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| **Supplementary Table S1. Age-adjusted baseline characteristics of cases by the availability of tumor *IRS1* and *IRS2* expression status in the Nurses’ Health Study (1988)**  |
|  | ***IRS1* unavailable** **cases (N = 1,093)**  | ***IRS1* available** **cases (N = 304)** | ***IRS2* unavailable** **cases (N = 1,089)** | ***IRS2* available** **cases (N = 308)** |
|  Age, years\* | 57.8 (6.4) | 58.2 (6.5) | 57.9 (6.4) | 58.1 (6.6) |
|  Race (White), % | 97.7 | 98.4 | 97.8 | 98.1 |
|  Body mass index, kg/m2  | 26.0 (5.2) | 26.1 (5.1) | 26.0 (5.3) | 26.1 (5.1) |
|  Family history of colorectal cancer, % | 16.1  | 17.3  | 16.0  | 17.6  |
|  History of sigmoidoscopy / endoscopy, % | 11.5 | 11.4 | 11.5 | 11.3 |
|  Postmenopausal status, % | 84.7 | 87.0 | 84.9 | 86.7 |
|  Postmenopausal hormone use, % | 37.9 | 42.7 | 38.0 | 42.4 |
|  Total activity, METS - hours/week§ | 14.8 (18.5) | 15.1 (21.6) | 14.8 (18.6) | 15.1 (21.5) |
|  Regular aspirin use (2 or more tablets/week), % | 33.5 | 40.1 | 33.6 | 39.9 |
|  Smoking status, % |  |  |  |  |
|  Never, % | 38.5 | 39.9 | 38.6 | 39.5 |
|  Smoking‚ pack years 0 - 10, % | 15.1 | 10.3 | 14.7 | 11.4 |
|  Pack years > 10, % | 45.0 | 46.6 | 45.3 | 46.0 |
|  Total alcohol intake, g/day | 6.5 (11.3) | 6.7 (11.5) | 6.5 (11.4) | 6.6 (11.3) |
|  Total vitamin D, IU/day | 333 (247) | 340 (246) | 332 (247) | 340 (245) |
|  Total folate intake, µg/day | 386 (214) | 410 (226) | 386 (214) | 408 (226) |
|  Total energy intake, kcal/day | 1761 (533) | 1778 (518) | 1760 (535) | 1780 (515) |
|  Red meat, servings/week | 2.2 (1.4) | 2.2 (1.4) | 2.2 (1.4) | 2.2 (1.4) |
|  Processed meat, servings/week | 1.1 (1.5) | 1.0 (1.3) | 1.1 (1.5) | 1.1 (1.3) |
|  Total calcium intake, mg/day | 1057 (498) | 1054 (512) | 1055 (499) | 1058 (511) |
|  Night shift work duration, % |  |  |  |  |
|  Never, % | 37.9 | 39.0 | 38.3 | 37.8 |
|  1 - 14 years, % | 52.4 | 49.9 | 52.0 | 51.4 |
|  ≥ 15 years, % | 9.7 | 11.1 | 9.7 | 10.8 |
|  Sleep duration, % |  |  |  |  |
|  Sleep < 6h, % | 3.8 | 3.3 | 3.8 | 3.2 |
|  Sleep 6h -< 7h, % | 22.7 | 20.4 | 22.8 | 20.2 |
|  Sleep 7h -< 8h, % | 47.8 | 45.3 | 47.6 | 45.9 |
|  Sleep 8h -< 9h, % | 21.6 | 26.3 | 21.7 | 26.1 |
|  Sleep ≥ 9h, % | 4.1 | 4.7 | 4.1 | 4.6 |
|  History of type 2 diabetes, % | 5.5 | 7.9 | 5.3 | 8.5 |
|  Tumor location\* |  |  |  |  |
|  Rectal cancer, % | 21.3 | 20.1 | 21.3 | 20.2 |
|  Distal colon, % | 28.0 | 29.0 | 28.2 | 28.3 |
|  Proximal colon, % | 50.7 | 50.8 | 50.5 | 51.5 |
|  Tumor stage\* |  |  |  |  |
|  Stage I, % | 22.2 | 21.4 | 22.1 | 21.8 |
|  Stage II, % | 24.9 | 31.6 | 24.9 | 31.5 |
|  Stage III, % | 21.8 | 30.9 | 22.0 | 29.9 |
|  Stage IV, % | 17.1 | 12.8 | 16.9 | 13.6 |
|  Unknown, % | 14.0 | 3.3 | 14.0 | 3.2 |
|  Tumor differentiation\* |  |  |  |  |
|  Well / moderate differentiation, % | 86.3 | 90.5 | 87.1 | 89.6 |
|  Poor differentiation, % | 13.7 | 9.5 | 12.9 | 10.4 |

Values were means (SD) or percentages and were standardized to the age distribution of the study population.

Values of polytomous variables may not sum to 100% due to rounding.

\* Value was not age adjusted.

§ METS, metabolic equivalent task score.