RESEARCH ARTICLE

Behavioural and Metabolic Risk Factors for Mortality from Colon and Rectum Cancer: Analysis of Data from the Asia-Pacific Cohort Studies Collaboration

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Abstract

Background: Colorectal cancer has several modifiable behavioural risk factors but their relationship to the risk of colon and rectum cancer separately and between countries with high and low incidence is not clear. Methods: Data from participants in the Asia Pacific Cohort Studies Collaboration (APCSC) were used to estimate mortality from colon (International Classification of Diseases, revision 9 (ICD-9) 153, ICD-10 C18) and rectum (ICD-9 154, ICD-10 C19-20) cancers. Data on age, body mass index (BMI), serum cholesterol, height, smoking, physical activity, alcohol and diabetes mellitus were entered into Cox proportional hazards models. Results: 600,427 adults contributed 4,281,239 person-years follow-up. The mean ages (SD) for Asian and Australia/New Zealand cohorts were 44.0 (9.5) and 53.4 (14.5) years, respectively. 455 colon and 158 rectum cancer deaths were observed. Increasing age, BMI and attained adult height were associated with increased hazards of death from colorectal cancer, and physical activity was associated with a reduced hazard. After multiple adjustment, any physical activity was associated with a 28% lower hazard of colon cancer mortality (HR 0.72, 95%CI 0.53-0.96) and lower rectum cancer mortality (HR 0.75, 95%CI 0.45-1.27). A 2cm increase in height increased colon and all colorectal cancer mortality by 7% and 6% respectively. Conclusions: Physical inactivity and greater BMI are modifiable risk factors for colon cancer in both Western and Asian populations. Further efforts are needed to promote physical activity and reduce obesity while biological research is needed to understand the mechanisms by which they act to cause cancer mortality.

Keywords: Cancer - colon - rectum - mortality - risk factors - anthropometric - behavioural

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Introduction

Cancers of the colon and rectum have the third and fourth highest incidences worldwide for women and men, respectively (Parkin et al., 2005). Incidence is 20% higher for men than women and higher in Western compared with Asian countries (Parkin et al., 2005). The most compelling evidence indicates that alcoholic beverages, body and abdominal fatness and attained adult height increase incidence while physical activity is protective (World Cancer Research Fund, 2007; Huxley et al., 2009). Poorer survival for patients from the most deprived, compared with the most affluent, socio-economic circumstances has also been reported (Mitry et al., 2008a; 2008b). Although the effect sizes of some risk factors differ between colon and rectum cancers, many studies treat them as a single cancer. Alcohol has been reported to have a stronger and more consistent relationship with colon cancers by some studies (Mizoue et al., 2006; 2008) and with rectum cancers by others (Huxley et al., 2009). Body mass index (BMI) is associated with colon cancer risk (World Cancer Research Fund, 2007) although the association is stronger for men than women (Renehan et al., 2008). A significant association has been reported between BMI and rectum cancer, for men only, by two meta-analyses (Larsson and Wolk, 2007; Renehan et al.,

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2008). Smoking increases both incidence and mortality from all colorectal cancers but has a stronger association with rectum than with colon cancer (Liang et al., 2009). Although there is little heterogeneity in the evidence that physical activity lowers the risk of colorectal cancer and that a dose-response relationship exists, the evidence is clearer for an association with colon than rectum cancer (World Cancer Research Fund, 2007).

The Asia Pacific Cohort Studies Collaboration (APCSC) (Woodward et al., 2006) has previously reported on risk factors for mortality from total colorectal cancer (Asia Pacific Cohort Studies Collaboration, 2007). This included estimates of mortality rates for individual studies and by region. Mortality rates were about three times higher in Australia and New Zealand compared with Asian cohorts (Asia Pacific Cohort Studies Collaboration, 2007). Height, BMI and cigarette smoking were all found to be significantly associated with increased risk of mortality from colorectal cancer while physical activity was found to be protective. No significant effect on colorectal cancer mortality was observed for alcohol consumption, waist circumference, fasting blood glucose or diabetes (Asia Pacific Cohort Studies Collaboration, 2007). Given the differential effects of alcohol, smoking and physical activity on cancers of the colon and rectum reported elsewhere, further work was indicated to refine outcome definitions and examine their relationships with risk factors. The present study aimed to analyse the particular relationships between anthropometric and potentially modifiable metabolic risk factors on mortality from cancers of the colon and rectum separately.

