP	T	C	0.022	0.003	0.008	0.009	−0.004	0.012	0.021	0.013	0.018	0.011	0.036	0.014	0.009	0.014	−0.003	0.014
rs6916994	6	87,991,236	GJB7	C	T	0.029	0.003	−0.005	0.009	−0.001	0.012	−0.006	0.013	−0.008	0.011	−0.030	0.014	0.015	0.014	0.009	0.014
rs670049	6	100,087,024	PRDM13	A	C	0.019	0.003	−0.005	0.009	0.002	0.013	−0.012	0.013	−0.003	0.011	−0.011	0.014	0.001	0.015	−0.004	0.014
rs9322822	6	105,369,598	LIN28B−AS1	C	T	0.015	0.003	0.003	0.009	0.016	0.013	−0.011	0.014	0.007	0.011	0.006	0.015	0.006	0.015	0.001	0.015
rs4946810	6	107,420,270	BEND3	A	C	−0.016	0.003	0.006	0.009	0.004	0.013	0.011	0.013	0.016	0.011	0.012	0.015	0.020	0.015	−0.004	0.014
rs218291	6	108,467,024	OSTM1/OSTM1−AS1	G	A	0.016	0.003	0.011	0.009	0.014	0.013	0.007	0.013	0.007	0.011	0.002	0.014	0.009	0.015	0.021	0.014
rs9398171	6	108,983,527	FOXO3	T	C	0.050	0.003	0.012	0.010	0.023	0.013	−0.002	0.014	0.022	0.012	0.027	0.015	0.024	0.015	−0.001	0.015
rs41285260	6	126,661,502	CENPW	T	G	0.039	0.004	-0.007	0.017	-0.012	0.024	-0.005	0.024	-0.012	0.020	0.004	0.026	-0.039	0.027	0.008	0.026
rs9321106	6	128,355,316	PTPRK	A	G	0.018	0.003	0.016	0.012	0.018	0.017	0.014	0.018	0.004	0.015	0.008	0.019	0.001	0.019	0.030	0.019
rs9398891	6	129,314,749	LAMA2	C	T	−0.017	0.003	−0.001	0.010	−0.002	0.013	0.001	0.014	0.000	0.011	−0.002	0.015	0.005	0.015	0.007	0.015

Supplementary Table 2. Continued

SNP	Chr	Position	Gene[a]	Effect allele	Other allele	Association parameters for the exposure		Association parameters for colorectal cancer		Association parameters for colorectal cancer men		Association parameters for colorectal cancer women		Association parameters for colon cancer		Association parameters for proximal colon cancer		Association parameters for distal colon cancer		Association parameters for rectal cancer	
						Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE
rs3890746	6	130,371,055	L3MBTL3	T	C	−0.020	0.003	0.004	0.009	0.014	0.012	−0.004	0.013	−0.006	0.011	−0.033	0.014	0.020	0.014	0.017	0.014
rs2786185	6	147,595,554	STXBP5	G	A	0.019	0.003	0.005	0.009	0.019	0.012	−0.008	0.013	0.004	0.011	−0.009	0.014	0.012	0.014	−0.001	0.014
rs7774230	6	152,164,239	ESR1	C	T	−0.026	0.003	0.011	0.009	0.007	0.012	0.016	0.013	0.008	0.011	0.013	0.014	0.004	0.014	0.010	0.014
rs790513	6	154,420,368	OPRM1	C	A	0.025	0.003	0.006	0.010	−0.015	0.014	0.027	0.015	−0.001	0.012	−0.027	0.016	0.012	0.016	0.011	0.016
rs7758644	6	156,583,467	snoRNA	C	A	−0.019	0.003	0.008	0.012	0.014	0.017	0.000	0.018	0.004	0.015	0.004	0.019	0.008	0.019	0.019	0.019
rs3127579	6	160,674,632	SLC22A2	G	A	−0.033	0.004	0.012	0.013	0.028	0.019	−0.008	0.019	−0.004	0.016	−0.016	0.021	0.005	0.021	0.028	0.021
rs12211977	6	161,252,770	lincRNA	G	A	−0.023	0.004	0.010	0.016	0.040	0.022	−0.022	0.022	0.024	0.018	0.061	0.024	−0.004	0.024	−0.007	0.024
rs504371	6	165,724,052	C6orf118	C	A	−0.015	0.003	−0.015	0.009	−0.006	0.013	−0.023	0.013	−0.018	0.011	−0.027	0.014	−0.006	0.015	−0.015	0.014
rs4709995	6	166,313,447	PDE10A	C	T	−0.042	0.003	−0.022	0.009	−0.023	0.013	−0.020	0.013	−0.026	0.011	−0.020	0.014	−0.041	0.014	−0.049	0.014
rs7802508	7	1,191,689	ZFAND2A	G	A	−0.021	0.003	−0.006	0.009	−0.012	0.013	0.001	0.013	−0.007	0.011	−0.012	0.014	−0.001	0.014	−0.023	0.014
rs12699547	7	2,015,970	MAD1L1	C	T	0.021	0.003	0.005	0.009	−0.009	0.013	0.022	0.013	0.008	0.011	0.004	0.014	0.010	0.015	0.016	0.014
rs1182174	7	2,875,420	GNA12	G	A	−0.021	0.003	0.028	0.010	0.029	0.014	0.026	0.014	0.037	0.012	0.036	0.015	0.031	0.015	0.003	0.015
rs2250243	7	6,690,240	ZNF316	T	C	−0.024	0.003	−0.011	0.010	−0.009	0.014	−0.015	0.015	−0.010	0.012	−0.008	0.016	−0.014	0.016	−0.016	0.016
rs4719393	7	14,219,213	DGKB	T	G	0.027	0.003	−0.008	0.010	−0.010	0.013	−0.005	0.014	−0.008	0.012	−0.013	0.015	−0.004	0.015	−0.009	0.015
rs10252510	7	31,023,108	GHRHR	G	A	0.020	0.003	0.001	0.010	−0.009	0.014	0.012	0.015	−0.001	0.012	−0.018	0.016	0.015	0.016	0.007	0.016
rs7790246	7	32,976,416	AVL9/RP9P	C	T	−0.017	0.003	−0.007	0.010	0.000	0.014	−0.013	0.014	0.001	0.012	0.004	0.015	0.005	0.015	0.006	0.015
rs1050327	7	44,808,017	ZMIZ2	G	A	−0.017	0.003	−0.010	0.009	−0.008	0.012	−0.013	0.013	−0.005	0.011	−0.003	0.014	−0.007	0.014	−0.010	0.014
rs870796	7	45,426,435	ELK1P1	G	A	0.017	0.003	−0.007	0.009	−0.006	0.013	−0.010	0.013	−0.004	0.011	0.002	0.014	−0.014	0.014	−0.014	0.014
rs2270628	7	45,949,570	IGFBP3	C	T	−0.033	0.003	0.023	0.011	0.030	0.015	0.019	0.016	0.024	0.013	0.017	0.017	0.043	0.018	0.048	0.017
rs74657816	7	46,670,682	HMGN1P19	T	G	0.047	0.005	0.012	0.019	0.002	0.026	0.021	0.027	−0.004	0.022	0.004	0.029	−0.022	0.029	−0.006	0.029
rs12538762	7	47,264,328	TNS3	C	T	0.026	0.004	0.001	0.014	0.002	0.020	−0.003	0.020	−0.004	0.017	−0.002	0.022	−0.006	0.023	−0.012	0.022
rs6974707	7	55,982,894	ZNF713	G	A	−0.019	0.003	0.009	0.011	0.024	0.015	−0.008	0.015	0.004	0.013	−0.008	0.016	0.023	0.017	0.012	0.017
rs35862187	7	69,625,029	AUTS2	A	G	0.031	0.006	0.002	0.020	−0.030	0.028	0.038	0.029	−0.015	0.024	−0.036	0.031	−0.003	0.031	−0.012	0.031
rs17145738	7	72,982,874	TBL2	C	T	−0.034	0.004	−0.016	0.014	−0.018	0.019	−0.016	0.019	−0.021	0.016	−0.005	0.021	−0.030	0.022	−0.034	0.021
rs411717	7	94,033,031	COL1A2	C	T	−0.015	0.003	0.009	0.009	0.017	0.012	−0.001	0.013	0.001	0.011	−0.007	0.014	0.010	0.014	0.022	0.014
rs34670419	7	99,130,834	ZKSCAN5	G	T	−0.036	0.006	0.001	0.024	−0.020	0.033	0.022	0.034	−0.024	0.028	−0.028	0.036	−0.020	0.037	0.045	0.037
rs34312198	7	99,674,870	ZNF3	C	A	−0.024	0.004	−0.020	0.014	−0.021	0.020	−0.020	0.021	−0.026	0.017	−0.020	0.022	−0.021	0.023	−0.010	0.022
rs7783012	7	114,116,881	FOXP2	A	G	−0.016	0.003	0.010	0.009	0.017	0.012	0.004	0.013	0.011	0.011	0.018	0.014	0.005	0.014	0.015	0.014
rs12666306	7	115,082,406	AC073901.1	G	A	0.017	0.003	−0.001	0.009	0.017	0.012	−0.020	0.013	−0.007	0.011	−0.003	0.014	−0.010	0.014	0.017	0.014
rs2896395	7	127,511,705	SND1	C	T	0.015	0.003	−0.010	0.010	−0.016	0.014	−0.003	0.014	−0.018	0.012	−0.015	0.015	−0.021	0.015	−0.007	0.015
rs11556924	7	129,663,496	ZC3HC1	T	C	−0.016	0.003	0.037	0.009	0.032	0.013	0.043	0.013	0.043	0.011	0.030	0.015	0.047	0.015	0.033	0.015
rs207212	7	130,547,217	LINC00513	C	T	0.028	0.004	0.058	0.016	0.075	0.022	0.045	0.022	0.068	0.019	0.057	0.024	0.063	0.025	0.049	0.024
rs1986692	7	133,743,393	EXOC4	A	G	−0.015	0.003	0.004	0.009	−0.003	0.013	0.011	0.013	0.008	0.011	0.012	0.014	0.003	0.014	−0.004	0.014
rs273956	7	137,603,188	CREB3L2	G	A	−0.021	0.003	0.011	0.009	0.007	0.013	0.016	0.013	0.012	0.011	0.016	0.014	0.023	0.015	0.021	0.014
rs114949263	7	150,498,245	TMEM 176B/ TMEM 176A	T	C	0.027	0.004	−0.013	0.014	−0.004	0.020	−0.020	0.021	−0.027	0.017	−0.019	0.022	−0.044	0.022	−0.023	0.022
rs10246481	7	156,184,748	lincRNA	A	G	−0.015	0.003	0.004	0.009	0.004	0.013	0.006	0.013	0.006	0.011	0.018	0.014	−0.020	0.014	0.002	0.014
rs9657541	8	10,643,164	SOX7/PINX1/ PINX1	C	T	0.020	0.003	−0.002	0.011	−0.010	0.016	0.007	0.016	−0.006	0.013	0.004	0.017	−0.015	0.017	−0.002	0.017
rs76393968	8	16,282,937	MSR1	G	A	0.060	0.010	0.035	0.034	0.018	0.048	0.060	0.051	0.029	0.044	0.036	0.058	0.025	0.059	0.015	0.057
rs1495741	8	18,272,881	NAT2	A	G	−0.026	0.003	0.010	0.010	0.010	0.015	0.009	0.015	0.011	0.013	0.012	0.016	0.013	0.017	0.012	0.016

