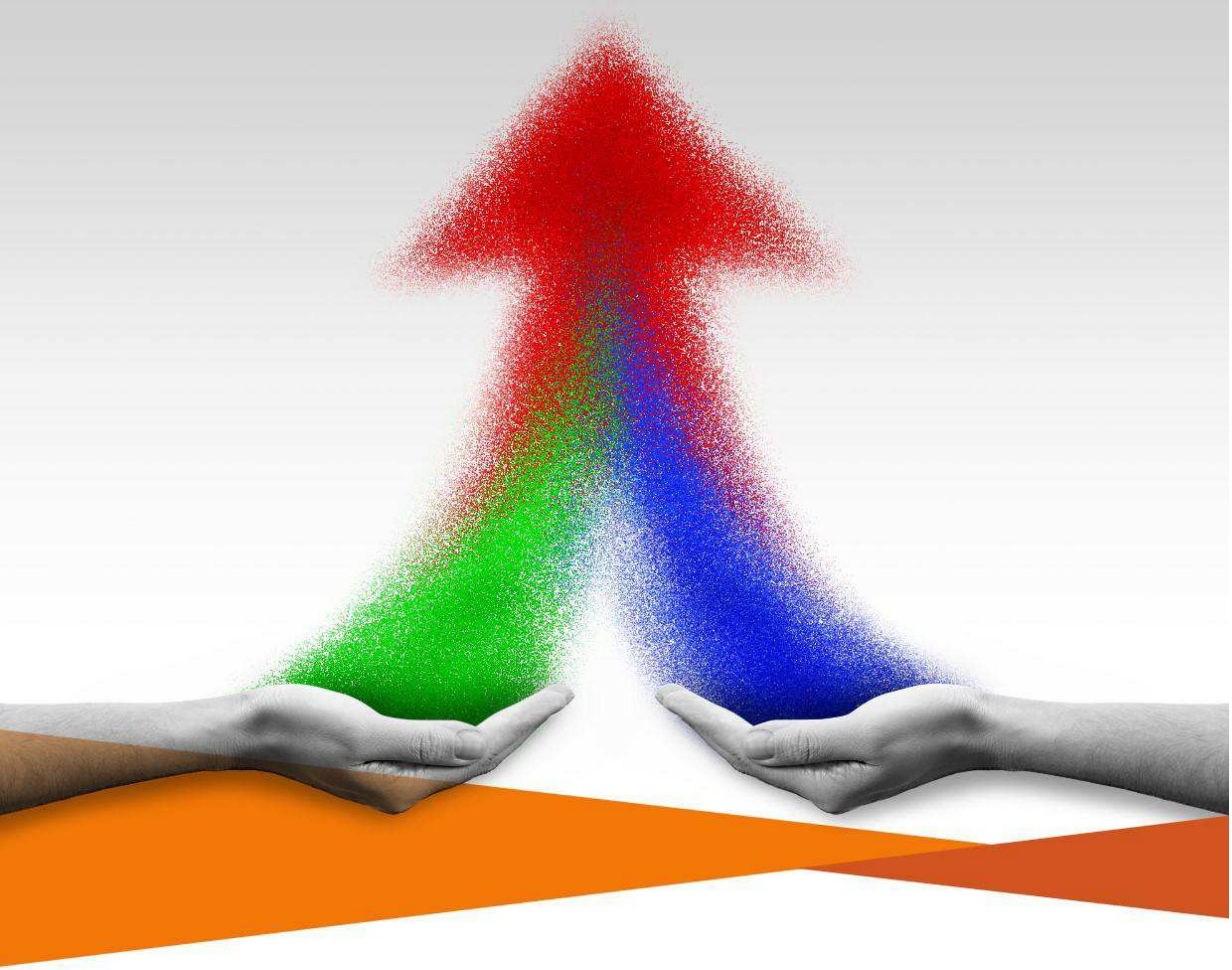

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BODY SIZE AND COLORECTAL-CANCER RISK

