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Original Contribution

Anthropometric Factors in Adulthood and Risk of Colorectal Adenomas

The French E3N-EPIC Prospective Cohort

Sophie Morois, Sylvie Mesrine, Marine Josset, Françoise Clavel-Chapelon, and Marie-Christine Boutron-Ruault*

* Correspondence to Dr. Marie-Christine Boutron-Ruault, INSERM, UMRS 1018, Centre for Research in Epidemiology and Population Health, Team 9, Paris South University, Institut Gustave Roussy, Espace Maurice Tubiana, 114 rue Edouard Vaillant, F-94805 Villejuif Cedex, France (e-mail: boutron@igr.fr).

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Anthropometric factors have been associated with colorectal cancer and adenomas but with conflicting results in women or regarding adenoma characteristics. The authors aimed to explore associations between anthropometric factors (height, weight, body mass index, waist and hip circumferences, and weight changes) and adenoma risk. They analyzed the 17,391 women of the French Etude épidémiologique des femmes de la Mutuelle Générale de l'Education Nationale (E3N)-European Prospective Investigation into Cancer and Nutrition (EPIC) cohort who underwent a colonoscopy during follow-up (1993–2002), including 1,408 who developed a first colorectal adenoma. In Cox multivariate proportional hazard regression models, obesity was associated with an increased colorectal adenoma risk (hazard ratio = 1.53, 95% confidence interval: 1.21, 1.94). This association was restricted to left colon adenomas ($P_{homogeneity} = 0.05$ and 0.01 for colon vs. rectum and right vs. left colon, respectively), with a dose-effect relation observed from 22 kg/m^2. A high waist circumference was also associated with left colon adenoma risk (hazard ratio = 1.81, 95% confidence interval: 1.36, 2.41). Mean weight gain over 0.5 kg/year was associated with a 23% increased colorectal adenoma risk. Associations did not differ between advanced and nonadvanced adenomas. In conclusion, study findings suggest that obesity and weight gain are associated with early colorectal carcinogenesis in women, and specifically regarding the distal colon.

adenoma; body mass index; body weight changes; cohort studies; colon, descending; colorectal neoplasms; obesity; waist circumference

Abbreviations: BMI, body mass index; CI, confidence interval; E3N, Etude épidémiologique des femmes de la Mutuelle Générale de l'Education Nationale; EPIC, European Prospective Investigation into Cancer and Nutrition.

Colorectal cancer is one of the most common malignancies in Western countries and the second cause of cancer-related mortality in women in France (1). A large proportion of colorectal cancers arises from adenomas, through the adenoma-carcinoma sequence (2). Although mass screening for colorectal tumors has proven efficient for the prevention of colorectal cancer (3), the acceptance rate is often low, and it is costly and not devoid of side effects. Thus, prevention of adenoma formation and growth remains an important option for preventing colorectal cancer. Migrant studies, or studies in countries with major dietary changes such as Japan, demonstrate that risk of colorectal cancer rapidly varies with changes in dietary habits (4, 5), and there is strong evidence of the role of dietary factors in colorectal carcinogenesis (1). However, few intervention studies demonstrated some efficacy on prevention of adenoma recurrence (6–9). A better understanding of the factors associated with adenoma risk is thus still requested.

Body fatness is a convincing and modifiable risk factor for colorectal cancer (1). It has also been positively associated with incidence or recurrence of colorectal adenomas (10–17), with exceptions (18–20).

Sex and gender specificities have been described regarding colorectal tumors. The sex ratio for colorectal cancer displays strong variations along the large bowel (21), there is some evidence for a role of female hormones in colorectal carcinogenesis (22), and there are some gender differences regarding dietary factors associated with colorectal cancer (1). Anthropometry is influenced by sex hormones, as demonstrated by a shift from gynecoid to android fatness after menopause (23); in previous studies, body mass index (BMI) has been more markedly associated with risk of colorectal cancer (24) or adenomas (10, 14, 25) in men than in women, although results for adenomas are conflicting (15, 26). Thus, additional information regarding anthropometry in relation to adenomas in women is needed.

Studies that considered adenoma characteristics, such as tumor site or histologic characteristics, in relation to anthropometry (10, 14–16, 18, 25–32) produced conflicting results. Moreover, most of them had a case-control design, included a limited number of cases, and/or concerned American or Asian populations, whose anthropometric characteristics differ from those of a European population.

We examined the relation between anthropometry in adulthood and risk of colorectal adenomas in a prospective study in French women, focusing on adenoma characteristics and site.

MATERIALS AND METHODS

The E3N-EPIC cohort study

The Etude épidémiologique des femmes de la Mutuelle Générale de l'Education Nationale (E3N)-European Prospective Investigation into Cancer and Nutrition (EPIC) cohort involves the 74,531 women from the E3N prospective cohort (33) who filled in a comprehensive dietary questionnaire sent in 1993. All women signed an informed consent, in compliance with the rules of the French National Commission for Data Protection and Individual Freedom (Commission National Informatique et Libertés) from which approval was obtained.

Self-administered questionnaires were completed approximately every 24 months and provided data on lifestyle factors, family, and personal history of disease, and age at menopause, as well as occurrence of medical events, especially colonoscopy and colorectal polyp, since the last follow-up questionnaire. Dietary data were collected between June 1993 and July 1995, by using a validated diet history questionnaire (33).

Anthropometric data

Self-reported weight was obtained from each of the 7 consecutive questionnaires considered for this study; self-reported height was obtained from the 1990 (first), 1995 (fourth), and 2000 (sixth) questionnaires; and self-reported waist and hip circumferences were obtained from the 1995 questionnaire. Waist circumference was defined as the smallest circumference between the base of the ribs and the high point of the iliac crest, and hip circumference was defined as the largest circumference below the umbilicus (34).

If Q_x is the considered questionnaire, Q_{x-1} the preceding questionnaire, and Q_1 the baseline questionnaire, we defined the mean annual weight gain as [Σ (weight Q_x − weight Q_{x-1})]/(year Q_x − year Q_1) and the mean annual weight fluctuation as [Σ absolute (weight Q_x − weight Q_{x-1})]/(year Q_x − year Q_1).

BMI was considered by use of World Health Organization cutoff points (1), further dividing normal BMI into over or below 22 kg/m^2 (close to our median BMI value). Height, weight, waist circumference, hip circumference, and the waist/hip ratio were categorized according to quartiles at baseline.

