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The impact of dietary and lifestyle risk factors on risk of colorectal cancer: A quantitative overview of the epidemiological evidence

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Colorectal cancer is a major cause of cancer mortality and is considered to be largely attributable to inappropriate lifestyle and behavior patterns. The purpose of this review was to undertake a comparison of the strength of the associations between known and putative risk factors for colorectal cancer by conducting 10 independent meta-analyses of prospective cohort studies. Studies published between 1966 and January 2008 were identified through EMBASE and MEDLINE, using a combined text word and MESH heading search strategy. Studies were eligible if they reported estimates of the relative risk for colorectal cancer with any of the following: alcohol, smoking, diabetes, physical activity, meat, fish, poultry, fruits and vegetables. Studies were excluded if the estimates were not adjusted at least for age. Overall, data from 103 cohort studies were included. The risk of colorectal cancer was significantly associated with alcohol: individuals consuming the most alcohol had 60% greater risk of colorectal cancer compared with non- or light drinkers (relative risk 1.56, 95% CI 1.42–1.70). Smoking, diabetes, obesity and high meat intakes were each associated with a significant 20% increased risk of colorectal cancer (compared with individuals in the lowest categories for each) with little evidence of between-study heterogeneity or publication bias. Physical activity was protective against colorectal cancer. Public-health strategies that promote modest alcohol consumption, smoking cessation, weight loss, increased physical activity and moderate consumption of red and processed meat are likely to have significant benefits at the population level for reducing the incidence of colorectal cancer.

Key words: meta-analysis; colorectal cancer; lifestyle; smoking; alcohol

Cancers of the colon and rectum (colorectal) constitute a significant proportion of the global burden of cancer morbidity and mortality, particularly in developed countries where these malignancies rank second in terms of both incidence and mortality, compared with fifth in less developed countries.[1] Annually, approximately 1 million new cases of colorectal cancer are diagnosed, and more than half a million people die from colorectal cancer, equivalent to approximately 8% of all cancer-related deaths worldwide.[2]

The occurrence of colorectal cancer varies at least 25-fold between countries[1,2] with the highest incidence rates for colorectal cancer seen in certain areas and ethnic groups in the United States, Canada, Japan and New Zealand.[3] The wide geographical variation in incidence rates for colorectal cancer, and data from migrant studies,[4] suggest that lifestyle risk factors, including diet,[5,6] physical activity,[7] obesity[8] and diabetes,[9] play a pivotal role in the aetiology of the disease.[10] A high consumption of different processed foods and alcohol intakes have also been associated with a higher colorectal cancer risk.[11] The proportion of colorectal cancer attributed to dietary factors has been estimated to be about 50%.[12] Further, approximately 66–77% of colorectal cancer has been suggested to be preventable by an appropriate combination of diet and physical activity.[13]

In 2007, the World Cancer Research Fund (WCRF)[14] released a report stating that there was convincing evidence of a causal role for red and processed meat, obesity and alcohol (in men; probable risk in women) in the aetiology of colorectal cancer. However, many studies were excluded from the analyses and the role of more putative risk factors, such as diabetes and smoking, was not explored. The aim of the current study was to quantify the risk of colorectal cancer associated with major modifiable lifestyle and dietary risk factors by updating previous meta-analyses or, in the absence of any previous reviews, to conduct a quantitative overview of the relationship between modifiable lifestyle risk factors with the risk of colorectal cancer. By doing so, we aim to determine the relative importance of these risk factors by comparing the magnitude of each of these associations with subsequent risk of colorectal cancer thereby highlighting possible areas for future intervention.

Material and methods

Data sources

Relevant studies were identified through EMBASE and MEDLINE using a combined text word and MESH heading search strategy with the terms: "colorectal cancer", "colorectal neoplasm", "colon cancer", "colon neoplasm", "rectal cancer", "rectal neoplasm", "cohort" and combined with "BMI" or "body mass index", "obesity", "overweight", "diabetes", "glucose intolerance", "smoking", "cigarette smoking", "alcohol", "physical activity", "exercise", "red meat", "processed meat", "fish", "poultry", "vegetables", "fruits", "diet", "lifestyle", "systematic review" and "meta-analysis". References from identified meta-analyses and cohort studies were also scanned to identify any other relevant studies.

Statistical methods

Studies were included if they had published quantitative estimates and standard errors (or some other measure of variability) of the association between each risk factor and colorectal cancer by January 2008. Studies were excluded if they provided only an estimate of effect, with no means by which to calculate the standard error, or if the estimates were not at least age adjusted.

For each risk factor, estimates of relative risk (RR) and 95% confidence intervals (95% CI) for colorectal cancer were extracted, where available, from each identified study in a standardized form—that which was most often reported in the literature. RRs (95% CI) for obesity were, thus, recorded as a comparison between the obese (BMI $\geq$ 30 kg/m^2) and those in the normal range of BMI ($\leq$25 kg/m^2). For cigarette smoking, the RR (95%

Additional Supporting Information may be found in the online version of this article.

