RESEARCH COMMUNICATION

The Role of Lifestyle Risk Factors on Mortality from Colorectal Cancer in Populations of the Asia Pacific Region

Asia Pacific Cohort Studies Collaboration*

Abstract

Although colorectal cancer is one of the leading malignancies worldwide, there are few data on aetiological relationships from the Asia-Pacific region. Therefore, a collaborative study was conducted involving over half a million subjects from 33 cohort studies in the region. Age-adjusted death rates from colorectal cancer, over an average of 6.8 years follow-up, were 12 and 14 per 100,000 person-years among Asian women and men, respectively; corresponding values in Australasia were 31 and 41. Height was strongly associated with death from colorectal cancer: an extra 5cm of height was associated with 10% (95% confidence interval, 3% - 18%) additional risk, after adjustment for other factors. Smoking increased risk by 43% (9% - 88%), although no significant dose-response relationship was discerned (p >0.05). Other significant (p <0.05) risk factors were body mass index and lack of physical activity. There was no significant effect on colorectal cancer mortality for alcohol consumption, waist circumference, fasting blood glucose or diabetes, although the latter conferred a notable 26% additional risk. Height may be a biomarker for some currently unknown genetic, or environmental, risk factors that are related both to skeletal growth and mutanogenesis. Understanding such mechanisms could provide opportunities for novel preventive and therapeutic intervention.

Keywords: Colorectal cancer - obesity - smoking - diabetes - Asia Pacific

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Introduction

Cancers of the colon and rectum (colorectal) constitute a significant proportion of the global burden of cancer morbidity and mortality, particularly in highly industrialised countries where these malignancies rank second in terms of both incidence and mortality, compared with fifth in less developed countries (Stewart and Kleihues, 2003). Annually, approximately 1 million new cases of colorectal cancer are diagnosed, more than 90% of which occurs among individuals older than 50 years of age (Parkin et al., 2002; Stewart and Kleihues, 2003). In the West, recent improvements in its detection and management have resulted in a five-year survival rate of more than 60% (although it remains low, at around 30% in developing countries) but nevertheless, every year, more than half a million people die from colorectal cancer, equivalent to approximately 8% of all cancer-related deaths worldwide (Parkin et al., 2002; Stewart and Kleihues, 2003).

The wide geographical variation in incidence rates for colorectal cancer, combined with reports of increasing incidence rates in countries that are undergoing rapid industrialisation (e.g. China), lends support to the theory that lifestyle risk factors, including diet, physical activity, obesity and diabetes, play a pivotal role in the aetiology of the disease (Potter et al., 1993). This is further evidenced by data from migrant studies which indicates that the incidence of colorectal cancer increases among groups migrating from low to high incidence areas within a couple of generations (Haenszel et al., 1968).

Data from large-scale epidemiological studies, and from several meta-analyses, have suggested modest (relative risk less than 2) associations between low levels of physical activity (Samad et al., 2005), diabetes (Larsson et al., 2005), obesity (Bianchin et al., 2002) and diets low in fibre, fruit and vegetables (Terry et al., 2001a; Gonzalez, 2006), with increased risk of colorectal cancer. The evidence for a causative role for cigarette smoking in the aetiology of colorectal cancer is more equivocal than it is for some of these other risk factors, possibly due to a long induction period (30-40 years) between the onset of smoking and the development of the neoplasm that has previously been postulated (Giovannucci et al., 1994).

To date, most of the studies that have examined the associations between major lifestyle risk factors and colorectal cancer have been conducted in populations from highly-industrialised countries. Consequently, little is known about these relationships among populations from lower- and middle-income countries, particularly those in Asia. This is of relevance given that large parts of the region are undergoing rapid economic development and industrialisation. The primary aim of this study therefore was to examine the strength and nature of the associations

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between selected lifestyle risk factors with mortality from colorectal cancer in diverse populations of the Asia Pacific Region using data from the Asia Pacific Cohort Studies Collaboration (APCSC).

