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Total calcium intake and colorectal adenoma in young women

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Abstract

Background—Total calcium intake appears to reduce occurrence of colorectal adenoma; however, the dose necessary for prevention in young women is unclear. We examined fine categories of calcium intake in relation to occurrence of first colorectal adenoma in a cohort of mostly premenopausal (88%) women aged 26–60 at time of endoscopy.

Design—We conducted an analysis among 41,403 participants in the Nurses'Health Study II and assessed intakes of calcium prior to endoscopy through participants'responses to biannual questionnaires.

Results—Between 1991–2007, we documented 2,273 colorectal adenoma cases. There was a significant trend across categories of calcium intakes with lowest intakes suggestive of higher occurrence of adenoma ($p=0.03$) and those in the distal colon ($p=0.03$) and rectum ($p=0.04$).

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Our paper is the first to examine a dose-response relationship between calcium intake and risk colorectal adenoma in a group of largely premenopausal women who have estrogen to assist in calcium absorption. Knowing the lowest dose of calcium required to reduce risk of the precursors to colorectal cancer is important because higher intakes of dairy increases may increase risk of other unhealthy outcomes. Calcium intake is easily modifiable and can have an important public health message.

Compared with 1001-1250 mg/day of calcium intake, ≤ 500 mg/day was suggestive of a modest increase in occurrence of adenoma (multivariable RR = 1.21, 95% CI: 0.90-1.61); there were also suggestions of an increased risk with >500 - ≤ 700 mg/day of calcium. The association between ≤ 500 mg/day of calcium intake and adenoma was stronger for multiple (RR = 2.27, 95% CI: 1.38, 3.72), large (≥ 1 cm) (RR = 2.01, 95% CI: 1.27, 3.21), and high risk adenoma (≥ 1 cm or mention of villous histology/high grade dysplasia) (RR = 1.76, 95% CI: 1.13, 2.72). No differences in associations were noted between jointly categorized calcium and phosphorus or magnesium intakes.

Conclusions—Our findings suggest that low intakes of calcium, <500 and possibly 500-700 mg/day, in younger women are associated with an increased risk of multiple and advanced colorectal adenoma.

Keywords

calcium; magnesium; phosphorus; premenopausal; estrogen; colorectal adenoma

Introduction

Animal studies suggest that calcium intake may reduce colorectal carcinogenesis,(1) perhaps through maintenance of cell differentiation, a reduction in cell proliferation in the colorectal mucosa. Effects may be mediated through the calcium-sensor receptor (CaSR) and may be modified by CASR gene polymorphisms.(2-4) Though a few epidemiological investigations have reported no reduction in risk with calcium intake and colorectal cancer(5, 6) most studies, including a pooled analysis,(7-11) have reported an inverse association between calcium intake and colorectal cancer or adenoma. This finding was confirmed in clinical trials of calcium supplementation for adenoma recurrence.(12-16) However, these trials used high doses of calcium, $\sim 1,200$ mg/day, which does not provide information on the dose response relationship. A study of an older cohort of women has examined the dose response of calcium intake and found 800 mg/day was adequate to reduce optimally occurrence of colorectal adenoma.(17) However, this cohort of women was largely post-menopausal and recent studies suggest calcium is not absorbed well in estrogen deplete individuals.(18, 19) Therefore, we studied the dose response relationship between calcium and colorectal adenoma occurrence in young women, who are primarily pre-menopausal, to explore whether the association might differ as a result of the estrogen status.

Of note, studies where the main source of calcium is from supplements tend to suggest a strong protective association,(8, 12) whereas those where dairy products are the main calcium source tend to be weaker or null.(5-7, 20) The null studies might be more susceptible to the antagonistic effects of phosphorus on calcium's actions(21) because their primary sources of calcium were from milk, which is an important dietary source of calcium and phosphorus. High levels of phosphorus may reduce the absorption of calcium in the gastrointestinal tract, thereby reducing its bioavailability.(11, 22, 23) Another reason for the null results of some studies investigating calcium intake could be due to the lack of consideration of the calcium to magnesium ratio. Calcium competes with magnesium for absorption and transport and magnesium is antagonistic to calcium in many biological actions.(24, 25)