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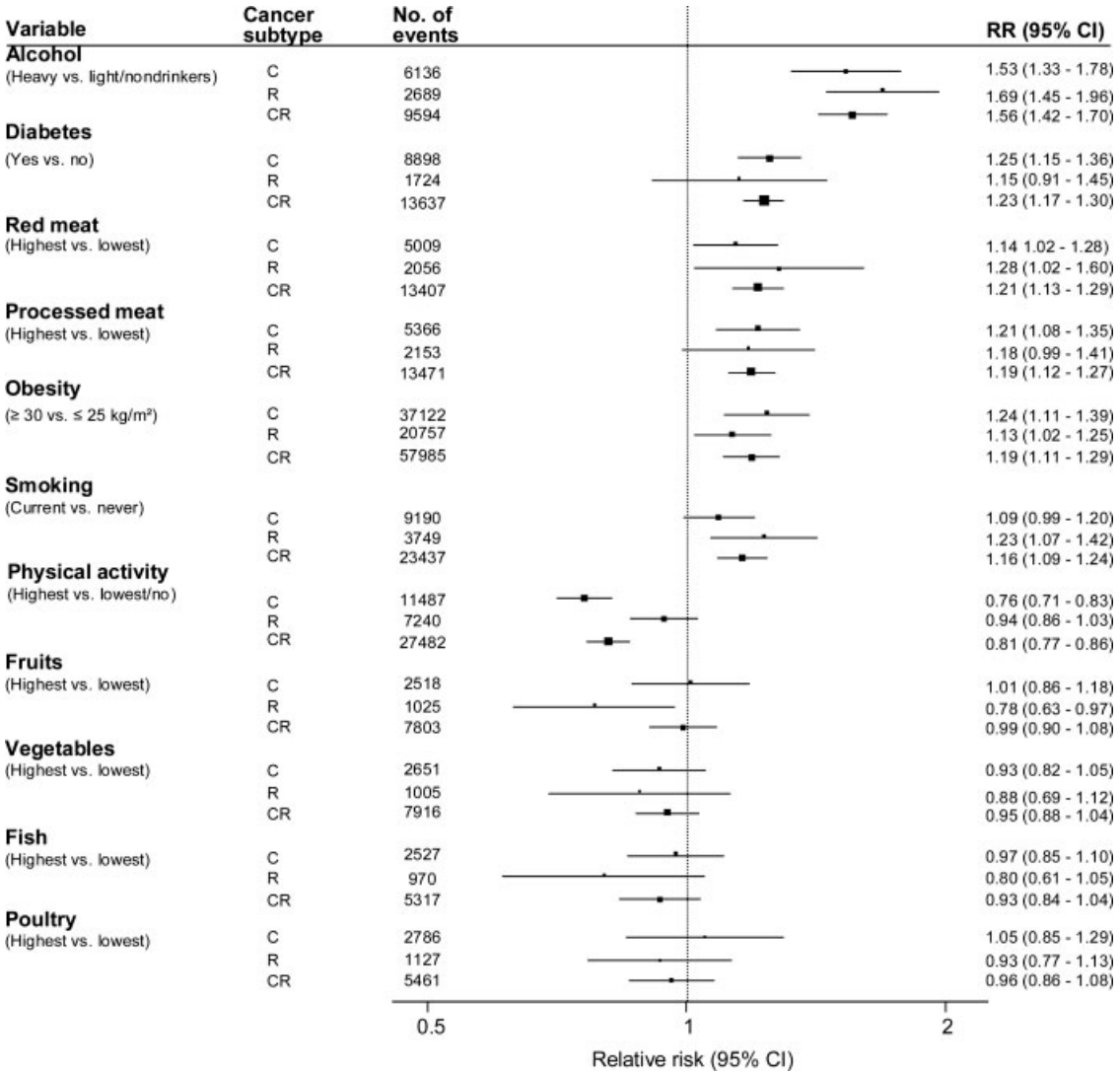

FIGURE 1 – Summary of the relationships between dietary and lifestyle risk factors and colorectal cancer. The pooled estimates of effect size are represented by a black square (with area proportional to statistical 'information', based on the inverse of variance of the summary odds ratio). The horizontal line represents the 95% confidence intervals for the observed effect in the pooled estimate. The diamond represents the pooled estimate. C, colon; R, rectum; CR, colorectal.

CI) of colorectal cancer due was based on the comparison between the risks for current smokers *versus* never smokers. For alcohol consumption, the RR (95% CI) was usually reported comparing the risk of colorectal cancer in the heaviest *versus* the lightest category of drinkers or nondrinkers. Similarly, the protective effect of physical activity was obtained for individuals with the highest level of physical activity compared with those in the lowest category of physical activity. We compared the risk of colorectal cancer among individuals with and without diabetes. Where there was a lack of consistency in the method of quantifying the exposure (*e.g.* where many studies reported by thirds and many by quarters) we compared the highest *versus* the lowest level of exposure.

Pooled estimates of RR and 95% CI were obtained by means of a random effects approach, and studies were weighted according to an estimate of its "statistical size" defined as the inverse of the variance of the log odds ratio (15). When a risk factor is protective, the pooled estimate of effect is reported as the relative risk reduction = $(1 - \text{RR}) \times 100$. Heterogeneity was estimated using the I^2 statistic and tested using the Q statistic.[15] Publication bias was investigated through Begg and Egger's test.[15,16] Where there was evidence of publication bias ($p < 0.05$) the pooled estimate was corrected using the trim-and-fill method.[17] All analyses were performed using Stata, version 10. For all the meta-analyses, we used a modified version of the MOOSE guidelines[18] for the conduct of meta-analysis of observational studies.

There have been no previous meta-analyses published of the relationship between cigarette smoking with colorectal cancer. Hence, we have included information on all of the eligible studies with information on smoking and colorectal cancer in this review. The remaining nine risk factors have all been the subject of meta-analyses, or systematic reviews, and so we have updated the most recent reviews and have provided descriptions of only those studies that had published subsequently in a series of Supporting Information (Webtables).

