**SUPPLEMENTARY MATERIALS**

***Barrett’s esophagus ascertainment***

Participants were asked if they had ever undergone upper gastrointestinal endoscopy as well as the date of the first procedure. In addition, participants were asked if they had been diagnosed with BE and the year of diagnosis. We requested written permission to acquire endoscopy and pathology records from participants reporting BE. A board-certified gastroenterologist (BCJ), blinded to exposure information, reviewed records to extract information on the initial date of diagnosis of BE, the length of columnar-lined esophagus seen at endoscopy and the presence or absence of specialized intestinal metaplasia (SIM) documented in biopsies taken from above the gastroesophageal junction. To minimize misclassification, BE is defined strictly by the presence of SIM (i.e., the presence of goblet cells) within columnar mucosa retrieved from biopsies of the esophagus. Corresponding endoscopy reports are used to verify biopsies were taken above the gastric folds.

To validate self-reporting of upper gastrointestinal endoscopy, and that failure to report BE was a reliable indication that a participant did not have the condition, we requested written permission to acquire records from 200 randomly-selected NHS participants who reported an upper gastrointestinal endoscopy but not BE. After one mailing attempt, we obtained records from 95 women. For none of these instances did the endoscopist suspect BE.(1,2)

To verify that blinded review of pathology reports accurately identifies participants with BE, we sought original slides and tissue blocks from health care providers for random NHS participants identified as having SIM by chart review. After centralized review of 251 slides by two expert gastrointestinal pathologists, we confirmed SIM in 97% of instances where the nurse was classified as having BE by chart review. When the original histology report only described columnar epithelium in the esophagus, this too was confirmed in 96% of instances. We conclude that our method of chart review of random NHS participants accurately classifies cases as having SIM.(3)

***Non-genetic (lifestyle) exposures***

*Body Mass Index (BMI) assessment:* Self-reported height and weight have been collected in all three cohorts. Height was reported at baseline questionnaire. Weight is updated every 2 years. Prior validation studies have demonstrated that self-reported height and weight are highly correlated (r=0.97) with weight measured by trained technicians.(4) For the purposes of the present study, we used weight at the time of DNA collection. We calculated BMI according to the standard formula (BMI = weight in kilograms/height in meters, squared). We categorized participants according to three BMI categories: <25.0, 25.0-29.9, and ≥30.0 kg/m2.

*Smoking assessment*: Smoking has been assessed on every biennial questionnaire for all three cohorts since inception and can be categorized according to number of cigarettes per day or pack-years of smoking. On the initial questionnaires, each participant was asked if she or he was a current smoker, past smoker, or never smoker. The past and current smokers were asked to indicate the average number of cigarettes they smoked per day, the age at which they began smoking, and among past smokers, the age at which they stopped smoking. Information on smoking status and the number of cigarettes smoked has been updated every two years. For the purposes of the present study, we also divided participants into two smoking categories: never-smokers versus ever-smokers, based on whether they reported any number of pack-years of smoking in the cycle before DNA collection.

*Alcohol consumption assessment:* Alcohol intake was measured several times with validated dietary questionnaires (FFQ). Previous studies have shown that our FFQs have reasonable validity and reproducibility for individual foods.(5) There were nine possible responses for each alcohol intake question, ranging from ‘almost never’ to ‘6+ servings per day’. Consumption of beer, wine, and liquor was ascertained in separate items. Each participant was asked how often, on average, she or he consumed each type of alcoholic beverage over the previous year, using standardized portion of each beverage (a 12-oz bottle or a can of beer, a 4-oz glass of wine, or a 1.5-oz serving of liquor). Alcohol intake (in g per day) was calculated as the sum of the daily number of drinks multiplied by the average alcohol content per type of each alcoholic beverage (beer 12.8 g, light beer 11.3 g, wine 11.0 g, liquor 14.0 g), using information obtained from US Department of Agriculture food-composition sources. Alcohol intake as measured by FFQ was highly correlated with intake, as calculated from diet record assessment completed by a sample of study participants (Spearman’s r=0.90).(6) For the purpose of the present study, we used information obtained from responses on the FFQs assessed in the cycle before DNA collection.

