European Journal of Cancer (2013) 49, 3526–3536

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Adult weight change and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition ☆

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Available online 15 July 2013

☆ *Funding/support:* The work described in the paper was carried out with the financial support of the 'Europe Against Cancer' Programme of the European Commission (SANCO); Deutsche Krebshilfe; German Cancer Research Center; German Federal Ministry of Education and Research; Danish Cancer Society; Cancer Research UK; Medical Research Council, UK; the Stroke Association, UK; British Heart Foundation; Department of Health, UK; Food Standards Agency, UK; the Wellcome Trust, UK; Hellenic Health Foundation, Athens, Greece; Italian Association for Research on Cancer; Italian National Research Council; Swedish Cancer Society; Swedish Scientific Council; and Regional Government of Skåne, Sweden.

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0959-8049/$ - see front matter
http://dx.doi.org/10.1016/j.ejca.2013.06.021

KEYWORDS
Body weight change
Colorectal neoplasms
Abdominal obesity
Cancer prevention

Abstract ***Aim:*** Weight change during adult life may reflect metabolic changes and influence colorectal cancer (CRC) development, but such role is not well established. We aimed to explore the association between adult weight change (from age 20 to 50) and CRC risk. In particular, we investigated differences according to colon and rectal cancer, sex and measures of attained adiposity.
Methods: We included 201,696 participants from six participating countries in the European Prospective Investigation into Cancer and Nutrition (1992–2010). During a mean follow-up of 11.2 years 2384 (1194 in men and 1190 in women) incident CRC cases occurred. Cox proportional hazard models adjusted for body mass index at age 20 and lifestyle factors at study recruitment were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).
Results: After multivariable adjustment, each kg of weight gained annually from age 20 to 50 was associated with a 60% higher risk of colon cancer (95% CI 1.20–2.09), but not rectal cancer (HR 1.13, 95% CI 0.79–1.62, $P_{\text{interaction}} = 0.04$). The higher risk of colon cancer was restricted to people with high attained waist circumference at age 50 (HR 1.82, 95%CI 1.14–2.91, $P_{\text{interaction}} = 0.02$). Results were not different in men and women ($P_{\text{interaction}} = 0.81$).
Conclusion(s): Adult weight gain, as reflected by attained abdominal obesity at age 50, increases colon cancer risk in both men and women. These data underline the importance of weight management and metabolic health maintenance in early adult life years for colon cancer prevention.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer in men (663,000 cases, 10.0% of the total) and the second in women (570,000 cases, 9.4% of the total) worldwide and prevention strategies for reducing cancer-associated burden are highly demanded.[1] Excess body weight has been identified as one of the modifiable lifestyle factors convincingly related to CRC risk.[2] However, an important question still to be answered is whether fluctuations in weight over time may also contribute to CRC risk. Weight change in different life periods can be regarded as a dynamic measure reflecting different health outcomes. History of weight gain in middle life may be indicative of the formation of metabolic processes or diet-lifestyle characteristics that are not reflected adequately by a static measure of body fatness like body mass index (BMI).[3] Middle life weight gain, even among those with initially healthy weight, has been related to a higher chronic disease risk and a reduced probability of healthy survival in older ages.[4] Since the year 2000, when the International Agency for Research on Cancer judged that evidence in support of the association between weight change and risk of CRC is limited,[5] a number of prospective cohort[6–9] and case-control studies[10–13] have explored these associations. However, the evidence remains inconclusive about whether associations may be different by colon and rectal cancer, sex and measures of attained adiposity. Current research indicates that the relation between obesity and CRC incidence is stronger for cancer of the colon than cancer of the rectum[14]; but it is not clear if this is true also with regard to weight change, as most of the studies to date have been of small sample size and did not report results by cancer site. Also, studies observed these associations to be present either in men only[18,22,25] or in women[15,16]; while the few studies combining data for men and women did not evaluate whether differences by sex were statistically significant. Finally, the potential influence of body size at young and late adult age on the association between weight change in middle life and CRC risk has not been sufficiently evaluated. Some studies have questioned whether weight change may be associated with disease incidence beyond its effect on attained adiposity.[17] In particular, it is of interest to explore whether the associations may be modified by attained abdominal obesity as measured by waist circumference (WC) which is more closely related to metabolic changes compared to general obesity as determined by BMI.[18] To help clarify this evidence, we prospectively investigated the association between adult weight change (from age 20 to 50) and CRC risk in a large prospective study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

2. Methods

2.1. Study population and collection of data

EPIC is a large prospective cohort study with approximately 520,000 participants enrolled between 1992 and 1998 from 23 centres in 10 European countries. The present analysis is based on participant data from study centres in Denmark, Germany (Potsdam), Greece, Italy (Naples,Varese), Sweden (Malmö) and the United Kingdom, with available information on recalled body

weight at age 20 years and measured anthropometric characteristics at study enrolment. After excluding participants with prevalent cancer, those with missing questionnaire data ($n = 252{,}623$); as well as those with missing data on measured anthropometric characteristics ($n = 92{,}011$), the study population eligible for the present analysis comprised of 74,091 men and 127,605 women. The follow-up was based on population cancer registries or a combination of methods including health insurance records, cancer and pathology registries and active follow-up through study subjects and their next-of-kin. The 10th Revision of the International Classification of Diseases (ICD) for injuries and causes of death was used for coding cancer incidence.

