**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/C  C/T  T/T | YTHDF3,  IFITM8P | (7) | 188  178  53 | 185  151  54 | 1.00  0.87  1.06 | 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 | 1.00  1.12  1.20 | Reference  (0.83-1.51)  (0.78-1.84) |  |
| **rs11010572** |  |  |  |  |  |  | 0.28 |
| G/G  A/G  A/A |  | (9) | 292  132  8 | 266  119  14 | 1.00  1.01  2.03 | Reference  (0.75-1.37)  (0.83-4.98) |  |
| **rs12733285** |  |  |  |  |  |  | 0.41 |
| C/C  C/T  T/T | ADIPOQ,  ADIPOR1 | (8,10) | 190  178  50 | 195  151  48 | 1.00  0.82  0.91 | Reference  (0.61-1.10)  (0.58-1.42) |  |
| **rs12880053** |  |  |  |  |  |  | 0.096 |
| C/C  A/C  A/A |  | (9) | 141  189  90 | 105  195  94 | 1.00  1.39  1.41 | Reference  (1.01-1.93)  (0.96-2.08) |  |
| **rs1342387** |  |  |  |  |  |  | 0.22 |
| C/C  A/C  A/A | ADIPOQ,  ADIPOR1 | (8,10) | 122  205  100 | 133  171  92 | 1.00  0.75  0.82 | Reference  (0.55-1.04)  (0.56-1.20) |  |
| **rs1391010** |  |  |  |  |  |  | 0.67 |
| C/C  C/T  T/T | LOC100505946,  LOC100506253 | (9,11) | 284  124  21 | 270  115  13 | 1.00  0.99  0.72 | Reference  (0.73-1.35)  (0.35-1.48) |  |
| **rs1431594** |  |  |  |  |  |  | 0.83 |
| C/C  C/T  T/T | IFITM8P, LOC286184 | (9,12) | 196  188  48 | 182  168  49 | 1.00  0.97  1.12 | Reference  (0.73-1.30)  (0.72-1.76) |  |
| **rs1497205** |  |  |  |  |  |  | 0.68 |
| T/T  C/T  C/C | PARM1,  RCHY1 | (13) | 216  182  32 | 191  170  36 | 1.00  1.01  1.26 | Reference (0.76-1.35)  (0.75-2.11) |  |
| **rs1501299** |  |  |  |  |  |  | 0.70 |
| G/G  G/T  T/T | ADIPOQ - ADIPOR1 | (8,14) | 211  180  41 | 201  166  31 | 1.00  0.96  0.80 | Reference (0.72-1.28)  (0.48-1.34) |  |
| **rs1532167** |  |  |  |  |  |  | 0.61 |
| G/G  G/T  T/T | LOC732275,  LOC401864 | (9,15) | 155  210  66 | 153  180  68 | 1.00  0.87  0.99 | Reference (0.64-1.17)  (0.66-1.49) |  |
| **rs1946518** |  |  |  |  |  |  | 0.88 |
| G/G  G/T  T/T | IL-18 promoter | (16) | 148  194  72 | 132  189  66 | 1.00  1.07  0.98 | Reference (0.78-1.46)  (0.65-1.48) |  |
| **rs1946518** |  |  |  |  |  |  | 0.50 |
| T/T  C/T  C/C | IL-18 promoter | (16) | 168  196  67 | 141  190  68 | 1.00  1.15  1.25 | Reference (0.85-1.56)  (0.83-1.88) |  |
| **rs2241766** |  |  |  |  |  |  | 0.69 |
| T/T  G/T  G/G | ADIPOQ | (8,17) | 338  90  3 | 310  84  5 | 1.00  1.03  1.85 | Reference (0.74-1.45)  (0.43-7.89) |  |
| **rs2241766** |  |  |  |  |  |  | 0.20 |
| G/G  A/G  A/A | ADIPOQ | (8,17) | 154  208  68 | 162  189  48 | 1.00  0.87  0.68 | Reference (0.64-1.17)  (0.44-1.04) |  |
| **rs266729** |  |  |  |  |  |  | 0.39 |
| C/C  C/G  G/G | ADIPOQ | (8,17) | 246  158  23 | 235  148  14 | 1.00  0.97  0.62 | Reference (0.73-1.30)  (0.31-1.24) |  |
| **rs2669333** |  |  |  |  |  |  | 0.71 |
| G/G  G/A  A/A | DIAPH3, TRDR3,  PCDH20 | (18) | 196  177  54 | 170  171  54 | 1.00  1.12  1.13 | Reference (0.83-1.51)  (0.73-1.74) |  |
| **rs2687201** |  |  |  |  |  |  | **0.019** |
| C/C  A/C  A/A | FOXP1 | (9) | 179  190  52 | 204  144  45 | 1.00  0.65  0.78 | Reference (0.48-0.88)  (0.50-1.23) |  |