Cases and noncases

Repeated mailings were sent to the women who reported intestinal polyps in the questionnaires and to their physicians, requesting pathologic and colonoscopy reports. We then coded the histologic features, size, number, and precise location of the tumors. Adenomas over 1 cm in diameter, with high-grade dysplasia (severe or in situ adenocarcinoma), or with a villous component were classified as advanced lesions. Women simultaneously diagnosed with advanced and nonadvanced adenomas were classified in the ''advanced adenoma'' category. Right colon included the cecum, ascending colon, hepatic flexure, and transverse colon; left colon included the splenic flexure, descending colon, and sigmoid colon; rectum included the rectosigmoid junction and rectum.

Because colonoscopy is required to diagnose adenomas, we restricted our population to women who underwent at least 1 colonoscopy during follow-up and considered women with adenoma-free colonoscopies (excluding those with hyperplastic polyps) as noncases.

Study period

Baseline was defined as the date the dietary questionnaire was returned for height, weight, BMI, and weight change variables and as the date the fourth questionnaire was returned for waist and hip circumferences. Subjects contributed person-years of follow-up until the date of adenoma diagnosis, the date of the last questionnaire with normal colonoscopy, the date of the questionnaire with normal colonoscopy prior to cancer diagnosis (24 colorectal and 886 other cancers), or July 2002 (the date of the seventh questionnaire mailing), whichever occurred first.

From the initial 74,531 E3N-EPIC women, we excluded 4,654 with prevalent cancer, 810 lost to follow-up after the baseline questionnaire, and 1,364 with extreme values of energy intake (33). In the remaining cohort, 20,852 underwent a colonoscopy during follow-up; we further excluded 193 women with inflammatory bowel disease, 9 with colectomy, 1 with familial adenomatous polyposis, 1,929 with a colorectal adenoma or unspecified polyp diagnosed before baseline, 783 with a hyperplastic polyp as the first diagnosed polyp, 115 whose removed polyp was not analyzed, and 421 with no available histologic report despite repeated mailings to women and/or their physicians. Finally, because menopause was a potential effect modifier, we excluded 6 women

Table 1. Baseline Characteristics of Participants, E3N-EPIC Cohort ($n = 17,391$), France, 1993–2002

	Noncases			All Adenoma Cases			Only Colon Cases			Only Right Colon Cases			Only Left Colon Cases			Only Rectal Cases		
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
No.	15,983			1,408			1,035			344			642			257		
Age at baseline, years			53.1 (6.5)			54.3 (6.6)			54.2 (6.6)			54.9 (6.8)			53.9 (6.4)			54.2 (6.7)
Age at diagnosis, years						58.7 (6.9)			58.7 (6.9)			59.3 (7.2)			58.3 (6.8)			58.7 (6.8)
Advanced adenomas				599	42.5		422	40.8		103	29.9		291	45.3		131	51.0	
At least villous component				482	80.5		331	78.4		85	82.5		223	76.6		112	85.5	
At least size over 1 cm				341	56.9		239	56.6		46	44.7		173	59.5		75	57.3	
At least severe dysplasia				148	24.7		100	23.7		17	16.5		74	25.4		33	25.2	
Anthropometric factors at baseline																		
Height, cm			161.7 (5.7)			161.8 (5.7)			161.8 (5.8)			162.1 (5.9)			161.6 (5.7)			162.1 (5.5)
Weight, kg[a]			59.6 (9.1)			60.4 (9.4)			60.6 (9.5)			60.1 (9.1)			60.9 (9.6)			59.7 (8.7)
Body mass index, kg/m^{2a}			22.8 (3.2)			23.1 (3.3)			23.2 (3.4)			22.8 (3.2)			23.3 (3.4)			22.7 (3.0)
Waist circumference, cm[a]			75.8 (8.8)			77.0 (9.2)			77.2 (9.4)			76.2 (9.2)			77.7 (9.4)			75.8 (8.1)
Hip circumference, cm[a]			96.6 (8.3)			97.5 (8.5)			97.7 (8.7)			97.3 (8.5)			98.0 (8.7)			96.4 (7.4)
Waist/hip ratio[a]			0.78 (0.06)			0.79 (0.06)			0.79 (0.06)			0.78 (0.05)			0.79 (0.06)			0.79 (0.05)
Adjustment variables at baseline																		
Total alcohol-free energy intake, kcal/day			2,101.3 (560.8)			2,090.6 (550.9)			2,085.0 (552.2)			2,066.9 (557.6)			2,093.5 (535.1)			2,121.1 (551.2)
Physical activity, METs/week			54.4 (30.1)			55.2 (30.8)			55.3 (30.4)			53.8 (28.9)			55.4 (30.4)			55.4 (32.6)
Alcohol intake, g/day			10.8 (13.7)			12.6 (15.6)			12.6 (15.3)			11.7 (12.9)			13.3 (16.7)			12.3 (15.3)
Smoking status[a]																		
Never	9,053	56.6		794	56.4		568	54.9		187	54.4		356	55.5		153	59.5	
Past	4,947	31.0		426	30.3		325	31.4		111	32.3		199	31.0		76	29.6	
Current smoker	1,982	12.4		188	13.4		142	13.7		46	13.4		87	13.5		28	10.9	
No. of years of schooling																		
<12	1,768	11.1		201	14.3		144	13.9		43	12.5		91	14.2		38	14.8	
12–14	8,567	53.6		757	53.8		564	54.5		181	52.6		353	55.0		130	50.6	
>14	5,648	35.3		450	32.0		327	31.6		120	34.9		198	30.8		89	34.6	
Family history of colorectal cancer	2,244	14.0		274	19.5		220	21.3		73	21.2		138	21.5		37	14.4	

Age at menopause, years[b]	50.4 (3.8)		50.6 (3.7)		50.6 (3.5)		50.6 (3.4)		50.6 (3.6)		50.6 (4.0)	
Ever use of MHT[c]	10,796	67.6	880	62.5	653	63.1	223	64.8	402	62.6	159	61.9

Abbreviations: BMI, body mass index; E3N, Etude épidémiologique des femmes de la Mutuelle Générale de l'Education Nationale; EPIC, European Prospective Investigation into Cancer and Nutrition; MET, metabolic equivalent; MHT, menopausal hormone therapy; SD, standard deviation.

[a] Missing values: for waist circumference ($n = 1,993$), hip circumference ($n = 2,006$), waist/hip ratio ($n = 2,047$), weight ($n = 3$), BMI ($n = 3$), and smoking status at baseline ($n = 1$), respectively.

