Review

Obesity and Risk of Colorectal Cancer: A Meta-analysis of 31 Studies with 70,000 Events

Alireza Ansary Moghaddam, Mark Woodward, and Rachel Huxley

The George Institute for International Health, Sydney, Australia

Abstract

Background: **Colorectal cancer is the second most common cause of death and illness in developed countries. Previous reviews have suggested that obesity may be associated with 30% to 60% greater risk of colorectal cancer, but little consideration was given to the possible effect of publication bias on the reported association.**
Methods: **Relevant studies were identified through EMBASE and MEDLINE. Studies were included if they had published quantitative estimates of the association between general obesity [defined here as body mass index (BMI) $\geq$30 kg/m^2] and central obesity (measured using waist circumference) and colorectal cancer. Random-effects meta-analyses were done, involving 70,000 cases of incident colorectal cancer from 31 studies, of which 23 were cohort studies and 8 were case-control studies.**
Results: **After pooling and correcting for publication bias, the estimated relative risk of colorectal cancer was 1.19 [95% confidence interval (95% CI), 1.11-1.29], comparing obese (BMI $\geq$30 kg/m^2) with normal weight (BMI <25 kg/m^2) people; and 1.45 (95% CI, 1.31-1.61), comparing those with the highest, to the lowest, level of central obesity. After correcting for publication bias, the risk of colorectal cancer was 1.41 (95% CI, 1.30-1.54) in men compared with 1.08 (95% CI, 0.98-1.18) for women ($P_{heterogeneity}$ <0.001). There was evidence of a dose-response relationship between BMI and colorectal cancer: for a 2 kg/m^2 increase in BMI, the risk of colorectal cancer increased by 7% (4-10%). For a 2-cm increase in waist circumference, the risk increased by 4% (2-5%).**
Conclusions: **Obesity has a direct and independent relationship with colorectal cancer, although the strength of the association with general obesity is smaller than previously reported.** (Cancer Epidemiol Biomarkers Prev 2007;16(12):2533–47)

Introduction

Cancers of the colon and rectum (colorectal) constitute a significant proportion of the global burden of cancer morbidity and mortality. This is particularly so in developed countries where these malignancies rank second in terms of both incidence and mortality, compared with fifth in less developed countries (1). Approximately 1 million new cases of colorectal cancer are diagnosed, and more than half a million people die from colorectal cancer each year (1, 2). The wide geographic variation in incidence rates for colorectal cancer, together with observations from migrant studies, suggest that lifestyle risk factors, including diet (3, 4), physical activity (5), obesity (6), and diabetes (7), play a pivotal role in the etiology of the disease (8).

Previous reviews (6, 9-11) have indicated that obesity is associated with 7% to 60% greater risk of colorectal cancer compared with normal weight individuals, with some suggestion that the relationship with obesity is stronger for cancer of the colon compared with rectal cancer. However, no overall quantitative estimate of this difference has previously been reported, possibly due to insufficient data on site-specific associations with obesity to allow reliable estimation. It seems that the excess risk of colorectal cancer may be higher among obese men compared with obese women, but findings of a sex difference have been inconsistently reported (6, 9-11). Moreover, there remains uncertainty regarding whether publication bias may be unduly influencing these estimates of effect as findings from the two most recent overviews provide conflicting results on this issue (10, 11).

Hence, the purpose of this current review is to summarize all of the available data to provide the most reliable estimation of the strength, and nature, of the association between measures of general and central obesity with cancers of the colon and rectum, in both men and women. To minimize the potential for bias, we restricted the review to include only studies that reported incident colon and rectal cancer and which used the same criteria to define overweight and obesity in the study population.

Materials and Methods

Data Sources. We adhered to the Meta-analysis of Observational Studies in Epidemiology guidelines for the conduct of meta-analysis of observational studies (12). Relevant studies were identified through EMBASE and MEDLINE using a combined text word and MESH

Received 8/2/07; revised 10/2/07; accepted 10/9/07.

Requests for reprints: Rachel Huxley, The George Institute for International Health, P.O. Box M201, Missenden Road, Sydney, NSW 2050 Australia. Phone: 61-2-9657-0358; Fax: 61-2-9657-0301. E-mail: rhuxley@thegeorgeinstitute.org

doi:10.1158/1055-9965.EPI-07-0708

heading search strategy with the terms colorectal cancer, colorectal neoplasm, colon cancer, colon neoplasm, rectal cancer, rectal neoplasm, cohort, and case-control studies combined with body mass index (BMI), obesity, and waist circumference. References from identified studies were also scanned to identify any other relevant studies.

Statistical Methods. Studies were included if they had published quantitative estimates and SEs (or some other measure of variability) of the association between general obesity (defined here as BMI $\geq$30 kg/m^2) or central obesity (measured using waist circumference) and colorectal cancer by April 2007. Studies were excluded if they provided only an estimate of effect, with no means by which to calculate the SE, or if the estimates were not, at least, age adjusted. Studies also excluded if reporting mortality from colorectal cancer. Information from the studies was extracted independently by two authors (A.A.M. and R.H.). Pooled estimates of relative risks (RR) were obtained using either hazard ratios (for cohort studies) or odds ratios (for case-control studies) by means of a random-effects approach. Studies were weighted according to an estimate of their ''statistical size,'' defined as the inverse of the variance of the log RR (13). Heterogeneity was estimated using the I^2 statistic and tested using the Q statistic (13).

Pooled RRs for general obesity were estimated continuously (per 2-unit increment in BMI) and using a binary measure [comparing obese individuals (BMI $\geq$30 kg/m^2) with those in the reference range of BMI (<25 kg/m^2)]. The RR and 95% confidence intervals (95% CI) per 2 units higher BMI were derived by multiplying both the estimated log RR and its SE by 2.

In addition, estimates from those studies that used the same three BMI categories were pooled separately to examine any dose-response effect; normal weight, BMI 18.5 to 24.9 kg/m^2; overweight, BMI 25 to 29.9 kg/m^2; and obese, BMI $\geq$30 kg/m^2. The results for the association between waist circumference and colorectal cancer risk are described continuously (per 2-cm increase in waist circumference), and by comparing risk in the highest with those in lowest category of waist circumference as defined in each qualifying study (there was no consistent categorization of central obesity across studies). Possible sources of heterogeneity were investigated by comparing the results for colon and rectal cancer, sex groups, study designs, and whether the study adjusted for risk factors, including cigarette smoking, alcohol consumption, physical activity, diabetes, and dietary variables.

Publication bias was investigated through funnel plots and tested using Egger's test (13, 14). Funnel plots are plots of the exposure estimated from individual studies against a measure of study size, and are so called because the precision in the estimation of the underlying exposure increases as the sample size of studies increases. If bias is absent, results from small studies will scatter relatively widely compared with larger studies, all around the same average. Corrections for publication bias were made using the trim-and-fill procedure, which essentially corrects the funnel plot by imputing where the missing studies would be most likely to fall, should they have been recorded (13). All analyses were done using STATA, version 10.

Results

The search identified 2,055 studies, of which 565 were potentially relevant (Fig. 1). A total of 79 reports from 23 cohort studies (15-40) and eight case-control studies

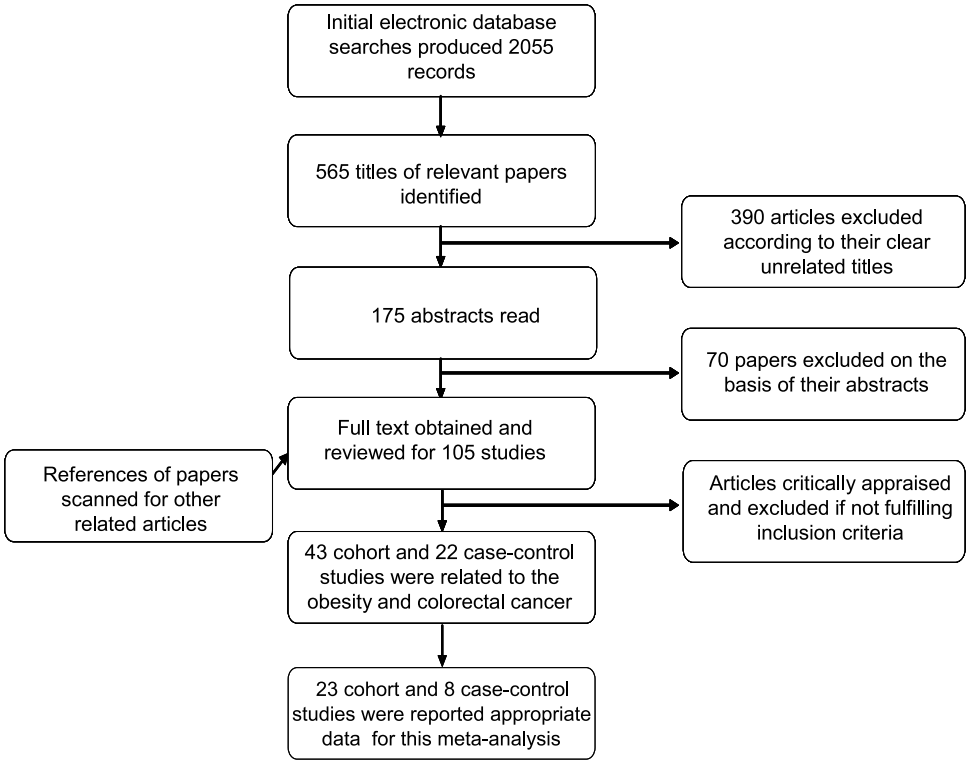

Figure 1. Flowchart of the literature search.