2.2. Assessment of weight change

We used two approaches to model adult weight change: as an absolute measure of total weight change and as an annual estimate per year of study participation. The absolute weight change was defined as the difference between measured weight at study recruitment at average age 50 and recalled weight at age 20 years as reported in baseline questionnaires, as described previously by Lahmann et al.[19] Based on this variable, weight change categories were defined as follows: –2 and +2 kg as the referent category (stable weight); more than –2 kg as weight loss; and more than +2 kg as weight gain. Five weight change categories were further defined (2.1–5.0, 5.1–10.0, 10.1–15.0, 15.1–20.0, >20 kg) to be comparable with those used in previous studies. Because study participation time may influence total absolute weight change such that participants with longer time may have larger absolute change compared with participants with shorter time, and weight change may have a different effect than total change, average yearly weight variable was additionally computed. Annual weight change (kilograms per year) was computed as the difference between measured weight at recruitment and recalled weight at age 20, divided by time between age at recalled weight and measured weight at study recruitment. Annual weight change is a continuous variable that can be interpreted either as the mean yearly weight change (kg/y) between baseline and first follow up, or as the slope of a subject's weight trajectory throughout that period.[20] Positive values will reflect weight gain, whereas negative values will indicate weight loss. In other terms, absolute weight change equals multiplied annual weight change by the number of years from age 20 to study recruitment.

2.3. Statistical analysis

Cox proportional hazard regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of CRC incidence for each weight change category. Age was used as the underlying (primary dependent) time variable in the counting process formulation, with entry time defined as the subject's age at recruitment, and exit time defined as the subject's age at cancer diagnosis or censoring date. The crude model was stratified by age at recruitment, study centre and sex (in analyses including all participants). The multivariable-adjusted model was adjusted for weight at age 20 (kg) and CRC risk factors, including smoking status, education, alcohol, physical activity, red and processed meat, fish and shellfish, fruits and vegetables, fibre, WC and BMI at age 50. In this analysis, missing dietary data ($n = 438$) were substituted with sex-specific median intakes in cases and controls. Trend tests were calculated on the basis of category-based scores, assigning a score from 1 to 7 to an individual according to absolute weight change categories. These associations were also examined continuously after including annual weight change (kg per year) in the model as an exposure variable. We also explored associations according to categories of annual weight change (<0.1, 0.1–0.3, 0.3–0.5, 0.5–1, >1 kg per year). Using the category <0.1 kg per year as a reference category, we calculated the hazard risks of CRC, colon and rectal cancer in men and women, associated with each of these categories of annual weight change. We tested for linear trend in these associations by assigning sex-specific median values according to annual weight change categories. Restricted cubic spline regression was used to investigate whether the association between weight change per year and risk of CRC, colon and rectal cancer in the multivariable-adjusted model was linear. Models were fitted with 4 knots (5th, 25th, 75th, 95th percentile) of the weight change variable and non-linearity was evaluated with a Wald chi-square test.[21]

Using annual weight change as an exposure variable, stratified analysis was performed across categories of BMI at age 20, BMI and WC at study recruitment; in women by menopausal status (pre-menopausal/post-menopausal) and in postmenopausal by hormonal replacement therapy use (yes/no). Effect modification on the multiplicative scale by cancer sub-site and sex, as well as by factors that may be relevant for CRC risk was tested by using with the likelihood-ratio test comparing regression models with and without interaction terms.[22] Main analyses were repeated excluding cases diagnosed with cancer during the first 2 years of follow-up to eliminate the possibility that the observed relationships were distorted by pre-existing disease. All P-values presented were two tailed, and $P < 0.05$ was considered statistically significant. All analyses were performed using SAS Enterprise Guide version 4.3 (SAS Institute, Inc., Cary, North Carolina, United States of America [USA]).

3. Results

During the follow-up period between 1992 and 2010, over an average of 11.2 ± 2.5 follow-up years, 2384 incident CRC cancer cases (1194 in men and 1190 in women) were identified. The average age at study recruitment was 54.5 ± 10.0 in men and 51.2 ± 11.5 in women. Baseline characteristics and details of established risk factors for CRC across weight change categories are shown in Table 1. Men and women who gained >20 kg weight had higher WC, were less educated, tending to be never or former smokers and eat more red and processed meat and less fibre, compared to the stable weight people.

In multivariable-adjusted Cox proportional hazard regression, annual weight change was statistically significantly associated with risk of CRC (Table 2). This association was present for colon cancer (HR 1.60, 95% CI 1.20–2.09, Table 3), but not for rectal cancer (HR 1.13, 95% CI 0.79–1.62, $P_{\text{interaction}} = 0.04$, Table 4). Relative to people who had an annual weight change of <0.1 kg per year, the HR-s for people with 0.1–0.3, 0.3–0.5, 0.5–1 and >1 kg of weight gain per year were as follows, 1.01 (95% CI 0.83–1.24), 1.21 (95% CI 0.98–1.50), 1.32 (95% CI 1.05–1.65) and 2.05 (95% CI 1.37–3.07), respectively; $P_{\text{trend}} = 0.003$. Overall, people who gained >20 kg of weight since age 20 had a 38% higher risk of colon cancer compared to those whose weight remained stable ($P_{\text{trend}} = 0.01$, Table 3). There was no evidence for a non-linear shape of the association between weight change and risk of CRC ($P_{\text{non-linearity}} = 0.99$), colon cancer ($P_{\text{non-linearity}} = 0.40$) and rectal cancer ($P_{\text{non-linearity}} = 0.08$), as assessed by cubic spline regression.

