**Supplementary Table S2. Night-shift work duration and colorectal cancer risk according to tumor *IRS1* and *IRS2* expression status by inverse probability weighting in the Nurses’ Health Study**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Night-shift work duration** |  |  |
| **Never** | **1 - 14 years** | **≥ 15 years** | ***Ptrend*\*** | ***Pheterogeneity*¶** |
| **Total colorectal cancer (with *IRS1*)** |  |  |  |  |  |
|  No. cases (N = 304) | 122 | 146 | 36 |  |  |
|  Age-adjusted HR (95% CI) | 1 (ref) | 0.91 (0.80 to 1.03) | 1.29 (1.05 to 1.58) | 0.01 |  |
|  Multivariable HR (95% CI)§ | 1 (ref) | 0.90 (0.79 to 1.02) | 1.21 (0.99 to 1.49) | 0.05 |  |
| ***IRS1*** |  |  |  |  |  |
| **Negative / weak** |  |  |  |  |  |
|  No. cases (N = 218) | 90 | 105 | 23 |  |  |
|  Age-adjusted HR (95% CI) | 1 (ref) | 0.90 (0.66 to 1.21) | 1.08 (0.67 to 1.72) | 0.75 | 0.001 |
|  Multivariable HR (95% CI)§ | 1 (ref) | 0.88 (0.66 to 1.18) | 1.02 (0.64 to 1.61) | 0.91 | 0.001 |
| **Moderate / intense** |  |  |  |  |  |
|  No. cases (N = 86) | 32 | 41 | 13 |  |  |
|  Age-adjusted HR (95% CI) | 1 (ref) | 0.95 (0.59 to 1.53) | 1.84 (0.95 to 3.57) | 0.06 |  |
|  Multivariable HR (95% CI)§ | 1 (ref) | 0.95 (0.60 to 1.52) | 1.73 (0.90 to 3.32) | 0.09 |  |
|  |  |  |  |  |  |
| **Total colorectal cancer (with *IRS2*)** |  |  |  |  |  |
|  No. cases (N = 308) | 119 | 153 | 36 |  |  |
|  Age-adjusted HR (95% CI) | 1 (ref) | 0.98 (0.86 to 1.11) | 1.32 (1.08 to 1.63) | 0.006 |  |
|  Multivariable HR (95% CI)§ | 1 (ref) | 0.97 (0.85 to 1.10) | 1.24 (1.01 to 1.53) | 0.03 |  |
| ***IRS2*** |  |  |  |  |  |
| **Negative / weak** |  |  |  |  |  |
|  No. cases (N = 206) | 90 | 98 | 18 |  |  |
|  Age-adjusted HR (95% CI) | 1 (ref) | 0.85 (0.63 to 1.15) | 0.79 (0.47 to 1.34) | 0.40 | 0.001 |
|  Multivariable HR (95% CI)§ | 1 (ref) | 0.85 (0.64 to 1.14) | 0.75 (0.45 to 1.26) | 0.29 | 0.001 |
| **Moderate / intense** |  |  |  |  |  |
|  No. cases (N = 102) | 29 | 55 | 18 |  |  |
|  Age-adjusted HR (95% CI) | 1 (ref) | 1.36 (0.86 to 2.16) | 2.87 (1.59 to 5.17) | 0.0003 |  |
|  Multivariable HR (95% CI)§ | 1 (ref) | 1.32 (0.84 to 2.09) | 2.65 (1.48 to 4.77) | 0.0007 |  |

CI, confidence interval; HR, hazard ratio.

Duplication-method Cox proportional cause-specific hazards regression weighted by inverse probabilities based on the availability of tumor *IRS1* or *IRS2* expression status for competing risks data was used to compute HRs and 95% CIs.

All analyses were stratified by age (in month) and year of questionnaire return.

\*: Linear trend test using the median years of each category.

¶: The Wald test was used to test for the heterogeneity of the associations between night-shift work duration (median) and colorectal cancer risk according to the expression of *IRS1* and *IRS2* (ordinal).

§: Multivariable hazard ratios were adjusted for age (in month), adult BMI (< 25, 25 -< 27.5, 27.5 -< 30, or ≥ 30 kg/m2), smoking (0, 1-10, or > 10 pack-years), history of colorectal cancer in a parent or sibling (yes or no), history of sigmoidoscopy / colonoscopy (yes or no), postmenopausal status and hormone use (premenopause, postmenopause and never use hormone, postmenopause and current use hormone, postmenopause and past use hormone), physical activity (< 3, 3 -< 27,≥ 27 METS - hours/week), regular aspirin use (yes or no), alcohol consumption (0 -< 5, 5 -< 15, or ≥ 15 g/day), total intake of vitamin D, folate, calcium, red meat and processed meat (all in tertiles), sleep duration (< 6h, 6 -< 7h, 7 -< 8h, 8 -< 9h, or ≥ 9h), and history of type 2 diabetes (yes or no).