Fasting glucose

	Study	Country	Design	Gender	Age(years)	cancer types and No. of cases/controls/cohort	unit of fasting glucose	Adjustment for covariates
1	Yamada et al,1998	Japan	case-control	F/M	34-73	CRC:129,control:258	mg/dl	age,sex,BMI,alcohol consumption
2	Schoen et al,1999	USA	cohort	F/M	73.9(mean)	CRC:602,cohort:5849	mg/dl	age, sex and physical activity
3	Jee et al,2005	Korea	cohort	F/M	30-95	CRC:3352,cohort:829770men,468615women	mg/dl	adjusted for age, age squared, amount of smoking, and alcohol use
4	Chung et al,2006	Korea	case-control	F/M	CRC:58.4,control:58.7	CRC:185,control:935	mg/dl	Adjusted for age, sex ,BMI,TG,cholesterol
5	Limburg et al,2006	Finland	nested case-control	M	50-69	CRC:139,control:399,cohort:29133	mg/dl	cigarette pack-years, body mass index, protein intake, fat intake, fiber intake, alcohol consumption, caloric intake, history of diabetes mellitus and occupational physical activity.
6	Rapp et al,2006	Austrian	cohort	F/M	44-8(mean)	CRC:677,cohort:6585men, 7722Bwomen	mmol/l	age, smoking status, occupational group, and BMI
7	Stattin et al 2007	Sweden	cohort	F/M	46(mean)	CC-147,RCB7,cohort-645/97	mmol/l	age, calendar year, smoking
8	Cuarer et al,2008	USA	nested case-control	F	50-79	CRC:438,control:816,cohort:5676	mg/dl	age
9	Stocks et al,2008	Sweden	nested case-control	F/M	50-70	CRC:306,control:595,cohort:104461	mmol/l	case-control status, sex, age, smoking status and fasting time before blood draw
10	Stocks et al,2009	Norway, Austria and	cohort	F/M	44.8(mean)	CC-2434,RC-1346,cohort:27413Omen,275818women	mmol/l	adjusted for baseline age, BMI, and smoking status, and RRs per 1 mmol/l were additionally adjusted for fasting time
11	Yamamoto et al,2010	Japan	case-control	F/M	53.8(mean)	CRC:22,control:056	mg/dl	BMI, smoking and drinking
12	Stocks et al,2011	Norway	cohort	F/M	44(mean)	CRC:4695,cohort:578100	mmol/l	adjusted for baseline age, birth year, smoking status, and quintiles of BMI
13	Kabat et al,2012	UK	nested case-control	F	50-79	CRC:81,control:6821,cohort:6902	mg/dl	Adjusted for age, body mass index, alcohol intake, physical activity, family history of colorectal cancer, ethnicity, and participation in the OS or treatment arm of each clinical trial.
14	Ollerding et al,2012	USA	nested case-control	F/M	45-75	CRC:1954,control:2587,cohort:215000	mg/dl	Adjusted for age, sex, race/ethnicity, history of colorectal polyp, family history of colorectal cancer, BMI, physical activity, processed meat intake, pack-years of smoking, alcohol consumption, and mutual adjustment for IGF-I and IGFBP-3.
15	Wulaningsih et al,2012	Sweden	cohort	F/M	43.8(mean)	CC-2472,RC-1510,cohort:548309	mg/dl	adjusted for glucose, TC and TG levels, age, gender, SES, and fasting status
16	Haluzuki et al,2013	Japan	case-control	F/M	48(mean)	CRC:29,control:440	mg/dl	age, gender, cholesterol, triglyceride, uric acid
17	Parekh et al,2013	USA	cohort	F/M	66.8(mean)	CRC:136,cohort:4615	mg/dl	age, sex, alcohol, smoking, BMI, smoking status
18	Shin et al,2014	Korea	cohort	F/M	42(mean)	CRC:320,cohort:175677	mg/dl	age, sex, body mass index, smoking, alcohol drinking, and regular exercise

1mol=1000mmol 1mmol/L=18mg/dl

1 Yamada1998

Relation of serum total cholesterol, serum triglycerides and fasting plasma glucose to colorectal carcinoma in situ

Japan 129CRC:258controls fasting glucose(mg/dl)

case-control **Numbers of cases and controls,odds ratio/OR\adjusted OR and 95% confidence interval/CI\ colorectalcarcinomainsituaccordino to the levels of serum lipids and fasting plasma glucose**

fasting glucose(mg/dl)	cases/controls	OR	adjusted OR	age,sex,BMI, smoking, alcohol consumption
<=95	52/103	1	1	
96-105	43/95	0.96(0.5-1.5)	1(0.6-1.7)	
106-115	14/38	0.7(0.4-1.5)	0.7(0.3-1.5)	
116<	20/22	1.8(0.9-3.6)	2(0.9-4.4)	
trend		p=0.12	p=0.11	

2 Schoen1999

Increased blood glucose and insulin, body size, and incident colorectal cancer

US 102CRC:584cohort fasting glucose(mg/dl)

cohort 77months

Relative risk of incident colorectal cancer in the Cardiovascular Health Study

fasting glucose range	Q1	Q2	Q3	Q4	linear model	adjusted for age, sex, and physical activity
men	81–96	97–103	104–115	116–448		
women	53–93	94–99	100–110	111–657		
case/subjects	22/1591	18/1352	29/1433	32/1393		
RR	1.0 (referent)	0.92(0.5–1.8)	1.4(0.8–2.4)	1.8(1.0–3.1)	1.2(1.0-1.5) p=0.02	

3 Jee2005

Fasting serum glucose level and cancer risk in Korean men and women

Korean 129838Scohort(829770men,468615women) age 30-95

10year prospective cohort fasting glucose(mg/dl)

Age-Adjusted Incidence Rate per 100 000 Men for All Cancer and Various Cancers by Fasting Serum Glucose Level in Korean Men,1993–2002

	<90	90-109	110-125	126-139	>=140	p	diabetes	adjusted for age, age squared, amount of smoking, and alcohol use
Men	429370	304362	58020	11459	26559		41858	
colon/rectum								
incidence rate/ 100000	52.4	57.8	63.1	53.5	58.2		60.1	
HR	1	1.08 (1.03-1.15)	1.14 (1.02-1.27)	1.03 (0.82-1.28)	1.13 (0.98-1.30)	0.35	1.11(1.00-1.24)	
women	270157	157040	22578	5657	12283		21056	
colon/rectum								
incidence rate/ 100000	36.8	38	38.5	45.1	54.2		53.8	
HR	1	1.04 (0.94-1.15)	1.11 (0.92-1.34)	0.80 (0.53-1.20)	1.07 (0.84-1.36)	0.84	1.17(0.98-1.40)	

4 Chung2006

Association of obesity, serum glucose and lipids with the risk of advanced colorectal adenoma and cancer: a case-control study in Korea

Korean 185CRC:105adenoma,335control age,58.4control:58.7cancer fasting glucose(mg/dl)

case-control **Multivariate-adjusted OR with 95% CI for advanced adenoma and cancer in relation to BMI, serum glucose and lipids**

glucose/mal/dl	cases/controls	OR			Adjusted for age, sex ,BMI,TG,cholesterol
<90	27/48	1			
90-109	44/44	2.0(0.9-4.4)			
>110	34/13	3.0(0.9-9.8)			

5 Limburg2006

Insulin, glucose, insulin resistance, and incident colorectal cancer in male smokers

Finland 134CRC:399controls,2933men age50-69

nested case-control **Associations Between Fasting Insulin, Glucose, HOMA-IR and Incident Colorectal Cancer, Overall and by Anatomic Subsite**

men	fasting Glucose(mol/l)										
	Q1	Q2	Q3	Q4	P		Insulin analyses are adjusted for cigarette pack-years, body mass index, protein intake, fat intake, fiber intake, alcohol consumption, caloric intake, history of diabetes mellitus and occupational physical activity.				
	<92	93-98	99-107	>107							
all CRC											
case/control	23/99	32/100	44/101	35/99							
HR(age)	1.00 (ref.)	1.35 (0.72–2.50)	2.08 (1.14–3.79)	1.70 (0.92–3.13)	0.04						
HR(multi)	1.00 (ref.)	1.19 (0.58–2.43)	1.95 (0.97–3.91)	1.65 (0.78–3.49)	0.16						
Proximal CRC											
case/control	8/99	14/100	15/101	10/99							
HR(age)	1.00 (ref.)	1.57 (0.62–3.98)	2.15 (0.85–5.41)	1.45 (0.55–3.84)	0.33						
HR(multi)	1.00 (ref.)	1.67 (0.59–4.73)	1.92 (0.66–5.58)	1.38 (0.42–4.52)	0.52						
Distal CRC											
case/control	15/99	18/100	29/101	25/99							
HR(age)	1.00 (ref.)	1.22 (0.58–2.57)	2.04 (1.02–4.09)	1.81 (0.90–3.66)	0.04						
HR(multi)	1.00 (ref.)	1.03 (0.42–2.51)	2.09 (0.89–4.91)	1.85 (0.77–4.45)	0.08						

6 Rapp2006

Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria

Austrian 喂 6385Bmen,77228women 8.4years follow up fasting Glucose(mmol/l) age and adjusted for smoking status (never, former, current), occupational group (white collar, blue collar, self-employed), and BMI

cohort	**MALE**										
fasting Glucose(mmol/l)	2.2-4.1		4.2-5.2		5.3-6		6.1-6.9		>=7		p
	n	HR	n	HR	n	HR	n	HR	n	HR	
Total participants	15505		30510		11636		3467		2467		
CRC	59	0.92(0.68-1.25)	148	1	66	1.02(0.76-1.36)	33	1.37(0.94-2.01)	27	1.19(0.79-1.81)	0.12
	Female										
Total participants	20562		39210		11784		3261		2291		
CRC	78	1.07(0.82-1.41)	159	1	57	0.97(0.71-1.32)	34	1.57(1.08-2.28)	16	0.88(0.52-1.48)	0.87

7 Stattin et al,2007

Prospective study of hyperglycemia and cancer risk

Colon				fasting Glucose(mmol/l)		
Fasting (n=147)	ref(Q1)	Q2	Q3	Q4	p	
IER (95% CI) 1		1.95 (0.55–1.62)	0.99 (0.56–1.46)	1.16 (0.74–1.85)	0.47	
Rectum						
Fasting (n=87)						
IER (95% CI)		1.1 18 (0.59–2.32)	0.99 (0.53–1.87)	1.13 (0.62–2.12)	0.782	

Risk was adjusted for age, calendar year, and smoking, by including these covariates into the statistical model.