For colon cancer, the multivariable-adjusted HR associated with each kg of weight change annually from age 20 to 50 years was 1.42 (95% CI 0.96–2.11) in men and 1.82 (95% CI 1.24–2.69) in women (Table 3). The differences by sex were not statistically significant ($P_{\text{interaction}} = 0.81$). In men, adjustment for individual risk factors of colon cancer slightly attenuated the risk estimates and this effect was partly accounted by fibre intake. Thus, the multivariable HR of colon cancer without fibre was 1.53 (95% CI 1.03–2.28); whereas after including fibre it was 1.42 (95% CI 0.96–2.11).

When in additional analyses the multivariable-adjusted model for colon cancer was also adjusted for WC at age 50, the association in all participants was no longer statistically significant (HR 1.33, 95% CI 0.83–2.14). Similar adjustment for BMI at age 50 did not appreciably change risk estimates (HR 1.84, 95% CI 1.05–3.22). Annual weight change was associated with colon cancer risk in the group with high WC (multivariable-adjusted HR 1.82, 95% CI 1.14–2.91); whereas no association was seen in the group with low WC (HR 1.03, 95% CI 0.57–1.58, $P_{\text{interaction}} = 0.02$). No statistically significant interaction was seen by BMI at age 20 and BMI at age 50 (Table 5). In women, annual weight change was associated with colon cancer in premenopausal women (multivariable-adjusted HR 10.9, 95% CI 1.46–82.5), whereas no significant association was observed in postmenopausal women (HR 1.31, 95% CI 0.77–2.23; however, these differences were not statistically significant ($P_{\text{interaction by menopausal status}} = 0.22$). No substantial differences in the associations were seen by hormonal replacement therapy in postmenopausal women (Table 1 Supplement). Additional analyses excluding cases incident during the first 2 years of follow-up ($n = 262$) did not substantially change the HRs. For example, the HR for CRC risk associated with each kg of weight change annually from age 20 to 50 years was 1.30 (95% CI 1.05–1.60).

4. Discussion

In this large prospective cohort study, weight change in middle life years (from age 20 to 50) was associated with higher risk of colon cancer in both men and women, but not with rectal cancer, independent of weight at age 20 and other established CRC risk factors. These associations were present only in the group of people with high attained WC at age 50 suggesting that it is particularly fat accumulation in the abdominal area that is important for the risk of colon cancer.

We were particularly interested in exploring the effect of long-term weight change from early to middle adulthood on one side because of the aetiological plausibility that metabolic changes occurring on the long run in adult life may influence CRC development; and on the other side because of the stronger potential for early cancer prevention at younger ages. Direct comparison with previous studies is somewhat difficult, since definitions of weight change differ in terms of assessment (prospective or retrospective), life periods considered or categories used to quantify change. Nevertheless, consistent with our study, most prior studies have used recalled weight between ages 18 and 25 years as the baseline weight.[6–8,10,23–26]

We observed an increased risk associated with weight change for colon cancer but not for rectal cancer. Previous evidence for these associations by colon and rectal cancer is limited and inconsistent.[9,10,27] A more recent study in the National Institutes of Health-AARP Cohort, based on 4076 incident CRC cases, reported that weight gained between the ages of 18 and 35 years and between 18 years of age and age at study recruitment (approximately 63 years) was associated with higher risk of colon cancer in men[9]; whereas no association was seen for rectal cancer. Our results confirm these findings as well as previous observations showing differences by cancer site in the associations with BMI

Table 1
Characteristics of study sample by categories of adult life weight change, the European Prospective Investigation into Cancer and Nutrition Study, 1992–2010.

