Table S1. Median baseline (1989) metabolic, inflammatory and dietary measures in colorectal cancer cases and matched controls (193 pairs) in CLUE II.

	Overall			Men			Women		
	Cases	Controls	p*	Cases	Controls	p*	Cases	Controls	p*
CRP (mg/L)	2.4	1.8	0.2	2.7	1.8	0.7	2.1	1.8	0.1
IL-6 (pg/mL)	2.3	1.8	0.2	2.6	2.2	0.9	2.1	1.6	0.01
HbA1c (%)	5.6	5.5	0.4	5.6	5.5	0.9	5.7	5.5	0.1
IGFBP1 (ng/mL)	12.4	19.5	0.4	7.8	10.6	0.9	21.3	25.7	0.2
Insulin (pmol/L)	13.8	13.5	0.7	14.7	15.6	0.6	13	11.9	0.9
TCH (mg/dL)	213	219	0.3	199	211	0.05	220	228	0.7
HDL (mg/dL)	43.2	43.8	0.8	39.3	35.7	0.2	46.8	47.3	0.5
Triglycerides (mg/dL)	145	146	0.6	149.5	161	0.5	137	144	0.1
Calcium (mg)**	715.3	840.8	0.4	821.3	882.6	0.2	656.7	807.9	0.9
Folate (μg)**	308.4	295.7	0.5	331.5	311.7	0.4	297.4	263	0.8
Fiber (g)**	11	12.2	0.5	11.7	12.8	0.9	10.6	12	0.5
Saturated fat (g)**	23.4	23	0.6	32.1	27.1	0.3	17.5	20.1	0.1
Calories (kcal)**	1571.8	1623.1	0.3	1890.3	1803.9	0.8	1330	1415.9	0.2
Red meat (g)**	69.3	67.8	0.9	114.3	83.6	0.6	59.4	50.2	0.9
Alcohol (g)**	4.7	5.9	0.6	7.2	6.3	0.8	4.7	2	0.4

*, from generalized linear model; TCH – total cholesterol; HDL – high-density cholesterol; intake of dietary factors was assessed through FFQ that was available for 105 (54%) and 128 (66%) of CRC cases and controls.

Table S2. Age and sex-adjusted Spearman correlation coefficients* of leptin, adiponectin and sTNFR2 concentrations with adiposity, inflammatory and metabolic markers in 193 controls in CLUE II

	Adiponectin						Leptin						sTNFR2					
	All	p	Men	p	Women	p	All	p	Men	p	Women	p	All	p	Men	p	Women	p
BMI	-0.28	<0.001	-0.25	0.02	-0.27	0.005	0.65	<0.001	0.70	<0.001	0.62	<0.001	0.21	0.004	0.10	0.1	0.22	0.03
Adult weight gain	-0.25	<0.001	-0.15	0.2	-0.29	0.003	0.60	<0.001	0.61	<0.001	0.60	<0.001	0.30	<0.001	0.42	<0.001	0.21	0.04
CRP	-0.23	0.004	-0.14	0.2	-0.31	0.004	0.29	<0.001	0.23	0.1	0.39	<0.001	0.29	<0.001	0.37	0.002	0.26	0.02
IL-6	-0.17	0.03	-0.01	0.9	-0.25	0.02	0.19	0.02	0.13	0.3	0.25	0.02	0.20	0.01	0.24	0.05	0.19	0.1
Insulin	-0.23	0.004	-0.21	0.1	-0.28	0.01	0.25	0.001	0.32	0.01	0.25	0.02	0.10	0.2	0.20	0.1	0.02	0.9
IGFBP-1	0.31	<0.001	0.26	0.03	0.34	0.001	-0.41	<0.001	-0.44	<0.001	-0.37	<0.001	-0.11	0.2	-0.03	0.8	-0.16	0.1
HbA1c	-0.08	0.3	0.04	0.8	-0.07	0.5	0.02	0.8	0.17	0.2	-0.07	0.5	0.02	0.8	-0.04	0.8	0.07	0.5
TCH	0.09	0.2	0.13	0.2	0.07	0.5	0.14	0.1	0.15	0.2	0.08	0.4	-0.09	0.2	-0.25	0.02	0.05	0.6
HDL	0.39	<0.001	0.33	0.01	0.41	<0.001	-0.24	0.004	-0.20	0.1	-0.30	0.01	-0.21	0.01	-0.31	0.01	-0.20	0.1
Triglycerides	-0.23	0.004	-0.28	0.02	-0.19	0.1	0.27	0.001	0.34	0.004	0.25	0.02	0.17	0.04	0.17	0.2	0.18	0.1
Leptin	-0.21	0.003	-0.19	0.1	-0.23	0.02	-						0.30	<0.001	0.16	0.1	0.43	<0.001
Adiponectin	-						-						0.01	0.9	-0.09	0.4	0.06	0.5

*, age and sex were adjusted for all participants; age was adjusted for analysis separate in men and women. TCH – total cholesterol; HDL – high-density cholesterol

Table S3. Odds ratio of colorectal cancer in men and women by sex-specific quartiles of concentration of leptin, adiponectin, and sTNFR2 in the CLUE II cohort accounting for BMI, diet, and other risk factors.

