**Pan-cancer DNA methylation signature quantification of lifestyle exposures and cancer prognosis**

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**SUPPLEMENTAL TABLES**

*S***upplemental Table S1**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Cancer  | Age median (± IQR) | Gender female/male | OS Events | TNM stage I/II/III/IV/NA | Follow-up time in days median (± IQR) | Alcohol 1 median (± IQR)  | BMI 1 median (± IQR)  | Smoking 1 median (± IQR)  |
| BLCA | 69 (60 - 76) | 107/302 | 181 | 2/131/139/135/2 | 536 (331 - 979) | -0.5 (-0.9 ~ -0.1) | -0.5 (-1.3 ~ -0.1) |  0.1 (-0.4 ~ 0.6) |
| BRCA | 58 (48 - 67) | 765/9 | 101 | 124/431/197/11/11 | 825 (492 - 1673) | -1.0 (-1.4- ~ -0.5) | -0.2 (-0.8 ~ 0.4) |  0.2 (-0.4 ~ 0.7) |
| CESC | 47 (38 - 56) | 299/0 | 67 | 0/0/0/0/299 | 636 (352 - 1243) | -0.4 (-0.9 ~ 0.3) | -0.3 (-1.0 ~ 0.2) | -0.1 (-0.8 ~ 0.5) |
| CHOL | 66 (56 - 72) | 20/16 | 18 | 19/9/1/7/0 | 645 (373 - 1173) | -0.3 ( -0.8 ~ 0.0) |  0.0 (-0.7 ~ 1.1) | -0.8 (-1.3 ~ -0.4) |
| COAD | 67 (55 - 75) | 133/157 | 69 | 44/114/82/40/10 | 670 (383 - 1173) | -0.6 (-1.0 ~ -0.2) |  0.2 (-0.1 ~ 0.5) | -0.2 (-0.8 ~ 0.3) |
| DLBC | 57 (46 - 67) | 25/22 | 9 | 0/0/0/0/47 | 791 (409 - 1477) | -0.8 (-1.3 ~ -0.4) | -0.8 (-1.2 ~ -0.3) | -0.2 (-0.6 ~ 0.4) |
| ESCA | 60 (53 - 72) | 26/148 | 68 | 18/79/55/8/14 | 401 (236 - 690) | -0.6 (-1.0 ~ -0.1) |  0.2 (-0.3 ~ 0.7) | -0.8 (-1.2 ~ 0.1) |
| GBM | 61 (52 - 70) | 54/70 | 82 | 0/0/0/0/124 | 276 (145 - 526) |  0.4 (0.0 ~ 0.8) |  1.0 (0.6 ~ 1.3) |  0.1 (-0.2 ~ 0.4) |
| HNSC | 61 (53 - 69) | 141/382 | 219 | 26/74/82/267/74 | 645 (378 - 1182) | -0.5 (-0.9 ~ -0.1) | -0.6 (-1.2 ~ -0.1) |  0.1 (-0.4 ~ 0.6) |
| KICH | 50 (42 - 61) | 27/39 | 10 | 21/25/14/6/0 | 2248 (920 - 3068) |  0.6 (-0.1 ~ 1.0) |  0.4 (-0.2 ~ 0.9) |  0.8 (-0.2 ~ 1.7) |
| KIRC | 61 (53 - 70) | 112/204 | 105 | 153/31/72/58/2 | 1091 (407 - 2005) |  0.3 (0.0 ~ 0.8) |  0.8 (0.3 ~ 1.0) |  0.4 (-0.1 ~ 1.1) |