	Weight change (kg)						
	Stable ±2 kg	Loss <–2 kg	Gain 2–5 kg	Gain 5–0 kg	Gain 10–15 kg	Gain 15–20 kg	Gain > 20 kg
N	25,072	16,801	25,220	43,879	35,960	24,076	30,688
Women, %	68.7	70.0	66.5	63.1	60.3	59.2	59.4
Age at study recruitment, y, mean (SD)	47.6 (13.7)	50.6 (13.4)	49.9 (11.9)	52.2 (10.5)	53.9 (9.4)	54.9 (8.8)	55.7 (8.3)
Weight at age 20[a], kg, mean (SD)	61.8 (10.0)	68.3 (12.9)	61.1 (9.8)	61.2 (10.1)	61.1 (10.3)	60.9 (10.5)	61.0 (11.1)
Weight at study recruitment, kg, mean (SD)	62.0 (10.0)	61.5 (11.1)	64.8 (9.9)	68.8 (10.2)	73.6 (10.4)	78.4 (10.6)	89.1 (13.6)
Absolute weight change[b], kg, mean (SD)	0.25 (1.2)	-6.8 (5.6)	3.7 (0.9)	7.6 (1.4)	12.5 (1.4)	17.5 (1.4)	28.0 (7.9)
Annual weight change, kg per year, mean (SD)	0.05 (1.7)	-0.35 (1.2)					
Body Mass Index at age 20, kg/m^{2}, mean (SD)	22.1 (2.6)	24.6 (3.9)	21.9 (2.5)	21.8 (2.5)	21.7 (2.6)	21.6 (2.7)	21.6 (3.0)
Body Mass Index at age 50[c], kg/m^2 , mean (SD)	22.2 (2.6)	22.2 (3.1)	23.2 (2.5)	24.6 (2.6)	26.2 (2.7)	27.9 (2.8)	31.6 (4.3)
Waist circumference, cm, mean (SD)	75.5 (9.9)	75.7 (10.5)	77.9 (9.9)	81.8 (10.3)	86.3 (10.2)	90.8 (10.3)	99.5 (11.9)
Education, %							
No school degree or primary school	17.8	23.9	19.3	23.7	28.8	33.9	41.2
Technical or professional school	40.2	38.5	40.8	41.2	41.2	39.6	36.4
Secondary school	35.3	29.8	33.4	28.3	23.7	20.6	17.4
University degree	6.7	7.9	6.5	6.8	6.3	5.9	5.0
Smoking status, %							
Never smokers	51.1	44.5	49.5	47.1	44.0	42.3	44.4
Former smokers	23.1	24.0	25.9	28.6	31.8	33.4	33.3
Current smokers	24.5	30.3	23.3	22.9	22.6	22.4	20.7
Missing	1.3	1.2	1.3	1.5	1.5	1.4	1.5
Physical activity, %							
Inactive	19.1	15.8	20.6	21.0	21.2	20.5	19.8
Moderately inactive	32.7	32.2	30.7	30.4	30.3	30.9	30.7
Moderately active	37.1	40.5	37.5	38.0	38.0	38.6	40.0
Active	10.5	10.8	10.6	9.8	9.6	9.1	8.8
Missing	0.8	0.7	0.7	0.9	0.9	0.8	0.8
Alcohol intake, g/day, median (IQR)	94.3 (22.1–225.7)	73.9 (13.8–208.4)	100.3 (24.9–239.5)	108.0 (27.5–260.0)	114.3 (28.0–280.0)	105.9 (23.4–275.6)	104.3 (23.6–268.4)
Dietary intakes							
Red and processed meat, g/day, median (IQR)	69.1 (9.8–112.2)	70.0 (16.0–112.9)	80.3 (34.1–120.1)	90.5 (54.6–128.9)	98.4 (65.5–136.3)	101.0 (70.5–139.7)	106.2 (74.7–147.2)
Fish and shellfish, g/day, median (IQR)	24.2 (7.2–42.1)	24.1 (8.2–42.5)	27.2 (12.5–44.5)	29.0 (15.9–46.5)	30.8 (17.2–48.3)	31.7 (18.1–49.1)	31.2 (18.2–48.9)
Fruits, g/day, median (IQR)	201.2 (114.6–323.3)	204.2 (115.3–337.1)	194.6 (111.9–308.7)	190.9 (110.1–305.6)	188.2 (106.6–304.9)	189.2 (107.5–312.4)	194.8 (107.5–324.7)
Vegetables, g/day, median (IQR)	209.7 (135.0–313.9)	212.9 (131.9–323.0)	200.3 (129.5–298.9)	193.3 (125.6–201.6)	186.0 (119.9–284.1)	184.9 (117.4–287.0)	186.1 (115.5–300.1)
Fibre intake, g/day, median (IQR)	23.3 (18.3–29.4)	23.3 (18.1–29.8)	22.9 (18.2–28.8)	22.7 (17.9–28.3)	22.2 (17.6–27.7)	22.0 (17.4–27.4)	21.9 (17.2–27.3)
Postmenopausal women, %	9.5	8.1	10.7	21.2	19.2	13.5	17.9
Hormonal replacement therapy use, %	9.8	7.2	12.1	24.4	20.3	12.8	13.4

Abbreviations: IQR, interquartile range; SD, standard deviation; *n*, number.

[a] Recalled weight at age 20 years, except for German cohort (recalled weight at age 25 years).

[b] Adult life weight change from age 20 to 50 was calculated as the difference between measured weight at study recruitment at average age 50 years and recalled weight at age 20 years.

[c] Average age at study recruitment.

Table 2
Hazard ratios and 95% confidence intervals for colorectal cancer in relation to adult weight change, the European Prospective Investigation into Cancer and Nutrition Study, 1992–2010.

