Supplementary table 1. Hazard ratios (95% CI) for the incidence of total cancer and cancer types by quartile of serum β-2-microglobulin (B2M), ARIC, 1990–2006

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Cancer | No. of cases | Quartiles of B2M (mg/L) | | | | |
| ≤1.66 | 1.67-1.88 | 1.89-2.15 | ≥2.16 | *P-trend* |
| Total cancer  Model 3a  Model 4b  Model 5c  Model 6d  Model 7e | 2,436 | 512  1 (reference)  1 (reference)  1 (reference)  1 (reference)  1 (reference) | 583  1.02 (0.90-1.16)  1.01 (0.89-1.16)  1.04 (0.91-1.19)  1.08 (0.93-1.24)  1.05 (0.92-1.21) | 659  1.20 (1.05-1.38)  1.18 (1.02-1.36)  1.24 (1.07-1.44)  1.29 (1.10-1.52)  1.15 (0.99-1.33) | 682  1.24 (1.05-1.47)  1.20 (1.01-1.42)  1.26 (1.06-1.51)  1.21 (0.96-1.51)  1.20 (1.00-1.43) | 0.002  0.008  0.002  0.004  0.03 |
| Colorectal cancer  Model 3  Model 4  Model 5  Model 6  Model 7 | 255 | 44  1 (reference)  1 (reference)  1 (reference)  1 (reference)  1 (reference) | 64  1.36 (0.89-2.09)  1.32 (0.86-2.02)  1.42 (0.91-2.08)  1.33 (0.85-2.08)  1.43 (0.91-2.25) | 77  1.90 (1.23-2.95)  1.80 (1.16-2.79)  1.95 (1.23-3.09)  1.80 (1.11-2.93)  1.84 (1.15-2.95) | 70  2.19 (1.31-3.68)  1.94 (1.14-3.28)  2.02 (1.15-3.54)  2.18 (1.18-4.04)  2.14 (1.23-3.74) | 0.001  0.006  0.01  0.004  0.05 |
| Lung cancer  Model 3  Model 4  Model 5  Model 6  Model 7 | 298 | 59  1 (reference)  1 (reference)  1 (reference)  1 (reference)  1 (reference) | 72  1.10 (0.75-1.62)  1.08 (0.73-1.59)  1.17 (0.78-1.75)  1.14 (0.74-1.74)  1.15 (0.76-1.76) | 66  0.98 (0.64-1.50)  0.94 (0.62-1.45)  0.94 (0.59-1.49)  1.10 (0.67-1.82)  0.95 (0.59-1.52) | 101  1.64 (1.03-2.60)  1.54 (0.96-2.46)  1.72 (1.04-2.83)  1.50 (0.82-2.77)  1.40 (0.83-2.34) | 0.06  0.11  0.08  0.29  0.34 |
| Breast cancer(women only)  Model 3\*f  Model 4\*  Model 5\*  Model 6\*  Model 7\* | 424 | 103  1 (reference)  1 (reference)  1 (reference)  1 (reference)  1 (reference) | 91  0.83 (0.57-1.21)  0.82 (0.56-1.19)  0.83 (0.55-1.23)  1.00 (0.66-1.50)  0.93 (0.62-1.40) | 103  1.14 (0.78-1.65)  1.06 (0.73-1.54)  1.22 (0.82-1.82)  1.32 (0.85-2.06)  1.10 (0.72-1.67) | 127  1.01 (0.78-1.65)  0.92 (0.58-1.45)  1.15 (0.70-1.87)  0.95 (0.50-1.82)  1.20 (0.74-1.96) | 0.59  0.95  0.29  0.53  0.36 |
| Prostate cancer  Model 3  Model 4  Model 5  Model 6  Model 7 | 524 | 119  1 (reference)  1 (reference)  1 (reference)  1 (reference)  1 (reference) | 153  1.12 (0.89-1.42)  1.16 (0.90-1.52)  1.17 (0.0-1.46)  1.23 (0.94-1.62)  1.14 (0.87-1.49) | 149  1.22 (0.92-1.63)  1.26 (0.94-1.67)  1.28 (0.96-1.70)  1.41 (1.03-1.94)  1.19 (0.88-1.60) | 103  0.95 (0.66-1.36)  1.02 (0.71-1.47)  1.04 (0.72-1.50)  0.58 (0.30-1.10)  0.93 (0.64-1.36) | 0.97  0.67  0.58  0.69  0.94 |
| Hematological cancers  Model 3  Model 4  Model 5  Model 6  Model 7 | 176 | 35  1 (reference)  1 (reference)  1 (reference)  1 (reference)  1 (reference) | 38  1.06 (0.62-1.79)  1.06 (0.62-1.80)  0.95 (0.55-1.64)  1.26 (0.71-2.23)  1.16 (0.67-2.01) | 43  1.17 (0.67-2.02)  1.17 (0.67-2.03)  1.06 (0.60-1.86)  1.13 (0.58-2.21)  1.13 (0.63-2.03) | 60  1.50 (0.80-2.80)  1.50 (0.80-2.84)  1.22 (0.64-2.36)  1.54 (0.67-3.58)  1.09 (0.54-2.18) | 0.19  0.19  0.47  0.44  0.87 |