Materials and Methods

Details of study identification, data collection and event verification in the Asia Pacific Cohort Studies Collaboration (APCSC) are described elsewhere (Zhang et al., 1999; Woodward et al., 2006). Briefly, studies were included if they had continued follow-up for at least 5000 person-years and had recorded vital status at the end of follow-up. Studies were excluded if entry was dependent upon a particular condition or risk factor. Mortality was classified according to the 9th Revision of the International Classification of Diseases (ICD): Colorectal cancer was selected as ICD 153 – 154. Studies were classified as Asian if their participants were recruited from mainland China, Hong Kong, Japan, Korea, Singapore, Taiwan or Thailand; and ANZ if from Australia or New Zealand.

All data on cigarette smoking (Woodward et al., 2005) were based on self-report at the time of entry into one of the included studies; smoking status was recorded as current, former or never-smoker. Of these studies, 19 additionally recorded the average number of cigarettes per day; groups of <20, and ≥20 cigarettes were chosen as 20 cigarettes corresponds to one standard pack.

At recruitment, information on alcohol consumption was recorded by some studies but few studies recorded the amount or type (beer, wine or spirits) of alcohol consumed. Hence, alcohol consumption was dichotomised into: 'yes' to indicate current drinkers at study baseline and 'no' to indicate no consumption of alcoholic beverages. Similarly, physical activity was recorded by 14 studies, but studies varied according to how well it was measured in terms of frequency, type and duration. We therefore classified PA into a binary variable with 'yes' indicating any type of PA and 'no' to indicate no physical activity.

Most studies in APCSC did not differentiate between type-1 and type-2 diabetes, and hence the analyses included all individuals with diabetes recorded at study baseline on the basis of either self-report (Woodward et al., 2003) or an oral glucose tolerance test (Lawes et al., 2004), or both. Using the values for height and weight measured at study baseline, BMI (Ni Mhurchu et al., 2004) was computed as weight in kilograms divided by height squared (kg/m^2). Some studies (3) additionally recorded waist circumference (cm). At recruitment, data were also collected on several risk factors, including blood pressure (Lawes et al., 2003), and cholesterol (Zhang et al., 2003).

Analyses used individual participant data and were restricted to individuals aged ≥20 years at enrolment. Cox proportional hazard models, stratified by study and sex and adjusted for age, were used to estimate hazard ratios and 95% confidence intervals (CIs) associated with putative risk factors both before and after adjustment for other risk factors. Associations between quantitative variables and colorectal cancer were assessed through hazard ratios and corresponding 95%CIs for a standard increment in each variable. Dose-response associations were explored by categorising study participants into equal quarters of continuous distributions. Due to the limited number of events (92) in the studies that had information on waist circumference, we did not examine the dose-response association with waist. Tests for regional and sex interactions were conducted by adding interaction terms to the Cox model. Linear trend was explored through analyses by quartiles. Confidence intervals were calculated using the floating absolute risk method (Easton et al., 1991).

Within prospective studies, values for risk factors measured at study baseline will fluctuate due to several factors, including measurement error or within-person variability, resulting in an underestimation of the true association with disease risk, which is termed "regression dilution bias" (MacMahon et al.,1990). By using repeat measurements of the risk factors from a sample of the total study population, attenuation coefficients were derived using a linear regression model that accounted for the heterogeneity of variance between studies, within-subject correlation, and the varying time intervals between measurements (Rosner et al., 1990). Information on repeat measures of blood pressure, total cholesterol, body mass index, waist circumference and fasting glucose were available on up to 16 studies for between one to seven occasions with a median of four years (1 to 29 yrs) after the baseline measurement. Regression attenuation coefficients were calculated in this way for, fasting glucose (1.6), body mass index (1.2) and waist circumference (1.4) and used to adjust the continuous associations between these risk factors and the risk of death from colorectal cancer. The log relative risks and standard errors obtained from Cox proportional hazard analysis were multiplied by an attenuation coefficient to produce an estimate with 95% confidence intervals of the association between the usual values of a risk factor with colorectal cancermortality.