Supplementary Table 2. Continued

SNP	Chr	Position	Gene[a]	Effect allele	Other allele	Association parameters for the exposure		Association parameters for colorectal cancer		Association parameters for colorectal cancer men		Association parameters for colorectal cancer women		Association parameters for colon cancer		Association parameters for proximal colon cancer		Association parameters for distal colon cancer		Association parameters for rectal cancer	
						Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE
rs11782452	8	26,361,601	BNIP3L	G	A	0.015	0.003	−0.002	0.009	0.000	0.013	−0.005	0.013	−0.002	0.011	0.009	0.014	−0.009	0.014	−0.001	0.014
rs56352849	8	73,769,173	KCNB2	G	A	−0.016	0.003	−0.011	0.010	−0.012	0.014	−0.005	0.014	−0.017	0.012	−0.038	0.015	−0.002	0.016	−0.010	0.015
rs1431015	8	77,131,580	HNF4G	C	T	0.020	0.003	0.008	0.009	0.014	0.012	−0.001	0.013	0.003	0.011	0.008	0.014	−0.001	0.014	0.016	0.014
rs6473015	8	78,178,485	lincRNA	A	C	−0.019	0.003	−0.028	0.010	−0.025	0.014	−0.034	0.014	−0.024	0.012	−0.031	0.015	−0.019	0.015	−0.035	0.015
rs445036	8	81,408,409	ZBTB10	T	C	0.019	0.003	−0.007	0.010	−0.008	0.013	−0.007	0.014	0.004	0.011	0.015	0.015	−0.012	0.015	−0.029	0.015
rs1786342	8	101,676,363	SNX31	T	C	0.017	0.003	0.022	0.009	0.030	0.013	0.011	0.013	0.023	0.011	0.014	0.014	0.032	0.014	0.016	0.014
rs60862542	8	109,275,071	EIF3E	G	A	0.017	0.003	−0.005	0.011	−0.018	0.015	0.008	0.015	−0.010	0.013	−0.007	0.016	−0.015	0.017	−0.010	0.016
rs2737205	8	116,610,180	TRPS1	C	T	−0.023	0.003	−0.013	0.009	−0.005	0.013	−0.021	0.013	−0.028	0.011	−0.023	0.014	−0.034	0.014	0.010	0.014
rs2978062	8	134,571,618	ST3GAL1	T	G	−0.019	0.003	−0.007	0.013	0.009	0.018	−0.023	0.018	−0.004	0.015	0.018	0.020	−0.035	0.020	0.019	0.020
rs716100	8	135,661,278	ZFAT	G	A	−0.019	0.003	−0.017	0.009	−0.018	0.013	−0.013	0.013	0.002	0.011	−0.001	0.015	0.005	0.015	−0.039	0.015
rs12549853	8	145,020,636	PLEC	G	A	−0.016	0.003	0.011	0.009	0.009	0.013	0.015	0.013	0.006	0.011	0.014	0.014	−0.004	0.014	0.009	0.014
rs10114121	9	19,440,136	ACER2	G	A	−0.020	0.004	−0.021	0.012	−0.025	0.017	−0.018	0.018	−0.019	0.015	−0.013	0.019	−0.023	0.019	−0.019	0.019
rs10757291	9	22,161,884	CDKN2B−AS1	A	G	−0.019	0.003	0.007	0.009	0.010	0.012	0.006	0.013	0.008	0.011	0.018	0.014	−0.008	0.014	0.011	0.014
rs10811787	9	22,871,816	AL391117.1	T	C	−0.015	0.003	−0.009	0.009	−0.011	0.012	−0.009	0.013	−0.010	0.011	−0.020	0.014	−0.008	0.014	−0.002	0.014
rs11557154	9	34,107,505	DCAF12	T	C	0.024	0.004	0.036	0.013	0.038	0.018	0.029	0.018	0.045	0.016	0.051	0.020	0.041	0.021	0.050	0.020
rs10869022	9	74,057,313	TRPM3	C	T	0.021	0.003	0.005	0.011	0.027	0.015	−0.016	0.015	0.020	0.013	0.019	0.017	0.024	0.017	−0.020	0.017
rs2378662	9	86,707,289	AL390838.1	A	G	−0.017	0.003	0.004	0.009	−0.007	0.012	0.019	0.013	0.008	0.011	0.020	0.014	−0.003	0.014	0.018	0.014
rs10908903	9	92,228,559	GADD45G	T	G	0.015	0.003	0.015	0.009	0.012	0.012	0.019	0.013	0.013	0.011	0.019	0.014	0.007	0.014	0.014	0.014
rs1055710	9	96,214,928	FAM120AOS	A	G	−0.018	0.003	−0.013	0.009	−0.014	0.013	−0.011	0.013	−0.011	0.011	−0.039	0.015	0.017	0.015	0.000	0.015
rs75660441	9	97,662,448	C9orf3	A	G	0.039	0.005	−0.029	0.018	−0.024	0.026	−0.030	0.026	−0.032	0.022	−0.049	0.028	−0.016	0.029	−0.038	0.028
rs28831479	9	98,254,526	PTCH1	C	A	0.022	0.003	0.001	0.010	0.007	0.014	−0.002	0.014	0.002	0.012	−0.016	0.016	0.015	0.016	0.001	0.016
rs7034716	9	101,858,382	TGFBR1	C	T	0.015	0.003	0.013	0.010	−0.030	0.014	0.006	0.014	−0.008	0.012	0.004	0.016	−0.024	0.016	−0.016	0.016
rs6479003	9	102,948,685	INVS	G	A	0.024	0.004	0.022	0.016	0.035	0.022	0.006	0.023	0.029	0.019	0.025	0.025	0.015	0.025	0.021	0.024
rs41277821	9	109,689,972	ZNF462	T	C	0.062	0.009	0.005	0.038	0.013	0.054	−0.005	0.055	−0.018	0.046	−0.007	0.060	−0.021	0.062	0.021	0.058
rs7872812	9	119,341,544	ASTN2	C	T	−0.026	0.004	−0.007	0.013	−0.023	0.017	0.004	0.018	−0.003	0.015	0.019	0.019	−0.027	0.019	−0.017	0.019
rs13301073	9	128,284,378	MAPKAP1	G	A	0.022	0.003	0.005	0.009	0.000	0.013	0.012	0.013	0.008	0.011	0.017	0.014	−0.005	0.015	−0.005	0.014
rs1832007	10	5,254,847	AKR1C4	A	G	−0.057	0.003	−0.034	0.012	−0.045	0.017	−0.023	0.018	−0.043	0.015	−0.043	0.019	−0.055	0.020	−0.009	0.019
rs2801482	10	12,459,773	CAMK1D	A	G	−0.050	0.008	−0.026	0.026	−0.016	0.036	−0.037	0.037	0.003	0.032	−0.010	0.041	0.033	0.041	−0.021	0.040
rs7921105	10	13,535,398	BEND7	T	C	−0.016	0.003	−0.001	0.009	−0.003	0.012	0.002	0.013	0.008	0.011	−0.001	0.014	0.010	0.014	−0.003	0.014
rs11012712	10	21,760,015	–	C	T	0.022	0.003	−0.026	0.011	−0.021	0.016	−0.032	0.016	−0.027	0.014	−0.039	0.017	−0.012	0.018	−0.035	0.017
rs10047326	10	22,839,463	PIP4K2A	A	C	0.017	0.003	−0.011	0.009	0.013	0.013	−0.034	0.013	−0.010	0.011	−0.019	0.014	−0.005	0.014	−0.026	0.014
rs293275	10	53,215,020	PRKG1	T	C	−0.014	0.003	0.003	0.009	0.009	0.012	−0.005	0.013	0.013	0.011	0.023	0.014	0.005	0.014	−0.008	0.014
rs10821713	10	62,055,781	ANK3	C	T	−0.017	0.003	−0.004	0.009	−0.004	0.012	−0.004	0.013	0.006	0.011	−0.007	0.014	0.018	0.014	−0.009	0.014
rs7910087	10	77,209,145	LRMDA	C	T	−0.017	0.003	−0.009	0.009	−0.020	0.012	0.001	0.013	−0.002	0.011	−0.009	0.014	0.006	0.014	−0.020	0.014
rs4418728	10	94,839,724	CYP26A1	G	T	0.024	0.003	−0.027	0.009	−0.029	0.012	−0.025	0.013	−0.029	0.011	−0.030	0.014	−0.028	0.014	−0.022	0.014
rs116454156	10	95,347,041	FFAR4	A	G	0.078	0.010	−0.013	0.033	−0.007	0.047	−0.024	0.049	−0.006	0.040	−0.003	0.051	−0.015	0.053	−0.006	0.051
rs11187838	10	96,038,686	PLCE1	G	A	0.024	0.003	−0.006	0.009	−0.002	0.012	−0.010	0.013	0.000	0.011	0.005	0.014	−0.004	0.014	−0.006	0.014
rs10509746	10	102,656,897	PAX2	C	T	0.027	0.003	0.006	0.009	0.031	0.013	−0.021	0.013	0.000	0.011	−0.002	0.014	0.001	0.014	0.011	0.014
rs4917962	10	103,931,931	NOLC1	G	T	−0.024	0.004	−0.024	0.013	−0.008	0.018	−0.042	0.019	−0.017	0.016	0.004	0.021	−0.032	0.021	−0.021	0.021
rs12244851	10	114,773,926	TCF7L2	C	T	−0.015	0.003	−0.010	0.010	−0.004	0.013	−0.014	0.014	−0.009	0.011	0.008	0.015	−0.021	0.015	−0.005	0.015
rs3858325	10	117,988,795	GFRA1	C	T	−0.019	0.003	0.006	0.009	0.000	0.012	0.011	0.013	0.004	0.011	0.015	0.014	−0.007	0.014	0.011	0.014