[b] A total of 247 women were still premenopausal at the end of follow-up.

[c] At the end of follow-up.

who never had any menstrual period and, thus, with undetermined menopausal age.

Thus, height, weight, and BMI were studied in 1,408 adenoma cases and 15,983 noncases; when studying waist circumference and hip circumference, we further excluded 2,834 women who did not provide information on these variables, leading to 1,025 cases and 13,532 noncases.

Statistical analyses

Cox proportional hazard models with age as timescale were used to estimate hazard ratios and 95% confidence intervals of colorectal adenoma risk. Weight, BMI, and annual weight variations were analyzed as time-dependent variables. When weight (and thus BMI) was missing at 1 questionnaire, the preceding value was considered until the next known value. Models were adjusted for alcohol-free energy intake, alcohol intake, total physical activity (time dependent), smoking status (time dependent), colorectal cancer in first degree relatives (time dependent), educational level, menopausal status (time dependent), and use of menopausal hormone therapy (time dependent). Data were missing for less than 5% of adjustment variables; we thus replaced missing values by the modal value. To test for linear trends across categories, we assigned ordinal values to each category of the variable. Hazard ratios according to adenoma site or risk category (advanced or nonadvanced) were estimated by using a competing risk method where adenoma cases other than those under study were censored at the date of diagnosis (35). We then tested homogeneity in associations between colon and rectum, right and left colon, and advanced and nonadvanced adenomas. We tested for potential interactions between BMI and family history of colorectal cancer, menopausal status, menopausal hormone therapy use, physical activity, and smoking status. All tests were 2 sided, and statistical significance (P value) was set at the 0.05 level. All analyses were performed by using SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

During 103,227 person-years of follow-up (mean = 5.9 years, standard deviation = 2.4), 1,408 women were diagnosed with at least 1 incident adenoma; 1,035 had exclusively colon adenomas (344 exclusively on the right colon, 642 exclusively on the left colon, 49 on both the left and right colon), 257 had exclusively rectal adenomas, 64 had both colon and rectal adenomas, and for 52 the site could not be retrieved. There were 599 advanced adenomas (43%). The mean age at diagnosis was 58.7 years (standard deviation = 6.9). Adenomas were diagnosed at first colonoscopy in 78.2% of the cases, while 51.4% of noncases had at least 2 colonoscopies during follow-up. The mean age at first colonoscopy was 55.4 years in noncases and 57.4 years in cases. Family history of colorectal cancer was most common in colon cases and least so in noncases. Alcohol intake was highest in left colon cases and lowest in noncases; never smokers were most common in rectal cases and least so in

colon cases. Advanced adenomas were most frequent in the rectum (Table 1).

Weight and BMI were positively associated with overall, colon, and left colon adenoma risk, while there was no association with rectal or right colon adenomas ($P_{homogeneity}$ colon vs. rectum = 0.05 for weight and 0.05 for BMI; $P_{homogeneity}$ right vs. left colon = 0.38 for weight and 0.01 for BMI) (Table 2). We observed a dose-effect relation from 22 kg/m^2 for left colon adenomas ($P_{trend} < 0.01$). Hazard ratios per 1-kg/m^2 increase in BMI were 1.04 (95% confidence interval (CI): 1.02, 1.05) and 1.05 (95% CI: 1.03, 1.08) for the colon and left colon, respectively. Height was associated with only right colon adenoma risk, with a borderline statistically significant positive association ($P_{trend} = 0.07$). Associations were not modified by family history of colorectal cancer, menopausal status, menopausal hormone therapy use, physical activity, or smoking status ($P_{interaction} > 0.10$; data not tabulated).

Waist circumference was also positively associated with overall, colon, and left colon adenoma risk and not with rectal or right colon adenomas ($P_{homogeneity}$ between colon and rectum and between right and left colon = 0.04 and <0.01, respectively) (Table 3). Waist circumference and BMI were highly correlated ($r = 0.78$), but the association with overall and left colon adenomas was slightly stronger for waist circumference than for BMI: Regarding all sites' adenomas, the hazard ratios associated with the fourth versus the first quartile were 1.27 (95% CI: 1.05, 1.53) and 1.17 (95% CI: 1.01, 1.37) for waist circumference and BMI, respectively; corresponding hazard ratios regarding left colon adenomas were 1.81 (95% CI: 1.36, 2.41) and 1.47 (95% CI: 1.17, 1.86), respectively. Mutual adjustment decreased relative risks associated with waist circumference and BMI, which became only borderline statistically significant (data not shown). Hip circumference was associated with a nonsignificant increased adenoma risk, and the test for heterogeneity between sites did not reach statistical significance. The waist/hip ratio was associated with only a borderline significant increased risk of left colon adenomas.

A mean annual weight gain over 0.5 kg/year was associated with a significant increased risk of 23% for all adenomas, 23% for colon adenomas, and 38% for left colon adenomas, as compared with no weight change (Table 4). In the opposite, mean annual weight fluctuation was not significantly associated with adenoma risk. Associations were not substantially modified by adjustment for BMI (data not shown).

All the above-described associations were similar in advanced and nonadvanced lesions (Appendix Tables 1 and 2). Further adjustments on dietary calcium, vitamin D, folate, and fiber intakes did not modify the associations.

DISCUSSION

Very few prospective studies have investigated adenoma risk in relation to adult anthropometric features, including height, BMI, weight gain, and type of obesity, while also considering adenoma location and characteristics. In one of the largest studies to date on adenoma incidence, we observed a positive statistically significant association between colorectal adenoma risk and BMI, waist circumference, and weight gain in French adult women. Associations were restricted to the left colon, and they were similar in advanced and nonadvanced adenomas.

Overweight and obesity have consistently been associated with the risk of colorectal adenomas and cancers, although associations are usually stronger in men (10, 14, 24, 25) than in women (15, 26). Our large-scale prospective study in women is thus of importance to further investigate the impact of anthropometry on female colorectal carcinogenesis. Because our population included a large proportion of lean women, we were able to demonstrate a significant increased risk of colorectal, and especially left colon, adenomas above a BMI of 22 kg/m^2, with a dose-effect relation. Obese women had a more than doubled risk, but overweight women had already a 34% increased risk. An important finding of our study is the association between BMI and colon but not rectal adenoma risk, consistent with previous studies on cancer (1, 24) or adenomas (10, 18, 28, 29) in women. However, the restriction to left colon adenomas is in conflict with the results of most other studies. Indeed, recent meta-analyses on cancer did not observe a heterogeneity between the right and left colon (24) and, among site-specific analyses on adenomas (10, 16, 18, 25, 27–30), only 2 described a stronger association with distal than with proximal colon adenomas (28, 29).