	Case/ Control	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Men													
Adiponectin													
1st Quartile	33/22	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref
2nd Quartile	14/22	0.46	0.19-1.09	0.48	0.19-1.24	0.47	0.15-1.48	0.49	0.19-1.27	0.43	0.15-1.28	0.43	0.12-1.62
3rd Quartile	14/24	0.45	0.19-1.03	0.45	0.18-1.11	0.30	0.09-0.99	0.50	0.20-1.24	0.40	0.15-1.08	0.25	0.07-0.96
4th Quartile	28/21	0.99	0.43-2.29	1.15	0.45-2.94	1.01	0.33-3.16	0.79	0.31-2.01	0.72	0.25-2.07	0.57	0.15-2.11
Per 50th percentile*		0.78	0.28-2.21	0.97	0.31-3.07	0.87	0.21-3.60	0.63	0.20-1.99	0.55	0.15-2.20	0.43	0.09-2.20
p-trend			0.6		0.9		0.9		0.4		0.4		0.3
Leptin													
1st Quartile	26/23	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref
2nd Quartile	11/21	0.40	0.14-1.12	0.33	0.11-1.02	0.37	0.10-1.38	0.45	0.14-1.43	0.37	0.10-1.33	0.39	0.08-1.89
3rd Quartile	31/23	1.19	0.52-2.75	0.90	0.33-2.45	0.71	0.20-2.54	1.50	0.60-3.76	1.25	0.42-3.76	1.09	0.26-4.53
4th Quartile	21/22	0.81	0.34-1.90	0.67	0.20-2.19	0.67	0.16-2.80	0.88	0.34-2.25	0.60	0.15-2.39	0.89	0.17-4.69
Per 50th percentile*		1.18	0.25-5.65	0.85	0.10-7.49	0.74	0.05-10.64	1.48	0.26-8.34	1.00	0.08-11.91	1.67	0.08-34.74
p-trend			0.8		0.9		0.8		0.7		0.9		0.7
sTNFR2													
1st Quartile	16/23	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref
2nd Quartile	14/21	1.07	0.38-3.03	1.16	0.39-3.43	0.70	0.19-2.60	1.08	0.34-3.42	1.34	0.38-4.74	0.74	0.16-3.29
3rd Quartile	19/24	1.40	0.51-3.85	1.68	0.57-4.88	1.03	0.29-3.72	1.21	0.40-3.66	1.62	0.49-5.34	0.95	0.22-4.08
4th Quartile	40/21	3.06	1.19-7.88	3.66	1.30-10.33	2.26	0.66-7.77	3.14	1.11-8.86	4.76	1.45-15.64	2.83	0.67-11.93
Per 50th percentile*		1.37	1.08-1.73	1.42	1.10-1.84	1.28	0.95-1.73	1.38	1.07-1.78	1.50	1.12-2.02	1.34	0.94-1.91
p-trend			0.01		0.01		0.1		0.01		0.01		0.1
Women													
Adiponectin													
1st Quartile	32/26	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref
2nd Quartile	24/27	0.68	0.31-1.51	0.72	0.29-1.77	0.74	0.29-1.90	0.70	0.31-1.60	0.74	0.29-1.89	0.81	0.30-2.20
3rd Quartile	35/25	1.02	0.51-2.02	0.90	0.41-2.01	0.98	0.42-2.26	1.02	0.49-2.13	0.86	0.37-2.01	0.98	0.41-2.39
4th Quartile	13/26	0.34	0.13-0.88	0.33	0.11-1.02	0.31	0.09-1.00	0.34	0.12-0.94	0.32	0.10-1.06	0.31	0.09-1.11
Per 50th percentile*		0.14	0.01-2.09	0.10	0.00-2.73	0.10	0.00-3.17	0.14	0.01-2.71	0.08	0.00-2.75	0.10	0.00-3.96
p-trend			0.2		0.2		0.2		0.2		0.2		0.3
Leptin													
1st Quartile	22/27	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref
2nd Quartile	29/25	1.45	0.67-3.14	1.17	0.49-2.80	0.89	0.35-2.24	1.49	0.66-3.36	1.30	0.53-3.21	1.00	0.38-2.60
3rd Quartile	31/26	1.44	0.69-3.02	1.18	0.47-2.98	0.89	0.32-2.46	1.14	0.50-2.59	1.05	0.39-2.83	0.82	0.27-2.44
4th Quartile	22/26	1.05	0.48-2.26	0.82	0.28-2.42	0.52	0.15-1.84	0.98	0.42-2.29	0.83	0.26-2.59	0.55	0.15-2.04
Per 50th percentile*		1.27	0.03-54.07	0.45	0.00-105.79	0.06	0.00-32.22	0.60	0.01-40.36	0.35	0.00-114.76	0.05	0.00-38.70
p-trend			0.9		0.8		0.4		0.8		0.7		0.4
sTNFR2													
1st Quartile	24/27	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref
2nd Quartile	26/25	1.18	0.54-2.57	1.50	0.62-3.61	1.23	0.48-3.15	1.13	0.50-2.56	1.47	0.60-3.63	1.22	0.45-3.37
3rd Quartile	29/26	1.29	0.57-2.97	1.35	0.50-3.63	1.51	0.53-4.34	1.21	0.49-2.96	1.34	0.48-3.75	1.55	0.50-4.78
4th Quartile	25/26	1.12	0.48-2.64	1.16	0.42-3.19	1.04	0.34-3.19	1.15	0.45-2.90	1.30	0.45-3.72	1.31	0.39-4.36
Per 50th percentile*		1.04	0.77-1.42	1.03	0.71-1.49	1.03	0.69-1.53	1.05	0.75-1.47	1.08	0.73-1.58	1.12	0.73-1.72
p-trend			0.8		0.9		0.9		0.8		0.7		0.6

