**Supplementary Methods**

**Statistical Analysis**

All statistical analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC), and all *P* values were two-sided. Our primary hypothesis testing was assessment of a statistical interaction (using the Wald test on the cross-product) between postdiagnosis physical activity levels (the median value of each decile category) and T cell densities in tumor tissue (the median value of each decile category) in the Cox proportional hazards regression model for colorectal cancer-specific mortality analysis. Variables for physical activity and T cell densities were treated as decile categorical variables to reduce the influential effect of a few arbitrary cut-off points. In our primary hypothesis testing on new discoveries, we used the α level of 0.005 ([1](#_ENREF_1)). All other analyses including evaluations of stratum-specific hazard ratios (HRs) and survival curves represented secondary analyses. In our secondary and other exploratory analyses, we recognized multiple comparisons associated with those analyses, and used the α level of 0.005. Outcome endpoints were colorectal cancer-specific mortality and overall mortality. Survival time was defined as the time since colorectal cancer diagnosis to death or the end of follow-up, whichever came first, and was left-truncated at the time of the first postdiagnosis questionnaire return.

In order to reduce bias due to the availability of postdiagnosis questionnaire data, the inverse probability weighting (IPW) method was used in all survival analyses ([2-4](#_ENREF_2)). We estimated the probability of questionnaire return after colorectal cancer diagnosis using the multivariable logistic regression model as previously described ([2](#_ENREF_2)), and used the inverse probability to weight each patient. When we performed sex-stratified IPW-adjusted Cox regression analyses without truncation of weight, the results remained consistent (data not shown). Multivariable sex-stratified Cox proportional hazards models initially included age at diagnosis (continuous), year of diagnosis (continuous), prediagnosis physical activity (sex-specific quartiles), postdiagnosis body mass index (< 25 vs. 25 to 29.9 vs. ≥ 30 kg/m2), history of colorectal cancer in any first-degree relatives (absent vs. present), tumor location (proximal colon vs. distal colon vs. rectum), tumor differentiation (well to moderate vs. poor), disease stage (I-II vs. III-IV), MSI status (MSI-high vs. non-MSI-high), CIMP (low/negative vs. high), LINE-1 methylation level (continuous), *BRAF* mutation (mutant vs. wild-type), *KRAS* mutation (mutant vs. wild-type), *PIK3CA* mutation (mutant vs. wild-type), nuclear *CTNNB1* expression (negative vs. positive), *PTGS2* expression (negative vs. positive), and *IRS1* expression (negative/low vs. high). A backward elimination was performed with a threshold of *P* = .05 to select variables for the final models. We also estimated HRs for a quartile-unit increase of postdiagnosis physical activity levels in strata of levels of T cell densities using a re-parameterization of the interaction term in a single regression model ([5](#_ENREF_5)). The cases with missing data (postdiagnosis body mass index, 7.9%; tumor location, 0.2%; tumor differentiation, 0.4%; MSI status, 0.6%; CIMP status, 0.9%; *BRAF* mutation, 1.3%; *KRAS* mutation, 1.3%; *PIK3CA* mutation, 8.5%; and nuclear *CTNNB1* expression, 4.0%) were included in the majority category of a given categorical covariate to limit the degrees of freedom of the models. For cases with missing data on LINE-1 methylation level (2.1%) and *IRS1* expression (12.0%), we assigned a separate indicator variable for each variable. We confirmed that excluding cases with missing information in any of the covariates did not alter our results substantially (data not shown). The proportionality of hazards assumption was evaluated using a time-dependent variable, which was the cross-product of the postdiagnosis physical activity variable and survival time (*P* > .05). Results of Cox regression analyses without IPW, which were similar to those with IPW, are shown in **Supplementary Table 1**. Survival probabilities were estimated using the IPW-adjusted Kaplan-Meier method and compared using the weighted log-rank test ([6](#_ENREF_6)). **References**

1. Benjamin D, Berger J, Johannesson M, et al. Redefine statistical significance. *Nat Hum Behav*. 2018;2:6-10.

2. Hamada T, Cao Y, Qian ZR, et al. Aspirin Use and Colorectal Cancer Survival According to Tumor CD274 (Programmed Cell Death 1 Ligand 1) Expression Status. *J Clin Oncol*. 2017;35(16):1836-1844.