8 Gunter2008

Insulin, insulin-like growth factor-I, endogenous estradiol, and risk of colorectal cancer in postmenopausal women

US 93676 women, 438CRC,816controls age50-79 fasting Glucose(mg/dl)

nested case-control **Age-adjusted and multivariate associations (HRs and 95% CI) of baseline IGF-I, free IGF-I, IGFBP-3, insulin, glucose, HOMA-IR index, estradiol, hormone therapy use, and obesity with incident colorectal cancer** Adjusted for age only

Glucose	<86	86-93.5	93.5-100	>=100	p	
cases/subcohort	99/200	109/210	98/195	129/207		
HR	1	0.94 (0.68–1.34)	0.91 (0.63–1.30)	1.16 (0.83–1.63)	0.4	

9 Stocks2008

Components of the metabolic syndrome and colorectal cancer risk; a prospective study

Sweden 306CRC,595control age50-70 fasting Glucose(mmol/l)

nested case-control **Odds ratios for colorectal cancer by quartiles**

	Q1	Q2	Q3	Q4	p	
Fasting glucose mmol/L	<5	5-5.3	5.3-5.6	>5.6		
cases/control	63/102	42/86	38/118	70/103		
OR	1	0.82 (0.55–1.32)	0.53 (0.32–0.87)	1.06 (0.67–1.68)	0.98	
OR adjusted for BMI	1	0.82 (0.55–1.33)	0.53 (0.33–0.88)	1.05 (0.68–1.68)	0.9	

10 Stocks2009

Blood glucose and risk of incident and fatal cancer in the metabolic syndrome and cancer project (me-can): analysis of six prospective cohorts

cohorts from Norway, Austria, and Sweden 274,126 men and 275,818 women age44.8,follow up10.4years 2 cohort fasted<8h, one cohort fasted<8h All participants in the VHM&PP and the MPP and 90% of participants in the VIP had fasted 8 h before the health examination, whereas 95% of participants in the Norwegian cohorts had fasted 8 h.

	cases	Q1	Q2	Q3	Q4	Q5	p	RR per 1mmol/L increment
colon								
men	1,455	1	0.93 (0.52–1.64)	0.97 (0.54–1.74)	0.73 (0.42–1.29)	1.33 (0.79–2.28)	0.2	1.02 (0.88–1.18)
women	979	1	0.97 (0.44–2.05)	1.1 (0.52–2.16)	1.03 (0.52–2.16)	1.53 (0.85–2.59)	0.5	0.99 (0.84–1.16)
rectum								
men	899	1	1.74 (0.81–3.69)	1.94 (0.90–4.22)	2.52 (1.21–5.10)	1.69 (0.81–3.53)	0.5	1.14 (0.94–1.37)
women	446	1	0.84 (0.28–2.52)	0.79 (0.28–2.28)	1.18 (0.44–3.29)	1.00 (0.37–2.79)	0.7	1.09 (0.85–1.40)

attained age as the time scale, was stratified by cohort and adjusted for baseline age, birth year, smoking status, and quintiles of BMI (except BMI) attained age as time scale, stratified by cohort, sex, and birth year, andadjusted for baseline age, BMI, and smoking status, and RRs per 1 mmol/l were additionally adjusted for fasting time.

11 Yamamoto2010

Visceral fat area and markers of insulin resistance in relation to colorectal neoplasia

Japan 22CRC:85controls fasting Glucose(mg/dl)

case-control **Associations of glucose, insulin, and HOMA-IR with the prevalence of adenoma and cancer in the colorectum**

	Q1	Q2	Q3	p	
fasting Glucose(mg/dl)	<99	99-108	>108		
case/control	4/21	5/22	12/23		Adjusted for smoking and alcohol drinking
OR	1	1.69 (0.36–7.98)	3.12 (0.76–12.74)	0.09	Additionally adjusted for BMI
adjusted OR1	1	1.76 (0.35–8.69)	4.40 (0.99–19.59)	0.04	
adjusted OR2	1	2.17 (0.41–11.50)	4.07 (0.86–19.37)	0.07	

12 Stocks2011

Metabolic factors and the risk of colorectal cancer in 580,000 men and women in the metabolic syndrome and cancer project (Me-Can)

Norway 578700cohort,2834CRC(M),1861CRC(F) age44,follow up 12years partly fasting<8h, fasting Glucose(mmol/l)

cohort **The Relative Risk of Incident Colorectal Cancer in Men and Women by Quintiles of Metabolic Factors**

	Men				Women		
	glucose(mmol/L)	cases	RR	glucose(mmol/L)	cases	RR	
Q1	4.2	490	1.00 (referent)	4.1	283	1.00 (referent)	attained age as the time scale, was stratified by cohort and adjusted for baseline age, birth year, smoking status, and quintiles of BMI (except BMI)
Q2	4.8	503	1.00 (0.63-1.55)	4.6	293	1.07 (0.58-1.92)	
Q3	5.1	537	1.19 (0.77-1.86)	5	392	1.11 (0.63-1.92)	
Q4	5.5	630	1.11 (0.74-1.75)	5.3	368	1.15 (0.66-2.02)	
Q5	6.9	668	1.15 (0.74-1.75)	6.5	520	1.41 (0.83-2.35)	
p			0.89			0.33	
	colon 1706	rectum 1074		colon 1237	rectum 588		
model 1	1.11 (0.94-1.31)	1.36 (0.95-1.43)		1.09 (0.93-1.32)	1.24 (0.95-1.62)	model 1	The RR from Cox regression model, with attained age as the time scale, was stratified by cohort and adjusted for baseline age, birth year, and smoking status. RRs are corrected for the regression dilution
model 2	0.98 (0.82-1.17)	1.08 (0.87-1.34)		1.08 (0.89-1.32)	1.22 (0.92-1.62)		ratio (RDR) and converted into uncorrected RRs, as described in Table 4.
						model 2	The RRs from Cox regression models, with attained age as the time scale, were stratified by cohort and adjusted for baseline age, birth year, smoking status, and all individualZscores (except in the MetS

analysis).Zscores derived from original values were calibrated

13 Kabat2012

A longitudinal study of serum insulin and glucose levels in relation to colorectal cancer risk among postmenopausal women

UK 4982 women,83CRC,11 cases follow up, 4821control age,64.3CRC,62.5control

nested case-control women fasting Glucose(mg/dl)

Association of baseline serum insulin, glucose, and HOMA-IR with risk of colorectal and colon cancer in the Women's Health Initiative

	Colorectal cancer			colon cancer		
Glucose mg/dl	case/non-case	HR(age)	HR(multi)	case	HR(age)	HR(multi)
<89.5	18/1520	1	1	15	1	1
89.5-99.5	28/1641	1.41(0.78-2.57)	1.32(0.72-2.4)	28	1.84(0.92-3.68)	1.72(0.85-3.48)
>=99.5	35/1660	1.73(0.98-3.06)	1.74(0.97-3.15)	22	2.18(1.11-4.29)	2.25(1.12-4.51)
p		0.06	0.06		0.03	0.02
Continous			1.03(1.009-1.054)			1.034(1.009-1.060)

Adjusted for age, body mass index , alcohol intake (drinks per week), physical activity (MET-hours per week), family history of colorectal cancer, ethnicity (white, black, other), and participation in the OS or treatment arm of each clinical trial.

14 Ollerding2012

Genetic variants, prediagnostic circulating levels of insulin-like growth factors, insulin, and glucose and the risk of colorectal cancer: the Multiethnic Cohort study

US 210000cohort, 1954cases,2587controls age45-75 fasting Glucose(mg/dl)

nested case-control **ORs and 95% CIs for tertiles of circulating IGF system biomarkers, insulin, glucose, and colorectal cancer**

	cases/controls	Q1	Q2	Q3	p	
fasting glucose mg/dl		77-18	89.87	111.89		model 1 Adjusted for age, sex, and race/ethnicity
model 1	258/1,701	1	0.90 (0.65–1.25)	1.03 (0.75–1.43)	0.738	model 3 Adjusted for age, sex, race/ethnicity, history of colorectal polyp, family history of colorectal cancer, BMI (kg/m
model 3	249/1,571	1	0.87 (0.62–1.23)	0.87 (0.62–1.22)	0.472	), moderate or vigorous

physical activity, processed meat intake, pack-years of smoking, alcohol consumption, and mutual adjustment for IGF-I and IGFBP-3, where appropriate

15 Wulaningsih2012

Serum Lipids and the Risk of Gastrointestinal Malignancies in the Swedish AMORIS Study

Swedish 540309cohort, 2472CC, 1510RC fasting Glucose(mmol/L) 1534fasting, 147not fasting, 791 missing

cohort **Hazard ratios and 95% confidence intervals for GI cancer for quartiles of lipid components, adjusted for age, gender, SES, fasting status, glucose (continuous), total cholesterol (continuous), and triglycerides (continuous).**

glucose mmol/L	n(colon)	Colon	n(Rectal)	rectal	
<4.4	310	1.00 (Ref)	242	1.00 (Ref)	adjusted for glucose, TC and TG levels (if not
4.4-4.8	572	1.14 (1.00–1.32)	338	0.85 (0.72–1.00)	strongly correlated with the covariate of interest), as well as
4.8-5.2	622	1.12 (0.98–1.28)	346	0.77 (0.65–0.91)	age, gender, SES, and fasting status
>=5.2	968	1.21 (1.05–1.40)	584	0.88 (0.74–1.05)	
p		0.03		0.23	

16 Haluzuki2013

Association of laboratory data on lifestyle-related factors with the risk of colorectal adenoma and cancer: A retrospective cohort study with long-term follow-up total colonoscopy

Japan 29CRC,440control age48CRC,45control,41-52 follow up 10years fasting Glucose(mg/dl)

case-control

glucose mg/dl	control	CRC	recalculated
<109	334	16	1
110-125	70	9	2.08(1.18-3.65)
>126	36	4	2.06(.81-5.21)

17 Parekh2013

Metabolic dysregulation of the insulin-glucose axis and risk of obesity-related cancers in the Framingham heart study-offspring cohort (1971-2008)

USA 4615cohort,136CRC, age66.8,follow up>37years fasting Glucose(mg/dl)

cohort **Exposure to markers of insulin–glucose metabolism and risk of commonly diagnosed obesity-related cancer sites**

	cases/cohort	HR(age)	HR(adjusted)	
fasting glucose	136/4192			
<110mg/dl		1	1	Adjusted for age, sex, alcohol, smoking, and BMI (<25, 25–30, and>30). Smoking status (never, past, and current smoker) was based
>110mg/dl		2.21(1.53-3.19)	2.2(1.48-3.27)	on self-reported data from each exam

18 Shin2014

Association between fasting serum glucose levels and incidence of colorectal cancer in Korean men: the Korean Cancer Prevention Study-II

Korea prospective cohort 175677 follow-up 4.7y fasting blood glucose mg/dl

Table 3 – Incidence rate and hazard ratio for developing colorectal cancer in individuals with high or low fasting serum glucose levels

		person-year	CRC	IR(incidence rate)	HR1	HR2	HR3	
	total							
<100	low	677,675.60	221	32.61	1	1	1	
>100	high	138,467.00	99	71.5	1.49(1.10-1.78)	1.45(1.11-1.90)	1.45(1.10-1.90)	1 adjusted for age and sex
	men							2 adjusted for age, sex, and body mass index
	low	375,362.60	145	38.63	1	1	1	3 adjusted for age, sex, body mass index, smoking, alcohol drinking, and regular exercise
	high	100,275.20	82	81.77	1.54(1.17-2.02)	1.51(1.12-2.05)	1.51(1.11-2.05)	
	women							
	low	302,313.00	76	25.14	1	1	1	
	high	38,191.80	17	44.51	0.99(0.57-1.70)	1.25(0.68-2.28)	1.23(0.67-2.26)	

Table 4 – Incidence rate and hazard ratio for developing proximal colon, distal colon, and rectal cancers in individuals with high or low fasting serum glucose levels.

	total	proximal colon	distal cancer	rectal cancer	
<100	low	1	1	1	
>100	high	1.42(0.77-2.62)	1.60(0.99-2.61)	1.49(1.00-2.24)	Cox proportional hazards regression analysis adjusted for age, sex, body mass index, smoking, alcohol drinking, and regular exercise.
	men				
	low	1	1	1	
	high	1.69(0.81-3.53)	1.53(0.88-2.64)	1.59(1.01-2.48)	
	women				
	low	1	1	1	
	high	1.11(1.06-1.15)	1.94(0.86-5.66)	1.12(0.41-3.06)	

