

## SUPPLEMENTARY MATERIAL

**Table S1.** Amsterdam criteria and Bethesda guidelines.

<p><b>Amsterdam I criteria (all criteria must be fulfilled)</b></p> <ul style="list-style-type: none"><li>• There are at least three relatives affected with CRC</li><li>• One affected person is a first-degree relative of the other two</li><li>• At least two successive generations are affected</li><li>• At least one person was diagnosed before the age of 50 years</li><li>• Familial adenomatous polyposis has been excluded</li><li>• Tumors have been verified by pathologic examination</li></ul>
<p><b>Amsterdam II criteria (all criteria must be fulfilled)</b></p> <ul style="list-style-type: none"><li>• There are at least three relatives with an HNPCC-associated cancer (large bowel, endometrium, small bowel, ureter, or renal pelvis, though not including stomach, ovary, brain, bladder, or skin)</li><li>• One affected person is a first-degree relative of the other two</li><li>• At least two successive generations are affected</li><li>• At least one person was diagnosed before the age of 50 years</li><li>• Familial adenomatous polyposis has been excluded</li><li>• Tumors have been verified by pathologic examination</li></ul>
<p><b>Modified Bethesda guidelines (at least one guideline must be fulfilled)</b></p> <ul style="list-style-type: none"><li>• CRC &lt; age 50 years</li><li>• Synchronous or metachronous colorectal or other HNPCC-associated tumors regardless of age</li><li>• CRC with MSI-positive morphology &lt; age 60 years</li><li>• CRC with one or more first-degree relatives with CRC or other HNPCC-related tumor, with one of the cancers &lt; age 50 years</li><li>• CRC with two or more first- or second-degree relatives with CRC or other HNPCC-related tumor (endometrial, stomach, ovarian, cervical, esophageal, leukemia, thyroid, bladder, ureter and renal pelvis, biliary tract, small bowel, breast, pancreas, liver, larynx, bronchus, lung, and brain (glioblastoma), sebaceous gland adenomas, and keratoacanthomas), regardless of age.</li></ul>

Abbreviations: CRC, colorectal cancer; HNPCC, hereditary nonpolyposis colon cancer; MSI, microsatellite instability.

**Table S2.** 95 CRC risk-associated variants obtained from the meta-analysis for CRC risk alleles performed by Huyghe et al. and used in this study.

*[Included as separate file]*

**Table S3.** Risk estimates (not adjusted by age or gender) for fCRC cases associated with the 92 CRC susceptibility alleles (wPRS). In bold, statistically significant results.

Clinical features	fCRC patients (%)	Mean wPRS (SD)	OR (95% CI)	P value
<i>Gender</i>				
Male	232 (55.63)	91.59 (6.62)		
Female	185 (44.36)	91.87 (5.96)	1.008 (0.977-1.039)	0.6278
<i>Deceased status</i>				
Alive	380 (91.12)	91.66 (6.39)		
Deceased	33 (7.91)	92.04 (5.77)	1.008 (0.953-1.066)	0.7879
<i>Age at diagnosis</i>				
<50years	271 (64.98)	91.18 (6.68)		
≥50years	146 (35.01)	92.70 (5.51)	<b>1.038 (1.005-1.072)</b>	<b>0.0252</b>
<i>HNPCC criteria</i>				
Amsterdam I/II	56 (13.43)	91.90 (5.83)		
Bethesda	361 (86.57)	91.68 (6.41)	0.994 (0.951-1.039)	0.7961
<i>FH CRC</i>				
No	192 (46.04)	91.06 (6.64)		
Yes	213 (51.07)	92.28 (6.09)	1.030 (0.999-1.063)	0.0575
<i>FH cancer</i>				
No	71 (17.02)	91.59 (6.69)		
Yes	334 (80.09)	91.72 (6.32)	1.003 (0.964-1.044)	0.8760
<i>Multiple CRC</i>				
No	385 (81.74)	91.47 (6.25)		
Yes	32 (7.67)	94.65 (6.64)	<b>1.088 (1.024-1.156)</b>	<b>0.0067</b>
<i>Multiple any cancer</i>				
No	364 (87.29)	91.42 (6.25)		
Yes	53 (12.71)	93.69 (6.55)	<b>1.06 (1.011-1.112)</b>	<b>0.0160</b>

Abbreviations: CI, confidence interval; CRC, colorectal cancer; fCRC, familial/early-onset CRC; FH, family history; HNPCC, hereditary nonpolyposis colorectal cancer; OR, odds ratio; SD, standard deviation; wPRS, weighted polygenic risk score.

**Figure S1.** Strategy followed in the study.