3. Liu L, Nevo D, Nishihara R, et al. Utility of inverse probability weighting in molecular pathological epidemiology. *Eur J Epidemiol*. 2017;33(4):381-392.

4. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res*. 2013;22(3):278-295.

5. Nosho K, Irahara N, Shima K, et al. Comprehensive biostatistical analysis of CpG island methylator phenotype in colorectal cancer using a large population-based sample. *PLoS One*. 2008;3(11):e3698.

6. Xie J, Liu C. Adjusted Kaplan-Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. *Stat Med*. 2005;24(20):3089-3110.

**Supplementary Table 1.** Colorectal cancer mortality according to postdiagnosis physical activity levels in all cases or in strata of quartiles of T cell densities without inverse probability weighting

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Colorectal cancer-specific mortality  hazard ratio (HR) for a quartile-unit increase of  postdiagnosis physical activity levels | | |  | Overall mortality  hazard ratio (HR) for a quartile-unit increase of  postdiagnosis physical activity levels | | |
|  | No. of  cases | No. of  events | Univariable HR  (95% CI) | Multivariable HR  (95% CI)\* |  | No. of  events | Univariable HR  (95% CI) | Multivariable HR  (95% CI)\* |
|  |  |  |  |  |  |  |  |  |
| ***CD3*+ cell density** |  |  |  |  |  |  |  |  |
| Quartile 1 (lowest) | 111 | 30 | 0.60 (0.41 to 0.86) | 0.56 (0.38 to 0.82) |  | 69 | 0.76 (0.60 to 0.96) | 0.77 (0.63 to 0.95) |
| Quartile 2 | 111 | 23 | 0.81 (0.55 to 1.20) | 0.82 (0.56 to 1.22) |  | 64 | 0.68 (0.55 to 0.84) | 0.73 (0.59 to 0.91) |
| Quartile 3 | 112 | 25 | 0.80 (0.53 to 1.20) | 0.75 (0.49 to 1.17) |  | 68 | 0.82 (0.65 to 1.04) | 0.84 (0.66 to 1.07) |
| Quartile 4 (highest) | 111 | 15 | 1.06 (0.74 to 1.54) | 1.15 (0.79 to 1.68) |  | 60 | 0.85 (0.67 to 1.08) | 0.93 (0.74 to 1.18) |
| *P*interaction† |  |  | .002 | < .001 |  |  | .35 | .24 |
|  |  |  |  |  |  |  |  |  |
| ***CD8*+ cell density** |  |  |  |  |  |  |  |  |
| Quartile 1 (lowest) | 110 | 34 | 0.67 (0.47 to 0.94) | 0.66 (0.46 to 0.95) |  | 66 | 0.72 (0.57 to 0.92) | 0.77 (0.59 to 1.00) |
| Quartile 2 | 109 | 23 | 0.92 (0.63 to 1.34) | 0.88 (0.61 to 1.27) |  | 65 | 0.83 (0.67 to 1.02) | 0.82 (0.66 to 1.02) |
| Quartile 3 | 109 | 18 | 0.60 (0.39 to 0.92) | 0.57 (0.34 to 0.96) |  | 59 | 0.63 (0.50 to 0.80) | 0.75 (0.59 to 0.95) |
| Quartile 4 (highest) | 109 | 19 | 1.03 (0.70 to 1.52) | 1.03 (0.68 to 1.57) |  | 64 | 0.87 (0.69 to 1.11) | 0.85 (0.70 to 1.04) |
| *P*interaction† |  |  | .097 | .18 |  |  | .31 | .66 |
|  |  |  |  |  |  |  |  |  |
| **CD45RO+ cell density** |  |  |  |  |  |  |  |  |
| Quartile 1 (lowest) | 113 | 33 | 1.01 (0.73 to 1.40) | 0.90 (0.64 to 1.26) |  | 73 | 0.75 (0.58 to 0.96) | 0.79 (0.64 to 0.97) |
| Quartile 2 | 113 | 34 | 0.71 (0.50 to 1.01) | 0.70 (0.49 to 1.00) |  | 69 | 0.76 (0.60 to 0.96) | 0.79 (0.63 to 1.00) |
| Quartile | 113 | 19 | 0.63 (0.42 to 0.94) | 0.64 (0.40 to 1.02) |  | 63 | 0.74 (0.60 to 0.92) | 0.80 (0.65 to 1.00) |
| Quartile 4 (highest) | 112 | 10 | 0.94 (0.52 to 1.72) | 0.90 (0.49 to 1.64) |  | 60 | 0.84 (0.67 to 1.04) | 0.93 (0.76 to 1.15) |
| *P*interaction† |  |  | .87 | .84 |  |  | .74 | .87 |
|  |  |  |  |  |  |  |  |  |
| ***FOXP3*+ cell density** |  |  |  |  |  |  |  |  |
| Quartile 1 (lowest) | 107 | 32 | 0.77 (0.55 to 1.08) | 0.81 (0.56 to 1.19) |  | 76 | 0.69 (0.55 to 0.87) | 0.76 (0.60 to 0.96) |
| Quartile 2 | 106 | 23 | 0.70 (0.48 to 1.02) | 0.70 (0.46 to 1.08) |  | 67 | 0.71 (0.58 to 0.88) | 0.74 (0.60 to 0.92) |
| Quartile 3 | 106 | 20 | 0.96 (0.64 to 1.45) | 1.04 (0.70 to 1.52) |  | 56 | 0.98 (0.76 to 1.27) | 1.06 (0.86 to 1.32) |
| Quartile 4 (highest) | 107 | 13 | 0.68 (0.44 to 1.05) | 0.66 (0.42 to 1.04) |  | 49 | 0.73 (0.56 to 0.95) | 0.78 (0.61 to 0.98) |
| *P*interaction† |  |  | .39 | .30 |  |  | .85 | .32 |
|  |  |  |  |  |  |  |  |  |