Menopausal status has sometimes been found to be an effect modifier of BMI-related cancer risk (36). In our study, the small proportion of premenopausal cases (17% of cases) limited the ability to investigate this aspect.

Only a few studies explored associations with anthropometry according to adenoma type. Early studies, mostly of a case-control design, described stronger associations for large than for small adenomas (26–29, 31). More recently, when advanced adenomas (including large adenomas and/or adenomas with a villous part and/or high-grade dysplasia) were compared with nonadvanced adenomas, associations with BMI were similar in women (14, 32), consistent with our findings, or they were observed only for nonadvanced adenomas (10, 15). Thus, findings from the most recent studies suggest that adult anthropometric factors may be associated with early rather than late events of colorectal carcinogenesis.

Waist circumference is considered to be a better marker of visceral adiposity than BMI (37, 38). Our results of a positive association with adenoma risk are in line with some previous studies (11, 31, 39, 40) but not all (12, 14, 15, 18, 20). The high correlation between BMI and waist circumference in our study, stronger than in others of similar design (31), precludes any strong inference about the specific role of visceral obesity, as opposed to overweight/obesity in itself. Like ours, some studies (18–20, 25), but not all (30, 31), failed to observe an association between colorectal adenoma risk and the waist/hip ratio, which may reflect both muscle and fat distribution (37), with the waist/hip ratio having been found to be a poorer predictor of the abdominal visceral fat level than is waist circumference (38).

It has been suggested that, independently of BMI, weight fluctuations or weight gain could represent independent risk

Table 2. Hazard Ratios and 95% Confidence Intervals for Colorectal Adenomas in Relation to Height, Weight, and BMI in the E3N-EPIC Cohort ($n = 17,391$), France, 1993–2002

	Person-Years	All Adenomas					Only Colon Adenomas[a]			Only Rectal Adenomas[a]			Only Right Colon Adenomas[b]			Only Left Colon Adenomas[b]		
		No. of Cases	HR[c]	95% CI	HR[d]	95% CI	No. of Cases	HR[d]	95% CI	No. of Cases	HR[d]	95% CI	No. of Cases	HR[d]	95% CI	No. of Cases	HR[d]	95% CI
Height (quartiles), cm[e]																		
<158.0	23,220	312	1.00	Referent	1.00	Referent	236	1.00	Referent	50	1.00	Referent	72	1.00	Referent	151	1.00	Referent
158.0–161.9	27,516	386	1.08	0.93, 1.25	1.07	0.92, 1.24	276	1.01	0.85, 1.20	75	1.30	0.91, 1.86	93	1.13	0.83, 1.54	171	0.97	0.78, 1.21
162.0–165.4	27,454	370	1.06	0.92, 1.24	1.07	0.92, 1.24	263	1.00	0.84, 1.19	69	1.23	0.85, 1.78	85	1.08	0.79, 1.48	167	0.98	0.78, 1.22
≥165.5	25,030	340	1.12	0.96, 1.31	1.12	0.96, 1.31	260	1.13	0.95, 1.36	63	1.27	0.87, 1.85	94	1.38	1.01, 1.88	153	1.02	0.81, 1.28
$P_{linear\ trend}$				0.19		0.19			0.21			0.31			0.07			0.86
Weight (time-dependent quartiles), kg[e]																		
<54.0	23,604	285	1.00	Referent	1.00	Referent	203	1.00	Referent	58	1.00	Referent	74	1.00	Referent	117	1.00	Referent
54.0–58.0	25,329	302	0.98	0.83, 1.15	0.96	0.82, 1.13	213	0.95	0.79, 1.15	68	1.05	0.74, 1.49	73	0.90	0.65, 1.25	127	0.98	0.76, 1.26
58.1–64.3	25,529	356	1.12	0.95, 1.30	1.09	0.93, 1.27	277	1.19	0.99, 1.43	50	0.74	0.51, 1.08	80	0.95	0.69, 1.31	187	1.39	1.10, 1.76
≥64.4	28,753	464	1.26	1.08, 1.46	1.24	1.06, 1.44	341	1.29	1.08, 1.54	81	1.02	0.72, 1.44	117	1.23	0.92, 1.65	210	1.38	1.10, 1.74
$P_{linear\ trend}$				<0.01		<0.01			<0.01			0.72			0.11			<0.01
BMI (WHO cutoff points), kg/m^2[e]																		
<18.5	3,705	44	0.97	0.72, 1.33	1.02	0.75, 1.39	36	1.22	0.86, 1.72	4	0.41	0.15, 1.12	14	1.24	0.71, 2.16	18	1.07	0.66, 1.74
18.5–21.9	40,350	481	1.00	Referent	1.00	Referent	336	1.00	Referent	106	1.00	Referent	123	1.00	Referent	195	1.00	Referent
22.0–24.9	35,711	499	1.08	0.95, 1.22	1.07	0.94, 1.21	376	1.16	1.00, 1.34	85	0.82	0.62, 1.09	120	1.00	0.78, 1.29	245	1.31	1.08, 1.58
25.0–29.9	19,350	300	1.16	1.00, 1.34	1.15	0.99, 1.33	223	1.24	1.05, 1.47	53	0.89	0.64, 1.25	75	1.13	0.84, 1.51	137	1.34	1.07, 1.67
≥30	4,098	83	1.53	1.21, 1.94	1.56	1.23, 1.97	63	1.75	1.33, 2.29	9	0.71	0.36, 1.41	12	0.90	0.50, 1.64	46	2.25	1.63, 3.12
$P_{linear\ trend}$				<0.01		<0.01			<0.01			0.65			0.92			<0.01
BMI per 1-kg/m^2 increase			1.03	1.01, 1.04	1.03	1.01, 1.04		1.04	1.02, 1.05		0.98	0.95, 1.02		1.00	0.97, 1.04		1.05	1.03, 1.08

Abbreviations: BMI, body mass index; CI, confidence interval; E3N, Etude épidémiologique des femmes de la Mutuelle Générale de l'Education Nationale; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; MHT, menopausal hormone therapy; WHO, World Health Organization.

[a] $P_{homogeneity}$ colon vs. rectum = 0.72, 0.05, 0.05, and 0.02 for height, weight, BMI with WHO cutoff points, and 1-kg/m^2 BMI increment, respectively.

