**Table S1.** Information about genotyping and imputation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Genotyping platform** | **Cases (N)** | **Controls (N)** | **Recruitment Period** | **Imputation** |
| Illumina HumanCytoSNP | 1694 | 1698 | 2003-2008 | Haplotype Reference Consortium (version r1.1.2016) |
| Illumina HumanOmniExpress  | 664 | 495 | 2007-2010 |
| Illumina HumanOmniExpress | 1182 | 624 | 2010-2015 |
| Illumina Infinium OncoArray | 896 | 650 | 2003-2016 |
| Illumina Global Screening Array | 650 | 653 | 2016-2017 |

**NOTE:** We excluded triallelic SNPs, genotyped SNPs which had a low call rate (<98%), lack of Hardy-Weinberg equilibrium in control individuals (P<1×10–4), or low minor allele frequency (<0.1%), and those not assigned an rs number. More details can be found in the previous studies by Peters et ala and Schumacher et alb.

aPeters U, Jiao S, Schumacher FR, et al. Identification of genetic susceptibility loci for colorectal tumors in a genome-wide meta-analysis. Gastroenterology 2013; 144:799–807.

bSchumacher FR, Schmit SL, Jiao S, et al. Genome-wide association study of colorectal cancer identifies six new susceptibility loci. Nat Commun 2015; 6:7138.

**Table S2.** Genetic risk equivalent for comparisons between smoking exposure categories in the whole population

|  |  |  |
| --- | --- | --- |
| **Exposure** | **Modelb****OR (95% CI)** | **GRE (95% CI)** |
| Smoking status |  |  |
|  Never  | Ref. | Ref. |
|  Former  | 1.26 (1.14, 1.40) | 17.6 (9.3, 26.0) |
|  Current  | 1.48 (1.27, 1.72) | 29.9 (17.7, 42.1) |
| PRSa | 1.14 (1.12, 1.16) |  |
|  |  |  |
| Pack-years of active smoking |  |  |
|  0 | Ref. | Ref. |
|  1-9 | 1.16 (1.02, 1.31) | 11.3 (1.5, 21.1) |
|  10-19 | 1.30 (1.11, 1.51) | 20.0 (8.1, 31.9) |
|  ≥20 | 1.50 (1.32, 1.71) | 30.9 (20.4, 41.5) |
| PRSa | 1.14 (1.12, 1.16) |   |

aORs for PRS are presented for increase in PRS by 10 percentiles with every 10 percentiles.

bVariables in the model included age, sex, education, body mass index, physical activity, alcohol consumption, red meat consumption, history of colonoscopy, history of diabetes, family history of colorectal cancer in a first-degree relative, use of statins and use of nonsteroidal anti-inflammatory drugs, smoking status (or pack-years of active smoking) and PRS.

**Abbreviations:** CI, confidence interval; GRE, genetic risk equivalent; OR, odds ratio; PRS, polygenic risk score; Ref., reference.

**Table S3.** Genetic risk equivalent for comparisons between smoking exposure categories by cancer sites

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Controls** | **CC Cases**  | **Modelb**  | **GRE (95% CI)** |  | **RC Cases**  | **Modelb**  | **GRE (95% CI)** |
|  |  **N (%)** | **N (%)** | **OR (95% CI)**  |  |  | **N (%)** | **OR (95% CI)**  |  |
| Smoking status |  |  |  |  |  |  |  |  |
|  Never  | 1393 (46.4) | 2057 (50.9) | Ref. |  |  | 800 (41.5) | Ref. |  |
|  Former  | 1180 (39.3) | 1544 (38.2) | 1.22 (1.08, 1.37) | 15.2 (6.0, 24.4) |  | 810 (42.1) | 1.35 (1.17, 1.56) | 22.9 (11.4, 34.4) |
|  Current  | 429 (14.3) | 440 (10.9) | 1.54 (1.30, 1.83) | 33.0 (19.2, 46.7) |  | 316 (16.4) | 1.41 (1.15, 1.71) | 26.2 (10.5, 41.9) |
| PRSa |  |  | 1.14 (1.11, 1.16) |  |  | 1.14 (1.12, 1.17) |  |
|  |  |  |  |  |  |  |  |  |
| Pack-years of active smoking |  |  |  |  |  |  |  |
|  0 | 1393 (46.4) | 2057 (50.9) | Ref. |  |  | 800 (41.5) | Ref. |  |
|  1-9 | 549 (18.3) | 795 (19.7) | 1.16 (1.00, 1.33) | 11.3 (0.4, 22.3) |  | 358 (18.6) | 1.19 (1.00, 1.41) | 13.3 (-0.1, 26.7) |
|  10-19 | 358 (11.9) | 446 (11.0) | 1.22 (1.03, 1.45) | 15.2 (1.9, 28.5) |  | 274 (14.2) | 1.37 (1.12, 1.67) | 24.0 (8.2, 39.8) |
|  ≥20 | 702 (23.4) | 743 (18.4) | 1.50 (1.30, 1.73) | 30.9 (19.3, 42.6) |  | 494 (25.6) | 1.56 (1.32, 1.85) | 33.9 (19.7, 48.1) |
| PRSa |   |   | 1.14 (1.11, 1.16) |   |  | 1.14 (1.12, 1.17) |   |

aORs for PRS are presented for increase in PRS by 10 percentiles with every 10 percentiles.

