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Jayasekara, H; English, DR; Haydon, A; Hodge, AM; Lynch, BM; Rosty, C; Williamson, EJ; Clendenning, M; Southey, MC; Jenkins, MA; Room, R; Hopper, JL; Milne, RL; Buchanan, DD; Giles, GG; MacInnis, RJ (2017) Associations of alcohol intake, smoking, physical activity and obesity with survival following colorectal cancer diagnosis by stage, anatomic site and tumor molecular subtype. *International journal of cancer Journal international du cancer*. ISSN 0020-7136 DOI: <https://doi.org/10.1002/ijc.31049>

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Associations for Alcohol Intake, Smoking, Physical Activity and Obesity with Survival Following Colorectal Cancer Diagnosis by Stage, Site and Tumor Molecular Subtype

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Keywords: Colorectal cancer; survival; alcohol intake; smoking; physical activity; obesity

Abbreviations: CI, confidence interval; CIMP, CpG island methylator phenotype; HR, hazard ratio; ICD-O-3, International Classification of Diseases for Oncology; MCCA, Melbourne Collaborative Cohort Study; MSI, microsatellite instability; MSS, microsatellite stable; VCR, Victorian Cancer Registry

Abstract: 275 words **Text:** 2,993 words **Figures:** 1 **Tables:** 5 **References:** 64

ABSTRACT

Purpose

While survival following colorectal cancer (CRC) has improved in countries with high CRC incidence, the effect of lifestyle factors on survival after diagnosis is not well established. We examined lifestyle factors measured before diagnosis as prognostic factors for CRC.

Patients and Methods

The Melbourne Collaborative Cohort Study collected data on alcohol intake, cigarette smoking and physical activity, and body measurements at baseline (1990-94) and wave 2 (2003-07). We included participants diagnosed to 31 August 2015 with incident stage I-III CRC within 10-years post exposure assessment. Information on tumor characteristics was obtained from the cancer registry and histopathologic review, while vital status was obtained from the cancer registry and national death indices. Tumor DNA was tested for somatic mutations in oncogenes *BRAF* and *KRAS*. Cox regression was used to estimate hazard ratios (HRs) for potential prognostic factors for overall and CRC-specific mortality.

Results

Of 724 eligible CRC cases, 339 died (including 170 from CRC) during an average of 9.0 years of follow-up. Exercise (non-occupational/leisure-time) was associated with better CRC-specific survival for stage II (HR, 0.25; 95% CI, 0.10 to 0.60) but not stage I or III disease (P for interaction = .01), and possibly for colon and *KRAS* wild-type tumors. Waist circumference was inversely associated with CRC-specific survival (HR, 1.256 per 10 cm increment; 95% CI, 1.08 to 1.44), independent of stage, site and tumor molecular status. Cigarette smoking was associated with lower overall survival, with suggestive evidence of worse survival for *BRAF* mutated CRC, but not with CRC-specific survival. Alcohol intake was not associated with survival.

Conclusion

We have identified pre-diagnostic predictors of survival following CRC that may have clinical and public health relevance.

INTRODUCTION

Survival following a diagnosis of colorectal cancer (CRC) has improved in recent decades but a substantial proportion of those diagnosed continue to die from CRC, making it important to identify potential prognostic factors.¹ Studies of factors associated with disease outcomes have predominantly examined the role of tumor characteristics, with stage at diagnosis being the most important prognostic factor,² but have also evaluated potentially modifiable lifestyle factors such as obesity, physical activity and diet.³⁻⁶ A previous analysis from the Melbourne Collaborative Cohort Study (MCCS) reported that physical activity prior to diagnosis was associated with better overall and CRC-specific survival for patients diagnosed with stage II or III CRC, while increased central obesity was associated with poorer survival.⁷ While the role of smoking has been examined widely,⁸⁻¹⁴ more recent studies have assessed alcohol intake.^{10,15-19} Studies of CRC survival by tumor molecular characteristics have mostly used microsatellite instability (MSI) status.²⁰

The present study updates and extends a previous analysis of MCCS data by including an additional 11 years of follow-up, additional lifestyle factors including smoking and alcohol intake, and survival by CRC subtype based on somatic mutations in the oncogenes *BRAF* (V600E) and *KRAS* (codons 12 and 13).

PATIENTS AND METHODS

Study Population

The MCCS is an Australian prospective cohort study of 41,513 people (99.2% aged 40-69 years; 58.9% women) recruited during 1990-94 from Melbourne residents.²¹ At study entry (baseline), participants attended clinics where demographic, anthropometric, lifestyle and dietary information was collected and anthropometric measurements performed. Additional information was collected between 2003 and 2007 (wave 2). Participants gave written informed consent to participate and for investigators to obtain access to their medical records. The study protocol was approved by the Cancer Council Victoria's Human Research Ethics Committee.

For this analysis, we selected participants who did not have a previous diagnosis of cancer at enrolment and had an incident CRC diagnosed during follow-up, within 10 years of exposure assessment at baseline or wave 2 (Appendix Fig A1). Individuals with metastatic disease (stage IV) were excluded for greater comparability with previous studies²²⁻²⁴ and to minimize potential effects of reverse causation such as undiagnosed advanced disease altering lifestyle patterns before diagnosis. Participants who had a CRC diagnosed less than 6 months after exposure assessment were also excluded. CRC cases were defined as having a first histopathological diagnosis of adenocarcinoma of the colon or rectum reported to the Victorian Cancer Registry (VCR), coded following the 3rd Revision of the International Classification of Diseases for Oncology (ICD-O-3) as colon (C180, C182-189) or rectum (C199, C209). Carcinomas of the appendix, anus and anal canal (including overlapping lesions of rectum, anus and anal canal) were excluded. In-situ lesions were also excluded. Participants with metachronous CRC were censored at the time of diagnosis of the second primary CRC for the CRC-specific survival analysis. Tumor site, stage and degree of

differentiation were obtained from VCR and standardized review of archival tumor tissue by a gastrointestinal histopathologist (CR).

Assessment of Demographic Information, Alcohol Intake, Smoking and Physical Activity

Structured interview schedules were used at baseline to obtain demographic information, and at both waves to collect information about alcohol intake, smoking and physical activity. At baseline, participants were asked whether they smoked at least seven cigarettes a week, and if so, the number of cigarettes they smoked per day and the duration of smoking. At wave 2, smokers at baseline were asked if they were still smoking, and if so the amount smoked. Alcohol intake for non-abstainers was recorded as frequency and quantity of intake per drinking occasion, for beer, wine and spirits, for decades of age starting from 20 years. Detailed information on the method of calculating lifetime intake (g/day) at baseline has been reported previously;²⁵ at wave 2, intake during the previous year was assessed similarly. Physical activity at baseline was assessed by three separate questions regarding frequency of non-occupational vigorous and moderate physical activity, and walking, as described by Haydon et al.⁷ Those who answered ‘not at all’ to vigorous and moderate physical activity were classified as ‘non-exercisers’ while those who reported any regular exercise (≥ 1 time per week) were classified as ‘exercisers’. Individuals were classified as ‘walkers’ if they walked for recreation and/or exercise at least once a week over the last six months, while individuals were classified as ‘non-walkers’ if they answered ‘not at all’ to all three physical activity questions. Additionally, the responses to each question were coded as 0 (‘none’), 1.5 (1-2 per week) and 4 (≥ 3 per week). Scores for walking and moderate exercise were added together along with two times the score for vigorous exercise to generate a physical activity score for each participant. A modified form of the long version of the International Physical

Activity Questionnaire (available at www.ipaq.ki.se) was used at wave 2.²⁶ It includes questions about duration and frequency of vigorous and moderate physical activity, and walking.

Assessment of Body Composition

Height was measured at baseline to 1 mm with a stadiometer. At both baseline and wave 2, weight was measured to 100 g using digital electronic scales and waist circumferences to 1 mm using a two-meter metal anthropometric tape.²⁷

Tumor Characterization

The American Joint Committee on Cancer (AJCC) staging system was used to categorize stage: stage I (T₁₋₂, N₀, M₀), stage II (T₃₋₄, N₀, M₀) and stage III (T_{any}, N₁₋₂, M₀). The tumor with the highest stage was used when synchronous CRCs were present. The degree of tumor differentiation was classified as ‘well’, ‘moderately’ and ‘poorly’ differentiated. Separate categories were used for cases with missing stage and degree of differentiation. For tumors diagnosed by June 2009, we attempted to obtain archival tumor tissue and to test tumor DNA for the V600E mutation in *BRAF*, which accounts for approximately 90% of *BRAF* mutations in colorectal cancer,²⁸ using a fluorescent allele-specific PCR discrimination method as previously described²⁹ and for mutations in exon 2 of *KRAS* by direct Sanger sequencing.³⁰

Ascertainment of Deaths and Cause of Death

Vital status was ascertained through the VCR and the National Death Index (NDI). Cause of death was assigned as reported in the NDI and VCR.