[b] $P_{homogeneity}$ right colon vs. left colon = 0.17, 0.38, 0.01, and 0.01 for height, weight, BMI with WHO cutoff points, and 1-kg/m^2 BMI increment, respectively.

[c] Age adjusted.

[d] Adjusted on alcohol-free energy intake (baseline), alcohol intake (baseline), total physical activity (time dependent), smoking status (time dependent), colorectal cancer in first degree relatives (time dependent), educational level (baseline), menopausal status (time dependent), and MHT use (time dependent).

[e] Missing values: for height ($n = 0$), weight ($n = 1$), and BMI ($n = 1$), respectively.

Table 3. Hazard Ratios and 95% Confidence Intervals for Colorectal Adenomas in Relation to Waist and Hip Circumferences and Waist/Hip Ratio in the E3N-EPIC Cohort ($n = 14,557$), France, 1995–2002

	Person-Years	All Adenomas					Only Colon Adenomas[a]			Only Rectal Adenomas[a]			Only Right Colon Adenomas[b]			Only Left Colon Adenomas[b]		
		No. of Cases	HR[c]	95% CI	HR[d]	95% CI	No. of Cases	HR[d]	95% CI	No. of Cases	HR[d]	95% CI	No. of Cases	HR[d]	95% CI	No. of Cases	HR[d]	95% CI
Waist circumference (quartiles), cm																		
<70.0	15,571	189	1.00	Referent	1.00	Referent	134	1.00	Referent	39	1.00	Referent	55	1.00	Referent	73	1.00	Referent
70.0–74.9	18,927	266	1.11	0.92, 1.34	1.09	0.90, 1.31	186	1.07	0.86, 1.34	57	1.13	0.75, 1.70	58	0.82	0.57, 1.19	114	1.20	0.90, 1.62
75.0–80.9	17,726	274	1.16	0.97, 1.40	1.13	0.93, 1.36	215	1.24	1.00, 1.54	40	0.80	0.51, 1.25	77	1.08	0.76, 1.53	131	1.40	1.05, 1.86
≥81.0	16,105	296	1.31	1.09, 1.57	1.27	1.05, 1.53	226	1.38	1.11, 1.72	48	0.97	0.62, 1.50	59	0.84	0.58, 1.23	157	1.81	1.36, 2.41
$P_{\text{linear trend}}$				<0.01		0.01			<0.01			0.49			0.75			<0.01
Hip circumference (quartiles), cm																		
<92.0	18,140	238	1.00	Referent	1.00	Referent	173	1.00	Referent	46	1.00	Referent	63	1.00	Referent	99	1.00	Referent
92.0–95.9	15,685	212	0.98	0.81, 1.18	0.96	0.80, 1.16	148	0.92	0.74, 1.15	49	1.16	0.78, 1.74	52	0.90	0.62, 1.30	88	0.95	0.72, 1.27
96.0–100.9	16,964	275	1.13	0.95, 1.34	1.10	0.92, 1.31	213	1.17	0.96, 1.43	40	0.83	0.54, 1.28	54	0.82	0.57, 1.18	149	1.43	1.11, 1.85
≥101.0	17,539	300	1.14	0.96, 1.36	1.12	0.94, 1.33	227	1.17	0.96, 1.43	49	0.92	0.61, 1.39	80	1.12	0.80, 1.58	139	1.27	0.98, 1.66
$P_{\text{linear trend}}$				0.05		0.10			0.03			0.40			0.56			0.01
Waist/hip ratio (quartiles)																		
<0.74	16,648	221	1.00	Referent	1.00	Referent	160	1.00	Referent	47	1.00	Referent	58	1.00	Referent	94	1.00	Referent
0.74–0.78	19,292	281	1.06	0.89, 1.26	1.04	0.87, 1.24	215	1.09	0.89, 1.34	43	0.76	0.50, 1.15	78	1.10	0.78, 1.54	127	1.10	0.84, 1.43
0.79–0.81	13,605	219	1.15	0.96, 1.39	1.13	0.93, 1.36	162	1.14	0.92, 1.42	39	0.95	0.62, 1.46	50	0.97	0.66, 1.42	103	1.24	0.94, 1.65
≥0.82	18,784	304	1.13	0.95, 1.34	1.09	0.91, 1.30	224	1.11	0.90, 1.36	55	0.93	0.63, 1.38	63	0.85	0.59, 1.22	151	1.29	0.99, 1.67
$P_{\text{linear trend}}$				0.13		0.26			0.34			0.96			0.25			0.04

Abbreviations: CI, confidence interval; E3N, Etude épidémiologique des femmes de la Mutuelle Générale de l'Education Nationale ; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; MHT, menopausal hormone therapy.

[a] $P_{\text{homogeneity}}$ colon vs. rectum = 0.04, 0.09, and 0.70 for waist circumference, hip circumference, and waist/hip ratio, respectively.

[b] $P_{\text{homogeneity}}$ right colon vs. left colon = <0.01, 0.29, and 0.03 for waist circumference, hip circumference, and waist/hip ratio, respectively.

[c] Age adjusted.

[d] Adjusted on alcohol-free energy intake (baseline), alcohol intake (baseline), total physical activity (time dependent), smoking status (time dependent), colorectal cancer in first degree relatives (time dependent), educational level (baseline), menopausal status (time dependent), and MHT use (time dependent).

Table 4. Hazard Ratios and 95% Confidence Intervals for Colorectal Adenoma Risk in Relation to Weight Change in the E3N-EPIC Cohort ($n = 17,391$), France, 1993–2002