Measure	Cases, *n*	All subjects		Cases, *n*	Men		Cases, *n*	Women	
		Crude model[a] HR (95%CI)	Multivariable model[b] HR (95%CI)		Crude model[a] HR (95%CI)	Multivariable model[b] HR (95%CI)		Crude model[a] HR (95%CI)	Multivariable model[b] HR (95%CI)
Absolute weight change (kg)									
Loss ⩽2 kg	170	1.11 (0.80–1.52)	1.06 (0.65–1.13)	68	1.00 (0.62–1.62)	0.97 (0.59–1.60)	102	1.20 (0.78–1.84)	1.13 (0.74–1.77)
Stable ±2 kg	217	1.00 [Reference]	1.00 [Reference]	112	1.00 [Reference]	1.00 [Reference]	105	1.00 [Reference]	1.00 [Reference]
Gain 2–5 kg	250	1.21 (0.91–1.62)	1.24 (0.92–1.66)	113	0.94 (0.61–1.45)	0.92 (0.59–1.44)	137	1.50 (1.01–2.21)	1.55 (1.04–2.29)
Gain 5–10 kg	471	1.12 (0.87–1.44)	1.12 (0.87–1.44)	229	1.14 (0.78–1.65)	1.11 (0.75–1.63)	242	1.11 (0.79–1.56)	1.15 (0.81–1.62)
Gain 10–15 kg	457	1.12 (0.87–1.45)	1.13 (0.87–1.47)	230	1.03 (0.71–1.51)	1.00 (0.68–1.48)	227	1.20 (0.84–1.71)	1.24 (0.87–1.79)
Gain 15–20 kg	351	1.30 (0.99–1.70)	1.31 (0.99–1.72)	186	1.19 (0.81–1.74)	1.15 (0.77–1.70)	165	1.41 (0.97–2.06)	1.47 (1.00–2.16)
Gain 20 kg	468	1.36 (1.05–1.76)	1.37 (1.05–1.78)	256	1.35 (0.93–1.95)	1.27 (0.86–1.86)	212	1.36 (0.94–1.96)	1.44 (0.99–2.09)
P for linear trend		0.01	0.01		0.02	0.08		0.23	0.12
Annual weight change (kg per year)		1.33 (1.08–1.64)	1.36 (1.10–1.69)		1.36 (1.01–1.83)	1.32 (0.96–1.80)		1.30 (0.97–1.75)	1.38 (1.01–1.88)
P-value		0.007	0.005		0.04	0.09		0.08	0.04
<0.1 kg per year	524	1.00 [Reference]	1.00 [Reference]	244	1.00 [Reference]	1.00 [Reference]	280	1.00 [Reference]	1.00 [Reference]
0.1–0.3 kg per year	723	1.02 (0.85–1.22)	1.09 (0.93–1.27)	352	1.06 (0.82–1.38)	1.07 (0.81–1.40)	371	0.99 (0.78–1.27)	1.02 (0.80–1.32)
0.3–0.5 kg per year	602	1.08 (0.89–1.30)	1.15 (0.98–1.35)	310	1.13 (0.86–1.49)	1.10 (0.83–1.47)	292	1.04 (0.81–1.35)	1.10 (0.84–1.43)
0.5–1 kg per year	454	1.28 (1.05–1.56)	1.28 (1.08–1.53)	254	1.51 (1.14–2.01)	1.46 (1.09–1.97)	200	1.07 (0.81–1.42)	1.11 (0.83–1.49)
>1 kg per year	81	1.32 (0.90–1.96)	1.50 (1.08–2.09)	34	1.05 (0.58–1.88)	1.03 (0.56–1.88)	47	1.64 (0.97–2.78)	1.75 (1.03–3.00)
P for linear trend		0.008	0.006		0.02	0.05		0.05	0.06

Abbreviations: HR, hazard ratio; CI, confidence interval.
Note: Analysis based on 74,091 men (1194 cases); 127,605 women (1190 cases).
P value for interaction by sex, 0.81.
[a] Crude model: Stratified by centre and age at recruitment. The model for all subjects was additionally stratified by sex.
[b] Multivariable model: Crude model was additionally adjusted for weight at age 20, smoking status (never, past, current or unknown), education (no school degree or primary school, technical or professional school, secondary school, university degree), alcohol intake (continuous), physical activity (inactive, moderately inactive, moderately active, active or missing), red and processed meat (g/day), fish and shellfish(g/day), fruits and vegetables (g/day) and fibre intake (g/day).

and WC,[14] but also with other lifestyle[28] and metabolic factors.[14,29]

In our study, adult weight change was associated with colon cancer in both men and in women. Similar associations for both genders have been reported by a small case-control study on colorectal adenomas,[25] as well as in a large international case-control study involving Colon Cancer Family Registry participants.[12] Our findings for men are in line with those reported by a number of prospective cohort[6–8] and case-control studies.[10–12] Interestingly, in our data the association between weight change and CRC risk in men was partly explained by intake of dietary fibre. Recent meta-analysis of prospective studies reported that dietary fibre, particularly cereal fibre and whole grains, was associated with a reduction in CRC risk.[30] Higher intakes of dietary fibre and whole grains are inversely related to weight change[31,28] and diabetes[18]; thus it may be plausible that fibre exerts its protective effects through controlling weight and insulin resistance.

Our findings for a statistically significant association between women's weight change and colon cancer risk contradict results from a number of case-control[10–12] and prospective studies.[8,23,26,27,32] For example, in the

Table 3
Hazard ratios and 95% confidence intervals for colon cancer in relation to adult weight change, the European Prospective Investigation into Cancer and Nutrition Study, 1992–2010.