Supplementary Table 2. Continued

SNP	Chr	Position	Gene[a]	Effect allele	Other allele	Association parameters for the exposure		Association parameters for colorectal cancer		Association parameters for colorectal cancer men		Association parameters for colorectal cancer women		Association parameters for colon cancer		Association parameters for proximal colon cancer		Association parameters for distal colon cancer		Association parameters for rectal cancer	
						Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE
rs61867536	11	1,513,700	MOB2	C	T	−0.018	0.003	−0.030	0.009	−0.019	0.012	−0.044	0.013	−0.023	0.011	−0.016	0.014	−0.025	0.014	−0.054	0.014
rs3213223	11	2,156,930	IGF2/INS −IGF−2	G	A	−0.076	0.003	0.007	0.011	0.011	0.015	0.004	0.016	0.021	0.013	0.028	0.017	0.012	0.017	−0.023	0.017
rs11029620	11	3,771,924	NUP98	C	T	0.022	0.003	−0.004	0.011	−0.009	0.015	0.003	0.015	0.004	0.013	−0.012	0.017	0.010	0.017	−0.011	0.017
rs67257872	11	8,530,218	STK33	A	G	0.014	0.003	−0.003	0.009	−0.003	0.012	0.000	0.013	0.000	0.011	0.000	0.014	0.010	0.014	0.000	0.014
rs7947951	11	13,356,030	ARNTL	G	A	0.020	0.003	−0.007	0.009	−0.008	0.013	−0.006	0.013	−0.016	0.011	−0.016	0.015	−0.015	0.015	−0.001	0.015
rs72858776	11	15,772,953	AC087379.1	G	T	0.030	0.005	−0.010	0.016	−0.006	0.022	−0.010	0.023	−0.008	0.019	−0.014	0.025	−0.002	0.026	−0.010	0.025
rs11024614	11	18,326,758	HPS5	T	C	−0.023	0.003	−0.008	0.009	−0.013	0.013	−0.001	0.013	−0.004	0.011	−0.007	0.014	−0.001	0.014	−0.021	0.014
rs34452566	11	27,793,470	AC103796.1	G	T	−0.018	0.003	−0.010	0.012	0.004	0.016	−0.026	0.017	−0.004	0.014	−0.002	0.018	−0.010	0.018	−0.021	0.018
rs11031058	11	30,375,889	ARL14EP	C	T	−0.022	0.003	0.015	0.012	0.019	0.017	0.008	0.017	0.014	0.014	0.013	0.018	0.018	0.019	0.007	0.018
rs117529631	11	46,159,633	AC024475.4	C	T	−0.041	0.006	−0.035	0.023	−0.058	0.031	−0.014	0.032	−0.024	0.027	−0.015	0.035	−0.037	0.036	−0.013	0.035
rs5896	11	46,745,003	F2	T	C	0.036	0.004	−0.023	0.013	−0.022	0.018	−0.021	0.019	−0.023	0.016	−0.016	0.021	−0.028	0.021	−0.026	0.021
rs1051006	11	47,306,585	MADD	A	G	0.040	0.003	−0.009	0.012	−0.013	0.016	−0.004	0.017	−0.012	0.014	−0.011	0.018	−0.019	0.019	−0.017	0.018
rs1039481	11	48,182,237	PTPRJ	A	G	−0.042	0.003	−0.013	0.010	0.000	0.014	−0.027	0.015	−0.010	0.012	−0.005	0.016	−0.013	0.016	−0.011	0.016
rs202676	11	49,227,620	FOLH1	G	A	0.021	0.003	0.002	0.010	−0.005	0.015	0.008	0.015	0.003	0.013	0.008	0.016	0.001	0.017	−0.017	0.017
rs10769621	11	49,860,463	TRIM51FP	T	C	0.020	0.003	0.012	0.010	0.002	0.013	0.025	0.014	0.011	0.012	0.017	0.015	0.004	0.015	0.009	0.015
rs11230983	11	55,541,284	OR5D13	A	G	0.035	0.004	0.009	0.014	−0.002	0.019	0.023	0.019	0.015	0.016	0.010	0.021	0.013	0.022	0.001	0.021
rs78460947	11	56,143,715	OR8U1	G	A	0.042	0.006	−0.006	0.027	0.023	0.037	−0.035	0.038	−0.013	0.032	0.019	0.041	−0.020	0.043	−0.029	0.041
rs146345029	11	59,596,007	GIF	G	A	−0.034	0.006	0.052	0.022	0.051	0.032	0.053	0.032	0.036	0.027	0.003	0.034	0.067	0.036	0.051	0.035
rs174554	11	61,579,463	FADS1/ FADS2	A	G	0.022	0.003	0.061	0.009	0.062	0.013	0.062	0.013	0.060	0.011	0.045	0.015	0.081	0.015	0.051	0.015
rs117104648	11	65,543,736	AP5B1	T	C	−0.036	0.005	0.001	0.019	0.008	0.027	0.000	0.027	−0.010	0.023	−0.012	0.029	−0.016	0.030	0.018	0.029
rs12790261	11	66,988,048	KDM2A	C	A	−0.031	0.005	−0.013	0.019	−0.003	0.027	−0.016	0.028	−0.015	0.023	0.006	0.030	−0.024	0.031	−0.030	0.030
rs4980661	11	69,306,579	CCND1	A	G	0.014	0.003	−0.012	0.009	−0.001	0.012	−0.024	0.013	−0.014	0.011	−0.010	0.014	−0.020	0.014	−0.002	0.014
rs2512525	11	77,923,019	USP35	T	C	0.024	0.003	−0.012	0.012	−0.018	0.016	−0.005	0.017	−0.007	0.014	−0.017	0.018	−0.005	0.019	−0.032	0.018
rs61904289	11	85,994,731	AP003084.1	C	T	−0.016	0.003	−0.002	0.009	0.001	0.013	−0.004	0.014	−0.005	0.011	0.000	0.015	−0.010	0.015	0.006	0.015
rs625245	11	94,192,103	MRE11	T	G	−0.016	0.003	0.009	0.009	−0.005	0.013	0.025	0.013	0.016	0.011	0.022	0.015	0.005	0.015	0.006	0.014
rs35023999	11	113,266,411	ANKK1	C	A	0.015	0.003	0.006	0.009	0.003	0.012	0.009	0.013	0.011	0.011	0.026	0.014	−0.006	0.014	−0.007	0.014
rs10892564	11	120,224,650	ARHGEF12	A	G	−0.017	0.003	0.012	0.009	−0.001	0.013	0.028	0.013	0.008	0.011	0.011	0.014	0.013	0.014	0.005	0.014
rs4936759	11	122,763,516	C11orf63	C	T	0.016	0.003	0.005	0.009	0.015	0.013	−0.001	0.013	0.006	0.011	0.008	0.014	0.009	0.014	0.014	0.014
rs10893499	11	126,241,979	ST3GAL4	G	A	0.022	0.004	0.025	0.013	0.001	0.018	0.050	0.018	0.022	0.016	0.024	0.020	0.018	0.020	0.046	0.020
rs11064536	12	905,582	WNK1	T	C	0.020	0.003	−0.016	0.012	0.016	0.017	−0.051	0.017	−0.021	0.014	−0.022	0.019	−0.025	0.019	−0.024	0.019
rs2856321	12	11,855,773	ETV6	A	G	−0.026	0.003	0.006	0.009	0.022	0.013	−0.009	0.013	−0.003	0.011	0.001	0.015	−0.006	0.015	0.018	0.015
rs10841649	12	20,954,879	SLCO1B3	C	T	0.021	0.004	−0.002	0.013	0.010	0.019	−0.011	0.019	−0.010	0.016	0.014	0.021	−0.017	0.021	0.016	0.021
rs9738365	12	31,997,635	–	C	A	−0.058	0.003	0.000	0.010	0.007	0.014	−0.009	0.014	−0.007	0.012	−0.001	0.016	−0.005	0.016	0.015	0.016
rs12231073	12	38,526,901	–	G	T	−0.017	0.003	0.011	0.009	0.022	0.012	0.001	0.013	0.010	0.011	0.013	0.014	0.012	0.014	0.008	0.014
rs11175935	12	40,693,806	LRRK2	G	T	0.020	0.003	0.000	0.011	0.019	0.015	−0.020	0.016	−0.006	0.013	−0.016	0.017	0.006	0.018	−0.002	0.017
rs247917	12	46,265,916	ARID2	C	T	−0.015	0.003	0.000	0.009	0.010	0.012	−0.009	0.013	−0.001	0.011	−0.006	0.014	0.006	0.014	−0.007	0.014
rs117564283	12	52,300,110	ACVRL1	C	T	−0.029	0.005	0.037	0.018	0.026	0.025	0.046	0.026	0.045	0.022	0.053	0.028	0.024	0.028	−0.006	0.028
rs773116	12	56,486,159	ERBB3	G	A	0.016	0.003	0.008	0.009	0.008	0.013	0.010	0.013	0.017	0.011	0.010	0.014	0.037	0.014	0.000	0.014
rs78607331	12	57,648,644	R3HDM2	T	C	−0.037	0.006	0.025	0.025	0.015	0.034	0.040	0.036	−0.001	0.030	−0.019	0.039	0.037	0.039	0.048	0.037
rs4547160	12	63,503,650	AVPR1A	G	T	−0.018	0.003	−0.018	0.009	−0.014	0.013	−0.020	0.013	−0.015	0.011	−0.008	0.015	−0.031	0.015	−0.013	0.015
rs1351394	12	66,351,826	HMGA2	C	T	0.024	0.003	0.018	0.009	0.018	0.012	0.015	0.013	0.012	0.011	0.018	0.014	0.001	0.014	0.023	0.014