Fasting insulin

	Study	Country	Design	Gender	Age(years)	cancer types and No. of cases/controls/cohort	unit of fasting insulin	Adjustment for covariates
1	Schoen et al,1999	USA	cohort	F/M	73.9(mean)	CRC:182,cohort:5849	IU/ml	age, sex and physical activity
2	Palmqvist et al,2003	Sweden	case-control	F/M	30-70	CC:110,RC:58,control:336	pmol/l	age, sex, BMI, smoking, IGFBP levels
3	Limburg et al,2006	Finland	nested case-control	M	50-69	CRC:139,control:399,cohort:29133	uIU/ml	cigarette pack-years, body mass index, protein intake, fat intake, fiber intake, alcohol consumption, caloric intake, history of diabetes mellitus and occupational physical activity.
4	Gunter et al,2008	USA	nested case-control	F	50-79	CRC:438,control:816,cohort:93676	uIU/ml	age
5	Yamamoto et al,2010	Japan	case-control	F/M	53.8(mean)	CRC:22,control:66	uIU/dl	BMI, smoking and drinking
6	Chen et al,2012	China	case-control	M	early cancer52.1,adv	CRC:165,control:102	mIU/l	age, BMI, WHR, SBP, TG, fasting insulin, HOMA-IR, total adiponectin, HMW adiponectin, lifestyle characteristics, medications, family history of CRC and diabetes
7	Dankner et al,2012	Four region	cohort	F/M	51.8(mean)	CRC:44,cohort:1695	mIU/l	Adjusted for age, sex, and ethnicity
8	Kabat et al,2012	UK	nested case-control	F	50-79	CRC:81,control:4821,cohort:4902	uIU/ml	Adjusted for age, body mass index , alcohol intake, physical activity, family history of colorectal cancer, ethnicity, and participation in the OS or treatment arm of each clinical trial.
9	Ollberding et al,2012	USA	nested case-control	F/M	45–75	CRC:1954,control:12587,cohort:215000	mIU/l	Adjusted for age, sex, race/ethnicity, history of colorectal polyp, family history of colorectal cancer, BMI,physical activity, processed meat intake, pack-years of smoking, alcohol consumption, and mutual adjustment for IGF-I and IGFBP-3,
10	Parekh et al,2013	USA	cohort	F/M	66.8(mean)	CRC:136,cohort:4615	pmol/l	age, sex, alcohol, smoking, BMI, smoking status

CRC-insulin

1uIU/ml=1mIU/L | insulin pmol/L = mIU/L×6.965 | 1000uIU=1IU=45.4ug insulin

1 Schoen/1999 — Increased blood glucose and insulin, body size, and incident colorectal cancer

US	102CRC,5849cohort		fasting insulin(IU/ml)			
cohort						
	Relative risk of incident colorectal cancer in the Cardiovascular Health Study					
fasting insulin range	Q1	Q2	Q3	Q4	linear model	adjusted for age, sex, and physical activity
men	4–10	11–13	14–18	19–400		
women	3–9	10–13	14–18	19–400		
case/subjects	29/1661	177/1538	29/1232	26/1297		
RR	1.0 (referent)	0.6(0.3–1.1)	1.4(0.8–2.3)	1.2(0.7–2.1)	NA	

2 Palmqvist/2003 — Plasma insulin, IGF-binding proteins-1 and -2 and risk of colorectal cancer: a prospective study in northern Sweden

Sweden	168CRC(110CC,58RC),336controls			pmol/l		
case-controls	**OR OF CANCER OF THE COLORECTUM, COLON OR RECTUM FOR QUARTILES OF BMI, SERUM INSULIN, IGFBP-1 AND IGFBP-2**					
insulin	Q1	Q2	Q3	Q4	p	
CRC						
OR	1	1(0.56–1.74)	1.21(0.69–2.12)	1.22(0.64–2.31)	0.41	adjusted for smoking
cases/controls	41/84	39/86	44/81	42/84		Analyses on both fasting and nonfasting subjects
Mean exposure	3.22	5.31	7.97	27.98		
Colon						
OR	1	1.43(0.70–2.95)	1.52(0.75–3.09)	1.2(0.52-2.77)	0.56	
cases/controls	22/54	31/56	31/56	26/54		
Mean exposure	3.19	5.32	7.98	27.26		
Rectum						
OR	1	0.48(0.17–1.31)	0.93(0.32–2.74)	1.37(0.46–4.08)	0.48	
cases/controls	19/30	8/30	13/25	16/30		
Mean exposure	3.27	5.3	7.95	29.22		

3 Limburg/2006 — Insulin, glucose, insulin resistance, and incident colorectal cancer in male smokers

Finland	134CRC,399controls,29133men			age50-69		
nested case-control	**Associations Between Fasting Insulin, Glucose, HOMA-IR and Incident Colorectal Cancer, Overall and by Anatomic Subsite**					
men	**fasting insulin(uIU/ml)**					
	Q1	Q2	Q3	Q4	P	Insulin analyses are adjusted for cigarette pack-years, body mass index, protein intake, fat intake, fiber intake, alcohol consumption, caloric intake, history of diabetes mellitus and occupational
	<2.8	2.9-4.1	4.2-6.1	>6.1		physical activity.
all CRC						
case/control	31/104	37/97	25/103	41/95		
HR(age)	1.00 (ref.)	1.40 (0.78–2.51)	0.94 (0.51–1.74)	1.84 (1.03–3.30)	0.12	
HR(multi)	1.00 (ref.)	1.43 (0.74–2.78)	0.77 (0.35–1.69)	1.74 (0.74–4.07)	0.4	
Proximal CRC						
case/control	13/104	13/97	9/103	12/95		
HR(age)	1.00 (ref.)	1.30 (0.56–3.04)	0.91 (0.36–2.33)	1.53 (0.62–3.76)	0.54	
HR(multi)	1.00 (ref.)	1.36 (0.53–3.52)	0.82 (0.26–2.65)	1.62 (0.45–5.86)	0.64	
Distal CRC						
case/control	18/104	24/97	16/103	29/95		
HR(age)	1.00 (ref.)	1.46 (0.72–2.97)	0.96 (0.46–1.99)	2.03 (1.04–3.97)	0.1	
HR(multi)	1.00 (ref.)	1.45 (0.65–3.27)	0.73 (0.28–1.87)	1.73 (0.63–4.77)	0.49	

4 Gunter/2008 — Insulin, insulin-like growth factor-I, endogenous estradiol, and risk of colorectal cancer in postmenopausal women

US	93676 women, 438CRC,816controls		age50-79	fasting insulin(uIU/ml)		
nested case-control	**Age-adjusted and multivariate associations (HRs and 95% CI) of baseline IGF-I, free IGF-I, IGFBP-3, insulin,**					
	glucose, HOMA-IR index, estradiol, hormone therapy use, and obesity with incident colorectal cancer					Adjusted for age only
Insulin	<3.6	3.6-5.7	5.7-9.5	>=9.5	p	
cases/subcohort	74/199	97/192	116/206	142/203		
HR	1	1.32(0.90-1.91)	1.45(1-2.09)	1.89(1.33-2.69)	0.0005	

5 Yamamoto/2010 — Visceral fat area and markers of insulin resistance in relation to colorectal neoplasia

Japan	22CRC,66controls			fasting insulin(uU/dl)		
case-control	**Associations of glucose, insulin, and HOMA-IR with the prevalence of adenoma and cancer in the colorectum**					
	Q1	Q2	Q3	p		
fasting insulin(uU/dl)	<5	5-7.8	>7.8			
case/control	5/21	8/22	8/23			Adjusted for smoking and alcohol drinking
OR	1	1.55 (0.45–5.32)	1.38 (0.40–4.76)	>0.2		Additionally adjusted for BMI
adjusted OR1	1	1.65 (0.38–7.28)	1.84 (0.47–7.15)	>0.2		
adjusted OR2	1	1.88 (0.39–9.03)	1.29 (0.28–5.84)	>0.2		

6 Chen/2012 — Association of plasma total and high-molecular-weight adiponectin with risk of colorectal cancer: an observational study in Chinese male

China	71early cancer,94	advanced cancer, 102control		male	Fasting insulin (mIU/L)			
case-control								
		case/control						age, BMI, WHR, SBP, TG, fasting insulin, HOMA-IR, total adiponectin, HMW adiponectin, lifestyle characteristics, medications,
early cancer		low	high	univariate analysis	p	Multi analysis	p	family history of CRC and diabetes
Fasting insulin (mIU/L	<6.8,>=6.8	22/47	49/55	2.117(0.934-7.281)	0.048	1.327(0.614-6.881)	0.292	
advanced cancer								
Fasting insulin (mIU/L	<6.8,>=6.8	36/47	58/55	3.209(0.911-9.336)	0.148	1.937(0.734-7.863)	0.285	age, BMI, WHR, SBP, TG, fasting insulin, HOMA-IR, total adiponectin,
								HMW adiponectin, lifestyle characteristics, medications, family history of CRC and diabetes

7 Dankner/2012 — Effect of elevated basal insulin on cancer incidence and mortality in cancer incident patients: the Israel GOH 29-year follow-up study

	1695cohort			age51.8, follow up 22 yr	Fasting insulin (mIU	Four region,European-American, North African, Yemenite, and Other Middle Eastern	
cohort	**Cancer incidence density (per 10000 person-years) of selected sites and HR (95% CI) for cancer events among 1,695 men**						
	and women according to quartiles of plasma values of basal insulin* (1, lowest quartile; 4, highest quartile)						
	total	Q1	Q2	Q3	Q4	HR of insulin Q4 compared with Q1-3	
n	1695	425	429	420	421		Adjusted for age, sex (except for breast and prostate cancers), and ethnicity
person-years follow u	37,276	9,414	9,670	9,077	9,115		
colon/rectum	11.8	12.7	11.4	13.2	9.9	0.82 (0.39–1.72)	

8 Kabat/2012 — A longitudinal study of serum insulin and glucose levels in relation to colorectal cancer risk among postmenopausal women

UK	4902 women,81CRC,11.9years follow up,		4821control		age,64.3CRC,62.5control		
nested case-control		women	fasting blood sample		uIU/ml		
	Association of baseline serum insulin, glucose, and HOMA-IR with risk of colorectal and colon cancer in the Women's Health Initiative						
	Colorectal cancer			**colon cancer**			
insulin uIU/ml	case/non-case	HR(age)	HR(multi)	case	HR(age)	HR(multi)	
<7.75	29/1561	1	1	21	1	1	
7.75-11.85	24/1545	0.85(0.5-1.47)	0.89(0.51-1.55)	25	1.03(0.56-1.89)	1.11(0.59-2.08)	Adjusted for age, body mass index , alcohol intake (drinks per week), physical activity (MET-hours per week), family history of colorectal cancer,
>=11.85	27/1563	0.99(0.59-1.68)	1.11(0.61-2.01)	18	1.11(0.61-2.02)	1.28(0.65-2.53)	ethnicity (white, black, other), and participation in the OS or treatment arm of each clinical trial.
p		0.99	0.75		0.73	0.48	
Continous			1.000(0.965-1.036)			1.003(0.964-1.044)	

9 Ollberding/2012 — Genetic variants, prediagnostic circulating levels of insulin-like growth factors, insulin, and glucose and the risk of colorectal cancer: the Multiethnic Cohort study

US	215000cohort, 1954	cases,2587controls	age45-75	Fasting insulin (mIU/mL)			
nested case-control	**ORs and 95% CIs for tertiles of circulating IGF system biomarkers, insulin, glucose, and colorectal cancer**						
	cases/controls	Q1	Q2	Q3	p		
Fasting insulin (mIU/mL)		3.04	5.75	11.41		model 1	Adjusted for age, sex, and race/ethnicity
model 1	258/1,701	1	1.16 (0.83–1.62)	1.47 (1.05–2.05)	0.022	model 3	Adjusted for age, sex, race/ethnicity, history of colorectal polyp, family history of colorectal cancer, BMI (kg/m
model 3	249/1,571	1	1.06 (0.75–1.51)	1.21 (0.84–1.75)	0.293		), moderate or vigorous
							physical activity, processed meat intake, pack-years of smoking, alcohol consumption, and mutual adjustment for IGF-I and IGFBP-3,