Table 1. Cohort studies reporting on the association between general obesity and risk of colorectal cancer

First author/ year (reference number)	Cohort			Outcome			BMI status (kg/m^2)			Level of adjustment
	Name (country)	No. (sex)	Source	Cancer subtype	No. events	Obesity definition (kg/m^2)	Per 2-unit increase	Groups		
							RR (95% CI)	BMI	RR (95% CI)	
Lukanova, 2006 (15)	NSHDC (Sweden)	33,424 (M)	NR	C	73	>30	NA	18.5-24.9	1.00	1,4,18
								25.0-29.9	1.57 (0.94-2.71)	
								≥30.0	1.43 (0.62-3.02)	
		35,362 (F)		C	76	>30	NA	18.5-24.9	1.00	
								25.0-29.9	1.28 (0.78-2.18)	
								≥30.0	2.25 (1.25-3.98)	
		M		R	58	>30	NA	18.5-24.9	1.00	
								25.0-29.9	0.80 (0.44-1.45)	
								≥30.0	1.96 (0.96-3.86)	
		F		R	31	>30	NA	18.5-24.9	1.00	
								25.0-29.9	1.31 (0.59-2.86)	
								≥30.0	1.30 (0.42-3.45)	
Larsson, 2006 (16)	COSM (Sweden)	45,906 (M)	CR,DC	CR	464	>30	1.08 (1.02-1.14)	<23.0	1.00	1,4,8,10,11,13
				C	284	>30		23.0-24.9	1.11 (0.77-1.61)	
								25.0-26.9	1.07 (0.73-1.56)	
								27.0-29.9	1.15 (0.78-1.70)	
								≥30.0	1.60 (1.03-2.48)	
				R	180	>30		<23.0	1.00	
								23.0-24.9	1.08 (0.65-1.80)	
								25.0-26.9	1.35 (0.83-2.19)	
								27.0-29.9	1.53 (0.93-2.51)	
								≥30.0	1.44 (0.79-2.61)	
MacInnis, 2006 (17)	MCCS (Australia)	17,049 (M)	CR,DC,MR	R	134	>30	1.04 (0.94-1.14)	<25.0	1.00	1,2,17
								25.0-29.9	1.70 (1.10-2.70)	
								≥30.0	1.30 (0.80-2.40)	
		24,479 (F)		R	95	>30	0.99 (0.91-1.08)	<25.0	1.00	
								25.0-29.9	0.70 (0.40-1.10)	
								≥30.0	1.10 (0.70-1.90)	
MacInnis, 2006 (18)	MCCS (Australia)	24,479 (F)	CR,DC,MR	C	212	>30	1.02 (0.96-1.08)	<25.0	1.00	1,8,13,17
								25.0-29.9	0.80 (0.60-1.20)	
								≥30.0	1.00 (0.70-1.40)	
Bowers, 2006 (19)	ATBCPS (Finland)	(28,983)	CR	C	227	>30	NA	<18.5	1.47 (0.36-5.98)	1,3,4
		M						18.5-25	1.00	
								25-30	1.07 (0.79-1.44)	
								>30	1.78 (1.25-2.55)	
				R	183	>30	NA	<18.5	0.96 (0.40-3.93)	
								18.5-25	1.00	
								25-30	1.18 (0.85-1.64)	
								>30	1.51 (0.99-2.29)	
Pischon, 2006 (20)	EPIC (Europe)	129,731 (M)	MR,CR, SR,P,PR	C	421	>30	1.10 (1.04-1.17)	18.5-24.9	1.00	1,2,4,5,11 12,13,19
								25-29.9	1.00 (0.80-1.26)	
								≥30	1.41 (1.06-1.88)	
		238,546 (F)		C	563	>30	1.04 (1.00-1.08)	18.5-24.9	1.00	
								25-29.9	1.16 (0.96-1.40)	
								≥30	1.07 (0.82-1.38)	
		M		R	295	NA	NA	<23.6	1.00	
								23.6-25.3	0.88 (0.60-1.30)	
								25.4-27.0	0.96 (0.66-1.40)	
								27.1-29.3	1.11 (0.77-1.62)	
								≥29.3	1.05 (0.72-1.55)	
		F		R	291	NA	NA	<21.7	1.00	
								21.7-23.5	0.78 (0.51-1.18)	
								23.6-25.7	1.14 (0.78-1.66)	
								25.8-28.8	0.95 (0.64-1.41)	
								≥28.9	1.06 (0.71-1.58)	

(*Continued on the following page*)

Table 1. Cohort studies reporting on the association between general obesity and risk of colorectal cancer (Cont'd)

First author/ year (reference number)	Cohort			Outcome			BMI status (kg/m^2)			Level of adjustment
	Name (country)	No. (sex)	Source	Cancer subtype	No. events	Obesity definition (kg/m^2)	Per 2-unit increase	Groups		
							RR (95% CI)	BMI	RR (95% CI)	
Ahmed, 2006 (21)	ARIC (USA)	14,109 (M+F)	SR,CR							1,2,4,5,8
		M		CR	107	NA	NA	<24.7	1.00	
								≥29.8	1.52 (0.90-2.70)	
		F		CR	87	NA	NA	<23.4	1.00	
								≥31.3	1.26 (0.60-2.60)	
Otani, 2005 (22)	JPHC (Japan)	49,158 (M)	NR	C	424	>30	NA	<25.0	1.00	1,2,4,5,12
								25-26.9	1.30 (1.02-1.70)	
								27-29.9	1.50 (1.08-2.10)	
								≥30.0	1.40 (0.70-2.80)	
		53,791 (F)		C	229	>30	NA	<25.0	1.00	
								25-26.9	1.30 (0.90-1.80)	
								27-29.9	0.90 (0.60-1.40)	
								≥30.0	0.50 (0.20-1.40)	
		M		R	202	>30	NA	<25.0	1.00	
								25-26.9	1.00 (0.70-1.50)	
								27-29.9	1.20 (0.70-1.90)	
								≥30.0	1.60 (0.60-3.90)	
		F		R	131	>30	NA	<25.0	1.00	
								25-26.9	1.20 (0.80-2.00)	
								27-29.9	1.00 (0.50-1.80)	
								≥30.0	1.30 (0.50-3.10)	
Rapp, 2005 (23)	VHM&PP (Austria)	67,447 (M)	CR,DC	C	260	>30	NA	18.5-24.9	1.00	1,4,14
								25.0-29.9	1.14 (0.86-1.50)	
								30.0-35.0	1.56 (1.06-2.30)	
								≥35.0	2.48 (1.15-5.39)	
		78,484 (F)		C	271	>30	NA	18.5-24.9		
								25.0-29.9	1.13 (0.86-1.47)	
								30.0-35.0	1.11 (0.76-1.62)	
								≥35.0	0.88 (0.43-1.81)	
		M		R	138	>30	NA	18.5-24.9	1.00	
								25.0-29.9	1.20 (0.82-1.75)	
								≥30.0	1.66 (1.01-2.73)	
		F		R	133	>30	NA	18.5-24.9	1.00	
								25.0-29.9	0.90 (0.62-1.31)	
								30.0-35.0	0.66 (0.36-1.23)	
								≥35.0	0.96 (0.38-2.39)	
Engeland, 2005 (24)	NHS (Norway)	963,709 (M)	CR,NR	C	13,805	>30	1.08 (1.08-1.10)	<18.5	0.73 (0.54-0.97)	1,16,20
								18.5-24.9	1.00	
								25.0-29.9	1.21 (1.17-1.26)	
								≥30.0	1.49 (1.39-1.60)	
		1,038,010 (F)		C	16,638	>30	NA	<18.5	0.95 (0.82-1.10)	
								18.5-24.9	1.00	
								25-29.9	1.03 (1.00-1.07)	
								≥30.0	1.07 (1.02-1.12)	
		M		R	9,182	>30	NA	<18.5	1.00 (0.74-1.34)	
								18.5-24.9	1.00	
								25-29.9	1.06 (1.02-1.11)	
								≥30.0	1.27 (1.16-1.38)	
		F		R	7,492	>30	NA	<18.5	1.25 (1.03-1.50)	
								18.5-24.9	1.00	
								25-29.9	0.98 (0.93-1.03)	
								≥30.0	1.04 (0.97-1.11)	
Kuriyama, 2005 (25)	Japan	12,485 (M)	CR,NR	C	88	>30	NA	18.5-24.9	1.00	1,4,5,12,16
								25.0-27.4	1.39 (0.82-2.37)	
								27.5-29.9	1.12 (0.40-3.08)	
								≥30.0	1.30 (0.32-5.37)	

(*Continued on the following page*)

Table 1. Cohort studies reporting on the association between general obesity and risk of colorectal cancer (Cont'd)