Statistical Analysis

We used Cox regression³¹ with time since CRC diagnosis as the time axis to estimate hazard ratios (HR) and 95% confidence intervals (CI) for overall and CRC-specific mortality. Analysis time began at date of diagnosis and ended at death or 31 August 2015 (the date at which ascertainment of deaths was complete), whichever came first. For CRC-specific survival, individuals were censored at death when the cause of death was anything other than CRC, but were excluded when no information was available on cause of death. Lifestyle factors included current and past alcohol intake (continuous: per 10 g/day increment; categorical: lifetime abstention, former drinker, >0-19, 20-39, \geq 40 g/day), cigarette smoking status (categorical: never, former, current smokers), number of cigarettes (categorical: 0, 1-10, 11-20, \geq 21 per day), duration of smoking (categorical: 0, >0-15, 16-30, \geq 31 years), time since quitting (categorical: <10, \geq 10 years), physical activity (categorical: score 0, >0-3.9, \geq 4-5.9, \geq 6), exercising (categorical: non-exercisers, exercisers), walking (categorical: non-walkers, walkers), BMI (continuous: per 5 kg/m²; categorical: normal <25 kg/m², overweight 25-29 kg/m², obese \geq 30 kg/m²),³² and waist circumference (continuous: per 10 cm; categorical: healthy <94 cm for males, <80 cm for females; action levels \geq 94 cm for males, \geq 80 cm for females).³³ Baseline exposure data were used for participants diagnosed with CRC within 10 years post study enrolment whereas wave 2 exposure data were used for participants diagnosed with CRC within 10 years post wave 2. All multivariate models were adjusted for age at diagnosis of CRC (categorical: <60, 60-69, \geq 70 years), year of diagnosis (categorical: <1999, 1999-2005, \geq 2006), sex and the country of birth (Australia/United Kingdom, Italy/Greece). We repeated the analyses adjusting additionally for AJCC stage (categorical: stage I, stage II, stage III), degree of differentiation (categorical: well/moderately, poorly differentiated) and anatomic site (colon, rectum), potential mediators of associations between the lifestyle factors and survival following CRC. A sensitivity

analysis performed to account for potential effects of reverse causation excluded participants with pre-existing diagnosis of heart attack, stroke, angina or diabetes. A subgroup analysis was performed to test differences in associations by *BRAF* and *KRAS* status for participants for whom tumor molecular data were available. We fitted interaction terms to test for differences in HRs for each lifestyle factor by stage, anatomic site, and *BRAF* and *KRAS* status. We compared nested models using the likelihood ratio test. We examined each model for outliers and influential points and used Schoenfeld residuals to assess the proportional hazard assumptions; there was no evidence that they were violated. All statistical analyses were performed using Stata 14.1 (StataCorp, College Station, TX).

RESULTS

Among eligible MCCS participants with no previous diagnosis of cancer at enrolment, 1,227 incident CRC cases were diagnosed. We excluded 43 diagnosed less than 6 months and 269 diagnosed more than 10 years after exposure measurement exposure measurement, 157 with stage IV disease and 34 with missing information on covariates, leaving 724 CRC cases (467 colon, 257 rectal) for the overall survival analysis (Appendix Fig A2). The median time from exposure measurement to CRC diagnosis was 4.9 years, and the average follow-up from CRC diagnosis was 9.0 years. During follow-up, 339 deaths occurred, of which 170 (50%) were CRC-specific; cause of death was unknown for 26. Characteristics of participants included in the analysis are shown in Table 1. Participants with unknown tumor molecular data did not differ from others in terms of age, sex or ethnicity (data not shown).

HR estimates for overall and CRC-specific mortality are shown in Table 2 and Table 3, respectively. Lifetime and past alcohol intakes were not associated with survival. Current alcohol intake was associated with better CRC-specific survival (i.e. lower mortality) (HR, 0.90 per 10 g/day increment; 95% CI, 0.82 to 0.99); the HR was 0.91 per 10 g/day increment (95% CI, 0.83 to 1.01) when former drinkers were excluded (data not shown). Cigarette smoking was not associated with CRC-specific survival although lower CRC-specific survival was evident for former smokers who quit ≥ 10 years ago (HR, 1.92; 95% CI, 1.04 to 3.55). A dose-dependent association between smoking and overall survival was observed (P for trend = .04 for number of cigarettes smoked per day). Higher waist circumference was associated with lower overall and CRC-specific survival (e.g. HR, 1.25 per 10 cm increment; 95% CI, 1.08 to 1.44 for CRC-specific survival); the association for BMI with survival was less clear (HR, 1.18 per 5 kg/m² increment; 95% CI, 0.98 to 1.42 for CRC-specific survival). Measures of physical activity were not associated with survival in this analysis. These

associations did not materially change when adjusted for primary CRC-related features, or when participants with pre-existing disease were excluded (Appendix Table A1).

Exercise prior to diagnosis was associated with improved CRC-specific survival for those diagnosed with stage II (HR, 0.25; 95% CI, 0.10 to 0.60) but not with stage I or III CRC (P for interaction = .01) (Table 4; additional results are shown in Appendix Table A2). There was also suggestive evidence that the better disease-specific survival in relation to exercise prior to diagnosis was limited to colon cancer (HR, 0.68; 95% CI, 0.44 to 1.05; P for interaction = .09) (Table 5) and to *KRAS* wild-type CRC (HR, 0.61; 95% CI, 0.38 to 0.98; P for interaction = .1) (Fig 1; Appendix Table A4). These associations were stronger after adjustment for primary CRC-related features (Appendix Table A3; Appendix Table A5). Differential survival observed for walking (lowest overall survival observed for stage III: HR, 1.84; 95% CI, 1.10 to 3.08; P for interaction = .01) was not evident when participants with existing illnesses were excluded (P for interaction = .2); excluding participants with existing illnesses did not change results for exercise (HR, 0.22; 95% CI, 0.08 to 0.57 for stage II CRC; P for interaction = .002 for CRC-specific survival) (data not shown).

There was weak evidence of approximately a two-fold lower survival for smokers with *BRAF* mutated CRC (HR, 1.82; 95% CI, 0.99 to 3.36; P for interaction = .08) (Fig 1; Appendix Table A4).

DISCUSSION

While lower CRC-specific survival was observed for individuals who were obese prior to CRC diagnosis, exercise was only associated with better disease-specific survival for stage II disease, and possibly, colon cancer and *KRAS* wild-type tumors. Although cigarette smoking prior to CRC diagnosis was associated with lower overall survival with suggestive evidence of worse survival for *BRAF* mutated CRC, smoking was not associated with CRC-specific survival. Pre diagnosis alcohol intake was not related to survival.

Smoking, a known risk factor³⁴ especially for *BRAF* mutated and MSI-high CRC incidence,³⁵ is a strong determinant of mortality.³⁶ The absence of an association with CRC-specific survival in our study contrasts with evidence from the North Central Cancer Treatment Group Phase III Trial N0147 which found adverse disease-free survival for smoking for *BRAF* wild-type and *KRAS* mutated colon cancer.¹⁴ However, the definition of survival outcome was different (time to colon cancer recurrence or death from any cause) and the study included only participants with stage III colon cancer.¹⁴ Using the same cohort of clinical trial participants, authors observed a potentially beneficial effect on survival from wine intake with no association for drinking overall.¹⁶ Long term alcohol intake is associated with a ~50% higher risk of CRC,³⁷ but evidence for differential risks by anatomic location³⁸⁻⁴⁰ or by molecular subtype (MSI,⁴¹⁻⁴⁵ *BRAF* and *CIMP*^{46,47}) has been inconsistent. The absence of an association between lifetime alcohol intake and survival in our study is consistent with existing evidence for alcohol.^{10,15,17,18} We believe that the apparent CRC-specific survival benefit seen for current intake in our study may have been influenced by the inclusion of ‘*sick quitters*’ within abstainers.⁴⁸ Authors of a recent analysis of a large population-based German cohort¹⁹ discussed the possible contamination of abstainers with ‘*sick quitters*’ as a possible explanation for poorer CRC-specific survival seen for abstainers among nonmetastatic CRC patients with current as well as lifetime intake; Rehm et al. have

shown that using lifetime abstention as the reference category may not completely avoid contamination.⁴⁹

Our findings for obesity and exercise are biologically plausible and replicate existing evidence^{6,13,22-24,50,51} considering the inverse relationship between the two. Among the postulated biological explanations for an association between obesity and survival following CRC are increased insulin resistance,³ inflammation and oxidative stress, and impaired immune surveillance,⁵² factors which might also be related to CRC incidence. On the other hand, physical activity favorably affects survival following CRC via increased insulin-like growth factor binding proteins,^{3,53} and by modulating oxidative DNA damage.⁵⁴ We replicated our previous findings for a detrimental association between obesity and survival following CRC that is more evident with waist circumference than with BMI, and for differential associations with exercise, which most likely differentiated those who were physically active from those who were not in our data, by disease stage.⁷ Contrary to others, we did not observe differential survival for obesity by disease stage.^{5,50} We speculate that evidence of differential survival by disease stage for walking status that diminished when participants with existing illness were excluded may have been due to reverse causation.

