**Supplementary Table 1.** Hazard ratios (HR) and 95% confidence intervals (CI) for associations between personal factors, initial colorectal cancer (CRC) tumour pathology features, lifestyle factors and surveillance interval and the risk of metachronous CRCusing only non-missing data

|  |  |  |
| --- | --- | --- |
|  | Univariable | Multivariable (Cases=18; Person-years=6,325) |
|  | Cases/Person-years | HR (95% CI) | *P* valuea | HR (95% CI) | *P* valuea |
| *Personal factors* |  |  |  |  |  |
| Age at initial diagnosis  |  |  |  |  |  |
|  <50 years | 52/18,336 | 1 |  | - |  |
|  ≥50 years | 90/33,706 | 0.97 (0.69-1.37) | 0.88 | - | - |
|  Per 10-year increment | 142/52,042 | 1.01 (0.88-1.17) | 0.85 | 1.02 (0.61-1.70) | 0.93 |
| Sex |  |  |  |  |  |
|  Male | 63/25,574 | 1 |  | 1 |  |
|  Female | 79/26,468 | 1.23 (0.88-1.71) | 0.22 | 1.04 (0.35-3.06) | 0.95 |
| First-degree family history of CRC |  |  |  |  |  |
|  No | 101/39,857 | 1 |  | 1 |  |
|  Yes | 41/12,185 | 1.36 (0.95-1.96) | 0.10 | 0.49 (0.11-2.21) | 0.35 |
|  |  |  |  |  |  |
| *Initial tumour features* |  |  |  |  |  |
| Synchronous CRC |  |  |  |  |  |
|  No | 109/40,713 | 1 |  | 1 |  |
|  Yes | 9/1,039 | 3.10 (1.57-6.13) | 0.001 | 13.77 (1.05-181.42) | 0.05 |
| Synchronous adenoma |  |  |  |  |  |
|  No | 62/20,331 | 1 |  | 1 |  |
|  Yes | 27/8,984 | 1.01 (0.64-1.59) | 0.96 | 0.17 (0.02-1.58) | 0.12 |
| Site of initial tumourb |  |  |  |  |  |
|  Proximal colon | 85/16,697 | 3.77 (2.62-5.41) | <0.001 | 3.32 (1.13-9.75) | 0.03 |
|  Distal colon/rectum | 45/33,718 | 1 |  | 1 |  |
|  Unspecified colon | 12/1,627 | 5.02 (2.65-9.50) | <0.001 | - | - |
| TNM stage |  |  |  |  |  |
|  I | 19/6,379 | 1 |  | 1 |  |
|  II | 13/5,515 | 0.78 (0.39-1.58) |  | 0.84 (0.23-3.03) |  |
|  III | 15/6,443 | 0.77 (0.39-1.53) |  | 0.51 (0.13-1.93) |  |
|  IV | 6/1,664 | 1.16 (0.45-2.96) | 0.82i | 0.84 (0.08-8.63) | 0.41i |
| Tumour grade |  |  |  |  |  |
|  Low | 94/30,447 | 1 |  | 1 |  |
|  High | 16/5,841 | 0.86 (0.51-1.46) | 0.58 | 0.64 (0.16-2.55) | 0.52 |
| Tumour mismatch repair status |  |  |  |  |  |
|  Proficient  | 89/30,718 | 1 |  | 1 |  |
|  Deficient  | 20/4,656 | 1.54 (0.94-2.49) | 0.08 | 0.52 (0.12-2.23) | 0.38 |
|  |  |  |  |  |  |
| *Lifestyle factors* |  |  |  |  |  |
| Cigarette smoking statusc |  |  |  |  |  |
|  Never | 58/23,479 | 1 |  | 1 |  |
|  Former | 66/23,231 | 1.15 (0.81-1.64) |  | 1.57 (0.55-4.44) |  |
|  Current | 18/5,332 | 1.33 (0.78-2.25) | 0.26i | 1.12 (0.12-10.48) | 0.59i |
| Alcohol intake |  |  |  |  |  |
|  Per 14 g/day increment | 103/38,536 | 1.00 (0.93-1.08) | 0.97 | 0.98 (0.72-1.36) | 0.93 |
| BMI recentd, kg/m2 |  |  |  |  |  |
|  <18.5 | 4/1,263 | 0.99 (0.36-2.76) |  | - |  |
|  18.5-<25 | 54/18,157 | 1 |  | - |  |
|  25-<30 | 44/19,463 | 0.76 (0.51-1.13) |  | - |  |
|  ≥30 | 40/13,159 | 1.01 (0.67-1.52) | 0.69i | - | - |
|  Per 5 kg/m2 | 142/52,042 | 0.99 (0.97-1.03) | 0.81 | 0.81 (0.51-1.30) | 0.39 |
| BMI at age 20 yearse, kg/m2 |  |  |  |  |  |
|  <18.5 | 18/5,046 | 1.35 (0.82-2.24) |  | - |  |
|  18.5-<25 | 90/35,812 | 1 |  | - |  |
|  25-<30 | 27/8,213 | 1.28 (0.83-1.97) |  | - |  |
|  ≥30 | 7/2,971 | 0.89 (0.41-1.92) | 0.48i | - | - |
|  Per 5 kg/m2 | 150/52,030 | 0.99 (0.97-1.02) | 0.61 | 0.87 (0.43-1.74) | 0.69 |
| Diabetes mellitusf |  |  |  |  |  |
|  No | 128/46,115 | 1 |  | 1 |  |
|  Yes | 14/5,927 | 0.83 (0.48-1.44) | 0.50 | 3.77 (1.15-12.31) | 0.03 |
| Aspirin intake  |  |  |  |  |  |
|  No | 103/36,765 | 1 |  | 1 |  |
|  Yes | 39/15,277 | 0.92 (0.64-1.33) | 0.67 | 0.46 (0.13-1.66) | 0.24 |
| Ibuprofen intake  |  |  |  |  |  |
|  No | 119/43,432 | 1 |  | 1 |  |
|  Yes | 23/8,610 | 0.98 (0.63-1.53) | 0.93 | 0.78 (0.20-2.99) | 0.71 |
| Multivitamin supplement intake |  |  |  |  |  |
|  No | 64/24,942 | 1 |  | 1 |  |
|  Yes | 78/27,100 | 1.21 (0.85-1.70)g | 0.29 | 0.75 (0.25-2.24) | 0.61 |
| Calcium supplement intake |  |  |  |  |  |
|  No | 107/37,886  | 1 |  | 1 |  |
|  Yes | 35/14,156 | 0.90 (0.61-1.32) | 0.58 | 1.20 (0.37-3.84) | 0.76 |
|  |  |  |  |  |  |
| Surveillance intervalh  |  |  |  |  |  |
|  ≤1 year | 12/2,006 | 1 |  | - | - |
|  >1-2 years | 31/9,181 | 0.59 (0.30-1.15) |  | - | - |
|  >2-3 years | 7/7,496 | 0.16 (0.06-0.42) |  | - | - |
|  >3 years | 42/16,716 | 0.44 (0.23-0.84) | 0.02i | - | - |
|  No colonoscopy | 1/913 | 0.19 (0.03-1.50) |  | - | - |