	Person-Years	All Adenomas					Only Colon Adenomas[a]			Only Rectal Adenomas[a]			Only Right Colon Adenomas[b]			Only Left Colon Adenomas[b]		
		No. of Cases	HR[c]	95% CI	HR[d]	95% CI	No. of Cases	HR[d]	95% CI	No. of Cases	HR[d]	95% CI	No. of Cases	HR[d]	95% CI	No. of Cases	HR[d]	95% CI
Mean annual weight gain (time-dependent variable), kg/year[e]																		
<0	19,852	266	1.11	0.92, 1.34	1.12	0.92, 1.35	181	1.01	0.81, 1.27	55	1.27	0.82, 1.96	70	1.02	0.71, 1.47	99	0.99	0.73, 1.33
0	15,475	178	1.00	Referent	1.00	Referent	133	1.00	Referent	33	1.00	Referent	50	1.00	Referent	76	1.00	Referent
0.1–0.49	31,815	477	1.26	1.06, 1.50	1.25	1.05, 1.49	359	1.25	1.02, 1.52	88	1.28	0.85, 1.90	112	1.03	0.74, 1.43	231	1.41	1.09, 1.83
≥0.5	35,781	483	1.24	1.04, 1.47	1.23	1.03, 1.46	360	1.23	1.01, 1.50	79	1.07	0.71, 1.61	112	1.03	0.74, 1.45	234	1.38	1.07, 1.79
$P_{\text{linear trend}}$				0.03		0.05			0.01			0.55			0.89			<0.01
Mean annual weight fluctuation (time-dependent variable), kg/year																		
0–0.49	28,543	366	1.00	Referent	1.00	Referent	261	1.00	Referent	79	1.00	Referent	91	1.00	Referent	156	1.00	Referent
0.5–1	34,296	512	1.18	1.03, 1.35	1.17	1.02, 1.34	380	1.22	1.04, 1.43	89	0.94	0.69, 1.27	136	1.26	0.97, 1.65	228	1.22	0.99, 1.50
>1	40,084	526	1.06	0.93, 1.21	1.06	0.93, 1.21	392	1.11	0.95, 1.30	87	0.79	0.58, 1.08	117	0.97	0.74, 1.28	256	1.21	0.99, 1.50
$P_{\text{linear trend}}$				0.36		0.55			0.26			0.13			0.69			0.08

Abbreviations: CI, confidence interval; E3N, Etude épidémiologique des femmes de la Mutuelle Générale de l'Education Nationale; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; MHT, menopausal hormone therapy.

[a] $P_{\text{homogeneity}}$ colon vs. rectum = 0.09; 0.06 for mean relative and mean absolute variations, respectively.

[b] $P_{\text{homogeneity}}$ right colon vs. left colon = 0.05; 0.17 for mean relative and mean absolute variations, respectively.

[c] Age adjusted.

[d] Adjusted on alcohol-free energy intake (baseline), alcohol intake (baseline), total physical activity (time dependent), smoking status (time dependent), colorectal cancer in first degree relatives (time dependent), educational level (baseline), menopausal status (time dependent), and MHT use (time dependent).

[e] Missing values: for mean relative and mean weight absolute variation ($n = 61$).

factors for colorectal adenomas (13, 15, 27, 30) or cancer (41). The definitions of weight changes differ considerably among studies in terms of assessment (prospective or retrospective) or period considered. We chose to consider time-dependent cumulative variables, which captured both the 2-year period prior to diagnosis as well as preceding weight changes. Indeed, we could consider only the date of adenoma diagnosis, which could be several years later than adenoma occurrence itself. Our results suggest that only weight gain, and not weight fluctuation, is associated with an increased risk of colon, specifically left colon, adenomas.

Height has been consistently associated with an increased risk of colorectal cancer (1), with the underlying hypothesis that factors promoting child growth rather than tallness itself (1) affect early stages of colorectal carcinogenesis. However, 2 (27, 28) of the 3 (20, 27, 28) studies that explored associations between height and colorectal adenomas failed to observe any association. Our results are in line with these studies, although the small proportion of tall women may have prevented us from finding an association; the borderline statistically significant positive association with right colon adenoma risk warrants further investigation.

Some hypotheses have been proposed to explain the observed associations. Obesity, particularly abdominal obesity, is related to insulin resistance, hyperinsulinemia, and the development of type 2 diabetes (42). Diabetes mellitus has been associated with both advanced and nonadvanced adenomas (43). An increased risk of colon cancer has been observed in women recently diagnosed with diabetes, but the association was weaker 15 years after diagnosis (44); this emphasizes a role for hyperinsulinemia, because high insulin levels predominate in the initial stages of impaired glucose tolerance, whereas hypoinsulinemia occurs in later stages of diabetes (42). Furthermore, high serum levels of C-peptide, a marker of insulin secretion, have been positively associated with colorectal neoplasia (42). The metabolic syndrome has also been associated with an increased risk of colorectal adenomas, especially proximal and advanced adenomas (40). Hyperinsulinemia appears, thus, to be a consistent marker of enhanced colon cancer risk; however, it remains unclear whether this is due to direct mitogenic and antiapoptotic effects of insulin on tumor growth or indirectly through insulin-like growth factor 1 (42, 45) that would inhibit apoptosis and stimulate cell proliferation. Indeed, high insulin-like growth factor 1 levels have been associated with a high risk of colorectal adenomas or cancers (46), although not consistently (47).

Inflammatory mechanisms have also been mentioned, because obesity is thought to induce a chronic low-grade inflammation (1). High C-reactive protein levels have been associated with colorectal neoplasia (48), and aspirin and nonsteroidal antiinflammatory drugs have been associated with reduced adenoma risk or recurrence (49). Adipocytes and macrophages in fat tissue secrete several proinflammatory molecules (45), such as interleukin 6 and tumor necrosis factor α, that could induce insulin resistance (42, 45).

There is no clear explanation for the restriction of our findings to the distal colon. Several anatomic, embryologic, and physiologic differences (2), as well as such epidemiologic features as sex ratio, trends in migrant populations, and time trends (21), indicate that right colon, left colon, and rectal cancers may have partly different etiologic pathways and should probably be considered as 3 separate entities. However, the impact of a given factor along the large bowel may differ according to the prevalence of other environmental factors and, thus, according to sex or country. We suggest that site-specific analyses should systematically be performed in future studies on the relation between anthropometry and colorectal tumors.

Strengths of our study include its prospective design, large population, long follow-up, biennial updating, and adjustment for many potential confounders. We excluded women with prevalent adenomas, previous hyperplastic polyps, or unspecified incident polyps for several reasons, including possible changes in risk behavior since the first adenoma diagnosis, difficulty in ascertaining the quality and homogeneity of pathologic analyses performed decades earlier, and differences in etiology between incident and recurrent adenomas. Bias was limited by histologic confirmation of all cases and inclusion of polyp-free subjects as noncases. Moreover, we requested colonoscopic and histologic details on the characteristics and location of adenomas, making it possible to perform subgroup analyses.