Results

The characteristics of the participants in the 33 cohort studies within the APCSC that contributed to these analyses are summarized in Table 1. In total, 539201 (35% female) individuals with a median follow-up of 6.8 years, and a mean age of 47 years, were included in the analysis. The mean values for height and BMI, and the prevalence of cigarette smoking, differed substantially between Asia and ANZ but the mean prevalence of diabetes was similar among cohorts from Asia and ANZ (Table 1).

Overall, there were 751 deaths from colorectal cancer (62% in cohorts from ANZ), during 3.7 million person-years of follow up (Table 2). The age-standardised mortality rates for colorectal cancer were approximately three times higher among individuals in ANZ compared with Asia in both males and females: 41 versus 14 and 31 versus 12 per 100,000 person-years in males and females from ANZ and Asia, respectively.

Age and colorectal cancer

The risk of colorectal cancer was strongly associated

Table1. Study Characteristics Including Values of Risk Factors at Baseline

Country	Study	Baseline	No. of subjects	Mean age (years)	Female (%)	Median FU (years)	CRC* deaths	Mean Height (cm)	Mean BMI (kg/m2)	Diabetic (%)	Current Smokers (%)	
											M	F
Australia	Busselton	1966-81	7,767	44.9	52	26.5	109	167	24.6	3.4	44	24
Australia	Canberra-Queanbeyan Longitudinal	1990-91	706	76.5	45	9.8	11	-	-	6.7	12	9
Australia	Long. Study of Aging	1992-93	1,610	78.1	48	4.6	4	163	26.0	8.3	8	8
Australia	Melbourne	1990-94	41,285	54.8	59	8.5	179	165	26.9	5.4	15	9
Australia	National Heart Foundation	1989-90	9,277	43.5	51	8.3	19	168	25.4	1.9	27	21
Australia	Newcastle	1983-94	5,929	51.7	50	8.9	29	167	26.7	3.5	28	18
Australia	Perth	1978-94	10,230	45.1	48	14.4	55	169	25.2	2.6	30	21
Australia	WA AAAScreenees	1996-99	12,203	72.2	0	3.2	50	171	26.9	11.7	11	-
NZ	Fletcher Challenge	1992-94	10,326	44.3	28	5.8	13	172	26.4	2.6	25	18
ANZ	Subtotal	1966-99	99,333	53.4	45	8.3	469	167	26.3	5.2	20	14
China	Anzhen	1991	8,378	53.8	55	4.3	4	162	23.9	-	51	10
China	East Beijing	1977-94	1,128	43.8	51	17.1	5	165	23.6	5.6	47	11
China	Guangzhou Occupational	1985-98	166,695	41.5	22	7.3	57	167	22.6	10.0	60	1
China	Huashan	1990-92	1,868	53.0	52	2.8	1	162	23.4	13.7	48	4
China	Seven Cities Cohorts	1987	10,811	53.9	55	2.7	14	162	22.6	1.2	57	17
China	Shanghai Factory workers	1972-78	9,347	48.5	31	14.0	33	-	-	-	61	7
China	Six Cohorts	1982-86	19,387	44.7	47	9.0	11	160	21.2	-	76	12
China	Tianjin	1984	9,335	54.6	51	6.1	13	162	23.5	-	63	39
China	Yunnan	1976	6,581	55.8	3	4.5	6	162	21.6	1.0	70	0
Hong Kong	Hong Kong	1985-91	2,983	78.6	57	2.5	13	154	21.9	8.6	29	11
Japan	Aita town	1980-83	1,130	50.8	59	16.4	2	156	22.6	3.4	66	2
Japan	Akabane	1985-86	1,834	54.5	56	11.0	5	155	22.5	2.5	62	1
Japan	Civil Service Workers	1990-92	9,240	46.7	33	6.7	9	162	22.5	1.8	51	11
Japan	Hisayama	1961	1,601	56.1	56	24.6	18	151	21.6	-	76	17
Japan	Miyama	1988-90	1,073	60.8	56	6.6	4	154	22.2	5.2	58	7
Japan	Saitama	1986-90	3,615	54.5	62	11.0	8	154	22.4	1.7	63	8
Japan	Shibata	1977	2,350	56.9	58	20.0	14	152	22.4	1.1	72	4
Japan	Shigaraki Town	1991-97	3,730	57.1	59	4.4	6	156	22.5	7.2	59	8
Japan	Shirakawa	1974-79	4,640	48.0	54	17.5	6	-	21.5	1.0	70	5
Singapore	Singapore Heart	1982-97	2,321	40.7	49	14.6	4	160	23.5	11.5	40	3
Singapore	Singapore NHS92	1992	3,305	39.2	52	6.2	4	161	23.3	9.7	35	3
South Korea	KMIC	1992	160,242	44.0	33	4.0	35	165	23.0	7.7	58	0
Taiwan	CVDFACTS	1988-96	5,729	47.2	55	6.0	8	160	23.5	2.7	48	1
Taiwan	Kinmen	1993-97	2,545	63.2	49	2.9	2	160	23.4	8.7	50	5
Asia	Subtotal	1961-98	439,868	44.9	32	6.4	282	164	22.8	6.4	59	5
Total		1961-99	539,201	46.5	35	6.8	751	165	23.7	6.0	53	7