Results

Overall, data from 103 cohort studies with information on one or more of these risk factors were eligible for inclusion in these analyses. Figure 1 summarises the relationship between colorectal cancer (and separately for cancers of the colon and rectum) with

each of the modifiable risk factors reviewed, comparing the excess risk of cancer in the highest *versus* the lowest category for each risk factor. The individual risk factor–disease relationships are described in more detail in the following section.

Alcohol consumption and colorectal cancer

A total of 21 cohort studies (41 reports)[19–24] with information on 9,594 individuals with colorectal cancer were included in these analyses. The summary characteristics of included studies are shown in Supporting Information Webtable 1. Most of the studies were from Western populations: North America ($n = 7$), Europe ($n = 5$) and the remaining nine studies were from Asia. The pooled estimate indicated that in individuals who were categorized as "heavy drinkers", the risk of colorectal cancer was approximately 60% greater compared with those individuals classed as light/nondrinkers: RR 1.56 (95% CI 1.42–1.70; Supporting Information Webfigure 1). There was no evidence of heterogeneity across studies ($p = 0.27$) nor was there evidence of a significant different in the estimates of effect size for cancer of the colon and for rectal cancer: [RR 1.53 (95% CI 1.33–1.78) and RR 1.69 (95% CI 1.45–1.96), respectively; $p = 0.56$]. There was no evidence of publication bias ($p = 0.56$).

Diabetes and colorectal cancer

A total of 15 cohort studies (30 reports)[9,25–27] with information on 13,637 individuals with colorectal cancer were included in these analyses. The summary characteristics of included studies are shown in Supporting Information Webtable 2. Most of the study populations were from Western populations: North America ($n = 7$), Europe ($n = 7$) and the remaining three studies were from the Asia-Pacific region. The pooled estimate suggested that in individuals with diabetes the risk of colorectal cancer was 20% higher compared with unaffected individuals: RR 1.23 (95% CI 1.17–1.30; Supporting Information Webfigure 2). There was no evidence of heterogeneity across studies ($p = 0.44$) nor was there a significant difference in the estimates for cancer of the colon and for rectal cancer: RR 1.25 (95% CI 1.15–1.36) and RR 1.15 (95% CI 0.91–1.45), respectively. There was no evidence of publication bias ($p = 0.14$).

Cigarette smoking and colorectal cancer

From the identified studies, a total of 22 cohort studies (39 reports)[23,25,28–46] with information on 23,437 individuals with colorectal cancer met inclusion criteria for these analyses. The summary characteristics of included studies are shown in Table I. Most of the study populations were from Western populations: North America ($n = 10$), Europe ($n = 4$) and the remaining eight studies were from the Asia-Pacific region. The pooled summary estimated indicated that smokers had a 16% greater risk compared with those who had never smoked (Fig. 2). There was evidence of heterogeneity across studies ($p < 0.001$), which was not explained by differences in the strength of the association by site or by sex: the estimated RR for cancer of the colon was nonsignificantly lower than for rectal cancer: 1.09 (95% CI: 0.99–1.20) *vs.* 1.23 (95% CI: 1.07–1.42); $p = 0.17$. Similarly, there was a nonsignificant difference in the summary estimate by sex: 1.09 (95% CI: 0.99–1.19) in females *vs.* 1.21 (95% CI: 1.10–1.33) in males; $p = 0.12$. There was no evidence of any regional difference in the strength of the association: pooled RR (95% CI) for Asian cohorts 1.17 (1.02–1.35) *vs.* 1.16 (95% CI: 1.08–1.24) in cohorts from other regions combined; p for heterogeneity = 0.91.

There was some suggestion that the risk of colorectal cancer increased with study duration such that in those studies with more than 25 years follow up, the RR of colorectal cancer associated with smoking was approximately 20% compared with less than 10% in those studies of less than 10 years follow-up (p for trend = 0.16; Fig. 3). Length of study may be a proxy for duration of smoking, and this may thus explain the heterogeneity found in the strength of the association between smoking and colorectal cancer.

Meat consumption and colorectal cancer

A total of 26 cohort studies (111 reports)[23,44,47–63] with information on 15,057 individuals with colorectal cancer examined the association between meat (red meat, processed meat, fish and/or poultry) and colorectal cancer. The summary characteristics of included studies are shown in Supporting Information Webtables 3 and 4. Most of the study populations were from Western populations: North America ($n = 13$), Europe ($n = 9$), Australia ($n = 1$) and the remaining three studies were from Asia.

The pooled estimate for the highest *versus* the lowest level of consumption for red meat was RR 1.21 (95% CI: 1.13–1.29; Supporting Information Webfigure 3). There was no evidence of heterogeneity across studies ($p = 0.72$) and there was no significant difference in the estimates for cancer of the colon and for rectal cancer: RR 1.14 (95% CI: 1.02–1.28) and RR 1.28 (95% CI: 1.02–1.60), respectively.

Individuals in the highest level compared with those in the lowest level of processed meat intake had a 20% increased risk for developing colorectal cancer RR 1.19 (95% CI: 1.12–1.27; Supporting Information Webfigure 4). There was no evidence of heterogeneity across studies ($p = 0.42$) and there was no significant difference in the estimates for cancer of the colon and for rectal cancer: RR 1.21 (95% CI: 1.08–1.35) and RR 1.18 (95% CI: 0.99–1.41), respectively.

We did not observe any apparent association between risk of colorectal cancer and consumption of either fish [RR 0.93 (95% CI: 0.84–1.04)] (Supporting Information Webfigure 5) or poultry [RR 0.96 (95% CI: 0.86–1.08)] (Supporting Information Webfigure 6).