Our finding suggestive of a greater survival benefit from exercise for colon but not rectal cancer is in line with findings from the Seattle Colon Cancer Family Registry,²² and may reflect a greater diagnostic delay and symptomatic disease at the time of diagnosis for rectal cancer.⁵⁵ Existing evidence for differential survival by anatomic site for obesity is inconsistent,^{5,51,56} and we did not observe any.

Few findings have been reported for subtypes defined by somatic mutations in oncogenes. Evidence of an association between obesity and the risk of *BRAF* mutated or CIMP+ CRC (which is highly correlated with somatic mutations in *BRAF*) is inconsistent.^{57,58} It is possible that we may not have observed lower survival associated with obesity for *BRAF* mutated

CRC in the present study due to the exclusion of stage IV tumors (stage IV tumors and *BRAF* mutated CRC have worse survival⁵⁹). We observed weak evidence suggestive of a survival benefit of exercise that was limited to *KRAS* wild-type CRC. The only comparable study that has considered subtypes based on *BRAF* and *KRAS* status did not observe evidence of differential survival.²² *BRAF* and *KRAS* are routinely assessed for screening for Lynch syndrome and for assessing response to therapy, respectively,^{60,61} and any potential survival benefit for *KRAS* wild-type CRC could have important clinical implications.

Strengths of this analysis include: prospective design; near complete follow-up; relatively large number of deaths; and availability of detailed information on lifestyle factors. This study also contributes to a sparse literature by examining the relationship between alcohol intake and survival following CRC¹⁰ and by evaluating survival by *BRAF* and *KRAS* status.^{14,22} the etiology of each CRC is unique⁶²⁻⁶⁴

There are several limitations. First, the unavailability of full details of treatment has prevented the evaluation of treatment as an effect modifier but disease stage is highly correlated with treatment. Second, we addressed the issue of reverse causation by excluding individuals with metastatic disease, who had a CRC diagnosed less than 6 months after exposure assessment, and, in a sensitivity analysis, with pre-existing illness prior to CRC diagnosis although ill health altering lifestyle patterns before CRC cannot be excluded completely. Third, measurement error and misclassification of alcohol intake, and inaccuracy of self-reported physical activity measurement may have attenuated associations. Fourth, archival tissue from the CRC was unavailable for a substantial number of cases. However, this may not have biased the observed associations by *BRAF* and *KRAS* status as cases with and without tumor molecular data varied little by demographic characteristics such as ethnicity and sex which were both strongly associated with molecular subtype. Finally, misclassification of underlying cause of death is also possible.

In conclusion, smoking, exercise and obesity are not only risk factors for CRC, but are associated with survival after diagnosis. Future research is necessary to determine whether exercising, losing weight and smoking cessation after diagnosis affect survival, and to examine underlying biological and molecular pathological mechanisms underpinning these associations.

ACKNOWLEDGEMENTS

We thank the original investigators and the diligent team, who recruited the participants and who continue working on follow-up, for their contribution. We also express our gratitude to the many thousands of Melbourne residents who continue to participate in the study.

Financial support

MCCS cohort recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further supported by Australian National Health and Medical Research Council grants 209057, 251553 and 504711 and by infrastructure provided by Cancer Council Victoria. BML is supported by a Fellowship from the National Breast Cancer Foundation. MAJ is an NHMRC Senior Research Fellow. JLH is a NHMRC Senior Principal Research Fellow. DDB is a University of Melbourne Research at Melbourne Accelerator Program (R@MAP) Senior Research Fellow. RR's position was funded by the Foundation for Alcohol Research and Education. The funding sources played no role in the study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Table 1. Characteristics for CRC cases in the Melbourne Collaborative Cohort Study, for all cases and according to smoking status, exercising and waist circumference

	All cases (n=724)	Cigarette smoking		Exercising		Waist circumference ^a	
		Ever smokers (n=350)	Never-smokers (n=374)	Exercisers (n=319)	Non-exercisers (n=405)	Healthy (n=259)	Action level (n=465)
Age at diagnosis (years)							
Median (range)	71 (44-87)	70 (44-87)	71 (44-87)	71 (45-87)	70 (44-87)	70 (44-87)	71 (45-87)
Sex (n, %)							
Male	357 (49.3)	231 (66.0)	126 (33.7)	154 (48.3)	203 (50.1)	122 (47.1)	235 (50.5)
Female	367 (50.7)	119 (34.0)	248 (66.3)	165 (51.7)	202 (49.9)	137 (52.9)	230 (49.5)
Country of birth (n, %)							
Australia/United Kingdom	585 (80.8)	279 (79.7)	306 (81.8)	277 (86.8)	308 (76.1)	226 (87.3)	359 (77.2)
Italy/Greece	139 (19.2)	71 (20.3)	68 (18.2)	42 (13.2)	97 (23.9)	33 (12.7)	106 (22.8)
AJCC stage (n, %)							
Stage I	200 (27.6)	105 (30.0)	95 (25.4)	84 (26.3)	116 (28.6)	72 (27.8)	128 (27.5)
Stage II	251 (34.7)	121 (34.6)	130 (34.8)	109 (34.2)	142 (35.1)	88 (34.0)	163 (35.1)
Stage III	232 (32.0)	101 (28.9)	131 (35.0)	107 (35.5)	125 (30.9)	85 (32.8)	147 (31.6)
Unknown	41 (5.7)	23 (6.6)	18 (4.8)	19 (6.0)	22 (5.4)	14 (5.4)	27 (5.8)
Degree of differentiation (n, %)							
Well	21 (2.9)	13 (3.7)	8 (2.1)	11 (3.4)	10 (2.5)	10 (3.9)	11 (2.4)
Moderate	466 (64.4)	219 (62.6)	247 (66.1)	205 (64.3)	261 (64.4)	163 (62.9)	303 (65.2)
Poor	163 (22.5)	74 (21.1)	89 (23.8)	72 (22.6)	91 (22.5)	62 (23.9)	101 (21.7)
Unknown	74 (10.2)	44 (12.6)	30 (8.0)	31 (9.7)	43 (10.6)	24 (9.3)	50 (10.7)
Anatomic site							
Colon	467 (64.5)	223 (63.7)	244 (65.2)	201 (63.0)	266 (65.7)	161 (62.2)	306 (65.8)
Rectum	257 (35.5)	127 (36.3)	130 (34.8)	118 (37.0)	139 (34.3)	98 (37.8)	159 (34.2)
<i>BRAF</i> status							
<i>BRAF</i> wild-type	383 (52.9)	186 (53.1)	197 (52.7)	167 (52.3)	216 (53.3)	151 (58.3)	232 (49.9)
<i>BRAF</i> mutated	82 (11.3)	39 (11.2)	43 (11.5)	42 (13.2)	40 (9.9)	31 (12.0)	51 (11.0)
Unknown	259 (35.8)	125 (35.7)	134 (35.8)	110 (34.5)	149 (36.8)	77 (29.7)	182 (39.1)
<i>KRAS</i> status							
<i>KRAS</i> wild-type	335 (46.3)	160 (45.7)	175 (46.8)	145 (45.4)	190 (46.9)	130 (50.2)	205 (44.1)
<i>KRAS</i> mutated	131 (18.1)	67 (19.1)	64 (17.1)	65 (20.4)	66 (16.3)	53 (20.5)	78 (16.8)

Unknown	258 (35.6)	123 (35.2)	135 (36.1)	109 (34.2)	149 (36.8)	76 (29.3)	182 (39.1)
Lifetime alcohol intake (n, %) ^b							
Mean (SD) (g/day)	19.5 (21.9)	24.3 (23.9)	13.2 (17.2)	18.9 (21.2)	20.0 (22.5)	18.2 (20.1)	20.2 (22.8)
Cigarette smoking (n, %)							
Never	374 (51.7)	-	-	169 (53.0)	205 (50.6)	135 (52.1)	239 (51.4)
Former	289 (39.9)	-	-	130 (40.7)	159 (39.3)	97 (37.5)	192 (41.3)
Current	61 (8.4)	-	-	20 (6.3)	41 (10.1)	27 (10.4)	34 (7.3)
Exercising (n, %)							
Non-exercisers	405 (55.9)	200 (57.1)	205 (54.8)	-	-	125 (48.3)	280 (60.2)
Exercisers	319 (44.1)	150 (42.9)	169 (45.2)	-	-	134 (51.7)	185 (39.8)
Walking (n, %) ^c							
Non-walkers	132 (20.8)	68 (21.9)	64 (19.7)	0 (0.0)	132 (32.6)	47 (21.4)	85 (20.5)
Walkers	503 (79.2)	243 (78.1)	260 (80.3)	230 (100.0)	273 (67.4)	173 (78.6)	330 (79.5)
BMI (n, %)							
<25 kg/m ²	206 (28.4)	98 (28.0)	108 (28.9)	104 (32.6)	102 (25.2)	162 (62.6)	44 (9.5)
25-29 kg/m ²	354 (48.9)	173 (49.4)	181 (48.4)	161 (50.5)	193 (47.6)	92 (35.5)	262 (56.3)
≥30 kg/m ²	164 (22.7)	79 (22.6)	85 (22.7)	54 (16.9)	110 (27.2)	5 (1.9)	159 (34.2)
Waist circumference (n, %)							
Healthy	259 (35.8)	124 (35.4)	135 (36.1)	134 (42.0)	125 (30.9)	-	-
Action level	465 (64.2)	226 (64.6)	239 (63.9)	185 (58.0)	280 (69.1)	-	-

SD, standard deviation; BMI, body mass index; AJCC, American Joint Committee on Cancer.