Abbreviations: CI = confidence interval.

\* The multivariable sex-stratified Cox regression model initially included age, year of diagnosis, family history of colorectal cancer, body mass index, prediagnosis physical activity, tumor location, tumor differentiation, disease stage, microsatellite instability, CpG island methylator phenotype, long interspersed nucleotide element-1 methylation level, *KRAS* mutation, *BRAF* mutation, *PIK3CA* mutation, nuclear *CTNNB1* (beta-catenin) expression, *PTGS2* (cyclooxygenase-2) expression, and *IRS1* expression. A backward elimination with a threshold of *P* = .05 was used to select variables in the final models.

† *Pinteraction* was calculated using the Wald test for the cross-product of postdiagnosis physical activity levels (the median value of each decile category) and each T cell subset (the median value of each decile category) in the sex-stratified Cox regression model.

**Supplementary Table 2.** Colorectal cancer mortality according to postdiagnosis physical activity levels in strata of *CD3*+ cell density (the final multivariable models)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Colorectal cancer-specific mortality  hazard ratio (HR) |  | Overall mortality  hazard ratio (HR) |
|  | Multivariable HR  (95% CI)\*† |  | Multivariable HR  (95% CI)\*† |
|  |  |  |  |
| Postdiagnosis physical activity levels  (per one-quartile increase) |  |  |  |
| *CD3*+ cell density |  |  |  |
| Quartile 1 (lowest) | 0.56 (0.38 to 0.83) |  | 0.76 (0.62 to 0.93) |
| Quartile 2 | 0.80 (0.54 to 1.18) |  | 0.72 (0.58 to 0.89) |
| Quartile 3 | 0.73 (0.47 to 1.11) |  | 0.83 (0.65 to 1.06) |
| Quartile 4 (highest) | 1.14 (0.79 to 1.65) |  | 0.96 (0.76 to 1.21) |
|  |  |  |  |
| Age (per 10-year increase) | Did not remain in this model |  | 2.12 (1.72 to 2.63) |
|  |  |  |  |
| Body mass index |  |  |  |
| < 25 kg/m2 | 1 (referent) |  | 1 (referent) |
| 25 to 29.9 kg/m2 | 0.79 (0.50 to 1.24) |  | 0.87 (0.67 to 1.12) |
| ≥ 30 kg/m2 | 0.32 (0.14 to 0.71) |  | 0.59 (0.39 to 0.89) |
|  |  |  |  |
| AJCC disease stage |  |  |  |
| I-II | 1 (referent) |  | 1 (referent) |
| III-IV | 3.03 (1.97 to 4.67) |  | 1.65 (1.28 to 2.12) |
|  |  |  |  |
| MSI status |  |  |  |
| Non-MSI-high | 1 (referent) |  | 1 (referent) |
| MSI-high | 0.32 (0.13 to 0.81) |  | 0.60 (0.38 to 0.94) |
|  |  |  |  |
| CIMP status | Did not remain in this model |  |  |
| Low/negative |  |  | 1 (referent) |
| High |  |  | 1.60 (1.03 to 2.50) |
|  |  |  |  |