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Individuals whose energy intake exceeds expenditure are at increased risk of colorectal cancer. To determine whether body-size measurements at different ages were risk factors for cancer of the colon-rectum, we carried out a hospital-based case-control study in 6 Italian areas, 2 of which were in the South. Interviews were conducted with 1,217 subjects of both genders with incident histologically confirmed cancer of the colon, 726 with cancer of the rectum, and 4,136 controls hospitalized for acute, non-neoplastic, non-digestive conditions. The questionnaire included information on sociodemographic factors, and physical activity, a validated dietary history, height, weight at diagnosis and at 12, 30 and 50 years of age and waist-to-hip ratio (WHR). After allowance for education, physical activity, energy intake, family history of colorectal cancer and recent change in weight, the body-mass index (BMI) was significantly associated with colorectal-cancer-risk in men (odds ratio, OR, in highest *vs.* lowest quintile = 1.7; 95% confidence interval, CI, 1.3–2.3), but not in women (corresponding OR = 0.9; 95% CI, 0.7–1.2). Cases of both gender tended to have higher BMI than controls in adolescence, young adulthood and middle age. Height appeared unrelated to risk. In women, but not in men, WHR was positively associated with risk, independently of BMI (OR for ≥0.90 *vs.* ≤0.81 = 1.6; 95% CI; 1.2–2.1). Thus, excessive weight predicts colorectal-cancer risk in men, whereas abdominal obesity (*i.e.,* a high WHR) represents a more reliable risk indicator in women. *Int. J Cancer* 78:161–165, 1998.
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Epidemiologic studies on risk factors for colorectal cancer have focused mainly on dietary factors (Potter, 1996; Franceschi *et al.,* 1997; Slattery *et al.,* 1997*a*). Weight and height have also been studied (Howe *et al.,* 1997), partly because they reflect the balance between energy intake and expenditure in different age periods. Individuals whose energy intake exceeds their energy expenditure through physical activity are at increased risk of colon cancer (Howe *et al.,* 1997; Slattery *et al.,* 1997*b*).

A few case-control studies showed no consistent association between body-size indices and colorectal-cancer risk (Howe *et al.,* 1997), but most (Gerhardsson de Verdier *et al.,* 1990; Kune *et al.,* 1990; Le Marchand *et al.,* 1992; Dietz *et al.,* 1995; Slattery *et al.,* 1997*b*) reported a direct association between body mass and colorectal cancer, clearer in men than in women (Gerhardsson de Verdier *et al.,* 1990; Kune *et al.,* 1990; Slattery *et al.,* 1997*b*). In ecological and prospective investigations, which are less susceptible to the problem of weight loss in proximity of cancer diagnosis, increased body-mass indices (BMI) have generally been associated with a moderate excess of colorectal cancer (Bostick *et al.,* 1994; Giovannucci *et al.,* 1995; Martinez *et al.,* 1997).

The influence of excessive weight on colorectal-cancer risk may be mediated, like that of sedentary lifestyle and high intake of refined sugar, by increased insulin resistance and hyperinsulinemia (Giovannucci, 1995). Then abdominal obesity may be the primary component of obesity linked to colorectal-cancer risk (Giovannucci, 1995). Information on waist-to-hip ratio (WHR) as an indicator of abdominal obesity and colorectal cancer risk is, however, scanty (Bostick *et al.,* 1994; Giovannucci *et al.,* 1995; Martinez *et al.,* 1997). Height, independently of weight, also appeared to be associated with increased colon-cancer risk in some studies (Giovannucci *et al.,* 1995; Howe *et al.,* 1997), but not all (Dietz *et al.,* 1995).

The present multicenter case-control study enabled us to elucidate further the role of various anthropometric measures, including WHR, on a large number of Italian colorectal-cancer cases and control subjects.

MATERIAL AND METHODS

A multicenter case-control study of cancer of the colon and rectum has been conducted between January 1992 and June 1996 in 6 Italian areas: the provinces of Pordenone and Gorizia in North-eastern Italy, the urban areas of Milan and Genoa, and the province of Forlì, in the North of the country, Latina, and the urban area of Naples in the South (Franceschi *et al.,* 1997).