10 Parekh/2013 — Metabolic dysregulation of the insulin-glucose axis and risk of obesity-related cancers in the Framingham heart study-offspring cohort (1971-2008)

USA	4615cohort,136CRC, age66.8,follow up>37years			fasting Insulin (pmol/L)			
cohort	**Exposure to markers of insulin–glucose metabolism and risk of commonly diagnosed obesityrelated cancer sites**						
	cases/cohort	HR(age)	HR(adjusted)				
Insulin (pmol/L)	71/3433						
<4.94		1	1			Adjusted for age, sex, alcohol, smoking, and BMI (<25, 25–30, and>30). Smoking status (never, past, and current smoker) was based	
4.94-10.08		1.01 (0.53–1.91)	1.11 (0.58–2.13)			on self-reported data from each exam	
>=10.09		2.02 (1.15–3.55)	2.10 (1.12–3.93)				
p		0.0157	0.0354				

HOMA-IR

	Study	Country	Design	Gender	Age(years)	cancer types and No. of cases/controls/cohort
1	Limburg et al,2006	Finland	nested case-control	M	50-69	CRC:139,control:399,cohort:29133
2	Gunter et al,2008	USA	nested case-control	F	50-79	CRC:438,control:816,cohort:93676
3	Yamamoto et al,2010	Japan	case-control	F/M	53.8(mean)	CRC:22,control:66
4	Chen et al,2012	China	case-control	M	early cancer62.1,advanced cancer61.8,control58.3	CRC:165,control:102
5	Kabat et al,2012	UK	nested case-control	F	50-79	CRC:81,control:4821,cohort:4902
6	Ollberding et al,2012	USA	nested case-control	F/M	45-75	CRC:1954,control:2587,cohort:215000
7	Parekh et al,2013	USA	cohort	F/M	66.8(mean)	CRC:136,cohort:4615
8	Erarslan et al,2014	Turkey	case-control	F/M	CRC58,control52.9	CRC:21,control:30

CRC-HOMA

HOMA-IR was derived as fasting insulin x fasting glucose/22.5

1 Limburg/2006

Insulin, glucose, insulin resistance, and incident colorectal cancer in male smokers

Finland	134CRC,399controls,29133men			age50-69	
nested case-control	**Associations Between Fasting Insulin, Glucose, HOMA-IR and Incident Colorectal Cancer, Overall and by Anatomic Subsite**				
men		**HOMA-IR**	fasting		
	Q1	Q2	Q3	Q4	P
	<92	93-98	99-107	>107	
all CRC					
case/control	33/102	37/99	18/98	46/100	
HR(age)	1.00 (ref.)	1.27 (0.71–2.26)	0.67 (0.35–1.30)	1.85 (1.06–3.24)	0.12
HR(multi)	1.00 (ref.)	1.30 (0.68–2.47)	0.51 (0.23–1.16)	**1.71 (0.77–3.78)**	0.38
Proximal CRC					
case/control	14/102	12/99	6/98	15/100	
HR(age)	1.00 (ref.)	1.11 (0.47–2.61)	0.63 (0.22–1.79)	1.70 (0.73–3.97)	0.4
HR(multi)	1.00 (ref.)	1.33 (0.52–3.42)	0.47 (0.13–1.67)	1.96 (0.56–6.91)	0.54
Distal CRC					
case/control	19/102	25/99	12/98	31/100	
HR(age)	1.00 (ref.)	1.36 (0.69–2.70)	0.70 (0.32–1.52)	1.94 (1.01–3.73)	0.15
HR(multi)	1.00 (ref.)	1.31 (0.60–2.87)	0.53 (0.20–1.38)	1.58 (0.63–3.93)	0.53

Insulin analyses are adjusted for cigarette pack-years, body mass index, protein intake, fat intake, fiber intake, alcohol consumption, caloric intake, history of diabetes mellitus and occupational physical activity.

2 Gunter/2008

Insulin, insulin-like growth factor-I, endogenous estradiol, and risk of colorectal cancer in postmenopausal women

US	93676 women, 438CRC,816controls		age50-79	fasting		
nested case-control	**Age-adjusted and multivariate associations (HRs and 95% CI) of baseline IGF-I, free IGF-I, IGFBP-3, insulin, glucose, HOMA-IR index, estradiol, hormone therapy use, and obesity with incident colorectal cancer**					Adjusted for age only
HOMA-IR	<0.71	0.71-1.14	1.14-1.93	>=1.93	p	
cases/subcohort	77/200	99/199	112/200	140/200		
HR	1	1.25(0.86-1.81)	1.35(0.94-1.94)	**1.85(1.3-2.64)**	0.001	

3 Yamamoto/2010

Visceral fat area and markers of insulin resistance in relation to colorectal neoplasia

Japan	22CRC,66controls			fasting		
case-control	**Associations of glucose, insulin, and HOMA-IR with the prevalence of adenoma and cancer in the colorectum**					
	Q1	Q2	Q3	p		
HOMA-IR	1.33	1.33-2.04	>2.04			
case/control	4/21	8/22	9/23		Adjusted for smoking and alcohol drinking	
OR	1	1.85 (0.52–6.62)	1.89 (0.51–6.94)	>0.2	Additionally adjusted for BMI	
adjusted OR1	1	2.60 (0.62–10.97)	3.10 (0.71–13.54)	0.15		
adjusted OR2	1	2.63 (0.60–11.41)	**2.20 (0.45–10.81)**	>0.2		

4 Chen/2012

Association of plasma total and high-molecular-weight adiponectin with risk of colorectal cancer: an observational study in Chinese male

China	71early cancer,94advanced cancer, 102control			male				
case-control								
		case/control						age, BMI, WHR, SBP, TG, fasting insulin, HOMA-IR, total adiponectin, HMW adiponectin, lifestyle characteristics, medications,
early cancer		low	high	univariate analysis	p	Multi analysis	p	family history of CRC and diabetes
HOMA-IR	<2.5,>=2.5	32/70	39/32	3.567(2.274-11.592	0.002	2.881(1.086-10.227)	0.029	
advanced cancer								
HOMA-IR	<2.5,>=2.5	58/70	46/32	2.089(0.934-7.673)	0.072	**1.834(0.785-8.153)**	0.142	age, BMI, WHR, SBP, TG, fasting insulin, HOMA-IR, total adiponectin, HMW adiponectin, lifestyle characteristics, medications, family history of CRC and diabetes

5 Kabat/2012

A longitudinal study of serum insulin and glucose levels in relation to colorectal cancer risk among postmenopausal women

UK	4902 women,81CRC,11.9years follow up, 4821control			age,64.3CRC,62.5control		
nested case-control		women		fasting blood sample		
	Association of baseline serum insulin, glucose, and HOMA-IR with risk of colorectal and colon cancer in the Women's Health Initiative					
	Colorectal cancer			**colon cancer**		
HOMA-IR	case/non-case	HR(age)	HR(multi)	case	HR(age)	HR(multi)
<31.2	27/1556	1	1	21	1	1
31.2-50.2	23/1560	0.86(0.5-1.51)	0.93(0.52-1.66)	24	1.02(0.55-1.89)	1.14(0.6-2.16)
>=50.2	30/1553	1.18(0.7-1.98)	**1.37(0.76-2.49)**	19	1.27(0.7-2.29)	1.51(0.77-2.98)
P		0.54	0.3		0.43	0.23
continous			1.001(0.995-1.007)			1.002(0.995-1.009)

Adjusted for age, body mass index , alcohol intake (drinks per week), physical activity (MET-hours per week), family history of colorectal cancer, ethnicity (white, black, other), and participation in the OS or treatment arm of each clinical trial.

6 Ollberding/2012

Genetic variants, prediagnostic circulating levels of insulin-like growth factors, insulin, and glucose and the risk of colorectal cancer: the Multiethnic Cohort study

US	215000cohort, 1954cases,2587controls		age45-75	Fasting			
nested case-control	**ORs and 95% CIs for tertiles of circulating IGF system biomarkers, insulin, glucose, and colorectal cancer**						
	cases/controls	Q1	Q2	Q3	p		
HOMA-IR		0.636	1.296	2.935		model 1	Adjusted for age, sex, and race/ethnicity
model 1	258/1,701	1	1.06 (0.75–1.48)	1.55 (1.12–2.16)	0.004	model 3	Adjusted for age, sex, race/ethnicity, history of colorectal polyp, family history of colorectal cancer, BMI (kg/m
model 3	249/1,571	1	0.94 (0.66–1.34)	**1.28 (0.88–1.85)**	0.1		), moderate or vigorous
							physical activity, processed meat intake, pack-years of smoking, alcohol consumption, and mutual adjustment for IGF-I and IGFBP-3, where appropriate

7 Parekh/2013

Metabolic dysregulation of the insulin-glucose axis and risk of obesity-related cancers in the Framingham heart study-offspring cohort (1971-2008)

USA	4615cohort,136CRC, age66.8,follow up>37years				
cohort	**Exposure to markers of insulin–glucose metabolism and risk of commonly diagnosed obesityrelated cancer sites**				
	cases/cohort	HR(age)	HR(adjusted)		
HOMA-IR	**71/3428**				
<2.6		1	1		Adjusted for age, sex, alcohol, smoking, and BMI (<25, 25–30, and>30). Smoking status (never, past, and current smoker) was based
>2.6		2.39 (1.49–3.85)	2.36 (1.40–4.00)		on self-reported data from each exam

8 Erarslan/2014

IGF-I levels and visceral fat accumulation in colonic neoplasia

Turkey	21CRC,30controls					
case-control	**Factors associated with colorectal adenoma and colorectal carcinoma in patients assessed by logistic regression analysis.**					
	colorectal carcinoma					
HOMA-IR	1.056(0.77—1.43)	0.73				

HbA1c

	Study	Country	Design	Gender	Age(years)	cancer types and No. of cases/controls/cohort	unit of HbA1c
1	Platz et al,1999	USA	nested case-control	F	44-69	CRC:79,control:156,cohort:121700	%
2	Soydah et al,2003	USA	case-control	F/M	>18	CC:132,RC:81,control:346	%
3	Khaw et al,2004	UK	cohort	F/M	45-79	CRC:67,cohort:9605	%
4	Lin et al,2005	USA	cohort	F	>=45	CRC:168,cohort:27110	%
5	Wei et al,2005	USA	nested case-control	F	30-55	CRC:582,control:350,cohort:32826	%
6	Rinaldi et al,2008	Europen countries	nested case-control	F/M	35-69	CRC:1026,control:1026,cohort:370000women,1	%
7	Stocks et al,2008	Sweden	nested case-control	F/M	50-70	CRC:386,control:395,cohort:104461	%
8	Parekh et al,2013	USA	cohort	F/M	66.8(mean)	CRC:136,cohort:4615	%

1 Platz/1999

Glycosylated hemoglobin and risk of colorectal cancer and adenoma (United States)

USA — Nurses' Health Study; 79CRC,156control; 201distal colorectal adenoma, 201control

nested case-control — Mean age in 1990 (years) CRC:61.2 ;Controls:61.1

(OR) and 95% confidence interval (CI) of colorectal cancer according to tertiles of HbA1cin the Nurses' Health Study, — HbA1c was determined (blinded to case status) by turbidometric immunoinhibition in red blood cells using the Hitachi 911 analyzer (Boehringer Mannheim).