Measure	Cases, *n*	All subjects		Cases, *n*	Men		Cases, *n*	Women	
		Crude model[a] HR (95%CI)	Multivariable model[b] HR (95%CI)		Crude model[a] HR (95%CI)	Multivariable model[b] HR (95%CI)		Crude model[a] HR (95%CI)	Multivariable model[b] HR (95%CI)
Absolute weight change (kg)									
Loss ⩽2 kg	107	0.95 (0.63–1.43)	0.89 (0.59–1.35)	37	0.90 (0.47–1.72)	0.84 (0.43–1.64)	70	1.00 (0.58–1.70)	0.97 (0.56–1.68)
Stable ±2 kg	133	1.00 [Reference]	1.00 [Reference]	67	1.00 [Reference]	1.00 [Reference]	66	1.00 [Reference]	1.00 [Reference]
Gain 2–5 kg	152	1.19 (0.82–1.72)	1.24 (0.85–1.81)	65	1.13 (0.65–1.97)	1.20 (0.67–2.14)	87	1.24 (0.75–2.04)	1.34 (0.81–2.23)
Gain 5–10 kg	280	0.98 (0.70–1.36)	1.00 (0.71–1.40)	122	0.95 (0.58–1.56)	0.97 (0.58–1.63)	158	1.01 (0.65–1.58)	1.07 (0.68–1.69)
Gain 10–15 kg	266	0.94 (0.67–1.32)	0.96 (0.68–1.36)	127	0.84 (0.51–1.39)	0.88 (0.53–1.48)	139	1.02 (0.64–1.63)	1.05 (0.65–1.69)
Gain 15–20 kg	226	1.19 (0.84–1.69)	1.21 (0.85–1.72)	114	1.09 (0.66–1.79)	1.09 (0.65–1.84)	112	1.30 (0.81–2.10)	1.36 (0.83–2.23)
Gain >20 kg	306	1.34 (0.96–1.88)	1.38 (0.97–1.95)	165	1.30 (0.80–2.11)	1.31 (0.78–2.19)	141	1.38 (0.86–2.20)	1.49 (0.92–2.42)
P for linear trend		0.02	0.01		0.12	0.13		0.09	0.05
Annual weight change (kg per year)		1.50 (1.15–1.96)	1.60 (1.20–2.09)		1.34 (0.92–1.94)	1.42 (0.96–2.11)		1.68 (1.16–2.43)	1.82 (1.24–2.69)
P-value		0.0003	0.001		0.13	0.08		0.005	0.002
<0.1 kg per year	326	1.00 [Reference]	1.00 [Reference]	141	1.00 [Reference]	1.00 [Reference]	185	1.00 [Reference]	1.00 [Reference]
0.1–0.3 kg per year	430	0.88 (0.70–1.12)	1.01 (0.83–1.24)	193	0.85 (0.60–1.21)	0.88 (0.62–1.27)	237	0.92 (0.67–1.27)	0.97 (0.70–1.34)
0.3–0.5 kg per year	373	1.06 (0.84–1.36)	1.21 (0.98–1.50)	188	1.09 (0.76–1.55)	1.10 (0.75–1.60)	185	1.05 (0.76–1.47)	1.10 (0.79–1.55)
0.5–1 kg per year	279	1.24 (0.96–1.61)	1.32 (1.05–1.65)	148	1.31 (0.90–1.90)	1.33 (0.90–1.98)	131	1.16 (0.81–1.67)	1.21 (0.83–1.77)
>1 kg per year	62	1.56 (0.97–2.52)	2.05 (1.37–3.07)	27	0.96 (0.46–1.99)	0.97 (0.46–2.08)	35	2.35 (1.23–4.48)	2.65 (1.37–5.13)
P for linear trend		0.005	0.003		0.16	0.18		0.01	0.005

Abbreviations: HR, hazard ratio; CI, confidence interval.
Note: Analysis based on 74,091 men (697 cases); 127,605 women (773 cases).
P value for interaction by sex, 0.97.
[a] Crude model: Stratified by centre and age at recruitment. The model for all subjects was additionally stratified by sex.
[b] Multivariable model: Crude model was additionally adjusted for weight at age 20, smoking status (never, past, current or unknown), education (no school degree or primary school, technical or professional school, secondary school, university degree), alcohol intake (continuous), physical activity (inactive, moderately inactive, moderately active, active or missing), red and processed meat (g/day), fish and shellfish(g/day), fruits and vegetables (g/day) and fibre intake (g/day).

National Institutes of Health-AARP Cohort Study, no associations were seen in women between weight gain and risk of either colon or rectal cancer.[9] Consistent with our results, in the French E3N cohort mean weight gain over 0.5 kg/year was associated with a 23% increased colorectal adenoma risk in French women.[33]

Our data suggest that weight change is associated with excess colon cancer risk in people with attained high WC at age 50, but not in those having low WC; whereas no such differences were seen by attained BMI. Previously in EPIC, we have shown that WC, but not BMI, is associated with colon cancer in both sexes, supporting the hypothesis that fat distribution is more important than body weight or BMI for colon cancer risk.[18] Abdominal obesity may reflect metabolic pathways implicated also in the development and progression of CRC,[3] including hyperinsulinemia,[34] hyperglycaemia,[35] dyslipidemia,[36] chronic low grade inflammation,[37] oxidative stress[38] and overall metabolic syndrome.[39] In addition, visceral adipose tissue secretes a number of cytokines and hormones that may be relevant for CRC, risk.[40,41] Our findings imply that it is fat accumulation in the abdominal area reflecting cumulative metabolic attack in the body over years that induce colon carcinogenesis.