Supplementary Table 2. Continued

SNP	Chr	Position	Gene[a]	Effect allele	Other allele	Association parameters for the exposure		Association parameters for colorectal cancer		Association parameters for colorectal cancer men		Association parameters for colorectal cancer women		Association parameters for colon cancer		Association parameters for proximal colon cancer		Association parameters for distal colon cancer		Association parameters for rectal cancer	
						Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE
rs2230281	12	89,917,518	GALNT4/POC1B–GALNT4	G	A	−0.016	0.003	−0.010	0.010	0.009	0.014	−0.033	0.014	−0.013	0.012	−0.021	0.015	−0.002	0.016	0.002	0.015
rs10777540	12	94,150,321	CRADD	T	G	−0.018	0.003	−0.014	0.009	−0.023	0.012	−0.005	0.013	−0.016	0.011	−0.023	0.014	−0.012	0.014	−0.013	0.014
rs10860237	12	98,157,010	AC007424.1	G	A	−0.030	0.003	−0.003	0.009	−0.013	0.013	0.007	0.014	0.001	0.012	0.000	0.015	0.006	0.015	−0.007	0.015
rs11111274	12	102,838,128	IGF1	A	G	−0.080	0.003	−0.013	0.010	−0.019	0.014	−0.007	0.014	−0.015	0.012	0.002	0.016	−0.041	0.016	0.002	0.016
rs10745954	12	103,483,094	AC068643.1	G	A	0.015	0.003	0.003	0.009	−0.003	0.012	0.008	0.013	0.005	0.011	0.010	0.014	0.008	0.014	0.000	0.014
rs7314285	12	111,522,026	CUX2	T	G	−0.052	0.005	0.011	0.017	−0.006	0.024	0.033	0.024	0.005	0.021	−0.019	0.027	0.029	0.028	0.002	0.027
rs1061657	12	115,108,136	TBX3	T	C	−0.022	0.003	−0.032	0.010	−0.018	0.014	−0.047	0.014	−0.029	0.012	−0.023	0.016	−0.029	0.016	−0.044	0.015
rs2460488	12	116,187,660	–	G	A	0.026	0.003	0.008	0.012	0.008	0.016	0.008	0.017	0.009	0.014	0.005	0.018	0.009	0.019	0.004	0.018
rs1800574	12	121,416,864	HNF1A	T	C	0.145	0.007	0.003	0.027	−0.009	0.038	0.019	0.039	0.019	0.032	−0.013	0.042	0.071	0.041	0.050	0.041
rs11057265	12	123,805,950	SBNO1	G	A	0.044	0.007	0.011	0.027	−0.013	0.037	0.035	0.038	0.005	0.032	−0.017	0.041	0.028	0.043	0.040	0.042
rs9532512	13	40,769,897	LINC00598	G	A	−0.043	0.003	−0.010	0.011	−0.004	0.016	−0.012	0.016	−0.015	0.013	−0.014	0.017	−0.027	0.018	−0.010	0.017
rs1170158	13	42,701,941	DGKH	T	G	0.021	0.003	−0.021	0.011	−0.036	0.015	−0.007	0.016	−0.034	0.013	−0.032	0.017	−0.038	0.017	−0.013	0.017
rs1535793	13	47,154,966	LRCH1	A	G	0.024	0.003	0.033	0.010	0.024	0.014	0.042	0.015	0.036	0.012	0.031	0.016	0.045	0.016	0.028	0.016
rs118081390	13	49,671,053	FNDC3A	G	A	0.028	0.005	−0.018	0.018	−0.049	0.025	0.014	0.025	−0.020	0.021	−0.012	0.027	−0.041	0.027	−0.019	0.027
rs9573360	13	74,771,429	KLF12	A	C	0.014	0.003	−0.010	0.009	0.003	0.012	−0.022	0.013	−0.011	0.011	−0.019	0.014	−0.004	0.014	−0.017	0.014
rs71432868	13	106,559,402	SNORA25	T	C	−0.028	0.005	0.016	0.022	0.023	0.030	0.009	0.031	0.032	0.026	0.038	0.034	0.020	0.034	0.011	0.034
rs9583151	13	107,666,257	–	C	T	0.014	0.003	0.001	0.009	0.000	0.012	0.001	0.013	0.001	0.011	0.011	0.014	−0.012	0.014	−0.001	0.014
rs7323205	13	110,365,525	LINC00676	C	T	0.015	0.003	−0.004	0.009	−0.014	0.013	0.004	0.013	−0.008	0.011	0.005	0.014	−0.022	0.015	0.002	0.014
rs6602909	13	114,551,993	GAS6	T	C	−0.020	0.003	−0.009	0.010	−0.001	0.014	−0.016	0.014	−0.009	0.012	−0.007	0.016	−0.004	0.016	0.006	0.015
rs8017377	14	24,883,887	NYNRIN	A	G	−0.017	0.003	−0.010	0.009	−0.012	0.012	−0.007	0.013	−0.007	0.011	−0.011	0.014	−0.007	0.014	−0.028	0.014
rs28396553	14	36,673,392	lincRNA	T	C	0.015	0.003	0.021	0.009	0.018	0.013	0.025	0.013	0.015	0.011	0.036	0.014	−0.004	0.014	0.010	0.014
rs33912345	14	60,976,537	SIX6	A	C	−0.023	0.003	0.008	0.009	0.023	0.013	−0.009	0.013	0.007	0.011	0.013	0.014	0.001	0.014	0.028	0.014
rs79936318	14	64,315,556	SYNE2	G	A	−0.017	0.003	−0.007	0.012	−0.017	0.017	0.009	0.018	−0.010	0.015	−0.045	0.019	0.027	0.020	0.001	0.019
rs168961	14	69,282,930	ZFP36L1	A	G	−0.018	0.003	−0.004	0.009	−0.013	0.012	0.006	0.013	−0.004	0.011	−0.004	0.014	0.001	0.014	−0.016	0.014
rs75088740	14	69,819,101	GALNT16	G	A	−0.019	0.003	−0.021	0.012	−0.018	0.017	−0.020	0.017	−0.025	0.014	−0.030	0.018	−0.019	0.019	−0.010	0.019
rs13379043	14	74,250,126	ELMSAN1	T	C	0.025	0.003	0.016	0.010	0.008	0.014	0.024	0.014	0.011	0.012	0.024	0.016	0.002	0.016	0.002	0.016
rs175043	14	75,471,803	EIF2B2	G	A	0.018	0.003	−0.021	0.009	−0.026	0.012	−0.017	0.013	−0.023	0.011	−0.037	0.014	−0.005	0.014	−0.024	0.014
rs1061638	14	77,928,525	AHSA1	G	A	0.018	0.003	0.008	0.010	0.013	0.013	0.007	0.014	0.008	0.011	0.013	0.015	−0.001	0.015	0.005	0.015
rs10145154	14	79,939,525	NRXN3	C	T	−0.018	0.003	−0.006	0.011	−0.002	0.016	−0.012	0.016	0.000	0.013	0.011	0.017	−0.009	0.017	−0.009	0.017
rs78598185	14	92,791,479	SLC24A4	A	G	−0.029	0.004	0.003	0.015	0.004	0.021	0.004	0.022	0.036	0.018	0.028	0.024	0.041	0.024	−0.023	0.023
rs1115897	14	93,910,816	UNC79	A	C	0.021	0.003	0.012	0.010	0.015	0.013	0.008	0.014	0.002	0.012	0.017	0.015	−0.018	0.015	0.003	0.015
rs28929474	14	94,844,947	SERPINA1	T	C	−0.063	0.009	−0.097	0.035	−0.139	0.051	−0.033	0.050	−0.117	0.043	−0.116	0.055	−0.087	0.057	−0.069	0.055
rs10136874	14	101,202,022	DLK1	G	T	0.023	0.003	−0.006	0.009	−0.017	0.013	0.007	0.013	0.002	0.011	0.011	0.014	−0.008	0.014	−0.021	0.014
rs17747633	15	40,916,237	KNL1	G	A	0.015	0.003	0.026	0.009	0.029	0.013	0.022	0.013	0.026	0.011	0.037	0.014	0.019	0.014	0.028	0.014
rs62020698	15	43,237,414	UBR1	C	T	0.047	0.004	0.008	0.016	0.011	0.023	−0.001	0.024	0.026	0.020	0.052	0.026	−0.005	0.026	−0.023	0.025
rs55707100	15	43,820,717	MAP1A	T	C	−0.151	0.008	−0.007	0.026	−0.011	0.036	−0.006	0.037	−0.002	0.030	−0.067	0.040	0.071	0.039	−0.001	0.040