Materials and Methods

Details of identification, data collection and verification of studies included in the APCSC are described elsewhere (Woodward et al., 2006; Zhang et al., 1999). Studies were included if they were based in the Asia Pacific region, used a cohort study design, and had at least 5000 person-years of follow-up. Mortality was classified using both International Classification of Diseases (ICD) versions 9 and 10. Colon cancer was defined as ICD-9 153 and ICD-10 C18. Rectum cancer, including rectosigmoid tumours, was defined as ICD-9 154, and ICD-10 C19 and C20. Studies were excluded if there was insufficient information in the ICD code to determine the sub-site of colorectal cancer. Cases with missing or zero follow-up were also excluded.

Continuous data items comprised age (in years); BMI (weight (kg)/height $(m)^2$); serum cholesterol (mmol/l) and height (cm). We grouped height into 2cm categories both to make any effect size clearer and because it is approximately equal to the imperial inch (2.54 cm), which is commonly used in the USA, Canada, Australia and the United Kingdom amongst other countries. Smoking, physical activity, alcohol consumption and diabetic status were classified as binary variables because of inconsistent approaches to their recording between studies. Smoking and alcohol consumption status were classified into "current" and "not current" groups. Because different studies recorded the frequency, type and duration of physical activity in a variety of ways, a simple binary variable "little or none" or "any" was created. Diabetes was defined as self reported history of diabetes or glucose levels according to Word Health Organisation cutoffs in mmol/l as follows: fasting serum≥6.1; fasting plasma≥7.0; non-fasting-serum≥10.0; and non-fasting plasma≥11.1. Information on educational attainment was available for some individuals. We compared those who had completed secondary education at 17-18 years old with those with only primary (up to 10 years old) or no educational attainment. All statistical analysis was performed with SAS 9.20 software (SAS Institute, Cary, NC). Person risk-time was calculated from entry into each cohort to cancer-specific death or censor date. Cox proportional hazards models (Cox, 1972) were used to estimate associations between cancer mortality and potential risk factors presented as hazard ratios (HRs) with 95% confidence intervals (CIs). All models were stratified by both sex and study and performed for colon, rectum and both cancer deaths. Schoenfeld residuals (Grambsch and Therneau, 1994) were generated to test the proportionality assumption for each covariate of the Cox models using the conventional threshold of p≥0.05

Results

The final sample comprised 600,427 participants with 4,281,239 person-years of follow-up. A total of 455 deaths from colon cancer and 158 deaths from rectum cancer were observed. Four fifths (83.4%, n=500,819) of participants were Asian. The mean ages (SD) of Asian and Australia/New Zealand cohorts were 44.0 (9.5) and 53.4 (14.5) years, respectively. Table 1 gives the sex, age, BMI, height, exercise, follow-up years and number of colorectal cancers for each study. The Schoenfeld residuals for all covariates had p-values above 0.05, indicating that the proportionality assumption was met.

Table 2 provides age-adjusted hazard ratios, by sub-site, for all participants for whom data on each variable were available. Increasing age was positively associated with both colon and rectum cancer mortality such that the hazard increased by 8-9% for each additional year. Each unit increase in BMI increased the hazard of colon cancer mortality by 3% (HR 1.03, 95%CI 1.00 to 1.05) but there was no significant effect on rectum cancer mortality. Overall hazards of colorectal mortality were associated with increasing age, BMI, and height and were reduced by taking any physical activity (HR 0.76, 95%CI 0.59 to 0.96).

