**Supplementary Table S1. Comparing characteristics of the study subjects from two medical centers**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 　 | KMUH | 　 | CCH | 　 |
| variable | case | control | 　 | case | control | 　 |
| 　 | N=285 | N=331 | P-value | N=162 | N=249 | P-value |
| Male, N (%) | 270(94.7) | 322(97.3) | 0.1037 | 160(98.7) | 243(97.3) | 0.4681 |
| Age, year (SD) | 53.8(13.7) | 51.2(10.4) | 0.01 | 61.1(8.9) | 51.6(12.8) | <.0001 |
| Tumor Stage, N (%) |  |  |  |  |  |  |
| I  | 97(34.5) |  |  | 22(37.9) |  | 0.6109 |
| II  | 32(11.4) |  |  | 7(12.1) |  |  |
| III  | 55(19.6) |  |  | 7(12.1) |  |  |
| IV  | 97(34.5) |  |  | 22(37.9) |  |  |
| Cigarette, N (%) |  |  |  |  |  |  |
| None | 39(13.7) | 176(53.2) | <.0001 | 16(9.5) | 122(49.0) | <.0001 |
| Ever | 110(38.6) | 58(17.5) |  | 103(61.5) | 50(20.1) |  |
| Current | 136(47.7) | 97(29.3) |  | 43(29.0) | 77(30.9) |  |
| Alcohol, N (%) |  |  |  |  |  |  |
| None | 92(32.3) | 260(78.6) | <.0001 | 32(19.6) | 174(69.9) | <.0001 |
| Ever | 94(33.0) | 21(6.3) |  | 97(58.1) | 19(7.6) |  |
| Current | 99(34.7) | 50(15.1) |  | 33(22.3) | 56(22.5 |  |
| BQ Chewing, N (%) |  |  |  |  |  |  |
| None | 51(17.9) | 311(93.9) | <.0001 | 24(14.9) | 194(77.9) | <.0001 |
| Ever | 194(68.1) | 20(6.1) |  | 109(65.5) | 37(14.9) |  |
| Current | 40(14.0) | 0(0) | 　 | 29(19.6) | 18(7.2) | 　 |

Abbreviations: KMUH:Kaohsiung Medical University Hospital; CCH: Changhua Christian Hospital.

aOSCC and control were recruited from the southern Taiwan(n=616)

bOSCC and control were recruited from the middle of Taiwan(n=411).