| KIRP | 62 (54 - 71) | 73/201 | 40 | 167/18/51/14/24 | 744 (404 - 1498) |  0.5 (0.1 ~ 0.9) | -0.2 (-0.7 ~ 0.3) |  0.0 (-0.4 ~ 1.0) |
| LGG | 41 (33 - 53) | 225/279 | 124 | 0/0/0/0/504 | 656 (400 - 1224) |  0.0 (-0.5 ~ 0.6) |  0.7 (0.4 ~ 0.9) |  0.1 (-0.2 ~ 0.3) |
| LIHC | 61 (51 - 69) | 121/254 | 131 | 175/87/84/5/24 | 595 (328 - 1090) |  0.6 (0.0 ~ 1.3) |  1.5 (0.9 ~ 1.9) |  0.2 (-0.7 ~ 1.2) |
| LUAD | 66 (59 - 72) | 243/212 | 163 | 247/111/73/20/4 | 642 (415 - 1092) |  0.6 (0.2 ~ 0.9) |  0.2 (0.0 ~ 0.6) |  0.4 (-0.2 ~ 0.9) |
| LUSC | 69 (62 - 74) | 95/270 | 157 | 169/133/56/4/3 | 666 (373 - 1263) |  0.1 (-0.3 ~ 0.5) |  0.0 (-0.4 ~ 0.5) | -0.3 (-0.9 ~ 0.3) |
| OV | 60 (55 - 66) | 10/0 | 5 | 0/0/0/0/10 | 498 (318 - 972) |  0.3 (0.1 ~ 1.3) |  0.2 (-0.6 ~ 0.2) | -0.9 (-1.2 ~ 0.1) |
| PAAD | 65 (57 - 73) | 82/102 | 99 | 21/151/4/5/3 | 467 (277 - 678) | -0.4 (-0.7 ~ -0.2) | -0.1 (-0.4 ~ 0.3) | -0.6 (-1.0 ~ - 0.1) |
| PRAD | 61 (56 - 66) | 0/484 | 9 | 0/0/0/0/484 | 916 (523 - 1461) | -0.2 (-0.5 ~ 0.1) |  0.2 (-0.2 ~ 0.6) | -0.8 (-1.0 ~ -0.5) |
| READ | 64 (57 - 72) | 43/51 | 16 | 9/29/35/12/9 | 690 (420 - 1143) | -0.5 (-1.0 ~ -0.1) |  0.4 (0.1 ~ 0.6) | -0.2 (-0.7 ~ 0.4) |
| STAD | 66 (58 - 72) | 135/258 | 151 | 52/125/173/32/11 | 447 (273 - 786) | -0.6 (-1.0 ~ -0.2) |  0.3 (-0.2 ~ 0.6) | -0.5 (-1.0 ~ -0.1) |
| THCA | 46 (35 - 58) | 367/135 | 16 | 283/52/112/53/2 | 945 (542 - 1504) |  1.7 (1.3 ~ 2.1) | -0.8 (-1.3 ~ -0.1) | -0.2 (-0.7 ~ 0.3) |
| UCEC | 64 (57 - 71) | 425/0 | 71 | 0/0/0/0/425 | 763 (450 - 1225) |  0.7 (0.1 ~ 1.3) |  0.2 (-0.3 ~ 0.7) | -0.2 (-0.8 ~ 0.5) |
| UCS | 68 (62 - 76) | 57/0 | 35 | 0/0/0/57 | 611 (371 - 979) |  0.4 (-0.1 ~ 1.0) |  0.5 (0.0 ~ 1.2) | -0.4 (-0.8 ~ 0.3) |

Abbreviations: body mass index (BMI), deoxyribonucleic acid methylation (DNAm), interquartile range (IQR), not applicable (NA) and tumour-node-metastasis (TNM); OS = overall survival.

