**Supplemental Table S1: Multivariable hazard ratio (HR, 95%CI) of proximal and distal colon adenomas and rectal adenomas by quartiles of heme iron intake according to dietary antioxidant intake**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Colon adenomas (n=1,035)** | | | | | | | | | | | | | |  | **Rectal adenomas (n=258)** | | | |
|  | **Proximal adenomas (n=344)** | | | | | | |  | **Distal adenomas (n=622)** | | | | | |  |
|  | **FRAP mmol/day** | | | | | | |  | **FRAP mmol/day** | | | | | |  | **FRAP mmol/day** | | | |
|  | **< 12.7** | | | | **≥ 12.7** | | |  | **< 12.7** | | | **≥ 12.7** | | |  | **< 12.7** | | **≥ 12.7** | |
|  | Cases | | | HR1 (95%CI) | Cases | | HR1 (95%CI) | Cases | | HR1 (95%CI) | Cases | | HR1 (95%CI) |  | Cases | HR1 (95%CI) | Cases | HR1 (95%CI) |
| **Total heme iron (mg/day)** | | | | |  |  | |  |  |  | |  |  | |  |  |  |  |  |
| < 0.75 | | 46 | 1.00 | | 29 | 1.00 | |  | 73 | 1.00 | | 57 | 1.00 | |  | 32 | 1.00 | 31 | 1.00 |
| [0.75 – 1.07[ | | 41 | 1.04 (0.68, 1.60) | | 42 | 1.36 (0.84, 2.20) | |  | 82 | 1.24 (0.90, 1.71) | | 76 | 1.25 (0.88, 1.78) | |  | 34 | 1.07 (0.65, 1.76) | 30 | 0.89 (0.53, 1.49) |
| [1.07 – 1.45[ | | 50 | 1.59 (1.02, 2.48) | | 54 | 1.59 (0.97, 2.61) | |  | 86 | 1.52 (1.08, 2.15) | | 95 | 1.43 (1.00, 2.06) | |  | 30 | 1.04 (0.60, 1.79) | 34 | 0.88 (0.51, 1.50) |
| ≥ 1.45 | | 40 | 1.84 (1.07, 3.17) | | 42 | 1.14 (0.64, 2.04) | |  | 68 | 1.54 (1.01, 2.35) | | 105 | 1.55 (1.03, 2.31) | |  | 36 | 1.47 (0.79, 2.73) | 31 | 0.74 (0.40, 1.37) |
| p-trend | |  | 0.013 | |  | 0.79 | |  |  | 0.028 | |  | 0.038 | |  |  | 0.25 |  | 0.35 |
| *p-inter* | |  | *0.25* | |  |  | |  |  | *0.75* | |  |  | |  |  | *0.026* |  |  |
| **Non-nitrosylated heme iron (mg/day)** | | | | | |  | |  |  |  | |  |  | |  |  |  |  |  |  |
| < 0.63 | | 47 | 1.00 | | 31 | 1.00 | |  | 73 | 1.00 | | 56 | 1.00 | |  | 33 | 1.00 | 29 | 1.00 |
| [0.63 – 0.92[ | | 39 | 0.90 (0.58, 1.39) | | 45 | 1.33 (0.83, 2.13) | |  | 85 | 1.27 (0.92, 1.75) | | 77 | 1.28 (0.90, 1.82) | |  | 30 | 0.91 (0.55, 1.51) | 32 | 1.00 (0.60, 1.69) |
| [0.92 – 1.24[ | | 57 | 1.44 (0.93, 2.21) | | 46 | 1.26 (0.77, 2.07) | |  | 75 | 1.27 (0.89, 1.80) | | 100 | 1.55 (1.09, 2.22) | |  | 35 | 1.10 (0.65, 1.85) | 37 | 1.06 (0.62, 1.82) |
| ≥ 1.24 | | 34 | 1.12 (0.64, 1.93) | | 45 | 1.13 (0.65, 1.98) | |  | 76 | 1.62 (1.08, 2.43) | | 100 | 1.50 (1.00, 2.23) | |  | 34 | 1.21 (0.66, 2.23) | 28 | 0.74 (0.39, 1.39) |
| p-trend | |  | 0.39 | |  | 0.89 | |  |  | 0.029 | |  | 0.059 | |  |  | 0.44 |  | 0.34 |
| *p-inter* | |  | *0.57* | |  |  | |  |  | *0.71* | |  |  | |  |  | *0.045* |  |  |
| **Nitrosylated heme iron (mg/day)** | | | | |  |  | |  |  |  | |  |  | |  |  |  |  |  |
| < 0.06 | | 44 | 1.00 | | 31 | 1.00 | |  | 86 | 1.00 | | 64 | 1.00 | |  | 34 | 1.00 | 33 | 1.00 |
| [0.06 – 0.13[ | | 49 | 1.28 (0.85, 1.93) | | 36 | 1.13 (0.69, 1.84) | |  | 65 | 0.79 (0.57, 1.09) | | 91 | 1.31 (0.95, 1.82) | |  | 35 | 1.06 (0.66, 1.70) | 24 | 0.68 (0.40, 1.17) |