The four variables with significant effects were entered into multivariate proportional hazards models (Model 1, Table 3). Age and height showed significant positive associations with colon cancer mortality while any physical activity had a protective effect, reducing the hazard by 28% (HR 0.72, 95%CI 0.53 to 0.96). Age, height and physical activity were also significant determinants of overall colorectal cancer mortality. Only age was a significant determinant of rectum cancer death. Additional variables-alcohol consumption, smoking, cholesterol, diabetes status and educational attainment - were added (Model 2, Table 3). Absence of complete data

Table 1. The Asia Pacific Cohort Studies Collaboration

Study name	Country	Female		Age (years)		BMI (kg/m^2)		Height (m)		Exercise	Follow-up (years)		No. of events		
		n	%	Mean	SD	Mean	SD	Mean	SD	%	Mean	SD	Colon	Rectal	All
Aito Town	Japan	1717	57	51	9.1	22.6	3	1.6	0.1	-	14.9	2.3	0	0	0
Akabane	Japan	1836	56	54.5	7.8	22.5	3	1.6	0.1	22	11.2	2	2	0	5
Anzhen	China	8378	55	53.8	12.8	23.9	3.8	1.6	0.1	-	4.2	0.4	0	4	4
Anzhen02	China	4152	51	47	8.2	24	3.3	1.6	0.1	-	2.8	0.5	0	0	0
Beijing Aging	China	2092	51	69.8	8.6	23.3	4	1.6	0.1	66	4.3	1.2	0	0	0
Beijing Steelworkers	China	8957	12	36.2	10.1	-	-	-	-	-	26.9	3.7	4	5	9
Capital Iron & Steel Company	China	5272	0	45.4	7.8	23.2	2.7	1.7	0.1	-	13.2	3.3	0	0	0
CISCH	China	2167	51	44.2	7.4	24.7	3.5	1.6	0.1	52	3.3	0.2	0	0	0
Civil Service Workers	Japan	9319	33	46.7	4.6	22.5	2.7	1.6	0.1	-	6.5	0.9	3	0	9
CVDFACTS	Taiwan	5730	55	47.2	15.2	23.5	3.4	1.6	0.1	-	6.4	1.9	7	0	8
East Beijing	China	1128	51	43.8	15.1	23.6	3.3	1.7	0.1	43	14.2	4.5	3	2	5
EGAT	Thailand	3497	23	43	5.1	23.1	3.1	1.6	0.1	-	10.1	3.6	0	0	0
Fangshan	China	2625	67	47.3	10	24.4	3.6	1.6	0.1	-	3.2	0.5	0	0	0
Guangzhou Occupational	China	167377	22	41.5	6.3	22.6	3.1	1.7	0.1	-	7.5	1.1	20	0	20
Hisayama	Japan	1616	56	56.3	11.2	21.6	2.7	1.5	0.1	-	18.5	8.3	12	0	19
Hong Kong	Hong Kong	3006	57	78.7	6.9	21.9	3.9	1.5	0.1	65	2.2	1	10	2	14
Huashan	China	1868	52	53	11.6	23.4	3.4	1.6	0.1	-	2.5	0.9	1	0	1
Kinmen	Taiwan	2793	48	62.7	9.6	23.4	3.4	1.6	0.1	34	2.7	1	2	0	2
