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BRIEF COMMUNICATION

Body Mass Index and Risk of Colorectal Cancer According to Fatty Acid Synthase Expression in the Nurses' Health Study

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Fatty acid synthase (FASN) plays an important role in energy metabolism of fatty acids and is overexpressed in some colon cancers. We investigated whether associations between body mass index (BMI) and risk of colorectal cancer varied according to FASN expression. During follow-up of 109 051 women in the ongoing prospective Nurses' Health Study, a total of 1351 incident colon and rectal cancers were diagnosed between 1986 and 2004. We constructed tissue microarrays of the available resected tumor samples (n = 536), and FASN expression was analyzed by immunohistochemistry. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models. All statistical tests were two-sided. High BMI was associated with an increased risk of FASN-negative (no or weak expression) colorectal cancer compared with normal BMI (high BMI [≥30 kg/m^2], ie, obese vs normal BMI [18.5–22.9 kg/m^2], HR = 2.25, 95% CI = 1.49 to 3.40, P_{trend} < .001) but not with FASN-positive (moderate to strong expression) colorectal cancer. A statistically significant heterogeneity in colorectal cancer risks was observed between FASN-negative and FASN-positive tumors ($P_{heterogeneity}$ = .033). The age-adjusted incidence rates for FASN-positive and FASN-negative colorectal cancers were 10.9 and 7.1, respectively, per 100 000 person-years. This molecular pathological epidemiology study supports a role of energy metabolism in colorectal cancer pathogenesis.

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Accumulating evidence suggests that obesity (body mass index [BMI] ≥ 30.0 kg/m^2) is associated with increased risk of cancer (1–21). Understanding the modifying effect of obesity on carcinogenic pathways may lead to a better cancer prevention strategy. Lipogenic enzyme fatty acid synthase (FASN) is physiologically regulated by energy intakes and expenditures (3,22) and may play a role in carcinogenesis (3,22,23). Overexpression of FASN has been observed in a subset of colorectal cancers (23–26), and its overexpression in colon and prostate cancers has been shown to interact with patient's BMI and modify tumor behavior and patient survival (26,27).

Thus, we conjectured that cellular response to energy balance status might differ according to cellular FASN expression status. We hypothesized that neoplastic colon epithelial cells expressing FASN might progress to malignancy independent of an individual's BMI (used as a surrogate of energy balance in this study), whereas malignant transformation of these cells with no FASN expression might be influenced by BMI. To test this hypothesis, we designed a molecular pathological epidemiology (MPE) study (28,29), to examine whether associations between BMI and risk of colorectal cancer varied according to FASN expression and whether obesity was associated with an increased risk of colorectal cancers that do not express FASN.

We used the Nurses' Health Study (NHS) (30), an ongoing prospective cohort study in which 121 701 nurses were sent questionnaires in 1976 and then every 2 years, to update information on weight, dietary and lifestyle factors, and to identify newly diagnosed cancer patients. The National Death Index was used to identify unreported patients with lethal cancers. We excluded 12 650 women with incomplete questionnaire return or a history of ulcerative colitis or cancer at baseline. To calculate BMI, we used height (m) reported in 1976 and the cumulative mean weight (kg), which was the mean of all available weight data up to the start of each 2-year follow-up period. This study was approved by the Human Subjects Committees at the Harvard School of Public Health and Brigham and Women's Hospital.

During follow-up of 109 051 eligible women, 1351 incident colon and rectal cancers were identified between 1986 and 2004. Written informed consent was obtained from all 1351 patients for analysis of tumor tissues. We obtained paraffin-embedded tissue blocks from hospitals where participants underwent tumor resections (31). Tissue microarrays were constructed (32), immunohistochemistry for FASN expression was performed on available tumors (n = 536), and expression levels were compared with normal colonic mucosa and adipose tissue as references using a semiquantitative scoring method, as described previously (33), where "strong," "moderate," and "weak" expression patterns have also been defined (details in Supplementary Methods, available online).