NZ=New Zealand; ANZ=Australia and New Zealand; CPD=cigarettes per day for current smokers; m=males; f=females

Table 2. Crude and Age-standardized Mortality Rates for Colorectal Cancer by Sex and Region in the Asia Pacific Cohort Studies Collaboration

Region	Sex	No. of subjects	Person-years	No. of Events	Crude mortality rate*	Age-standardized mortality rate (95% CI)*
ANZ	Male	54,353	454,143	271	60	41 (35 - 48)
	Female	44,980	466,834	198	42	31 (26 - 37)
	Overall	99,333	920,977	469	51	36 (32 - 40)
Asia	Male	297,776	1867,029	183	10	14 (12 - 16)
	Female	142,092	923,023	99	11	12 (10 - 15)
	Overall	439,868	2790,052	282	10	13 (12 - 15)
Total	Male	352,129	2321,172	454	20	21 (19 - 23)
	Female	187,072	1389,857	297	21	19 (17 - 22)
	Overall	539,201	3711,029	751	20	20 (19 - 21)

*per 100,000 person-years, ANZ = Australia and New Zealand

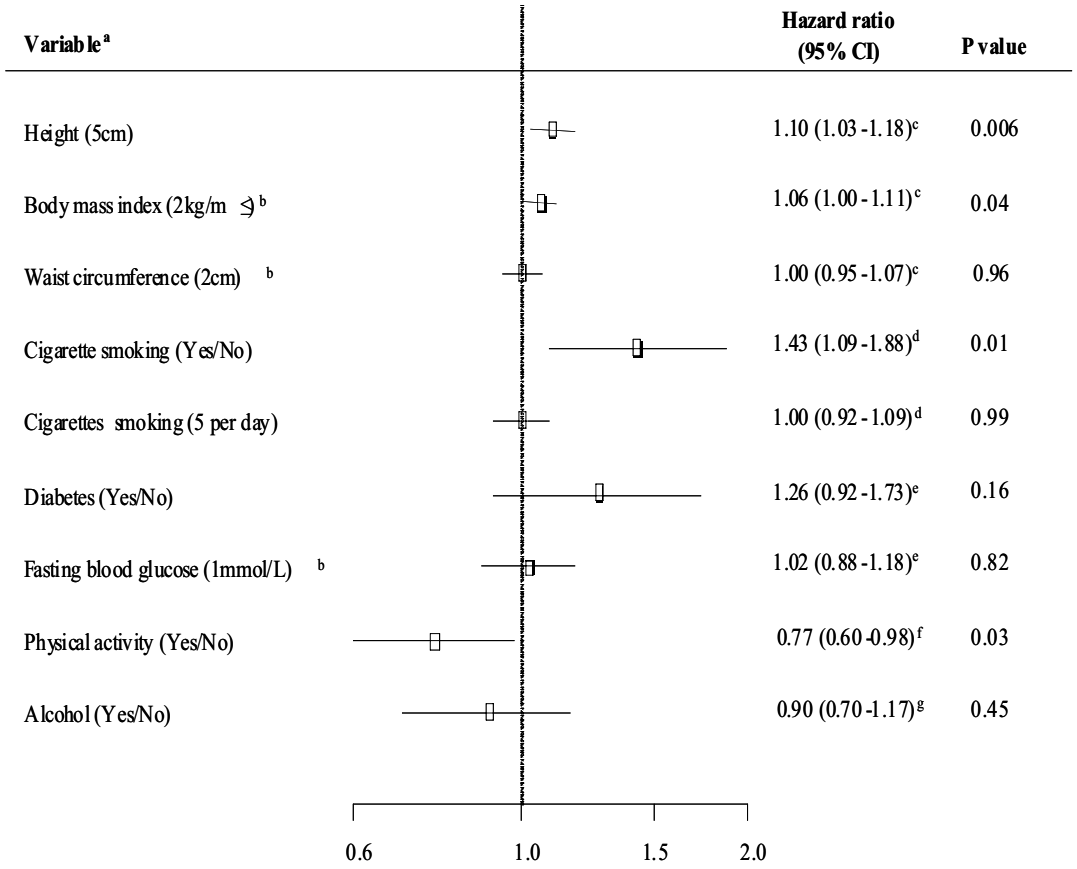

Figure 1. Multiple-adjusted Hazard Ratios and 95% Confidence Intervals for the Associations between Risk Factors with Mortality from Colorectal Cancer in APCSC. a =the units of examining the associations for all variables are given in brackets; b =regression attenuation coefficients were 1.2, 1.4, and 1.6 for fasting glucose, body mass index, waist circumference, and fasting glucose respectively; c= adjusted for smoking, diabetes, and alcohol; d=adjusted for diabetes, BMI, and alcohol; e =adjusted for smoking, BMI and alcohol; f =adjusted for smoking, diabetes, and alcohol; g =adjusted for smoking, diabetes, and BMI