bVariables in the model included age, sex, education, body mass index, physical activity, alcohol consumption, red meat consumption, history of colonoscopy, history of diabetes, family history of colorectal cancer in a first-degree relative, use of statins and use of nonsteroidal anti-inflammatory drugs, smoking status (or pack-years of active smoking) and PRS.

**Abbreviations:** CC, colon cancer; CI, confidence interval; GRE, genetic risk equivalent; OR, odds ratio; PRS, polygenic risk score; RC, rectum cancer; Ref., reference.

**Table S4.** Genetic risk equivalent for comparisons between smoking exposure categories by sex

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Sex** | **Exposure** | **Cases**  | **Controls**  | **Modelb** | **GRE** |
| **N (%)** | **N (%)** |  **OR (95% CI)**  | **(95% CI)** |
| Female | Smoking status |  |  |  |  |
|  |  Never  | 1224 (63.2) | 1054 (67.7) | Ref. |  |
|  |  Former  | 438 (22.6) | 343 (22.0) | 1.33 (1.11, 1.60) | 21.8 (7.1, 36.4) |
|  |  Current  | 274 (14.2) | 160 (10.3) | 1.63 (1.28, 2.08) | 37.3 (17.2, 57.4) |
|  | PRSa |  |  | 1.14 (1.11, 1.17) |  |
|  |  |  |  |  |  |
|  | Pack-years of active smoking |  |  |  |
|  |  0 | 1224 (63.2) | 1054 (67.7) | 1.20 (0.98, 1.48) | 13.9 (-2.2, 30.0) |
|  |  1-9 | 301 (15.5) | 263 (16.9) | 1.56 (1.17, 2.09) | 33.9 (10.8, 57.1) |
|  |  10-19 | 168 (8.7) | 103 (6.6) | 1.75 (1.37, 2.25) | 42.7 (21.8, 63.7) |
|  |  ≥20 | 243 (12.6) | 137 (8.8) | 1.14 (1.11, 1.17) |  |
|  | PRSa |  |  |  |  |
|  |  |  |  |  |  |
| Male | Smoking status |  |  |  |
|  |  Never | 969 (32.4) | 1003 (40.4) | Ref. |  |
|  |  Former | 1552 (51.9) | 1201 (48.3) | 1.23 (1.08, 1.41) | 15.8 (5.4, 26.2) |
|  |  Current | 471 (15.7) | 280 (11.3) | 1.38 (1.14, 1.68) | 24.6 (9.1, 40.1) |
|  | PRSa |  |  | 1.14 (1.11, 1.16) |  |
|  |  |  |  |  |  |
|  | Pack-years of active smoking |  |  |  |
|  |  0 | 969 (32.4) | 1003 (40.4) | Ref. |  |
|  |  1-9 | 606 (20.3) | 532 (21.4) | 1.13 (0.96, 1.34) | 9.3 (-3.3, 21.9) |
|  |  10-19 | 464 (15.5) | 343 (13.8) | 1.20 (1.00, 1.45) | 13.9 (-0.3, 28.1) |
|  |  ≥20 | 953 (31.9) | 606 (24.4) | 1.42 (1.21, 1.65) | 26.8 (14.3, 39.3) |
|   | PRSa |   |   | 1.14 (1.11, 1.16) |   |

aORs for PRS are presented for increase in PRS by 10 percentiles with every 10 percentiles.

bVariables in the model included age, education, body mass index, physical activity, alcohol consumption, red meat consumption, history of colonoscopy, history of diabetes, family history of colorectal cancer in a first-degree relative, use of statins and use of nonsteroidal anti-inflammatory drugs, smoking status (or pack-years of active smoking) and PRS.

**Abbreviations:** CI, confidence interval; GRE, genetic risk equivalent; OR, odds ratio; PRS, polygenic risk score; Ref., reference.