First author/ year (reference number)	Cohort			Outcome			BMI status (kg/m^2)			Level of adjustment
	Name (country)	No. (sex)	Source	Cancer subtype	No. events	Obesity definition (kg/m^2)	Per 2-unit increase	Groups		
							RR (95% CI)	BMI	RR (95% CI)	
		15,054 (F)		C	72	>30	NA	18.5-24.9	1.00	
								25.0-27.4	1.11 (0.69-1.80)	
								27.5-29.9	1.28 (0.68-2.43)	
								≥30.0	2.06 (1.03-4.13)	
		M		R	67	>30	NA	18.5-24.9	1.00	
								25.0-27.4	0.67 (0.30-1.49)	
								27.5-29.9	2.38 (1.07-5.30)	
								≥30.0	2.41 (0.74-7.85)	
		F		R	42	>30	NA	18.5-24.9	1.00	
								25.0-27.4	1.34 (0.65-2.80)	
								27.5-29.9	0.88 (0.27-2.90)	
								≥30.0	1.21 (0.29-5.14)	
Oh, 2005 (26)	Korea	781,283 (M)	CR,MR,DC	C	953	>30	NA	<18.5	1.00 (0.62-1.63)	1,4,5,10,11,14
								18.5-22.9	1.00	
								23.0-24.9	1.24 (1.07-1.43)	
								25.0-26.9	1.33 (1.13-1.57)	
								27.0-29.9	1.07 (0.83-1.38)	
								≥30.0	1.92 (1.15-3.22)	
		M		R	1,563	>30	NA	<18.5	0.64 (0.362-1.13)	
								18.5-22.9	1.00	
								23.0-24.9	1.06 (0.92-1.22)	
								25.0-26.9	1.29 (1.10-1.52)	
								27.0-29.9	1.15 (0.91-1.46)	
								≥30.0	1.08 (0.56-2.10)	
Lin, 2004 (27)	WHS (USA)	39,876 (F)	MR,SR,P	C	158	>30	NA	<23.0	1.00	1,2,4,5,8,10,11,16
								23.0-24.9	1.59 (0.99-2.54)	
								25.0-26.9	1.26 (0.74-2.16)	
								27.0-29.9	1.90 (1.17-3.10)	
								≥30.0	1.73 (1.05-2.85)	
				R	40	>30	NA	<23.0	1.00	
								23.0-24.9	0.66 (0.23-1.89)	
								25.0-26.9	1.38 (0.55-3.46)	
								27.0-29.9	1.03 (0.38-2.80)	
								≥30.0	1.55 (0.64-3.77)	
MacInnis, 2004 (28)	MCCS (Australia)	17,049 (M)	CR, MR	C	153	NA	1.11 (1.02-1.21)	<24.8	1.00	1,13,17
								24.8-26.9	1.30 (0.80-2.20)	
								27.0-29.2	1.40 (0.80-2.30)	
								>29.2	1.70 (1.10-2.80)	
Wei, 2004 (29)	NHS and HPFS (USA)	46,632 (M)	NR, MR	C	452	>30	NA	<23.0	1.00	1,4,5,8,10,11,12
								23-24.9	1.33 (0.97-1.83)	
								25-29.9	1.54 (1.15-2.07)	
								≥30.0	1.85 (1.26-2.72)	
		87,733 (F)		C	671	>30	NA	<23.0	1.00	
								23-24.9	1.10 (0.88-1.36)	
								25-29.9	1.11 (0.91-1.35)	
								≥30.0	1.28 (1.01-2.42)	
		M		R	132	>30	NA	<23.0	1.00	
								23-24.9	1.16 (0.70-1.94)	
								25-29.9	0.93 (0.57-1.53)	
								≥30.0	1.03 (0.49-2.14)	
		F		R	204	>30	NA	<23.0	1.00	
								23-24.9	1.37 (0.92-2.02)	
								25-29.9	1.40 (0.98-2.01)	
								≥30.0	1.56 (1.01-2.42)	
Moore, 2004 (30)	Framingham (USA)	1,684 (M) 30-45 y	NR,MR,DC	C	71	>30	NA	<25.0	1.00	1,2,4,5,11,20
								25.0-29.9	1.10 (0.67-1.90)	
								≥30.0	2.00 (0.98-4.20)	
		2,080 (F) 30-45 y		C	86	>30	NA	<25.0	1.00	
								25.0-29.9	1.50 (0.92-2.40)	
								≥30.0	1.30 (0.62-2.70)	

(*Continued on the following page*)

Table 1. Cohort studies reporting on the association between general obesity and risk of colorectal cancer (Cont'd)

First author/ year (reference number)	Cohort			Outcome			BMI status (kg/m^2)			Level of adjustment
	Name (country)	No. (sex)	Source	Cancer subtype	No. events	Obesity definition (kg/m^2)	Per 2-unit increase	Groups		
							RR (95% CI)	BMI	RR (95% CI)	
		1,661 (M) 55-79 y		C	72	>30	NA	<25.0	1.00	
								25.0-29.9	2.10 (1.10-4.00)	
								≥30.0	3.70 (1.70-8.10)	
		2,141 (F) 55-79 y		C	80	>30	NA	<25.0	1.00	
								25.0-29.9	1.70 (1.00-2.80)	
								≥30.0	1.90 (0.98-3.50)	
Terry, 2002 (31)	NBSS (Canada)	89,835 (F)	NR,CR	C	363	>30	NA	<25.0	1.00	1,4,8,11,13,15
								25-<30	1.13 (0.89-1.43)	
								≥30.0	0.95 (0.67-1.34)	
				R	164	>30	NA	<25.0	1.00	
								25-<30	0.83 (0.57-1.21)	
								≥30.0	1.35 (0.87-2.07)	
Ford, 1999 (32)	NHANES (USA)	13,420 (M+F)	DC, MR, PR, P	C	222	>30	1.12 (1.06-1.21)			1,2,4,5,7,9,11
		M		C	104	>30	NA	<22.0	1.00	
								22.0-<24.0	1.58 (0.57-4.36)	
								24.0-<26.0	1.59 (0.59-4.25)	
								26.0-<28.0	2.41 (<1.00-5.82)	
								28.0-<30	3.72 (1.41-8.83)	
								≥30	2.95 (0.99-8.74)	
		F		C	118	>30	NA	<22.0	1.00	
								22.0-<24.0	2.03 (0.87-5.17)	
								24.0-<26.0	2.17 (0.78-6.04)	
								26.0-<28.0	2.49 (0.83-7.47)	
								28.0-<30	3.64 (1.27-10.5)	
								≥30	2.74 (1.04-7.25)	
Chyou, 1996 (33)	USA	7945 (M)	MR,CR	C	330	NA	1.12 (1.06-1.21)	<21.7	1.00	1
								21.7-23.8	1.16 (0.84-1.61)	
								23.8-25.8	1.36 (0.99-1.86)	
								≥25.8	1.38 (1.01-1.90)	
				R	123	NA	NA	<21.7	1.00	
								21.7-23.8	0.68 (0.42-1.10)	
								23.8-25.8	0.73 (0.45-1.17)	
								≥25.8	0.63 (0.38-1.04)	
Bostick, 1994 (34)	IWHS (USA)	35,215 (F)	NR,CR	Colon	212	NA	NA	<22.9	1.00	1,12,15,20
								22.9-25.0	0.97 (0.59-1.59)	
								25.0-27.5	1.69 (1.10-2.61)	
								27.5-30.6	1.51 (0.97-2.37)	
								>30.6	1.41 (0.90-2.23)	
Lee, 1992 (35)	USA	17,595 (M)	SR,DC,MR	C	302	NA	1.17 (1.08-1.28)	<22.5	1.00	1,10,11
								22.5-<23.5	1.30 (0.84-1.94)	
								23.5-<24.5	1.10 (0.75-1.61)	
								24.5-<26.0	1.34 (0.93-1.94)	
								≥26.0	1.52 (1.06-2.17)	
Kreger, 1991 (36)	Framingham (USA)	5,209 (M+F) M	MR,PR	C	56	NA	1.15 (1.00-1.32)	NA	NA	1
		F		C	66	NA	1.06 (0.96-1.14)			
		M		R	19	NA	0.83 (0.64-1.10)			
		F		R	20	NA	0.98 (0.80-1.21)			
Klatsky, 1988 (37)	USA	106,203 (M+F)	MR	C	203	NA	2.20 (1.49-3.21)	NA	NA	1,4,5,7,9,13
				R	66	NA	1.00 (0.44-2.19)	NA	NA	

NOTE: Level of adjustment—1, age; 2, sex; 3, diabetes; 4, smoking; 5, alcohol; 6, hypertension; 7, hypercholesteremia; 8, medication; 9, race; 10, family history; 11, physical activity; 12, diet; 13, education; 14, socioeconomic status; 15, pregnancy for women; 16, menstruation; 17, place of birth; 18, calendar year; 19, study centre; 20, height; 21, marital status; 22, birth cohort.

Abbreviations: Subtype—C, colon; R, rectum; CR, colorectal. Source of cancer diagnosis—CRG, cancer registry; MR, medical records; DC, death certificate; SR, self-report; P, proxy provided information; NR, national registry; PR, pathology records. Sex—M, male; F, female. Cohort name—NSHDC, the Northern Sweden Health and Disease Cohort; NHANES, the National Health and Nutrition Examination Survey; NBSS, the National Breast Screening Study; JPHC, the Japan Public Health Center–based Prospective study; WHS, the Women's Health Study; VHM&PP, the Vorarlberg Health Monitoring and Promotion Program; MCCS, the Melbourne Collaborative Cohort Study; ATBCPS, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; EPIC, the European Prospective Investigation into Cancer and Nutrition; NHS, the Norwegian Health survey; NHS, the Nurses' Health Study; HPFS, the Health Professionals Follow-up Study; COSM, the cohort of Swedish men. NA, not available.