KMIC	South Korea	183600	37	44.1	6.7	23	2.5	1.6	0.1	-	4	0.3	20	30	50
Konan	Japan	1226	55	51.7	15.9	21.9	3	1.6	0.1	-	6.3	2.7	0	0	0
Miyama	Japan	1078	56	60.8	9.6	22.1	3	1.5	0.1	21	6.3	1.2	2	0	4
Ohasama	Japan	2240	64	59.5	11.5	23.3	3.2	1.5	0.1	-	4.2	0.4	0	0	0
Saitama	Japan	3624	62	54.5	11.8	22.4	2.9	1.5	0.1	21	10.2	2	6	0	9
Seven Cities Cohorts	China	10811	55	53.9	12.1	22.6	3.7	1.6	0.1	-	6.1	3.9	3	0	4
Shibata	Japan	2350	58	56.9	11.2	22.4	3	1.5	0.1	-	15.9	6.1	5	0	14
Shigaraki Town	Japan	3758	59	57.2	14	22.5	3.1	1.6	0.1	-	3.9	1.7	3	3	6
Shinghai Factory Workers	China	9347	31	48.5	7.1	-	-	-	-	-	14.3	3.4	0	0	0
Shirakawa	Japan	4643	54	48	12.3	21.5	2.8	-	-	-	16.6	3	4	2	6
Singapore Heart	Singapore	2325	49	40.7	13.5	23.5	4.4	1.6	0.1	13	12.3	4.7	2	2	4
Singapore NHS92	Singapore	3305	52	39.2	12.5	23.2	4.2	1.6	0.1	33	6.2	0.5	3	1	4
Six Cohorts	China	19387	47	44.7	7	21.2	2.6	1.6	0.1	-	8.3	1.2	3	4	7
Tanno/Soubetsu	Japan	1984	53	51.1	6.9	23.6	3.2	1.6	0.1	-	15.3	3.9	0	0	0
Tianjin	China	9335	51	54.6	12.1	23.5	4	1.6	0.1	-	5.8	1.1	4	8	13
Xi'an	China	1695	34	44.4	6.1	-	-	-	-	-	18.1	4.7	0	0	0
Yunnan	China	6581	3	55.8	9.3	21.6	2.9	1.6	0.1	-	4.4	0.7	0	6	6
Total Asia		500819	34	45	9.5	22.9	2.9	1.6	0.1	37	6.7	4.3	119	69	188
Australian Longitudinal Study of Aging	Australia	1613	48	78.1	6.5	26	4.1	1.6	0.1	5	4.9	2.9	3	0	4
Australian National Heart Foundation	Australia	9277	51	43.5	13.5	25.4	4.3	1.7	0.1	47	8.2	1	13	3	18
Busselton	Australia	7866	52	44.9	17	24.6	3.8	1.7	0.1	-	24.8	9.2	87	18	110
Canberra	Australia	833	45	76.7	5.1	-	-	-	-	78	8.6	4.3	3	0	7
Fletcher Challenge	NZ	10366	28	44.3	15	26.4	4.2	1.7	0.1	79	5.7	0.7	7	6	13
Melbourne	Australia	41286	59	54.8	8.7	26.9	4.4	1.7	0.1	38	8.6	1.4	125	37	175
Newcastle	Australia	5934	50	51.7	10.5	26.7	4.5	1.7	0.1	34	9.1	4.6	23	6	29
Perth	Australia	10230	48	45.1	12.9	25.2	4	1.7	0.1	-	12.9	6.2	46	6	54
Western Australia AAA Screenees	Australia	12203	0	72.2	4.4	26.9	3.7	1.7	0.1	74	3.2	0.7	29	13	48
Total ANZ		99608	45	53.4	14.5	26.3	4.3	1.7	0.1	49	9.3	6.3	336	89	425
Total		600427	36	46.4	10.9	23.7	3.6	1.7	0.1	47	7.1	4.8	455	158	613