Fruit and vegetable intake and colorectal cancer

Among 16 eligible cohort studies (57 reports)[23,31,57,64–68] for these analyses, 7,956 individuals were diagnosed with colorectal cancer. The summary characteristics of included studies are shown in Supporting Information Webtable 5. Most of the study populations were from Western populations: North America ($n = 8$), Europe ($n = 4$) and the remaining four studies were from Asia.

There was no evidence of an association between fruit intake and risk of colorectal cancer. The pooled estimate of colorectal cancer for the highest *versus* lowest level of fruit intake was 0.99 (95% CI: 0.90–1.08; Supporting Information Webfigure 7) with limited evidence of statistical heterogeneity across studies ($p = 0.11$). There was no evidence of publication bias ($p = 0.30$). When the association was examined by cancer site, there was a significant inverse association between fruit intake with rectal cancer but not for colon cancer: RR 0.78 (95% CI: 0.63–0.97) *versus* 1.01 (95% CI: 0.86–1.18); p for heterogeneity = 0.06.

As with fruit intake, there was no evidence of a significant association between vegetable consumption and risk of colorectal cancer. The pooled estimate comparing the highest with the lowest category of vegetable intake was RR 0.95 (95% CI: 0.88–1.04; Supporting Information Webfigure 8). There was no evidence of heterogeneity across studies ($p = 0.18$) and there was no significant difference in the summary estimates for cancer of the colon and for rectal cancer: RR 0.93 (95% CI: 0.82–1.05) and 0.88 (95% CI: 0.69–1.12), respectively. Neither was there evidence of publication bias ($p = 0.29$).

Obesity and colorectal cancer

We have previously published a meta-analysis of the association between overweight, obesity and colorectal cancer.[69] A brief summary of the published findings are presented here. A total of 18 cohort studies (51 reports) with information on 57,985 individuals with colorectal cancer examined the association between obesity and colorectal cancer. The pooled estimate indicated that

TABLE 1 – COHORT STUDIES REPORTING ON THE ASSOCIATION BETWEEN SMOKING AND COLORECTAL CANCER

First author/Year	Cohort/Country	No. (Sex)	Cancer subtype	Events	Source	Smoking status				Level of adjustment
						Ex-smokers	Current vs. Never Smokers			
							Yes/No	CPD		
						RR (95% CI)	RR (95% CI)	No.	RR (95% CI)	
Akhter 2007[28]	Japan	25,729 (M)	CR	188	CR,DC	1.73 (1.04–2.87)	1.47 (0.93–2.34)	Never	1.00	1,3,4,6,7
								1–19	1.32 (0.75–2.31)	
								≥20	1.60 (0.99–2.58)	
A–Moghaddam 2007[25]	Asia-Pacific	539,201 (M+F)	CR	751	CP	1.55 (1.19–2.02)	1.34 (1.03–1.74)	Never	1.00	1,3,4,12
								1–19	1.38 (0.92–2.08)	
								≥20	0.89 (0.54–1.48)	
Tsong 2007[22]	Singapore	63,527 (M+F)	C	516	CR,MR, VS	0.96 (0.73–1.27)	0.83 (0.67–1.06)	Never	1.00	1,2,3,4,6,7,9
								<13	0.84 (0.64–1.11)	
								≥13	0.91 (0.71–1.17)	
			R	329		1.43 (1.04–2.01)	1.63 (1.23–2.17)	Never	1.00	
								<13	1.38 (0.99–1.90)	
								≥13	1.71(1.28–2.28)	
Paskett 2007[29]	USA	146,877	C	1075	MR,PR	1.12 (0.97–1.29)	1.03 (0.77–1.38)	Never	1.00	1,5,6,7,8,12,13,14,20
								<25	1.05 (0.90–1.21)	
								≥25	1.47 (1.16–1.85)	
			R	176		1.15 (0.80–1.67)	1.95 (1.10–3.47)	Never	1.00	
								<25	1.29 (0.90–1.86)	
								≥25	1.14 (0.59–2.18)	
Yun 2005[30]	Korea	733,134 (M)	C	417	CR	1.37 (1.06–1.77)	0.81 (0.63–1.05)	Never	1.00	1,3,4,6,8
								1–9	0.97 (0.66–1.43)	
								10–19	0.78 (0.59–1.04)	
								=20	0.76 (0.51–1.15)	
			R	453	CR	1.17 (0.91–1.52)	0.97 (0.76–1.24)	Never	1.00	
								1–9	0.95 (0.65–1.39)	
								10–19	0.95 (0.73–1.24)	
								=20	1.05 (0.74–1.50)	
Sanjoaquin 2004[31]	UK	10,998 (M+F)	CR	95	NHSCR	1.80 (1.13–2.85)	1.70 (0.92–3.15)			1,2,4
Otani 2003[32]	Japan	42,540 (M)	C	299	CR,DC, MR	1.50 (1.02–2.10)	1.60 (1.10–2.10)			1,3,4,5,8,17
			R	148		1.20 (0.70–2.00)	1.40 (0.90–2.30)			
Wakai 2003[33]	Japan	25,280 (M)	C	219	CR,DC	1.07(0.72–1.59)	1.23 (0.85–1.78)	Never	1.00	1,3,4,5,6,7, 8,9
								0–19	1.05 (0.70–1.58)	
								20–39	1.30 (0.89–1.89)	
								≥40	0.69 (0.33–1.43)	
		34,819 (F)	C	189		1.07 (0.39–2.92)	1.06 (0.55–2.02)			
		M	R	147		0.88 (0.56–1.39)	0.83 (0.55–1.26)	Never	1.00	
								0–19	0.95 (0.60–1.50)	
								20–39	0.79 (0.51–1.22)	
								≥40	0.80 (0.38–1.69)	
		F	R	57		1.05 (0.14–2.69)	0.36 (0.05–2.65)			
Terry 2002[34]	Canada	89,835 (F)	C	363	MR,CR	1.03 (0.80–1.33)	0.93 (0.71–1.24)	Never	1.00	1,3,4,5,7,18
								1–9	0.89 (0.61–1.28)	
								10–19	0.94 (0.67–1.32)	
								20–29	1.16 (0.87–1.53)	
								30–39	0.87 (0.26–1.52)	
								≥40	0.63 (0.26–1.52)	
			R	164		1.44 (1.00–2.06)	1.17 (0.78–1.75)	Never	1.00	
								1–9	1.31 (0.80–2.14)	
								10–19	1.98 (1.32–2.96)	
								20–29	0.97 (0.61–1.56)	
								30–39	0.72 (0.23–2.29)	
								≥40	0.90 (0.28–2.85)	