1989to94

	HbA1c					
	Q1	Q2	Q3	p-trend	top 10% HbA1c vs below	
	5.20%	5.50%	5.80%		>=5.9%	cases and controls were matched on year of birth, month of blood draw, and fasting state
CRC(case/control)	22/48	31/60	26/48		13/24	
OR	1 ref	1.2(0.6-2.5)	1.2(0.6-2.7)	0.6	**1.1(0.5-2.6)**	
CC(case/control)	18/36	22/47	15/28		7/11	
OR	1 ref	0.9(0.4-2.2)	1.2(0.5-3)	0.7	1.3(0.5-3.8)	
Advanced CRC(case	7/24	12/29	18/20		8/12	
OR	1 ref	1.9(0.5-6.8)	4.6(1.2-17.1)	0.02	1.6(0.5-5.2)	

2 Saydah/2003

Association of markers of insulin and glucose control with subsequent colorectal cancer risk

USA — 173CRC/133CC,418RC),346controls

case-control — **OR(95% CI) of colorectal cancer according to fourths of markers of insulin and glucose control, CLUE II cohort of Washington County, Maryland,1989-2000**

	HbA1c					
	Q1	Q2	Q3	Q4	p	Cases and controls were matched on age, sex, race, time since last meal, and date of blood draw
	<5.38%	5.38-5.54%	5.54-5.78%	>5.78%		
CRC(case/control)	39/87	29/86	43/86	62/87		
OR	1	0.77(0.43-1.36)	1.12(0.65-1.91)	**1.57(0.94-2.60)**	0.02	
Colon	1.97(1.11-3.48)	0.003				
Proximal colon	2.1(1.4-4)	0.02				
Distal colon	1.61(0.72-3.58)	0.13				
Rectum	0.91(0.36-2.26)	0.69				

3 Khaw/2004

Preliminary communication: glycated hemoglobin, diabetes, and incident colorectal cancer in men and women: a prospective analysis from the European prospective investigation into cancer-Norfolk study

UK — 960Cohort,67CRC — 6 years follow up — age45-79

cohort — Incident colorectal cancer rates and RRs* adjusted for age and age, sex, smoking, and BMI by category of glycated HbA1c level and known diabetes status in 9,605 men and women ages 45 to 79 years without known cancer at baseline, 1995 to 2003

	Level of glycated HbA1c (%)						
	<5%	5-5.9%	6-6.9%	>=7%	Known diabetes	P	
Men and Women	2,627	5,721	899	137	221		
cases	10	35	13	3	6	<0.001	
RR(age, sex)	1	1.13 (0.56-2.30)	1.93 (0.83-4.47)	2.94 (0.80-10.85)	4.02 (1.44-11.22)		
RR(age, sex, BMI and	1	1.07 (0.53-2.20)	1.95 (0.84-4.56)	**2.85 (0.76-10.7)**	3.35 (1.12-10.00)		
men	1,152	2,634	434	76	149	4,445	
cases	4	18	7	2	5	36	<0.001
RR(age, sex)	1	1.64 (0.55-4.85)	3.10 (0.90-10.73)	4.94 (0.89-27.35)	8.96 (1.84-26.34)		
RR(age, sex, BMI and	1	1.61 (0.54-4.82)	3.40 (0.97-11.92)	**5.19 (0.92-29.38)**	6.02 (1.47-24.65)		
women	1,475	3,087	465	61	72	5,160	0.03
cases	6	17	6	1	1	31	
RR(age, sex)	1	0.77 (0.30-1.98)	1.14 (0.36-3.68)	1.58 (0.19-13.46)	1.57 (0.19-13.14)		
RR(age, sex, BMI and	1	0.70 (0.27-1.82)	1.08 (0.33-3.50)	**1.36 (0.15-12.04)**	1.38 (0.16-11.76)		

连续升高,多元调整, model3

All incident colorectal cancer (n = 67/9,605)

HbA1c (per 1% increa 1.39 (1.04-1.81) 0.02

Men only, all incident colorectal cancers (n = 36/4,445)

HbA1c (per 1% increa 1.35 (1.04-1.76) 0.02

Women only, all incident colorectal cancers (n = 31/5,160)

HbA1c (per 1% increa 1.20 (0.81-1.78) 0.26

4 Lin/2005

Hemoglobin A1c concentrations and risk of colorectal cancer in women

US — 27110women,168CRC — age>=45

women cohort — **RRs and 95% CIs of colorectal cancer according to quartiles of HbA1clevels in the Women's Health Study**

	Quartile of HbA1c				
	Q1	Q2	Q3	Q4	p
HbA1c %	2.3-4.8	>4.8-5.0	>5.0-5.2	>5.2	
CRC					
No. of cases	36	41	46	45	
RR1	1	1.00 (0.64-1.57)	1.03 (0.66-1.60)	0.89 (0.57-1.40)	0.59
RR2	1	1.02 (0.65-1.61)	0.95 (0.60-1.50)	**0.83 (0.52-1.33)**	0.35
CC					
No. of cases	29	27	33	38	
RR1	1	0.81 (0.48-1.36)	0.89 (0.54-1.47)	0.90 (0.55-1.47)	0.84
RR2	1	0.83 (0.49-1.41)	0.81 (0.48-1.38)	0.86 (0.51-1.44)	0.65
Tumor location					
Proximal colon cancer					
No. of cases	15	17	19	17	
RR1	1	0.96 (0.48-1.93)	0.95 (0.48-1.89)	0.74 (0.36-1.50)	0.37
RR2	1	0.89 (0.44-1.79)	0.73 (0.36-1.48)	0.51 (0.25-1.08)	0.06
Distal colon cancer					
No. of cases	14	10	14	21	
RR1	1	0.63 (0.28-1.42)	0.81 (0.39-1.72)	1.09 (0.54-2.17)	0.51
RR2	1	0.74 (0.32-1.69)	0.91 (0.42-2.00)	1.47 (0.70-3.08)	0.17
Rectal cancer					
No. of cases	7	12	12	6	
RR1	1	1.84 (0.65-4.18)	1.61 (0.63-4.12)	0.77 (0.26-2.33)	0.53
RR2	1	1.64 (0.64-4.18)	1.55 (0.60-4.01)	0.60 (0.18-1.99)	0.34
Tumor stage					
Duke's A					
No. of cases	15	9	17	11	
RR1	1	0.55 (0.24-1.28)	1.14 (0.56-2.30)	0.95 (0.42-2.16)	0.72
RR2	1	0.45 (0.16-1.29)	1.53 (0.59-3.99)	1.23 (0.40-3.78)	0.48
Duke's B					
No. of cases	5	13	11	11	
RR1	1	2.12 (0.74-6.05)	2.05 (0.70-6.04)	2.58 (0.86-7.78)	0.14
RR2	1	3.19 (0.83-12.26)	4.98 (1.22-20.34)	4.69 (1.14-19.30	0.04
Duke's C					
No. of cases	15	18	17	21	
RR1	1	1.09 (0.53-2.21)	1.07 (0.52-2.18)	1.54 (0.76-3.12)	0.21
RR2	1	1.35 (0.59-3.06)	0.72 (0.30-1.74)	1.27 (0.52-3.18)	0.74

1 Model was adjusted for age and random treatment assignment

2 Model was adjusted for age, random treatment assignment, body mass index, family history of colorectal cancer in a first-degree relative, history of colon polyps, physical activity, smoking status, red meat intake, alcohol consumption, total energy intake, multivitamin use, menopausal status, and baseline postmenopausal hormone use

5 Wei/2005

A prospective study of C-peptide, insulin-like growth factor-I, insulin-like growth factor binding protein-1, and the risk of colorectal cancer in women

US — 32826women,182CRC,350controls — follow up 10years — age30-55

nested case-control — **RR and 95% CI of colorectal cancer according to quartiles of plasma levels of C-peptide, IGFBP-1, and HbA1c in the**

women — **Nurses' Health Study, 1989-2000**

	Q1	Q2	Q3	Q4	p
HbA1c %	5.1	5.4	5.6	5.8	
CRC					
case/control	41/73	40/89	48/87	46/83	
RR1	1	0.82 (0.48-1.41)	1.01 (0.59-1.73)	0.99 (0.57-1.71)	
RR2	1	0.75 (0.43-1.30)	0.94 (0.54-1.65)	**0.85 (0.47-1.51)**	0.74
colon					
case/control	33/55	26/70	41/66	35/64	
RR1	1	0.66 (0.35-1.23)	1.08 (0.59-1.98)	0.95 (0.51-1.76)	
RR2	1	0.57 (0.29-1.10)	1.02 (0.53-1.95)	0.82 (0.42-1.61)	0.91

1 RR from conditional logistic regression

2 RR from conditional logistic regression additionally adjusted for BMI, physical activity, pack-years smoked, and alcohol intake as continuous variables, family history of colorectal cancer, aspirin use, history of screening, menopausal status, and use of postmenopausal hormones

6 Rinaldi/2008

Glycosylated hemoglobin and risk of colorectal cancer in men and women, the European prospective investigation into cancer and nutrition

10 western Europen — 1026CRC,1026controls,370000women,150000men

nested case-control — age35-65

Odds ratios of colorectal cancer (95% CI) by increase in HbA1c in cases and in matched controls in the study population, by cancer site

	Q1	Q2	Q3	Q4	Q5	OR per 10% increase in HbA1c
Colorectum	<=5.4	5.4-5.6	5.6-5.8	5.8-6.1	>6.1	
cases/control	214/218	193/212	189/224	234/211	196/155	
OR(crude)	1	0.93 (0.71-1.23)	0.87 (0.66-1.16)	1.11 (0.84-1.47)	1.33 (0.98-1.80)	1.11 (1.03-1.20)
OR(adjusted)	1	0.96 (0.73-1.27)	0.88 (0.66-1.17)	1.13 (0.85-1.49)	**1.30 (0.96-1.77)**	1.10 (1.01-1.19)
nondiabetics	<=5.4	5.4-5.6	5.6-5.7	5.7-5.9	>5.9	
cases/control	202/192	173/189	95/99	156/180	206/172	
OR(adjusted1)	1	0.89 (0.66-1.19)	0.94 (0.66-1.33)	0.84 (0.61-1.14)	1.15 (0.85-1.57)	1.07 (0.90-1.27)
Colon	<5.4	5.4-5.6	5.6-5.8	5.8-6.1	>6.1	
cases/control	130/129	121/129	119/152	158/142	118/92	
OR(crude)	1	0.93 (0.65-1.33)	0.78 (0.55-1.11)	1.10 (0.77-1.55)	1.30 (0.88-1.91)	1.12 (1.01-1.24)
OR(adjusted)	1	0.97 (0.67-1.39)	0.80 (0.56-1.14)	1.10 (0.77-1.56)	**1.25 (0.84-1.84)**	1.09 (0.98-1.22)
nondiabetics	<5.4	5.4-5.6	5.6-5.7	5.7-5.9	>5.9	
cases/control	122/115	108/112	60/88	97/117	144/119	
OR(adjusted1)	1	0.93 (0.64-1.37)	0.86 (0.55-1.34)	0.80 (0.54-1.17)	1.15 (0.79-1.68)	1.09 (0.88-1.34)
Rectum	<5.4	5.4-5.6	5.6-5.8	5.8-6.1	>6.1	
cases/control	84/89	72/83	70/72	78/75	78/63	
OR(crude)	1	0.93 (0.61-1.44)	1.08 (0.68-1.73)	1.15 (0.72-1.83)	1.40 (0.86-2.27)	1.10 (0.98-1.24)
OR(adjusted)	1	0.91 (0.59-1.42)	1.07 (0.66-1.73)	1.15 (0.72-1.85)	**1.45 (0.88-2.38)**	1.10 (0.97-1.25)
nondiabetics	<5.4	5.4-5.6	5.6-5.7	5.7-5.9	>5.9	
cases/control	80/77	65/77	35/31	59/63	62/53	
OR(adjusted1)	1	0.81 (0.51-1.29)	1.12 (0.62-2.02)	0.91 (0.54-1.53)	1.17 (0.68-2.01)	1.04 (0.78-1.38)