| [0.13 – 0.23[ | | 34 | 1.06 (0.67, 1.69) | | 59 | 1.75 (1.10, 2.77) | |  | 80 | 1.04 (0.76, 1.43) | | 82 | 1.06 (0.75, 1.50) | |  | 38 | 1.27 (0.78, 2.05) | 32 | 0.86 (0.51, 1.44) |
| ≥ 0.23 | | 50 | 1.98 (1.25, 1.14) | | 41 | 1.16 (0.68, 1.96) | |  | 78 | 1.15 (0.81, 1.62) | | 96 | 1.15 (0.80, 1.64) | |  | 25 | 0.88 (0.50, 1.56) | 37 | 0.95 (0.55, 1.65) |
| p-trend | |  | 0.006 | |  | 0.61 | |  |  | 0.19 | |  | 0.87 | |  |  | 0.72 |  | 0.75 |
| *p-inter* | |  | *0.17* | |  |  | |  |  | *0.20* | |  |  | |  |  | *0.86* |  |  |

1 Cox’s proportional hazards model with individuals’ age as the time scale, and adjusted by colorectal cancer in first degree relatives, educational level, smoking status, menopausal status, physical activity, body mass index, total energy, and energy-adjusted intake alcohol, fibers, dietary and supplemental calcium, and dietary zinc. Nitrosylated and non-nitrosylated heme iron were simultaneously included in the model.

**Supplemental Table S2: Multivariable hazard ratio (HR, 95%CI) of proximal and distal colon adenomas and rectal adenomas by quartiles of heme iron intake according to TRAP intake**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Colon adenomas (n=1,035)** | | | | | | | | | | | | | |  | **Rectal adenomas (n=258)** | | | |
|  | **Proximal adenomas (n=344)** | | | | | | |  | **Distal adenomas (n=622)** | | | | | |  |
|  | **TRAP mmol/day** | | | | | | |  | **TRAP mmol/day** | | | | | |  | **TRAP mmol/day** | | | |
|  | **< 4.57** | | | | **≥ 4.57** | | |  | **< 4.57** | | | **≥ 4.57** | | |  | **< 4.57** | | **≥ 4.57** | |
|  | Cases | | | HR1 (95%CI) | Cases | | HR1 (95%CI) | Cases | | HR1 (95%CI) | Cases | | HR1 (95%CI) |  | Cases | HR1 (95%CI) | Cases | HR1 (95%CI) |
| **Total heme iron (mg/day)** | | | | |  |  | |  |  |  | |  |  | |  |  |  |  |  |
| < 0.75 | | 44 | 1.00 | | 31 | 1.00 | |  | 66 | 1.00 | | 64 | 1.00 | |  | 30 | 1.00 | 33 | 1.00 |
| [0.75 – 1.07[ | | 36 | 0.93 (0.59, 1.45) | | 47 | 1.49 (0.94, 2.37) | |  | 84 | 1.36 (0.97, 1.89) | | 74 | 1.13 (0.80, 1.59) | |  | 34 | 1.13 (0.68, 1.86) | 30 | 0.87 (0.52, 1.44) |
| [1.07 – 1.45[ | | 55 | 1.73 (1.11, 2.68) | | 49 | 1.45 (0.88, 2.37) | |  | 84 | 1.55 (1.09, 2.20) | | 97 | 1.42 (1.00, 2.01) | |  | 31 | 1.08 (0.62, 1.87) | 33 | 0.85 (0.50, 1.45) |
| ≥ 1.45 | | 38 | 1.70 (0.98, 2.97) | | 44 | 1.22 (0.70, 2.15) | |  | 69 | 1.60 (1.04, 2.46) | | 104 | 1.50 (1.01, 2.22) | |  | 38 | 1.55 (0.83, 2.89) | 29 | 0.70 (0.38, 1.30) |
| p-trend | |  | 0.017 | |  | 0.71 | |  |  | 0.029 | |  | 0.033 | |  |  | 0.19 |  | 0.27 |
| *p-inter* | |  | *0.28* | |  |  | |  |  | *0.62* | |  |  | |  |  | *0.0099* |  |  |
| **Non-nitrosylated heme iron (mg/day)** | | | | | |  | |  |  |  | |  |  | |  |  |  |  |  |  |
| < 0.63 | | 46 | 1.00 | | 32 | 1.00 | |  | 67 | 1.00 | | 62 | 1.00 | |  | 31 | 1.00 | 31 | 1.00 |