aModel 3 – adjusted for age, sex, race, and study center, for education, BMI, smoking status and pack-years of smoking, use of aspirin, hormone replacement therapy (in women), and eGFR (i.e., all variables in Model 2, Table 2) and + WHR

bModel 4 – adjusted for all variables in Model 2 + log transformed hs-CRP

cModel 5 – adjusted for all variables in Model 2 and excluding people with hs-CRP >10 mg/ l, i.e. those with potential acute inflammation

dModel 6 – adjusted for all variables in Model 2 and excluding people with eGFR greater than 90 mL/min/1.73 m2, i.e., those with potential kidney dysfunction

eModel 7 – adjusted for all variables in Model 2 and excluding first three years of follow-up

fModel\* – adjusted for all variables in Model 2 + menopausal status, age at menarche, and number of live births

Supplementary table 2a. Hazard ratios(95% CI) a for colorectal cancer incidence in strata of select characteristics. ARIC, 1990–2006

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Characteristics | No. of cases/participants | Quartiles of B2M (mg/L) | | | | |
| ≤1.66 | 1.67-1.88 | 1.89-2.15 | ≥2.16 | *P-interaction* |
| Age  ≤60  >60 | 165/8,588  90/3,712 | 1 (reference)  1 (reference) | 1.46 (0.90-2.37)  0.99 (0.42-2.37) | 1.64 (0.96-2.78)  2.24 (1.00-5.02) | 2.00 (1.06-3.73)  2.44 (0.98-6.07) | 0.45 |
| Sex  Men  Women | 129/5,489  126/6,811 | 1 (reference)  1 (reference) | 1.57 (0.89-2.78)  1.19 (0.62-2.27) | 1.93 (1.05-3.56)  2.06 (1.09-3.86) | 2.50 (1.21-5.16)  2.13 (1.01-4.61) | 0.99 |
| Race  White  Black | 186/9,158  69/3,142 | 1 (reference)  1 (reference) | 1.88 (1.07-3.31)  0.84 (0.40-1.75) | 2.70 (1.52-4.80)  1.05 (0.47-2.35) | 2.75 (1.41-5.37)  1.87 (0.77-4.59) | 0.19 |
| Smoking  Ever  Never | 156/7,485  99/4,795 | 1 (reference)  1 (reference) | 1.26 (0.75-2.13)  1.54 (0.74-3.21) | 1.45 (0.83-2.53)  3.01 (1.46-6.19) | 1.78 (0.92-3.42)  3.16 (1.34-7.44) | 0.38 |
| BMI  Overweight  Non-overweight | 188/8,512  67/3,788 | 1 (reference)  1 (reference) | 1.49 (0.89-2.50)  1.08 (0.50-2.35) | 1.97 (1.16-3.34)  1.91 (0.87-4.20) | 2.34 (1.26-4.36)  1.87 (0.71-4.92) | 0.88 |
| Aspirin in last 2 weeks  Yes  No | 127/6,217  126/6,048 | 1 (reference)  1 (reference) | 1.16 (0.62-2.18)  1.58 (0.88-2.83) | 2.13 (1.15-3.95)  1.76 (0.95-3.29) | 1.92 (0.91-4.06)  2.51 (1.22-5.12) | 0.38 |
| HRT use (in women)  Yes  No | 34/1749  71/3,705 | 1 (reference)  1 (reference) | 0.67 (0.19-2.34)  1.55 (0.71-3.34) | 2.31 (1.05-5.09)  2.11 (0.74-5.99) | 2.33 (0.92-5.92)  1.89 (0.55-6.46) | 0.35 |

a Multivariable model (Model 2, Table 2) – adjusted for age, sex, race, and study center, education, BMI, smoking status and pack-years of smoking, use of aspirin, hormone replacement therapy (in women) and eGFR.

