COLORECTAL CANCER

Obesity and colorectal cancer risk in women

P D Terry, A B Miller, T E Rohan

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See end of article for authors' affiliations

Correspondence to:
Dr P Terry, Department of
Epidemiology and Social
Medicine, Albert Einstein
College of Medicine,
1300 Morris Park Avenue,
1301-A, Bronx, NY
10461, USA;
pterry@aecom.yu.edu

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Background: Several large studies of obesity and colorectal cancer risk have found no association among women but a reasonably consistent positive association among men. In women, a positive association that is stronger among, or limited to, those who are premenopausal has been suggested by studies that stratified analyses by age, although no previous study has examined the association by menopausal status.

Methods: We used proportional hazards analyses to estimate hazard ratios relating obesity to colorectal cancer risk among 89 835 women aged 40-59 years at recruitment into the Canadian National Breast Screening Study, a multicentre randomised controlled trial of mammography screening for breast cancer. During an average 10.6 years of follow up (936 433 person years), a total of 527 women were diagnosed with incident colorectal cancer (363 colon and 164 rectal).

Results: We found that obesity (body mass index ≥ 30 kg/m²) was associated with an approximately twofold increased risk of colorectal cancer among women who were premenopausal at baseline (hazard ratio 1.88, 95% confidence interval 1.24-2.86). There was no association among postmenopausal women (p for interaction=0.01), and there was only a weak positive association in the entire cohort.

Conclusions: Our data suggest that obesity is associated with a twofold increased risk of colorectal cancer in premenopausal women but is not associated with altered risk in postmenopausal women. Effect modification by menopausal status may better explain the inconsistent or weak findings in previous studies than the presumed lack of an association among women.

There is some interest in the possibility that a high relative body weight may be associated with an increased risk of colorectal cancer through the mitogenic effects of increased blood levels of insulin.¹ In both the American Cancer Society Cohort² and the Seventh Day Adventists' Cohort,³ a high body mass index (BMI) was associated with an increased risk of colorectal cancer mortality among men. However, in these same cohorts, there was no association among women. Perhaps noteworthy, the latter study reported an inverse association among "younger women" but did not specify the age range of these women.³ In two other prospective cohort studies, a twofold increased risk of colon cancer was observed with high BMI in a relatively young cohort of nurses⁴ while no association with colorectal cancer was observed in an older cohort of retired subjects.⁵ Of the four case control studies that examined the association between BMI and colorectal cancer risk among women by age strata,⁶⁻⁹ all found a stronger association among younger women.

Most recently, the hypothesis that a positive association between obesity and colorectal cancer among women may diminish with age has been examined in a large prospective cohort study that found a positive association only among women less than 55 years of age.¹⁰ Although the latter study did not have information on menopausal status, the possibility that the association may be stronger among (or limited to) premenopausal women was suggested. Such effect modification may help to explain the inconsistent findings among women and would also have clear relevance for prevention. Therefore, given the novelty of this hypothesis and the paucity of prospective data on colorectal cancer incidence, we examined the association between obesity and colorectal cancer risk in a large cohort of women that included information on menopausal status.

SUBJECTS AND METHODS

Study population

The investigation was conducted using data from the Canadian National Breast Screening Study (NBSS). The NBSS is a multi-

centre randomised controlled trial of mammography screening for breast cancer in 89 835 women aged 40-59 years at recruitment.¹¹ Participants were recruited between 1980 and 1985 by various means, including personal invitation by letter, group mailings to employees of large institutions and to members of professional associations, advertisements in newspapers, and public service announcements on radio and television.