with age. Among individuals over the age of 65 years the risk of dying from the neoplasm was eight times that of those individuals less than 55 years of age (HR 8.05, 95% CI: 6.18 – 10.5). The association was approximately linear in that for every extra 10 years of increase in age, the risk of colorectal cancer more than doubled: HR 2.30, 95%

Table 3. Hazard Ratios (95% CIs) for the Dose-Response Associations between Risk Factors and Mortality from Colorectal Cancer

Risk Factor	No of Subjects	No of Deaths	Adjusted for Age, Sex & Study	Multiple-Adjusted
Cigarettes per day				
Never smoked*	58,151	211	1	1[a]
<20cpd	11,088	32	1.34 (0.89-2.01)	1.38 (0.92-2.08)
≥20cpd	10,243	20	0.88 (0.53-1.47)	0.89 (0.54-1.48)
Blood glucose (mmol/L)				
<5.1*	108,778	52	1	1[b]
5.1-5.4	34,960	54	0.92 (0.61-1.40)	0.93 (0.61-1.40)
5.4-6.0	30,602	52	0.75 (0.49-1.15)	0.74 (0.48-1.14)
≥6.0	19,278	50	0.87 (0.57-1.35)	0.85 (0.55-1.32)
BMI (kg/m^2)				
<20*	31,610	36	1	1[c]
20-<25	173,408	181	1.01 (0.70-1.47)	1.02 (0.70-1.48)
25-28	64,665	161	1.37 (0.92-2.02)	1.37 (0.93-2.04)
≥28	36,994	137	1.25 (0.83-1.88)	1.24 (0.83-1.87)
Height (cm)				
≤158*	77,737	130	1	1[c]
159-165	86,624	125	1.11 (0.84-1.46)	1.11 (0.85-1.47)
166-172	89,930	141	1.39 (1.02-1.90)	1.40 (1.03-1.92)
≥173	52,721	121	1.54 (1.08-2.20)	1.57 (1.10-2.24)