**Supplementary Table S2**. **Association of selected SNPs within 13 betel related candidate genes in all OSCC cases and controls.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP ID | Gene | Role | Alleles | case | control | ＊P-value | ＋P-value | ＆P-value |
| rs2070833 | BRCA1 | Intron | A/C | 277 | 280 | 0.0794  | 0.0294  | 0.0257  |
| rs3737559 | BRCA1 | Intron | A/G | 277 | 280 | 0.2120  | 0.4411  | 0.4307  |
| rs8176199 | BRCA1 | Intron | A/C | 278 | 279 | 0.8834  | 0.6818  | 0.6811  |
| rs1406844 | COL9A1 | Intron | C/T | 277 | 280 | 0.4344  | 0.9119  | 0.9125  |
| rs3806091 | COL9A1 | Intron | A/G | 274 | 274 | 0.4280  | 0.2698  | 0.2884  |
| rs3828777 | COL9A1 | Intron | A/G | 277 | 281 | 0.4902  | 0.2939  | 0.2977  |
| rs495558 | COL9A1 | Intron | G/T | 276 | 280 | 0.4100  | 0.1981  | 0.2098  |
| rs518558 | COL9A1 | Intron | A/G | 276 | 279 | 0.1467  | 0.0521  | 0.0544  |
| rs544179 | COL9A1 | Intron | A/G | 278 | 281 | 0.2466  | 0.1056  | 0.1070  |
| rs550675 | COL9A1 | Intron | C/T | 278 | 281 | 0.0174  | 0.0061  | 0.0050  |
| rs616621 | COL9A1 | Intron | A/G | 279 | 280 | 0.8777  | 0.6015  | 0.6215  |
| rs679521 | COL9A1 | Intron | C/G | 278 | 279 | 0.7010  | 0.4027  | 0.4057  |
| rs9455009 | COL9A1 | Intron | C/G | 278 | 280 | 0.7238  | 0.4787  | 0.4812  |
| rs9455039 | COL9A1 | Promoter | A/T | 273 | 273 | 0.9055  | 0.6436  | 0.6568  |
| rs997953 | COL9A1 | Downstream | A/G | 277 | 280 | 0.0046  | 0.8264  | 0.8268  |
| rs1846158 | COL9A2 | Intron | C/T | 276 | 278 | 0.8640  | 0.7128  | 0.7148  |
| rs209918 | COL9A2 | Intron | C/T | 275 | 279 | 0.9393  | 0.7236  | 0.7244  |
| rs2273195 | COL9A2 | Intron | G/T | 240 | 253 | 0.5789  | 0.6093  | 0.5789  |
| rs1097134 | DNAJA1 | Promoter | A/G | 279 | 280 | 0.6882  | 0.9068  | 0.9063  |
| rs3758276 | DNAJA1 | Promoter | C/T | 278 | 280 | 0.6925  | 0.8917  | 0.8896  |
| rs4879658 | DNAJA1 | Intron | C/T | 275 | 279 | 0.6525  | 0.9949  | 0.9948  |
| rs1054564 | GDF15 | 3' UTR | C/G | 279 | 279 | 0.9830  | 0.8764  | 0.8747  |
| rs1041889 | HDGFRP | Promoter | C/T | 274 | 279 | 0.4954  | 0.7084  | 0.7006  |
| rs1042112 | HDGFRP | Promoter | C/T | 262 | 266 | 0.3719  | 0.1959  | 0.3591  |
| rs2822638 | HSPA13 | 3' UTR | C/T | 277 | 277 | 0.8053  | 0.4996  | 0.5139  |
| rs2822641 | HSPA13 | Intron | A/C | 277 | 279 | 0.0389  | 0.0134  | 0.0119  |
| rs2822644 | HSPA13 | Intron | G/T | 274 | 278 | 0.8854  | 0.7068  | 0.7015  |
| rs2822648 | HSPA13 | Intron | A/G | 277 | 280 | 0.5049  | 0.2550  | 0.2503  |
| rs7282521 | HSPA13 | Downstream | C/T | 184 | 172 | 0.8349  | 0.6632  | 0.7571  |
| rs2072744 | MAOA | Intron | A/G | 277 | 275 | 0.9396  | 0.9361  | 0.9544  |
| rs2283725 | MAOA | Intron | A/G | 274 | 271 | 0.6013  | 0.3410  | 0.4937  |
| rs4301558 | MAOA | Promoter | A/C | 278 | 280 | 0.6880  | 0.4897  | 0.6197  |
| rs5906883 | MAOA | Intron | A/C | 156 | 163 | 0.6791  | 0.4231  | 0.5661  |
| rs522616 | MMP3 | Promoter | A/G | 276 | 280 | 0.6435  | 0.6219  | 0.6167  |
| rs605949 | MMP3 | Downstream | C/T | 278 | 280 | 0.6661  | 0.6757  | 0.6661  |
| rs139994842 | NOTCH1 | Exon | A/G | 277 | 279 | 0.0466  | 0.0493  | 0.0466  |
| rs200699541 | NOTCH1 | Exon | C/T | 278 | 280 | 0.3186  | 0.3188  | 0.3186  |
| rs201174576 | NOTCH1 | Exon | G/T | 282 | 280 | 0.1551  | 0.1555  | 0.1551  |
| rs1119064 | PTGS2 | Promoter | A/G | 278 | 278 | 0.3459  | 0.3560  | 0.3459  |
| rs689466 | PTGS2 | Promoter | A/G | 278 | 280 | 0.9076  | 0.6675  | 0.6619  |
| rs1165705 | CHAF1A | Downstream | G/T | 278 | 280 | 0.6060  | 0.3725  | 0.3683  |
| rs3006475 | S100A1 | Downstream | A/C | 277 | 281 | 0.2303  | 0.1894  | 0.1806  |
| rs243402 | SH3GL1 | Intron | G/T | 275 | 279 | 0.0541  | 0.5718  | 0.5603  |
| rs243404 | SH3GL1 | Intron | C/T | 275 | 279 | 0.7011  | 0.4801  | 0.4764  |
| rs73234 | SH3GL1 | Intron | C/G | 275 | 280 | 0.1810  | 0.3095  | 0.3058  |
| rs2233678 | UBL5 | Downstream | C/G | 279 | 280 | 0.3667  | 0.3711  | 0.3667  |
| rs2233679 | UBL5 | Downstream | C/T | 276 | 280 | 0.4252  | 0.3359  | 0.3296  |
| rs1044510 | UBXN6 | Coding exon | A/G | 274 | 276 | 0.7809  | 0.7420  | 0.7414  |
| rs932276 | UBXN6 | Downstream | A/G | 277 | 280 | 0.0369  | 0.6931  | 0.6906  |
| rs1130214 | CHAF1B | Promoter | G/T | 277 | 281 | 0.9883  | 0.9012  | 0.9039  |

＊Genotype test, ＋allele test, ＆trend test

**Supplementary Table S3. Interaction between GRSs and consuming quantities of betel nut**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| GRSs | Betel nut use | Case | control | aOR(95%CI)＊  |  |
| 0 | 0 | 24 | 184 | 1 |  |
| 0 | 1--10 | 32 | 12 | 20.44(9.29-44.96) |  |
| 0 | 10<  | 50 | 10 | 38.33(17.20-85.41) |  |
| 1--3 | 0 | 41 | 313 | 1.14(0.59-.172) |  |
| 1--3 | 1--10 | 119 | 23 | 39.67(21.41-73.49) |  |
| 1--3 | 10<  | 166 | 29 | 43.88(24.59-78.39) |  |
| 4 | 0 | 4 | 8 | 3.83(1.07-13.69) |  |
| 4 | 1--10 | 1 | 0 | 47.44(5.70-394.69) |  |
| 4 | 10<  | 10 | 1 | 76.67(9.39-625.55) |  |

GRS: genetic risk scores.

＊Odds ratios were adjusted for continuous age in a stratified analysis.

**Supplementary Table S4. Associations between tumor stage, GRS and BQ chewing.**

|  |  |  |
| --- | --- | --- |
|  | **Tumor stage** |  |
| **Variables** | **Mean(SD)** | **P for tend** |
| BQ chewing |  |  |
| **No** | 0.26(0.83) | <0.001 |
| **Yes** | 2.03(1.57) |  |
| Genetic risk score  |  |  |
| 0 | 0.72(1.33) | 0.05  |
| 1--3 | 0.99(1.47) |  |
| 4 | 1.53(1.76) | 　 |

We used generalized linear model (GLM) to analyze relations among the tumor stage, Genetic risk score (GRS) and BQ chewing. GRS (*P* =0.05) and BQ chewing (*P* < .01) were found to be associated with oral cancer stage.

**Supplementary Figure S1**. Comparison of areas under the ROC curves of early and advanced stage oral cancer sensitivity and specificity. GRS has higher AUC for early stage oral cancer than advanced stage oral cancer. However, BQ chewing has higher AUC for advanced stage oral cancer than early stage oral cancer.