TABLE I – COHORT STUDIES REPORTING ON THE ASSOCIATION BETWEEN SMOKING AND COLORECTAL CANCER (CONTINUED)

First author/Year	Cohort/Country	No. (Sex)	Cancer subtype	Events	Source	Smoking status				Level of adjustment
						Ex-smokers	Current vs. Never Smokers			
							Yes/No	CPD		
						RR (95% CI)	RR (95% CI)	No.	RR (95% CI)	
Rohan 2000[35]	USA	56,837 (F)	CR	90	MD	1.52 (0.91–2.56)	1.15 (0.61–2.16)	Never	1.00	1,3,4,5,6
								1–9	1.78 (0.94–3.38)	
								10–19	1.21 (0.60–2.47)	
								≥20	1.21 (0.66–2.20)	
Chao 2000[36]	CPS–II (USA)	508,351 (M)	CR	4,513 (Deaths)	DC,NDI, ACSV	1.32 (1.16–1.49)	1.15 (1.04–1.27)	Never	1.00	1,3,4,5,6,7,8,11,15
								<20	1.29 (1.07–1.55)	
								20	1.25 (1.05–1.50)	
								21–39	1.33 (1.08–1.62)	
								≥40	1.46 (1.19–1.79)	
		676,306 (F)	CR	4,252 (Deaths)		1.41 (1.26–1.58)	1.22 (1.09–1.37)	Never	1.00	1,3,4,5,6,7,8,11,15,16
								<20	1.32 (1.13–1.55)	
								20	1.52 (1.29–1.79)	
								21–39	1.26 (0.97–1.65)	
								≥40	1.65 (1.24–2.21)	
Strumer 2000[37]	USA	2,2071 (M)	CR	351	SR,MR	1.49 (1.17–1.89)	1.81 (1.28–2.55)	Never	1.00	1,3,4,5,6,15
								<20	1.32 (0.73–2.40)	
								≥20	2.14 (1.45–3.14)	
Hsing 1998[23]	USA	17,633 (M)	C	120	DC	1.50 (0.80–2.70)	1.40 (0.70–2.70)	Never	1.00	1,4,9
								1–19	1.30 (0.20–9.70)	
								20–29	2.40 (1.00–5.30)	
								≥30	1.20 (0.60–2.40)	
			R	25		1.10 (0.70–1.80)	1.00 (0.60–1.70)	Never	1.00	
								1–19	0.80 (0.40–1.60)	
								20–29	1.10 (0.50–2.10)	
								≥30	1.70 (0.70–3.80)	
Liaw,1998[38]	Taiwan	11,096 (M)	CR	42	CR		0.80 (0.40–1.50)			1
Nordlund 1997[39]	Sweden	26,000 (F)	CR	559	CR	1.16 (0.72–1.86)	0.88 (0.67–1.16)	Never	1.00	1,9
								1–7	0.90 (0.63–1.27)	
								8–15	0.66 (0.39–1.12)	
								≥16	1.42 (0.77–2.60)	
Nyren 1996[40]	Sweden	135,000	C	713	CR,NDR	1.02 (0.84–1.24)	0.98 (0.82–1.17)	Never	1.00	1
								1–4	0.91 (0.72–1.16)	
								5–14	0.82 (0.67–0.99)	
								15–24	1.09 (0.86–1.38)	
								≥25	1.07 (0.63–1.82)	
			R	505		1.22 (0.97–1.54)	1.16 (0.94–1.44)	Never	1.00	
								1–4	1.07 (0.82–1.41)	
								5–14	0.80 (0.62–1.04)	
								15–24	1.20 (0.91–1.58)	
								≥25	1.08 (0.58–2.03)	
Engeland 1996[41]	Norway	11,863 (M)	C	230	CR,DC, MR	1.00 (0.60–1.50)	1.20 (0.80–1.60)			1
		14,269 (F)	C	300		1.30 (0.90–2.00)	1.10 (0.80–1.40)			
		M	R	139		0.80 (0.40–1.60)	1.60 (1.00–2.60)			
		F	R	141		1.30 (0.80–2.40)	0.80 (0.50–1.30)			
Chyou 1996[42]	USA	7,945 (M)	C	330	CR,MR	1.27 (0.95–1.70)	1.42 (1.09–1.85)			1
			R	123		1.31 (0.78–2.20)	1.95 (1.25–3.04)			
Heineman 1995[43]	USA	248,046 (M)	C	3,812	VA,DC	1.30 (1.20–1.50)	1.20 (1.10–1.40)	Never	1.00	1,9,14
								1–9	1.10 (1.00–1.30)	
								10–20	1.20 (1.10–1.40)	
								21–39	1.30 (1.10–1.40)	
								≥40	1.60 (1.20–2.00)	

