**Supplementary Text 1**

**Study populations**

***European Consortium***

**Colorectal Transdisciplinary (CORECT) Study**

Individuals included in the current analysis participated in the original CORECT Study and were of European ancestral heritage from North America, Australia, and Europe. This analysis includes observational studies genotyped with high-density SNP arrays and imputed to the 1000 Genomes Project, March 2012 reference panel. Study populations, sample collection, genotyping, QC, imputation procedures, and statistical analysis have been described in detail previously (PMID: 23266556; PMID: 26151821; PMID: 29917119).

**Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO)**

The GECCO GWAS consisted of participants within the French Association Study Evaluating RISK for sporadic colorectal cancer (ASTERISK); the Colon Cancer Family Registry (CCFR 1-4); Hawaiian Colorectal Cancer Studies 2 and 3 (Colo2&3); Darmkrebs: Chancen der Verhütung durch Screening (DACHS); Diet, Activity, and Lifestyle Study (DALS); Health Professionals Follow-up Study (HPFS); Multiethnic Cohort (MEC); Nurses’ Health Study (NHS); Physician’s Health Study (PHS); Prostate, Lung, Colorectal Cancer, and Ovarian Cancer Screening Trial (PLCO); VITamins And Lifestyle (VITAL); and the Women’s Health Initiative (WHI). The details of description of the study population for each involved study could be found in previous publications (PMID: 23266556; PMID: 26151821; PMID: 29917119).

**CORSA (Colorectal Cancer Study of Austria)**

In the ongoing CRC study of Austria (CORSA), more than 13,000 Caucasian participants have been recruited within the province-wide screening project, “Burgenland Prevention Trial of Colorectal Disease with Immunological Testing” (B-PREDICT), since 2003 (PMID: 21422235). All inhabitants between 40 and 80 years of age from the Austrian province of Burgenland are annually invited to participate in fecal immunochemical testing. Participants who receive positive Haemoccult tests are then recommended to undergo a follow-up colonoscopy. Controls received a complete colonoscopy and were free of CRC and polyps. CORSA participants have been recruited in the four KRAGES hospitals in Burgenland, Austria, and additionally, at the Medical University of Vienna (Department of Surgery), the Viennese hospitals: “Rudolfstiftung” and “Sozialmedizinisches Zentrum Süd,” and at the Medical University of Graz (Department of Internal Medicine). Distribution of the factors sex and age (5-year strata) were evenly matched between cases and controls. All participants were genotyped using the Affymetrix Axiom Genome-Wide Human Origins 1 Array.

**UK Biobank**

We previously constructed a CRC and advanced adenoma nested case-control dataset from the UK Biobank resource (application number 8614) (PMID: 29917119). CRC cases were defined as subjects diagnosed with primary invasive CRC, or who died from CRC. Eligible control participants were required to be free of invasive colorectal cancer. All participants were genotyped using the Affymetrix UK Biobank Axiom Array.

***Asia Colorectal Cancer Consortium***

This study included genotyping data from 13,675 CRC cases and 17,379 controls of East Asians ancestry from 10 studies conducted in the Asia Colorectal Cancer Consortium (ACCC). Details of genotyping, genotype calling, and quality control were performed in previous GWAS by the CRC consortia (PMID: 31826910). All participants provided written informed consent, and each study was approved by the relevant research ethics committee or institutional review board. Details on sample selection and matching, sample numbers, and demographic characteristics of study participants have been described previously.

**The Shanghai CRC Study**

This study included 4,168 cases and 7,104 controls from four case-control sets conducted in Shanghai, China (Shanghai-1, Shanghai-2, Shanghai-3, and Shanghai-4). CRC cases for the Shanghai-1, Shanghai-2, and Shanghai-4 studies were identified from two cohort studies: the Shanghai Women’s Health Study (SWHS) and the Shanghai Men’s Health Study (SMHS). Cancer-free controls were identified from the SWHS and the SMHS [Shanghai-1, Shanghai-2 and Shanghai-4]. The SWHS and the SMHS are both population-based cohort studies which are being conducted in urban Shanghai, China. The SWHS includes 75,049 Chinese women who were between the ages of 40 and 70 years at enrollment (1997 to 2000) and lived in urban Shanghai. In-person interviews were conducted to collect exposure information, and anthropometrics were measured. The response rate was 92% for the baseline interview. Approximately 88% of the study participants provided biological samples; either a blood sample (n = 56,833) or an exfoliated buccal cell sample (n = 8,921). Using similar study protocols, the SMHS enrolled 61,582 men between the ages of 40 and 74 years in urban Shanghai between 2001 and 2006, with an overall response rate of 74% for the baseline interview. Approximately 90% of the study participants provided either a blood sample (76%) or a buccal cell sample (14%). Ongoing follow-up for cancer incidence and cause-specific mortality is being conducted for both the SMHS and SWHS via a combination of periodic in-person surveys and annual linkage with data routinely collected by the population-based Shanghai Cancer Registry and Vital Statistics Unit (for death certificates). CRC cases for the Shanghai-3 study were identified from the population-based Shanghai Cancer Registry. In-person interviews and saliva sample collections were completed for 2,575 cases. Controls (n = 1336) for these cases were selected from members of the SWHS and SMHS who were free of any cancer.