Our results further suggest an association between annual weight gain and colon cancer in premenopausal women but not in post-menopausal women. Similar

Table 4
Hazard ratios and 95% confidence intervals for rectal cancer in relation to adult weight change, the European Prospective Investigation into Cancer and Nutrition Study, 1992–2010.

Measure	Cases, *n*	All subjects		Cases, *n*	Men		Cases, *n*	Women	
		Crude model[a] HR (95%CI)	Multivariable model[b] HR (95%CI)		Crude model[a] HR (95%CI)	Multivariable model[b] HR (95%CI)		Crude model[a] HR (95%CI)	Multivariable model[b] HR (95%CI)
Absolute weight change (kg)									
Loss ⩽2 kg	63	1.39 (0.83–2.31)	1.37 (0.81–2.32)	31	1.17 (0.56–2.43)	1.15 (0.53–2.49)	32	1.71 (0.83–3.51)	1.77 (0.84–3.76)
Stable ±2 kg	84	1.00 [Reference]	1.00 [Reference]	45	1.00 [Reference]	1.00 [Reference]	39	1.00 [Reference]	1.00 [Reference]
Gain 2–5 kg	98	1.23 (0.78–1.95)	1.24 (0.77–1.99)	48	0.70 (0.35–1.42)	0.64 (0.30–1.35)	50	2.03 (1.08–3.80)	2.15 (1.12–4.11)
Gain 5–10 kg	191	1.35 (0.92–1.99)	1.34 (0.90–2.00)	107	1.42 (0.80–2.51)	1.37 (0.74–2.52)	84	1.26 (0.74–2.14)	1.34 (0.78–2.31)
Gain 10–15 kg	191	1.41 (0.95–1.99)	1.46 (0.97–2.19)	103	1.31 (0.73–2.32)	1.28 (0.69–2.35)	88	1.51 (0.87–2.62)	1.65 (0.93–2.93)
Gain 15–20 kg	125	1.44 (0.94–2.21)	1.56 (1.00–2.43)	72	1.33 (0.74–2.39)	1.22 (0.65–2.30)	53	1.60 (0.85–2.99)	1.82 (0.94–3.51)
Gain >20 kg	162	1.36 (0.90–2.04)	1.40 (0.92–2.14)	91	1.39 (0.78–2.48)	1.36 (0.73–2.52)	71	1.30 (0.72–2.35)	1.45 (0.79–2.66)
P for linear trend		0.35	0.23		0.12	0.16		0.78	0.96
Annual weight change (kg per year)		1.08 (0.77–1.53)	1.13 (0.79–1.62)		1.40 (0.87–2.28)	1.42 (0.83–2.39)		0.82 (0.50–1.35)	0.82 (0.48–1.40)
P - value		0.65	0.51		0.17	0.19		0.44	0.46
<0.1 kg per year	198	1.00 Reference]	1.00 [Reference]	103	1.00 [Reference]	1.00 [Reference]	95	1.00 [Reference]	1.00 [Reference]
0.1–0.3 kg per year	293	1.24 (0.94–1.63)	1.21 (0.95–1.54)	159	1.40 (0.94–2.09)	1.41 (0.92–2.16)	134	1.14 (0.78–1.66)	1.18 (0.79–1.78)
0.3–0.5 kg per year	229	1.09 (0.81–1.47)	1.08 (0.83–1.39)	122	1.20 (0.77–1.86)	1.17 (0.74–1.86)	107	1.02 (0.67–1.55)	1.12 (0.72–1.73)
0.5–1 kg per year	175	1.32 (0.97–1.80)	1.24 (0.94–1.64)	106	1.84 (1.18–2.86)	1.83 (1.14–2.93)	69	0.93 (0.59–1.45)	0.98 (0.61–1.57)
>1 kg per year	19	0.90 (0.44–1.81)	0.79 (0.43–1.47)	7	1.17 (0.43–3.15)	1.27 (0.46–3.54)	12	0.72 (0.26–1.94)	0.62 (0.22–1.81)
P for linear trend		0.46	0.33		0.07	0.08		0.46	0.52

Abbreviations: HR, hazard ratio; CI, confidence interval.
Note: Analysis based on 74,091 men (497cases); 127,605 women (417 cases); *P value for* interaction by sex, 0.82.
[a] Crude model: Stratified by centre and age at recruitment. The model for all subjects was additionally stratified by sex.
[b] Multivariable model: Crude model was additionally adjusted for weight at age 20, smoking status (never, past, current or unknown), education (no school degree or primary school, technical or professional school, secondary school, university degree), alcohol intake (continuous), physical activity (inactive, moderately inactive, moderately active, active or missing), red and processed meat (g/day), fish and shellfish(g/day), fruits and vegetables (g/day) and fibre intake (g/day).