Table 2. Case-control studies reporting on the association between obesity and risk of colorectal cancer

First author/year (reference number)	Country	Cancer cases			Controls			BMI status (kg/m^2)			Level of adjustment
		Source	Cancer sub type	No.	Source	No.	Obesity definition (kg/m^2)	Per 2-unit increase	Groups		
								RR	Class	RR (95% CI)	
Elwing, 2006 (41)	USA	Newly diagnose patients	CR (F)	159	Hospital	610	>30	NA	≤30.0	1.00	1,3,6,7,8,9
									>30.0	1.82 (1.26-2.62)	
Guilera, 2005 (42)	USA	Hospital	CR (M+F)	226	Hospital	494	>30	NA	<25.0	100	1,2
									25.0-30.0	1.00 (0.70-1.50)	
									>30.0	1.70 (1.10-2.50)	
Pan, 2004 (43)	Canada	Newly diagnosed patients	C (M)	959	Community	5,039	>30	NA	<25.0	1.00	1,4,5,10,12, 14,15,16
			C (F)	768			>30	NA	25.0-30.0	1.54 (1.27-1.86)	
									≥30.0	2.16 (1.68-2.78)	
									<25.0	1.00	
									25.0-30.0	1.22 (0.98-1.52)	
									≥30.0	1.77 (1.35-2.32)	
			R (M)	858			>30	NA	<25.0	1.00	
									25.0-30.0	1.41 (1.15-1.71)	
									≥30.0	1.75 (1.35-2.28)	
			R (F)	589			>30	NA	<25.0	1.00	
									25.0-30.0	1.28 (1.02-1.61)	
									≥30.0	1.50 (1.11-2.02)	
Slattery, 2003 (44)	USA	CRG	C (M)	1,095	Community	1,286	>30	NA	<23	1.00	1
									23-24	0.96 (0.64-1.44)	
									25-27	1.13 (0.79-1.63)	
									28-30	1.54 (1.06-2.23)	
									>30	1.88 (1.29-2.74)	
			C (F)	877		1,100	>30	NA	<23	1.00	
									23-24	1.22 (0.90-1.65)	
									25-27	1.27 (0.96-1.67)	
									28-30	1.30 (0.96-1.76)	
									>30	1.45 (1.09-1.92)	
Slattery, 2003 (45)	USA	CRG	R (M)	556	Community	626	>30	NA	<23.0	1.00	
									23.0-25.0	0.80 (0.50-1.30)	
									25.1-28.0	0.90 (0.60-1.30)	
									28.1-30.0	0.70 (0.50-1.10)	
									>30.0	1.00 (0.70-1.60)	1
			R (F)	390		525	>30	NA	<23.0	1.00	
									23.0-25.0	0.90 (0.60-1.30)	
									25.1-28.0	0.80 (0.50-1.40)	
									28.1-30.0	0.80 (0.50-1.40)	
									>30.0	1.10 (0.80-1.60)	
Russo, 1998 (46)	Italy	Patients	CR (M)	1,124	Hospital	2,067	NA	NA	<22.7	1.00	1,11,12, 13,19
									22.7-24.6	1.32 (1.00-1.76)	
									24.6-26.5	1.19 (0.89-1.57)	
									26.5-28.7	1.45 (1.09-1.92)	
									>28.7	1.68 (1.25-2.27)	
			CR (F)	819		2,069	NA	NA	<22.7	1.00	
									22.7-24.6	0.91 (0.70-1.18)	
									24.6-26.5	0.84 (0.64-1.12)	
									26.5-28.7	1.16 (0.86-1.55)	
									>28.7	0.87 (0.65-1.17)	
Slattery, 1997 (47)	USA	Newly diagnosed patients	C (M)	1,099	Community	1,290	>30	NA	<23.8	1.00	1,8,10, 11,12
									23.8-25.5	1.23 (0.93-1.63)	
									25.5-27.3	1.32 (1.00-1.74)	
									27.3-30.0	1.78 (1.36-2.33)	
									>30.0	1.94 (1.49-2.54)	
			C (F)	894		1,120	>30	NA	<23.8	1.00	
									23.8-25.5	1.26 (0.94-1.68)	

(*Continued on the following page*)

Table 2. Case-control studies reporting on the association between obesity and risk of colorectal cancer (Cont'd)

First author/year (reference number)	Country	Cancer cases			Controls			BMI status (kg/m^2)			Level of adjustment
		Source	Cancer sub type	No.	Source	No.	Obesity definition (kg/m2)	Per 2-unit increase	Groups		
								RR	Class	RR (95% CI)	
Kune, 1990 (48)	Australia	Newly diagnosed patients	CR (M)	388	Community	398	≥31	NA	25.5-27.3 27.3-30.0 >30.0 <19.0	1.19 (0.89-1.60) 1.38 (1.03-1.85) 1.45 (1.08-1.94) 0.47 (0.20-1.20)	1,12
			CR (F)	327		329	≥31	NA	20.0-25.0 26.0-30.0 ≥31.0 <18.0 19.0-24.0 25.0-30.0 ≥31.0	1.00 1.38 (1.00-2.00) 1.70 (0.80-3.60) 0.39 (0.20-0.90) 1.00 0.70 (0.50-1.00) 0.71 (0.40-1.40)	
			C (M)	202		398	≥31	1.06 (0.96-1.17)	<19.0	0.09 (0.00-0.70)	
			C (F)	190		329	≥31	0.96 (0.90-1.04)	20.0-25.0 26.0-30.0 ≥31.0 <18.0	1.00 1.18 (0.80-1.80) 1.17 (0.50-2.90) 0.41 (0.20-1.10)	
			R (M)	186		398	≥31	NA	19.0-24.0 25.0-30.0 ≥31.0 <19.0	1.00 0.74 (0.50-1.20) 0.73 (0.30-1.60) 0.93 (0.30-2.50)	
			R (F)	137		329	≥31	NA	20.0-25.0 26.0-30.0 ≥31.0 <18.0 19.0-24.0 25.0-30.0 ≥31.0	1.00 1.54 (1.00-2.40) 2.09 (0.90-5.00) 0.32 (0.10-1.00) 1.00 0.60 (0.40-1.00) 0.61 (0.20-1.50)	

(41-48), with information on a total of 70,906 individuals with colorectal cancer (~66% colon; 49% female) were eligible for inclusion in these analyses. The summary characteristics of included studies are shown online (Tables 1, 2–3). Most of the study populations were from Western populations: North America (n = 19), Europe (n = 7), and Australia (n = 2). The remaining three studies were from Asia.

General Obesity and Risk of Colorectal Cancer. A total of 26 studies, with information on 69,619 events, reported on the association between general obesity and colorectal cancer, with some studies reporting both sex-specific and site-specific associations. Hence, the overall number of reported associations exceeded the number of contributing studies. The pooled estimate indicated that individuals with a BMI ≥30 kg/m^2 had a 40% greater risk of colorectal cancer compared with individuals with a BMI <25 kg/m^2 (RR, 1.40; 95% CI, 1.31-1.51). There was evidence of significant heterogeneity across studies (P < 0.001) that was not explained by differences in study design; the summary estimate for the association between obesity and colorectal cancer from case-control studies was nonsignificantly higher than that obtained from cohort studies: RR 1.50 (95% CI, 1.31-1.72) versus RR 1.35 (95% CI, 1.24-1.46; $P_{heterogeneity}$ = 0.19; Fig. 2).

Subsequent analyses were restricted to cohort studies for which there was evidence of heterogeneity across cohort studies (P < 0.001). Furthermore, as shown in the funnel plot (Fig. 3), there was evidence of publication bias (P = 0.003) and the trim-and-fill analysis indicated that the true estimate of effect for the association between obesity and colorectal cancer may be closer to 20%: RR 1.19 (95% CI, 1.11-1.29).

Some of the observed heterogeneity in study estimates was explained by differences in the magnitude of the association of obesity with site-specific cancers. The pooled estimate of the association between obesity and colon cancer was significantly higher than that of the association between obesity and cancer of the rectum: RR 1.44 (95% CI, 1.28-1.63) versus RR 1.21 (95% CI, 1.10-1.34; $P_{heterogeneity}$ = 0.04; Fig. 4). However, after correcting for the presence of publication bias, this difference was reduced and became nonsignificant: the RR was 1.24 (95% CI, 1.11-1.39) for colon cancer and 1.13 (95% CI, 1.02-1.25) for rectal cancer ($P_{heterogeneity}$ = 0.23).