^aWaist circumference: healthy, <94 cm for males and <80 cm for females; action level, ≥94 cm for males and ≥80 cm for females.

^bExcluding lifetime abstainers (n=183).

^cPeople who only reported exercising were excluded.

Table 2 Hazard ratios (HR) and 95% confidence intervals (CI) for overall mortality by alcohol intake, cigarette smoking, physical activity, exercise, walking, BMI and waist circumference

	No.	No. of events	Primary model ^a		Model adjusted for primary CRC-related features ^b		
			HR	95% CI	HR	95% CI	
<i>Alcohol intake</i>							
Lifetime intake (per 10 g/day)	724	339	1.01	0.95 to 1.07	1.03	0.97 to 1.09	
<i>P</i> value			0.8		0.3		
Current intake (per 10 g/day)	724	339	0.97	0.91 to 1.03	0.97	0.91 to 1.03	
<i>P</i> value			0.3		0.3		
Lifetime abstention	183	89	Reference		Reference		
Former drinkers	82	40	1.10	0.74 to 1.63	1.30	0.87 to 1.93	
>0-19 g/day	281	126	0.86	0.64 to 1.14	0.99	0.74 to 1.33	
20-39 g/day	103	49	0.96	0.66 to 1.40	1.04	0.71 to 1.53	
≥40 g/day	75	35	0.80	0.52 to 1.23	0.89	0.58 to 1.38	
<i>P</i> for trend ^c			0.4		0.8		
Age 20-29 intake (per 10 g/day)	724	339	1.02	0.97 to 1.07	1.04	0.99 to 1.09	
<i>P</i> value			0.5		0.2		
Age 30-39 intake (per 10 g/day)	724	339	1.01	0.96 to 1.06	1.03	0.98 to 1.08	
<i>P</i> value			0.8		0.3		
Age 40-49 intake (per 10 g/day)	724	339	1.02	0.97 to 1.06	1.03	0.98 to 1.08	
<i>P</i> value			0.5		0.2		
<i>Cigarette smoking</i>							
Smoking status							
Never	374	154	Reference		Reference		
Ever	350	185	1.27	1.00 to 1.60	1.32	1.04 to 1.67	
<i>P</i> for trend			0.05		0.02		
Smoking status							
Never	374	154	Reference		Reference		
Former	289	153	1.25	0.98 to 1.59	1.29	1.01 to 1.65	
Current	61	32	1.37	0.92 to 2.05	1.44	0.96 to 2.15	
Number of cigarettes per day							
0	374	154	Reference		Reference		
1-10	111	54	1.17	0.85 to 1.61	1.22	0.89 to 1.68	
11-20	140	78	1.36	1.02 to 1.82	1.37	1.02 to 1.83	
≥21	95	52	1.33	0.93 to 1.88	1.49	1.04 to 2.13	
Unknown	4	1	-		-		
<i>P</i> for trend			0.04		0.01		
Duration of smoking (years)							
0	374	154	Reference		Reference		
>0-15	67	34	1.24	0.85 to 1.83	1.26	0.86 to 1.85	
16-30	116	58	1.20	0.87 to 1.66	1.46	1.05 to 2.03	
≥31	167	93	1.32	0.99 to 1.74	1.26	0.95 to 1.67	
<i>P</i> for trend			0.05		0.05		
Time since quitting (years) ^d							
<10	70	33	Reference		Reference		
≥10	219	120	1.31	0.88 to 1.97	1.48	0.98 to 2.23	
<i>P</i> for trend			0.2		0.06		
<i>Physical activity</i>							
Physical activity score							
0	132	72	Reference		Reference		

>0-3.9	112	46	0.85	0.58 to 1.24	0.89	0.61 to 1.31
≥4-5.9	313	147	0.96	0.71 to 1.29	0.93	0.69 to 1.26
≥6	167	74	0.86	0.61 to 1.21	0.86	0.61 to 1.21
<i>P</i> for trend				0.4		0.6
Exercising						
Non-exercisers	405	197	Reference		Reference	
Exercisers	319	142	0.86	0.69 to 1.07	0.84	0.67 to 1.05
<i>P</i> for trend				0.2		0.1
Walking^e						
Non-walkers	132	72	Reference		Reference	
Walkers	503	231	0.95	0.72 to 1.27	0.95	0.71 to 1.26
<i>P</i> for trend				0.7		0.7
Body size						
BMI (per 5 kg/m ²)	724	339	1.14	0.99 to 1.30	1.13	0.99 to 1.29
<i>P</i> value				0.06		0.08
Normal	206	89	Reference		Reference	
Overweight	354	175	1.22	0.94 to 1.60	1.39	1.06 to 1.82
Obese	164	75	1.17	0.85 to 1.61	1.14	0.82 to 1.56
<i>P</i> for trend				0.2		0.3
Waist circumference ^f (per 10 cm)	724	339	1.19	1.07 to 1.32	1.18	1.06 to 1.31
<i>P</i> value				0.001		0.002
Healthy	259	112	Reference		Reference	
Action levels	465	227	1.24	0.98 to 1.56	1.29	1.02 to 1.64
<i>P</i> for trend				0.07		0.03

^aAdjusted for age at diagnosis, year of diagnosis, sex and country of birth in addition to the exposures shown in the table.

^bAdjusted for age at diagnosis, year of diagnosis, sex, country of birth, American Joint Committee on Cancer stage, degree of differentiation and anatomic site in addition to the exposures shown in the table.

^cCalculated excluding former drinkers.

^dIncludes only former smokers.

^ePeople who only reported exercising were excluded.

^fWaist circumference categorized as healthy (<94 cm for males; <80 cm for females) and action levels (≥94 cm for males; ≥80 cm for females).

Table 3 Hazard ratios (HR) and 95% confidence intervals (CI) for CRC-specific mortality by alcohol intake, cigarette smoking, physical activity, exercise, walking, BMI and waist circumference

	No.	No. of events	Primary model ^a		Model adjusted for primary CRC-related features ^b	
			HR	95% CI	HR	95% CI
<i>Alcohol intake</i>						
Lifetime intake (per 10 g/day)	698	170	0.97	0.89 to 1.05	0.99	0.91 to 1.08
<i>P</i> value			0.4		0.8	
Current intake (per 10 g/day)	698	170	0.90	0.82 to 0.99	0.88	0.79 to 0.98
<i>P</i> value			0.03		0.02	
Lifetime abstention	177	46	Reference		Reference	
Former drinkers	80	24	1.24	0.73 to 2.08	1.50	0.89 to 2.53
>0-19 g/day	268	63	0.80	0.54 to 1.21	0.92	0.61 to 1.39
20-39 g/day	100	24	0.81	0.47 to 1.39	0.86	0.50 to 1.47
≥40 g/day	73	13	0.55	0.28 to 1.06	0.57	0.29 to 1.13
<i>P</i> for trend ^c			0.09		0.2	
Age 20-29 intake (per 10 g/day)	698	170	0.98	0.91 to 1.06	1.01	0.94 to 1.08
<i>P</i> value			0.7		0.8	
Age 30-39 intake (per 10 g/day)	698	170	0.99	0.93 to 1.06	1.02	0.95 to 1.09
<i>P</i> value			0.8		0.6	
Age 40-49 intake (per 10 g/day)	698	170	0.98	0.91 to 1.05	1.00	0.93 to 1.08
<i>P</i> value			0.5		0.9	
<i>Cigarette smoking</i>						
Smoking status						
Never	366	81	Reference		Reference	
Ever	332	89	1.28	0.92 to 1.79	1.34	0.96 to 1.86
<i>P</i> for trend			0.1		0.09	
Smoking status						
Never	366	81	Reference		Reference	
Former	274	76	1.33	0.94 to 1.88	1.37	0.97 to 1.93
Current	58	13	1.07	0.58 to 1.96	1.18	0.64 to 2.17
Number of cigarettes per day						
0	366	81	Reference		Reference	
1-10	104	31	1.48	0.96 to 2.28	1.47	0.96 to 2.27
11-20	134	36	1.25	0.82 to 1.89	1.25	0.82 to 1.90
≥21	91	22	1.11	0.66 to 1.85	1.33	0.78 to 2.25
Unknown	3	0	-		-	
<i>P</i> for trend			0.4		0.2	
Duration of smoking (years)						
0			Reference		Reference	
>0-15	366	81	1.63	0.99 to 2.67	1.65	1.00 to 2.71
16-30	63	21	1.10	0.69 to 1.76	1.49	0.92 to 2.39
≥31	111	27	1.26	0.84 to 1.89	1.14	0.76 to 1.72
<i>P</i> for trend	158	41	0.3		0.4	
Time since quitting (years) ^d						
<10	68	13	Reference		Reference	
≥10	206	63	1.92	1.04 to 3.55	2.29	1.21 to 4.31
<i>P</i> for trend			0.04		0.01	
<i>Physical activity</i>						
Physical activity score						
0	124	34	Reference		Reference	