Some studies report significant changes by subgroups of different risk factors in the assessment of calcium intakes and risks of colorectal cancer or adenoma reoccurrence. In the Cancer Prevention Study II Nutrition Cohort, the inverse association between calcium intake and colorectal cancer was attenuated by phosphorus intake.(26) A case-control study from the Tennessee Colorectal Polyp Study found children who consumed a high amount of calcium and the Recommended Dietary Allowance of magnesium were in negative magnesium balance.(27) A recent case-control study found total calcium intake was associated with a lower risk of colorectal adenoma only when the ratio of calcium to magnesium was low. This study also reported that a trend of increasing calcium to magnesium intake ratios corresponded with an increased risk of colorectal adenoma.(28) However, other studies have not found these interactions to be significant.(8, 12, 26, 29)

To our knowledge, no studies have performed a detailed examination of low doses of calcium intake among those with high phosphorus or low magnesium and risk of colorectal adenomas and occurrence of adenomas in a population of young women. Our study design allows us to consider women's exposures up to 14 years in the past, and these early life exposures could be important if there is a long induction period between dietary and lifestyle exposures and occurrence of adenoma. Because women in this cohort are predominately premenopausal and pre-menopausal women absorb calcium much more efficiently than post-menopausal women, the dose response between calcium intake and colorectal cancer might differ by menopausal status.(30) Additionally, because the correlation between calcium, phosphorus, and magnesium intakes are high, large samples sizes, such as the ones provided by the Nurses'Health Study II (NHS II) cohort, are needed to estimate their separate and joint effects.

Subjects and Methods

Study population

The NHS II began in 1989, when 116,671 female registered nurses completed a mailed questionnaire about lifestyle factors and medical history. Every two years participants in the NHS II are mailed follow-up questionnaires to update information on possible risk factors for disease, as well as to identify newly diagnosed illnesses. Response rates for each questionnaire have been ~ 90%. The follow up for this analysis began in 1991 because this is the year that diet was first assessed through a semi-quantitative food frequency questionnaire. Participants were aged 26–46 years at the start of follow-up.

We excluded women if they did not complete a dietary questionnaire in 1991, or if they had any diagnosis of cancer (excluding nonmelanoma skin cancer), inflammatory bowel disease, familial polyposis, or colorectal polyp before 1991. We only included women who had their first lower gastrointestinal endoscopic procedure (colonoscopy or sigmoidoscopy) during the study period. 41,403 women were eligible for this analysis, which was approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard School of Public Health.

Ascertainment of colorectal adenoma

The ascertainment of adenoma cases and controls has been previously described. (31) Briefly, women who indicated a new diagnosis of colorectal polyp on a follow-up questionnaire were mailed a consent form to ask for medical records. Study investigators, who were blinded to the exposure status of the women, collected information on the anatomic location, histological type, and size of the reported polyps. Only those adenoma cases that were confirmed by pathology report were considered in this analysis. Between 1991 and 2007, we documented 2,273 women with adenomas in the proximal or distal colon or rectum, or any combination of the three locations. We found 1,008 proximal colon, 1,106 distal colon, and 398 rectal adenomas. 1,597 women were classified as having all small (<1 cm) adenomas, 554 women had one or more large (≥ 1 cm) adenoma, and 122 women had missing information on adenoma size, mainly as a result of biopsy procedures which left the size inestimable. 1,008 were classified as having low risk (small and tubular), 694 had high risk (large or villous), and 491 women had missing information on adenoma stage because of similar issues with biopsy procedures.

Dietary assessment

In 1991, a FFQ was mailed to women in NHSII. This questionnaire asked how often over the past year they consumed specified portions of certain foods. The dairy foods listed in 1991 were: skim or low fat milk, whole milk, cream, sour cream, sherbet/ ice milk or frozen yogurt, ice cream, yogurt, cottage cheese or ricotta cheese, cream cheese, other cheese (American, cheddar, etc.) plain or as part of a main dish, and butter. The 1999 questionnaire asked more detailed questions about milk with separate questions for skim, 1% or 2% milk, whole milk, and soy milk. Average daily intakes of calcium were calculated by multiplying the nutrient content by the frequency of consumption and then adding all of the nutrient contributions from each food item. Total intakes of calcium, phosphorus, and magnesium contained the nutrient components from food as well as from multivitamins and specific supplements. All nutrient intakes were energy adjusted using the residual method.(32)