Questionnaires

On enrolment in the NBSS, all participants completed a questionnaire that sought data on demographic characteristics (including height and weight), lifestyles, menstrual and reproductive history, and use of oral contraceptives and replacement oestrogens. Participants were asked the following series of questions regarding menopausal status: "Are you still having menstrual periods (yes, no, uncertain)", "When was your last menstrual period (day, month, year)", "Do you think your menstrual periods are (or were) regular (yes, no)", "Has your womb been removed (that is, have you had a hysterectomy) (yes, no)", and "Have you had both ovaries removed (yes, no, uncertain)". Starting in 1982, a questionnaire regarding diet and physical activity was distributed to all new attendees at all screening centres, and to women returning to the screening centres for rescreening. By the time that the dietary questionnaire was introduced, some women had already been enrolled in the study and were not seen again at the screening centres. A total of 56 837 women returned completed dietary questionnaires. Therefore, analyses were performed both on the entire cohort and in women for whom information on physical activity was available (see below). Although we did not measure the validity of self reported BMI

Abbreviations: BMI, body mass index; RR, hazard ratio; NBSS, Canadian National Breast Screening Study; IGF, insulin-like growth factor.

Table 1 Baseline characteristics of the study cohort according to relative body weight and menopausal status

Characteristic	Premenopausal women			Postmenopausal women		
	Non-obese* (n=27 712)	Pre-obese† (n=10 715)	Obese‡ (n=4579)	Non-obese* (n=17 818)	Pre-obese† (n=28 184)	Obese‡ (n=4525)
Person years	298 239	113 659	48 060	189 156	108 003	46 649
Median BMI (kg/m ²)	22.3	26.7	33.0	22.3	26.8	32.7
Mean age at baseline (y)	44.3	45.0	45.0	53.1	53.8	53.6
Smoking (% current smokers)	22.6	20.0	20.1	24.7	20.5	18.1
Education (% post-secondary)	35.5	28.7	22.9	25.4	20.7	16.4
Oral contraceptive use (%)	71.6	66.5	62.7	47.9	41.5	37.9
HRT (%)	6.4	7.1	7.5	48.7	47.2	39.5
Parity (mean No of children)	2.2	2.5	2.6	2.5	2.8	3.0

BMI, body mass index: *BMI <25.0 kg/m²; †BMI 25.0–30 kg/m²; ‡BMI >30.0 kg/m².
p values for trend (χ^2 two sided) were <0.05 for all covariates listed.

in our data, a previous study among women with a similar age structure to that of the women in our cohort found a high Pearson correlation coefficient between reported and actual BMI ($r=0.893$).¹²

Case definition and ascertainment

Outcome (incident colorectal cancer or death) was ascertained by means of computerised record linkage to the National Mortality Database and to the Canadian Cancer Database (a composite of cancer incidence data collected by the provincial population based cancer registries), both of which are maintained by Statistics Canada. There is good evidence from the NBSS and from other sources that the use of record linkage to ascertain incident cancer cases and deaths in Canada is both accurate and complete.^{13–14} After excluding 66 women with prevalent colorectal cancer at baseline, we identified 527 incident colorectal cancers (363 colon and 164 rectal) in total. For analyses by colon cancer subsite, proximal colon cancers were defined as those occurring from the caecum through to the splenic flexure ($n=172$), and distal colon cancers were defined as those occurring from the descending colon through to the sigmoid colon ($n=148$); the location of 43 colon cancers was not specified.

Statistical analysis

Follow up of the cohort was censored at the date of diagnosis, the date of death, or at the end of the follow up period (31 December 1993), whichever was earliest. For the purposes of the analysis, women were categorised according to the criteria for obesity established by the World Health Organization,¹⁵ namely “pre-obese” (BMI 25.0 to <30 kg/m²) and “obese” (BMI ≥ 30 kg/m²); those with a BMI <25.0 kg/m² were classified as “non-obese.” Cox proportional hazards models were used to estimate hazard ratios (RR) with 95% confidence intervals (CI) for the association between obesity and colorectal cancer risk. Multivariate models included age in five year age groups, smoking (never, past, current), education level (less than high school, high school, and university), oral contraceptive use (never + four levels of duration), hormone replacement therapy (never + four levels of duration), parity (quintiles), and vigorous physical activity (hours per day in tertiles). Physical activity was categorised as “low,” “medium,” “high,” and “missing,” where the latter group was comprised of women who did not complete the questionnaire regarding physical activity and diet. Women in whom this information was missing were included in multivariate analyses as a separate risk category. To assess the possibility of residual confounding among women with missing information on physical activity, we conducted additional analyses limited to the 56 837 women who completed questionnaires regarding physical activity and diet. For tests of trend in risk across successive levels of categorical variables, median values of each category were fitted in the risk models as successive integers.