>0-3.9	109	21	0.88	0.50 to 1.53	0.97	0.55 to 1.69
≥4-5.9	304	77	1.13	0.74 to 1.72	1.08	0.71 to 1.66
≥6	161	38	1.04	0.64 to 1.69	1.09	0.67 to 1.78
<i>P</i> for trend				0.5		0.6
Exercising						
Non-exercisers	387	99	Reference		Reference	
Exercisers	311	71	0.88	0.64 to 1.20	0.83	0.61 to 1.14
<i>P</i> for trend				0.4		0.3
Walking^c						
Non-walkers	124	34	Reference		Reference	
Walkers	485	113	1.06	0.71 to 1.60	1.07	0.71 to 1.61
<i>P</i> for trend				0.8		0.7
Body size						
BMI (per 5 kg/m ²)	698	170	1.18	0.98 to 1.42	1.19	0.99 to 1.43
<i>P</i> value				0.08		0.06
Normal	196	39	Reference		Reference	
Overweight	343	87	1.33	0.90 to 1.97	1.65	1.10 to 2.46
Obese	159	44	1.39	0.88 to 2.17	1.41	0.90 to 2.21
<i>P</i> for trend				0.1		0.1
Waist circumference ^f (per 10 cm)	698	170	1.25	1.08 to 1.44	1.26	1.09 to 1.45
<i>P</i> value				0.002		0.001
Healthy	247	53	Reference		Reference	
Action levels	451	117	1.35	0.97 to 1.89	1.52	1.08 to 2.14
<i>P</i> for trend				0.08		0.02

^aAdjusted for age at diagnosis, year of diagnosis, sex and country of birth in addition to the exposures shown in the table.

^bAdjusted for age at diagnosis, year of diagnosis, sex, country of birth, American Joint Committee on Cancer stage, degree of differentiation and anatomic site in addition to the exposures shown in the table.

^cCalculated excluding former drinkers.

^dIncludes only former smokers.

^ePeople who only reported exercising were excluded.

^fWaist circumference categorized as healthy (<94 cm for males; <80 cm for females) and action levels (≥94 cm for males; ≥80 cm for females).

Table 4. Hazard ratios (HR) and 95% confidence intervals (CI) for overall and CRC-specific mortality by alcohol intake, cigarette smoking, physical activity, exercise, walking, BMI and waist circumference, by AJCC stage

	Stage I		Stage II		Stage III		<i>P</i> for interaction
	HR ^a	95% CI	HR ^a	95% CI	HR ^a	95% CI	
<i>Overall mortality</i>							
Lifetime alcohol intake (per 10 g/day)	1.12	1.02 to 1.23	1.01	0.92 to 1.12	0.99	0.91 to 1.08	0.1
Ever smokers	1.16	0.70 to 1.93	1.28	0.85 to 1.91	1.45	1.01 to 2.07	0.8
Physical activity score ≥ 4	0.83	0.50 to 1.38	0.85	0.57 to 1.26	1.13	0.78 to 1.65	0.5
Exercisers	0.96	0.58 to 1.58	0.60	0.40 to 0.90	0.91	0.64 to 1.28	0.2
Walkers ^b	0.65	0.37 to 1.15	0.75	0.47 to 1.18	1.84	1.10 to 3.08	0.01
BMI (per 5 kg/m ²)	1.21	0.90 to 1.62	1.17	0.91 to 1.51	1.14	0.94 to 1.39	0.9
Waist circumference (per 10 cm)	1.24	1.02 to 1.52	1.26	1.06 to 1.49	1.11	0.96 to 1.29	0.4
<i>CRC-specific mortality</i>							
Lifetime alcohol intake (per 10 g/day)	1.13	0.96 to 1.34	0.94	0.78 to 1.13	0.98	0.88 to 1.09	0.3
Ever smokers	1.31	0.46 to 3.74	1.40	0.71 to 2.75	1.44	0.94 to 2.20	0.9
Physical activity score ≥ 4	0.80	0.28 to 2.26	0.85	0.43 to 1.67	1.18	0.76 to 1.85	0.6
Exercisers	0.88	0.31 to 2.49	0.25	0.10 to 0.60	0.98	0.65 to 1.46	0.01
Walkers ^b	0.64	0.19 to 2.13	0.67	0.32 to 1.38	1.83	0.98 to 3.42	0.07
BMI (per 5 kg/m ²)	1.71	0.95 to 3.06	1.19	0.78 to 1.79	1.18	0.94 to 1.49	0.5
Waist circumference (per 10 cm)	1.88	1.22 to 2.90	1.28	0.97 to 1.69	1.19	0.99 to 1.42	0.1

BMI, body mass index.

^aAdjusted for age at diagnosis, year of diagnosis, sex and country of birth in addition to the exposures shown in the table.

^bPeople who only reported exercising were excluded.

Table 5. Hazard ratios (HR) and 95% confidence intervals (CI) for overall and disease-specific mortality by alcohol intake, cigarette smoking, physical activity, exercise, walking, BMI and waist circumference, by anatomic site

	Colon		Rectum		<i>P</i> for interaction
	HR ^a	95% CI	HR ^a	95% CI	
<i>Overall mortality</i>					
Lifetime alcohol intake (per 10 g/day)	1.01	0.94 to 1.08	1.00	0.92 to 1.09	0.9
Ever smokers	1.47	1.10 to 1.97	1.01	0.70 to 1.44	0.1
Physical activity score ≥ 4	1.01	0.75 to 1.37	0.99	0.69 to 1.42	0.9
Exercisers	0.78	0.59 to 1.04	1.00	0.70 to 1.42	0.3
Walkers ^b	0.98	0.67 to 1.42	0.92	0.61 to 1.41	0.8
BMI (per 5 kg/m ²)	1.11	0.94 to 1.31	1.22	0.97 to 1.53	0.5
Waist circumference (per 10 cm)	1.20	1.06 to 1.35	1.19	1.02 to 1.39	0.9
<i>Disease-specific mortality</i>					
Lifetime alcohol intake (per 10 g/day)	0.99	0.89 to 1.10	0.93	0.82 to 1.05	0.4
Ever smokers	1.47	0.95 to 2.27	1.09	0.69 to 1.74	0.3
Physical activity score ≥ 4	1.32	0.82 to 2.12	1.09	0.68 to 1.75	0.6
Exercisers	0.68	0.44 to 1.05	1.18	0.74 to 1.86	0.09
Walkers ^b	1.46	0.78 to 2.73	0.86	0.49 to 1.49	0.2
BMI (per 5 kg/m ²)	1.17	0.92 to 1.48	1.23	0.93 to 1.63	0.8
Waist circumference (per 10 cm)	1.31	1.10 to 1.56	1.21	1.00 to 1.48	0.5

BMI, body mass index.

^aAdjusted for age at diagnosis, year of diagnosis, sex and country of birth in addition to the exposures shown in the table.

^bPeople who only reported exercising were excluded.