Physical activity has been identified as a potential confounder of relationship between BMI and cancer (6). In the NHS cohort, detailed leisure-time physical activity was first assessed in 1986. To evaluate the influence of BMI adjusted for physical activity, follow-up for the current analysis started in June 1986 and ended on date of colorectal cancer diagnosis, date of death, or June 2004, whichever came first. We used multivariable Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) adjusted for potential confounders including age, physical activity, smoking status, intakes of alcohol, folate, vitamin D, calcium, calories, and red meat, use of multivitamins, aspirin, and hormone

CONTEXT AND CAVEATS

Prior knowledge

The lipogenic enzyme fatty acid synthase (FASN), regulated by cellular energy balance, is often overexpressed in cancer cells and has been shown to play a role in carcinogenesis.

Study design

A molecular pathological epidemiology study was designed to examine whether neoplastic colon epithelial cells that express FASN progress to malignancy independent of an individual's body mass index (BMI; a surrogate of energy balance), whereas cells that do not express FASN are dependent on BMI. Tumor samples obtained from women diagnosed with incident colorectal cancers in the prospective Nurses' Health Study were analyzed for FASN expression. Associations between BMI and risk of colorectal cancer were assessed according to FASN expression.

Contribution

Obesity (BMI ≥ 30 kg/m^2) and higher BMI (≥25 kg/m^2) were associated with an increased risk of FASN-negative (no or weak expression) colorectal cancer compared with normal BMI (18.5–22.9 kg/m^2) but not with a risk of FASN-positive (moderate to strong expression) colorectal cancer.

Implication

FASN-inactive cells may depend on excess energy balance, reflected by higher BMI, for malignant transformation.

Limitations

BMI used as a surrogate may not be a perfect measure of energy balance. Results may not be generalizable to men. Residual confounding cannot be ruled out.

From the Editors

Table 1. Baseline characteristics of colorectal cancer patients according to FASN data availability*

Characteristics	Without FASN data	With FASN data	*P*†
Participants, No.	815	536	—
Cumulative BMI, kg/m^2, mean (SD)	25.0 (4.6)	25.4 (4.6)	.065
Age, y, mean (SD)	55.6 (6.4)	55.6 (6.6)	.89
Former and current smoker, %	57	60	.28
Physical activity‡, METs wk, mean (SD)	13.2 (16.8)	12.0 (16.2)	.24
Family history of colorectal cancer in any first-degree relative, %	10	13	.15
History of sigmoidoscopy, %	3	3	.48
Menopause status, %	79	79	.97
Multivitamin use, %	33	37	.19
Regular aspirin use§, %	24	28	.076
Calorie‖, kcal/d, mean (SD)	1679.2 (472.2)	1696.0 (461.8)	.54
Alcohol, g/d, mean (SD)	7.6 (12.0)	7.0 (10.2)	.25
Folate‖,¶, μg/d, mean (SD)	379.2 (223.6)	365.6 (174.6)	.25
Vitamin D‖,¶, IU/d, mean (SD)	326.2 (238.0)	313.8 (215.4)	.36
Calcium‖,¶, mg/d, mean (SD)	849.4 (333.2)	848.6 (309.0)	.97
Red meat, servings per d, mean (SD)	1.2 (0.6)	1.2 (0.6)	.59

* Participants were included from the ongoing prospective Nurses' Health Study. A total of 1351 incident colorectal cancers were identified between 1986 and 2004. Tumor samples available from 536 patients were analyzed for FASN expression by immunohistochemistry (with FASN data), and the remaining 815 participants were without FASN data. Cumulative mean BMI was calculated using baseline height (m) and cumulative mean weight (kg), which was the mean of all available weight data from 1976 to 1986. BMI = body mass index; FASN = fatty acid synthase; IU = international unit; MET = metabolic equivalent task; SD = standard deviation; — = not applicable.

† *P* values were calculated using a two-sided χ^2 test for a comparison of percentages or by a two-sided Student's *t* test for a comparison of means.