Men

	Q1	Q2	Q3	Q4	Q5	OR per 10% increase in HbA1c
Colorectum	<5.4	5.4-5.6	[5.6-5.8]	[5.8-6.1]	>6.1	
cases/control	118/127	109/103	104/110	116/120	114/101	
OR(crude)	1	1.14 (0.79-1.65)	1.03 (0.71-1.51)	1.05 (0.72-1.54)	1.25 (0.84-1.86)	1.06 (0.96-1.18)
OR(adjusted)	1	1.17 (0.80-1.69)	1.04 (0.71-1.53)	1.09 (0.74-1.60)	**1.25 (0.83-1.86)**	1.06 (0.95-1.17)
nondiabetics	<5.4	5.4-5.6	[5.6-5.7]	[5.7-5.9]	>5.9	
cases/control	112/112	94/90	56/46	73/93	101/101	
OR(adjusted1)	1	1.05 (0.71-1.56)	1.27 (0.78-2.05)	0.87 (057-1.33)	0.99 (0.65-1.51)	0.94 (0.75-1.17)
Colon	<5.4	5.4-5.6	[5.6-5.8]	[5.8-6.1]	>6.1	
cases/control	68/74	70/63	63/72	74/75	67/58	
OR(crude)	1	1.23 (0.75-2.03)	0.98 (0.60-1.61)	1.10 (0.67-1.80)	1.32 (0.78-2.23)	1.10 (0.96-1.26)
OR(adjusted)	1	1.31 (0.79-2.16)	1.03 (0.62-1.70)	1.12 (0.68-1.85)	**1.27 (0.75-2.17)**	1.08 (0.94-1.24)
nondiabetics	<5.4	5.4-5.6	[5.6-5.7]	[5.7-5.9]	>5.9	
cases/control	65/65	60/52	38/30	43/57	65/67	
OR(adjusted1)	1	1.19 (0.69-2.05)	1.31 (0.71-2.43)	0.82 (0.46-1.45)	0.92 (0.54-1.58)	0.92 (0.68-1.23)
Rectum	<5.4	5.4-5.6	[5.6-5.8]	[5.8-6.1]	>6.1	
cases/control	50/53	39/40	41/38	42/45	47/43	
OR(crude)	1	1.03 (0.59-1.78)	1.15 (0.64-2.10)	1.01 (0.55-1.85)	1.19 (0.65-2.19)	1.02 (0.87-1.19)
OR(adjusted)	1	0.94 (0.53-1.65)	1.19 (0.63-2.20)	1.04 (0.55-1.94)	**1.35 (0.71-2.56)**	1.03 (0.88-1.21)
nondiabetics	<5.4	5.4-5.6	[5.6-5.7]	[5.7-5.9]	>5.9	
cases/control	47/47	34/38	18/16	36/36	36/34	
OR(adjusted1)	1	0.84 (0.46-1.53)	1.34 (0.60-3.02)	1.01 (0.52-1.99)	1.17 (0.58-2.35)	0.97 (0.67-1.38)

Women

	Q1	Q2	Q3	Q4	Q5	OR per 10% increase in HbA1c
Colorectum	<5.4	[5.4-5.6]	[5.6-5.8]	[5.8-6.1]	>6.1	
cases/control	96/91	84/109	85/114	118/97	82/54	
OR(crude)	1	0.72 (0.47-1.09)	0.71 (0.46-1.09)	1.14 (0.75-1.73)	1.46 (0.91-2.33)	1.19 (1.04-1.35)
OR(adjusted)	1	0.74 (0.48-1.13)	0.71 (0.46-1.10)	1.13 (0.74-1.71)	**1.40 (0.87-2.24)**	1.16 (1.01-1.32)
nondiabetics	<5.4	[5.4-5.6]	[5.6-5.7]	[5.7-5.9]	>5.9	
cases/control	90/80	79/99	39/53	77/87	105/71	
OR(adjusted1)	1	0.72 (0.46-1.13)	0.69 (0.41-1.16)	0.78 (0.49-1.23)	1.32 (0.83-2.10)	1.28 (0.99-1.67)
Colon	<5.4	[5.4-5.6]	[5.6-5.8]	[5.8-6.1]	>6.1	
cases/control	62/55	51/66	56/80	82/67	51/34	
OR(crude)	1	0.67 (0.39-1.13)	0.62 (0.37-1.04)	1.09 (0.66-1.79)	1.34 (0.75-2.38)	1.15 (0.97-1.37)
OR(adjusted)	1	0.69 (0.40-1.18)	0.63 (0.37-1.05)	1.09 (0.66-1.82)	1.30 (0.72-2.33)	1.12 (0.93-1.34)
nondiabetics	<5.4	[5.4-5.6]	[5.6-5.7]	[5.7-5.9]	>5.9	
cases/control	57/50	48/60	22/38	54/60	79/52	
OR(adjusted1)	1	0.73 (0.42-1.27)	0.55 (0.28-1.06)	0.79 (0.46-1.37)	1.38 (0.80-2.38)	1.32 (0.96-1.80)
Rectum	<5.4	[5.4-5.6]	[5.6-5.8]	[5.8-6.1]	>6.1	
cases/control	34/36	33/43	29/34	36/30	31/20	
OR(crude)	1	0.84 (0.41-1.72)	0.95 (0.44-2.06)	1.29 (0.61-2.74)	1.75 (0.78-3.92)	1.24 (1.01-1.52)
OR(adjusted)	1	0.86 (0.41-1.78)	0.95 (0.44-2.07)	1.28 (0.60-2.73)	1.67 (0.74-3.78)	1.22 (0.99-1.50)
nondiabetics	<5.4	[5.4-5.6]	[5.6-5.7]	[5.7-5.9]	>5.9	
cases/control	33/30	31/39	17/15	23/27	26/19	
OR(adjusted1)	1	0.71 (0.32-1.55)	0.99 (0.40-2.46)	0.72 (0.30-1.72)	1.15 (0.47-2.79)	1.21 (0.74-1.97)

adjust — Analysis matched on EPIC recruitment center, gender, age at blood donation, time of the day at blood donation, follow-up time, fasting status and, in women, menopausal status and phase of the menstrual cycle for premenopausal women

adjust1 — Adjustment for WHR and alcohol (g/d).

7 Stocks/2008

Components of the metabolic syndrome and colorectal cancer risk; a prospective study

Sweden — 306CRC,595control — age50-70

nested case-control — **Odds ratios for colorectal cancer by quartiles**

	Q1	Q2	Q3	Q4	p
HbA1c %	<4.3	4.3-4.5	4.5-4.7	>4.7	
cases/control	53/98	22/90	76/114	69/114	
OR	1	0.47 (0.26–0.85)	1.19 (0.74–1.92)	**1.17 (0.71–1.93)**	0.11

8 Parekh/2013

Metabolic dysregulation of the insulin-glucose axis and risk of obesity-related cancers in the Framingham heart study-offspring cohort (1971-2008)

USA — 461Cohort,136CRC — age66.8,follow up>37years

cohort — **Exposure to markers of insulin–glucose metabolism and risk of commonly diagnosed obesityrelated cancer sites**

	cases/cohort	HR(age)	HR(adjusted)
Hemoglobin A1c (%)	**45/2881**		
<5.25		1	1
5.25-5.72		0.80 (0.34–1.89)	0.78 (0.33–1.86)
>=5.73		2.10 (1.05–4.22)	**2.18 (1.06–4.51)**
P		0.0206	0.0159

Adjusted for age, sex, alcohol, smoking, and BMI (<25, 25–30, and>30). Smoking status (never, past, and current smoker) was based on self-reported data from each exam

C-peptide

	Study	Country	Design	Gender	Age(years)	cancer types and No. of cases/controls/cohor	unit of c-peptide
1	Kaaks et al,2000	USA	nested case-control	F	35-65	CRC:102,control:200,cohort:14275	pmol/ml
2	Ma et al,2004	USA	nested case-control	M	40-84	CRC:176,control:294,cohort:14916	pmol/ml
3	Stattin et al,2004	Norway	nested case-control	M	45(mean)	CC:235,RC:143,control:378,cohort:600000	ng/ml
4	Wei et al,2005	USA	nested case-control	F	30-55	CRC:182,control:350,cohort:32826	ng/ml
5	Jenab et al,2007	10 European countries	nested case-control	F/M	36.7-76.9	CRC:1078,control:1078,cohort:520000	ng/ml
6	Otani et al,2007	Japan	nested case-control	F/M	40-69	CRC:375,control:750,cohort:38373	ng/ml
7	Stocks et al,2008	Sweden	nested case-control	F/M	50-70	CRC:306,control:595,cohort:104461	ng/ml
8	Nakajima et al,2010	Japan	case-control	F/M	CRC:63.7,cotrol:63.5	CRC:115,control:115	x
9	Wu et al,2011	USA	nested case-control	M	40-75	CRC:499,control:992,cohort:51129	x

3.02ng/ml=1pmol/ml

1 Kaaks/2000

Serum C-Peptide, Insulin-Like Growth Factor (IGF)-I,IGF-Binding Proteins, and Colorectal Cancer Risk in women

USA; 14275cohort, 1027CRC, 200controls; nested case-control; C-peptide, pmol/mL

Odds ratios (ORs) of cancer of the colorectum or of the colon for quintiles of serum insulin-like growth factor (IGF)-I, IGF-binding proteins (IGFBPs), C-peptide, and body mass index (BMI)

C-peptide	Q1	Q2	Q3	Q4	Q5	p
Colorectum						
OR	1	0.56 (0.22–1.38)	1.92 (0.90–4.09)	1.26 (0.53–3.02)	**2.92 (1.26–6.75)**	0.001
case/controls	17/44	11/47	25/35	19/43	30/30	
mean exposure	0.41	0.57	0.74	1.01	1.67	
colon						
OR	1	0.41 (0.13–1.27)	1.42 (0.60–3.34)	1.99 (0.68–5.85)	3.96 (1.49–10.50)	<.001
case/controls	13/32	5/36	17/30	16/27	24/21	
mean exposure	0.42	0.55	0.72	0.99	1.73	

2 Ma/2004

A prospective study of plasma C-peptide and colorectal cancer risk in men

US; Male; 14916cohort，176cases，294controls; age40-84; C-peptide, pmol/mL

nested case-control; **Association between the risk for colorectal cancer and quintiles of plasma C-peptide concentration**

	Q1	**Q2**	Q3	Q4	Q5	p	
C-peptide，pmo	0.14 (0.06–0.20)	0.24 (0.20–0.30)	0.38 (0.30–0.44)	0.54 (0.44–0.73)	0.97 (0.74–2.02)		
Overall follow-up							
case/control	19/58	29/59	46/59	39/59	43/59		
RR* (95% CI)	1.0 (referent)	1.4 (0.7 to 3.0)	2.5 (1.2 to 5.2)	2.3 (1.1 to 4.7)	2.5 (1.1 to 5.6)	0.06	age and smoking status and adjusted for fasting status
Multivariable RR	1.0 (referent)	1.5 (0.7 to 3.3)	2.2 (1.0 to 4.8)	1.6 (0.7 to 3.5)	**2.5 (1.2 to 5.6)**	0.04	age and smoking status and adjusted for fasting status
							BMI, alcohol consumption, vigorous exercise, and aspirin assignment
							number of markers for insulin resistance defined as the number of any of the following four factors
							insulin-like growth factor I (IGF-I) and IGF binding protein 3 (IGFBP-3)
Excludingfirst 5 years of follow-up							
case/control	16/50	22/42	40/50	24/43	35/48		
RR* (95% CI)	1.0 (referent)	1.6 (0.7 to 3.8)	2.8 (1.2 to 6.3)	2.1 (0.9 to 4.8)	3.3 (1.4 to 8.2)	0.03	age and smoking status and adjusted for fasting status
Multivariable RR	1.0 (referent)	1.6 (0.7 to 3.8)	2.6 (1.1 to 6.0)	2.0 (0.8 to 4.7)	3.4 (1.3 to 8.8)	0.03	age and smoking status and adjusted for fasting status
							BMI, alcohol consumption, vigorous exercise, and aspirin assignment

3 Stattin/2004

Obesity and colon cancer: does leptin provide a link?