rs4273010	15	44,947,434	SPG11	T	C	0.128	0.008	0.014	0.029	0.008	0.040	0.023	0.043	−0.016	0.035	0.024	0.046	−0.066	0.045	0.027	0.045

Supplementary Table 2. Continued

SNP	Chr	Position	Gene[a]	Effect allele	Other allele	Association parameters for the exposure		Association parameters for colorectal cancer		Association parameters for colorectal cancer men		Association parameters for colorectal cancer women		Association parameters for colon cancer		Association parameters for proximal colon cancer		Association parameters for distal colon cancer		Association parameters for rectal cancer	
						Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE
rs4545755	15	51,549,044	MIR4713HG/CYP19A1	G	A	0.016	0.003	0.018	0.009	0.019	0.012	0.015	0.013	0.014	0.011	0.025	0.014	0.013	0.014	0.023	0.014
rs12442867	15	62,489,128	AC126323.2	C	A	−0.017	0.003	0.003	0.009	−0.020	0.013	0.027	0.013	0.004	0.011	0.010	0.014	−0.005	0.014	0.008	0.014
rs79076440	15	63,803,863	USP3	A	G	0.019	0.003	−0.024	0.012	−0.023	0.017	−0.024	0.017	−0.023	0.014	−0.040	0.018	−0.017	0.019	−0.026	0.018
rs10851736	15	64,940,718	ZNF609	C	T	−0.027	0.005	0.013	0.015	−0.003	0.021	0.029	0.022	0.001	0.018	−0.010	0.024	0.000	0.024	0.011	0.024
rs8024330	15	67,443,926	SMAD3	C	T	0.018	0.003	−0.015	0.010	−0.018	0.013	−0.013	0.014	−0.021	0.012	−0.014	0.015	−0.033	0.015	−0.019	0.015
rs8033075	15	68,353,652	PIAS1	A	G	0.045	0.005	0.032	0.021	0.013	0.030	0.053	0.030	0.018	0.025	0.018	0.033	0.005	0.033	0.034	0.033
rs5742915	15	74,336,633	PML	C	T	0.025	0.003	−0.003	0.009	0.001	0.013	−0.007	0.013	−0.005	0.011	0.000	0.014	−0.002	0.014	0.002	0.014
rs12593755	15	89,111,712	AC013489.2	G	T	−0.016	0.003	−0.002	0.009	0.013	0.013	−0.019	0.013	−0.005	0.011	−0.018	0.014	0.017	0.014	−0.005	0.014
rs11856160	15	93,452,846	CHD2	A	G	0.021	0.003	0.003	0.012	0.006	0.017	0.002	0.018	0.002	0.015	0.018	0.019	−0.011	0.020	0.013	0.019
rs12912439	15	95,828,705	LINC01197	C	T	−0.022	0.003	−0.005	0.010	−0.003	0.013	−0.006	0.014	−0.014	0.012	−0.020	0.015	−0.003	0.015	0.008	0.015
rs34040697	15	97,125,666	–	A	G	0.016	0.003	−0.009	0.009	0.005	0.013	−0.022	0.013	−0.014	0.011	−0.012	0.014	−0.026	0.014	−0.009	0.014
rs142354201	15	99,524,022	PGPEP1L	G	A	0.034	0.006	−0.020	0.022	−0.037	0.031	−0.006	0.032	−0.025	0.026	−0.059	0.033	−0.001	0.034	0.005	0.034
rs4988483	16	1,129,010	SSTR5	A	C	−0.172	0.006	−0.048	0.026	−0.039	0.036	−0.054	0.037	−0.015	0.031	0.016	0.040	−0.041	0.041	−0.119	0.041
rs72761177	16	1,833,508	NUBP2	A	G	0.077	0.004	−0.020	0.016	−0.018	0.022	−0.024	0.023	−0.027	0.019	−0.026	0.025	−0.030	0.026	−0.019	0.025
rs11077337	16	3,492,048	AC025283.2/ZNF597	T	G	0.015	0.003	0.006	0.009	0.014	0.012	0.000	0.013	0.007	0.011	0.014	0.014	0.002	0.014	0.012	0.014
rs8182173	16	4,420,787	CORO7−PAM16	C	T	−0.018	0.003	−0.009	0.010	−0.017	0.015	0.001	0.015	−0.016	0.013	−0.046	0.016	0.009	0.017	0.000	0.016
rs74774288	16	5,922,263	RBFOX1	G	T	0.027	0.003	0.020	0.012	0.003	0.017	0.036	0.017	0.011	0.014	0.005	0.018	0.015	0.019	0.001	0.018
rs4985062	16	8,996,636	USP7	T	C	0.015	0.003	0.002	0.009	0.002	0.013	0.001	0.013	0.010	0.011	0.011	0.014	0.007	0.014	−0.009	0.014
rs1532824	16	10,532,211	ATF7IP2	C	A	−0.017	0.003	0.005	0.010	0.009	0.014	0.002	0.014	0.001	0.012	−0.012	0.015	0.015	0.016	0.011	0.015
rs12935465	16	17,476,853	XYLT1	T	C	0.016	0.003	−0.002	0.009	−0.005	0.012	0.003	0.013	−0.001	0.011	0.007	0.014	0.001	0.014	0.008	0.014
rs2023762	16	19,276,597	SYT17	T	C	0.015	0.003	−0.001	0.009	−0.020	0.013	0.017	0.013	0.000	0.011	0.002	0.015	−0.002	0.015	−0.005	0.015
rs12927172	16	27,325,021	IL4R	G	A	−0.015	0.003	0.006	0.009	0.021	0.013	−0.013	0.013	0.015	0.011	0.002	0.014	0.033	0.015	0.012	0.014
rs7498665	16	28,883,241	SH2B1	G	A	0.019	0.003	0.006	0.009	0.009	0.013	0.003	0.013	0.008	0.011	0.015	0.014	0.013	0.014	0.008	0.014
rs4788220	16	30,063,780	FAM57B	A	G	−0.017	0.003	−0.003	0.009	−0.002	0.012	−0.003	0.013	−0.006	0.011	0.000	0.014	−0.008	0.014	0.004	0.014
rs750952	16	31,093,954	ZNF646	C	T	0.032	0.003	−0.014	0.009	−0.012	0.013	−0.015	0.013	−0.015	0.011	−0.034	0.014	0.000	0.014	−0.008	0.014
rs116971887	16	51,170,026	SALL1	G	T	0.036	0.006	−0.018	0.022	0.023	0.030	−0.047	0.031	−0.025	0.026	−0.034	0.033	−0.007	0.034	−0.009	0.034
rs12597502	16	53,170,069	CHD9	A	G	−0.015	0.003	−0.001	0.010	−0.002	0.014	−0.001	0.014	0.005	0.012	0.004	0.015	0.006	0.015	−0.018	0.015
rs1548917	16	56,109,333	CES5A	C	T	−0.015	0.003	−0.010	0.009	−0.010	0.012	−0.010	0.013	−0.009	0.011	−0.021	0.014	0.003	0.014	−0.002	0.014
rs111792934	16	69,131,293	HAS3	C	T	0.022	0.003	0.018	0.012	0.001	0.017	0.039	0.017	0.023	0.015	0.042	0.019	0.018	0.019	0.005	0.019
rs17299478	16	69,775,500	–	C	T	0.032	0.003	−0.008	0.012	−0.009	0.017	−0.009	0.018	−0.021	0.015	−0.018	0.019	−0.014	0.020	0.003	0.019
rs12935091	16	71,525,208	ZNF19	A	G	−0.035	0.006	−0.022	0.023	−0.080	0.032	0.032	0.032	−0.022	0.027	0.001	0.036	−0.053	0.036	−0.061	0.035
rs147491123	16	72,567,795	LINC01572	C	T	0.036	0.007	0.026	0.024	0.025	0.034	0.030	0.035	0.025	0.029	0.004	0.037	0.060	0.039	0.062	0.038
rs8059803	16	81,603,001	CMIP	A	G	0.031	0.003	0.005	0.010	−0.010	0.014	0.019	0.014	0.001	0.012	−0.005	0.015	0.003	0.015	−0.008	0.015
rs11149612	16	83,980,965	AC009119.2	C	T	0.027	0.003	0.010	0.009	−0.001	0.013	0.022	0.014	0.002	0.011	0.003	0.015	0.005	0.015	0.015	0.015
rs8054322	16	85,201,405	GSE1	G	A	−0.015	0.003	−0.009	0.009	−0.009	0.013	−0.009	0.013	0.000	0.011	0.004	0.014	−0.002	0.014	−0.014	0.014
rs7502910	17	1,638,718	WDR81	A	G	0.016	0.003	0.009	0.009	0.009	0.012	0.011	0.013	0.016	0.011	0.006	0.014	0.031	0.014	0.008	0.014