Tests for interaction were based on likelihood ratio tests comparing models with and without product terms representing the variables of interest. The likelihood ratio test that all of the interaction parameters were zero was performed by referring $-2 \times$ the difference in the log likelihoods of models with and without interaction terms to the χ^2 distribution on degrees of freedom equal to the number of interaction parameters.

Analyses were conducted overall and by menopausal status. Women who at recruitment were reported as having regular menstrual periods within the past 12 months were considered to be premenopausal while those in whom menstrual periods ceased prior to 12 months before assessment were considered to be postmenopausal, as were women who had previously undergone oophorectomy (with or without a history of hysterectomy). To examine the association between obesity at recruitment and colorectal cancer occurring among those women who were premenopausal and postmenopausal at diagnosis, we estimated menopausal status at diagnosis using an algorithm developed by investigators analysing data from the Nurses' Health Study.¹⁶ Specifically, cancers occurring at or below age 51 years were considered premenopausal and those occurring at or after age 55 years were considered postmenopausal (the respective ages by which approximately 50% and 90% of the cohort became postmenopausal). As with the aforementioned study,¹⁶ menopausal status of women between these ages was considered uncertain. Women who were deemed to be perimenopausal were excluded from analyses that were stratified by menopausal status.

RESULTS

Mean duration of follow up of the cohort was 10.6 years (936 433 person years). Mean ages at diagnosis of colon and rectal cancer were 59 and 58 years, respectively. Median BMI varied from 22.5 kg/m² among non-obese women to 26.8 kg/m² among pre-obese women to 32.8 kg/m² among obese women (table 1). Parity was related positively to BMI while cigarette smoking, percentage of women with post-secondary education, and proportion of women who had ever used oral contraceptives were related inversely to BMI. Among premenopausal women, the proportion of women who had ever used hormone replacement therapy was highest among obese women while among postmenopausal women the proportion of women who had ever used hormone replacement therapy was lowest among obese women.

In the entire cohort, obesity was associated with a statistically non-significant 8% increased risk of colorectal cancer (table 2). When examined by subsite, there were statistically non-significant 30–35% increases in the risk of cancers of the distal colon and rectum while the risk of proximal colon cancer was slightly decreased among obese women. Among premenopausal women, obesity was associated with a statistically significant nearly twofold increased risk of colorectal

Table 2 Multivariate adjusted* rate ratios of colorectal cancer risk according to relative body weight by menopausal status

	Colorectal	Colon†	Proximal colon	Distal colon	Rectum
Baseline menopausal status					
Entire cohort					
No of cases	527	363	172	148	164
Non-obese	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Pre-obese	1.03 (0.84–1.26)	1.13 (0.89–1.43)	1.08 (0.77–1.52)	1.24 (0.85–1.82)	0.83 (0.57–1.21)
Obese	1.08 (0.82–1.41)	0.95 (0.67–1.34)	0.81 (0.48–1.38)	1.31 (0.79–2.16)	1.35 (0.87–2.07)
p for trend‡	0.57	0.97	0.61	0.22	0.35
Premenopausal					
No of cases	176	118	49	57	58
Non-obese	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Pre-obese	1.06 (0.74–1.53)	1.19 (0.77–1.85)	1.32 (0.69–2.55)	0.91 (0.45–1.84)	0.83 (0.43–1.61)
Obese	1.88 (1.24–2.86)	1.95 (1.15–3.29)	1.78 (0.76–4.14)	2.42 (1.19–4.91)	1.75 (0.88–3.49)
p for trend‡	0.007	0.02	0.16	0.04	0.21
Postmenopausal					
No of cases	275	184	93	70	91
Non-obese	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Pre-obese	0.98 (0.75–1.28)	1.06 (0.77–1.46)	0.90 (0.56–1.43)	1.53 (0.91–2.57)	0.83 (0.51–1.35)
Obese	0.73 (0.48–1.10)	0.62 (0.36–1.08)	0.61 (0.29–1.31)	0.79 (0.33–1.92)	0.92 (0.49–1.75)
p for trend‡	0.18	0.18	0.21	0.92	0.66