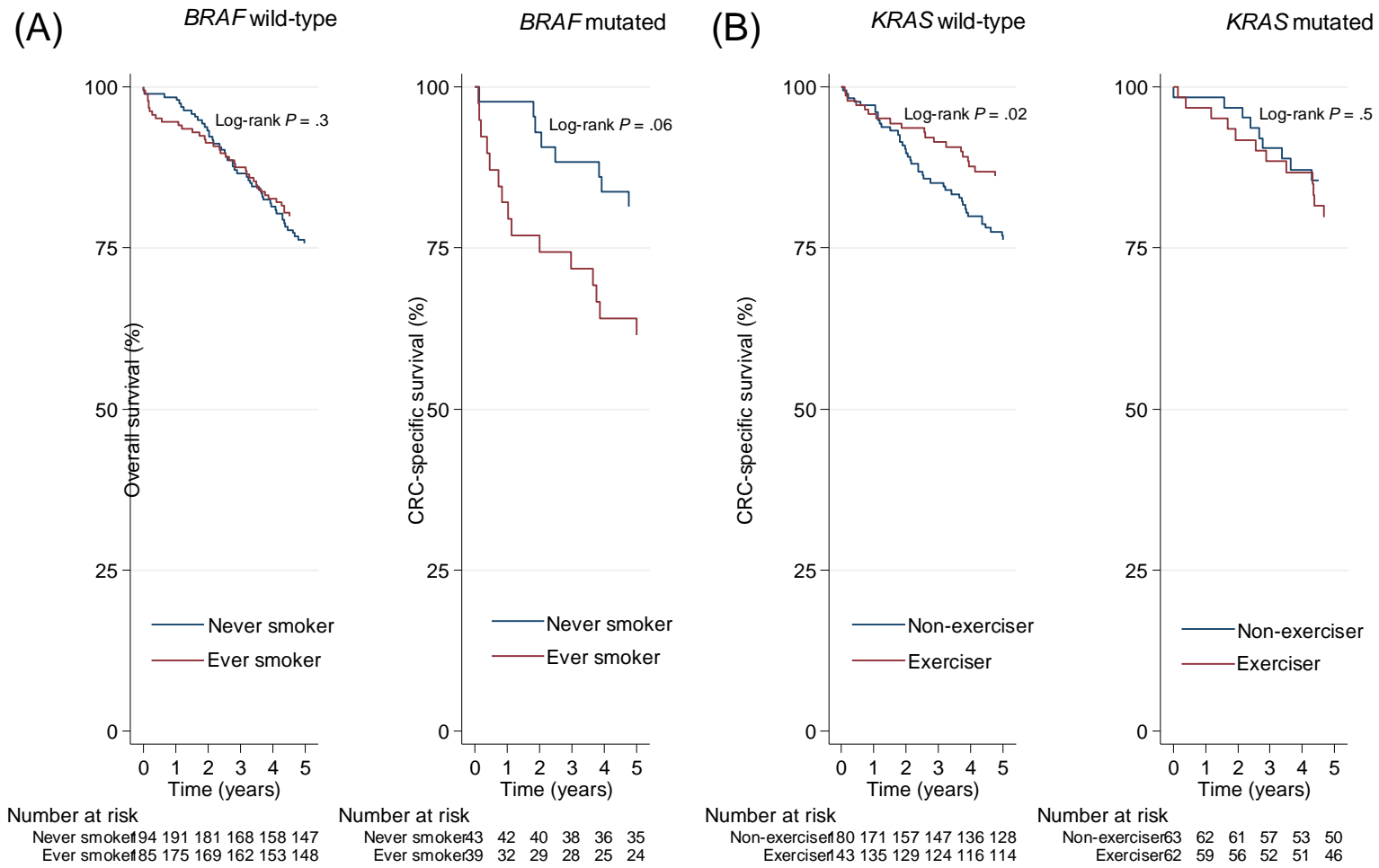


Fig 1. Kaplan-Meier curves for (A) overall survival for cigarette smoking by *BRAF* status and (B) CRC-specific survival for exercise by *KRAS* status.

Appendix

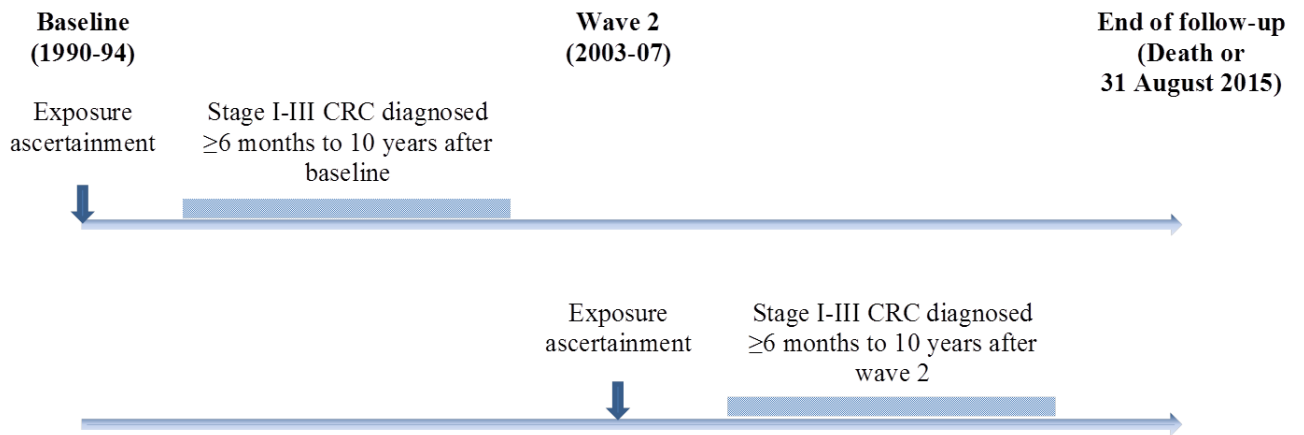


Fig A1. Diagram showing exposure ascertainment and colorectal cancer (CRC) diagnosis for Melbourne Collaborative Cohort Study participants.

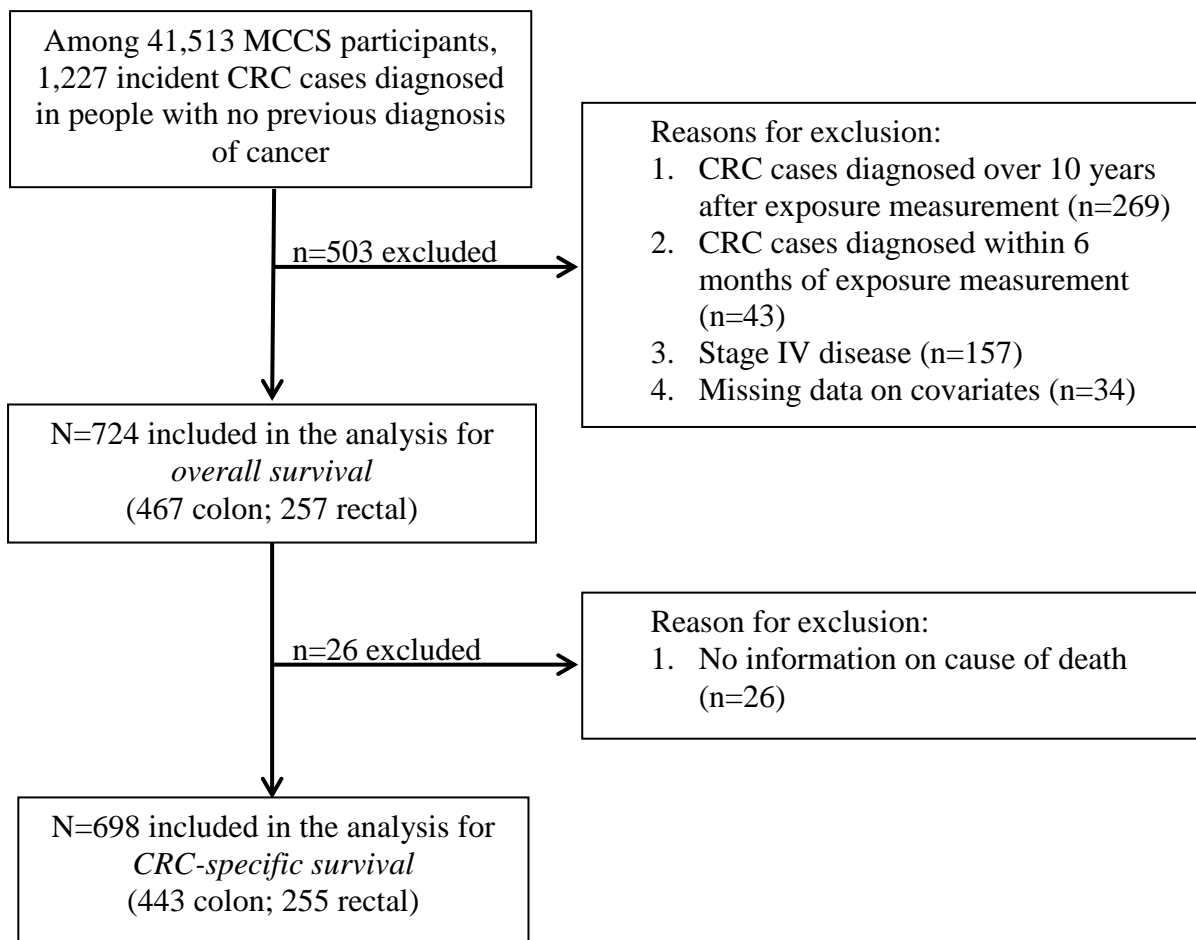


Fig A2. Flow diagram showing selection of participants.