Abbreviations: AJCC = American Joint Committee on Cancer; CI = confidence interval; CIMP = CpG island methylator phenotype; IPW = inverse probability weighting; MSI = microsatellite instability.

\* IPW was applied to reduce a bias due to the availability of questionnaire data after cancer diagnosis (see “Statistical Analysis” subsection for details).

† The multivariable sex-stratified IPW-adjusted Cox regression model initially included age, year of diagnosis, family history of colorectal cancer, body mass index, prediagnosis physical activity, tumor location, tumor differentiation, disease stage, MSI, CIMP, long interspersed nucleotide element-1 methylation level, *KRAS* mutation, *BRAF* mutation, *PIK3CA* mutation, nuclear *CTNNB1* (beta-catenin) expression, *PTGS2* (cyclooxygenase-2) expression, and *IRS1* expression. A backward elimination with a threshold of *P* = .05 was used to select variables for the final models.

**Supplementary Table 3.** Colorectal cancer mortality for a 10 METS-hours/week-unit increase of postdiagnosis physical activity levels in all cases or in strata of quartiles of T cell densities

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Colorectal cancer-specific mortality  hazard ratio (HR) for  a 10 METS-hours/week-unit increase of  postdiagnosis physical activity levels\* | | |  | Overall mortality  hazard ratio (HR) for  a 10 METS-hours/week-unit increase of  postdiagnosis physical activity levels\* | | |
|  | No. of  cases | No. of  events | Univariable HR  (95% CI)† | Multivariable HR  (95% CI)†‡ |  | No. of  events | Univariable HR  (95% CI)† | Multivariable HR  (95% CI)†‡ |
|  |  |  |  |  |  |  |  |  |
| **All colorectal cancer cases** | 470 | 100 | 0.90 (0.80 to 1.00) | 0.92 (0.82 to 1.03) |  | 275 | 0.93 (0.87 to 0.98) | 0.97 (0.92 to 1.02) |
|  |  |  |  |  |  |  |  |  |
| ***CD3*+ cell density** |  |  |  |  |  |  |  |  |
| Quartile 1 (lowest) | 111 | 30 | 0.75 (0.55 to 1.02) | 0.70 (0.51 to 0.96) |  | 69 | 0.91 (0.82 to 1.02) | 0.93 (0.84 to 1.02) |
| Quartile 2 | 111 | 23 | 0.90 (0.72 to 1.12) | 0.91 (0.73 to 1.14) |  | 64 | 0.87 (0.77 to 0.99) | 0.91 (0.82 to 1.02) |
| Quartile 3 | 112 | 25 | 0.89 (0.71 to 1.12) | 0.90 (0.72 to 1.12) |  | 68 | 0.91 (0.81 to 1.03) | 0.99 (0.88 to 1.10) |
| Quartile 4 (highest) | 111 | 15 | 1.10 (0.89 to 1.36) | 1.15 (0.93 to 1.42) |  | 60 | 1.02 (0.90 to 1.16) | 1.07 (0.94 to 1.22) |