Multivariable model included personal factors, initial tumour pathology features, lifestyle factors and surveillance interval as shown in the table, and country of data collection (United States; Canada; Australia). HRs reported using BMI recent in the multivariate model; HR for BMI at 20 years reported using BMI at 20 years in place of BMI recent in the model.

aWald P-value.

bAccording to International Classification of Diseases for Oncology, Third Edition anatomical site codes: C18.0, C18.2, C18.3, C18.4 (proximal colon); C18.5, C18.6, C18.7, C19.9, C20.9 (distal colon/rectum); C18.8, C18.9, C26.0 (unspecified colon).

cCigarette smoking was defined as ever smoking one cigarette per day for 3 months or longer. Current smoking was indicated when persons reported smoking in the referent period (defined as two years prior to enrolment); former smoking was indicated when persons stopped smoking before the referent period.

dDerived from pre-diagnosis recent body weight (defined as “weight 2 years prior to enrolment”) in kg divided by height in meters squared.

eDerived from body weight at age 20 years in kg divided by height in meters squared.

fSelf-report that diabetes mellitus was diagnosed by a physician, excluding gestational diabetes.

gAdjusted for country of data collection (United States; Canada; Australia).

hDerived from time since initial colorectal cancer diagnosis divided by number of post-diagnosis surveillance colonoscopies: multivariable-adjusted HRs omitted due to exceedingly small values.

iP-value for trend: calculated from Cox regression models with ordinal variables as continuous measures.