*Heartburn assessment:* Participants were asked if they experienced heartburn/acid-reflux symptoms, the frequency of reflux symptoms as well as the duration of reflux symptoms (in years). As for other covariables, we assessed the presence of reflux prior to DNA collection. Heartburn information was available for a total of 380 of the included cases (95%) and 405 of the controls (93%).

**Supplementary Table 1.** Main effect of the SNPs from candidate genes included in the Genetic Risk Score on Barrett’s Esophagus.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **SNP** | **Gene** | **Reference** | **Controls** | **Cases** | **OR1** | **95% CI** | **p-value** |
| **rs10112358** |  |  |  |  |  |  | 0.56 |
| C/CC/TT/T | YTHDF3,IFITM8P | (7) | 188178 53 | 185151 54 | 1.000.871.06 | Reference(0.65-1.18)(0.69-1.64) |  |
| **rs10920531** |  |  |  |  |  |  | 0.63 |
| C/C A/C A/A | ADIPOQ, ADIPOR1 | (8) | 172 200 58 | 147 192 58 | 1.001.121.20 | Reference(0.83-1.51)(0.78-1.84) |  |
| **rs11010572** |  |  |  |  |  |  | 0.28 |
| G/GA/GA/A |  | (9) | 292132 8 | 266119 14 | 1.001.012.03 | Reference(0.75-1.37)(0.83-4.98) |  |
| **rs12733285** |  |  |  |  |  |  | 0.41 |
| C/CC/TT/T | ADIPOQ,ADIPOR1 | (8,10) | 190178 50 | 195151 48 | 1.000.820.91 | Reference (0.61-1.10)(0.58-1.42) |  |
| **rs12880053** |  |  |  |  |  |  | 0.096 |
| C/CA/CA/A |  | (9) | 141189 90 | 105195 94 | 1.001.391.41 | Reference(1.01-1.93)(0.96-2.08) |  |
| **rs1342387** |  |  |  |  |  |  | 0.22 |
| C/CA/CA/A | ADIPOQ,ADIPOR1 | (8,10) | 122205 100 | 133171 92 | 1.000.750.82 | Reference(0.55-1.04)(0.56-1.20) |  |
| **rs1391010** |  |  |  |  |  |  | 0.67 |
| C/CC/TT/T | LOC100505946,LOC100506253 | (9,11) | 284124 21 | 270115 13 | 1.000.990.72 | Reference(0.73-1.35)(0.35-1.48) |  |
| **rs1431594** |  |  |  |  |  |  | 0.83 |
| C/CC/TT/T | IFITM8P, LOC286184 | (9,12) | 196188 48 | 182168 49 | 1.000.971.12 | Reference(0.73-1.30)(0.72-1.76) |  |
| **rs1497205** |  |  |  |  |  |  | 0.68 |
| T/TC/TC/C | PARM1,RCHY1 | (13) | 216182 32 | 191170 36 | 1.001.011.26 | Reference (0.76-1.35)(0.75-2.11) |  |
| **rs1501299** |  |  |  |  |  |  | 0.70 |
| G/GG/TT/T | ADIPOQ - ADIPOR1 | (8,14) | 211180 41 | 201166 31 | 1.000.960.80 | Reference (0.72-1.28)(0.48-1.34) |  |
| **rs1532167** |  |  |  |  |  |  | 0.61 |
| G/GG/TT/T | LOC732275,LOC401864 | (9,15) | 155210 66 | 153180 68 | 1.000.870.99 | Reference (0.64-1.17)(0.66-1.49) |  |
| **rs1946518** |  |  |  |  |  |  | 0.88 |
| G/GG/TT/T | IL-18 promoter | (16) | 148194 72 | 132189 66 | 1.001.070.98 | Reference (0.78-1.46)(0.65-1.48) |  |