| [0.63 – 0.92[ | | 35 | 0.81 (0.52, 1.27) | | 49 | 1.45 (0.92, 2.30) | |  | 83 | 1.33 (0.95, 1.84) | | 79 | 1.21 (0.86, 1.70) | |  | 30 | 0.96 (0.57, 1.60) | 32 | 0.96 (0.58, 1.61) |
| [0.92 – 1.24[ | | 58 | 1.43 (0.93, 2.21) | | 45 | 1.26 (0.77, 2.06) | |  | 77 | 1.37 (0.95, 1.96) | | 98 | 1.46 (1.03, 2.07) | |  | 37 | 1.20 (0.71, 2.02) | 35 | 0.98 (0.58, 1.67) |
| ≥ 1.24 | | 34 | 1.10 (0.63, 1.91) | | 45 | 1.15 (0.66, 2.00) | |  | 76 | 1.70 (1.12, 2.57) | | 100 | 1.43 (0.96, 2.12) | |  | 35 | 1.28 (0.69, 2.35) | 27 | 0.69 (0.37, 1.30) |
| p-trend | |  | 0.38 | |  | 0.93 | |  |  | 0.017 | |  | 0.078 | |  |  | 0.34 | 0.25 |  |
| *p-inter* | |  | *0.56* | |  |  | |  |  | *0.47* | |  |  | |  |  | *0.022* |  |  |
| **Nitrosylated heme iron (mg/day)** | | | | |  |  | |  |  |  | |  |  | |  |  |  |  |  |
| < 0.06 | | 42 | 1.00 | | 33 | 1.00 | |  | 84 | 1.00 | | 66 | 1.00 | |  | 34 | 1.00 | 33 | 1.00 |
| [0.06 – 0.13[ | | 47 | 1.27 (0.84, 1.94) | | 38 | 1.14 (0.70, 1.83) | |  | 64 | 0.79 (0.57, 1.09) | | 92 | 1.30 (0.95, 1.80) | |  | 34 | 1.00 (0.62, 1.62) | 25 | 0.75 (0.44, 1.26) |
| [0.13 – 0.23[ | | 34 | 1.06 (0.67, 1.70) | | 59 | 1.73 (1.11, 2.72) | |  | 80 | 1.03 (0.74, 1.42) | | 82 | 1.08 (0.77, 1.52) | |  | 40 | 1.22 (0.75, 1.97) | 30 | 0.89 (0.53, 1.50) |
| ≥ 0.23 | | 50 | 1.93 (1.21, 3.08) | | 41 | 1.19 (0.71, 2.00) | |  | 75 | 1.04 (0.73, 1.48) | | 99 | 1.24 (0.87, 1.77) | |  | 25 | 0.77 (0.43, 1.37) | 37 | 1.11 (0.64, 1.91) |
| p-trend | |  | 0.008 | |  | 0.50 | |  |  | 0.49 | |  | 0.48 | |  |  | 0.42 | 0.44 |  |
| *p-inter* | |  | *0.19* | |  |  | |  |  | *0.58* | |  |  | |  |  | *0.93* |  |  |

1 Cox’s proportional hazards model with individuals’ age as the time scale, and adjusted by colorectal cancer in first degree relatives, educational level, smoking status, menopausal status, physical activity, body mass index, total energy, and energy-adjusted intake alcohol, fibers, dietary and supplemental calcium, and dietary zinc. Nitrosylated and non-nitrosylated heme iron were simultaneously included in the model.

**Legend for Supplemental Figure S1:** **Risk of colorectal adenomas according to the total heme iron / TRAP ratio.** Hazard ratios were calculated fromCox’s proportional hazards model based on restricted cubic splines with individuals’ age as the time scale, and adjusted by colorectal cancer in first degree relatives, educational level, smoking status, menopausal status, physical activity, body mass index, total energy, and intake of alcohol, fibers,dietary and supplemental calcium, dietary zinc, and TRAP. The knots were located at the 25th, 50th and 75th percentiles, corresponding to 0.15 g/mol, 0.23 g/mol and 0.36 g/mol, respectively for the heme/TRAP ratio. The 25th percentile was used as the reference value. **Hatched lines** represent the 95% confidence intervals for the adjusted estimate (**solid line**). The vertical axis is on a log-scale.