*Multivariate models included age in five year age groups, smoking (never, past, current), educational level (less than high school, high school, and university), vigorous physical activity (hours per day in tertiles, and "missing"), oral contraceptive use (never+four levels of duration), hormone replacement therapy (never+four levels of duration), and parity (quintiles).

†43 cases of colon cancer were of unspecified location.

‡ All p values are from two sided tests.

cancer. This association was strongest for cancers of the distal colon but was evident for cancers of the rectum and proximal colon also. In contrast, there was no positive association between obesity and colorectal cancer risk among postmenopausal women. If anything, there was a tendency towards a small to moderate decreased risk among obese postmenopausal women, particularly for colon cancer. A formal test of interaction between obesity and menopausal status in relation to colorectal cancer risk was statistically significant ($p=0.01$). Overall, multivariate adjusted results were very similar to age adjusted results (not shown), although the former (shown in table 2) were slightly stronger than the latter among premenopausal women. For example, for colorectal cancer, the age adjusted RR for obese compared with non-obese women was 1.72 (95% CI 1.14–2.59; p for trend=0.02).

In additional analyses, we examined the association between obesity and cancers occurring among women who were premenopausal and postmenopausal at diagnosis, respectively. The multivariate adjusted RRs for colorectal cancers diagnosed among premenopausal women (pre-obese and obese compared with non-obese women) were 1.26 (95% CI 0.66–2.42) and 2.83 (95% CI 1.43–5.58), respectively (p for trend=0.005). The corresponding RRs for cancers occurring among women who were postmenopausal at diagnosis were 1.01 (95% CI 0.79–1.28) and 0.88 (95% CI 0.63–1.25), respectively (p for trend=0.55). The results of our study were also similar when, instead of using categories according to criteria for obesity established by the World Health Organization,¹⁵ we categorised BMI by quintiles. The increased risk among premenopausal obese women became slightly stronger when we excluded cases that occurred during the first year of follow up, perhaps reflecting weight loss among women with early (undetected) colorectal cancer (RR 2.07, 95% CI 1.36–3.17; p for trend=0.002). Exclusion of cases occurring up to five years after follow up began did not alter the relative risk estimates further. The results were also similar when we restricted the analyses to the 56 837 women who completed questionnaires regarding physical activity (and diet), although statistical precision was reduced. For example, obesity was associated with an increased risk of colorectal cancer among premenopausal women (RR 1.75, 95% CI 1.01–3.03) while for postmenopausal women RR was 0.57 (95% CI 0.31–1.05).

In a separate analysis, we examined the association between obesity and colorectal cancer risk among women who

were perimenopausal at recruitment (data not shown). The associations observed in this group were essentially similar to those observed among postmenopausal women, although only 76 cases were observed among such women and the confidence intervals were wide.

DISCUSSION

We found that obesity (BMI ≥ 30 kg/m²) was associated with a nearly twofold increased risk of colorectal cancer among women who were premenopausal at baseline. In postmenopausal women, there was essentially no association, or a small reduction in risk at most. Due to the greater number of cases among women who were postmenopausal at baseline, there was only a weak positive association in the entire cohort.