TABLE 1 – COHORT STUDIES REPORTING ON THE ASSOCIATION BETWEEN SMOKING AND COLORECTAL CANCER (CONTINUED)

First author/Year	Cohort/Country	No. (Sex)	Cancer subtype	Events	Source	Smoking status					Level of adjustment
						Ex-smokers	Current vs. Never Smokers				
							Yes/No	CPD			
						RR (95% CI)	RR (95% CI)	No.	RR (95% CI)		
			R	1,100		1.40 (1.10–1.70)	1.40 (1.20–1.70)	Never	1.00		
								1–9	1.30 (1.00–1.70)		
								10–20	1.40 (1.10–1.70)		
								21–39	1.60 (1.30–2.10)		
								≥40	1.70 (1.10–2.60)		
Bostick 1994[44]	USA	35,215 (F)	C	212	SHR	0.92 (0.64–1.32)	1.09 (0.74–1.59)				1,6,10,13
Akiba 1994[45]	Japan	61,505 (M+F)	C	324	CR,MD	0.90 (0.60–1.40)	1.20 (0.90–1.60)				1,2
Chute 1991[46]	USA	118,404 (F)	C	191	SR, MR, DC	1.20 (0.90–1.70)	1.00 (0.70–1.40)	Never	1.00		1
								1–14	1.00 (0.60–1.70)		
								15–24	1.00 (0.00–1.60)		
								>24	1.00 (0.60–1.70)		
			R	49		1.90 (1.00–3.60)	1.10 (0.50–1.30)	Never	1.00		
								1–14	1.20 (0.40–3.70)		
								>14	1.10 (0.50–2.50)		

individuals with a BMI $\geq$ 30 kg/m^2 had a 40% greater risk of colorectal cancer compared with individuals with a BMI $\leq$ 25 kg/m^2. There was evidence of both heterogeneity ($p < 0.001$) and publication bias ($p = 0.03$) across studies. The revised estimate, after correcting for publication bias, of the RR was 1.19 (95% CI: 1.11–1.29).

Some of the observed heterogeneity in study estimates was explained by differences in the magnitude of association in terms of sex. The RR for colorectal cancer, obese *versus* normal weight, was 1.41 (95% CI: 1.30–1.54) in men compared with 1.08 (95% CI: 98–1.18) in women (p heterogeneity < 0.001). The pooled estimate of the association between obesity and colon cancer was nonsignificantly higher than that of the association between obesity and rectal cancer: RR 1.24 (95% CI: 1.11–1.39) *versus* 1.13 (95% CI: 1.02–1.25); p for heterogeneity = 0.23.

Physical activity and colorectal cancer

From the identified studies, a total of 27 cohort studies (56 reports)[7,25,31,70–80] with information on 27,482 individuals with colorectal cancer were eligible for these analyses. The summary characteristics of included studies are shown in Supporting Information Webtable 6. Most of the study populations were from Western populations: North America ($n = 13$), Europe ($n = 10$), and the remaining four studies were from the Asia-pacific region.

The pooled estimate showed that individuals with high level of physical activity had a 20% lower risk of colorectal cancer compared with inactive individuals: RR 0.81 (95% CI: 0.77–0.86; Supporting Information Webfigure 9). There was evidence of statistical heterogeneity across studies ($p = 0.028$), some of which was explained by differences in the strength of the association between cancer sites. For colon cancer, the inverse association with physical activity was significantly stronger than for rectal cancer: relative risk reduction 24% (95% CI: 18–29%) *versus* 6% (95% CI: −3 to 14%) for rectum; p for heterogeneity < 0.001.

There was also some evidence of a sex difference in the magnitude of the association, such that the protective effect conferred by physical activity was observed to be slightly stronger in men than in women: 22% (95% CI: 16–28%) *versus* 13% (95% CI: 4–21%); p for heterogeneity = 0.04. Some of the heterogeneity may also have been because of the forms of physical activity undertaken with the association being nonsignificantly stronger for recreational or leisure-time physical activity compared with occupational physical activity: 26% (95% CI: 17–39%) *versus* 17% (95% CI: 10–24%); p for heterogeneity = 0.13.

Discussion

Evidence from this comprehensive series of meta-analyses indicates that the risk of colorectal cancer is increased by high alcohol intake such that individuals in the top category for consumption had an approximate 60% greater risk compared with those in the lowest category. And, although not directly comparable, these findings suggest that the relationship between risk of colorectal cancer with high BMI, diabetes, high consumption of red and processed meat, and cigarette smoking is broadly equivalent, with individuals in the highest categories for each of these risk factors having a 20% greater risk of the cancer compared with those in the lowest categories. Conversely, those individuals reporting the highest levels of physical activity—recreational or otherwise—had 20% lower risk of colorectal cancer when compared with the most sedentary individuals. There was no evidence to support an association between the consumption of fish, poultry, fruit or vegetables with risk of the neoplasm. These findings agree broadly with those published in the WCRF report,[14] but importantly, the current overview additionally provides evidence to implicate aetiological roles for cigarette smoking and diabetes in colorectal cancer. With the exception of alcohol, the strength of the associations between each of these four lifestyle risk factors with colorectal cancer was remarkably consistent at around 20%. Importantly,