Sex differences in the strength of the association between obesity and colorectal cancer were also a source of heterogeneity. The risk of colorectal cancer was RR 1.46 (95% CI, 1.36-1.56) in obese men compared with RR 1.15 (95% CI, 1.06-1.24) for obese women ($P_{heterogeneity}$ < 0.001; Fig. 4). The sex difference was apparent for both cancers of the colon (P = 0.003) and rectum (P < 0.001). Restricting the analysis to only those 10 studies that reported separate estimates for men and women gave similar findings: RR 1.44 (95% CI, 1.32-1.58) in men

Table 3. Cohort studies reporting on the association between central obesity and risk of colorectal cancer

First author/ year (reference number)	Cohort		Outcome			Waist circumference (cm)			Level of adjustment
	Country	No. (sex)	Source	Cancer subtype	Events	Per 2-unit increase	Groups		
						RR (95% CI)	Class	RR (95% CI)	
Pischon, 2006 (20)	EPIC (Europe)	129,731 (M)	MR,CR, SR,P,PR	C	421	1.05 (1.02-1.07)	<86	1.00	1,2,4,5,11,12, 13,19,20
							86.0-91.8	0.73 (0.50-1.04)	
							91.9-96.5	0.97 (0.69-1.36)	
							96.6-102.9	1.10 (0.79-1.53)	
							≥103	1.39 (1.01-1.93)	
		238,546 (F)		C	563	1.02 (0.99-1.04)	<70.2	1.00	
							70.2-75.8	1.10 (0.80-1.52)	
							75.9-80.9	1.23 (0.90-1.68)	
							81.0-88.9	1.25 (0.91-1.70)	
							≥89	1.48 (1.08-2.03)	
		M		R	295	NA	<86	1.00	
							86.0-91.8	1.06 (0.70-1.61)	
							91.9-96.5	1.15 (0.76-1.73)	
							96.6-102.9	1.18 (0.78-1.77)	
							≥103	1.27 (0.84-1.91)	
		F		R	291	NA	<70.2	1.00	
							70.2-75.8	1.10 (0.73-1.66)	
							75.9-80.9	0.94 (0.62-1.42)	
							81.0-88.9	1.22 (0.82-1.83)	
							≥89	1.23 (0.81-1.86)	
Larsson, 2006 (16)	COSM (Sweden)	45,906 (M)	CR, DC	CR	496	NA	<88	1.00	1,4,8,10,11,13,20
							88.0-92.0	1.06 (0.73-1.55)	
							93.0-97.0	1.32 (0.92-1.88)	
							98.0-103	1.37 (0.96-1.96)	
							≥103	1.29 (0.90-1.85)	
Ahmed, 2006 (21)	ARIC (USA)	14,109 (M+F)	SR,CR	CR	194	NA	Low	1.00	1,2,4,5,8
							High	1.40 (1.00-1.90)	
MacInnis, 2006 (18)	MCCS (Australia)	24,479 (F)	CR,DC,MR	C	212	1.03 (1.00-1.05)	<80.0	1.00	1,8,13,17
							80.0-87.0	1.40 (1.00-1.90)	
							≥88.0	1.40 (1.00-1.90)	
MacInnis, 2006 (17)	MCCS (Australia)	41,528 (M+F)	CR,DC,MR	R	229	1.01 (0.95-1.08)	<94/<80	1.00	1,2,17
							94-102/80-87.9	1.20 (0.90-1.60)	
							≥102/≥88	1.40 (1.00-1.90)	
		M		R		1.04 (0.94-1.14)	<94	1.00	
							94-102	1.30 (0.90-1.90)	
							≥102	1.40 (0.90-2.20)	
		F		R		0.99 (0.91-1.08)	<80	1.00	
							80-87.9	1.00 (0.60-1.70)	
							≥88	1.40 (0.80-2.20)	
Moore, 2004 (30)	Framingham (USA)	3,764 (M+F)	NR,MR,DC	C	157	NA	Small	1.00	1,2,4,5,11,13,20
							Medium	1.10 (0.66-2.00)	
							Large	1.60 (0.91-2.90)	
							X-large	2.00 (1.10-3.70)	
		M 30-45 y		C	71	NA	<83.8	1.00	
							83.8-<94.0	1.10 (0.49-2.30)	
							94.0-<101.6	1.60 (0.73-3.60)	
							≥101.6	2.40 (0.99-5.70)	
		F 30-45 y		C	72	NA	<81.3	1.00	
							81.3-<91.4	1.20 (0.53-2.50)	
							91.4-<99.1	1.60 (0.71-3.70)	
							≥99.1	1.80 (0.78-4.30)	
		M 55-79 y		C	71	NA	<83.8	1.00	
							83.8-<94.0	1.30 (0.51-3.10)	
							94.0-<101.6	2.20 (0.87-5.40)	
							≥101.6	3.30 (1.30-8.80)	
		F 55-79 y		C	72	NA	<81.3	1.00	
							81.3-<91.4	1.50 (0.58-3.90)	

(*Continued on the following page*)

Table 3. Cohort studies reporting on the association between central obesity and risk of colorectal cancer (Cont'd)

First author/ year (reference number)	Cohort		Outcome			Waist circumference (cm)			Level of adjustment
	Country	No. (sex)	Source	Cancer subtype	Events	Per 2-unit increase	Groups		
						RR (95% CI)	Class	RR (95% CI)	
							91.4-<99.1	2.00 (0.75-5.30)	
							≥99.1	2.30 (0.86-6.30)	
MacInnis, 2004 (28)	MCCS (Australia)	17,049 (M)	CR, MR	Colon	153	1.06 (1.03-1.10)	<87.0	1.00	1,13,17
							87.0-92.9	0.80 (0.40-1.40)	
							93.0-99.3	1.70 (1.00-2.80)	
							>99.3	2.10 (1.30-3.50)	
Schoen, 1999 (38)	CHS (USA)	5,849 (M+F)	MR,SR	Colorectal	102	NA	Quartile1	1.00	1,2,11
							Quartile2	2.20 (1.20-4.00)	
							Quartile3	1.40 (0.70-2.70)	
							Quartile4	2.20 (1.20-4.10)	
Martinez, 1997 (39)	NHS (USA)	89,448 (F)	MR,NR,P, PR,PS	Colon	393	NA	<27.5 in.	1.00	1,4,5,8,10,11,12
							>34.0 in.	1.48 (0.89-2.46)	
Giovannucchi, 1995 (40)	HPFS (USA)	47,723 (M)	SR,P,MR, PR	Colon	203	NA	<35 in.	1.00	1,4,5,8,10,11,12
							35.0-36.9	0.56 (0.27-1.14)	
							37.0-38.9	1.09 (0.59-2.01)	
							39.0-42.9	1.61 (0.91-2.85)	
							≥43 in.	2.56 (1.33-4.96)	

compared with 1.09 (95% CI, 1.01-1.17) in women ($P_{difference} < 0.001$). There was, again, evidence of publication bias in studies that published sex-specific results: After correction for publication bias, the sex difference was RR 1.41 (95% CI, 1.30-1.54) versus RR 1.08 (95% CI, 0.98-1.18; $P_{heterogeneity} < 0.001$).

The ability to adjust for potential confounders, such as high-fat diets, alcohol consumption, diets low in fiber and low levels of physical activity, differed between studies, and hence may have contributed to between-study variation. Comparison of the summary estimate from the 32 reports that had adjusted for at least one of the above variables with that from the 19 reports that did not adjust for any of these variables indicated that adjustment for diet and physical activity did not attenuate the association: RR 1.30 (95% CI, 1.16-1.45) versus 1.38 (95% CI, 1.25-1.53; $P_{heterogeneity} = 0.44$; Fig. 4). Restricting the analysis to those three studies that reported both unadjusted and adjusted estimates yielded similar results ($P = 0.98$). After correcting for publication bias, the difference between the unadjusted and adjusted remained unchanged: RR 1.18 (95% CI, 1.06-1.31) versus RR 1.25 (95% CI, 1.12-1.41), respectively ($P_{heterogeneity} = 0.47$).

Dose-Response Relationship between Overall Obesity and Risk of Colorectal Cancer. A total of nine studies reported on the dose-response association between BMI and colorectal cancer risk using BMI categories representing normal weight, overweight, and obesity. Pooling the estimates within these three categories showed evidence of a dose-response relationship between excess weight and the risk of colorectal cancer in both men and women, with some suggestion that the association was stronger for cancer of the colon compared with the rectum, particularly among men (Table 4). However, after correcting for publication bias, the dose-response relationships, particularly for colon cancer, were weakened such that there was no clear difference in the strength of the association between obesity and cancers of the colon and rectum (Table 4). Overall, 11 studies reported an estimate of the RR for colorectal cancer per unit increase in BMI. Pooling these data indicated that for every 2 kg/m^2 increment in BMI (equivalent to ~5 kg extra weight), the risk of colorectal cancer increased by 7% (95% CI, 4-10%). Correction for publication bias reduced this association by 1% (RR, 1.06; 95%CI, 1.03-1.09).