| **rs1946518** |  |  |  |  |  |  | 0.50 |
| T/TC/TC/C | IL-18 promoter | (16) | 168196 67 | 141190 68 | 1.001.151.25 | Reference (0.85-1.56)(0.83-1.88) |  |
| **rs2241766** |  |  |  |  |  |  | 0.69 |
| T/TG/TG/G | ADIPOQ  | (8,17) | 33890 3 | 31084 5 | 1.001.031.85 | Reference (0.74-1.45)(0.43-7.89) |  |
| **rs2241766** |  |  |  |  |  |  | 0.20 |
| G/GA/GA/A | ADIPOQ  | (8,17) | 154208 68 | 162189 48 | 1.000.870.68 | Reference (0.64-1.17)(0.44-1.04) |  |
| **rs266729** |  |  |  |  |  |  | 0.39 |
| C/CC/GG/G | ADIPOQ  | (8,17) | 246158 23 | 235148 14 | 1.000.970.62 | Reference (0.73-1.30)(0.31-1.24) |  |
| **rs2669333** |  |  |  |  |  |  | 0.71 |
| G/GG/AA/A | DIAPH3, TRDR3,PCDH20 | (18) | 196177 54 | 170171 54 | 1.001.121.13 | Reference (0.83-1.51)(0.73-1.74) |  |
| **rs2687201** |  |  |  |  |  |  | **0.019** |
| C/CA/CA/A | FOXP1 | (9) | 179190 52 | 204144 45 | 1.000.650.78 | Reference (0.48-0.88)(0.50-1.23) |  |
| **rs3005897** |  |  |  |  |  |  | 0.45 |
| C/CC/TT/T |  | (9) | 214175 35 | 181172 43 | 1.001.131.33 | Reference (0.85-1.52)(0.81-2.18) |  |
| **rs3111601** |  |  |  |  |  |  | 0.87 |
| T/TC/TC/C | FOXF1 | (19) | 190186 53 | 181171 47 | 1.000.970.89 | Reference (0.72-1.30)(0.57-1.39) |  |
| **rs3784262** |  |  |  |  |  |  | 0.50 |
| T/TC/TC/C | ALDH1A2 | (9,13) | 135207 86 | 113204 82 | 1.001.211.17 | Reference (0.88-1.66)(0.78-1.73) |  |
| **rs3897234** |  |  |  |  |  |  | 0.34 |
| T/TC/TC/C |  | (9) | 270145 16 | 244132 23 | 1.000.991.63 | Reference (0.74-1.33)(0.84-3.17) |  |
| **rs4523255** |  |  |  |  |  |  | 0.93 |
| C/CC/TT/T | MFHAS1 | (13) | 166200 65 | 151191 58 | 1.001.061.01 | Reference (0.79-1.43)(0.67-1.54) |  |
| **rs4611855** |  |  |  |  |  |  | 0.18 |
| C/CC/TT/T | OSBPL10 | (20,21) | 158181 82 | 144190 59 | 1.001.170.81 | Reference (0.86-1.59)(0.54-1.22) |  |
| **rs4800353** |  |  |  |  |  |  | 0.93 |
| A/AA/GG/G | RNU7-17P,GATA6-AS1 | (9) | 31997 7 | 29788 5 | 1.000.990.80 | Reference (0.71-1.37)(0.25-2.58) |  |
| **rs4973786** |  |  |  |  |  |  | 0.24 |
| G/GA/GA/A | VENTXP4,LRRC3B | (9,22) | 155210 64 | 146177 77 | 1.000.891.25 | Reference (0.66-1.21)(0.83-1.87) |  |
| **rs576425** |  |  |  |  |  |  | 0.28 |
| C/CC/TT/T |  | (9) | 120223 85 | 131185 83 | 1.000.780.90 | Reference (0.56-1.07)(0.61-1.33) |  |
| **rs6099816** |  |  |  |  |  |  | 0.35 |
| C/CA/CA/A | PMEPA1,MIR4532 | (9,23) | 174190 66 | 179159 58 | 1.000.800.88 | Reference (0.60-1.08)(0.58-1.33) |  |
| **rs6214** |  |  |  |  |  |  | 0.31 |
| C/CC/TT/T | IGF-1 | (24) | 165206 58 | 157176 68 | 1.000.901.24 | Reference (0.67-1.22)(0.82-1.88) |  |
| **rs6449586** |  |  |  |  |  |  | 0.94 |