**Supplementary Table 2.** Hazard ratios (HR) and 95% confidence intervals (CI) for associations between personal factors, initial colorectal cancer (CRC) tumour pathology features, lifestyle factors and surveillance interval and the risk of metachronous CRCwithout censoring at the age at diagnosis of metachronous colorectal adenoma (Cases=143; Person-years=52,560)

|  |  |  |
| --- | --- | --- |
|  | HR (95% CI) | *P* valuea |
| *Personal factors* |  |  |
| Age at initial diagnosis  |  |  |
|  Per 10-year | 0.93 (0.79-1.10) | 0.40 |
| Sex |  |  |
|  Male | 1 |  |
|  Female | 1.31 (0.90-1.90) | 0.16 |
| First-degree family history of colorectal cancer |  |  |
|  No | 1 |  |
|  Yes | 1.16 (0.80-1.69) | 0.44 |
|  |  |  |
| *Initial tumour features* |  |  |
| Synchronous CRCb |  |  |
|  No | 1 |  |
|  Yes | 3.11 (1.52-6.37) | 0.002 |
| Synchronous adenomab |  |  |
|  No  | 1 |  |
|  Yes | 0.81 (0.47-1.39) | 0.44 |
| Site of initial tumourc |  |  |
|  Proximal colon | 4.06 (2.74-6.01) | <0.001 |
|  Distal colon/rectum | 1 |  |
|  Unspecified colon | 5.83 (2.95-11.56) | <0.001 |
| TNM stageb |  |  |
|  I | 1 |  |
|  II | 0.64 (0.34-1.18) |  |
|  III | 0.51 (0.21-1.19) |  |
|  IV | 0.37 (0.09-1.59) | 0.14j |
| Tumour gradeb |  |  |
|  Low | 1 |  |
|  High | 0.69 (0.39-1.22) | 0.20 |
| Tumour mismatch repair statusb |  |  |
|  Proficient  | 1 |  |
|  Deficient  | 0.99 (0.57-1.71) | 0.97 |
|  |  |  |
| *Lifestyle factors* |  |  |
| Cigarette smoking statusd |  |  |
|  Never | 1 |  |
|  Former | 1.21 (0.83-1.75) |  |
|  Current | 1.31 (0.75-2.31) | 0.26j |
| Alcohol intakeb |  |  |
|  Per 14 g/day increment | 1.01 (0.92-1.10) | 0.91 |
| BMI recente, kg/m2 |  |  |
|  Per 5 kg/m2 | 0.99 (0.97-1.02) | 0.70 |
| BMI at age 20 yearsf, kg/m2 |  |  |
|  Per 5 kg/m2 | 0.99 (0.97-1.01) | 0.55 |
| Diabetes mellitusg |  |  |
|  No | 1 |  |
|  Yes | 0.84 (0.48-1.47) | 0.55 |
| Aspirin intake  |  |  |
|  No | 1 |  |
|  Yes | 0.91 (0.61-1.34) | 0.62 |
| Ibuprofen intake  |  |  |
|  No | 1 |  |
|  Yes | 0.95 (0.61-1.50) | 0.84 |
| Multivitamin supplement intake |  |  |
|  No | 1 |  |
|  Yes | 1.20 (0.84-1.72) | 0.31 |
| Calcium supplement intake |  |  |
|  No | 1 |  |
|  Yes | 0.79 (0.52-1.20) | 0.27 |
|  |  |  |
| Surveillance intervalb,i  |  |  |
|  ≤1 year | 1 |  |
|  >1-2 years | 0.67 (0.35-1.28) |  |
|  >2-3 years | 0.30 (0.12-0.80) |  |
|  >3 years | 0.53 (0.26-1.09) | 0.10j |
|  No colonoscopy | 0.22 (0.03-1.78) |  |

Multivariable model included personal factors, initial tumour pathology features, lifestyle factors and surveillance interval as shown in the table, and country of data collection (United States; Canada; Australia). HRs reported using BMI recent in the multivariate model; HR for BMI at 20 years reported using BMI at 20 years in place of BMI recent in the model.

aWald P-value.

bHRs calculated using imputed values from multiple imputation method for missing values.

cAccording to International Classification of Diseases for Oncology, Third Edition anatomical site codes: C18.0, C18.2, C18.3, C18.4 (proximal colon); C18.5, C18.6, C18.7, C19.9, C20.9 (distal colon/rectum); C18.8, C18.9, C26.0 (unspecified colon).

dCigarette smoking was defined as ever smoking one cigarette per day for 3 months or longer. Current smoking was indicated when persons reported smoking in the referent period (defined as two years prior to enrolment); former smoking was indicated when persons stopped smoking before the referent period.

eDerived from pre-diagnosis recent body weight (defined as “weight 2 years prior to enrolment”) in kg divided by height in meters squared.

fDerived from body weight at age 20 years in kg divided by height in meters squared.

gSelf-report that diabetes mellitus was diagnosed by a physician, excluding gestational diabetes.

hAdjusted for country of data collection (United States; Canada; Australia).

iDerived from time since initial colorectal cancer diagnosis divided by number of post-diagnosis surveillance colonoscopies.

jP-value for trend: calculated from Cox regression models with ordinal variables as continuous measures.