Model 1 – Matched model (matched for age, race, date of blood draw and time since last meal)
Model 2 – Model 1 plus mutually adjusted for BMI (continuous), smoking (never, current, former), alcohol (continuous), NSAID use, diabetic medication use, hormone use, and CRC family history
Model 3 – Model 2 plus adjusted for intake of calcium (continuous), folate (continuous), fiber (continuous), red meat (continuous), saturated fat (continuous), calories (continuous), and missing diet indicator
Model 4 – Model 1 plus mutually adjusted for leptin, adiponectin, and sTNFR2
Model 5 – Model 4 plus adjusted for BMI (continuous), smoking (never, current, former), alcohol (continuous), NSAID use, diabetic medication use, hormone use, and family history
Model 6 – Model 5 plus adjusted for intake of calcium (continuous), folate (continuous), fiber (continuous), red meat (continuous), saturated fat (continuous), calories (continuous), and missing diet indicator
*The 25th to 75th percentile delta is based on the biomarker concentration distribution for men and women combined.
**The 25th to 75th percentile delta is based on the biomarker concentration distribution separately in men and women.

Table S4. Odds ratio of adenoma in men and women by sex-specific quartiles of concentration of leptin, adiponectin, and sTNFR2 in CLUE II accounting for BMI, diet, and other risk factors.