‡ Leisure-time physical activity was assessed every 2 years since 1986. Subjects reported duration of participation (ranging from 0 to 11 or more h/wk) on walking (along with usual pace), jogging, running, bicycling, swimming laps, racket sports, other aerobic exercises, lower intensity exercise (yoga, toning, stretching), or other vigorous activities. Each activity on the questionnaire was assigned a MET score. One MET is the energy expenditure for sitting quietly. MET scores are defined as the ratio of the metabolic rate associated with specific activities divided by the resting metabolic rate. The values from the individual activities were summed for a total MET h/wk score.

§ Regular aspirin use of at least two standard 325 mg tablets per week in 1984.

‖ Based on cumulative mean intake from 1980 to 1986.

¶ Energy-adjusted intake (ie, nutrient intake divided by total calorie intake).

therapy, endoscopy screening, and family history of colorectal cancer. Proportionality of hazards assumptions were assessed by a time-varying covariate (ie, an interaction term of time and BMI; $P = .97$ for FASN-positive cancer event; $P = .31$ for FASN-negative cancer event). All *P* values were two-sided, and values less than .05 were considered to be statistically significant. All analyses were performed using SAS software, version 9.1.3 (SAS Institute, Cary, NC).

FASN expression was analyzed in 536 tumors. A total of 217 (40%) tumors were FASN negative (defined as no to weak expression), and 319 (60%) tumors were FASN positive (defined as moderate to strong expression) (Supplementary Figure 1, available online). The baseline characteristics of patients with FASN data were similar to those without FASN data (Table 1).

The baseline characteristics of the study population (n = 109 051 women) according to cumulative mean BMI from 1976 to 1986 are summarized in Table 2. The characteristics of the population did not differ substantially by BMI, except for physical activity and alcohol intake. Participants with higher BMI tended to report less physical activity and lower intake of alcohol.

The associations between the cumulative mean BMI and risk of colorectal cancer according to FASN status (n = 536 women) are shown in Table 3. Women with higher BMI (≥25.0 kg/m^2) were associated with a statistically significantly increased risk of FASN-negative colorectal cancer compared with women with normal BMI (18.5–22.9 kg/m^2) (BMI ≥30.0, ie, obese, vs 18.5–22.9 kg/m^2, multivariable HR = 2.25, 95% CI = 1.49 to 3.40; BMI 25.0–29.9 vs 18.5–22.9 kg/m^2, multivariable HR = 1.78, 95% CI = 1.25 to 2.54) ($P_{trend} < .001$). In contrast, women with higher BMI were not associated with a statistically significantly increased risk of FASN-positive colorectal cancer compared with women with normal BMI (BMI ≥30.0 vs 18.5–22.9 kg/m^2, multivariable HR = 1.27, 95% CI = 0.88 to 1.83; BMI 25.0–29.9 vs 18.5–22.9 kg/m^2, multivariable HR = 1.23, 95% CI = 0.92 to 1.63) ($P_{trend} = .16$). A statistically significant heterogeneity in colorectal cancer risks was noted between FASN-negative and FASN-positive tumors ($P_{heterogeneity} = .033$). The age-adjusted incidence rates for FASN-positive and FASN-negative colorectal cancers in the entire study population

Table 2. Age-adjusted baseline characteristics of the study population in 1986 according to cumulative mean body mass index from 1976 to 1986*