| *P*interaction§ |  |  | .003 | < .001 |  |  | .26 | .18 |
|  |  |  |  |  |  |  |  |  |
| ***CD8*+ cell density** |  |  |  |  |  |  |  |  |
| Quartile 1 (lowest) | 110 | 34 | 0.84 (0.65 to 1.08) | 0.91 (0.70 to 1.17) |  | 66 | 0.90 (0.76 to 1.06) | 0.99 (0.84 to 1.16) |
| Quartile 2 | 109 | 23 | 0.86 (0.71 to 1.03) | 0.85 (0.70 to 1.02) |  | 65 | 0.92 (0.84 to 1.01) | 0.94 (0.85 to 1.03) |
| Quartile 3 | 109 | 18 | 0.77 (0.54 to 1.09) | 0.84 (0.59 to 1.18) |  | 59 | 0.83 (0.71 to 0.97) | 0.93 (0.80 to 1.07) |
| Quartile 4 (highest) | 109 | 19 | 1.11 (0.91 to 1.35) | 1.07 (0.87 to 1.33) |  | 64 | 1.02 (0.93 to 1.13) | 1.02 (0.93 to 1.12) |
| *P*interaction§ |  |  | .061 | .13 |  |  | .28 | .42 |
|  |  |  |  |  |  |  |  |  |
| **CD45RO+ cell density** |  |  |  |  |  |  |  |  |
| Quartile 1 (lowest) | 113 | 33 | 1.02 (0.87 to 1.20) | 1.01 (0.84 to 1.20) |  | 73 | 0.94 (0.83 to 1.06) | 0.99 (0.88 to 1.12) |
| Quartile 2 | 113 | 34 | 0.85 (0.71 to 1.03) | 0.81 (0.67 to 1.00) |  | 69 | 0.96 (0.87 to 1.06) | 0.98 (0.89 to 1.08) |
| Quartile 3 | 113 | 19 | 0.60 (0.39 to 0.92) | 0.62 (0.37 to 1.04) |  | 63 | 0.83 (0.72 to 0.95) | 0.87 (0.77 to 0.98) |
| Quartile 4 (highest) | 112 | 10 | 1.13 (0.82 to 1.56) | 1.13 (0.81 to 1.57) |  | 60 | 0.98 (0.88 to 1.11) | 1.04 (0.93 to 1.16) |
| *P*interaction§ |  |  | .95 | 1.00 |  |  | .93 | .63 |
|  |  |  |  |  |  |  |  |  |
| ***FOXP3*+ cell density** |  |  |  |  |  |  |  |  |
| Quartile 1 (lowest) | 107 | 32 | 0.95 (0.78 to 1.15) | 1.03 (0.85 to 1.25) |  | 76 | 0.84 (0.72 to 0.99) | 0.89 (0.76 to 1.03) |
| Quartile 2 | 106 | 23 | 0.80 (0.59 to 1.07) | 0.84 (0.64 to 1.10) |  | 67 | 0.85 (0.75 to 0.97) | 0.89 (0.79 to 1.00) |
| Quartile 3 | 106 | 20 | 0.96 (0.79 to 1.17) | 0.99 (0.82 to 1.19) |  | 56 | 1.08 (0.98 to 1.19) | 1.09 (0.99 to 1.19) |
| Quartile 4 (highest) | 107 | 13 | 0.84 (0.64 to 1.10) | 0.88 (0.68 to 1.13) |  | 49 | 0.91 (0.78 to 1.06) | 0.99 (0.88 to 1.11) |
| *P*interaction§ |  |  | .47 | .36 |  |  | .63 | .21 |
|  |  |  |  |  |  |  |  |  |

Abbreviations: CI = confidence interval; IPW = inverse probability weighting; METS = metabolic equivalent task score.

\* Postdiagnosis physical activity levels (continuous) were truncated at the value of 95 percentile (72.1 METS-hours/week) to reduce influences of outliers.

† IPW was applied to reduce a bias due to the availability of questionnaire data after cancer diagnosis (see “Statistical Analysis” subsection for details).