findings have been reported with regard to the association of obesity and CRC.[42,43] It was hypothesised that oestrogen up-regulates IGF-I receptors in the colon, which in turn increases susceptibility to obesity-induced increased levels of insulin.[43,44] While in premenopausal women oestrogen is mainly produced in ovaries, in menopause adipose tissue becomes the main source of this hormone. Oestrogen derived from the adipose tissue may supersede in lowering CRC risk in menopausal obese women. Thus, effect modification by menopausal status, was suggested to explain the inconsistent or weak findings in previous studies among women. In our data, though, no significant statistical interaction was observed by menopausal status or HRT use and interpretation of findings is limited due to the low number of cases in sub-group analyses.

To our knowledge, our study is one of the largest prospective studies to date on weight change and CRC risk. The large sample size and long follow-up period allowed us to examine the relation by cancer site and sex with sufficient power. Another major strength of this study is that all anthropometric measures assessed at study recruitment were directly measured, in contrast to the self-reported data used in the majority of previous studies. Thus, non-differential misclassification of weight at age 50 should be minimal.

Our study has several limitations. We used long-term recall of body weight at age 20. However, previous

Table 5
Multivariable-adjusted[a] hazard ratios and 95% confidence intervals for colorectal cancer in relation to annual weight change (kg per year), by selected anthropometric measures, the European Prospective Investigation in- Cancer and Nutrition Study, 1992–2010.

	Cases, *n*	HR (95%CI)	*P*	Cases, *n*	HR (95%CI)	*P*	$P_{interaction}$
	Low BMI at age 20[b]			High BMI at age 20[b]			
Colorectal cancer	1151	1.17 (0.65–2.09)	0.60	1233	1.40 (0.94–2.09)	0.9	0.32
Colon cancer	711	1.28 (0.59–2.75)	0.52	759	1.53 (0.93–2.53)	0.10	0.86
Rectal cancer	405	0.84 (0.30–2.40)	0.75	509	1.22 (0.61–2.42)	0.57	0.20
	Low BMI at age 50[c]			High BMI at age 50[c]			
Colorectal cancer	1016	1.17 (0.65–2.09)	0.61	1368	1.40 (0.94–2.09)	0.09	0.42
Colon cancer	611	1.28 (0.60–2.75)	0.52	859	1.52 (0.93–2.53)	0.10	0.20
Rectal cancer	405	0.84 (0.30–2.40)	0.74	509	1.22 (0.61–2.42)	0.57	0.60
	Low waist circumference at age 50[d]			High waist circumference at age 50[d]			
Colorectal cancer	954	1.06 (0.63–1.79)	0.83	1430	1.56 (1.08–2.24)	0.02	0.09
Colon cancer	554	1.03 (0.57–1.58)	0.92	916	1.82 (1.14–2.91)	0.01	0.02
Rectal cancer	400	0.92 (0.34–2.51)	0.88	514	1.21 (0.66–2.20)	0.54	0.86

Abbreviations: HR, hazard ratio; CI, confidence interval.

[a] Multivariable model: Stratified by centre and age at recruitment, adjusted for weight at age 20, smoking status (never, past, current or unknown), education (no school degree or primary school, technical or professional school, secondary school, university degree or unknown), alcohol intake (continuous), physical activity (inactive, moderately inactive, moderately active, active or missing), red and processed meat (g/day), fish and shellfish(g/day), fruits and vegetables (g/day) and fibre intake (g/day);

[b] BMI at age 20. Categories defined based on median sex-specific cutoff points: 22.6 kg/m^2 in men, 21.2 kg/m^2 in women;

[c] BMI at age 50 years (average age at study recruitment). Categories defined based on sex to specific median cutoff points: 26 kg/m^2 in men, 24.4 kg/m^2 in women;

[d] Waist circumference categories defined based on median sex to specific cutoff points $\geqslant$93.1 cm in men, $\geqslant$77 cm in women.

validation studies of self-reports of past body weight over a similar period to that used in our study show moderate to strong correlations with measured weight in the range of 0.64–0.95 and the accuracy of self-reports has been generally supported in epidemiologic studies.[45–47] An increase of BMI in earlier adulthood (25–40 years) has been more strongly associated with unfavorable metabolic profile than in later adulthood (40–55 years)[3]; however we were not able to differentiate between these time periods. Finally, although we adjusted our analyses for a wide range of potentially confounding factors we cannot exclude the possibility of residual confounding by other unmeasured factors.

In conclusion, our data suggest that weight gain during adult life is associated with colon cancer in men and women, independent of BMI at age 20 and other potential CRC risk factors; whereas no association was seen for rectal cancer. The risk was particularly higher in abdominally obese people usually characterised by unfavorable metabolic profile. This evidence adds to the rationale of investing in weight control management and metabolic health maintenance in early adulthood for the prevention of colon cancer.

Conflict of interest statement

None declared.

Acknowledgments

We thank Ellen Kohlsdorf (EPIC-Potsdam, Germany) for her work on data management and technical assistance. We thank all participants in the EPIC study for their outstanding cooperation.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2013.06.021.

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