The reproducibility and validity of the FFQ in a similar prospective cohort (NHS I) have been previously noted.(33, 34) The correlation coefficients between 41-week dietary records from the NHS I validation study and the 1980 FFQ were found to be reasonably high at 0.56 for energy-adjusted total calcium, 0.51 for dietary calcium, and 0.51 for energy-adjusted phosphorus.(35) A validation study using the food frequency questionnaire and two 1-week diet records in the NHS I cohort found a correlation of 0.76 for magnesium.(36)

Assessment of other covariates

Information on height, body weight, recreational physical activity, pack-years of smoking, aspirin use, and solar ultraviolet radiation were collected by questionnaire every two years. Body mass index (BMI; kg/m^2) was calculated using height and weight. Solar ultraviolet radiation (UV-B in Roberston-Berger meter units) was collected from 30 photosensitive meters across the U.S. and was matched to place of residence.(37) These variables were adjusted for in multivariate models because they were potential confounders of the calcium intake and colorectal adenoma association by being jointly associated with calcium intake and risk of adenoma.

Statistical analysis

We analyzed calcium by creating categories of intakes based on 100 mg/day increments; above 800 mg the increments were 801-1000, 1001-1250 (recommended daily intake and reference group), 1251-1500, and 1501-6000 mg/day. All categories were defined *a priori*. We analyzed calcium intake in relation to risk of single and multiple colorectal adenoma, and then performed separate analyses of adenomas in the proximal colon, distal colon, and rectum. In addition, we considered multiple adenoma (2 or more), large (>1cm) adenomas and small ($\leq$ 1cm) adenomas as well as high risk (large or villous) and low risk (small and tubular).

We also performed joint analyses of calcium intake by diet and supplement use. Using cut points of calcium intake that have been suggested as important for reducing risk of colon cancer,(11) we categorized calcium by diet by $\leq$ 700, 701-1,000, 1,001-1250, and $\geq$ 1251 mg/day; then cross classified by high ($\leq$ 250mg/day) and low calcium supplement ($>$ 251mg/day) use to create 8 categories of calcium intake. We used a similar analysis strategy for exploring calcium intake by high and low magnesium and phosphorus intakes. We used the same 4 categories of total calcium intake and cross classified by high and low magnesium phosphorus intakes. High versus low intake cut points for magnesium and phosphorus were determined by the study population's median intakes.

Multivariable logistic regression models were used to calculate odds ratios to approximate relative risks (RR) of diagnosed adenoma in the large bowel. To control for potential confounders, we created one model with known risk factors for adenoma: age in 5 year intervals, time period of endoscopy (2 year study period interval), reason for endoscopy (screening vs. symptoms), family history of colorectal cancer (first degree relative), height (categories in inches: 39-62, 63-64, 65-66, and 67-81), BMI (in quintiles), physical activity (MET in quintiles), smoking (pack years of cigarettes smoked per year in quintiles), aspirin use (never, past only, current use 1 day/week, current use 2-3 days/week, current use 4-5 days/week, current use $\geq$ 6 days/week), solar ultraviolet flux (UV-B in Roberston-Berger meter units in quintiles), and energy adjusted intakes of folate (mcg/day) and vitamin B6 (milligrams/day), alcohol (grams in categories/day 0, $>$ 0 to $<$ 5, 5 to $<$ 15, and $>$ 15), red meat (servings/day), and processed meat (servings/day). We also performed restricted cubic spline analyses to investigate a non-linear relationship between calcium intake and risk of colorectal adenoma.

Non-cases consisted of women who did not have adenoma detected during endoscopy, although they may have had hyperplastic polyps. Cumulative averaging of all available dietary and non-dietary measures up to the start of each 2-year interval was used to obtain the most accurate representation of the women's long term dietary intake and lifestyle patterns. For example, this method uses dietary data from the 1991 questionnaire to predict colorectal adenoma detected between June 1991 and June 1995; the average of the 1991 and 1995 dietary intake was used to predict diagnoses between 1995 and 1999, and so on. We tested for trend by using the median of each calcium intake category as a continuous variable in our logistic models, which controlled for multiple covariates. All reported P

values are two-sided. We conducted all analyses using SAS version 9 (SAS Institute, Inc., Cary, NC).