‡ The multivariable sex-stratified IPW-adjusted Cox regression model initially included age, year of diagnosis, family history of colorectal cancer, body mass index, prediagnosis physical activity, tumor location, tumor differentiation, disease stage, microsatellite instability, CpG island methylator phenotype, long interspersed nucleotide element-1 methylation level, *KRAS* mutation, *BRAF* mutation, *PIK3CA* mutation, nuclear *CTNNB1* (beta-catenin) expression, *PTGS2* (cyclooxygenase-2) expression, and *IRS1* expression. A backward elimination with a threshold of *P* = .05 was used to select variables for the final models.

§ *P*interaction was calculated using the Wald test for the cross-product of postdiagnosis physical activity levels (continuous) and each T cell subset (the median value of each decile category) in the sex-stratified IPW-adjusted Cox regression model.

**Supplementary Table 4.** Colorectal cancer mortality according to postdiagnosis physical activity levels in strata of quartiles of T cell densities in stage I-III patients

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Colorectal cancer-specific mortality  hazard ratio (HR) for a quartile-unit increase of  postdiagnosis physical activity levels | | |  | Overall mortality  hazard ratio (HR) for a quartile-unit increase of  postdiagnosis physical activity levels | | |
|  | No. of  cases | No. of  events | Univariable HR  (95% CI)\* | Multivariable HR  (95% CI)\*† |  | No. of  events | Univariable HR  (95% CI)\* | Multivariable HR  (95% CI)\*† |
|  |  |  |  |  |  |  |  |  |
| ***CD3*+ cell density** |  |  |  |  |  |  |  |  |
| Quartile 1 (lowest) | 99 | 22 | 0.52 (0.34 to 0.81) | 0.47 (0.30 to 0.73) |  | 59 | 0.77 (0.60 to 0.98) | 0.76 (0.62 to 0.93) |
| Quartile 2 | 104 | 17 | 0.92 (0.58 to 1.45) | 0.75 (0.48 to 1.17) |  | 57 | 0.70 (0.57 to 0.88) | 0.75 (0.60 to 0.94) |
| Quartile 3 | 106 | 19 | 0.92 (0.58 to 1.46) | 0.74 (0.42 to 1.30) |  | 62 | 0.87 (0.68 to 1.11) | 0.86 (0.67 to 1.11) |
| Quartile 4 (highest) | 109 | 14 | 1.06 (0.73 to 1.56) | 1.03 (0.70 to 1.51) |  | 59 | 0.84 (0.66 to 1.08) | 0.93 (0.73 to 1.18) |
| *P*interaction‡ |  |  | .002 | < .001 |  |  | .45 | .31 |
|  |  |  |  |  |  |  |  |  |
| ***CD8*+ cell density** |  |  |  |  |  |  |  |  |
| Quartile 1 (lowest) | 101 | 26 | 0.66 (0.44 to 1.00) | 0.45 (0.29 to 0.70) |  | 58 | 0.72 (0.55 to 0.95) | 0.82 (0.62 to 1.09) |
| Quartile 2 | 101 | 16 | 1.21 (0.78 to 1.87) | 1.03 (0.66 to 1.60) |  | 58 | 0.89 (0.72 to 1.10) | 0.90 (0.73 to 1.11) |
| Quartile 3 | 104 | 14 | 0.60 (0.38 to 0.96) | 0.53 (0.30 to 0.92) |  | 54 | 0.63 (0.50 to 0.81) | 0.76 (0.60 to 0.96) |
| Quartile 4 (highest) | 105 | 17 | 0.96 (0.64 to 1.43) | 0.83 (0.53 to 1.29) |  | 61 | 0.87 (0.68 to 1.10) | 0.84 (0.68 to 1.03) |
| *P*interaction‡ |  |  | .31 | .51 |  |  | .57 | .96 |
|  |  |  |  |  |  |  |  |  |
| **CD45RO+ cell density** |  |  |  |  |  |  |  |  |
| Quartile 1 (lowest) | 102 | 24 | 1.14 (0.76 to 1.72) | 0.86 (0.57 to 1.29) |  | 63 | 0.77 (0.58 to 1.01) | 0.80 (0.63 to 1.01) |
| Quartile 2 | 105 | 28 | 0.70 (0.48 to 1.02) | 0.55 (0.37 to 0.81) |  | 63 | 0.76 (0.60 to 0.97) | 0.78 (0.62 to 0.99) |
| Quartile 3 | 107 | 14 | 0.71 (0.46 to 1.10) | 0.57 (0.32 to 1.02) |  | 57 | 0.78 (0.62 to 0.97) | 0.81 (0.65 to 1.00) |
| Quartile 4 (highest) | 110 | 9 | 1.06 (0.58 to 1.95) | 0.98 (0.53 to 1.80) |  | 58 | 0.85 (0.68 to 1.06) | 0.91 (0.74 to 1.13) |
| *P*interaction‡ |  |  | 1.00 | .86 |  |  | .68 | .84 |
|  |  |  |  |  |  |  |  |  |
| ***FOXP3*+ cell density** |  |  |  |  |  |  |  |  |
| Quartile 1 (lowest) | 94 | 20 | 0.97 (0.64 to 1.46) | 0.90 (0.57 to 1.42) |  | 63 | 0.74 (0.58 to 0.94) | 0.78 (0.61 to 0.99) |
| Quartile 2 | 99 | 19 | 0.71 (0.47 to 1.08) | 0.55 (0.34 to 0.87) |  | 61 | 0.73 (0.59 to 0.91) | 0.74 (0.59 to 0.92) |
| Quartile 3 | 102 | 17 | 0.96 (0.61 to 1.50) | 0.83 (0.53 to 1.30) |  | 53 | 0.97 (0.74 to 1.28) | 1.06 (0.84 to 1.32) |
| Quartile 4 (highest) | 104 | 11 | 0.70 (0.44 to 1.10) | 0.57 (0.34 to 0.94) |  | 47 | 0.75 (0.57 to 0.98) | 0.81 (0.63 to 1.05) |
| *P*interaction‡ |  |  | .33 | .26 |  |  | .84 | .097 |
|  |  |  |  |  |  |  |  |  |