Norway; 235CC,143RC,378control; age45; follow up 17years; C-peptide, ng/mL

nested case-cor; **ODDS RATIOS AND 95% CONFIDENCE INTERVAL OF CANCER OF THE COLON AND OF THE RECTUM FOR QUARTILES OF C-PEPTIDE**

	Q1	Q2	Q3	Q4	p	
Colon	<0.18	0.18-0.31	0.31-0.7	>=0.7		
All						
cases/control	52/65	63/54	60/58	60/58		Adjustment for leptin by adding it as continuous variable to the model.
OR(crude)	1	1.68 (0.92–3.05)	1.53 (0.82–2.86)	1.81 (0.67–4.86)	0.19	
OR(adjusted lep	1	1.69 (0.93–3.09)	1.53 (0.82–2.86)	**1.74 (0.65–4.69)**	0.21	
right colon						
cases/control	24/25	25/25	24/25	26/24		
OR(crude)	1	1.04 (0.49–2.23)	1.12 (0.44–2.82)	3.35 (0.29–38.6)	0.65	
OR(adjusted lep	1	1.04 (0.49–2.23)	1.12 (0.44–2.82)	3.35 (0.29–38.6)	0.65	
Left colon						
cases/control	31/32	29/34	34/29	32/31		
OR(crude)	1	0.91 (0.41–2.02)	1.32 (0.57–3.07)	1.31 (0.41–4.17)	0.47	
OR(adjusted lep	1	0.91 (0.40–2.03)	1.27 (0.54–2.98)	1.23 (0.38–3.97)	0.55	
Rectum	<0.18	0.18 0.36	0.36 1.06	>=1.06		
cases/control	37/34	38/34	33/38	35/37		
OR(crude)	1	0.89 (0.41–1.95)	0.61 (0.24–1.55)	0.44 (0.10–1.99)	0.21	
OR(adjusted lep	1	0.90 (0.41–1.98)	0.63 (0.24–1.68)	**0.46 (0.10–2.17)**	0.27	

4 Wei/2005

A prospective study of C-peptide, insulin-like growth factor-I, insulin-like growth factor binding protein-1, and the risk of colorectal cancer in women

US; 32826women,182CRC,350controls; follow up 10years; age30-55; C-peptide, ng/mL

nested case-cor; **RR and 95% CI of colorectal cancer according to quartiles of plasma levels of C-peptide, IGFBP-1, and HbA1c in the women**

Nurses' Health Study, 1989-2000

	Q1	Q2	Q3	Q4	p
C-peptide	0.9	1.4	2	3.6	
CRC					
case/control	35/87	50/86	54/89	43/88	
RR1	1	1.46 (0.86-2.45)	1.50 (0.88-2.57)	1.22 (0.70-2.13)	
RR2	1	1.46 (0.84-2.53)	1.41 (0.79-2.55)	**1.17 (0.63-2.20)**	0.94
colon					
case/control	23/70	41/65	42/71	34/62	
RR1	1	1.88 (1.04-3.42)	1.83 (0.96-3.48)	1.65 (0.88-3.09)	
RR2	1	1.88 (1.00-3.56)	1.85 (0.92-3.74)	1.76 (0.85-3.63)	0.38

1 RR from conditional logistic regression

2 RR from conditional logistic regression additionally adjusted for BMI, physical activity, pack-years smoked, and alcohol intake as continuous variables, family history of colorectal cancer, aspirin use, history of screening, menopausal status, and use of postmenopausal hormones

5 Jenab/2007

Serum C-peptide, IGFBP-1 and IGFBP-2 and risk of colon and rectal cancers in the European Prospective Investigation into Cancer and Nutrition

10 western European countries; 1078CRC,1078controls,520000cohort; C-peptide, ng/mL

nested case-cor; **ASSOCIATION OF SERUM C-PEPTIDE WITH CANCER RISK IN THE COLON, RECTUM AND COLON AND RECTUM COMBINED, BY FASTING STATU**

c-peptide	fasting and nonfasting combined		fasting subjects only			nonfasting subject		
	cases/control	crude OR	adjusted OR	**cases/control**	crude OR	adjusted OR	**cases/control**	crude OR	adjusted OR
colon									
1	104/121	1	1	27/32	1	1	77/89	1	1
2	139/150	1.08 (0.76–1.55)	1.05 (0.73–1.50)	40/41	1.15 (0.58–2.26)	1.20 (0.59–2.45)	99/109	1.06 (0.70–1.61)	1.04 (0.68–1.59)
3	120/136	1.07 (0.75–1.55)	1.06 (0.72–1.54)	32/38	0.99 (0.48–2.04)	0.98 (0.47–2.06)	88/98	1.10 (0.72–1.69)	1.10 (0.71–1.70)
4	143/136	1.29 (0.89–1.86)	1.17 (0.80–1.71)	38/36	1.27 (0.62–2.62)	1.22 (0.56–2.67)	105/100	1.30 (0.85–1.98)	1.19 (0.77–1.85)
5	168/131	1.67 (1.14–2.46)	1.48 (0.98–2.25)	41/31	1.66 (0.80–3.45)	1.58 (0.70–3.56)	127/100	1.66 (1.06–2.65)	1.49 (0.91–2.42)
p		<0.01	<0.01		0.18	0.49		0.01	0.01
rectum									
1	78/93	1	1	15/18	1	1	63/75	1	1
2	71/68	1.26 (0.80–1.99)	1.25 (0.79–1.99)	12/11	1.37 (0.46–4.10)	1.25 (0.41–3.83)	59/57	1.25 (0.75–2.06)	1.25 (0.75–2.09)
3	94/80	1.43 (0.93–1.20)	1.29 (0.82–2.04)	20/13	1.99 (0.60–5.72)	1.62 (0.49–5.39)	74/67	1.33 (0.83–2.15)	1.26 (0.76–2.08)
4	68/81	1.02 (0.65–1.20)	0.94 (0.59–1.51)	14/16	0.92 (0.30–2.80)	0.68 (0.20–2.31)	54/65	1.03 (0.63–1.68)	0.97 (0.58–1.63)
5	93/82	1.42 (0.90–2.25)	1.25 (0.76–2.03)	15/18	1.11 (0.38–3.25)	0.78 (0.23–2.58)	78/64	1.53 (0.92–2.55)	1.37 (0.80–2.36)
p		0.35	0.78		0.86	0.16		0.25	0.49
colorectum									
1	182/214	1	1	42/50	1	1	140/164	1	1
2	210/218	1.14 (0.87–1.51)	1.11 (0.84–1.47)	52/52	1.20 (0.68–2.12)	1.20 (0.67–2.16)	158/166	1.13 (0.82–1.55)	1.09 (0.79–1.51)
3	214/216	1.20 (0.91–1.59)	1.13 (0.85–1.51)	52/51	1.24 (0.69–1.21)	1.11 (0.61–2.03)	162/165	1.20 (0.87–1.55)	1.14 (0.82–1.58)
4	211/217	1.19 (0.90–1.58)	1.09 (0.81–1.46)	52/52	1.22 (0.67–2.21)	1.09 (0.57–2.05)	159/165	1.19 (0.86–1.63)	1.10 (0.79–1.53)
5	261/213	1.56 (1.16–2.09)	1.37 (1.00–1.88)	56/49	1.41 (0.78–2.55)	**1.22 (0.64–2.35)**	205/164	1.61 (1.15–2.26)	1.44 (1.00–2.06)
p		<0.01	0.03		0.31			0.01	0.02

fasting subjects	Q1	Q2	Q3	Q4	Q5	
	<2.2	2.2-2.8	2.8-3.2	3.2-3.8	>=3.8	ng/ml
non-fasting subj	Q1	Q2	Q3	Q4	Q5	
	<2.7	2.7-3.8	3.8-5	5-6.8	>=6.8	ng/ml

Values for Crude are OR (95%CI) derived from univariate models conditioned on the matching factors

Values for Adjusted are OR (95% CI) derived from univariate models conditioned on the matching factors and further adjusted for body mass index and physical activity.–

6 Otani/2007

Plasma C-peptide, insulin-like growth factor-I, insulin-like growth factor binding proteins and risk of colorectal cancer in a nested case-control study: the Japan public health center-based prospective study

Japan; C,750control,38373cohort; 11.5year follow up; C-peptide, ng/mL

nested case-cor; **ODDS RATIO (OR) AND 95% CONFIDENCE INTERVAL (CI) OF COLORECTAL CANCER FOR BASELINE CONCENTRATIONS OF PLASMA C-PEPTIDE, INSULIN-LIKE GROWTH FACTOR-I (IGF-I) AND INSULIN-LIKE GROWTH FACTOR BINDING PROTEINS**

	Q1	Q2	Q3	Q4	p
Colorectum					
Men					
c-peptide	1.1	1.9	3.3	5.6	
case/control	25/86	49/92	50/93	56/88	
OR	1	2.3 (1.2–4.5)	2.8 (1.3–6.1)	**3.2 (1.4–7.6)**	0.0072
women					
c-peptide	1.1	1.9	2.8	4.8	
case/control	51/80	32/77	46/93	46/88	
OR	1	0.71 (0.39–1.3)	0.75 (0.40–1.4)	**0.78 (0.38–1.6)**	
Colon					
Men	1	2.1 (0.96–4.6)	2.6 (1.0–6.3)	3.5 (1.2–10)	0.025
women	1	0.65 (0.29–1.4)	0.92 (0.41–2.0)	0.72 (0.28–1.8)	0.54
rectum					
Men	1	1.8 (0.40–8.0)	3.8 (0.83–18)	2.2 (0.47–10)	0.24
women	1	0.88 (0.34–2.3)	0.46 (0.14–1.5)	0.76 (0.23–2.5)	0.82

ORs estimated using matched pairs with adjustment for pack-years of smoking (continuous), alcohol consumption (g/week ethanol, continuous), body mass index (continuous), physical exercise (less than once a week, or once a week or more), family history of colorectal cancer and following plasma measurements mutually:

7 Stocks/2008

Components of the metabolic syndrome and colorectal cancer risk; a prospective study

Sweden; 306CRC,595contr; age50-60; C-peptide, ng/mL

nested case-cor; **Odds ratios for colorectal cancer by quartiles**

C-peptide ng/ml	Q1	Q2	Q3	Q4	p
fasting <4h	<2.6	2.6-3.7	3.7-5.2	>5.2	
fasting>4h	<1.5	1.5-1.9	1.9-2.5	>2.5	
cases/control	74/136	72/138	72/137	73/138	
OR	1	0.94 (0.63–1.40)	0.93 (0.62–1.39)	**0.94 (0.62–1.41)**	0.82

8 Nakajima/2010

Adipocytokines as new promising markers of colorectal tumors: adiponectin for colorectal adenoma, and resistin and visfatin for colorectal cancer

Japan; 115CRC,115contr; age,63.7CRC,63.5controls

case-control; **Univariate and multivariate analysis of patients with colorectal cancer and controls**

	Univariate		Multi	
	OR	P	OR	P
c-peptide	).711 (0.550–0.920	0.01	**0.983 (0.663–1.458)**	0.93