Supplementary Table 2. Continued

SNP	Chr	Position	Gene[a]	Effect allele	Other allele	Association parameters for the exposure		Association parameters for colorectal cancer		Association parameters for colorectal cancer men		Association parameters for colorectal cancer women		Association parameters for colon cancer		Association parameters for proximal colon cancer		Association parameters for distal colon cancer		Association parameters for rectal cancer	
						Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE
rs2309401	17	5,471,902	NLRP1	T	G	0.015	0.003	0.006	0.009	0.019	0.013	−0.009	0.013	−0.001	0.011	−0.006	0.014	0.007	0.014	0.030	0.014
rs9892862	17	7,439,014	POLR2A	G	A	0.022	0.003	−0.002	0.010	−0.002	0.015	−0.006	0.015	0.008	0.013	0.007	0.017	0.014	0.017	−0.017	0.016
rs6416868	17	15,924,370	TTC19	G	A	−0.019	0.003	−0.010	0.009	−0.025	0.012	0.006	0.013	−0.007	0.011	−0.002	0.014	−0.013	0.014	−0.010	0.014
rs8075153	17	17,622,666	RAI1	C	T	0.021	0.003	−0.020	0.009	−0.021	0.012	−0.017	0.013	−0.022	0.011	−0.034	0.014	−0.006	0.014	−0.004	0.014
rs8079923	17	19,869,544	AKAP10	C	T	0.016	0.003	0.004	0.010	0.000	0.014	0.010	0.015	−0.007	0.012	−0.028	0.016	0.004	0.016	0.021	0.016
rs56030650	17	38,131,187	GSDMA	A	C	−0.022	0.003	0.005	0.009	−0.007	0.012	0.022	0.013	0.004	0.011	−0.010	0.014	0.013	0.014	0.023	0.014
rs668799	17	40,716,235	COASY	C	T	0.018	0.003	−0.022	0.010	−0.038	0.014	−0.004	0.014	−0.032	0.012	−0.022	0.016	−0.036	0.016	−0.027	0.016
rs199525	17	44,847,834	WNT3	T	G	−0.020	0.003	0.014	0.011	−0.006	0.015	0.034	0.016	0.011	0.013	0.006	0.017	0.016	0.017	−0.002	0.017
rs11079157	17	53,360,799	HLF	G	T	−0.020	0.003	0.003	0.011	−0.011	0.015	0.021	0.016	0.019	0.013	−0.001	0.017	0.039	0.018	−0.025	0.017
rs2250014	17	57,836,134	VMP1	T	C	−0.021	0.003	−0.029	0.012	−0.030	0.017	−0.022	0.017	−0.038	0.014	−0.056	0.018	−0.011	0.019	0.001	0.019
rs142377191	17	61,649,170	DCAF7	G	A	−0.125	0.009	0.028	0.036	0.012	0.050	0.049	0.052	0.059	0.043	0.110	0.057	0.004	0.056	−0.025	0.055
rs76708468	17	62,206,299	ERN1	T	C	−0.087	0.006	0.009	0.030	−0.013	0.042	0.028	0.043	0.023	0.036	0.002	0.047	0.013	0.048	−0.033	0.046
rs78357146	17	64,305,051	PRKCA	A	G	−0.090	0.007	0.048	0.028	0.018	0.039	0.083	0.041	0.027	0.033	−0.002	0.043	0.072	0.044	0.100	0.044
rs77542162	17	67,081,278	ABCA6	G	A	0.054	0.009	0.031	0.037	0.055	0.052	−0.008	0.054	0.025	0.044	0.024	0.057	0.055	0.058	0.049	0.057
rs6501601	17	71,124,903	SLC39A11	G	A	0.015	0.003	−0.009	0.010	−0.025	0.013	0.006	0.014	−0.020	0.011	−0.029	0.015	−0.007	0.015	−0.007	0.015
rs4789227	17	73,794,354	UNK	T	C	0.015	0.003	0.004	0.009	0.018	0.013	−0.012	0.013	0.002	0.011	0.001	0.014	0.011	0.015	0.012	0.014
rs4075483	17	79,074,817	BAIAP2	C	T	0.017	0.003	0.000	0.009	−0.015	0.013	0.015	0.013	0.008	0.011	0.001	0.014	0.018	0.015	−0.033	0.014
rs8095538	18	1,616,505	–	T	G	−0.020	0.003	0.003	0.010	0.011	0.013	−0.005	0.014	−0.004	0.011	−0.012	0.015	−0.005	0.015	0.009	0.015
rs8084351	18	50,726,559	DCC	G	A	0.015	0.003	−0.011	0.009	−0.008	0.012	−0.013	0.013	−0.014	0.011	−0.014	0.014	−0.022	0.014	−0.001	0.014
rs11152071	18	56,087,417	AC105105.3	C	T	0.020	0.003	0.007	0.010	−0.003	0.014	0.016	0.015	0.007	0.012	−0.007	0.016	0.020	0.016	0.012	0.016
rs190102446	18	57,048,571	–	C	T	0.041	0.007	−0.007	0.023	−0.018	0.032	0.011	0.034	−0.013	0.028	0.010	0.036	−0.044	0.036	0.002	0.036
rs585187	18	58,177,124	MRPS5P4	T	G	0.015	0.003	−0.008	0.009	−0.010	0.012	−0.005	0.013	−0.013	0.011	−0.026	0.014	0.001	0.014	−0.006	0.014
rs12454712	18	60,845,884	BCL2	T	C	0.018	0.003	0.003	0.009	−0.005	0.013	0.012	0.013	0.007	0.011	0.003	0.015	0.012	0.015	−0.003	0.015
rs8097893	18	74,983,055	GALR1	A	G	0.058	0.006	−0.009	0.021	0.018	0.030	−0.034	0.031	−0.007	0.026	0.023	0.034	−0.020	0.034	0.041	0.034
rs67868323	19	4,048,561	ZBTB7A	T	G	0.016	0.003	−0.006	0.010	0.016	0.014	−0.028	0.014	0.007	0.012	0.032	0.016	−0.031	0.016	−0.033	0.015
rs2602717	19	4,902,950	UHRF1/ ARRDC5	C	T	0.019	0.003	0.024	0.011	0.034	0.016	0.017	0.017	0.030	0.014	0.019	0.018	0.033	0.018	0.033	0.018
rs8112883	19	7,179,320	INSR	G	T	0.017	0.003	0.007	0.010	0.011	0.014	0.005	0.014	0.006	0.012	0.004	0.015	0.014	0.015	0.028	0.015
rs8105174	19	10,347,032	DNMT1	C	T	0.050	0.003	0.010	0.012	0.018	0.016	0.004	0.017	0.021	0.014	0.014	0.018	0.030	0.018	−0.003	0.018
rs6510033	19	30,710,785	AC005597.1	A	G	0.020	0.003	0.007	0.010	0.001	0.014	0.015	0.014	0.012	0.012	0.000	0.015	0.022	0.016	0.002	0.015
rs6510177	19	31,211,647	ZNF536	C	T	−0.023	0.003	0.032	0.013	0.024	0.017	0.042	0.018	0.035	0.015	0.021	0.019	0.063	0.020	0.040	0.020
rs62102136	19	34,700,561	LSM14A	C	T	0.016	0.003	−0.007	0.010	0.008	0.014	−0.022	0.014	−0.014	0.012	−0.010	0.015	−0.011	0.015	−0.002	0.015