Table 2. Age-adjusted, Sex And Study-Stratified, Hazard Ratios (HR) of Colorectal Cancer Mortality in the APCSC

Variables	No. of participants	Colon (n=455), HR	Rectum (n=158), HR	All colorectal (n=613), HR
Age (years)	600427	1.09 (1.08-1.10)*	1.08 (1.06-1.10)*	1.08 (1.08-1.09)*
BMI (kg/m^2)	429518	1.03 (1.00-1.05)*	1.03 (0.98-1.07)	1.03 (1.00-1.05)*
Current smoker	600427	0.93 (0.73-1.19)	0.96 (0.64-1.44)	0.97 (0.79-1.18)
Physical activity (any)	101657	0.73 (0.54-0.97)	0.76 (0.45-1.29)	0.76 (0.59-0.96)*
Current drinker (alcohol)	600427	0.94 (0.72-1.21)	0.66 (0.43-1.01)	0.88 (0.71-1.09)
Cholesterol (mmol/l)	380468	1.05 (0.96-1.15)	1.01 (0.85-1.20)	1.04 (0.96-1.12)
Diabetes	182569	1.28 (0.82-2.01)	0.94 (0.38-2.35)	1.29 (0.89-1.87)
Height (2 cm increase)	510785	1.03 (1.00-1.06)*	1.02 (0.97-1.08)	1.03 (1.01-1.06)*
Education (secondary)	310342	1.11 (0.86-1.45)	1.27 (0.79-2.06)	1.16 (0.93-1.44)

*p≤0.05

for all variables reduced the sample from 99 555 to 71 484 persons. Increasing age and height were associated with greater hazards of colorectal cancer mortality while physical activity reduced the hazard by 36% (HR 0.64, 95%CI 0.48 to 0.86). There was no interaction between age and height on mortality. None of the additional variables was significantly associated with either colon or rectum cancers.

Table 3. Multivariate Adjusted Hazard Ratio of Colorectal Cancer Mortality in APCSC

Variables	Model 1 (n=99,555)			Model 2 (n=71,484)		
	Colon	Rectum	All colorectal	Colon	Rectum	All colorectal
Age (years)	1.10 (1.08 -1.12)*	1.09 (1.06-1.12)*	1.10 (1.08-1.11)*	1.10 (1.08-1.13)*	1.11 (1.07-1.15)*	1.10 (1.09-1.12)*
BMI (kg/m^2)	1.02 (0.99-1.06)	1.02 (0.96-1.08)	1.02 (0.99-1.05)	1.03 (0.99-1.06)	1.04 (0.97-1.11)	1.03 (1.00-1.06)
Physical activity (any)	0.72 (0.53-0.96)*	0.75 (0.45-1.27)	0.75 (0.59-0.96)*	0.59 (0.42-0.84)*	0.68 (0.37-1.26)	0.64 (0.48-0.86)*
Height (2 cm increase)	1.07 (1.03-1.11)*	1.04 (0.97-1.12)	1.06 (1.03-1.10)*	1.07 (1.02-1.12)*	1.05 (0.96-1.14)	1.06 (1.02-1.11)*
Current drinker (alcohol)				0.54 (0.25-1.17)	0.95 (0.26-3.50)	0.74 (0.39-1.39)
Current smoker				1.09 (0.67-1.76)	0.83 (0.32-2.15)	1.08 (0.72-1.62)
Cholesterol (mmol/l)				1.00 (0.86-1.16)	0.93 (0.71-1.23)	0.96 (0.84-1.09)
Diabetes				1.13 (0.59-2.17)	0.32 (0.04-2.39)	1.04 (0.59-1.85)
Education (secondary)				1.12 (0.79-1.59)	1.19 (0.64-2.24)	1.16 (0.87-1.55)

*p≤0.05. Model 1; age, BMI, physical activity and height (2cm) were included in the sex and study stratified model; Model 2; age, BMI, physical activity, height (2cm), drink, smoke, cholesterol, diabetes and education were included in the sex and study stratified model

