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| --- |
| **Supplementary Table S3. Night-shift work duration and colorectal cancer risk according to tumor *IRS1* and *IRS2* expression status by tumor location (colon and rectum)** |
|  | **Night-shift work duration** |  |  |
| **Never** | **1 - 14 years** | **≥ 15 years** | ***Ptrend*\*** | ***Pheterogeneity*¶** |
| ***IRS1* in colon cancer** |  |  |  |  |  |
| **Negative / weak** |  |  |  |  |  |
|  No. cases (N = 176) | 76 | 83 | 17 |  |  |
|  Age-adjusted HR (95% CI) | 1 (ref) | 0.83 (0.61 to 1.13) | 1.06 (0.63 to 1.80) | 0.80 | 0.36 |
|  Multivariable HR (95% CI)§ | 1 (ref) | 0.81 (0.60 to 1.11) | 0.97 (0.57 to 1.66) | 0.95 | 0.35 |
| **Moderate / intense** |  |  |  |  |  |
|  No. cases (N = 67) | 26 | 32 | 9 |  |  |
|  Age-adjusted HR (95% CI) | 1 (ref) | 0.94 (0.56 to 1.57) | 1.63 (0.76 to 3.50) | 0.18 |  |
|  Multivariable HR (95% CI)§ | 1 (ref) | 0.92 (0.55 to 1.55) | 1.51 (0.70 to 3.25) | 0.26 |  |
|  |  |  |  |  |  |
| ***IRS1* in rectal cancer** |  |  |  |  |  |
| **Negative / weak** |  |  |  |  |  |
|  No. cases (N = 42) | 14 | 22 | 6 |  |  |
|  Age-adjusted HR (95% CI) | 1 (ref) | 1.18 (0.60 to 2.30) | 2.15 (0.82 to 5.67) | 0.12 | 0.50 |
|  Multivariable HR (95% CI)§ | 1 (ref) | 1.15 (0.58 to 2.25) | 1.88 (0.70 to 5.02) | 0.21 | 0.58 |
| **Moderate / intense** |  |  |  |  |  |
|  No. cases (N = 19) | 6 | 9 | 4 |  |  |
|  Age-adjusted HR (95% CI) | 1 (ref) | 1.17 (0.42 to 3.32) | 3.57 (0.99 to 12.92) | 0.04 |  |
|  Multivariable HR (95% CI)§ | 1 (ref) | 1.19 (0.42 to 3.39) | 2.89 (0.79 to 10.60) | 0.09 |  |
|  |  |  |  |  |  |
| ***IRS2* in colon cancer** |  |  |  |  |  |
| **Negative / weak** |  |  |  |  |  |
|  No. cases (N = 161) | 73 | 74 | 14 |  |  |
|  Age-adjusted HR (95% CI) | 1 (ref) | 0.77 (0.56 to 1.07) | 0.92 (0.52 to 1.64) | 0.79 | 0.10 |
|  Multivariable HR (95% CI)§ | 1 (ref) | 0.77 (0.56 to 1.07) | 0.84 (0.47 to 1.51) | 0.58 | 0.09 |
| **Moderate / intense** |  |  |  |  |  |
|  No. cases (N = 85) | 27 | 46 | 12 |  |  |
|  Age-adjusted HR (95% CI) | 1 (ref) | 1.30 (0.81 to 2.10) | 2.08 (1.05 to 4.13) | 0.04 |  |
|  Multivariable HR (95% CI)§ | 1 (ref) | 1.26 (0.78 to 2.04) | 1.92 (0.96 to 3.83) | 0.07 |  |
|  |  |  |  |  |  |
| ***IRS2* in rectal cancer** |  |  |  |  |  |
| **Negative / weak** |  |  |  |  |  |
|  No. cases (N = 45) | 17 | 24 | 4 |  |  |
|  Age-adjusted HR (95% CI) | 1 (ref) | 1.07 (0.57 to 1.99) | 1.24 (0.41 to 3.71) | 0.71 | 0.02 |
|  Multivariable HR (95% CI)§ | 1 (ref) | 1.03 (0.55 to 1.93) | 1.05 (0.34 to 3.19) | 0.94 | 0.02 |
| **Moderate / intense** |  |  |  |  |  |
|  No. cases (N = 17) | 2 | 9 | 6 |  |  |
|  Age-adjusted HR (95% CI) | 1 (ref) | 3.55 (0.76 to 16.50) | 14.79 (2.92 to 74.88) | 0.0002 |  |
|  Multivariable HR (95% CI)§ | 1 (ref) | 3.56 (0.76 to 16.69) | 12.69 (2.47 to 65.22) | 0.0008 |  |

CI, confidence interval; HR, hazard ratio.

Duplication-method Cox proportional cause-specific hazards regression 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 likelihood ratio 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* (binary).

§ 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).