rs7254601	19	36,147,315	COX6B1	A	G	−0.016	0.003	0.017	0.010	0.027	0.014	0.005	0.015	0.014	0.012	0.005	0.016	0.022	0.016	−0.013	0.016
rs58560372	19	38,758,752	SPINT2	C	T	0.020	0.003	0.011	0.013	0.023	0.018	−0.004	0.018	−0.012	0.015	−0.016	0.020	−0.023	0.020	0.016	0.020
rs15052	19	41,813,375	HNRN PUL1/ TGFB1	T	C	−0.018	0.003	−0.014	0.013	−0.037	0.018	0.010	0.018	−0.001	0.015	−0.011	0.020	0.015	0.020	−0.039	0.020
rs11671304	19	47,564,643	ZC3H4	T	C	−0.018	0.003	0.007	0.010	−0.006	0.014	0.022	0.014	0.003	0.012	0.013	0.015	−0.012	0.015	0.009	0.015
rs296361	19	48,389,363	SULT2A1	G	A	−0.025	0.003	0.008	0.012	0.018	0.017	−0.005	0.017	0.016	0.014	−0.001	0.019	0.021	0.019	0.004	0.019
rs2287922	19	49,232,226	RASIP1	A	G	−0.030	0.003	0.022	0.009	0.020	0.013	0.025	0.013	0.034	0.011	0.044	0.014	0.023	0.014	−0.006	0.014
rs7256521	19	53,837,110	ZNF845	A	G	−0.015	0.003	−0.002	0.009	−0.005	0.013	0.001	0.013	−0.006	0.011	0.008	0.014	−0.013	0.015	−0.003	0.014
rs12975366	19	54,759,361	LILRB5	C	T	−0.020	0.003	−0.002	0.009	0.014	0.013	−0.021	0.013	−0.005	0.011	−0.002	0.014	−0.018	0.015	0.006	0.014
rs6037508	20	3,217,989	SLC4A11	T	G	−0.017	0.003	−0.020	0.011	−0.019	0.015	−0.022	0.016	−0.029	0.013	−0.045	0.017	−0.020	0.017	0.001	0.017

Supplementary Table 2. Continued

SNP	Chr	Position	Gene[a]	Effect allele	Other allele	Association parameters for the exposure		Association parameters for colorectal cancer		Association parameters for colorectal cancer men		Association parameters for colorectal cancer women		Association parameters for colon cancer		Association parameters for proximal colon cancer		Association parameters for distal colon cancer		Association parameters for rectal cancer	
						Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE	Effect	SE
rs7267595	20	10,643,850	JAG1	A	C	0.015	0.003	0.005	0.009	0.023	0.012	−0.012	0.013	−0.004	0.011	−0.015	0.014	0.006	0.014	0.012	0.014
rs2273058	20	20,033,319	CRNKL1	G	A	−0.022	0.003	−0.005	0.009	−0.002	0.012	−0.008	0.013	−0.011	0.011	−0.013	0.014	−0.009	0.014	−0.002	0.014
rs6106324	20	20,964,988	AL133465.1	T	C	0.019	0.003	−0.011	0.009	−0.009	0.013	−0.012	0.013	−0.008	0.011	−0.011	0.014	−0.007	0.014	−0.010	0.014
rs2424396	20	21,630,280	LINC01726	A	G	−0.033	0.004	0.016	0.016	0.003	0.022	0.026	0.022	0.025	0.019	0.034	0.024	0.022	0.025	0.020	0.024
rs6088579	20	33,284,624	PIGU/NCOA6	G	A	0.027	0.003	−0.016	0.012	−0.021	0.017	−0.011	0.017	−0.010	0.014	−0.016	0.019	−0.004	0.019	−0.045	0.019
rs2207132	20	39,142,516	MAFB	G	A	0.048	0.007	0.059	0.028	0.033	0.039	0.090	0.042	0.033	0.034	0.046	0.045	0.000	0.045	0.059	0.045
rs17265513	20	39,832,628	ZHX3	C	T	−0.022	0.003	−0.016	0.011	−0.029	0.016	−0.001	0.016	−0.018	0.014	−0.014	0.017	−0.017	0.018	−0.005	0.017
rs16995311	20	49,201,102	PTPN1	A	C	0.040	0.005	0.024	0.018	0.036	0.024	0.010	0.025	0.015	0.021	0.006	0.027	0.027	0.028	0.032	0.027
rs2104476	20	54,852,856	–	A	G	−0.020	0.003	0.006	0.010	0.012	0.014	−0.001	0.014	0.003	0.012	0.006	0.015	0.003	0.016	−0.004	0.015
rs2738787	20	62,328,375	RTEL 1−TNFRSF6B/RTEL1	G	A	−0.037	0.005	−0.028	0.017	−0.060	0.023	0.007	0.024	−0.005	0.020	0.001	0.026	0.000	0.026	−0.064	0.025
rs9978775	21	40,694,526	BRWD1−AS1	G	A	0.019	0.003	0.009	0.009	0.021	0.012	−0.001	0.013	0.008	0.011	0.008	0.014	0.001	0.014	0.011	0.014
rs8138950	22	29,448,643	ZNRF3	C	T	0.015	0.003	0.016	0.009	0.013	0.012	0.020	0.013	0.005	0.011	−0.004	0.014	0.010	0.014	0.032	0.014
rs2412973	22	30,529,631	HORMAD2	C	A	−0.014	0.003	0.024	0.009	0.011	0.012	0.035	0.013	0.028	0.011	0.037	0.014	0.022	0.014	0.016	0.014
rs12106594	22	31,885,316	DRG1/EIF4ENIF1/SFI1	C	T	−0.036	0.006	0.007	0.020	−0.017	0.028	0.030	0.029	0.008	0.024	0.010	0.031	−0.004	0.031	0.003	0.031
rs5755948	22	36,179,095	RBFOX2	G	A	−0.028	0.004	0.003	0.013	0.008	0.018	−0.005	0.019	0.011	0.016	0.028	0.020	−0.005	0.021	−0.001	0.020
rs6519133	22	39,096,602	JOSD1	T	C	0.029	0.003	0.011	0.009	0.012	0.013	0.011	0.013	0.005	0.011	0.013	0.014	0.002	0.015	0.024	0.014
rs9611565	22	41,767,486	TEF	T	C	0.029	0.003	0.001	0.010	0.010	0.014	−0.010	0.015	0.006	0.012	−0.001	0.016	0.006	0.016	−0.015	0.016
rs4823324	22	46,238,123	ATXN10	T	C	0.016	0.003	0.002	0.009	0.001	0.013	0.003	0.013	0.006	0.011	0.023	0.014	−0.013	0.014	0.000	0.014
IGFBP3 - n SNPs = 4																					
rs4234798	4	7,219,933	*SORCS2*	G	T	0.095	0.011	0.012	0.009	0.020	0.013	0.003	0.013	0.005	0.011	−0.003	0.014	0.015	0.014	0.015	0.014
rs11977526	7	46,008,110	*IGFBP3*	A	G	0.287	0.011	0.037	0.009	0.034	0.013	0.042	0.013	0.042	0.011	0.042	0.014	0.042	0.014	0.037	0.014
rs700753	7	46,753,684	*TNS3*	G	C	0.158	0.011	−0.006	0.009	−0.006	0.013	−0.007	0.013	−0.009	0.011	0.001	0.014	−0.025	0.015	−0.010	0.014
rs1065656	16	1,838,836	*NUBP2*	G	C	0.111	0.011	0.010	0.010	0.015	0.013	0.006	0.014	−0.003	0.012	0.004	0.015	−0.010	0.015	0.017	0.015