Central Obesity and Risk of Colorectal Cancer. Overall, 8 of the 23 cohort studies reported on the association between waist circumference and subsequent risk of colorectal cancer. Although there was a lack of uniformity across the studies in how central obesity was defined, with studies using quartiles, quintiles or highest versus lowest category of waist circumference (e.g., ≥102 versus <94 cm; or ≥88 versus <80 cm), the estimates of effect were relatively consistent across the studies ($P_{heterogeneity} = 0.80$; Fig. 5). The pooled estimate indicated that individuals in the highest category of waist circumference had ~50% greater risk compared with individuals in the lowest category (RR, 50%; 95% CI, 35-67%; Fig. 5). There was some evidence of publication bias ($P = 0.001$) but the results from the trim-and-fill analysis did not materially reduce the summary estimate of effect (RR, 1.45; 95% CI, 1.31-1.61). Two studies additionally reported on the continuous relationship between waist circumference and colorectal cancer; for

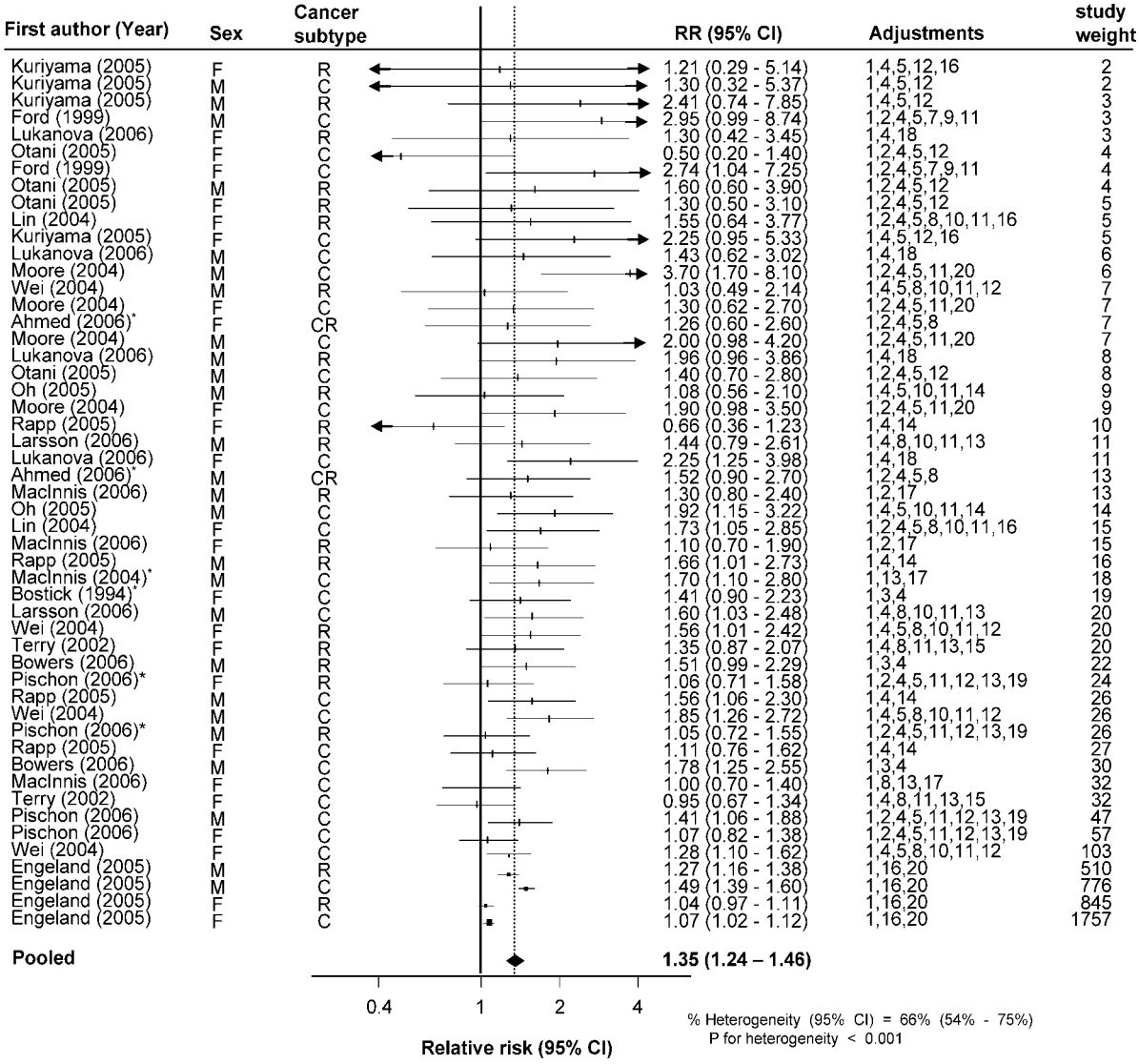

Figure 2. RRs and 95% CIs for colorectal cancer comparing obese (BMI $\geq$30 kg/m^2) with nonobese individuals (BMI <25 kg/m^2). *Black square,* point estimate (with area proportional to statistical "information"); *horizontal line,* 95% CI for observed effect in each study. *Diamond,* pooled estimate and 95% CI for meta-analysis. C, colon; R, rectum; CR, colorectal. *, these studies defined obesity as BMI >28 kg/m^2.

every 2-cm increment in waist circumference, the risk of colorectal cancer increased by 4% (95% CI, 2-5%). Correction for publication bias did not have an effect on this association.

Discussion

The findings from this meta-analysis, which includes information on 70,000 cases of colorectal cancer, indicate that obesity has a direct, and independent, relationship with colorectal cancer, although the magnitude of the association is smaller than previously estimated. Based on these data, individuals with a BMI $\geq$30 kg/m^2 have an ~20% greater risk of developing colorectal cancer compared with those considered to be of normal weight (BMI <25 kg/m^2). However, the association between BMI, a measure of general obesity, and risk of colorectal cancer seems to be continuous down to low levels of BMI. For every 2 kg/m^2 increase in BMI, the risk of developing colorectal cancer increased by 7%. Similarly, a 2-cm increase in waist circumference, a measure of central obesity, was associated with a 4% greater risk of colorectal cancer. These estimates are smaller, but compatible, with those reported by Larsson and colleagues in a previous review (11).

In agreement with some previous reports (6, 15, 17-25, 30), there was an indication that the carcinogenic effects of excess weight differed according to cancer site, being greater for cancer of the colon compared with that of the rectum. The data also indicated a sex difference in the strength of the association, such that the risk of

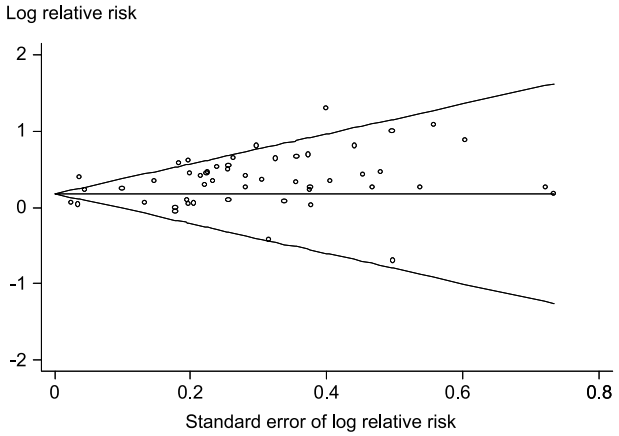

Figure 3. Funnel plot with 95% pseudo–confidence limits for the data from Fig. 2.

developing colorectal cancer is 30% higher in obese men compared with obese women.

The mechanisms that might underlie the association between excess weight and cancers of the colon and rectum remain unclear. It has been speculated that obesity serves as a surrogate marker of the cumulative effect of a chronic imbalance in dietary intake and physical activity over the life course. Experimental studies (49-52) have shown that severe caloric restriction has a protective effect against the development of several site-specific tumors, including colon cancer. There is also good evidence that physical activity is protective against colon/colorectal cancer (5, 53). A recent review (53) of the epidemiologic evidence (n = 46) reported that the average reduction in risk of colon cancer across studies was 40% to 50% among the most physically active group compared with the least active, which was independent of diet, BMI, and other potential confounders.

Dietary components may confound the association between obesity and colorectal cancer (54). A recent meta-analysis (55) of 15 cohort studies (~8,000 events) suggested that the highest versus the lowest intake categories of red and processed meat were significantly associated with 28% and 21% increased risk of colorectal cancer, respectively. Likewise, a large prospective study (56) reported that high intake of red and processed meat (>160 g/d compared with <20 g/d) increased the risk of colorectal cancer by 35% with evidence of a dose-response relationship (P_{trend} = 0.03).

In the current analyses, we attempted to disentangle the effects of diet and physical activity from obesity, by comparing studies that had adjusted for some measure of diet and physical activity with unadjusted studies. The relationship between obesity and subsequent risk of colorectal cancer, however, was similar irrespective of the level of adjustment, supporting a direct effect of obesity on risk. Recently, there has been speculation as to a possible etiologic role of insulin resistance or, hyperinsulinemia, in colorectal cancer (57, 58), a hypothesis that has received some support from studies demonstrating a positive association between glucose levels and diabetes with the malignancy (7). Further, diabetes has been reported to elevate the risk of other site-specific cancers [e.g., pancreas (59), breast (60), and bladder (61)