9 Wu/2011

Interactions between plasma levels of 25-hydroxyvitamin D, insulin-like growth factor (IGF)-1 and C-peptide with risk of colorectal cancer

US; male,499cases,992control; age40-75

nested case-cor; **Multivariable adjusted odds ratios (OR) of colorectal and colon cancer by median of plasma analyte level, HPFS and NHS combined**

	colorectal cancer		colon cancer		
c-peptide	low	high	low	high	
cases/control	197/455	277/460	140/337	211/339	Models for C-Peptide only included participants without self-reported diabetes mellitus.
OR	1	**1.37(1.05-1.78)**	1	1.58(1.16-2.16)	

total

	Study	Country	Design	Gender	Age(years)	cancer types and No. of cases/controls/cohort	CRC Diagnosis	Adjustment for covariates
1	Yamada et al.1998	Japan	case-control	F/M	34-79	CRC:129,control:258	histologically confirmed colorectal carcinoma in situ /do not penetrate beyond the muscularis mucosae/ with no history of IBD	sex,sex,BMI,alcohol consumption
2	Potter et al.1999	USA	nested case-control	F	50-74	CRC:79,control:158,cohort:121700	Review of histopathologic reports	age, sex, BMI, menopausal status, and fasting state
3	Schoen et al.1999	USA	cohort	F/M	72-94(mean)	CRC:102,cohort:5848	ICD-9 codes for colon(153.0-153.4 and 153.6-153.9) and rectal(154.0,154.1 and 154.8)	age, sex and physical activity
4	Kraaks et al.2000	USA	nested case-control	F	35-65	CRC:102,control:200,cohort:14275	Medical records reviewed to confirm pathologic diagnosis of cancer	age, menopausal status, day of menstrual cycle (for premenopausal women), and time of last food consumption and smoking status
5	Palmqvist et al.2003	Sweden	case-control	F/M	30-70	CC:110,RC:58,control:336	verified histologically by reviewing medical records.	sex, sex, BMI, smoking, IGFBP levels
6	Sayduh et al.2003	USA	case-control	F/M	>18	CC:132,RC41,control:346	ICD-9 codes for colon (153) and rectum (154); and confirmed by pathology report	age, sex, race, time since last meal, and date of blood draw
7	Khaw et al.2004	UK	cohort	F/M	45-79	CRC:97,cohort:9635	ICD-9 153-154.1 and 159	sex,BMI,smoking habit
8	Ma et al.2004	USA	nested case-control	M	40-84	CRC:176,control:294,cohort:14916	Medical records	age, smoking status, fasting status, BMI, alcohol consumption, vigorous exercise, and aspirin assignment
9	Stattin et al.2004	Norway	nested case-control	M	45(mean)	CC:191,RC:143,control:378,cohort:600000	linkage with the Norwegian cancer and all-cause mortality registries	Adjustment for testin by addina it as continuous variable to the model.
10	Lin et al.2005	USA	cohort	F	>=66	CRC:168,cohort:27110	Medical history	age, random treatment assignment, BMI, family history of CRC and colon polyps,physical activity, smoking status, red meat intake, alcohol consumption, total energy intake, multivitamin use, menopausal status, and baseline postmenopausal hormone use
11	Jee et al.2005	Korea	cohort	F/M	30-95	CRC:1667,cohort:707men,46861women	Korean National Cancer Registry and/or a hospital admission for cancer diagnosis	age, sex, BMI, smoking, and alcohol use
12	Wei et al.2005	USA	nested case-control	F	30-55	CRC:182,control:350,cohort:32826	Medical records	BMI, physical activity, pack-years smoked, and alcohol intake as continuous variables, family history of CRC, aspirin use, history of screening, menopausal status, and use of postmenopausal hormones
13	Chung et al.2006	Korea	case-control	F/M	CRC58.4,control58.7	CRC:105,control:105	histopathologic diagnosis of adenocarcinoma and subsite information were confirmed through colonoscopy or surgery	Adjusted for age, sex, BMI.TG,cholesterol
14	Lindlaug et al.2006	Finland	nested case-control	M	50-69	CRC:139,control:396,cohort:29633	Finnish Cancer Registry, medical records and ICD-9 153.0-153.4, 153.6-153.9 and 154.0-154.1	cigarette pack-years, body mass index, protein intake, fat intake, fiber intake, alcohol consumption, caloric intake, history of diabetes mellitus and occupational physical activity.
15	Rapp et al.2006	Austrian	cohort	F/M		CRC:677,cohort:6358Smen,7722Iwomen	histologically verified and according to ICD-9	age, smoking status, occupational group, and BMI
16	Jenab et al.2007	10 Europeanc	nested case-control	F/M	36.7-76.9	CRC:1078,control:1078,cohort:520000	record linkage with national cancer registries or health insurance records, contacts with caner and patholiov reaistries and active follow-us	Age, aender,BMI, physical activity, laboratory analysis and case-control status
17	Otani et al.2007	Japan	nested case-control	F/M	40-69	CRC:375,control:750,cohort:38373	pathologically confirmed as adenocarcinoma and ICD-O-3 for colon C180-C189 and rectum C199-C209	adjustment for pack-years of smoking, alcohol consumption, BMI, physical exercise, family history of colorectal cancer and following plasma measurements mutually
18	Stattin et al.2007	Sweden	cohort	F/M	46(mean)	CC:147,RC87,cohort:64587	NA	age, calendar year, smoking
19	Gunter et al.2008	USA	nested case-control	F	50-79	CRC:638,control:816,cohort:93676	ICD-9 153.0-153.4, 153.6-153.9 and 154.0-154.1	sex
20	Hjartaker et al.2008	Western coun	nested case-control	F/M	35-70	CRC:1329,control:1329,cohort:500000women,160000men	record linkage with regional cancer registries or health insurance records, contacts with caner and pathology registries and active follow-up	sex, gender, age at blood donation, time of the day at blood donation, follow-up time, fasting status and, in women, menopausal status and phase of the menstrual cycle for premenopausal women
21	Slocks et al.2008	Sweden	nested case-control	F/M	50-70	CRC:356,control:556,cohort:519452	medical records and pathology reports, ICD9 codes153.0 and 153.2-153.9 and ecrtum (19.9 and 20.9)	case-control status, sex, age, smoking status and fasting time before blood draw.
22	Slocks et al.2009	Norway, Austri	cohort	F/M	44.8(mean)	CC:2434,RC:1145,cohort:271626men,275816women	ICD 7	adjusted for baseline age, BMI, and smoking status, and RRs per 1 mmol/l were additionally adjusted for fasting time
23	Nakajima et al.2010	Japan	case-control	F/M	CRC:63.7,control:63.6	CRC:115,control:115	pathologically diagnosed with colorectal cancer by biopsy using colonoscopy	Age, aender, BMI, tumor stage,and tumor location
24	Yamamoto et al.2010	Japan	case-control	F/M	53.8(mean)	CRC:22,control:66	histologically confirmed carcinoma in situ or cancer invading within the submucosa	BMI, smoking and drinking
25	Slocks et al.2011	Norway	cohort	F/M	44(mean)	CRC:4686,cohort:578650	ICD-7 colon (153) and rectum (154)	adjusted for baseline age, birth year, smoking status, and quintiles of BMI
26	Wu et al.2011	USA	nested case-control	M	40-75	CRC:699,control:992	medical and pathology records	Age, gender, BMI, month of blood donation, smoking status, physical activity, intake of alcohol, methionine, folate, retinol, red and processed meat, calcium intake, family history of CRC, fasting status
27	Chen et al.2012	China	case-control	M	early cancer62.1 adva	CRC:165,control:102	pathologically diagnosed	sex, BMI, WHR, SBP, TG, fasting insulin, HOMA-IR, total adiponectin, HMW adiponectin, lifestyle characteristics, medications, family history of CRC and diabetes
28	Dankner et al.2012	Four region	cohort	F/M	51.8(mean)	CRC:44,cohort:1696	linkage of the GCH database with the Israel National Cancer Registry	Adjusted for age, sex, and ethnicity
29	Kabat et al.2012	UK	nested case-control	F	50-79	CRC:91,control:4321,cohort:4902	pathology reports, discharge summaries, operative and radiology reports and tumor registry abstracts	Adjusted for age, body mass index , alcohol intake, physical activity, family history of colorectal cancer, ethnicity, and participation in the OS or treatment arm of each clinical trial.
30	Ulbersdine et al.2012	USA	nested case-control	F/M	45-75	CRC:1964,control:2587,cohort:210000	ICD-O-3 colon(C18.0-18.9) and rectum(20.9)	Adjusted for age, sex, race/ethnicity, history of colorectal polyp, family history of colorectal cancer, BMI,physical activity, processed meat intake, pack-years of smoking, alcohol consumption, and mutual adjustment for IGF-I and IGFBP-3
31	Wolaningeh et al.2012	Sweden	cohort	F/M	58.2(mean)	CRC:1248,cohort:540369	Swedish Cancer Registry and the Cause of Death Register	age, gender, BMI, smoking status, calendar, SES, and fasting status
32	Hakozaki et al.2013	Japan	case-control	F/M	65(mean)	CRC:29,control:440	advanced colorectal cancer and not as a cancer lesion penetrating beyond the lamina propria mucosae	age, gender ,cholesterol, triglyceride, uric acid
33	Parekh et al.2013	USA	cohort	F/M	66.8(mean)	CRC:136,cohort:6615	pathologic reports and ICD codes	age, sex, alcohol, smoking, BMI, smoking status
34	Scanlan et al.2014	Turkey	case-control	F/M	CRC58.control62.8	CRC:21,control:20	total colonoscopy	sex, BMI, VFA, serum IGF-1, fastina insulin and alucose
35	Shin et al.2014	Korea	cohort	F/M	42(mean)	CRC:320,cohort:175677	positive report from National Cancer Registry or hospital admission for a cancer diagnosis. ICD-10 CRC(C18-C20)	age, sex, body mass index, smoking, alcohol drinking, and regular exercise.

	Study	cases	controls	cohort
1	Yamada et al.1998	139	528	0
2	Potter et al.1999	79	158	121700
3	Schoen et al.1999	102	0	5848
4	Kraaks et al.2000	102	200	14275
5	Palmqvist et al.2003	168	336	0
6	Sayduh et al.2003	173	346	0
7	Khaw et al.2004	97	0	9635
8	Ma et al.2004	176	294	14916
9	Stattin et al.2004	378	378	600000
10	Lin et al.2005	168	0	27110
11	Jee et al.2005	3352	0	1296385
12	Wei et al.2005	182	350	32826
13	Chung et al.2006	105	105	0
14	Lindlaug et al.2006	139	396	29633
15	Rapp et al.2006	677	0	143913
16	Jenab et al.2007	1078	1078	520000
17	Otani et al.2007	375	750	38373
18	Stattin et al.2007	234	0	64587
19	Gunter et al.2008	638	816	93676
20	Rinaldi et al.2008	1026	1026	520000
21	Slocks et al.2008	356	595	104461
22	Slocks et al.2009	3779	0	549644
23	Nakajima et al.2010	115	115	0
24	Yamamoto et al.2010	22	66	0
25	Slocks et al.2011	4686	0	578650
26	Wu et al.2011	699	992	0
27	Chen et al.2012	165	102	0
28	Dankner et al.2012	44	0	1696
29	Kabat et al.2012	91	4321	4902
30	Ulbersdine et al.2012	1964	2587	210000
31	Wolaningeh et al.2012	4252	0	540369
32	Hakozaki et al.2013	29	440	0
33	Parekh et al.2013	136	0	6615
34	Scanlan et al.2014	21	20	0
35	Shin et al.2014	320	0	175677
	Total	25566	16510	5706361