Abbreviations: CI = confidence interval; IPW = inverse probability weighting.

\* IPW was applied to reduce a bias due to the availability of questionnaire data after cancer diagnosis (see “Statistical Analysis” subsection for details).

† The multivariable sex-stratified IPW-adjusted Cox regression model initially included age, year of diagnosis, family history of colorectal cancer, body mass index, prediagnosis physical activity, tumor location, tumor differentiation, disease stage, microsatellite instability, CpG island methylator phenotype, long interspersed nucleotide element-1 methylation level, *KRAS* mutation, *BRAF* mutation, *PIK3CA* mutation, nuclear *CTNNB1* (beta-catenin) expression, *PTGS2* (cyclooxygenase-2) expression, and *IRS1* expression. A backward elimination with a threshold of *P* = .05 was used to select variables for the final models.

‡ *P*interaction was calculated using the Wald test for the cross-product of postdiagnosis physical activity levels (the median value of each decile category) and each T cell subset (the median value of each decile category) in the sex-stratified IPW-adjusted Cox regression model.

**Supplementary Table 5**. Colorectal cancer mortality according to postdiagnosis physical activity levels in strata of each lymphocytic reaction component

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Colorectal cancer-specific mortality  hazard ratio (HR) for a quartile-unit increase of  postdiagnosis physical activity levels | | |  | Overall mortality  hazard ratio (HR) for a quartile-unit increase of  postdiagnosis physical activity levels | | |
|  | No. of  cases | No. of  events | Univariable HR  (95% CI)\* | Multivariable HR  (95% CI)\*† |  | No. of  events | Univariable HR  (95% CI)\* | Multivariable HR  (95% CI)\*† |
|  |  |  |  |  |  |  |  |  |
| **Crohn’s-like lymphoid reaction** |  |  |  |  |  |  |  |  |
| Negative/low | 270 | 70 | 0.75 (0.60 to 0.95) | 0.74 (0.58 to 0.94) |  | 158 | 0.72 (0.62 to 0.84) | 0.76 (0.65 to 0.89) |
| Intermediate | 69 | 13 | 0.71 (0.45 to 1.12) | 0.70 (0.46 to 1.07) |  | 44 | 0.71 (0.55 to 0.92) | 0.88 (0.70 to 1.11) |
| High | 41 | 4 | 0.93 (0.50 to 1.73) | 1.14 (0.62 to 2.13) |  | 24 | 1.01 (0.76 to 1.36) | 0.97 (0.73 to 1.29) |
| *P*interaction‡ |  |  | .80 | .91 |  |  | .70 | .56 |
|  |  |  |  |  |  |  |  |  |
| **Peritumoral lymphocytic reaction** |  |  |  |  |  |  |  |  |
| Negative/low | 35 | 13 | 0.45 (0.25 to 0.82) | 0.47 (0.25 to 0.88) |  | 20 | 0.60 (0.39 to 0.94) | 0.57 (0.37 to 0.88) |