| **rs3005897** |  |  |  |  |  |  | 0.45 |
| C/C  C/T  T/T |  | (9) | 214  175  35 | 181  172  43 | 1.00  1.13  1.33 | Reference (0.85-1.52)  (0.81-2.18) |  |
| **rs3111601** |  |  |  |  |  |  | 0.87 |
| T/T  C/T  C/C | FOXF1 | (19) | 190  186  53 | 181  171  47 | 1.00  0.97  0.89 | Reference (0.72-1.30)  (0.57-1.39) |  |
| **rs3784262** |  |  |  |  |  |  | 0.50 |
| T/T  C/T  C/C | ALDH1A2 | (9,13) | 135  207  86 | 113  204  82 | 1.00  1.21  1.17 | Reference (0.88-1.66)  (0.78-1.73) |  |
| **rs3897234** |  |  |  |  |  |  | 0.34 |
| T/T  C/T  C/C |  | (9) | 270  145  16 | 244  132  23 | 1.00  0.99  1.63 | Reference (0.74-1.33)  (0.84-3.17) |  |
| **rs4523255** |  |  |  |  |  |  | 0.93 |
| C/C  C/T  T/T | MFHAS1 | (13) | 166  200  65 | 151  191  58 | 1.00  1.06  1.01 | Reference (0.79-1.43)  (0.67-1.54) |  |
| **rs4611855** |  |  |  |  |  |  | 0.18 |
| C/C  C/T  T/T | OSBPL10 | (20,21) | 158  181  82 | 144  190  59 | 1.00  1.17  0.81 | Reference (0.86-1.59)  (0.54-1.22) |  |
| **rs4800353** |  |  |  |  |  |  | 0.93 |
| A/A  A/G  G/G | RNU7-17P,  GATA6-AS1 | (9) | 319  97  7 | 297  88  5 | 1.00  0.99  0.80 | Reference (0.71-1.37)  (0.25-2.58) |  |
| **rs4973786** |  |  |  |  |  |  | 0.24 |
| G/G  A/G  A/A | VENTXP4,  LRRC3B | (9,22) | 155  210  64 | 146  177  77 | 1.00  0.89  1.25 | Reference (0.66-1.21)  (0.83-1.87) |  |
| **rs576425** |  |  |  |  |  |  | 0.28 |
| C/C  C/T  T/T |  | (9) | 120  223  85 | 131  185  83 | 1.00  0.78  0.90 | Reference (0.56-1.07)  (0.61-1.33) |  |
| **rs6099816** |  |  |  |  |  |  | 0.35 |
| C/C  A/C  A/A | PMEPA1,  MIR4532 | (9,23) | 174  190  66 | 179  159  58 | 1.00  0.80  0.88 | Reference (0.60-1.08)  (0.58-1.33) |  |
| **rs6214** |  |  |  |  |  |  | 0.31 |
| C/C  C/T  T/T | IGF-1 | (24) | 165  206  58 | 157  176  68 | 1.00  0.90  1.24 | Reference (0.67-1.22)  (0.82-1.88) |  |
| **rs6449586** |  |  |  |  |  |  | 0.94 |
| T/T  C/T  C/C | RPS10P12,  ISL1 | (9,25) | 136  207  84 | 125  193  82 | 1.00  0.99  1.06 | Reference (0.72-1.35)  (0.71-1.56) |  |
| **rs6479527** |  |  |  |  |  |  | 0.87 |
| G/G  A/G  A/A | PTPDC1 | (9) | 107  220  98 | 103  204  91 | 1.00  0.93  0.91 | Reference (0.66-1.30)  (0.61-1.35) |  |
| **rs6848890** |  |  |  |  |  |  | 0.22 |
| C/C  C/T  T/T |  | (9) | 300  111  11 | 265  113  18 | 1.00  1.14  1.88 | Reference (0.83-1.56)  (0.87-4.09) |  |
| **rs6898743** |  |  |  |  |  |  | 0.19 |
| G/G  C/G  C/C | GHR | (24) | 243  159  27 | 250  122  26 | 1.00  0.76  0.93 | Reference (0.57-1.02)  (0.53-1.65) |  |
| **rs732392** |  |  |  |  |  |  | **0.023** |
| T/T  G/T  G/G | GALNT18 | (9) | 231  167  33 | 190  158  52 | 1.00  1.16  1.94 | Reference (0.87-1.56)  (1.20-3.14) |  |
| **rs7539542** |  |  |  |  |  |  | 0.45 |
| C/C  C/G  G/G | ADIPOR1 | (8,26) | 204  181  38 | 184  171  45 | 1.00  1.05  1.36 | Reference (0.78-1.40)  (0.84-2.21) |  |
| **rs7691721** |  |  |  |  |  |  | 0.82 |
| T/T  C/T  C/C |  | (27) | 217  177  34 | 190  171  35 | 1.00  1.07  1.15 | Reference (0.80-1.42)  (0.69-1.93) |  |