* Reference group [a]Adjusted for diabetes, BMI, and alcohol; [b]Adjusted for smoking , BMI and alcohol; [c]Adjusted for smoking, diabetes and alcohol

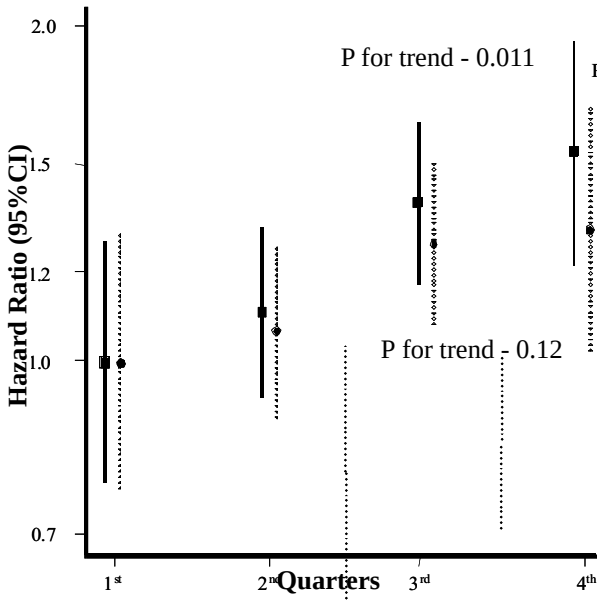

Figure 2. Hazard Ratios (95% CI) for the Association between Height (cm) and Mortality (quartiles) before (solid line) and after (dashed line) Adjustment for Current Weight

CI 2.10 – 2.55. The strength of the relationship did not differ significantly between the regions (p for interaction = 0.58) or by sex (p for interaction = 0.24).

Body anthropometry and colorectal cancer

In analyses adjusted for age and gender, there was a significant dose-response relationship between height and mortality from colorectal cancer (p for trend = 0.011; Figure 2), such that a 5 cm greater height was associated with an approximate 10% (95% CI 3 - 18%). This relationship was slightly strengthened after adjusting for smoking and diabetes (Table 3). Overall, individuals in the highest quarter for height had about 50% greater risk of mortality from colorectal cancer compared with those in the lowest quarter. The relationship was also observed, and of a similar magnitude, in cohorts from both Asia and ANZ and in both sexes (both p-values for interaction >0.7). After adjustment for current weight, however, the positive relationship between height and fatal colorectal cancer was attenuated and the dose-response relationship was significantly weakened, such that the excess risk, comparing individuals in the top to the bottom quarter, was reduced to 30% (p for trend = 0.12; Figure 2).

There was some evidence of a continuous dose-response relationship between BMI and mortality from colorectal cancer: in a multiple adjusted analysis, individuals in the highest quarter of BMI had an approximate 25% greater risk compared with those in the lowest quarter (Table 3; p for trend = 0.06). Overall, for every 2 kg/m^2 increment in BMI (equivalent to about 5 kg extra weight) the risk of mortality from colorectal cancer rose by 6% (95% CI: 0 – 11%). There was no evidence to suggest that the association differed between regions or by sex (both p-values for interaction >0.7). Among the subgroup of 27,572 individuals (92 events) with information on waist circumference, there was no association between central obesity and risk of mortality from colorectal cancer (Figure 1).