Results

Table 1 shows the age-standardized characteristics at time of their endoscopy procedure according to calcium intake in eight categories. Women who had higher intakes of calcium were more likely to have screening as a reason for endoscopy, engage in physical activity for more hours per week, have fewest pack years of smoking cigarettes, and consume more phosphorus, retinol, folate, magnesium, and vitamin B6 and less red and processed meats (Table 1). These differences were relatively small. Approximately 88% of the women in this cohort were premenopausal at the time of their endoscopy procedure.

There was a significant trend across intakes of calcium categories with the lowest intakes of calcium suggesting increased occurrence of colorectal adenoma as compared to the recommended calcium intake category, 1,001-1250 mg/day ($p=0.03$) (Table 2). The lowest intake of calcium ≤ 500 mg/day as compared to the reference group was suggestive of an increased risk of colorectal adenoma occurrence (RR=1.21, 95% CI: 0.90-1.61). Calcium intakes in the >500 to ≤ 700 mg/day range were also suggestive of an association with increased risk of adenoma (Table 2). Restricted cubic spline analysis for calcium intake were suggestive of a higher risk at lower intakes and a plateau with higher intakes (test for non-linear relationship, $P=0.10$). A sensitivity analysis was conducted restricting the analysis to only those women who were premenopausal ($n=2,127$); results did not change (data not shown).

Significant trends across calcium intake categories were also seen with occurrence of adenoma in the distal colon and rectum (distal: p for trend=0.04, rectum: p for trend=0.03), where the lowest intake of calcium as compared to the recommended intake for calcium were suggestive of increased risk (Table 2). Again, none of the specific categories of calcium intake were significantly associated with occurrence of adenoma in separate analyses of the proximal or distal colon or rectum.

We then examined calcium intake by sub-types of adenoma (Table 3). We found significant associations between the lowest intakes of calcium, ≤ 500 mg/day, as compared to 1,001-1,250 mg/day and increased occurrence of adenoma for multiple adenoma (RR=2.27, 95% CI 1.38-3.72); large adenoma (RR=2.01, 95% CI: 1.27-3.21); and high risk adenoma (RR=1.76, 95% CI: 1.13-2.72). For large and high-risk adenomas, a statistically significant inverse association was also noted in the 601-700 mg/day range. Large adenoma and high risk adenoma also had significant trend tests with lowest intakes being associated with highest occurrence of adenoma as compared to the recommended intake category (large $p=0.005$ and high risk $p=0.006$). When we combined the sub-types of multiple and large and villous adenoma, which we called “highest risk”, we similarly estimated the lowest calcium intake category to be associated with an increased risk (RR= 2.05, 95% CI: 1.19-3.54, p trend 0.10). In contrast, no association was observed for calcium with small or low risk adenoma.

When we considered calcium intake by food and supplement jointly all categories of intake compared to the lowest category (≤ 700 mg/day of dietary and < 250 mg/day of supplemental calcium) were suggestive of a small inverse association with colorectal adenoma occurrence (data not shown). The highest dietary (≥ 1251 mg/day) and supplement (≥ 250 mg/day) calcium intake category had the greatest suggestive inverse association with occurrence of adenoma (RR=0.84, 95% CI 0.66-1.06); this association was most pronounced in the rectum (RR=0.66, 95% CI 0.39-1.10).

There were little differences noted in the associations between jointly categorized calcium and phosphorus and occurrence of adenoma (Table 4). However, all categories of calcium and phosphorus intake compared to the lowest (≤ 700 mg/day of total calcium intake and ≤ 1365 mg/day of phosphorus) intakes had a suggestive inverse association with adenoma; and the two highest categories of calcium intake $\geq 1,251$ mg/day in both the low phosphorus and high phosphorus categories had a significant inverse association. Similarly, there were little differences in the effect sizes of jointly categorized calcium and magnesium intake with adenoma occurrence. Again it appeared that the highest intakes of the calcium categories, both 1,001-1250 and $\geq 1,251$ mg/day in the low and high magnesium intake categories had significant inverse associations with risk of colorectal adenoma as compared to the lowest calcium magnesium intake group.