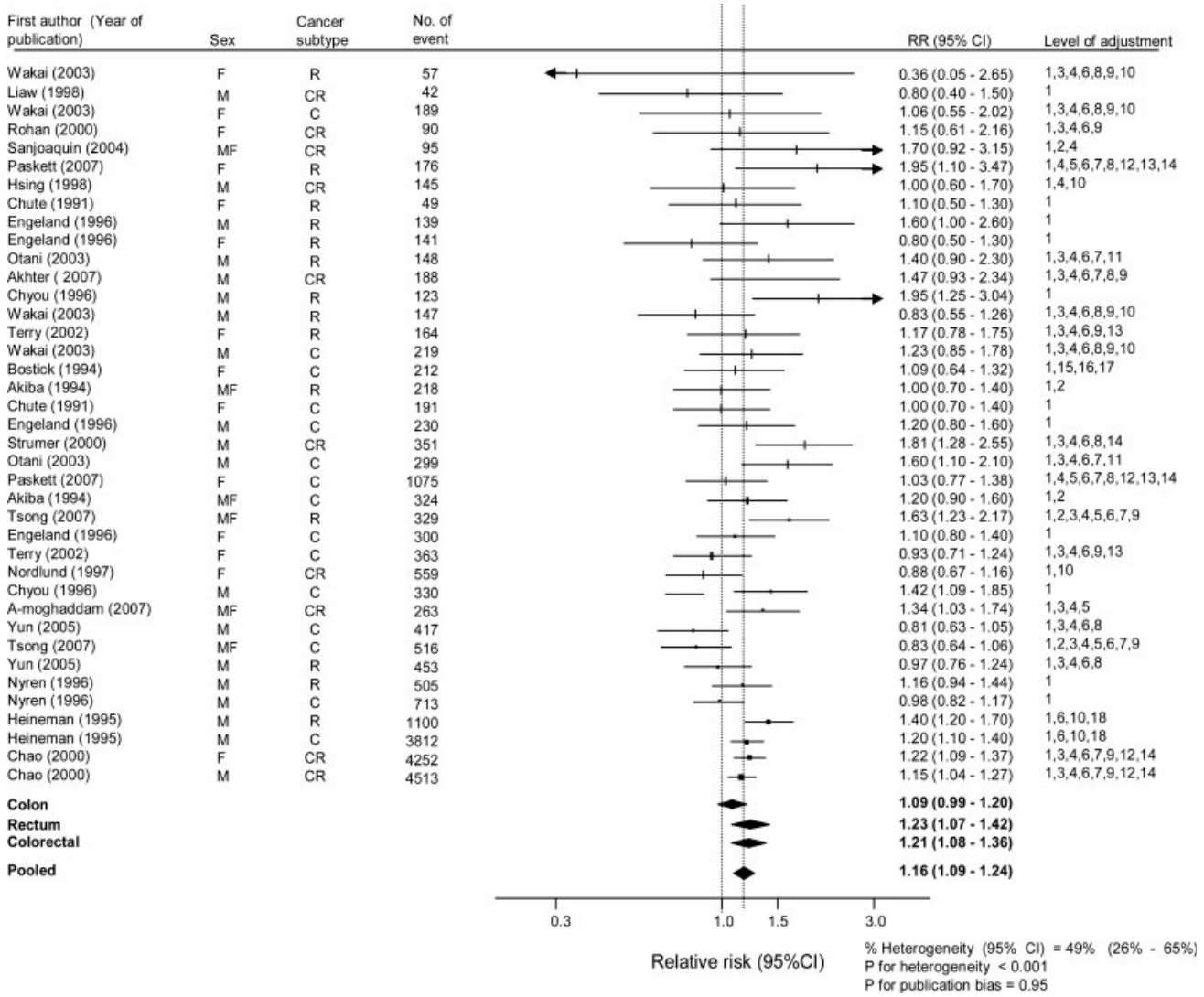

FIGURE 2 – The association between cigarette smoking and colorectal cancer (current *vs*. never smokers). Level of adjustment: the published estimates extracted from each of the studies that reported on the association between a risk factor with colorectal cancer differed in the level of adjustment for possible confounders. These adjustments are indicated in the figure by the following: 1, age; 2, sex; 3, BMI; 4, alcohol; 5, diabetes; 6, physical activity; 7, family history; 8, diet; 9, education; 10, socio-economic status; 11, center; 12, ethnicity; 13, hormone replacement therapy; 14, medication; 15, parity; 16, height; 17, vitamin supplementary intake; 18, calendar year; 19, menstruation for women; 20, waist circumference. The individual estimates of effect size from each of the studies are represented by a black square (with area proportional to statistical 'information', based on the inverse of variance of the odds ratio provided by each study). The horizontal line represents the 95% confidence intervals for the observed effect in each study. The diamond represents the pooled estimate. C, colon; R, rectum; CR, colorectal; M, Male; F, Female.

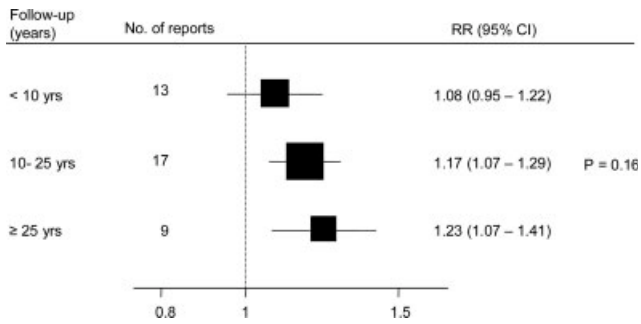

FIGURE 3 – The relationship between cigarette smoking and risk of colorectal cancer by duration of study. Conventions as in Fig. 2. *p* value for trend.