**Table S5.** Genetic risk equivalent for comparisons between smoking exposure categories by age

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Age** | **Exposure** | **Cases**  | **Controls**  | **Modelb** | **GRE (95% CI)** |
| **N (%)** | **N (%)** |  **OR (95% CI)**  |
| ≤55y | Smoking status |  |  |  |  |
|  |  Never  | 236 (36.7) | 225 (47.1) | Ref. |  |
|  |  Former  | 203 (31.6) | 131 (27.4) | 1.40 (1.03, 1.90) | 27.5 (0.2, 54.9) |
|  |  Current  | 204 (31.7) | 122 (25.5) | 1.43 (1.04, 1.96) | 29.3 (1.2, 57.3) |
|  | PRSa |  |  | 1.13 (1.08, 1.18) |  |
|  |  |  |  |  |  |
|  | Pack-years of active smoking |  |  |  |
|  |  0 | 236 (36.7) | 225 (47.1) | Ref. |  |
|  |  1-9 | 141 (21.9) | 96 (20.1) | 1.38 (0.98, 1.94) | 26.4 (-3.1, 55.8) |
|  |  10-19 | 109 (17.0) | 74 (15.5) | 1.26 (0.87, 1.84) | 18.9 (-12.3, 50.2) |
|  |  ≥20 | 157 (24.4) | 83 (17.4) | 1.60 (1.12, 2.30) | 38.5 (6.0, 70.9) |
|  | PRSa |  |  | 1.13 (1.08, 1.18) |  |
|  |  |  |  |  |  |
| >55y | Smoking status |  |  |  |
|  |  Never | 1957 (45.7) | 1832 (51.4) | Ref. |  |
|  |  Former | 1787 (41.7) | 1412 (39.7) | 1.25 (1.12, 1.40) | 17.0 (8.1, 25.9) |
|  |  Current | 541 (12.6) | 318 (8.9) | 1.41 (1.19, 1.68) | 26.2 (12.6, 39.8) |
|  | PRSa |  |  | 1.14 (1.12, 1.16) |  |
|  |  |  |  |  |  |
|  | Pack-years of active smoking |  |  |  |
|  |  0 | 1957 (45.7) | 1832 (51.4) | Ref. |  |
|  |  1-9 | 766 (17.9) | 699 (19.6) | 1.12 (0.98, 1.29) | 8.6 (-1.9, 19.2) |
|  |  10-19 | 523 (12.2) | 372 (10.4) | 1.29 (1.10, 1.53) | 19.4 (6.4, 32.5) |
|  |  ≥20 | 1039 (24.2) | 660 (18.5) | 1.46 (1.27, 1.67) | 28.9 (17.7, 40.1) |
|   | PRSa |   |   | 1.14 (1.12, 1.16) |   |

aORs for PRS are presented for increase in PRS by 10 percentiles with every 10 percentiles.

bVariables in the model included sex, education, body mass index, physical activity, alcohol consumption, red meat consumption, history of colonoscopy, history of diabetes, family history of colorectal cancer in a first-degree relative, use of statins and use of nonsteroidal anti-inflammatory drugs, smoking status (or pack-years of active smoking) and PRS.

**Abbreviations:** CI, confidence interval; GRE, genetic risk equivalent; OR, odds ratio; PRS, polygenic risk score; Ref., reference.

**Table S6.** Genetic risk equivalent for comparisons between smoking exposure categories by history of colonoscopy

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **History of colonoscopy** | **Exposure** | **Cases**  | **Controls**  | **Modelb** | **GRE (95% CI)** |
| **N (%)** | **N (%)** |  **OR (95% CI)**  |
| No | Smoking status |  |  |  |  |
|  |  Never  | 1578 (43.6) | 822 (51.0) | Ref. |  |
|  |  Former  | 1439 (39.7) | 566 (35.1) | 1.35 (1.17, 1.55) | 21.5 (10.7, 32.3) |
|  |  Current  | 606 (16.7) | 223 (13.8) | 1.55 (1.28, 1.88) | 31.4 (16.7, 46.0) |
|  | PRSa |  |  | 1.15 (1.13, 1.18) |  |
|  |  |  |  |  |  |
|  | Pack-years of active smoking |  |  |  |
|  |  0 | 1578 (43.6) | 822 (51.0) | 1.30 (1.09, 1.55) | 18.8 (6.0, 31.5) |
|  |  1-9 | 669 (18.5) | 284 (17.6) | 1.29 (1.06, 1.57) | 18.2 (3.8, 32.7) |
|  |  10-19 | 479 (13.2) | 206 (12.8) | 1.60 (1.35, 1.90) | 33.6 (20.2, 47.0) |
|  |  ≥20 | 897 (24.8) | 299 (18.6) | 1.15 (1.13, 1.18) |  |
|  | PRSa |  |  |  |  |
|  |  |  |  |  |  |
| Yes | Smoking status |  |  |  |
|  |  Never | 615 (47.1) | 1235 (50.8) | Ref. |  |
|  |  Former | 551 (42.2) | 978 (40.2) | 1.17 (1.00, 1.36) | 13.9 (-0.2, 27.9) |
|  |  Current | 139 (10.7) | 217 (8.9) | 1.35 (1.05, 1.74) | 26.5 (3.4, 49.5) |
|  | PRSa |  |  | 1.12 (1.09, 1.15) |  |
|  |  |  |  |  |  |
|  | Pack-years of active smoking |  |  |  |
|  |  0 | 615 (47.1) | 1235 (50.8) | Ref. |  |
|  |  1-9 | 238 (18.2) | 511 (21.0) | 1.00 (0.82, 1.21) | 0.0 (-16.8, 16.8) |
|  |  10-19 | 153 (11.7) | 240 (9.9) | 1.33 (1.05, 1.69) | 25.2 (3.6, 46.8) |
|  |  ≥20 | 299 (22.9) | 444 (18.3) | 1.40 (1.15, 1.69) | 29.7 (11.4, 48.0) |
|   | PRSa |   |   | 1.12 (1.09, 1.15) |   |