1 DNAm exposure z-scores

**Supplementary Table S2**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Cancer | N | Rsquared - Alcohol | Logrank-P - Alcohol | Rsquared - BMI | Logrank-P - BMI | Rsquared - smoking | Logrank-P - smoking |
| BLCA | 409 | 0.107 | 2.62E-09 | 0.098 | 3.94E-09 | 0.095 | 8.36E-09 |
| BRCA | 774 | 0.056 | 6.76E-09 | 0.070 | 5.72E-12 | 0.052 | 6.37E-09 |
| CESC | 299 | 0.040 | 1.69E-02 | 0.037 | 1.23E-02 | 0.038 | 9.95E-03 |
| CHOL | 36 | 0.075 | 5.93E-01 | 0.024 | 8.35E-01 | 0.037 | 7.15E-01 |
| COAD | 290 | 0.086 | 4.35E-05 | 0.085 | 1.67E-05 | 0.086 | 1.33E-05 |
| DLBC | 47 | 0.175 | 9.55E-02 | 0.063 | 4.48E-01 | 0.174 | 4.91E-02 |
| ESCA | 174 | 0.123 | 1.96E-04 | 0.099 | 5.67E-04 | 0.099 | 5.77E-04 |
| GBM | 124 | 0.222 | 8.29E-07 | 0.215 | 3.01E-07 | 0.212 | 3.85E-07 |
| HNSC | 523 | 0.032 | 1.92E-03 | 0.025 | 4.55E-03 | 0.024 | 4.89E-03 |
| KICH | 66 | 0.198 | 6.33E-03 | 0.212 | 1.47E-03 | 0.192 | 3.09E-03 |
| KIRC | 316 | 0.222 | 3.12E-16 | 0.202 | 2.61E-15 | 0.219 | 1.02E-16 |
| KIRP | 274 | 0.170 | 1.45E-09 | 0.139 | 3.13E-08 | 0.139 | 2.99E-08 |
| LGG | 504 | 0.145 | 6.35E-17 | 0.113 | 7.93E-14 | 0.114 | 6.43E-14 |
| LIHC | 375 | 0.070 | 4.34E-05 | 0.066 | 2.52E-05 | 0.066 | 2.62E-05 |
| LUAD | 455 | 0.063 | 1.12E-05 | 0.056 | 1.75E-05 | 0.056 | 1.75E-05 |
| LUSC | 365 | 0.042 | 4.84E-03 | 0.031 | 1.13E-02 | 0.040 | 2.43E-03 |
| OV | 10 | 0.532 | 1.08E-01 | 0.386 | 1.81E-01 | 0.181 | 5.73E-01 |
| PAAD | 184 | 0.039 | 1.30E-01 | 0.118 | 4.49E-05 | 0.035 | 9.02E-02 |
| PRAD | 484 | 0.010 | 1.99E-01 | 0.002 | 6.32E-01 | 0.007 | 1.81E-01 |
| READ | 94 | 0.138 | 1.33E-02 | 0.161 | 1.84E-03 | 0.136 | 5.98E-03 |
| STAD | 393 | 0.082 | 1.95E-06 | 0.064 | 1.68E-05 | 0.075 | 1.99E-06 |
| THCA | 502 | 0.099 | 1.26E-10 | 0.093 | 1.31E-10 | 0.097 | 5.02E-11 |
| UCEC | 425 | 0.110 | 5.39E-10 | 0.109 | 1.43E-10 | 0.109 | 1.42E-10 |
| UCS | 57 | 0.152 | 5.15E-02 | 0.161 | 1.83E-02 | 0.151 | 2.51E-02 |

Supplementary Table 3

|  |  |  |  |
| --- | --- | --- | --- |
| **Alcohol** |  |  |  |
| Cancer  | Multivariable - survival (Age+stage) | Multivariable - survival (Age+stage+Response) |
|   | HR (95% CI) | P-value  | N  | HR (95% CI) | P-value  | N  |
| BLCA | **1.30 (1.00 - 1.60)** | **0.02** | 407 | 1.26 (1.00 - 1.58) | 0.049 | 407 |
| BRCA | 1.30 (0.97 - 1.70) | 0.087 | 763 | NA | NA | NA |
| CESC | 1.10 (0.86 - 1.40) | 0.4 | 292 | 1.26 (0.93 - 1.71) | 0.134 | 292 |
| CHOL | 1.70 (0.70 - 4.10) | 0.24 | 36 | NA | NA | NA |
| COAD | 1.00 (0.67 - 1.60) | 0.92 | 280 | 0.86 (0.39 - 1.89) | 0.708 | 280 |