Characteristics	Cumulative mean BMI, kg/m²				
	<18.5	18.5–22.9	23.0–24.9	25.0–29.9	≥30
Participants, No.	1774	46972	22180	26751	11374
Age, y, mean (SD)	50.7 (7.4)	51.0 (7.2)	52.8 (7.2)	53.5 (7.1)	53.2 (6.9)
Former and current smoker, %	55	54	52	50	47
Physical activity†, METs per wk, mean (SD)	15.2 (22.9)	16.3 (23.3)	13.9 (19.3)	12.4 (19.2)	9.5 (14.3)
Menopause status and hormone use, %					
Premenopausal	26	31	32	31	31
Postmenopausal and never use	20	22	24	27	30
Postmenopausal and former use	11	11	12	12	11
Postmenopausal and current use	15	16	14	12	8
Family history of colorectal cancer in any first-degree relative, %	6	7	7	7	7
History of sigmoidoscopy, %	3	3	3	3	3
Multivitamin use, %	35	38	36	35	32
Regular aspirin use‡, %	24	25	27	28	31
Dietary intakes					
Calorie§, kcal/d, mean (SD)	1739 (512)	1672 (457)	1666 (453)	1677 (464)	1730 (486)
Alcohol, g/d, mean (SD)	7.3 (11.5)	7.7 (10.7)	6.7 (10.1)	5.3 (9.2)	3.2 (7.5)
Folate§,||, μg/d, mean (SD)	374 (199)	388 (213)	381 (206)	377 (210)	367 (203)
Vitamin D§,||, IU/d, mean (SD)	320 (217)	331 (228)	327 (222)	327 (228)	324 (223)
Calcium§,||, mg/d, mean (SD)	829 (336)	880 (343)	877 (335)	870 (332)	853 (344)
Red meat, servings per d, mean (SD)	1.3 (0.7)	1.2 (0.6)	1.2 (0.6)	1.3 (0.6)	1.4 (0.7)

* Participants were included from the Nurses' Health Study. Cumulative mean BMI was calculated in 109051 eligible women using baseline height (m) and cumulative mean weight (kg), which was the mean of all available weight data from 1976 to 1986. BMI = body mass index; IU = international unit; MET = metabolic equivalent task; SD = standard deviation.

† Leisure-time physical activity has been assessed every 2 years since 1986. Subjects reported duration of participation (ranging from 0 to 11 or more h/wk) on walking (along with usual pace), jogging, running, bicycling, swimming laps, racket sports, other aerobic exercises, lower intensity exercise (yoga, toning, stretching), or other vigorous activities. Each activity on the questionnaire was assigned a MET score. One MET is the energy expenditure for sitting quietly. MET scores are defined as the ratio of the metabolic rate associated with specific activities divided by the resting metabolic rate. The values from the individual activities were summed for a total MET h/wk score.

‡ Regular aspirin use of at least two standard 325 mg tablets per week in 1984.

§ Based on cumulative mean intake from 1980 to 1986.

|| Energy-adjusted intake (ie, nutrient intake divided by total calorie intake).

(n = 109051 women) were 10.9 and 7.1, respectively, per 100000 person-years; the age-adjusted incidence rates for FASN-positive and FASN-negative colorectal cancers in each BMI category are shown in Table 3.

We performed secondary analyses to assess associations between BMI and risk of colorectal cancer according to FASN status in different colorectal cancer subsets defined by tumor subsite location (ie, colon, proximal colon, distal colon, and rectum) (Supplementary Table 1, available online). Although statistical power was limited in subsite analyses for proximal colon cancers, distal colon cancers, and rectal cancers, the results were generally similar to our main analysis, which included all colorectal cancers. In an analysis restricted to total colon cancers, women with higher BMI were associated with a statistically significantly increased risk of FASN-negative colon cancer compared with women with normal BMI (BMI ≥30.0 vs 18.5–22.9 kg/m², multivariable HR = 2.06, 95% CI = 1.29 to 3.27; BMI 25.0–29.9 vs 18.5–22.9 kg/m², multivariable HR = 1.65, 95% CI = 1.11 to 2.45) (P_{trend} < .001). In contrast, women with higher BMI were not associated with a statistically significantly increased risk of FASN-positive colon cancer (BMI ≥30.0 vs 18.5–22.9 kg/m², multivariable HR = 1.15, 95% CI = 0.76 to 1.74; BMI 25.0–29.9 vs 18.5–22.9 kg/m², multivariable HR = 1.07, 95% CI = 0.77 to 1.49) (P_{trend} = .44).