Table A1. Hazard ratios (HR) and 95% confidence intervals (CI) for overall and CRC-specific mortality by alcohol intake, cigarette smoking, physical activity, exercise, walking, BMI and waist circumference for participants with no pre-existing illness*

	Overall mortality				CRC-specific mortality			
	No.	No. of events	HR ^a	95% CI	No.	No. of events	HR ^a	95% CI
<i>Alcohol intake</i>								
Lifetime intake (per 10 g/day)	597	265	1.00	0.94 to 1.07	577	141	0.93	0.84 to 1.04
<i>P</i> value			0.9				0.2	
Current intake (per 10 g/day)	597	265	0.97	0.91 to 1.04	577	141	0.91	0.82 to 1.01
<i>P</i> value			0.4				0.08	
Lifetime abstention	152	68	Reference		148	38	Reference	
Former drinkers	63	28	1.02	0.64 to 1.64	62	18	1.15	0.63 to 2.10
>0-19 g/day	229	101	0.92	0.66 to 1.28	218	53	0.86	0.55 to 1.34
20-39 g/day	90	40	0.93	0.60 to 1.43	87	21	0.84	0.47 to 1.52
≥40 g/day	63	28	0.89	0.55 to 1.46	62	11	0.61	0.29 to 1.26
<i>P</i> for trend ^b			0.6				0.2	
Age 20-29 intake (per 10 g/day)	597	265	1.03	0.97 to 1.09	577	141	0.97	0.89 to 1.07
<i>P</i> value			0.4				0.6	
Age 30-39 intake (per 10 g/day)	597	265	1.00	0.95 to 1.06	577	141	0.97	0.89 to 1.05
<i>P</i> value			0.9				0.4	
Age 40-49 intake (per 10 g/day)	597	265	1.01	0.95 to 1.06	577	141	0.95	0.87 to 1.03
<i>P</i> value			0.9				0.2	
<i>Cigarette smoking</i>								
Smoking status								
Never	313	124	Reference		306	73	Reference	
Ever	284	141	1.25	0.95 to 1.63	271	68	1.11	0.77 to 1.60
<i>P</i> for trend			0.1				0.6	
Smoking status								
Never	313	124	Reference		306	73	Reference	
Former	228	112	1.20	0.91 to 1.59	217	56	1.15	0.78 to 1.68
Current	56	29	1.45	0.94 to 2.24	54	12	0.97	0.51 to 1.85
Number of cigarettes per day								
0	313	124	Reference		306	73	Reference	
1-10	95	43	1.12	0.78 to 1.61	90	25	1.24	0.77 to 1.99
11-20	112	59	1.39	1.00 to 1.94	109	28	1.13	0.71 to 1.79
≥21	73	38	1.30	0.87 to 1.95	69	15	0.94	0.51 to 1.71
Unknown	4	1	-		3	0	-	
<i>P</i> for trend			0.07				0.9	
Duration of smoking (years)								
0	313	124	Reference		306	73	Reference	
>0-15	57	26	1.25	0.81 to 1.94	54	17	1.48	0.86 to 2.55
16-30	96	45	1.17	0.81 to 1.69	92	19	0.84	0.49 to 1.44
≥31	131	70	1.30	0.94 to 1.78	125	32	1.15	0.74 to 1.81
<i>P</i> for trend			0.1				0.8	
Time since quitting (years) ^c								
<10	56	24	Reference		54	9	Reference	
≥10	172	88	1.45	0.90 to 2.34	163	47	2.05	0.98 to 4.26
<i>P</i> for trend			0.1				0.06	
<i>Physical activity</i>								
Physical activity score								
0	108	56	Reference		102	29	Reference	
>0-3.9	91	38	0.94	0.61 to 1.44	88	19	0.97	0.54 to 1.76

≥4-5.9	256	109	0.96	0.68 to 1.36	250	60	1.06	0.66 to 1.71
≥6	142	62	0.95	0.64 to 1.40	137	33	1.09	0.64 to 1.86
<i>P</i> for trend			0.8				0.5	
Exercising								
Non-exercisers	326	146	Reference		313	79	Reference	
Exercisers	271	119	0.94	0.73 to 1.21	264	62	0.96	0.68 to 1.36
<i>P</i> for trend			0.6				0.8	
Walking^d								
Non-walkers	108	56	Reference		102	29	Reference	
Walkers	412	178	1.03	0.74 to 1.43	398	91	1.07	0.68 to 1.69
<i>P</i> for trend			0.9				0.8	
Body size								
BMI (per 5 kg/m ²)	597	265	1.16	1.00 to 1.36	577	141	1.16	0.95 to 1.42
<i>P</i> value			0.05				0.2	
Normal	185	75	Reference		176	36	Reference	
Overweight	283	134	1.27	0.94 to 1.71	275	70	1.29	0.85 to 1.97
Obese	129	56	1.20	0.83 to 1.73	126	35	1.32	0.80 to 2.16
<i>P</i> for trend			0.2				0.2	
Waist circumference ^e (per 10 cm)	597	265	1.22	1.08 to 1.37	577	141	1.27	1.08 to 1.48
<i>P</i> value			0.001				0.003	
Healthy	231	93	Reference		220	45	Reference	
Action levels	366	172	1.34	1.03 to 1.74	357	96	1.51	1.04 to 2.18
<i>P</i> for trend			0.03				0.03	

*Pre-existing illness defined as myocardial infarction, stroke, angina and diabetes mellitus.

^aAdjusted for age at diagnosis, year of diagnosis, sex and country of birth in addition to the exposures shown in table.

^bCalculated excluding former drinkers.

^cIncludes only former smokers.

^dPeople who only reported exercising were excluded.

^eWaist circumference categorized as healthy (<94 cm for males; <80 cm for females) and action levels (≥94 cm for males; ≥80 cm for females).

Table A2. Hazard ratios (HR) and 95% confidence intervals (CI) for overall and CRC-specific mortality by alcohol intake, cigarette smoking, physical activity, exercise, walking, BMI and waist circumference, by AJCC stage

	Stage I		Stage II		Stage III		<i>P</i> for interaction
	HR ^a	95% CI	HR ^a	95% CI	HR ^a	95% CI	
<i>Overall mortality</i>							
Lifetime alcohol intake (per 10 g/day)	1.11	1.01 to 1.22	1.01	0.92 to 1.12	0.99	0.91 to 1.08	0.2
Ever smokers	1.14	0.69 to 1.89	1.27	0.85 to 1.90	1.40	0.98 to 2.00	0.8
Physical activity score ≥ 4	0.89	0.53 to 1.47	0.87	0.58 to 1.30	1.11	0.76 to 1.63	0.6
Exercisers	0.97	0.59 to 1.60	0.60	0.39 to 0.90	0.92	0.65 to 1.30	0.2
Walkers ^b	0.68	0.38 to 1.21	0.73	0.46 to 1.16	1.79	1.07 to 3.00	0.01
BMI (per 5 kg/m ²)	1.18	0.88 to 1.59	1.17	0.91 to 1.50	1.17	0.96 to 1.43	0.9
Waist circumference (per 10 cm)	1.24	1.01 to 1.52	1.26	1.06 to 1.50	1.13	0.97 to 1.30	0.5
<i>CRC-specific mortality</i>							
Lifetime alcohol intake (per 10 g/day)	1.12	0.94 to 1.34	0.94	0.78 to 1.13	0.98	0.87 to 1.09	0.3
Ever smokers	1.30	0.45 to 3.70	1.40	0.71 to 2.76	1.38	0.90 to 2.11	0.9
Physical activity score ≥ 4	0.84	0.30 to 2.40	0.91	0.46 to 1.79	1.17	0.74 to 1.84	0.8
Exercisers	0.88	0.31 to 2.49	0.25	0.10 to 0.60	0.98	0.65 to 1.46	0.01
Walkers ^b	0.70	0.21 to 2.33	0.71	0.34 to 1.47	1.82	0.96 to 3.44	0.1
BMI (per 5 kg/m ²)	1.70	0.94 to 3.05	1.16	0.77 to 1.74	1.21	0.96 to 1.53	0.5
Waist circumference (per 10 cm)	1.92	1.23 to 2.99	1.29	0.98 to 1.70	1.20	1.00 to 1.43	0.1

BMI, body mass index.

^aAdjusted for age at diagnosis, year of diagnosis, sex, country of birth, degree of differentiation and anatomic site in addition to the exposures shown in the table.

^bPeople who only reported exercising were excluded.