| DLBC | 1.20 (0.25 - 5.60) | 0.84 | 41 | 1.66 (0.32 - 8.69) | 0.547 | 41 |
| ESCA | **1.50 (1.00 - 2.10)** | **0.03** | 168 | 1.33 (0.74 - 2.4) | 0.340 | 168 |
| GBM | 1.20 (0.88 - 1.70) | 0.23 | 124 | NA | NA | NA |
| HNSC | **1.30 (1.00 - 1.60)** | **0.042** | 523 | 0.99 (0.77 - 1.27) | 0.943 | 523 |
| KICH | 0.79 (0.41 - 1.50) | 0.5 | 66 | NA | NA | NA |
| KIRC | 0.83 (0.60 - 1.20) | 0.27 | 314 | 0.65 (0.17 - 2.44) | 0.521 | 314 |
| KIRP | **0.47 (0.29 - 0.76)** | **\*** | 256 | 0.52 (0.28 - 0.95) | 0.033 | 256 |
| LGG | **1.60 (1.30 - 1.90)** | **\*\*\*** | 504 | NA | NA | NA |
| LIHC | 1.10 (0.92 - 1.40) | 0.24 | 351 | NA | NA | NA |
| LUAD | 0.79 (0.61 - 1.00) | 0.064 | 451 | 0.82 (0.61 - 1.1) | 0.177 | 451 |
| LUSC | 1.10 (0.87 - 1.40) | 0.46 | 362 | 1.11 (0.83 - 1.5) | 0.480 | 362 |
| OV | 7.10 (0.98 - 52.00) | 0.052 | 10 | NA | NA | NA |
| PAAD | 1.20 (0.81 - 1.60) | 0.43 | 181 | 1.17 (0.78 - 1.77) | 0.444 | 181 |
| PRAD | 1.90 (0.59 - 6.50) | 0.28 | 484 | NA | NA | NA |
| READ | 0.75 (0.19 - 2.90) | 0.68 | 85 | NA | NA | NA |
| STAD | 1.30 (0.96 - 1.60) | 0.1 | 382 | 1.36 (1.05 - 1.76) | 0.021 | 382 |
| THCA | 0.59 (0.23 - 1.50) | 0.27 | 500 | NA | NA | NA |
| UCEC | 1.10 (0.83 - 1.40) | 0.56 | 425 | 0.92 (0.7 - 1.21) | 0.560 | 425 |
| UCS | 1.10 (0.67 - 1.70) | 0.79 | 57 | 1.19 (0.74 - 1.89) | 0.473 | 57 |
| **BMI** |  |  |  |
| Cancer | Multivariable - survival (Age+stage) | Multivariable - survival (Age+stage+Response) |
|   | HR (95% CI) | P-value  | N  | HR (95% CI) | P-value  | N  |
| BLCA  | **1.20 (1.00 - 1.40)** | **0.015** | 407 | 1.14 (0.95 - 1.35) | 0.149 | 407 |
| BRCA1 | 1.84 (0.95 - 3.55) | 0.07 | 165 | NA | NA | NA |
| BRCA2 | **1.44 (1.06 - 1.96)** | **0.018** | 492 | NA | NA | NA |
| CESC | 0.96 (0.73 - 1.30) | 0.78 | 292 | 0.98 (0.68 - 1.41) | 0.911 | 292 |
| CHOL | 1.10 (0.72 - 1.80) | 0.57 | 36 | NA | NA | NA |
| COAD | 0.86 (0.57 - 1.30) | 0.47 | 280 | 0.64 (0.35 - 1.15) | 0.136 | 280 |
| DLBC | 0.95 (0.38 - 2.40) | 0.92 | 41 | 1.18 (0.31 - 4.54) | 0.811 | 41 |
| ESCA | 1.10 (0.75 - 1.50) | 0.77 | 168 | 0.86 (0.51 - 1.44) | 0.557 | 168 |
| GBM  | 0.82 (0.49 - 1.40) | 0.45 | 124 | NA | NA | NA |
| HNSC | 1.00 (0.89 - 1.20) | 0.57 | 523 | 1 (0.83 - 1.2) | 0.991 | 523 |
| KICH | 2.00 (0.67 - 5.80) | 0.22 | 66 | NA | NA | NA |
| KIRC | 0.84 (0.63 - 1.10) | 0.26 | 314 | 0.34 (0.09 - 1.37) | 0.129 | 314 |
| KIRP | 0.91 (0.61 - 1.40) | 0.65 | 256 | 0.52 (0.3 - 0.89) | 0.018 | 256 |
| LGG | 1.10 (0.72 - 1.60) | 0.74 | 504 | NA | NA | NA |
| LIHC | 0.96 (0.77 - 1.20) | 0.68 | 351 | NA | NA | NA |