Cases were subjects at first histologically confirmed colorectal cancer, diagnosed no longer than one year prior to the interview, and with no previous diagnoses of cancer; 8 cases of cancer of the colon and 2 of the rectum were excluded because information on weight or height were missing. Thus, 1,217 subjects with cancer of the colon (687 men and 530 women, median age 62, range 19–74 years) and 726 with cancer of the rectum and recto-sigmoid junction (437 men and 289 women, median age 62, range 23–74 years) were included in the present analysis (Table I).

Controls were patients with no history of cancer, admitted to major teaching and general hospitals in the same catchment areas of cases for acute, non-neoplastic, non-gynecological conditions, unrelated to hormonal or digestive-tract diseases; 6 men and 12 women were excluded because of lack of information on either height or weight. Thus, the present analyses included 2,067 men and 2,069 women (median age 58, range 23–74) belonging to the following diagnostic categories: traumas, mostly fractures and sprains (27%); other orthopedic disorders, such as low back pain and disc disorders (24%); acute surgical conditions (18%); eye diseases (24%); and other miscellaneous diseases, such as ear, nose and throat, skin and dental conditions (7%). Controls were younger than cases (Table I), since they were collected within the framework of a multi-site case-control study including cancer sites whose age distribution was different from that of cancer of the colon-rectum (*e.g.,* breast). Thus, we allowed carefully for the age imbalance in statistical analyses. On average, about 4% of cases

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TABLE I – DISTRIBUTION OF 1,217 CASES OF COLON CANCER, 726 OF RECTAL CANCER, AND 4,136 CONTROLS[1] BY GENDER, AGE GROUP, PHYSICAL ACTIVITY, TOTAL ENERGY INTAKE AND FAMILY HISTORY OF COLORECTAL CANCER, ITALY, 1992–1996

Characteristic	Cancer cases		Controls number (%)
	Colon number (%)	Rectum number (%)	
Gender			
Males	687 (56)	437 (60)	2,067 (50)
Females	530 (44)	289 (40)	2,069 (50)
Age group (years)			
<40	55 (4)	26 (4)	344 (8)
40–49	114 (9)	67 (9)	731 (18)
50–59	320 (26)	197 (27)	1,239 (30)
60–69	514 (42)	306 (42)	1,351 (33)
≥70	214 (18)	130 (18)	471 (11)
Physical activity			
Low	443 (36)	231 (32)	1,377 (33)
Medium	446 (37)	257 (35)	1,468 (36)
High	328 (27)	238 (33)	1,291 (31)
χ^2_1 (trend)[2]	35.02[3]	0.64	
Total energy intake (quintiles)			
I	222 (18)	140 (19)	853 (21)
II	241 (20)	135 (19)	840 (20)
III	244 (20)	152 (21)	820 (20)
IV	246 (20)	130 (18)	840 (20)
V	264 (22)	169 (23)	783 (19)
χ^2_1 (trend)[2]	10.89[3]	6.34[4]	
Family history of colorectal cancer			
No	1,083 (89)	674 (93)	3,990 (96)
Yes	134 (11)	52 (7)	146 (4)
χ^2_1 [2]	87.46[3]	20.76[3]	

[1]Some figures do not add up to the total because of some missing values.–[2]Compared with the control group, adjusted for age and study centre.–[3]$p < 0.01$.–[4]$p < 0.05$.

and controls approached during their hospital stay refused to be interviewed.