Supplementary table 2b. Hazard ratiosa (95% CI) for lung cancer incidence in strata of selected participants’ characteristics; ARIC, 1990–2006

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Characteristics | No. of cases/participants | Quartiles of B2M (mg/L) | | | | |
| ≤1.66 | 1.67-1.88 | 1.89-2.15 | ≥2.16 | *P-interaction* |
| Age  ≤60  >60 | 148/8,588  150/3,712 | 1 (reference)  1 (reference) | 1.14 (0.70-1.88)  1.13 (0.58-2.18) | 0.93 (0.52-1.67)  1.18 (0.60-2.32) | 1.77 (0.93-3.36)  1.65 (0.81-3.37) | 0.52 |
| Sex  Men  Women | 187/5,489  111/6,811 | 1 (reference)  1 (reference) | 1.08 (0.67-1.73)  1.13 (0.57-2.23) | 1.08 (0.64-1.82)  0.78 (0.36-1.66) | 2.04 (1.16-3.56)  1.03 (0.44-2.39) | 0.69 |
| Race  White  Black | 234/9,158  66/3,142 | 1 (reference)  1 (reference) | 1.42 (0.91-2.21)  0.53 (0.25-1.16) | 1.11 (0.68-1.79)  0.83 (0.38-1.85) | 2.02 (1.20-3.40)  1.01 (0.40-2.56) | 0.30 |
| Smoking  Ever  Neverb | 261/7,485  18/4,795 | 1 (reference) | 1.03 (0.71-1.51) | 0.86 (0.56-1.32) | 1.55 (0.97-2.47) | 0.20 b |
| BMI  Overweight  Non-overweight | 164/8,512  134/3,788 | 1 (reference)  1 (reference) | 0.98 (0.57-1.69)  1.19 (0.68-2.07) | 0.93 (0.52-1.67)  0.96 (0.51-1.81) | 1.59 (0.78-2.97)  1.62 (0.80-3.28) | 0.95 |
| Aspirin in last 2 weeks  Yes  No | 161/6,217  136/6,048 | 1 (reference)  1 (reference) | 0.95 (0.54-1.65)  1.26 (0.73-2.19) | 0.88 (0.48-1.59)  1.15 (0.62-2.24) | 1.76 (0.94-3.29)  1.53 (0.76-3.07) | 0.19 |
| HRT use (in women)  Ever  Never | 24/1749  76/3,705 | 1 (reference)  1 (reference) | 0.95 (0.34-2.69)  1.42 (0.57-3.54) | 0.40 (0.11-1.52)  1.15 (0.43-3.06) | 0.46 (0.10-2.04)  1.63 (0.55-4.83) | 0.90 |

a Multivariable model (Model 2, Table 2) – adjusted for age, sex, race, study center, education, BMI, smoking status and pack-years of smoking, use of aspirin, hormone replacement therapy (in women) and eGFR.

b The numberof lung cases for never smokers were too small and the data are unreliable.

Supplementary table 3. Hazard ratios (95% CIs)a for colorectal cancer by quartiles of combined scores based on B2M and CRP; ARIC, 1990–2006

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Biomarker | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | p-value |
| Combined Score 2b  Number of cases/participants  HR (95% CI) | ≤ -1.06  49/3,073  1 (reference) | -1.05– (-0.13)  52/3,074  1.02 (0.66-1.56) | -0.12–0.90  73/3,074  1.59 (1.05 -2.41) | >0.90  81/3,074  2.12 (1.36-3.32) | 0.0001 |
| Combined Score 3c  Number of cases/participants  HR (95% CI) | ≤ -0.26  46/3,073  1 (reference) | -0.25 –(0.04)  56/3,075  1.14 (0.74-1.76) | -0.03–0.20  75/3,073  1.79 (1.18-2.73) | >0.20  78/3,074  2.19 (1.36-3.51) | 0.0002 |

a Multivariable model (Model 2, Table 2) – adjusted for age, sex, race, study center, education, BMI, smoking status and pack-years of smoking, use of aspirin, hormone replacement therapy (in women) and eGFR.

b Sum of two normalized log-transformed biomarkers: B2M and hs-CRP: Combined Score 2=B2M+hs-CRP.

c Linear combination of normalized log-transformed biomarkers (B2M and hs-CRP) multiplied by corresponding beta-estimate for each biomarker. Beta-estimates were derived from Cox model for colorectal cancer, when two biomarkers were put simultaneously into the model:

Combined Score 3=0.30\*B2M+0.19\*hs-CRP;