| LUAD | 0.96 (0.72 - 1.30) | 0.8 | 451 | 0.89 (0.64 - 1.23) | 0.475 | 451 |
| LUSC  | 0.92 (0.72 - 1.20) | 0.47 | 362 | 0.84 (0.63 - 1.13) | 0.247 | 362 |
| OV | 12.00 (0.93 - 150) | 0.057 | 10 | NA | NA | NA |
| PAAD | **2.10 (1.50 - 3.00)** | **\*\*\*** | 181 | 2.01 (1.34 - 3.01) | 0.001 | 181 |
| PRAD | 0.76 (0.32 - 1.80) | 0.54 | 484 | NA | NA | NA |
| READ | 3.00 (0.78 - 11.00) | 0.11 | 85 | NA | NA | NA |
| STAD | 1.20 (0.91 - 1.50) | 0.25 | 382 | 0.99 (0.77 - 1.27) | 0.922 | 382 |
| THCA | 1.40 (0.74 - 2.60) | 0.31 | 500 | NA | NA | NA |
| UCEC | 1.00 (0.76 - 1.40) | 0.86 | 425 | 0.89 (0.64 - 1.23) | 0.472 | 425 |
| UCS | 1.20 (0.80 - 1.90) | 0.34 | 57 | 1.35 (0.83 - 2.18) | 0.223 | 57 |
| **Smoking** |  |  |  |
| Cancer | Multivariable - survival (Age+stage) | Multivariable - survival (Age+stage+Response) |
|   | HR (95% CI) | P-value  | N | HR (95% CI) | P-value  | N  |
| BLCA  | **1.20 (1.00 - 1.50)** | **0.034** | 407 | 1.36 (1.11 - 1.67) | 0.003 | 407 |
| BRCA | 0.96 (0.76 - 1.20) | 0.74 | 763 | NA | NA | NA |
| CESC | 1.10 (0.84 - 1.50) | 0.46 | 292 | 1.28 (0.89 - 1.82) | 0.179 | 292 |
| CHOL | 1.50 (0.65 - 3.20) | 0.36 | 36 | NA | NA | NA |
| COAD | 0.86 (0.63 - 1.20) | 0.32 | 280 | 0.65 (0.38 - 1.12) | 0.120 | 280 |
| DLBC | **2.70 (1.10 - 6.50)** | **0.028** | 41 | 3.1 (1.3 - 7.39) | 0.011 | 41 |
| ESCA | 0.97 (0.74 - 1.30) | 0.82 | 168 | 0.93 (0.61 - 1.42) | 0.727 | 168 |
| GBM  | 0.95 (0.65 - 1.40) | 0.77 | 124 | NA | NA | NA |
| HNSC | 1.00 (0.87 - 1.20) | 0.68 | 523 | 1.07 (0.86 - 1.32) | 0.548 | 523 |
| KICH | 0.99 (0.55 - 1.80) | 0.98 | 66 | NA | NA | NA |
| KIRC | **0.70 (0.54 - 0.90)** | **\*** | 314 | 0.58 (0.21 - 1.58) | 0.288 | 314 |
| KIRP | 0.90 (0.62 - 1.30) | 0.59 | 256 | 0.8 (0.51 - 1.26) | 0.337 | 256 |
| LGG | 1.10 (0.81 - 1.60) | 0.46 | 504 | NA | NA | NA |
| LIHC | 1.00 (0.88 - 1.20) | 0.76 | 351 | NA | NA | NA |
| LUAD | 0.97 (0.80 - 1.20) | 0.8 | 451 | 1.02 (0.81 - 1.28) | 0.858 | 451 |
| LUSC  | **1.20 (1.00 - 1.50)** | **0.049** | 362 | 1.2 (0.96 - 1.49) | 0.102 | 362 |
| OV | 170 (0.21 - 15000) | 0.13 | 10 | NA | NA | NA |
| PAAD | 1.30 (0.94 - 1.80) | 0.12 | 181 | 0.89 (0.62 - 1.28) | 0.531 | 181 |
| PRAD | 0.26 (0.05 - 1.40) | 0.12 | 484 | NA | NA | NA |
| READ | 1.00 (0.60 - 1.70) | 0.99 | 85 | NA | NA | NA |
| STAD | **1.30 (1.10 - 1.70)** | **0.016** | 382 | 1.2 (0.96 - 1.51) | 0.114 | 382 |
| THCA | 0.49 (0.21 - 1.10) | 0.099 | 500 | NA | NA | NA |
| UCEC | 1.00 (0.79 - 1.30) | 0.84 | 425 | 1.16 (0.86 - 1.55) | 0.326 | 425 |
| UCS | 1.10 (0.75 - 1.60) | 0.64 | 57 | 1.67 (1.02 - 2.73) | 0.041 | 57 |