The same structured questionnaire and coding manual were used in each center, and all interviewers were centrally trained and routinely supervised. Data checking for consistency and reliability was also conducted centrally. The questionnaire included information on sociodemographic characteristics, such as education and occupation, lifetime smoking and alcohol-drinking habits, and physical activity. Dietary habits were investigated through a validated food-frequency-consumption section (Decarli *et al.,* 1996). To compute energy intake, Italian food-composition databases were used. For anthropometric measurements, study subjects were asked to report their habitual height and weight in the year before cancer diagnosis or interview (in control subjects). Self-reported values were validated by means of medical records. In addition, weight at 30 and 50 years of age, and highest (outside pregnancy) and lowest weight in adult life were elicited. Perceived body size at 12 years of age was also explored (*i.e.,* thinner than, same as, heavier than peers). In order to compute WHR, the interviewer measured the circumference of waist (2 cm above the umbilicus) and hip (maximal protrusion). In 490 cases and 762 control subjects, waist and/or hip measurements could not be taken. The BMI was computed as weight in kilograms divided by height in square meters. Change in BMI was computed as the difference between BMI at diagnosis or interview (for controls) and BMI at age 30 for subjects with age at diagnosis less than 55 and at age 50 for subjects with age at diagnosis above 55 years. Quintiles of height, weight and waist/hip ratio were defined from the joint distribution of cases and controls separately for men and women. Cut-off points for BMI quintiles at various ages were the same in the 2 genders (*i.e.,* 22.7, 24.6, 26.5 and 28.7 for BMI at diagnosis; 20.4, 22.5, 23.9 and 25.6 for BMI at age 30; and 22.5, 24.3, 25.9, 28.1 for BMI at age 50 years).

Odds ratio (OR) and corresponding 95% confidence intervals (CI) were computed using unconditional multiple-logistic-regression models (Breslow and Day, 1980). All the regression equations included terms for age (continuous and in quinquennia), study center, years of education, occupational physical activity (tertiles), total energy intake (quintiles), and, when mentioned, change in BMI. Distribution of the risk factors in cases and corresponding OR were used to compute attributable risks and corresponding CI. Interaction terms between BMI or WHR and selected characteristics were evaluated by means of the Wald Chi-squared test.

RESULTS

Table I shows the distribution of cases of cancer of the colon and rectum and control subjects according to gender, physical activity, energy intake and family history of colorectal cancer. Colon-cancer but not rectal-cancer cases reported lower levels of physical activity than control subjects. Colon- and rectal-cancer cases alike reported higher levels of energy intake and more frequent positive family cancer history than controls.

The distribution of cases and controls by quintiles of different body-size measurements at diagnosis, OR and corresponding 95% CI are shown in Table II, separately for men and women. No clear risk pattern emerged for height in either gender. In cases and in controls, median height was 171 cm in men and 160 cm in women. Weight at diagnosis was unrelated to colorectal-cancer risk in men (median weight 76 kg in cases and 77 kg in controls), but inversely associated in women (median weight 64 kg in cases and 65 kg in controls, OR in highest *vs.* lowest quintile = 0.7; 95% CI, 0.5–0.9). WHR seemed to influence colorectal-cancer risk in the opposite direction in men (median 0.94 in cases, 0.95 in controls) and women (0.85 in cases, 0.83 in controls). Men in the highest WHR quintile were at significantly reduced cancer risk (OR = 0.6; 95% CI, 0.4–0.8), whereas women were at elevated risk (OR = 1.7; 95% CI, 1.2–2.3).

In both genders, significantly fewer cases than controls reported an increase in BMI in years before diagnosis (OR = 0.8 and 0.7 in men and women respectively) (Table II). Thus, BMI change was allowed for. A significant positive association with BMI at diagnosis emerged in men, while no association was seen in women. Men in the highest BMI quintile showed an OR of 1.7 (95% CI, 1.3–2.3) as compared with those in the lowest one. Corresponding OR in women was 0.9 (95% CI, 0.7–1.2).

The relationship between colorectal-cancer risk and body-size indices at different ages is considered in Table III. Perceived body size at age 12 years showed a moderate positive association, which attained borderline significance in women only. In both genders, there were significant trends of increasing risk with the increase of BMI at age 30 (OR in highest *vs.* lowest quintile, 1.8 in men and 1.3 in women). At age 50 years, however, such an association was restricted to men (OR in highest quintile = 1.7; 95% CI, 1.3–2.3).