Chr, chromosome; SE, standard error.
[a]Overlapped or nearest gene (sourced from: https://snp-nexus.org/index.html). Where blank, gene unknown.

Supplementary Table 3. Risk (HRs) of Colorectal Cancer Associated With Circulating IGF1 Levels With Those Participants With Circulating HbA1c Levels ≥48 mmol/mol (or 6.5%, the Cutoff for Type 2 Diabetes) Excluded

	Q1	Q2	Q3	Q4	Q5	*P*-trend	HR per 1-SD increment	HR per 1-SD increment (adjusted)[a]
Colorectal cancer								
Both sexes	1	1.13 (1.00–1.27)	1.14 (1.01–1.29)	1.12 (0.98–1.27)	1.34 (1.18–1.53)	<0.0001	1.09 (1.04–1.14)	1.12 (1.06–1.18)
Colon cancer								
Both sexes	1	1.06 (0.91–1.22)	1.09 (0.94–1.26)	1.06 (0.91–1.24)	1.34 (1.15–1.57)	0.002	1.08 (1.03–1.14)	1.11 (1.04–1.19)
Proximal colon cancer								
Both sexes	1	1.15 (0.94–1.40)	1.22 (1.00–1.50)	0.97 (0.77–1.21)	1.35 (1.08–1.68)	0.09	1.08 (1.00–1.16)	1.10 (1.00–1.21)
Distal colon cancer								
Both sexes	1	0.96 (0.77–1.20)	0.97 (0.77–1.23)	1.18 (0.94–1.48)	1.31 (1.03–1.65)	0.01	1.09 (1.00–1.18)	1.12 (1.01–1.24)
Rectal cancer								
Both sexes	1	1.29 (1.05–1.59)	1.27 (1.02–1.57)	1.25 (1.00–1.56)	1.36 (1.08–1.72)	0.02	1.10 (1.02–1.19)	1.14 (1.03–1.25)

NOTE. Multivariable Cox regression model using age as the underlying time variable and stratified by sex, Townsend deprivation index (quintiles), region of the recruitment assessment center, and age at recruitment. Models adjusted for waist circumference (per 5 cm), total physical activity (<10, 10 to <20, 20 to <40, 40 to <60, ≥60 metabolic equivalent hours per week, unknown), height (per 10 cm), alcohol consumption frequency (never, special occasions only, 1–3 times per month, 1–2 times per week, 3–4 times per week, daily/almost daily, unknown), smoking status and intensity (never, former, current- <15 per day, current- ≥15 per day, current- intensity unknown, unknown), frequency of red and processed meat consumption (<2, 2 to <3, 3 to <4, ≥4 occasions per week, unknown), family history of colorectal cancer (no, yes, unknown), educational level (Certificates of secondary education [CSEs]/Ordinary [O]-levels/General Certificates of Secondary Education [GCSEs] or equivalent, National Vocational Qualification [NVQ]/Higher National Diploma [HND]/Higher National Certificate [HNC]/Advanced [A]-levels/Advanced Subsidiary [AS]-levels or equivalent, other professional qualifications, college/university degree, none of the above, unknown), regular aspirin/ibuprofen use (no, yes, unknown), ever use of hormone replacement therapy (no, yes, unknown), and circulating levels (sex-specific quintiles, missing/unknown) of CRP (mg/L), HbA1c (mmol/mol), testosterone (nmol/L), and SHBG (nmol/L).

[a]HRs per SD increment were additionally corrected for regression dilution using a regression dilution ratio (0.76) obtained from the subsample of participants with repeat IGF1 measurements.

Supplementary Table 4. MR Pleiotropy Sensitivity Tests for the Circulating IGF1 and IGFBP3 Levels and Risk of Colorectal Cancer

			Weighted median approach				MR-Egger test								MR-PRESSO		
	n SNPs	Group	OR	LCI	UCI	P	Intercept	LCI	UCI	P	OR	LCI	UCI	P	*P* Horizontal pleiotropy	*P* distortion	Outlier SNPs
IGF1	413	Colorectal cancer, both sexes	1.12	1.04	1.20	2.9E−03	−7.1E−04	−3.0E−03	1.6E−03	0.54	1.11	0.98	1.27	0.11	<1e−04	.91	rs1150752 rs174554
		Colorectal cancer, men	1.07	0.97	1.18	0.15	−1.4E−03	−4.5E−03	1.8E−03	0.4	1.18	1.00	1.38	0.05	<1e−04	–	–
		Colorectal cancer, women	1.07	0.97	1.18	0.2	−1.9E−05	−3.3E−03	3.3E−03	0.99	1.06	0.89	1.25	0.53	<1e−04	.82	rs174554
		Colon cancer, both sexes	1.12	1.03	1.23	0.01	−1.7E−03	−4.5E−03	9.9E−04	0.21	1.14	0.98	1.32	0.09	<1e−04	.83	rs174554
		Proximal colon cancer, both sexes	1.08	0.97	1.21	0.16	5.8E−04	−3.0E−03	4.1E−03	0.75	1.02	0.84	1.23	0.84	<1e−04	.90	rs33932084
		Distal colon cancer, both sexes	1.10	0.98	1.23	0.11	−4.2E−03	−7.8E−03	−5.5E−04	0.02	1.26	1.05	1.50	0.01	<1e−04	.82	rs174554
		Rectal cancer, both sexes	1.01	0.90	1.13	0.88	−4.2E−04	−4.0E−03	3.1E−03	0.82	1.09	0.91	1.30	0.36	<1e−04	.85	rs1150752 rs61867536 rs9267488
IGFBP3	4	Colorectal cancer, both sexes	1.14	1.07	1.20	1.1E−05	−0.01	−0.05	0.03	0.35	1.18	1.07	1.31	0.08	.29	–	–
		Colorectal cancer, men	1.13	1.04	1.22	2.8E−03	0.00	−0.06	0.05	0.82	1.14	0.98	1.34	0.23	.72	–	–
		Colorectal cancer, women	1.13	1.04	1.22	3.9E−03	−0.02	−0.08	0.04	0.26	1.25	1.18	1.32	0.02	.18	–	–
		Colon cancer, both sexes	1.13	1.05	1.21	7.9E−04	−0.03	−0.07	0.02	0.16	1.27	1.16	1.38	0.03	.04	–	–
		Proximal colon cancer, both sexes	1.12	1.02	1.23	0.01	−0.02	−0.08	0.04	0.28	1.25	1.21	1.29	0.01	.21	–	–
		Distal colon cancer, both sexes	1.13	1.03	1.24	0.01	−0.03	−0.10	0.03	0.17	1.29	1.01	1.65	0.18	.03	–	–
		Rectal cancer, both sexes	1.14	1.05	1.25	2.6E−03	−0.01	−0.07	0.05	0.57	1.18	1.01	1.39	0.18	.62	–	–

LCI, lower confidence interval; UCI, upper confidence interval.

Supplementary Table 5. MR leave-one-out analysis for IGFBP3 Levels and Risk of Colorectal Cancer

	MR	
SNP excluded	Likelihood-based approach OR (95% CI) per 1-SD increment	*P* value
rs11977526	1.02 (0.92–1.13)	0.7
rs4234798	1.11 (1.04–1.18)	1.E−03
rs700750	1.15 (1.08–1.23)	2.E−05
rs9923699	1.12 (1.05–1.19)	4.E−04