Discussion

In this large study of mainly pre-menopausal women with prospective dietary information, there were significant trends between the lower intakes of calcium and higher risk of colorectal adenoma compared to 1,001-1,250 mg/day of calcium. This trend also appeared in the distal colon and rectum. The association between the lowest intakes of calcium, ≤ 500 mg/day as compared to 1,001-1,150 mg/day, and increase occurrence of adenoma was strongest for multiple, large, and high risk adenoma. Calcium intakes in the 500-700 mg/day range were also suggestive of an increased occurrence of these high risk subgroups of adenoma. For most endpoints, there was no suggestion of lower risk above 700 mg/day. There was a suggestion of higher risk of colorectal adenoma among those with dietary calcium intakes of < 700 mg/day and not taking a calcium supplement. There were no differences noted in the relationship between calcium intake and adenoma by intake levels of phosphorus or magnesium. However, the highest intakes of calcium categories were both significantly inversely related to risk of colorectal adenoma as compared to the lowest intake of calcium in both the high and low phosphorus and magnesium intake categories.

The mechanisms by which calcium is thought to affect colorectal carcinogenesis are through binding bile and fatty acids in the lumen of the large bowel, by increasing apoptosis, through inhibition of the proliferation of colonic epithelial cells, and through CaSR genetic polymorphisms.(4, 38-41) It has been hypothesized that phosphorus could interfere with the absorption of calcium(11, 22, 23) which could reduce the protective effects that calcium has on adenoma occurrence. Additionally, it has been suggested that calcium competes with magnesium for absorption and transport and magnesium could be antagonistic to calcium in many biological actions.(24, 25) However, our study found no difference in associations between calcium and risk of adenoma by levels of phosphorus or magnesium intakes. A

larger study may be needed to investigate the possibility of phosphorus or magnesium playing an antagonistic role to calcium's actions on adenoma occurrence.

In the NHS cohort, greater than 800 mg/day, compared to ≤ 500 mg/day of calcium intake was significantly associated with large adenoma and marginally significantly associated with adenoma in the distal colon(17). The Calcium Polyp Prevention Study randomized trial found 1200mg/day of calcium compared to placebo resulted in a statistically significant decreased risk of recurrent adenoma ($RR=0.81$; 95%CI= 0.67 to 0.99).(12) A trial from Europe also found a modest reduction in risk with 2000 mg/day of calcium and recurrent adenoma; however, it was not statistically significant (0.66; 95% CI 0.38 to 1.17).(42) These studies support a protective role of higher calcium intakes on risk of colorectal adenoma; however, our study of primarily pre-menopausal women finds only those with the lowest intakes of calcium have an increased risk of colorectal adenoma. The difference in the dose response of calcium intake and risk of colorectal adenoma in these previous studies compared to our study of young women may be the result of the role estrogen plays in calcium absorption. In a recent study, menopausal status was found to be a potent factor for calcium absorption, possibly stronger than $1,25(OH)_2D$.(30) Estrogen deficiency is thought to lower intestinal calcium absorption,(18, 19) therefore older populations of women, may need larger intakes of calcium before lowering risk of colorectal adenoma occurrence.

Some studies of colorectal cancer that have suggested there may be a threshold level of calcium for reducing risk of adenoma. In a pooled analysis, total calcium of up to 1,000 mg/day of calcium was significantly inversely associated with colorectal cancer risk, with little protection being gained from greater intakes.(7) A recent epidemiological study of women and men(11) suggested a threshold effect of calcium of 700 mg/day beyond which may not be beneficial for reducing risk of colon cancer. Our results suggest a similar threshold effect of 700 mg/day of calcium for colorectal adenoma. Although the actual threshold level has varied across epidemiologic studies, the data on the whole do suggest that avoidance of very low calcium intakes is most important and that there may be diminishing benefits at very high intakes. It should be noted that our study population had a higher mean intake of calcium (1,122 mg/day) as compared to the national average intake of similarly aged women in NHANES (797 mg/day); thus, in the general population, there is a much higher proportion of individuals at the low levels of calcium intake.(43) Additionally, because most of the women in our cohort were pre-menopausal, estrogen could still be working to assist in intestinal calcium absorption(18, 19) and therefore smaller amounts of calcium may be needed by these younger individuals.