Cigarette smoking, alcohol consumption and colorectal cancer

In age-adjusted analyses, cigarette smoking was associated with about 40% greater risk of colorectal cancer compared with non-smokers (Figure 1). The association was noticeably weaker in cohorts from Asia compared with those from ANZ; HR 1.16 (95% CI 0.69 – 1.95) versus HR 1.54 (95% CI 1.13 – 2.11), although the difference was not statistically significant (p-value for interaction = 0.36). Overall, there was no evidence of a dose-response association (Table 3), nor was there any evidence to suggest that smoking cessation was associated with any reduction in the risk of colorectal cancer. Indeed, individuals who reported to have stopped smoking at study baseline had a non-significant greater risk of mortality from colorectal cancer compared with current smokers; HR 1.55 (95% CI 1.19 – 2.02) versus 1.34 (95% CI: 1.03 – 1.74), p-value = 0.27. The data were left-censored to preclude the possibility of reverse causality, but the estimates remained largely unaltered after excluding the first five years of study follow up (data not shown).

As we lacked the necessary information to examine the relationship between duration of smoking and fatal colorectal cancer, we used duration of study follow up as a proxy marker for the number of smoking years. There was some indication that increasing duration of study follow up was associated with a greater risk of colorectal cancer such that for every five years of follow up the risk associated with smoking increased by 12%: (95% CI -2% –29%; p = 0.11). In a further subgroup analysis among 316663 individuals (515 deaths) there was no evidence to suggest an association between alcohol consumption and fatal colorectal cancer (Figure 1).

Diabetes, blood glucose and colorectal cancer

A diagnosis of diabetes at study baseline was associated with a non-significant 31% (95%CI: -4%-80%) greater risk of fatal colorectal cancer compared with individuals without diabetes that was slightly weakened by adjustment for potential confounders (Figure 1). The magnitude of the association was similar in both regions and in both sexes (both p-values for interaction > 0.1). Among a smaller subgroup of individuals (n=193618) with information on blood glucose, there was no evidence of a dose-response association (Table 3).

Physical activity, alcohol consumption and colorectal cancer

Based on a subsample of 94500 individuals (310 deaths) there was some evidence to suggest a protective effect of physical activity on the risk of fatal colorectal cancer. In fully adjusted analyses, among those individuals who reported participating in some form of physical activity at the study baseline, the risk of colorectal cancer was 23% (95% CI: 2% - 40%) lower as compared with those individuals who did not report doing any form of physical activity (p=0.03; Figure 1). The relationship was similar between regions (p = 0.97) and in both sexes (p = 0.07).

Discussion

Findings from the current study, with individual participant data on nearly 540,000 individuals, lend support for a modest role of potentially modifiable risk factors in the aetiology of fatal colorectal cancer in ethnically diverse populations of the Asia-Pacific region. In particular, being overweight, having diabetes and a low level of physical activity were each compatible with an increased risk of dying from the malignancy. The magnitude of each of these associations was largely in agreement with findings from previous studies that were conducted predominantly within Caucasian populations.

A previous meta-analysis of 20 observational studies reported relative risks for incident colorectal cancer of 1.6 and 1.3 in men and women, respectively, within the highest category of BMI compared with those in the lowest category, respectively (Bianchini et al., 2002). Data from the current study, indicating an approximate 25% greater risk of fatal colorectal cancer among individuals within the highest, compared to the lowest, 25% of BMI values are compatible with this estimate, although there was no evidence to suggest a stronger association in men compared with women. In practical terms, a 2 unit increment in BMI (which is equivalent to an approximate 10 kg increase in weight) would be associated with about a 5% greater risk of dying from the disease. However, given that we were unable to adjust for the effects of various dietary constituents such as fruit, vegetable, fibre and meat that are all potential risk factors for the disease, it is possible that the association between BMI and fatal colorectal disease is partly, or wholly, due to confounding. A dose-response association between stature and fatal colorectal cancer was observed such that individuals within the top 25% of the height distribution had a 50% significantly greater risk of dying from the neoplasm compared with those in the lowest 25%. However, the magnitude of the association was significantly attenuated after adjustment for current weight and became more similar to that obtained by a meta-analysis of more than 5000 events, which reported a 30% greater risk of incident colorectal cancer among individuals in the top compared to the bottom 20% for height (Howe et al., 1997). As discussed in a recent review article by Gunnell and colleagues (Gunnell et al., 2001), a causal relationship between height and colorectal cancer (and several other site-specific cancers including breast and prostate) is improbable, rather, height may serve as a biomarker for some currently unknown genetic, or environmental risk factors, such as post-natal nutrition or infection, that are related both to skeletal growth and mutanogenesis. Understanding such mechanisms that link height with cancer risk could provide opportunities for novel therapeutic intervention.