| Intermediate | 365 | 80 | 0.82 (0.67 to 1.00) | 0.83 (0.66 to 1.04) |  | 210 | 0.78 (0.68 to 0.88) | 0.83 (0.73 to 0.94) |
| High | 68 | 7 | 0.81 (0.39 to 1.69) | 0.81 (0.42 to 1.59) |  | 43 | 0.78 (0.61 to 0.99) | 0.82 (0.65 to 1.03) |
| *P*interaction‡ |  |  | .10 | .39 |  |  | .19 | .37 |
|  |  |  |  |  |  |  |  |  |
| **Intratumoral periglandular reaction** |  |  |  |  |  |  |  |  |
| Negative/low | 35 | 12 | 0.42 (0.22 to 0.81) | 0.43 (0.22 to 0.83) |  | 19 | 0.60 (0.37 to 0.96) | 0.56 (0.35 to 0.88) |
| Intermediate | 364 | 81 | 0.84 (0.69 to 1.03) | 0.85 (0.68 to 1.06) |  | 211 | 0.79 (0.70 to 0.90) | 0.84 (0.74 to 0.95) |
| High | 69 | 7 | 0.56 (0.30 to 1.05) | 0.59 (0.33 to 1.04) |  | 43 | 0.71 (0.56 to 0.90) | 0.74 (0.60 to 0.91) |
| *P*interaction‡ |  |  | .36 | .61 |  |  | .54 | .82 |
|  |  |  |  |  |  |  |  |  |
| **Tumor-infiltrating lymphocytes** |  |  |  |  |  |  |  |  |
| Negative/low | 334 | 82 | 0.74 (0.60 to 0.91) | 0.73 (0.58 to 0.92) |  | 192 | 0.74 (0.65 to 0.85) | 0.79 (0.69 to 0.90) |
| Intermediate | 72 | 13 | 1.01 (0.68 to 1.49) | 1.16 (0.77 to 1.76) |  | 42 | 0.83 (0.63 to 1.10) | 0.97 (0.75 to 1.26) |
| High | 62 | 5 | 0.60 (0.26 to 1.39) | 0.61 (0.22 to 1.70) |  | 39 | 0.81 (0.64 to 1.02) | 0.85 (0.67 to 1.08) |
| *P*interaction‡ |  |  | .69 | .34 |  |  | .43 | .20 |
|  |  |  |  |  |  |  |  |  |

Abbreviations: CI = confidence interval; IPW = inverse probability weighting.

\* IPW was applied to reduce a bias due to the availability of questionnaire data after cancer diagnosis (see “Statistical Analysis” subsection for details).

† The multivariable sex-stratified IPW-adjusted Cox regression model initially included age, year of diagnosis, family history of colorectal cancer, body mass index, prediagnosis physical activity, tumor location, tumor differentiation, disease stage, microsatellite instability, CpG island methylator phenotype, long interspersed nucleotide element-1 methylation level, *KRAS* mutation, *BRAF* mutation, *PIK3CA* mutation, nuclear *CTNNB1* (beta-catenin) expression, *PTGS2* (cyclooxygenase-2) expression, and *IRS1* expression. A backward elimination with a threshold of *P* = .05 was used to select variables for the final models.

‡ *P*interaction was calculated using the Wald test for the cross-product of postdiagnosis physical activity levels (the median value of each decile category) and each of the lymphocytic reaction variables (ordinal) in the sex-stratified IPW-adjusted Cox regression model.