The combined influence of excessive weight (*i.e.,* BMI ≥ 25) and WHR is shown in Table IV. Although WHR differed substantially in the 2 genders, an attempt was made to compare men and women, at least in some common categories. In both genders, the 2 factors seemed to interact multiplicatively. Among men, excessive weight was associated with elevated OR in each stratum of WHR and overall, after allowance for it. Among women, the same held true for WHR, whose positive association with cancer risk emerged among normal as well as overweight women. However, among overweight individuals of both genders, no risk difference was seen between WHR 0.82–0.89 and ≥0.90 (Table IV).

The 2 body-size indices associated with colorectal-cancer risk in the 2 genders are re-examined in Table V in separate strata of selected co-variates. In men, the effect of excessive weight appeared somewhat, albeit not significantly, weaker at an early age (<55 years), and more marked for cancer of the left colon than of

TABLE II – DISTRIBUTION OF CASES OF COLORECTAL CANCER AND CONTROLS, OR[1,2] AND CORRESPONDING 95% CI[3] BY VARIOUS BODY-SIZE MEASUREMENTS AND GENDER, ITALY, 1992–1996

Variable	Quintile	Males		Females	
		Cases:Controls	OR (95% CI)	Cases:Controls	OR (95% CI)
Height (cm)	1[4]	241:393	1	152:413	1
	2	164:321	0.84 (0.65–1.09)	122:293	1.15 (0.86–1.54)
	3	262:485	0.96 (0.76–1.21)	227:529	1.17 (0.91–1.50)
	4	254:438	1.03 (0.81–1.30)	161:400	1.06 (0.80–1.39)
	5	203:430	0.86 (0.67–1.11)	157:434	0.89 (0.68–1.17)
χ_1^2 (trend)			0.14; $p = 0.71$		0.92; $p = 0.34$
Weight (kg)	1[4]	242:433	1	171:397	1
	2	242:423	1.07 (0.85–1.35)	162:405	0.87 (0.70–1.14)
	3	193:338	1.09 (0.85–1.39)	152:455	0.66 (0.50–0.86)
	4	227:451	0.99 (0.78–1.25)	175:360	0.94 (0.72–1.23)
	5	220:422	1.08 (0.86–1.37)	159:452	0.66 (0.50–0.86)
χ_1^2 (trend)			0.08; $p = 0.77$		6.06; $p = 0.01$
Waist-to-hip ratio (WHR)	1[4]	177:318	1	94:373	1
	2	184:314	1.06 (0.80–1.38)	115:352	1.20 (0.87–1.65)
	3	167:335	0.82 (0.62–1.08)	143:327	1.47 (1.07–2.01)
	4	141:359	0.65 (0.49–0.86)	135:334	1.30 (0.95–1.79)
	5	132:361	0.59 (0.44–0.78)	165:301	1.70 (1.24–2.32)
χ_1^2 (trend)			22.66; $p < 0.001$		10.27; $p = 0.001$
Change in body-mass index (BMI)[5]	Decrease	213:295	1.10 (0.88–1.37)	141:287	0.93 (0.71–1.20)
	Equal[4]	428:728	1	273:563	1
	Increase	436:978	0.75 (0.63–0.88)	353:1137	0.66 (0.54–0.80)
χ_1^2 (trend)			15.97; $p < 0.001$		13.63; $p < 0.001$
Body-mass index (BMI) (kg/m²)[6]	1[4]	137:252	1	242:583	1
	2	241:413	1.32 (1.00–1.76)	155:408	0.91 (0.70–1.18)
	3	233:493	1.19 (0.89–1.57)	127:363	0.84 (0.64–1.12)
	4	282:497	1.45 (1.09–1.92)	146:291	1.16 (0.86–1.55)
	5	231:412	1.68 (1.25–2.27)	149:424	0.87 (0.65–1.17)
χ_1^2 (trend)			10.80; $p = 0.001$		0.08; $p = 0.77$

[1]Odds ratio.–[2]Estimates from multiple-logistic-regression equations including terms for age, study centre, education, physical activity and caloric intake.–[3]Confidence interval.–[4]Reference category.–[5]Change in BMI from age 30 years or 50 years to cancer diagnosis or interview.–[6]Adjusted also for change in BMI.