Benefits of calcium intake have been thought to be most important for the proximal colon because effects of fatty acids and bile acids on colon cell proliferation may be stronger in that region.(5, 44) However, in some studies which have investigated associations by cancer site, there is growing support for calcium's effect to be more pronounced in the distal region. Two case-control, three cohort studies, and a pooling project of prospective studies all found inverse associations between calcium intake and colon cancer risk tended to be strongest in the sigmoid colon.(7, 45-48) In contrast, the two trials which investigated cancer site do not support calcium's effects being more prominent in the distal colon. Bonithon-Kopp et al.'s

trial found inverse associations between calcium supplements and adenoma to be only in the proximal region(42); Baron et al.'s trial found no difference in colon subsite.(12)

Our study also found calcium's association to be greatest for advanced, large and multiple adenoma, subtypes of adenomas with a greater propensity to progress to malignancy. In fact, individuals with a single, small tubular adenoma are not considered to be at appreciably higher risk of malignancy. Only a few studies have investigated the relationship between calcium intake and histological type of colorectal adenoma. Two observational studies found no difference in association between non-advanced and advanced stage adenomas.(49, 50) However, a study using Baron's et al. randomized control trial found calcium supplementation had greater antineoplastic effects on advanced colorectal adenoma compared with any other type of adenoma.

To our knowledge, this is the first study to investigate the relation of calcium intake on risk of colorectal adenoma in a largely premenopausal cohort of women using prospective data. Strengths of our study include its prospective design, a high follow-up response rate, repeated assessments of diet and supplement use, and detailed data on many potential confounders. These factors reduce the chance that bias or confounders influenced our results. Lifestyle factors were controlled for in this study; yet it is possible that there was residual confounding due to errors in measurement of these covariates. However, it is unlikely that this potential residual confounding could explain our results because we found only small differences in magnitude of associations between the age-adjusted analyses and the multivariate analyses that controlled for these "health conscious" traits.

One limitation of our study is that calcium intake was assessed by questionnaires, which is likely to result in some misclassification of exposure. However, these errors should not be associated with the outcome because dietary collection was prospective. Therefore, these errors of misclassification would tend to bias the results toward the null. It should also be noted that this study was comprised of only women, who were primarily premenopausal; therefore it may not be generalizable to postmenopausal women or to men.

In conclusion, our results suggest that those with the lowest intakes of calcium, 500 or less, and possibly 500-700, mg per day may be at increased risk of colorectal adenoma in young, primarily premenopausal women. Additionally, the inverse association of calcium intake may be greater for multiple, large and high risk adenoma.

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Table 1
Age-standardized characteristics according to categories of calcium intake in women at time of first endoscopy

	Categories of calcium intake (mg/day)									
	<=500	501-600	601-700	701-800	801-1000	1001-1250	1251-1500	1501-6000		
Participants (n)	987	1733	2,850	3,675	8,291	9,728	7,010	7,129		
Calcium (mg)	436	554	653	751	899	1,121	1,364	1,822		
Age (years)	45.9	46.1	46.3	46.4	47.3	47.7	48.1	48.7		
Family history of colorectal cancer (%)	16.4	15.7	16.7	16.4	15.8	14.9	14.9	14.1		
Reason for endoscopy was screening (%)	63.2	63.6	66.6	65.6	68.5	69.1	70.3	71.8		
Aspirin use										
Never user (%)	51.2	49.8	50.1	49.0	48.0	46.8	47.0	45.8		
Past user (%)	26.1	26.1	26.8	27.7	27.5	27.8	25.5	25.3		
Current user (%)	22.7	24.1	23.1	23.3	24.5	25.4	27.5	28.9		
Height (inches)	64.4	64.6	64.8	64.7	64.9	65.0	65.1	65.0		
Body mass index (kg/m ²)	27.4	27.3	27.4	27.2	27.0	26.7	26.5	26.1		
Physical activity (METs-hrs/ week)	14.1	16.3	16.9	18.4	19.2	20.6	22.0	24.7		
Pack-years of smoking (years)	11.0	8.1	8.5	10.1	8.6	7.6	8.2	7.8		
UV-B Flux (R-B meter units)	130	127	126	126	125	124	124	127		
Phosphorus (mg/day)	1,046	1,140	1,202	1,257	1,320	1,406	1,491	1,578		
Folate (mcg/day)	287	314	367	387	434	478	529	617		
Magnesium (mg/day)	236	263	279	290	306	322	340	363		
Vitamin B6 (mg/day)	4.8	4.3	5.4	6.1	6.6	7.9	10.2	15.0		
Unprocessed red meat (servings/day)	0.62	0.59	0.57	0.56	0.52	0.51	0.46	0.39		
Processed meat (servings/day)	0.23	0.21	0.21	0.20	0.20	0.19	0.18	0.13		
Alcohol (gm/day)	2.9	3.9	3.9	4.0	4.1	3.7	3.7	3.3		