In this study, we examined FASN expression in the resected tumor samples from participants in the Nurses' Health Study who were diagnosed with incident colorectal cancer between 1986 and 2004 to determine whether associations between BMI and colorectal cancer risk differed by FASN expression status. We found that high BMI (≥25 kg/m²) was statistically significantly associated with increased risk of FASN-negative colorectal cancer but not with increased risk of FASN-positive colorectal cancer. Similar associations were obtained when we restricted the analysis to colon cancer. Associations between BMI and rectal cancer risk by FASN expression status showed similar patterns, although the analysis had limited statistical power.

Accumulating evidence suggests that FASN acts as a "metabolic oncogene" by conferring a selective growth advantage to cells upon nutritional deprivation (3). FASN inhibition results in apoptosis of cancer cells and decreases tumor size in experimental models (35–38). Cancer cells treated with FASN inhibitors can be rescued by supraphysiological amounts of dietary fatty acids (39). These findings suggest that FASN activity promotes tumor cell proliferation and survival, by allowing tumor cells to be autonomous from host metabolic status. Therefore, it is conceivable that FASN-inactive cells may depend on excess energy balance for malignant transformation,

Table 3. Body mass index and colorectal cancer risk according to FASN expression status*

Colorectal cancer subtype	Cumulative mean BMI†, kg/m²					P_{trend}‡	$P_{heterogeneity}$§
	<18.5	18.5–22.9	23.0–24.9	25.0–29.9	≥30		
All colorectal cancers (n = 536)							
No. of cancers/ person-years	5/23 128	143/686 819	107/387 121	189/521 008	92/230 130	—	
Age-adjusted incidence rate||	12.6	14.4	19.3	20.0	23.1	—	
Age-adjusted HR (95% CI)	1.06 (0.43 to 2.58)	1 (referent)	1.17 (0.91 to 1.50)	1.46 (1.17 to 1.82)	1.63 (1.25 to 2.12)	<.001	
Multivariable HR (95% CI)	1.09 (0.44 to 2.66)	1 (referent)	1.13 (0.88 to 1.45)	1.42 (1.14 to 1.78)	1.61 (1.22 to 2.13)	<.001	
FASN-negative colorectal cancers (n = 217)							
No. of cancers/ person-years	2/23 132	50/686 898	36/387 181	84/521 094	45/230 166	—	
Age-adjusted incidence rate||	4.0	5.0	6.3	9.0	10.6		
Age-adjusted HR (95% CI)	1.23 (0.30 to 5.06)	1 (referent)	1.09 (0.71 to 1.68)	1.83 (1.29 to 2.60)	2.27 (1.51 to 3.40)	<.001	
Multivariable HR (95% CI)	1.25 (0.30 to 5.15)	1 (referent)	1.05 (0.68 to 1.62)	1.78 (1.25 to 2.54)	2.25 (1.49 to 3.40)	<.001	
FASN-positive colorectal cancers (n = 319)							.033
No. of cancers/ person-years	3/23 128	93/686 863	71/387 154	105/521 087	47/230 173	—	
Age-adjusted incidence rate||	8.6	9.4	13.0	11.0	12.5	—	
Age-adjusted HR (95% CI)	0.96 (0.30 to 3.05)	1 (referent)	1.21 (0.89 to 1.65)	1.26 (0.95 to 1.67)	1.29 (0.91 to 1.83)	.11	
Multivariable HR (95% CI)	1.00 (0.32 to 3.17)	1 (referent)	1.18 (0.86 to 1.61)	1.23 (0.92 to 1.63)	1.27 (0.88 to 1.83)	.16	