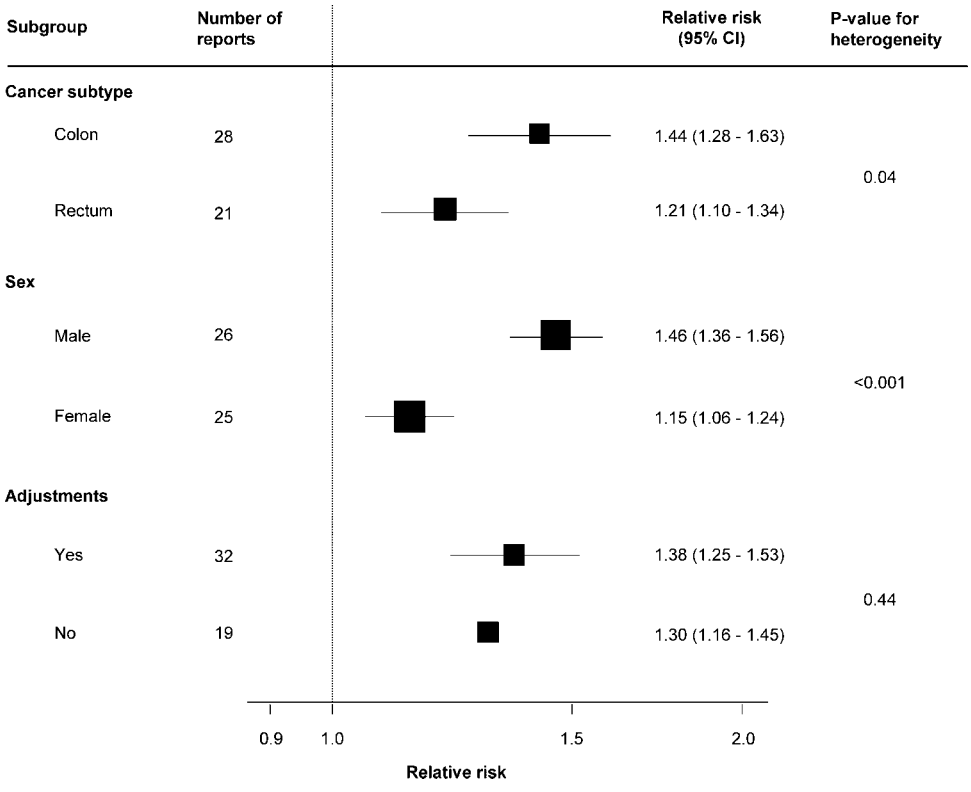

Figure 4. Subgroup analyses of general obesity and colorectal cancer for the data from Fig. 2. Conventions as in Fig. 2.

Table 4. Dose-response association between general obesity and colorectal cancer before and after correction for publication bias (reference group is BMI <25 kg/m^2; normal weight)

Cancer type/sex	No. reports	No. events	BMI (kg/m^2)			
			Uncorrected for publication bias		Corrected for publication bias	
			25-29.9 overweight	≥30 Obese	25-29.9 Overweight	≥30 Obese
Colon						
Male	9	15,745	1.25 (1.14-1.37)	1.51 (1.42-1.61)	1.23 (1.11-1.36)	1.53 (1.33-1.75)
Female	9	18,674	1.09 (0.99-1.20)	1.16 (1.01-1.34)	1.05 (0.95-1.16)	1.09 (0.93-1.28)
All	18	34,419	1.18 (1.09-1.28)	1.38 (1.20-1.59)	1.11 (1.02-1.19)	1.21 (1.06-1.38)
Rectum						
Male	6	9,846	1.08 (0.97-1.20)	1.29 (1.19-1.40)	1.08 (0.97-1.20)	1.27 (1.17-1.37)
Female	6	8,303	1.02 (0.88-1.17)	1.08 (0.92-1.26)	0.97 (0.83-1.14)	1.02 (0.85-1.22)
All	12	18,149	1.04 (0.97-1.12)	1.21 (1.05-1.39)	1.03 (0.95-1.12)	1.12 (0.98-1.28)
Colorectal						
Male	15	25,591	1.19 (1.09-1.30)	1.47 (1.33-1.61)	1.16 (1.07-1.27)	1.40 (1.33-1.47)
Female	15	26,977	1.05 (0.99-1.11)	1.11 (1.03-1.20)	1.03 (0.96-1.10)	1.07 (0.97-1.18)
All	30	52,568	1.13 (1.06-1.19)	1.31 (1.19-1.45)	1.09 (1.02-1.15)	1.19 (1.08-1.30)

by ~50%]. Given that the data did not permit exploration of the effect of diabetes on colorectal cancer risk, we are unable to exclude the possibility that the association between obesity and colorectal cancer is not explained by diabetic status.

The observed sex difference in the strength of the association between obesity with cancers of the colon and rectum may be related, in part, to differences in hormonal levels (in particular, estrogen) in women. Some, but not all, studies (31, 44, 62) have reported that the positive association between obesity and the risk of colorectal cancer is apparent in premenopausal but not in postmenopausal women. Slattery and colleagues (44) reported a positive association between high BMI and risk of colon cancer for premenopausal and women who used hormone replacement therapy, but no association among postmenopausal women. In contrast, the European Prospective Investigation into Cancer and Nutrition study (20) reported the largely opposing finding that, in postmenopausal women, waist circumference is weakly associated with the risk of colon cancer only among non–hormone replacement therapy users.

An inherent limitation of meta-analysis, particularly of observational studies, is the presence of publication bias

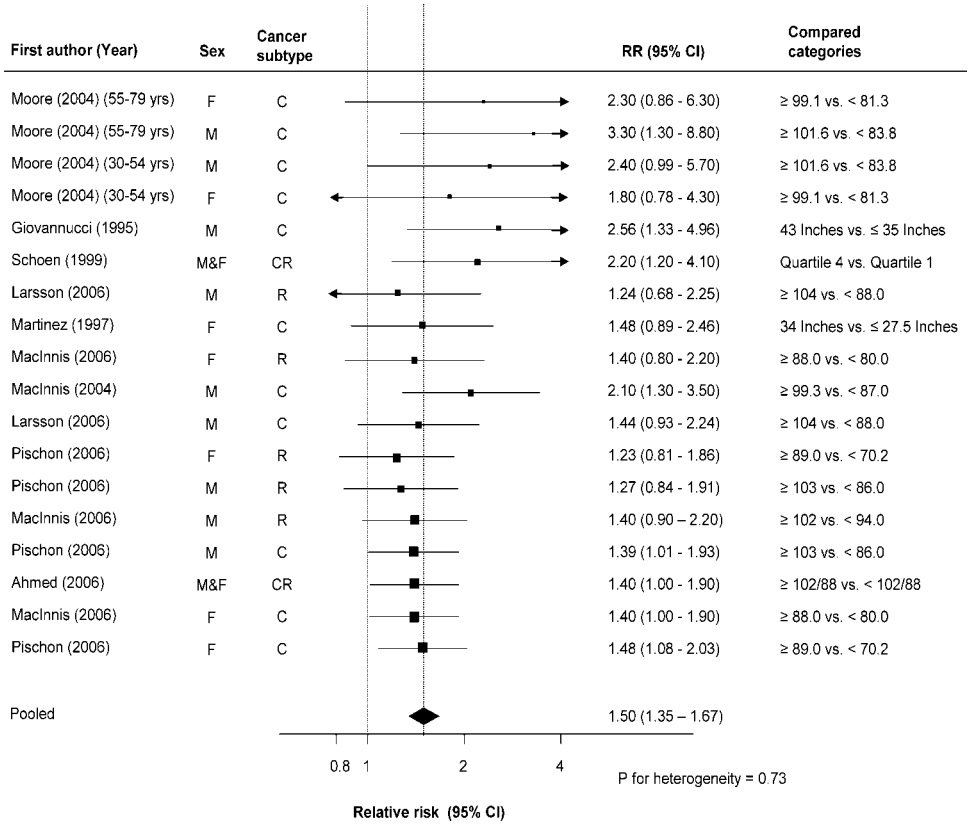

Figure 5. RR and 95% CI for colorectal cancer comparing highest versus lowest category of waist circumference. Conventions as in Fig. 2.

that might artificially inflate the magnitude of any reported association. Our findings suggest that previous reports of around 50% greater risk of colorectal cancer associated with obesity may have substantially overestimated the true strength of the underlying relationship. This finding is in contrast to previous reviews that reported no evidence of publication bias (10, 11), or in the case of one review, only found evidence of it in the association between colon cancer and BMI in women (11). Differences in the study inclusion criteria and methods of analysis between previous reviews and the current meta-analysis may account in part for the discrepant findings. After correcting for the presence of publication bias in the current analyses, the magnitude of the association between obesity and colorectal cancer was approximately halved, from 40% to 20%. Moreover, because we were unable to adjust for potential confounders (e.g., physical activity, alcohol, diet) at the level of the individual, even this reduced estimate of the size of the association might be an overestimate. Finally, as the individual studies used different methods to verify colorectal cancers, the lack of standardization could have had some unpredictable effect on the results. This, as well as the considerable variation in the sets of variables used for adjustment, is reflected in the high degree of heterogeneity between studies of BMI and colorectal cancer, which adds a note of caution to the interpretation of the pooled estimate of association found here in any specific situation.

The global prevalence of obesity is currently estimated to be 300 million, a figure that is expected to increase to 700 million by 2015 (63, 64). Assuming that obesity increases the risk of colorectal cancer by 20%, then each year ~10,000 cases of colorectal cancer worldwide are due to severe excess weight, a figure that is likely to increase to >25,000 by 2015. As these estimates do not take into account the vast number of individuals who are overweight, then these figures are likely to substantially underestimate the true global burden of colorectal cancer that is attributable to excess weight.

Acknowledgments

We thank Dr. Federica Barzi for comments on earlier versions of the manuscript.