| **rs7835508** |  |  |  |  |  |  | 0.76 |
| T/T  C/T  C/C | PLEKHA2 | (9,28) | 157  207  64 | 148  180  67 | 1.00  0.93  1.07 | Reference (0.68-1.25)  (0.71-1.61) |  |
| **rs7904985** |  |  |  |  |  |  | 0.95 |
| G/G  A/G  A/A | GRID1 | (9) | 210  173  45 | 196  157  45 | 1.00  0.96  1.02 | Reference (0.72-1.29)  (0.65-1.62) |  |
| **rs8045253** |  |  |  |  |  |  | 0.87 |
| T/T  C/T  C/C | FOXF1,  LINC00917,  AC092327.1,  LOC732275 | (29) | 154  209  64 | 136  202  60 | 1.00  1.08  1.02 | Reference (0.80-1.47)  (0.67-1.57) |  |
| **rs822395** |  |  |  |  |  |  | 0.37 |
| A/A  A/C  C/C | ADIPOQ,  ADIPOR1 | (8,14) | 171  206  45 | 173  176  46 | 1.00  0.83  1.05 | Reference (0.62-1.11)  (0.66-1.68) |  |
| **rs822396** |  |  |  |  |  |  | 0.47 |
| A/A  A/G  G/G | ADIPOQ,  ADIPOR1 | (8,14) | 263  145  20 | 260  122  16 | 1.00  0.85  0.77 | Reference (0.63-1.15)  (0.39-1.52) |  |
| **rs889838** |  |  |  |  |  |  | 0.30 |
| G/G  A/G  A/A |  | (9) | 141  216  73 | 128  187  85 | 1.00  0.95  1.28 | Reference (0.70-1.30)  (0.86-1.90) |  |
| **rs917997** |  |  |  |  |  |  | 0.82 |
| C/C  C/T  T/T | SLC9A4,  IL18RAP,  IL1R1 | (16,30) | 259  141  31 | 238  137  25 | 1.00  1.04  0.87 | Reference (0.78-1.40)  (0.50-1.52) |  |
| **rs9257809** |  |  |  |  |  |  | 0.70 |
| A/A  A/G  G/G | TRNAI25 | (31) | 375  49  3 | 341  55  3 | 1.00  1.19  1.00 | Reference (0.79-1.81)  (0.20-4.98) |  |
| **rs9837992** |  |  |  |  |  |  | 0.19 |
| G/G  A/G  A/A | MITF,  FOXP1,  EIF4E3 | (18) | 175  195  58 | 186  160  46 | 1.00  0.77  0.76 | Reference (0.58-1.04)  (0.49-1.19) |  |
| **rs9936833** |  |  |  |  |  |  | 0.70 |
| T/T  C/T  C/C | LINC00917, FENDRR | (31) | 156  201  70 | 155  176  70 | 1.00  0.88  0.96 | (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 CA  REF | 131 CO, 127 CA  OR=0.87  95%CI= 0.52-1.44 |
| High unweighted GRSB | 65 CO, 60 CA  OR=0.89  95%CI= 0.48-1.64 | 64 CO, 82 CA  OR=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 CA  REF | 119 CO, 122 CA  OR=1.08  95%CI= 0.64-1.80 |
| High unweighted GRSB | 71 CO, 62 CA  OR=1.12  95%CI= 0.63-2.01 | 58 CO, 81 CA  OR=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 CA  REF | 58 CO, 106 CA  OR=1.89  95%CI= 1.17-3.08 |
| High unweighted GRSB | 49 CO, 40 CA  OR=1.04  95%CI= 0.59-1.81 | 21 CO, 63 CA  OR=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 CA  REF | 112 CO, 98 CA  OR=1.47  95%CI= 0.84-2.58 |
| High GRSC | 76 CO, 95 CA  OR=2.71  95%CI= 1.49-5.01 | 86 CO, 116 CA  OR=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 CA  REF | 106 CO, 90 CA  OR=1.22  95%CI= 0.70-2.12 |
| High GRSC | 89 CO, 95 CA  OR=2.11  95%CI= 1.21-3.71 | 72 CO, 117 CA  OR=2.40  95%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 CA  REF | 49 CO, 78 CA  OR=2.27  95%CI= 1.33-3.92 |
| High GRSC | 54 CO, 62 CA  OR=2.02  95%CI= 1.17-3.52 | 31 CO, 92 CA  OR=4.67  95%CI= 2.64-8.44 |

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

P-interaction = 0.78

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