TABLE III – DISTRIBUTION OF CASES OF COLORECTAL CANCER AND CONTROLS, OR[1] AND CORRESPONDING 95% CI BY VARIOUS BODY-SIZE MEASUREMENTS AND GENDER AT AGES 12, 30 AND 50, ITALY, 1992–1996

Variable	Quintile	Males OR (95% CI)	Females OR (95% CI)
Perceived body size at age 12	Thinner[2]	1	1
	Same	1.20 (1.01–1.42)	1.16 (0.95–1.42)
	Heavier	1.08 (0.88–1.33)	1.24 (1.00–1.55)
χ_1^2 (trend)		1.10; $p = 0.29$	3.91; $p = 0.05$
Body-mass index (BMI) at age 30 (kg/m²)	1[2]	1	1
	2	1.21 (0.89–1.64)	1.20 (0.94–1.53)
	3	1.35 (1.01–1.80)	1.36 (1.04–1.78)
	4	1.72 (1.30–2.28)	1.58 (1.20–2.07)
	5	1.77 (1.33–2.36)	1.29 (0.97–1.70)
χ_1^2 (trend)		22.81; $p < 0.001$	7.59; $p = 0.006$
Body-mass index (BMI) at age 50 (kg/m²)	1[2]	1	1
	2	1.33 (1.00–1.78)	0.92 (0.70–1.22)
	3	1.09 (0.82–1.45)	1.33 (0.99–1.78)
	4	1.21 (0.91–1.60)	1.06 (0.78–1.43)
	5	1.72 (1.29–2.30)	0.92 (0.68–1.24)
χ_1^2 (trend)		9.40; $p = 0.002$	0.00; $p = 0.98$

[1]Estimates from multiple logistic regression equations including terms for age, study centre, education, physical activity and caloric intake.–[2]Reference category.

the right colon or the rectum. Furthermore, no association with excessive weight was found in men with a family history of colorectal cancer. In women, the influence of WHR appeared consistent in different strata of age, cancer site, energy intake, and family history of cancer. However, no association between WHR and cancer risk was observed in women who reported high levels of physical activity. The interaction between WHR and physical activity was significant ($p < 0.05$).

All analyses were replicated in strata of different study centres and by use of each major control category only (*i.e.,* orthopedic, surgical, eye and other conditions). No significant heterogeneity in major study findings was discovered.

DISCUSSION

This large case-control investigation on colorectal cancer showed a positive association between BMI at various ages and colorectal-cancer risk in men. As in some other investigations (Le Marchand *et al.,* 1992; Dietz *et al.,* 1995), this association seemed stronger for the left colon than for the right colon or the rectum. In women, although cases were found to have larger body mass than control subjects in adolescence and young adulthood, BMI at middle age and cancer diagnosis was unrelated to risk. In contrast, high WHR represented a significant risk indicator.

Several case-control studies (Gerhardsson de Verdier *et al.,* 1990; Kune *et al.,* 1990; Le Marchand *et al.,* 1992; Dietz *et al.,* 1995; Slattery *et al.,* 1997*b*), though not all (Howe *et al.,* 1997), showed positive associations between various body-size measurements and colorectal cancer. When genders were assessed separately, the association was stronger in men (Gerhardsson de Verdier *et al.,* 1990; Slattery *et al.,* 1997*b*) or, as in the present investigation, restricted to men (Kune *et al.,* 1990). A greater tendency in women than in men to under-report their weight has been suggested (Howe *et al.,* 1997). In a combined analysis of 13 studies, on a total of 5,287 cases and 10,470 controls, Howe *et al.,* (1997) found no relationship between BMI at cancer diagnosis in men, and an inverse association in women. However, colorectal-cancer development is likely to interfere with weight, as shown by our data where adjustment for changes in BMI in the years before cancer diagnosis allowed a clearer risk pattern to emerge.