there was little statistical heterogeneity between the individual studies (with the exception of cigarette smoking). Neither was there any evidence of publication bias which increases the likelihood that these studies represent the majority of published cohort studies that have examined the impact of these risk factors on cancer risk.[15,16]

The evidence for a causative role of cigarette smoking in the aetiology of colorectal cancer is more equivocal than it is for some of these other, more established, risk factors. Some commentators have suggested that the lack of an association between smoking and colorectal cancer observed by some studies, is because of an extraordinary long induction period of more than 30 years.[81] Data from the current study provide some support to this latter theory as there was some evidence to support a trend between increasing duration of study follow-up (used as a marker

of duration of smoking) with greater risk. A previous review of 27 studies[82] concluded that long-term cigarette smoking (over three to four decades) is an important risk factor for colorectal cancer and should be added to the list of tobacco-associated malignancies. It is likely that some of the heterogeneity observed in the current review between the studies of smoking and colorectal cancer risk is because of variation in the duration of smoking, as well as in the type and amount of cigarettes smoked and the age of initiation of smoking by study participants.

The major limitation of the meta-analyses presented here is that the data are reliant on published estimates and hence, we were unable to examine the impact of adjustment for possible confounders or to explore at what level these risk factors interact. An example of this is the possible confounding effect of smoking on the relationship between alcohol and colorectal cancer. Most of the studies included in the review would only have had information on whether an individual was a smoker, and in some studies, the amount smoked. However, the impact of smoking on disease risk is influenced by several additional factors such as age of commencement and duration of smoking. Unless there is adequate information on such variables then it is difficult to fully quantify and hence, adjust for the totality of the confounding effect due to smoking and so the potential for residual confounding remains high. Ideally, to preclude this possibility, one would analyse the relationship between alcohol consumption and colorectal cancer only in nonsmokers, but such an analysis was not possible because of the reliance on published estimates.

Further, given the frequent co-occurrence of smoking, alcohol, physical inactivity and diets that are high in meat (both processed and nonprocessed meat), it is impossible to disentangle the individual effects that each of these variables may have on risk. This would only be possible through the conduct of a large-scale individual participant data meta-analysis which would also have enabled sex-specific comparisons to be performed. Moreover, individual participant data would afford the flexibility to examine the observed associations in much more detail. For example, the association between excess weight and colorectal cancer may differ in women according to menopausal status.[83] The pooled relative risks for the association between alcohol, diabetes, cigarette smoking, red and processed meat consumption and risk of colorectal cancer risk were all less than two, and hence the potential for residual confounding to explain wholly, or in part, the observed relationships cannot be ruled out.

A further limitation of this review is that we did not conduct a specific overview for fibre and risk of colorectal cancer largely because fibre is considered to be a marker of dietary consumption of foods containing it such as vegetables and fruits, although specific mechanisms pertaining to a beneficial effect of fibre on colorectal cancer have been suggested.[14] The Pooling Project of Prospective Studies of Diet and Cancer which comprised 13 cohort studies with information on 8,081 colorectal cancer cases[84] examined the relationship between dietary fibre and risk of colorectal cancer. In age-adjusted analyses, there was a protective effect of high fibre intakes of approximately 10–20% but the effect was significantly attenuated after adjustment for other dietary and nondietary risk factors: pooled age-adjusted relative risk 0.84 (95% CI 0.77–0.92) *versus* RR 0.94 (95% CI 0.86–1.03) in the fully adjusted model. This finding is supported by the data for fruits and vegetables which, overall, provide little evidence of a protective effect of fruit and vegetables on subsequent colorectal cancer risk. However, these finding conflicts with those from the European Prospective Investigation into Cancer and Nutrition (EPIC), a prospective study from 10 European countries with 1,721 cases of colorectal cancer, that was not included in the Pooling Project. In EPIC, a significant inverse association of dietary fibre with colorectal cancer was observed with the relative risk for people in the highest *versus* the lowest fifth of dietary fibre intake of 0.79 (95% CI: 0.63–0.99) after adjustment for dietary and nondietary covariates.[85] A possible explanation for the heterogeneity between these two studies may be due to differences in the predominant source of dietary fibre. In EPIC, cereal fibre, which was the major source of fibre in half of the countries, was reported to confer a greater benefit on risk compared with fibre derived from fruit, vegetables and legumes. Whether this is an important distinction merits further investigation by future studies.

The similarity of the association between diabetes and obesity suggests that insulin resistance may underlie the increased risk observed in both cases but the mediator is not clear. Although elevated insulin like growth factor 1 is associated with colorectal cancer,[86] it tends to be lower in type-2 diabetes[87] and insulin levels in type-2 diabetes can be very variable being high initially and then falling with longer duration of the disease. Low level inflammation occurs in both colorectal cancer and type-2 diabetes[88] and indeed there is some evidence that C-reactive protein, a nonspecific but sensitive inflammatory marker, is associated with colorectal cancer.[89] Exercise reduces insulin resistance and lowers inflammation[90] suggesting a similar pathway for this lifestyle variable. Further, inflammation is known to increase oxidative DNA damage[91] and common inflammatory conditions like rheumatoid arthritis are associated with increased cancer risk[92] although interestingly not colorectal or breast cancer.

In conclusion, modest changes at the population level in the consumption of alcohol and red and processed meat, weight loss, smoking cessation and increased levels of physical activity may translate into significant reductions in the incidence of colorectal cancer. The public-health potential would be particularly great not only for higher-income countries but for many lower- and middle-income countries that are experiencing epidemics of obesity, type-2 diabetes and cigarette smoking, and hence, are projected to shoulder a substantial burden of chronic and degenerative disease in the next two decades.

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