References

1. Stewart BW, Kleihues P, editors. World Cancer Report. Lyon: IARC Press; 2003.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
3. Terry P, Giovannucci E, Michels KB, et al. Fruit, vegetables, dietary fiber, and risk of colorectal cancer. J Natl Cancer Inst 2002; 93:525–33.
4. Gonzalez CA. Nutrition and cancer: the current epidemiological evidence. Br J Nutr 2006;96:42–5.
5. Samad AK, Taylor RS, Marshall T, Chapman MA. A meta-analysis of the association of physical activity with reduced risk of colorectal cancer. Colorectal Dis 2005;7:204–13.
6. Bianchini F, Kaaks R, Vainio H. Overweight, obesity, and cancer risk. Lancet Oncol 2002;3:565–74.
7. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst 2005;97: 1679–87.
8. Potter JD, Slattery ML, Bostick RM, Gapstur SM. Colon cancer: a review of the epidemiology. Epidemiol Rev 1993;15:499–545.
9. Bergstrom A, Pisani P, Tenet V, Wolk A, Adami HO. Overweight as an avoidable cause of cancer in Europe. Int J Cancer 2001;91:421–30.
10. Dai Z, Xu YC, Niu L. Obesity and colorectal cancer risk: a meta-analysis of cohort studies. World J Gastroenterol 2007;13: 4199–206.
11. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. Am J Clin Nutr 2007;86:556–65.
12. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
13. Woodward M. Epidemiology: study design and data analysis. 2nd ed. Boca Raton: Chapman and Hall/CRC; 2004.
14. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315: 629–34.
15. Lukanova A, Bjor O, Kaaks R, et al. Body mass index and cancer: results from the Northern Sweden Health and Disease Cohort. Int J Cancer 2006;118:458–66.
16. Larsson SC, Rutegard J, Bergkvist L, Wolk A. Physical activity, obesity, and risk of colon and rectal cancer in a cohort of Swedish men. Eur J Cancer 2006;42:2590–7.
17. MacInnis RJ, English DR, Haydon AM, Hopper JL, Gertig DM, Giles GG. Body size and composition and risk of rectal cancer (Australia). Cancer Causes Control 2006;17:1291–7.
18. MacInnis RJ, English DR, Hopper JL, Gertig DM, Haydon AM, Giles GG. Body size and composition and colon cancer risk in women. Int J Cancer 2006;118:1496–500.
19. Bowers K, Albanes D, Limburg P, et al. A prospective study of anthropometric and clinical measurements associated with insulin resistance syndrome and colorectal cancer in male smokers. Am J Epidemiol 2006;164:652–64.
20. Pischon T, Lahmann PH, Boeing H, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). J Natl Cancer Inst 2006;98:920–31.
21. Ahmed RL, Schmitz KH, Anderson KE, Rosamond WD, Folsom AR. The metabolic syndrome and risk of incident colorectal cancer. Cancer 2006;107:28–36.
22. Otani T, Iwasaki M, Inoue M; Shoichiro Tsugane for the Japan Public Health Center-Based Prospective Study Group. Body mass index, body height, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan public health center-based prospective study. Cancer Causes Control 2005;16:839–50.
23. Rapp K, Schroeder J, Klenk J, et al. Obesity and incidence of cancer: a large cohort study of over 145,000 adults in Austria. Br J Cancer 2005; 93:1062–7.
24. Engeland A, Tretli S, Austad G, Bjorge T. Height and body mass index in relation to colorectal and gallbladder cancer in two million Norwegian men and women. Cancer Causes Control 2005;16:987–96.
25. Kuriyama S, Tsubono Y, Hozawa A, et al. Obesity and risk of cancer in Japan. Int J Cancer 2005;113:148–57.
26. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. J Clin Oncol 2005;23:4742–54.
27. Lin J, Zhang SM, Cook NR, Rexrode KM, Lee IM, Buring JE. Body mass index and risk of colorectal cancer in women (United States). Cancer Causes Control 2004;15:581–9.
28. MacInnis RJ, English DR, Hopper JL, Haydon AM, Gertig DM, Giles GG. Body size and composition and colon cancer risk in men. Cancer Epidemiol Biomarkers Prev 2004;13:553–9.
29. Wei EK, Giovannucci E, Wu K, et al. Comparison of risk factors for colon and rectal cancer. Int J Cancer 2004;108:433–42.
30. Moore LL, Bradlee ML, Singer MR, et al. BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. Int J Obes Relat Metab Disord 2004; 28:559–67.
31. Terry PD, Miller AB, Rohan TE. Obesity and colorectal cancer risk in women. Gut 2002;51:191–4.
32. Ford ES. Body mass index and colon cancer in a national sample of adult US men and women. Am J Epidemiol 1999;150:390–8.
33. Chyou PH, Nomura AM, Stemmermann GN. A prospective study of colon and rectal cancer among Hawaii Japanese men. Ann Epidemiol 1996;6:276–82.
34. Bostick RM, Potter JD, Kushi LH, et al. Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). Cancer Causes Control 1994;5:38–52.
35. Lee IM, Paffenbarger RS, Jr. Quetelet's index and risk of colon cancer in college alumni. J Natl Cancer Inst 1992;84:1326–31.
36. Kreger BE, Anderson KM, Schatzkin A, Splansky GL. Serum cholesterol level, body mass index, and the risk of colon cancer. The Framingham Study. Cancer 1992;70:1038–43.
37. Klatsky AL, Armstrong MA, Friedman GD, Hiatt RA. The relations

of alcoholic beverage use to colon and rectal cancer. Am J Epidemiol 1988;28:1007–15.
38. Schoen RE, Tangen CM, Kuller LH, et al. Increased blood glucose and insulin, body size, and incident colorectal cancer. J Natl Cancer Inst 1999;91:1147–54.
39. Martinez ME, Giovannucci E, Spiegelman D, Hunter DJ, Willett WC, Colditz GA; Nurses' Health Study Research Group. Leisure-time physical activity, body size, and colon cancer in women. J Natl Cancer Inst 1997;89:948–55.
40. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med 1995;122:327–34.
41. Elwing JE, Gao F, Davidson NO, Early DS. Type 2 diabetes mellitus: the impact on colorectal adenoma risk in women. Am J Gastroenterol 2006;101:1866–71.
42. Guilera M, Connelly-Frost A, Keku TO, Martin CF, Galanko J, Sandler RS. Does physical activity modify the association between body mass index and colorectal adenomas? Nutr Cancer 2005;51:140–5.
43. Pan SY, Johnson KC, Ugnat AM, Wen SW, Mao Y; Canadian Cancer Registries Epidemiology Research Group. Association of obesity and cancer risk in Canada. Am J Epidemiol 2004;159:259–68.
44. Slattery ML, Ballard-Barbash R, Edwards S, Caan BJ, Potter JD. Body mass index and colon cancer: an evaluation of the modifying effects of estrogen (United States). Cancer Causes Control 2003;14:75–84.
45. Slattery ML, Caan BJ, Benson J, Murtaugh M. Energy balance and rectal cancer: an evaluation of energy intake, energy expenditure, and body mass index. Nutr Cancer 2003;46:166–71.
46. Russo A, Franceschi S, La Vecchia C, et al. Body size and colorectal-cancer risk. Int J Cancer 1998;78:161–5.
47. Slattery ML, Potter J, Caan B, et al. Energy balance and colon cancer-beyond physical activity. Cancer Res 1997;57:75–80.
48. Kune GA, Kune S, Watson LF. Body weight and physical activity as predictors of colorectal cancer risk. Nutr Cancer 1990;13:9–17.
49. Reddy BS, Wang CX, Maruyama H. Effect of restricted caloric intake on azoxymethane-induced colon tumor incidence in male F344 rats. Cancer Res 1987;47:1226–8.
50. Engelman RW, Day NK, Good RA. Calorie intake during mammary development influences cancer risk: lasting inhibition of C3H/HeOu mammary tumorigenesis by peripubertal calorie restriction. Cancer Res 1994;54:5724–30.
51. Birt DF, Barnett T, Pour PM, Copenhaver J. High-fat diet blocks the inhibition of skin carcinogenesis and reductions in protein kinase C by moderate energy restriction. Mol Carcinog 1996;16:115–20.
52. Zhu Z, Haegele AD, Thompson HJ. Effect of caloric restriction on pre-malignant and malignant stages of mammary carcinogenesis. Carcinogenesis 1997;18:1007–12.
53. Friedenreich CM. Physical activity and cancer prevention: from observational to intervention research. Cancer Epidemiol Biomarkers Prev 2001;10:287–301.
54. Maskarinec G, Takata Y, Pagano I, et al. Trends and dietary determinants of overweight and obesity in a multiethnic population. Obesity 2006;14:717–26.
55. Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. Int J Cancer 2006;119:2657–64.
56. Norat T, Bingham S, Ferrari P, et al. Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. J Natl Cancer Inst 2005;97:906–16.
57. Giovannucci E. Insulin and colon cancer. Cancer Causes Control 1995;6:164–79.
58. McKeown-Eyssen G. Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? Cancer Epidemiol Biomarkers Prev 1994;3:687–95.
59. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer 2005;92:2076–83.
60. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer 2007;121:856–62.
61. Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis. Diabetologia 2006;49:2819–23.
62. Hou L, Ji BT, Blair A, et al. Body mass index and colon cancer risk in Chinese people: menopause as an effect modifier. Eur J Cancer 2006;42:84–90.
63. International obesity taskforce. The Global epidemic. Available from: http://www.iotf.org/globalepidemic.asp (accessed 20 July 2007).
64. WHO. Obesity and overweight. Available from: http://www.who.int/infobase/report.aspx (accessed 20 July 2007).