| T/TC/TC/C | RPS10P12,ISL1 | (9,25) | 136207 84 | 125193 82 | 1.000.991.06 | Reference (0.72-1.35)(0.71-1.56) |  |
| **rs6479527** |  |  |  |  |  |  | 0.87 |
| G/GA/GA/A | PTPDC1 | (9) | 107220 98 | 103204 91 | 1.000.930.91 | Reference (0.66-1.30)(0.61-1.35) |  |
| **rs6848890** |  |  |  |  |  |  | 0.22 |
| C/CC/TT/T |  | (9) | 300111 11 | 265113 18 | 1.001.141.88 | Reference (0.83-1.56)(0.87-4.09) |  |
| **rs6898743** |  |  |  |  |  |  | 0.19 |
| G/GC/GC/C | GHR | (24) | 243159 27 | 250122 26 | 1.000.760.93 | Reference (0.57-1.02)(0.53-1.65) |  |
| **rs732392** |  |  |  |  |  |  | **0.023** |
| T/TG/TG/G | GALNT18 | (9) | 231167 33 | 190158 52 | 1.001.161.94 | Reference (0.87-1.56)(1.20-3.14) |  |
| **rs7539542** |  |  |  |  |  |  | 0.45 |
| C/CC/GG/G | ADIPOR1 | (8,26) | 204181 38 | 184171 45 | 1.001.051.36 | Reference (0.78-1.40)(0.84-2.21) |  |
| **rs7691721** |  |  |  |  |  |  | 0.82 |
| T/TC/TC/C |  | (27) | 217177 34 | 190171 35 | 1.001.071.15 | Reference (0.80-1.42)(0.69-1.93) |  |
| **rs7835508** |  |  |  |  |  |  | 0.76 |
| T/TC/TC/C | PLEKHA2 | (9,28) | 157207 64 | 148180 67 | 1.000.931.07 | Reference (0.68-1.25)(0.71-1.61) |  |
| **rs7904985** |  |  |  |  |  |  | 0.95 |
| G/GA/GA/A | GRID1 | (9) | 210173 45 | 196157 45 | 1.000.961.02 | Reference (0.72-1.29)(0.65-1.62) |  |
| **rs8045253** |  |  |  |  |  |  | 0.87 |
| T/TC/TC/C | FOXF1,LINC00917,AC092327.1,LOC732275 | (29) | 154209 64 | 136202 60 | 1.001.081.02 | Reference (0.80-1.47)(0.67-1.57) |  |
| **rs822395** |  |  |  |  |  |  | 0.37 |
| A/AA/CC/C | ADIPOQ,ADIPOR1 | (8,14) | 171206 45 | 173176 46 | 1.000.831.05 | Reference (0.62-1.11)(0.66-1.68) |  |
| **rs822396** |  |  |  |  |  |  | 0.47 |
| A/AA/GG/G | ADIPOQ,ADIPOR1 | (8,14) | 263145 20 | 260122 16 | 1.000.850.77 | Reference (0.63-1.15)(0.39-1.52) |  |
| **rs889838** |  |  |  |  |  |  | 0.30 |
| G/GA/GA/A |  | (9) | 141216 73 | 128187 85 | 1.000.951.28 | Reference (0.70-1.30)(0.86-1.90) |  |
| **rs917997** |  |  |  |  |  |  | 0.82 |
| C/CC/TT/T | SLC9A4,IL18RAP,IL1R1 | (16,30) | 259141 31 | 238137 25 | 1.001.040.87 | Reference (0.78-1.40)(0.50-1.52) |  |
| **rs9257809** |  |  |  |  |  |  | 0.70 |
| A/AA/GG/G | TRNAI25 | (31) | 37549 3 | 34155 3 | 1.001.191.00 | Reference (0.79-1.81)(0.20-4.98) |  |
| **rs9837992** |  |  |  |  |  |  | 0.19 |
| G/GA/GA/A | MITF, FOXP1, EIF4E3 | (18) | 175195 58 | 186160 46 | 1.000.770.76 | Reference (0.58-1.04)(0.49-1.19) |  |
| **rs9936833** |  |  |  |  |  |  | 0.70 |
| T/TC/TC/C | LINC00917, FENDRR | (31) | 156201 70 | 155176 70 | 1.000.880.96 | (0.65-1.19)(0.64-1.43) |  |