Our study has some limitations. First, similarly to most studies, we assessed adenoma diagnosis rather than occurrence, which may have happened years earlier, leading to errors in estimating the period at risk. However, avoiding this problem would require a baseline polyp-free colonoscopy in a very large cohort, followed up with regular colonoscopies, and, thus, adenoma occurrence has little feasibility. Mass screening for colorectal tumors in France, based on the fecal occult blood test, was set up in 2003. Thus, during the study period, complete colonoscopy was mostly performed for bowel symptoms or for screening first degree relatives of subjects with colorectal cancer. Because of potential bias, we restricted the adenoma study population to women who underwent at least 1 colonoscopy during follow-up. When comparisons were made between women aged 50 or more years during follow-up without colonoscopy and the women included in the present analyses, the main characteristics were similar, except for a smaller proportion with a family history of colorectal cancer. Our 8.8 ratio of cases to noncases is lower than the ratios in other studies (13.5 in Hermann et al. (18) and 22.1 in a study evaluating the French colorectal cancer screening pilot program (50)). This is in agreement with French reports prior to the national screening campaign, which suggested that basing colonoscopies on symptoms had a poor efficiency in terms of tumor detection (51). The high mean educational level of the women in our cohort may explain an easy access to gastroenterologists and the prescription of colonoscopies for minor symptoms; thus, extrapolation to the general population should be cautious. Another potential limitation of our study refers to the reliability of the anthropometric indicators. Participants were not weighed or measured, and we used self-reported weight and height to calculate BMI. However, a validation study proved that these measures were accurate (52). Regarding the estimation of weight gain and fluctuations, we could consider only weight changes from one questionnaire to another and, thus, missed

seasonal changes as well as some short-term variations. Thus, we may have underestimated weight fluctuations and reduced our ability to find a significant association with adenoma risk.

In conclusion, obesity and weight gain were associated with early events of colorectal carcinogenesis in women, and specifically regarding the distal colon. This adds to the list of benefits of weight control in middle and late adulthood, which could reduce the burden of chronic diseases, especially cancer.

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(Appendix Tables 1 and 2 follow)

Appendix

Appendix Table 1. Hazard Ratios and 95% Confidence Intervals for Colorectal Adenomas and Anthropometric Factors According to Stage in the Adenoma-Carcinoma Sequence, E3N-EPIC Cohort, France, for Height, Weight, BMI, Mean Weight Gain, and Variation ($n = 17,391$) and for Waist Circumference, Hip Circumference, and Waist/Hip Ratio ($n = 14,557$), 1993–2002

	Person-Years	Nonadvanced Adenomas			Advanced Adenomas			$P_{homogeneity}$
		No. of Cases	HR[a]	95% CI	No. of Cases	HR[a]	95% CI	
Height (quartiles), cm								
<158.0	23,220	174	1.00	Referent	138	1.00	Referent	0.54
158.0–161.9	27,516	217	1.07	0.88, 1.31	169	1.07	0.85, 1.34	
162.0–165.4	27,454	219	1.12	0.92, 1.37	151	0.99	0.79, 1.25	
≥165.5	25,030	199	1.15	0.94, 1.41	141	1.08	0.85, 1.37	
$P_{linear\ trend}$				0.16			0.70	
Weight (time-dependent quartiles), kg[b]								
<54.0	23,604	161	1.00	Referent	124	1.00	Referent	0.86
54.0–58.0	25,329	177	1.00	0.81, 1.24	125	0.91	0.71, 1.17	
58.1–64.3	25,529	215	1.18	0.96, 1.44	141	0.98	0.77, 1.25	
≥64.4	28,753	255	1.22	1.00, 1.49	209	1.25	1.00, 1.57	
$P_{linear\ trend}$				0.02			0.02	
BMI (WHO cutoff points), kg/m^{2}[b]								
<18.5	3,705	23	0.91	0.60, 1.40	21	1.18	0.75, 1.85	0.88
18.5–21.9	40,350	281	1.00	Referent	200	1.00	Referent	
22.0–24.9	35,711	296	1.11	0.94, 1.30	203	1.02	0.83, 1.24	
25.0–29.9	19,350	159	1.08	0.88, 1.31	141	1.25	1.00, 1.55	
≥30	4,098	49	1.61	1.18, 2.18	34	1.49	1.03, 2.16	
$P_{linear\ trend}$				0.02			0.03	
BMI per 1-kg/m^{2} increase			1.03	1.01, 1.05		1.03	1.01, 1.05	0.86
Mean annual weight gain (time-dependent variable), kg/year[b]								
<0	19,852	154	1.01	0.79, 1.28	112	1.32	0.97, 1.79	0.60
0	15,475	115	1.00	Referent	63	1.00	Referent	
0.1–0.49	31,815	250	1.02	0.82, 1.27	227	1.67	1.27, 2.21	
≥0.5	35,781	289	1.12	0.90, 1.39	194	1.43	1.07, 1.90	
$P_{linear\ trend}$				0.26			0.10	
Mean annual weight fluctuation (time-dependent variable), kg/year[b]								
0–0.49	28,543	201	1.00	Referent	165	1.00	Referent	0.64
0.5–1	34,296	304	1.26	1.06, 1.51	208	1.06	0.86, 1.30	
>1	40,084	303	1.10	0.92, 1.31	223	1.01	0.82, 1.24	
$P_{linear\ trend}$				0.45			0.97	
Waist circumference (quartiles), cm								
<70	15,571	106	1.00	Referent	83	1.00	Referent	0.51
70–74.9	18,927	142	1.05	0.82, 1.36	124	1.14	0.86, 1.50	
75–80.9	17,726	160	1.21	0.94, 1.54	114	1.03	0.78, 1.37	
≥81	16,105	162	1.30	1.01, 1.67	134	1.23	0.93, 1.64	
$P_{linear\ trend}$				0.02			0.24	

Table continues

Appendix Table 1. Continued

	Person-Years	Nonadvanced Adenomas			Advanced Adenomas			$P_{homogeneity}$
		No. of Cases	HR[a]	95% CI	No. of Cases	HR[a]	95% CI	
Hip circumference (quartiles), cm								
<92	18,140	129	1.00	Referent	109	1.00	Referent	0.85
92.0–95.9	15,685	123	1.04	0.81, 1.33	89	0.88	0.66, 1.16	
96.0–100.9	16,964	157	1.18	0.93, 1.49	118	1.01	0.78, 1.31	
≥101.0	17,539	161	1.14	0.90, 1.45	139	1.09	0.84, 1.41	
$P_{linear\ trend}$				0.18			0.34	
Waist/hip ratio (quartiles)								
<0.74	16,648	128	1.00	Referent	93	1.00	Referent	0.62
0.74–0.78	19,292	149	0.96	0.76, 1.21	132	1.15	0.88, 1.50	
0.79–0.81	13,605	119	1.08	0.84, 1.38	100	1.19	0.90, 1.58	
≥0.82	18,784	174	1.11	0.88, 1.40	130	1.07	0.82, 1.40	
$P_{linear\ trend}$				0.24			0.70	

Abbreviations: BMI, body mass index; CI, confidence interval; E3N, Etude épidémiologique des femmes de la Mutuelle Générale de l'Education Nationale; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; MHT, menopausal hormone therapy; WHO, World Health Organization.