aORs for PRS are presented for increase in PRS by 10 percentiles with every 10 percentiles.

 bVariables in the model included age, sex, education, body mass index, physical activity, alcohol consumption, red meat consumption, history of diabetes, family history of colorectal cancer in a first-degree relative, use of statins and use of nonsteroidal anti-inflammatory drugs, smoking status (or pack-years of active smoking) and PRS.

**Abbreviations:** CI, confidence interval; GRE, genetic risk equivalent; OR, odds ratio; PRS, polygenic risk score; Ref., reference.

**Table S7.** Genetic risk equivalent for comparisons between smoking exposure categories by FH

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **FH** | **Exposure** | **Cases**  | **Controls**  | **Modelb** | **GRE (95% CI)** |
| **N (%)** | **N (%)** |  **OR (95% CI)**  |
| No | Smoking status |  |  |  |  |
|  |  Never  | 1886 (44.9) | 1825 (50.7) | Ref. |  |
|  |  Former  | 1687 (40.1) | 1375 (38.2) | 1.23 (1.10, 1.38) | 16.9 (7.4, 26.4) |
|  |  Current  | 632 (15.0) | 399 (11.1) | 1.41 (1.20, 1.66) | 28.1 (14.2, 42.0) |
|  | PRSa |  |  | 1.13 (1.11, 1.15) |  |
|  |  |  |  |  |  |
|  | Pack-years of active smoking |  |  |  |
|  |  0 | 1886 (44.9) | 1825 (50.7) | Ref. |  |
|  |  1-9 | 769 (18.3) | 696 (19.3) | 1.16 (1.01, 1.33) | 12.1 (0.9, 23.4) |
|  |  10-19 | 545 (13.0) | 401 (11.1) | 1.27 (1.08, 1.49) | 19.6 (6.0, 33.1) |
|  |  ≥20 | 1005 (23.9) | 677 (18.8) | 1.41 (1.23, 1.62) | 28.1 (16.2, 40.0) |
|  | PRSa |  |  | 1.13 (1.11, 1.15) |  |
|  |  |  |  |  |  |
| Yes | Smoking status |  |  |  |
|  |  Never | 307 (42.5) | 232 (52.5) | Ref. |  |
|  |  Former | 303 (41.9) | 169 (38.2) | 1.51 (1.11, 2.06) | 23.7 (5.0, 42.4) |
|  |  Current | 113 (15.6) | 41 (9.3) | 2.21 (1.40, 3.55) | 45.6 (17.2, 74.0) |
|  | PRSa |  |  | 1.19 (1.14, 1.25) |  |
|  |  |  |  |  |  |
|  | Pack-years of active smoking |  |  |  |
|  |  0 | 307 (42.5) | 232 (52.5) | Ref. |  |
|  |  1-9 | 138 (19.1) | 99 (22.4) | 1.19 (0.83, 1.70) | 10.0 (-10.8, 30.8) |
|  |  10-19 | 87 (12.0) | 45 (10.2) | 1.58 (1.00, 2.53) | 26.3 (-1.0, 53.6) |
|  |  ≥20 | 191 (26.4) | 66 (14.9) | 2.52 (1.72, 3.72) | 53.1 (27.4, 78.9) |
|   | PRSa |   |   | 1.19 (1.14, 1.25) |   |

aORs for PRS are presented for increase in PRS by 10 percentiles with every 10 percentiles.

bVariables in the model included age, sex, education, body mass index, physical activity, alcohol consumption, red meat consumption, history of colonoscopy, history of diabetes, use of statins and use of nonsteroidal anti-inflammatory drugs, smoking status (or pack-years of active smoking) and PRS.

**Abbreviations:** CI, confidence interval; FH, family history of colorectal cancer in a first-degree relative; GRE, genetic risk equivalent; OR, odds ratio; PRS, polygenic risk score; Ref., reference.