* Subanalyses were done by stratifying colorectal cancers according to FASN expression status in the tumors. To compare the associations of BMI and FASN-positive colorectal cancer risk with that of FASN-negative colorectal cancer risk, we used a data duplication method in Cox proportional hazards model (34). We assessed the difference between the hazard ratio estimates according to tumor FASN status by likelihood ratio test that compared the model that allowed for separate associations of BMI by FASN status with a model that assumed a common association. The analysis was stratified by 1-year age and adjusted for age. In multivariable analyses, we adjusted for potential confounders, including age, physical activity (MET score per week in quintiles), energy-adjusted dietary and supplmental folate (μg/d), vitamin D (IU/d), and calcium (mg/d) intakes (in quintiles), total calorie in kcal/d (continuous), red meat intake (servings per day in quintiles), current smoking status (current, former, never), pack-years of smoking before 30 years of age (0, 1–4, 5–10, ≥11), alcohol intake (0, 0.1–4.9, 5–14.9, ≥15 g/d), multivitamin use (yes, no), regular aspirin use of at least two standard 325-mg tablets/wk (yes, no), previous sigmoidoscopy (never, ever), family history of colorectal cancer in any first-degree relative (yes, no), and menopausal status and postmenopausal hormone replacement therapy use (premenopausal, postmenopausal and never use, postmenopausal and former use, postmenopausal and current use). Colorectal cancers without FASN expression data were censored observations at the date of diagnosis. BMI = body mass index; CI = confidence interval; FASN = fatty acid synthase; HR = hazard ratio; — = not applicable.

† Cumulative mean BMI was calculated using baseline height and cumulative mean weight, which was the mean of all available weight data up to the start of each 2-year follow-up period. BMI of 18.5–22.9 kg/m² is considered as normal, 25.0–29.9 kg/m² as overweight (pre-obese), and 30.0 kg/m² or greater as obese by World Health Organization.

‡ *P* values for a linear trend were calculated using a two-sided Wald test in women with cumulative mean BMI of 18.5 kg/m² or higher.

§ *P* value for heterogeneity between FASN-positive and FASN-negative cancer risks in women with cumulative mean BMI of 18.5 kg/m² or higher was calculated using two-sided likelihood ratio test (for a multivariable linear trend).

|| Incidence rate per 100 000 person-years. Age-adjusted incidence rates were standardized to the age distribution of the study population.

whereas FASN-active cells may progress to cancer independent of energy balance status.

This study has a few limitations. First, there is a possibility of residual confounding. However, the multivariable hazard ratios, which were adjusted for many potential confounders, did not substantially differ from the age-adjusted hazard ratios. Second, tumor tissues were not available from all 1351 colorectal cancer patients. Nonetheless, the distribution of each risk factor in patients with available tumor tissue did not appreciably differ from patients without tumor tissue. Third, although we used BMI as a surrogate of energy balance status, BMI is not a perfect measure of energy balance. Fourth, our results may not be generalizable to men.

This study has several strengths. First, because we collected updated information on weight during more than 20 years of follow-up, we were able to evaluate the long-term effect of BMI. The use of cumulative mean BMI could increase the likelihood of correct classification. Second, we prospectively collected weight information, eliminating recall bias. Furthermore, because we also collected updated data on potential confounders and had a high follow-up rate, we could adjust for those potential

confounders. Last, our tumor tissue database enabled us to conduct an MPE research, which is an integrated analysis of an exposure (ie, BMI), cancer risk, and a tumor biomarker (ie, FASN) to gain insights into the pathogenesis of cancer development (28,29).

In conclusion, this MPE study suggests that obesity may be associated with increased risk of FASN-negative colorectal cancer in women, in contrast to no statistically significant association between obesity and risk of FASN-positive colorectal cancer. The results support the hypothesis that cellular FASN status may determine a cell's dependence on energy balance status for malignant transformation, and provide further evidence for a role of energy balance status in a specific carcinogenesis pathway.