[a] Adjusted on alcohol-free energy intake (baseline), alcohol intake (baseline), total physical activity (time dependent), smoking status (time dependent), colorectal cancer in first degree relatives (time dependent), educational level (baseline), menopausal status (time dependent), and MHT use (time dependent).

[b] Missing values: for weight ($n = 1$), BMI ($n = 1$), mean annual weight gain ($n = 61$), and mean annual weight fluctuation ($n = 61$), respectively.

Appendix Table 2. Hazard Ratios and 95% Confidence Intervals for Left Colon Adenomas and Anthropometric Factors According to Stage in the Adenoma-Carcinoma Sequence, E3N-EPIC Cohort, France, for Height, Weight, BMI, Mean Annual Weight Gain, and Fluctuation ($n = 17,391$) and for Waist Circumference, Hip Circumference, and the Waist/Hip Ratio ($n = 14,557$), 1993–2002

	Person-Years	Nonadvanced Adenomas			Advanced Adenomas			$P_{homogeneity}$
		No. of Cases	HR[a]	95% CI	No. of Cases	HR[a]	95% CI	
Height (quartiles), cm								
<158.0	23,220	85	1.00	Referent	66	1.00	Referent	0.66
158.0–161.9	27,516	90	0.89	0.66, 1.20	81	1.07	0.77, 1.48	
162.0–165.4	27,454	92	0.94	0.70, 1.26	75	1.03	0.74, 1.43	
≥165.5	25,030	84	0.96	0.70, 1.30	69	1.10	0.78, 1.55	
$P_{linear\ trend}$				0.87			0.66	
Weight (time-dependent quartiles), kg[b]								
<54.0	23,604	65	1.00	Referent	52	1.00	Referent	0.95
54.0–58.0	25,329	66	0.92	0.65, 1.29	61	1.06	0.73, 1.54	
58.1–64.3	25,529	109	1.47	1.08, 2.00	78	1.30	0.91, 1.85	
≥64.4	28,753	110	1.32	0.97, 1.81	100	1.45	1.03, 2.04	
$P_{linear\ trend}$				0.01			0.01	
BMI (WHO cutoff points), kg/m^{2b}								
<18.5	3,705	10	1.10	0.58, 2.12	8	1.03	0.50, 2.12	0.73
18.5–21.9	40,350	106	1.00	Referent	89	1.00	Referent	
22.0–24.9	35,711	144	1.45	1.13, 1.87	101	1.15	0.86, 1.53	
25.0–29.9	19,350	64	1.20	0.87, 1.64	73	1.49	1.09, 2.04	
≥30	4,098	26	2.42	1.57, 3.75	20	2.06	1.26, 3.37	
$P_{linear\ trend}$				<0.01			<0.01	
BMI per 1-kg/m^2 increase			1.05	1.02, 1.08		1.06	1.03, 1.09	0.68
Mean annual weight gain (time-dependent variable), kg/year[b]								
<0	19,852	59	0.98	0.67, 1.45	40	0.99	0.62, 1.59	0.28
0	15,475	46	1.00	Referent	30	1.00	Referent	
0.1–0.49	31,815	113	1.15	0.81, 1.61	118	1.82	1.22, 2.72	
≥0.5	35,781	132	1.26	0.90, 1.77	102	1.57	1.04, 2.36	
$P_{linear\ trend}$				0.07			<0.01	
Mean annual weight fluctuation (time-dependent variable), kg/year[b]								
0–0.49	28,543	82	1.00	Referent	74	1.00	Referent	0.55
0.5–1	34,296	124	1.25	0.95, 1.66	104	1.18	0.88, 1.59	
>1	40,084	144	1.28	0.97, 1.68	112	1.13	0.84, 1.52	
$P_{linear\ trend}$				0.09			0.46	
Waist circumference (quartiles), cm								
<70	15,571	44	1.00	Referent	29	1.00	Referent	0.43
70–74.9	18,927	65	1.15	0.79, 1.69	49	1.28	0.81, 2.03	
75–80.9	17,726	65	1.18	0.80, 1.73	66	1.72	1.11, 2.68	
≥81	16,105	83	1.67	1.15, 2.43	74	2.02	1.30, 3.14	
$P_{linear\ trend}$				0.01			<0.01	

Table continues

Appendix Table 2. Continued

	Person-Years	Nonadvanced Adenomas			Advanced Adenomas			$P_{homogeneity}$
		No. of Cases	HR[a]	95% CI	No. of Cases	HR[a]	95% CI	
Hip circumference (quartiles), cm								
<92	18,140	59	1.00	Referent	40	1.00	Referent	0.06
92.0–95.9	15,685	54	0.98	0.68, 1.42	34	0.91	0.58, 1.44	
96.0–100.9	16,964	78	1.28	0.91, 1.79	71	1.66	1.12, 2.45	
≥101.0	17,539	66	1.05	0.73, 1.50	73	1.60	1.08, 2.37	
$P_{linear\ trend}$				0.50			<0.01	
Waist/hip ratio (quartiles)								
<0.74	16,648	50	1.00	Referent	44	1.00	Referent	0.13
0.74–0.78	19,292	63	1.03	0.71, 1.50	64	1.17	0.79, 1.72	
0.79–0.81	13,605	55	1.28	0.87, 1.88	48	1.20	0.80, 1.81	
≥0.82	18,784	89	1.48	1.04, 2.10	62	1.08	0.73, 1.60	
$P_{linear\ trend}$				0.01			0.78	

Abbreviations: BMI, body mass index; CI, confidence interval; E3N, Etude épidémiologique des femmes de la Mutuelle Générale de l'Education Nationale; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; MHT, menopausal hormone therapy WHO, World Health Organization.

[a] Adjusted on alcohol-free energy intake (baseline), alcohol intake (baseline), total physical activity (time dependent), smoking status (time dependent), colorectal cancer in first degree relatives (time dependent), educational level (baseline), menopausal status (time dependent), and MHT use (time dependent).

[b] Missing values: for weight ($n = 1$), BMI ($n = 1$), mean annual weight gain ($n = 61$), and mean annual weight fluctuation ($n = 61$), respectively.