Data from the current study suggested that individuals with diabetes have a 26% greater risk of dying from colorectal cancer compared with individuals without diabetes. Although this was not significant in this study, the estimate here agrees exactly with the findings of a meta-analysis of 15 studies which reported a relative risk of 1.26 (95% CI 1.05 – 1.50) for the same association (Larsson et al., 2005). The same meta-analysis reported that diabetes conferred a slightly higher, 30%, increased risk of fatal or non-fatal colorectal cancer.

Despite the inherent difficulties involved in accurately measuring physical activity in epidemiological studies, an inverse association between physical activity with colorectal cancer, particularly colon cancer, has been consistently reported (Colditz et al., 1997). A recent review of the epidemiological evidence reported that the average reduction in risk across studies was 40-50% among the most physically active group compared with the least active, which was independent of diet, BMI and other potential confounders (Friedenreich, 2001). Furthermore, a consistent dose-response relation has been demonstrated with those exhibiting the highest level of activity being at significantly lower risk of developing colon cancer compared with the least active group (Colditz et al., 1997). Our data also support a protective role of physical activity against fatal colorectal cancer in populations of the Asia Pacific region. However, given the variety of methods used to measure physical activity across studies in APCSC, which necessitated the categorisation of physical activity into a single variable with binary outcomes, it would be inappropriate to draw any more inference regarding the strength of the association from these data.

It is a matter of ongoing debate as to whether cigarette smoking is a risk factor for colorectal cancer. Although many studies (Giovannucci et al., 2001; Chao et al., 2000; Surgeon General's Report, 2004) published over the past couple of decades have found a statistically significant increased risk for colorectal cancer among smokers, the strength of the association was relatively weak, ranging from between 1.2 and 1.6. However, as most of these studies were unable to control for physical activity or diet, it is difficult to determine whether the observed relationship between smoking and colorectal cancer is causal or due to confounding. Some commentators have suggested that the lack of an association between smoking and colorectal cancer observed by some studies, is due to an extraordinary long induction period of more than 30 years. Data from the current study provide some support to this latter theory. Overall, smoking was positively associated with fatal colorectal cancer, particularly in cohorts from Australia and New Zealand that are at a much later stage of the smoking epidemic compared with many countries in Asia. Moreover, there was also a positive trend towards increased duration of follow up (as a proxy for duration of smoking) with colorectal risk. However, the lack of a clear dose-response relationship between the number of cigarettes smoked with colorectal risk, in conjunction with no significant reduction in risk among ex-smokers, and the inability to adjust for known confounders of the relationship, reflects the current state of uncertainty regarding the relationship between smoking and colorectal cancer.

In addition to the lack of information on duration, frequency and type of physical activity and alcohol consumed, all of which would have diluted the strength of any associations, there are several other limitations that warrant discussion. The analyses were based on self-reported cigarette and alcohol consumption, which may

have introduced bias. In addition, measurement error may have been present especially for waist circumference, which is more difficult to reliably measure than either weight or height. Finally, the individual studies used different methods to verify mortality from colorectal cancer, whilst the methods used will also have varied over time; consequently, the lack of standardization could have had some unpredictable effect on the results.

Appendix

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