References

1. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ*. 2007; 335(7630):1134.
2. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer*. 2008; 8(12):915–928.
3. Menendez JA, Lupu R. Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. *Nat Rev Cancer*. 2007;7(10):763–777.
4. Laake I, Thune I, Selmer R, Tretli S, Slattery ML, Veierod MB. A prospective study of body mass index, weight change, and risk of cancer in the proximal and distal colon. *Cancer Epidemiol Biomarkers Prev*. 2010;19(6):1511–1522.
5. Oxentenko AS, Bardia A, Vierkant RA, et al. Body size and incident colorectal cancer: a prospective study of older women. *Cancer Prev Res (Phila)*. 2010;3(12):1608–1620.
6. Martinez ME, Giovannucci E, Spiegelman D, Hunter DJ, Willett WC, Colditz GA. Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. *J Natl Cancer Inst*. 1997;89(13): 948–955.
7. Adams KF, Leitzmann MF, Albanes D, et al. Body mass and colorectal cancer risk in the NIH-AARP cohort. *Am J Epidemiol*. 2007; 166(1):36–45.
8. Engeland A, Tretli S, Austad G, Bjorge T. Height and body mass index in relation to colorectal and gallbladder cancer in two million Norwegian men and women. *Cancer Causes Control*. 2005;16(8):987–996.
9. Otani T, Iwasaki M, Inoue M. Body mass index, body height, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan public health center-based prospective study. *Cancer Causes Control*. 2005;16(7):839–850.
10. Pischon T, Lahmann PH, Boeing H, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *J Natl Cancer Inst*. 2006;98(13):920–931.
11. Larsson SC, Rutegard J, Bergkvist L, Wolk A. Physical activity, obesity, and risk of colon and rectal cancer in a cohort of Swedish men. *Eur J Cancer*. 2006;42(15):2590–2597.
12. MacInnis RJ, English DR, Hopper JL, Gertig DM, Haydon AM, Giles GG. Body size and composition and colon cancer risk in women. *Int J Cancer*. 2006;118(6):1496–1500.
13. Terry P, Giovannucci E, Bergkvist L, Holmberg L, Wolk A. Body weight and colorectal cancer risk in a cohort of Swedish women: relation varies by age and cancer site. *Br J Cancer*. 2001;85(3):346–349.
14. Chyou PH, Nomura AM, Stemmermann GN. A prospective study of colon and rectal cancer among Hawaii Japanese men. *Ann Epidemiol*. 1996;6(4):276–282.
15. Bassett JK, Severi G, English DR, et al. Body size, weight change, and risk of colon cancer. *Cancer Epidemiol Biomarkers Prev*. 2010;19(11): 2978–2986.
16. MacInnis RJ, English DR, Hopper JL, Haydon AM, Gertig DM, Giles GG. Body size and composition and colon cancer risk in men. *Cancer Epidemiol Biomarkers Prev*. 2004; 13(4):553–559.
17. Campbell PT, Cotterchio M, Dicks E, Parfrey P, Gallinger S, McLaughlin JR. Excess body weight and colorectal cancer risk in Canada: associations in subgroups of clinically defined familial risk of cancer. *Cancer Epidemiol Biomarkers Prev*. 2007;16(9):1735–1744.
18. Terry PD, Miller AB, Rohan TE. Obesity and colorectal cancer risk in women. *Gut*. 2002;51(2): 191–194.
19. Slattery ML, Ballard-Barbash R, Edwards S, Caan BJ, Potter JD. Body mass index and colon cancer: an evaluation of the modifying effects of estrogen (United States). *Cancer Causes Control*. 2003;14(1):75–84.
20. Vrieling A, Kampman E. The role of body mass index, physical activity, and diet in colorectal cancer recurrence and survival: a review of the literature. *Am J Clin Nutr*. 2010;92(3): 471–490.
21. Campbell PT, Jacobs ET, Ulrich CM, et al. Case-control study of overweight, obesity, and colorectal cancer risk, overall and by tumor microsatellite instability status. *J Natl Cancer Inst*. 2010;102(6):391–400.