Results similar to ours were observed in a large cohort of Swedish women¹⁰ that found a twofold increased risk among obese women less than 55 years of age compared with their normal weight counterparts, but found no association among older women. In agreement with those results, although no association was observed overall in a large cohort of female Seventh Day Adventists,³ the investigators reported a clear association among "younger women" without specifying the age range. Similarly, a twofold increased risk of colon cancer was observed among women who were obese at enrolment into the Nurses' Health Study,⁴ a large prospective cohort study of female American nurses who were between the ages of 34 and 59 at enrolment, while no association between BMI and risk was observed among women in the Leisure World cohort of retired people⁵ who were mostly over 65 years of age at baseline (the exact age range was not reported). In addition, four case control studies examined the association by age and all observed stronger associations among younger compared with older women.^{6–9} Two of these studies^{6,8} compared obesity at stages of life that included very youthful ages, ages 15, 25, and 35 years,⁸ and ages 12 and 30 years,⁶ respectively. In both studies, obesity at very young ages (12 and 15 years) was associated with an increased risk of colorectal cancer at magnitudes similar to those associated with obesity among older women who were still premenopausal (25, 30, and 35 years). Overall, these studies suggest that among premenopausal women the positive association between obesity and colorectal cancer risk may be as strong and consistent as that which has been observed previously among men.^{17,18} The results of previous studies also

suggest that a positive association among premenopausal women might be stronger in the distal colon and rectum than in the proximal colon.¹⁰ Our results offer some support for this hypothesis in that the greatest increased risk was observed among obese women for cancers of the distal colon although statistically non-significant positive associations were also observed for cancers of the proximal colon and rectum.

Among the strengths of our study was the large sample size of our cohort of women and the relatively long term follow up. The completeness of follow up of the cohort^{13,14} reduces the likelihood that our results reflect bias due to differential follow up of obese compared with non-obese women. Moreover, the large number of cases in our study allowed us to examine associations according to menopausal status with reasonable statistical power. On the other hand, although we adjusted our estimates for a wide range of potentially confounding variables, we cannot exclude the possibility of residual confounding by other factors.

We can only speculate on the biological mechanisms underlying our observations. Adiposity is positively related to blood insulin levels.¹ An increase in blood insulin levels lowers insulin-like growth factor (IGF) binding protein 1 and may subsequently lead to increased levels of free IGF-1.¹⁹ IGF-1 has been positively associated with the risk of colorectal cancer in men²⁰ and women.²¹ Oestrogen on the other hand appears to be associated with a lower risk of colorectal cancer. For example, hormone replacement therapy has been associated with a reduced risk of colorectal cancer²² and such benefits have been found to be stronger in the distal colon and rectum.^{23,24} In addition, the observation that hormone replacement therapy may confer greater benefits regarding both colorectal cancer^{25,26} and colorectal adenomas²⁷ among lean women than among obese women suggests that hormone replacement therapy offers no additional benefit over and above that from oestrogen derived from adipose tissue in postmenopausal obese women, which is the main source of endogenous oestrogen after the menopause.²⁸ Moreover, early age at menopause was associated with an increased risk of colorectal cancer in a cohort of Dutch women²⁹ but only among lean women. Thus in postmenopausal women, the potentially deleterious effects of obesity through increased insulin and IGF-1 levels might be offset by the ameliorative effect of obesity on endogenous oestrogen levels. In contrast, in premenopausal women, oestrogen derived from adipose tissue is a relatively unimportant source of this hormone compared with that derived from the ovaries²⁸ and, therefore, would not significantly offset the deleterious effects of obesity on colorectal cancer risk.

In conclusion, our data suggest that obesity is associated with a twofold increase in the risk of colorectal cancer in premenopausal women, and that at most it is associated with a small reduction in risk in postmenopausal women. Effect modification by menopausal status may therefore better explain the inconsistent or weak findings in previous studies of women than the presumed lack of an association among women.^{17,18} Given the relatively high incidence of colorectal cancer in Western populations,³⁰ and the rising prevalence of obesity, especially in younger age groups,³¹ the possible benefits with respect to this disease should be added to the list of potential advantages of weight control.³²

Authors' affiliations

P D Terry, T E Rohan, Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Bronx, NY, USA
A B Miller, Division of Clinical Epidemiology, Deutsches Krebsforschungszentrum, Heidelberg, Germany

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