TABLE IV – COMBINED EFFECTS OF BODY-MASS INDEX (BMI) AND WAIST-TO-HIP RATIO (WHR) ON COLORECTAL-CANCER RISK BY GENDER, ITALY, 1992–1996

BMI	OR (95% CI),[1]				
	WHR				
	≤0.81	0.82–0.89	0.90–0.95	≥0.96	All
Men					
<25		1	0.93 (0.67–1.30)	0.68 (0.45–1.01)	1
≥25		1.40 (0.96–2.06)	1.22 (0.89–1.65)	0.75 (0.54–1.03)	1.28 (1.05–1.56)
All		1	0.91 (0.72–1.15)	0.58 (0.45–0.76)	
Women					
<25	1	1.23 (0.92–1.65)	1.86 (1.23–2.83)		1
≥25	0.82 (0.58–1.17)	1.27 (0.94–1.71)	1.25 (0.87–1.80)		0.88 (0.71–1.10)
All	1	1.37 (1.10–1.71)	1.61 (1.20–2.14)		

[1]Estimates from multiple-logistic-regression equations including terms for age, study centre, education, physical activity, energy intake and change in BMI.

TABLE V – OR[1,2] AND CORRESPONDING 95% CI[3] FOR COLORECTAL CANCER BY BODY MASS INDEX (BMI) IN MEN AND WAIST-TO-HIP RATIO (WHR) IN WOMEN IN SEPARATE STRATA OF SELECTED COVARIATES. ITALY, 1992–1996

Variable	Males	Females		
	BMI[4]	WHR[5]		
	≥25 OR (95% CI)	0.82–0.89 OR (95% CI)	≥0.90 OR (95% CI)	χ^2_1 (trend)
Age (yrs)				
<55	1.04 (0.74–1.45)	1.48 (1.04–2.13)	1.70 (0.95–3.04)	5.75[6]
55–69	1.20 (0.97–1.48)	1.32 (0.97–1.79)	1.60 (1.11–2.31)	6.58[6]
≥70	1.19 (0.78–1.82)	1.56 (0.83–2.95)	1.61 (0.81–3.20)	1.84
Site				
Colon				
Right	1.17 (0.75–1.82)	1.21 (0.67–2.21)	1.60 (0.78–3.30)	1.60
Left	1.45 (1.12–1.88)	1.32 (0.95–1.84)	1.70 (1.14–2.55)	6.88[7]
Both	1.24 (1.02–1.51)	1.33 (1.03–1.72)	1.57 (1.14–2.16)	8.50[7]
Rectum	1.11 (0.88–1.39)	1.45 (1.04–2.01)	1.62 (1.08–2.43)	6.41[6]
Total energy intake (tertile)				
Low	1.15 (0.77–1.72)	1.55 (0.85–2.81)	1.35 (0.60–3.06)	1.05
Intermediate	1.11 (0.74–1.67)	1.44 (0.82–2.53)	1.82 (0.87–3.81)	2.87
High	1.06 (0.71–1.58)	1.37 (0.77–2.44)	1.73 (0.89–3.36)	2.72
Physical activity				
Low	1.06 (0.69–1.64)	1.69 (0.97–2.95)	2.33 (1.15–4.73)	6.31[6]
Intermediate	1.25 (0.81–1.93)	1.51 (0.90–2.55)	1.76 (0.93–3.32)	3.38
High	1.04 (0.73–1.49)	0.99 (0.51–1.94)	0.68 (0.28–1.65)	0.59
Family history				
No	1.15 (0.91–1.46)	1.30 (0.92–1.84)	1.58 (1.04–2.41)	4.80[6]
Yes	0.21 (0.04–1.16)	7.11 (1.79–28.26)	1.82 (0.28–12.02)	2.42

[1]Odds ratio.–[2]Estimates from multiple logistic regression equations including terms for age, study centre, change in BMI, and education, physical activity, energy intake as appropriate.–[3]Confidence interval.–[4]Men with BMI <25 as reference category.–[5]Women with WHR <0.82 as reference category.–[6]$p < 0.05$.–[7]$p < 0.01$.

Cohort studies, which are less affected than case-control studies by the possible weight loss in pre-diagnostic years, generally found a small-to-moderate association between BMI and colon-cancer risk among women (Bostick *et al.,* 1994; Martinez *et al.,* 1997) and men (Giovannucci *et al.,* 1995).