**The Aichi-2 CRC Study**

This study included 224 cases and 457 controls. The study was conducted as part of the Hospital-based Epidemiologic Research Program at the Aichi Cancer Center in Japan. All study participants (n = 28,766) were recruited between December 2000 and November 2005. CRC case status was confirmed via the Hospital-based Epidemiologic Research Program database, as well as the hospital-based cancer registry at the Aichi Cancer Center.

**The Hwasun Cancer Epidemiology Study-Colon and Rectum Cancer (HCES-CRC)**

HCES-CRC consisted of two studies: the first included 3,130 cases and 4,625 controls, and the second (HCES2-CRC) included 3,381 cases and 1,635 controls. These were hospital-based case-control studies conducted in South Korea that included multiple cancers. Cases were CRC patients at Chonnam National University Hwasun Hospital, Jeollanam-do, South Korea, newly diagnosed from April 2004 to October 2014. Cancer-free controls were randomly selected from participants in the Korean Community Health Survey, an annual nationwide health interview survey, conducted from 2010 to 2012 in the Jindo and Bosung counties, Jeollanam-do, South Korea. We added 1,757 female Korean controls to this study from an ongoing breast cancer project that was genotyped using the same platform.

**The Korean-National Cancer Center CRC Study**

This study (Korea-NCC) contributed 1,313 cases and 1,223 controls to the current study. It was a hospital-based case-control study of CRC, conducted in South Korea. Cases were histologically confirmed patients with CRC who received surgery between 2000 and 2004 at the Korean National Cancer Center (NCC). A total of 1,392 patients participated and provided a blood sample. Controls (n = 1,329) were selected from participants of the Cancer Screening Cohort of the NCC, recruited between August 2002 and December 2004.

**The Seoul CRC Study**

This study (Korea-Seoul) is a multicenter case-control study conducted in South Korea. Cases were CRC patients who were admitted to two university hospitals or one general cancer hospital in the Seoul Metropolitan Area between 1995 and 2004. Controls were patients of the same hospitals during the same time period from a wide spectrum of inpatients with non-neoplastic conditions. A total of 773 cases and 619 controls providing a blood sample were included in the current study.

**The Guangzhou-1 CRC Study**

This study included 638 cases and 971 controls and was conducted in Guangzhou, China. Cases were recruited from the Sun Yat-Sen University Cancer Center, Guangdong, China, from January 2002 to January 2012. Controls were cancer-free men and women recruited from the physical examination centers of several large hospitals in Guangdong during the same time period.

**The Aichi CRC Study**

This study had two collections (Aichi-1 and Aichi-2) with a total of 624 cases and 1,391 controls. The study was conducted as part of the Hospital-based Epidemiologic Research Program at the Aichi Cancer Center in Japan. All study participants (n = 28,766) were recruited between December 2000 and November 2005. CRC case status was confirmed via the Hospital-based Epidemiologic Research Program database, as well as the hospital-based cancer registry at the Aichi Cancer Center.

**The Korean Cancer Prevention Study-II CRC**

This study (KCPS-II) included 325 cases and 975 controls. The study was conducted as part of the Korean Cancer Prevention Study-II, a cohort study with 266,258 individuals, aged 20-77, who visited 16 health promotion centers nationwide from April 2004 to December 2008 in South Korea. Cancer status was confirmed via the National Cancer Registry and hospitalization records. Cancer-free controls were randomly selected from the same cohort study.

**The BioBank Japan CRC Study**

This study (BBJ) includes 6,692 cases and 27,178 controls. DNA samples of both CRC cases and cancer-free controls were obtained from the BioBank Japan of the Personalized Medicine Project (http://biobankjp.org/). In addition to healthy individuals as controls, we also included participants with diabetes, myocardial infarction, brain infarction, arteriosclerosis obliterans, atrial fibrillation, cholangiocarcinoma, drug eruption, liver cirrhosis, amytrophic lateral sclerosis and rheumatoid arthritis to increase the statistical power.