A total of 46 SNPs were included in this candidate-gene-based GRSC (unweighted). SNPs that were not in HW equilibrium in controls (N=8) and monomorphic SNPS (N=2) were excluded.

**Supplementary Table 2**

*a. Joint effect of smoking and unweighted GRSB on Barrett’s esophagus risk.*

|  |  |  |
| --- | --- | --- |
|  | Never Smokers | Ever Smokers |
| Low unweighted GRSB | 116 CO, 95 CAREF  | 131 CO, 127 CAOR=0.87 95%CI= 0.52-1.44 |
| High unweighted GRSB | 65 CO, 60 CAOR=0.89 95%CI= 0.48-1.64 | 64 CO, 82 CAOR=1.51 95%CI= 0.84-2.76 |

ORs adjusted by cohort, alcohol, energy intake, and heartburn duration

P-interaction = 0.22

*b. Joint effect of alcohol and unweighted GRSB on Barrett’s esophagus risk.*

|  |  |  |
| --- | --- | --- |
|  | Low Alcohol (0-2.8 g/day) | High Alcohol(>2.8-81.7 g/day) |
| Low unweighted GRSB | 125 CO, 100 CAREF | 119 CO, 122 CAOR=1.0895%CI= 0.64-1.80 |
| High unweighted GRSB | 71 CO, 62 CAOR=1.12 95%CI= 0.63-2.01 | 58 CO, 81 CAOR=1.59 95%CI= 0.89-2.87 |

ORs adjusted by cohort, smoking, energy intake, and heartburn duration

P-interaction = 0.64

*c. Joint effect of heartburn duration and unweighted GRSB on Barrett’s esophagus risk.*

|  |  |  |
| --- | --- | --- |
|  | Heartburn duration<= 5 years | Heartburn duration > 5 years |
| Low unweighted GRSB | 76 CO, 64 CAREF | 58 CO, 106 CAOR=1.8995%CI= 1.17-3.08 |
| High unweighted GRSB | 49 CO, 40 CAOR=1.04 95%CI= 0.59-1.81 | 21 CO, 63 CAOR=3.16 95%CI= 1.73-5.93 |

ORs adjusted by cohort, alcohol, energy intake, and smoking

P-interaction = 0.18

**Supplementary Table 3**

*a. Joint effect of smoking and unweighted GRSC on Barrett’s esophagus risk.*

|  |  |  |
| --- | --- | --- |
|  | Never Smokers | Ever Smokers |
| Low GRSC | 106 CO, 60 CAREF | 112 CO, 98 CAOR=1.47 95%CI= 0.84-2.58 |
| High GRSC | 76 CO, 95 CAOR=2.71 95%CI= 1.49-5.01 | 86 CO, 116 CAOR=2.42 95%CI= 1.37-4.33 |

ORs adjusted by cohort, alcohol, energy intake, and heartburn duration

P-interaction = 0.11

*b. Joint effect of alcohol and unweighted GRSC on Barrett’s esophagus risk.*

|  |  |  |
| --- | --- | --- |
|  | Low Alcohol (0-2.8 g/day) | High Alcohol(>2.8-81.7 g/day) |
| Low GRSC | 110 CO, 68 CAREF | 106 CO, 90 CAOR=1.22 95%CI= 0.70-2.12 |
| High GRSC | 89 CO, 95 CAOR=2.11 95%CI= 1.21-3.71 | 72 CO, 117 CAOR=2.4095%CI= 1.36-4.27 |

ORs adjusted by cohort, smoking, energy intake, and heartburn duration

P-interaction = 0.72

*c. Joint effect of heartburn duration and unweighted GRSC on Barrett’s esophagus risk.*

|  |  |  |
| --- | --- | --- |
|  | Heartburn duration<= 5 years | Heartburn duration > 5 years |
| Low GRSC | 73 CO, 43 CAREF | 49 CO, 78 CAOR=2.27 95%CI= 1.33-3.92 |
| High GRSC | 54 CO, 62 CAOR=2.02 95%CI= 1.17-3.52 | 31 CO, 92 CAOR=4.6795%CI= 2.64-8.44 |

ORs adjusted by cohort, alcohol, energy intake, and smoking

P-interaction = 0.78

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