22. Menendez JA, Vazquez-Martin A, Ortega FJ, Fernandez-Real JM. Fatty acid synthase: association with insulin resistance, type 2 diabetes, and cancer. *Clin Chem*. 2009;55(3):425–438.
23. Uddin S, Hussain AR, Ahmed M, et al. High prevalence of fatty acid synthase expression in colorectal cancers in Middle Eastern patients and its potential role as a therapeutic target. *Am J Gastroenterol*. 2009;104(7):1790–1801.
24. Rashid A, Pizer ES, Moga M, et al. Elevated expression of fatty acid synthase and fatty acid synthetic activity in colorectal neoplasia. *Am J Pathol*. 1997;150(1):201–208.
25. Visca P, Alo PL, Del Nonno F, et al. Immunohistochemical expression of fatty acid synthase, apoptotic-regulating genes, proliferating factors, and ras protein product in colorectal adenomas, carcinomas, and adjacent nonneoplastic mucosa. *Clin Cancer Res*. 1999;5(12):4111–4118.
26. Ogino S, Nosho K, Meyerhardt JA, et al. Cohort study of fatty acid synthase expression and patient survival in colon cancer. *J Clin Oncol*. 2008;26(35):5713–5720.
27. Nguyen PL, Ma J, Chavarro JE, et al. Fatty acid synthase polymorphisms, tumor expression, body mass index, prostate cancer risk, and survival. *J Clin Oncol*. 2010;28(25):3958–3964.
28. Ogino S, Stampfer M. Lifestyle factors and microsatellite instability in colorectal cancer: the evolving field of molecular pathological epidemiology. *J Natl Cancer Inst*. 2010;102(6):365–367.
29. Ogino S, Chan AT, Fuchs CS, Giovannucci E. Molecular pathological epidemiology of colorectal neoplasia: an emerging transdisciplinary and interdisciplinary field. *Gut*. 2011; 60(3):397–411.
30. Colditz GA, Hankinson SE. The Nurses' Health Study: lifestyle and health among women. *Nat Rev Cancer*. 2005;5(5):388–396.
31. Morikawa T, Kuchiba A, Yamauchi M, et al. Association of CTNNB1 (beta-catenin) alterations, body mass index, and physical activity with survival in patients with colorectal cancer. *JAMA*. 2011;305(16):1685–1694.
32. Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. *N Engl J Med*. 2007; 356(21):2131–2142.
33. Ogino S, Brahmandam M, Cantor M, et al. Distinct molecular features of colorectal carcinoma with signet ring cell component and colorectal carcinoma with mucinous component. *Mod Pathol*. 2006;19(1):59–68.
34. Lunn M, McNeil D. Applying Cox regression to competing risks. *Biometrics*. 1995;51(2): 524–532.
35. Pizer ES, Chrest FJ, DiGiuseppe JA, Han WF. Pharmacological inhibitors of mammalian fatty acid synthase suppress DNA replication and induce apoptosis in tumor cell lines. *Cancer Res*. 1998;58(20):4611–4615.
36. Kridel SJ, Axelrod F, Rozenkrantz N, Smith JW. Orlistat is a novel inhibitor of fatty acid synthase with antitumor activity. *Cancer Res*. 2004;64(6):2070–2075.
37. Menendez JA, Mehmi I, Verma VA, Teng PK, Lupu R. Pharmacological inhibition of fatty acid synthase (FAS): a novel therapeutic approach for breast cancer chemoprevention through its ability to suppress Her-2/neu (erbB-2) oncogene-induced malignant transformation. *Mol Carcinog*. 2004;41(3):164–178.
38. Pizer ES, Wood FD, Heine HS, Romantsev FE, Pasternack GR, Kuhajda FP. Inhibition of fatty acid synthesis delays disease progression in a xenograft model of ovarian cancer. *Cancer Res*. 1996;56(6):1189–1193.
39. Menendez JA, Ropero S, Mehmi I, Atlas E, Colomer R, Lupu R. Overexpression and hyperactivity of breast cancer-associated fatty

acid synthase (oncogenic antigen-519) is insensitive to normal arachidonic fatty acid-induced suppression in lipogenic tissues but it is selectively inhibited by tumoricidal alpha-linolenic and gamma-linolenic fatty acids: a novel mechanism by which dietary fat can alter mammary tumorigenesis. *Int J Oncol.* 2004;24(6):1369–1383.

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