* Means, unless otherwise noted

** Except for the data on mean age and % users, all data shown are standardized to the age distributions of the cohort

*** Nutrient intakes are energy adjusted

Table 2
Relative risks of colorectal adenoma among women in the Nurses' Health Study II, 1991-2007, by categories of calcium

Calcium (mg/ day)	RR and (95% CI) by Category								P trend ^{a/b}
	<=500	501-600	601-700	701-800	801-1000	1001-1250	1251-1500	1501-6000	
Adenoma									
#Ca/ #Co	61/926	104/1,629	176/2,674	212/3,463	483/7,808	521/9,207	362/6,648	354/6,775	
Age Adjusted RR [†]	1.32(1.00-1.73)	1.23(0.99-1.33)	1.25(1.05-1.50)	1.15(0.97-1.35)	1.12(0.99-1.27)	1.00	0.95(0.83-1.09)	0.90(0.79-1.04)	<0.001
Multivariable RR [§]	1.21(0.90-1.61)	1.14(0.91-1.43)	1.18(0.98-1.41)	1.09(0.92-1.29)	1.09(0.96-1.24)	1.00	0.98(0.85-1.12)	0.99(0.85-1.14)	0.03
Proximal colon									
#Ca/ #Co	24/926	40/1,629	67/2,674	89/3,463	209/7,808	250/9,207	156/6,648	173/6,775	
Age Adjusted RR [†]	1.19(0.78-1.83)	1.06(0.76-1.49)	1.06(0.80-1.39)	1.06(0.83-1.35)	1.03(0.86-1.24)	1.00	0.85(0.69-1.04)	0.90(0.74-1.10)	0.03
Multivariable RR [§]	1.07(0.69-1.68)	0.97(0.68-1.38)	0.98(0.74-1.31)	1.00(0.77-1.28)	1.00(0.83-1.21)	1.00	0.87(0.71-1.07)	1.00(0.81-1.23)	0.71
Distal colon									
#Ca/ #Co	36/926	50/1,629	89/2,674	106/3,463	249/7,808	243/9,207	181/6,648	152/6,775	
Age Adjusted RR [†]	1.56(1.09-2.24)	1.21(0.89-1.65)	1.31(1.02-1.67)	1.19(0.94-1.50)	1.22(1.02-1.46)	1.00	1.02(0.84-1.25)	0.84(0.68-1.03)	<0.001
Multivariable RR [§]	1.39(0.95-2.03)	1.10(0.80-1.51)	1.21(0.94-1.56)	1.11(0.88-1.41)	1.18(0.99-1.42)	1.00	1.06(0.87-1.29)	0.94(0.76-1.16)	0.03
Rectum									
#Ca/ #Co	14/926	20/1,629	33/2,674	43/3,463	79/7,808	86/9,207	61/6,648	62/6,775	
Age Adjusted RR [†]	1.78(1.00-3.16)	1.40(0.86-2.29)	1.40(0.93-2.09)	1.36(0.96-2.01)	1.10(0.81-1.50)	1.00	0.97(0.70-1.35)	0.96(0.69-1.33)	0.007
Multivariable RR [§]	1.68(0.92-3.06)	1.36(0.82-2.26)	1.37(0.91-2.08)	1.37(0.94-2.00)	1.10(0.81-1.50)	1.00	0.97(0.69-1.35)	0.99(0.70-1.39)	0.04

Adenoma found in proximal and/or distal colon and/or rectum

[†] Odds ratio and 95% confidence interval from age (5 yr cats) and time period (2 yr study period intervals) adjusted logistic regression

[§] Odds ratio and 95% confidence interval from logistic regression with adjustment for the following covariates: age, family history of colorectal cancer (first degree relative), reason for endoscopy (screening vs. symptoms), height (inches), BMI (quintiles), physical activity (METs-hrs/wk in quintiles), pack years of smoking, aspirin use (never, past, current 1 dy/wk, current 2-3 dy/wk, current 4-5 dy/wk, current >=6 dy/wk), UV-B flux (Robertson-Berger meter units in quintiles), energy adjusted intakes of folate (mcg/dy), vitamin B6 (mg/dy), alcohol (gm in cats: 0, >0 to <5, 5 to <15, and >=15/dy), unprocessed red meat (servings/d), and processed meats (servings/d)