Table A3. Hazard ratios (HR) and 95% confidence intervals (CI) for overall and disease-specific mortality by alcohol intake, cigarette smoking, physical activity, exercise, walking, BMI and waist circumference, by anatomic site

	Colon		Rectum		<i>P</i> for interaction
	HR ^a	95% CI	HR ^a	95% CI	
<i>Overall mortality</i>					
Lifetime alcohol intake (per 10 g/day)	1.04	0.98 to 1.12	1.00	0.92 to 1.09	0.4
Ever smokers	1.51	1.13 to 2.03	1.05	0.73 to 1.51	0.1
Physical activity score ≥ 4	0.98	0.73 to 1.33	0.91	0.63 to 1.31	0.7
Exercisers	0.72	0.54 to 0.95	1.09	0.76 to 1.55	0.08
Walkers ^b	0.99	0.68 to 1.44	0.90	0.59 to 1.37	0.7
BMI (per 5 kg/m ²)	1.05	0.89 to 1.24	1.31	1.04 to 1.64	0.1
Waist circumference (per 10 cm)	1.14	1.01 to 1.29	1.26	1.07 to 1.47	0.3
<i>Disease-specific mortality</i>					
Lifetime alcohol intake (per 10 g/day)	1.04	0.93 to 1.15	0.93	0.82 to 1.06	0.2
Ever smokers	1.50	0.97 to 2.31	1.16	0.73 to 1.85	0.4
Physical activity score ≥ 4	1.20	0.75 to 1.93	1.02	0.63 to 1.64	0.6
Exercisers	0.61	0.39 to 0.94	1.22	0.77 to 1.94	0.03
Walkers ^b	1.39	0.74 to 2.59	0.84	0.49 to 1.46	0.2
BMI (per 5 kg/m ²)	1.10	0.87 to 1.39	1.35	1.01 to 1.80	0.3
Waist circumference (per 10 cm)	1.22	1.03 to 1.46	1.32	1.07 to 1.62	0.6

BMI, body mass index.

^aAdjusted for age at diagnosis, year of diagnosis, sex, country of birth, American Joint Committee on Cancer stage and degree of differentiation in addition to the exposures shown in the table.

^bPeople who only reported exercising were excluded.

Table A4. Hazard ratios (HR) and 95% confidence intervals (CI) for overall and CRC-specific mortality by alcohol intake, cigarette smoking, physical activity, exercise, walking, BMI and waist circumference, by tumor molecular subtype

	<i>BRAF</i> wild-type		<i>BRAF</i> mutated		<i>P</i> for interaction	<i>KRAS</i> wild-type		<i>KRAS</i> mutated		<i>P</i> for interaction
	HR ^a	95% CI	HR ^a	95% CI		HR ^a	95% CI	HR ^a	95% CI	
<i>Overall mortality</i>										
Lifetime alcohol intake (per 10 g/day)	1.02	0.96 to 1.09	1.16	0.97 to 1.39	0.2	1.03	0.95 to 1.11	1.04	0.94 to 1.14	0.9
Ever smokers	1.01	0.74 to 1.38	1.82	0.99 to 3.36	0.08	1.20	0.87 to 1.66	1.00	0.59 to 1.68	0.5
Physical activity score ≥ 4	1.08	0.80 to 1.46	0.95	0.51 to 1.78	0.7	0.95	0.69 to 1.30	1.45	0.83 to 2.51	0.2
Exercisers	0.89	0.66 to 1.20	0.65	0.35 to 1.20	0.4	0.78	0.57 to 1.07	1.06	0.64 to 1.75	0.3
Walkers ^c	1.09	0.77 to 1.55	0.86	0.40 to 1.87	0.6	1.11	0.77 to 1.59	0.93	0.46 to 1.86	0.7
BMI (per 5 kg/m ²)	1.17	0.97 to 1.42	1.14	0.78 to 1.66	0.9	1.20	0.99 to 1.47	1.07	0.78 to 1.47	0.5
Waist circumference (per 10 cm)	1.14	0.99 to 1.30	1.28	0.99 to 1.66	0.4	1.17	1.01 to 1.34	1.15	0.92 to 1.43	0.9
<i>CRC-specific mortality</i>										
Lifetime alcohol intake (per 10 g/day)	0.99	0.90 to 1.10	1.09	0.85 to 1.39	0.5	1.01	0.89 to 1.13	0.99	0.86 to 1.14	0.9
Ever smokers	1.02	0.65 to 1.59	2.18	0.92 to 5.17	0.1	1.15	0.73 to 1.83	1.27	0.62 to 2.59	0.8
Physical activity score ≥ 4	1.15	0.75 to 1.76	1.04	0.42 to 2.54	0.8	0.93	0.59 to 1.47	1.90	0.85 to 4.23	0.1
Exercisers	0.77	0.50 to 1.18	0.69	0.29 to 1.64	0.8	0.61	0.38 to 0.98	1.23	0.62 to 2.42	0.1
Walkers ^c	1.12	0.68 to 1.82	1.56	0.44 to 5.52	0.6	1.21	0.72 to 2.03	1.07	0.40 to 2.89	0.8
BMI (per 5 kg/m ²)	1.26	0.98 to 1.62	1.06	0.61 to 1.84	0.6	1.33	1.01 to 1.75	1.01	0.67 to 1.52	0.3
Waist circumference (per 10 cm)	1.23	1.02 to 1.49	1.20	0.84 to 1.70	0.9	1.25	1.03 to 1.53	1.18	0.88 to 1.58	0.7

BMI, body mass index.

^aAdjusted for age at diagnosis, year of diagnosis, sex and country of birth in addition to the exposures shown in the table.

^bPeople who only reported exercising were excluded.

Table A5. Hazard ratios (HR) and 95% confidence intervals (CI) for overall and CRC-specific mortality by alcohol intake, cigarette smoking, physical activity, exercise, walking, BMI and waist circumference, by tumor molecular subtype

	<i>BRAF</i> wild-type		<i>BRAF</i> mutated		<i>P</i> for interaction	<i>KRAS</i> wild-type		<i>KRAS</i> mutated		<i>P</i> for interaction
	HR ^a	95% CI	HR ^a	95% CI		HR ^a	95% CI	HR ^a	95% CI	
<i>Overall mortality</i>										
Lifetime alcohol intake (per 10 g/day)	1.01	0.94 to 1.08	1.15	0.97 to 1.38	0.2	1.01	0.94 to 1.09	1.05	0.95 to 1.16	0.5
Ever smokers	1.03	0.75 to 1.42	2.10	1.14 to 3.89	0.04	1.27	0.92 to 1.76	0.99	0.58 to 1.68	0.4
Physical activity score ≥ 4	1.09	0.80 to 1.48	0.85	0.45 to 1.61	0.5	0.94	0.68 to 1.30	1.41	0.81 to 2.46	0.2
Exercisers	0.92	0.68 to 1.24	0.57	0.30 to 1.05	0.2	0.75	0.55 to 1.04	1.12	0.67 to 1.86	0.2
Walkers ^b	1.19	0.83 to 1.70	0.77	0.35 to 1.68	0.3	1.14	0.79 to 1.66	1.00	0.49 to 2.01	0.7
BMI (per 5 kg/m ²)	1.22	1.01 to 1.47	1.03	0.72 to 1.49	0.4	1.21	0.99 to 1.47	1.08	0.77 to 1.51	0.6
Waist circumference (per 10 cm)	1.17	1.02 to 1.35	1.19	0.92 to 1.54	0.9	1.17	1.02 to 1.35	1.19	0.94 to 1.49	0.9
<i>CRC-specific mortality</i>										
Lifetime alcohol intake (per 10 g/day)	0.98	0.89 to 1.09	1.08	0.85 to 1.39	0.5	0.97	0.86 to 1.09	1.04	0.90 to 1.21	0.5
Ever smokers	1.09	0.70 to 1.70	2.68	1.12 to 6.39	0.06	1.29	0.81 to 2.06	1.29	0.63 to 2.64	0.9
Physical activity score ≥ 4	1.10	0.71 to 1.71	0.81	0.32 to 2.02	0.5	0.84	0.53 to 1.34	1.85	0.82 to 4.18	0.09
Exercisers	0.77	0.50 to 1.19	0.52	0.22 to 1.27	0.4	0.56	0.35 to 0.90	1.29	0.65 to 2.58	0.05
Walkers ^b	1.17	0.71 to 1.93	1.13	0.31 to 4.09	0.9	1.17	0.68 to 2.01	1.13	0.42 to 3.05	0.9
BMI (per 5 kg/m ²)	1.33	1.03 to 1.71	0.85	0.50 to 1.43	0.1	1.31	1.01 to 1.72	1.02	0.66 to 1.58	0.3
Waist circumference (per 10 cm)	1.32	1.09 to 1.59	1.00	0.70 to 1.41	0.2	1.25	1.03 to 1.52	1.30	0.94 to 1.79	0.8

BMI, body mass index.

^aAdjusted for age at diagnosis, year of diagnosis, sex, country of birth, American Joint Committee on Cancer stage, degree of differentiation and anatomic site in addition to the exposures shown in the table.

^bPeople who only reported exercising were excluded.