Discussion

Participants in cohort studies included in the Asia Pacific Cohort Studies Collaboration who reported taking any physical activity had a reduced risk of colorectal cancer death of over a third. While "reverse causality" might explain some of this association – that is, colorectal cancer causes a reduction in physical activity rather than physical activity reducing cancer risk – a true causal association is probable. We also found that BMI, height and increasing age were associated with colorectal cancer mortality. Although the mechanisms by which these factors operate is still unclear, physical activity is largely assumed to protect against colorectal cancers through its systemic metabolic effects, including reductions in blood pressure and insulin resistance, but it also increases gut motility. Our finding that physical activity was associated with a clearer benefit for colon (HR 0.72, 95%CI 0.53-0.96) compared with rectum cancers (HR 0.75, 95%CI 0.45-1.27) is consistent with previously published findings (World Cancer Research Fund, 2007). Body and abdominal adiposity may increase risk through systemic effects in which insulin and oestrogen levels encourage carcinogenesis and discourage apoptosis. BMI was associated with increased colon and colorectal cancer mortality in the age-adjusted model but we were unable to detect a significant relationship with rectum cancer. The non-significant associations for rectal cancer were possibly due to the smaller number of rectal cancer deaths. Although not significant, the point estimates for rectal cancer were the same or greater than those for colon cancer. After adjustment for other significant factors, the effect of BMI became non-significant. Alcohol might exert its effects through carcinogenic acetaldehyde metabolites, through its solvent effects increasing mucosal absorption of other carcinogens, or through the production of prostaglandins, lipid peroxidation and the generation of free radical oxygen species (World Cancer Research Fund, 2007). In contrast to some previously published results, (Mizoue et al., 2006; 2008) we found that participants who reported current drinking had, if anything, lower hazards of colorectal cancer mortality. However, such non-significant results have been reported elsewhere (Adams et al., 2006; Bofetta and Hashibe, 2006) and do not change the overall conclusion that alcohol is a risk factor for the disease (World Cancer Research Fund, 2007). An increase in attained adult height of 5cm has previously been reported by the APCSC to be associated with a colorectal cancer hazard of 1.10 (95%CI 1.03-1.18) (Asia Pacific Cohort Studies Collaboration, 2007) which does not significantly differ between Asian and Caucasian populations (Batty et al., 2010). We found that height was a significant predictor of colon and all colorectal cancers, but not rectum cancer separately. This might have been because we used a smaller sample in the current study due to requirements for colon/rectum specific death records. It is not clear what biological mechanism may underlie the association between height and cancer mortality although a number of factors – including genetic predisposition and foetal and early life nutritional factors have been suggested (World Cancer Research Fund, 2007). We did not find an association between diabetes mellitus or circulating serum cholesterol levels and colon or rectum cancer mortality. Thus, there was inconclusive evidence to support the hypothesis that features of the metabolic syndrome (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults , 2001) may be part of the causal pathway for colorectal cancers (Renehan et al., 2008). We found no convincing relationship between smoking and colorectal cancer mortality. A recent meta-analysis (Liang et al., 2009) reported that current smokers had higher colorectal cancer mortality compared with never smokers, but the absence of any significant association between former smokers and colorectal cancer mortality or between smoking and site-specific cancer mortality, suggested that further research was needed.

General limitations of the APCSC include non-standardisation of data collection methods for both risk factors and outcomes, necessitating reduction of some factors to binary measures and exclusion of many participants. The dichotomous variables used for smoking, alcohol consumption and exercise may have been too crude to have detected dose-response effects, for example, between current, former or never smokers or drinkers. Specific limitations of the dataset for cancer analyses include the relatively short follow-up period available between baseline measures and outcomes, the relatively young age of participants and, for many studies, the availability of only mortality but not incidence data.

In conclusion, physical activity and BMI are potentially modifiable risk factors for colon cancer mortality although their effects on rectum cancer remain less clear. As physical

activity levels have fallen and obesity has increased in westernized countries, a relatively larger increase in incidence and mortality of colon, compared with rectum, cancers has been observed since the 1970s (Brewster and Rowan, 2005) which is consistent with these findings on mortality. Further efforts are needed to promote physical activity and to reduce obesity to reduce incidence and mortality from colorectal cancers. New research is needed to explore the biological mechanisms that underpin the relationships between metabolic risk factors and both colon and rectum cancers. Larger collaborative studies for meta-analysis of individual data with more precise exposure measures are needed to examine the interaction of the known and controversial risk factors on colon and rectum cancer separately.

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