In our study, in agreement with others (Le Marchand *et al.,* 1992; Lee and Paffenbarger, 1992; Must *et al.,* 1992), the positive association with excessive weight earlier in life, most notably at age 30, seemed at least equally, if not more important (*i.e.,* in women), than recent excessive weight. The association of risk with BMI at different ages is, obviously, affected by the precision of the particular measurement and the correlation between them. Our data, however, support the possibility that excessive weight and/or factors related to positive energy balance may act on late as well as early stages of colon carcinogenesis. In fact, obesity has also been shown to be directly associated with risk for colorectal adenomas (Giovannucci *et al.,* 1995), particularly large ones (Giovannucci *et al.,* 1995).

Adult height may be a proxy of positive energy balance during childhood, and is correlated with the total length of the colon. At variance with some studies (Giovannucci *et al.,* 1995; Howe *et al.,* 1997), however, tall persons of either gender were not at elevated risk of colon cancer in our study population.

Data on colorectal-cancer risk and WHR are scanty. In the highest compared with the lowest quintile of WHR, Bostick *et al.* (1994) and Martinez *et al.* (1997) reported OR of 1.2 and 1.5 respectively (not significant) in women, while Giovannucci *et al.* (1995) found an OR of 3.4 in men. Interest in this topic stems from the hypothesis that the best-known risk factors for colorectal cancer (*i.e.,* a diet high in refined sugar and calories but low in fibers, a sedentary life, and excessive weight) may act through insulin resistance and hyperinsulinemia (Giovannucci, 1995). Human colon cancer is known to express insulin and insulin-like growth-factor-1 receptors (Adenis *et al.,* 1995), and insulin has been shown to be a colon-tumor promoter in a rat model (Tran *et al.,* 1996) and *in vitro* (Bjork *et al.,* 1993).

Centrally located adipocytes may have specific metabolic roles in the pathogenesis of insulin resistance and hyperinsulinemia (Bjorntorp, 1990). The general tendency in males towards abdominal distribution of fat and higher insulin levels may account for the stronger association between high body mass and colorectal-cancer risk in men than in women. Conversely, in women, where fat distribution is more variable, the importance of WHR can emerge more clearly. The inverse association with risk we found for WHR in men is, apparently, at variance with the data from Giovannucci *et al.* (1995) and very difficult to explain. If not due to extreme chance or bias, the discrepancy may derive from the difference between the 2 male populations examined (upper class, sedentary professionals in Giovannucci *et al.* (1995); general population, including 60% manual workers, in our study). Although more data on WHR and colorectal-cancer risk are clearly needed, it is of interest that WHR seemed uninfluential in most active women, as if high levels of physical activity may counterbalance insulin resistance (Giovannucci, 1995). Finally, the other significant interaction which emerged in our study (*i.e.,* the lack of association with excessive weight in men with a family history of colorectal cancer) suggests that the influence of relatively weak environmental factors is difficult to quantify in the presence of high baseline risk.

This study was sufficiently large to obtain reasonably precise risk estimates. Limitations and strengths are common to most hospital-based case-control studies (Breslow and Day, 1980). Hospital controls may differ from the general population in several respects, but we checked the consistency of body-size measurements across major diagnostic categories of controls and the comparability with a representative sample of the general Italian population (Pagano and La Vecchia, 1994). Participation was almost complete, and risk estimates could be adjusted for major identified confounding factors, including total energy and physical activity. Interestingly, the results of a study of breast cancer, based, in large part, on the same control group, were substantially different, particularly with respect to WHR (Franceschi *et al.,* 1996).

In conclusion, the major findings of our study are that excessive weight at various ages predicts colorectal-cancer risk in men while, in women, abdominal obesity, as indicated by a high WHR, represents a more reliable risk indicator. If all men could reduce their BMI below 25, about 9% of male colorectal cancer might be avoided in Italy. A decrease of WHR below 0.82 might reduce colorectal cancer in women by 19%.

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