	Case/ Control	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Men													
Adiponectin													
1st Quartile	14/16	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref
2nd Quartile	15/17	1.02	0.36-2.88	1.10	0.36-3.41	0.74	0.18-3.09	1.11	0.38-3.23	1.12	0.34-3.62	0.78	0.18-3.50
3rd Quartile	11/17	0.79	0.24-2.56	0.91	0.26-3.21	0.86	0.19-3.98	0.85	0.25-2.93	0.85	0.22-3.28	0.98	0.18-5.31
4th Quartile	27/17	1.96	0.66-5.82	2.88	0.81-10.21	2.62	0.62-11.12	2.39	0.75-7.64	3.01	0.82-11.09	2.52	0.56-11.40
Per 50th percentile*		2.36	0.65-8.65	3.73	0.83-16.77	4.72	0.88-25.17	2.78	0.71-10.96	3.67	0.80-16.89	4.33	0.77-24.25
p-trend			0.2		0.1		0.1		0.1		0.1		0.1
Leptin													
1st Quartile	12/16	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref
2nd Quartile	16/17	1.25	0.49-3.22	1.16	0.41-3.28	2.05	0.59-7.17	1.12	0.39-3.18	0.88	0.27-2.86	1.58	0.35-7.06
3rd Quartile	23/17	1.84	0.68-4.97	1.95	0.60-6.30	3.99	0.91-17.44	2.09	0.72-6.05	1.70	0.48-6.06	3.33	0.66-16.79
4th Quartile	16/17	1.26	0.46-3.51	1.28	0.36-4.53	2.51	0.50-12.72	1.44	0.46-4.45	1.03	0.25-4.23	2.04	0.33-12.49
Per 50th percentile*		2.09	0.23-18.55	1.53	0.31-7.63	3.12	0.42-23.00	3.26	0.30-35.79	1.33	0.23-7.66	2.64	0.31-22.19
p-trend			0.5		0.6		0.3		0.3		0.8		0.4
sTNFR2													
1st Quartile	16/16	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref
2nd Quartile	18/17	0.97	0.36-2.64	1.09	0.39-3.08	1.45	0.45-4.70	0.85	0.29-2.46	0.99	0.32-3.11	1.42	0.38-5.39
3rd Quartile	21/18	1.12	0.41-3.07	1.27	0.45-3.61	1.81	0.56-5.86	0.78	0.26-2.40	0.89	0.28-2.89	1.45	0.38-5.50
4th Quartile	12/16	0.69	0.21-2.27	0.74	0.21-2.57	1.02	0.26-3.97	0.53	0.14-1.98	0.64	0.16-2.48	0.90	0.20-4.01
Per 50th percentile*		0.91	0.60-1.37	0.79	0.18-3.44	1.09	0.22-5.31	0.81	0.51-1.27	0.56	0.11-2.86	0.81	0.14-4.58
p-trend			0.6		0.7		0.9		0.9		0.5		0.8
Women													
Adiponectin													
1st Quartile	14/16	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref
2nd Quartile	15/16	1.14	0.37-3.50	1.33	0.40-4.49	1.66	0.33-8.26	1.08	0.30-3.81	1.15	0.29-4.51	1.09	0.15-8.03
3rd Quartile	24/16	1.66	0.64-4.30	1.77	0.60-5.21	2.90	0.77-10.96	1.62	0.55-4.77	1.56	0.46-5.37	2.44	0.51-11.70
4th Quartile	11/16	0.71	0.24-2.13	0.74	0.22-2.55	0.65	0.14-3.01	0.57	0.16-1.99	0.56	0.14-2.25	0.40	0.06-2.77
Per 50th percentile*		1.00	0.05-22.09	0.94	0.03-30.45	2.00	0.03-147.29	0.58	0.02-18.92	0.41	0.01-20.25	0.95	0.01158.27
p-trend			0.9		0.9		0.8		0.8		0.7		0.9
Leptin													
1st Quartile	20/16	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref
2nd Quartile	12/16	0.58	0.21-1.62	0.44	0.13-1.53	0.27	0.06-1.26	0.53	0.17-1.69	0.34	0.09-1.36	0.21	0.04-1.23
3rd Quartile	18/16	0.87	0.31-2.40	0.76	0.22-2.64	0.73	0.15-3.57	0.74	0.22-2.48	0.59	0.13-2.66	0.60	0.07-5.00
4th Quartile	14/16	0.66	0.22-1.94	0.53	0.11-2.50	0.41	0.06-2.61	0.49	0.13-1.84	0.37	0.06-2.36	0.27	0.02-3.30
Per 50th percentile*		0.17	0.00-130.66	0.29	0.00-34.35	0.26	0.00-70.21	0.03	0.00-89.99	0.09	0.00-28.17	0.06	0.00-112.70
p-trend			0.6		0.6		0.6		0.4		0.4		0.5
sTNFR2													
1st Quartile	13/16	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref	1	Ref
2nd Quartile	17/16	1.47	0.43-5.04	0.72	0.17-3.09	0.78	0.12-5.22	1.70	0.44-6.57	0.75	0.15-3.75	0.82	0.08-8.12
3rd Quartile	15/16	1.33	0.39-4.55	0.78	0.19-3.16	0.66	0.11-3.99	1.82	0.42-7.88	1.05	0.20-5.53	0.82	0.08-9.02
4th Quartile	19/16	1.59	0.52-4.84	1.01	0.28-3.61	0.97	0.22-4.30	2.03	0.53-7.75	1.26	0.26-6.09	1.03	0.15-6.91
Per 50th percentile*		1.10	0.84-1.44	1.65	0.04-68.80	1.16	0.02-79.62	1.17	0.84-1.63	3.87	0.03-450.26	1.39	0.00-421.29
p-trend			0.5		0.8		0.9		0.9		0.6		0.9

Model 1 – Matched model (matched for age, race, date of blood draw and time since last meal)
Model 2 – Model 1 plus adjusted for BMI (continuous), smoking (never, current, former), alcohol (continuous), hormone use
Model 3 – Model 2 plus adjusted for intake of calcium (continuous), folate (continuous), fiber (continuous), red meat (continuous), saturated fat (continuous), calories (continuous), and missing diet indicator
Model 4 – Model 1 plus adjusted for leptin, adiponectin, and sTNF-R2
Model 5 – Model 4 plus adjusted for BMI (continuous), smoking (never, current, former), alcohol (continuous), hormone use,
Model 6 – Model 5 plus adjusted for intake of calcium (continuous), folate (continuous), fiber (continuous), red meat (continuous), saturated fat (continuous), calories (continuous), and missing diet indicator
*The 25th to 75th percentile delta is based on the biomarker concentration distribution for men and women combined.
**The 25th to 75th percentile delta is based on the biomarker concentration distribution separately in men and women.