^{ab} Calculated using median intakes of calcium

Table 3
Multivariable relative risks of different stages of colorectal adenoma among women in the Nurses'Health Study II, 1991-2007, by categories of calcium intake

		RR and (95% CI) by category of calcium intake								P trend [¶]
Calcium (mg/day)		<=500	501-600	601-700	701-800	801-1000	1001-1250	1251-1500	1501-6000	
Highest risk adenoma ^β										
No. of Cases/ No. of Controls		34/39	36/90	82/129	86/159	181/364	197/391	138/231	109/268	
Multivariable RR [§]		2.05(1.19-3.54)	0.84(0.53-1.32)	1.33(0.93-1.90)	1.13(0.81-1.58)	0.98(0.75-1.27)	1.00	1.24(0.93-1.65)	0.83(0.61-1.13)	0.10
High risk adenoma										
No. of Cases/ No. of Controls		27/948	31/1,672	65/2,754	69/3,564	153/8,039	154/9,473	103/6,826	92/6,942	
Multivariable RR [‡]		1.76(1.13-2.72)	1.07(0.71-1.60)	1.40(1.03-1.90)	1.13(0.84-1.52)	1.14(0.91-1.44)	1.00	0.94(0.73-1.21)	0.91(0.69-1.19)	0.006
Multiple adenoma										
No. of Cases/ No. of Controls		22/965	16/1,717	34/2,816	43/3,632	103/8,188	106/9,622	71/6,939	70/7,059	
Multivariable RR [§]		2.27(1.38-3.72)	0.85(0.49-1.46)	1.12(0.75-1.68)	1.11(0.77-1.59)	1.13(0.86-1.49)	1.00	0.93(0.68-1.26)	0.95(0.69-1.30)	0.09
Large adenoma										
No. of Cases/ No. of Controls		25/926	24/1,629	52/2,674	58/3,463	128/7,808	120/9,207	73/6,648	74/6,775	
Multivariable RR [§]		2.01(1.27-3.21)	1.02(0.64-1.63)	1.41(1.01-1.99)	1.20(0.87-1.66)	1.22(0.94-1.57)	1.00	0.86(0.64-1.15)	0.95(0.70-1.29)	0.005
Low risk adenoma										
No. of Cases/ No. of Controls		22/953	43/1,660	80/2,739	101/3,532	231/7,961	266/9,361	178/6,751	167/6,867	
Multivariable RR [‡]		0.91(0.57-1.45)	1.00(0.71-1.40)	1.08(0.83-1.41)	1.06(0.83-1.34)	1.04(0.87-1.25)	1.00	0.93(0.76-1.13)	0.90(0.73-1.11)	0.14
Small adenoma										
No. of Cases/ No. of Controls		33/926	74/1,629	115/2,674	144/3,463	336/7,808	369/9,207	264/6,648	262/6,775	
Multivariable RR [§]		1.01(0.69-1.48)	1.23(0.94-1.60)	1.13(0.91-1.42)	1.08(0.89-1.33)	1.09(0.94-1.27)	1.00	0.98(0.83-1.16)	1.00(0.85-1.19)	0.15

Adenoma found in proximal and/or distal colon and/or rectum

^βHighest risk adenoma: advanced stage or multiple (2 or more adenoma)

High risk adenoma: advanced stage (>=1cm or any mention of villous histology or high grade dysplasia); low-risk adenoma: non-advanced stage <1cm and tubular

[‡]Odds ratio and 95% confidence interval from logistic regression adjusted for variables mentioned in Table 2

[§]Odds ratio and 95% confidence interval from logistic regression adjusted for variables mentioned in Table 2

§ Odds ratio and 95% confidence interval from logistic regression adjusted for variables mentioned in Table 2

¶ Calculated using median intakes of calcium

Table 4
Multivariable relative risks of colorectal adenoma among women in the NHS II, 1991-2007, by joint categories of calcium among those with high phosphorus intake (≥ 1365 mg/day) versus low phosphorus intake (< 1365 mg/day) and high magnesium intake (≥ 329 mg/day) versus low magnesium intake (< 329 mg/day)

Total calcium (mg/day)	RR and (95% CI) by Category			
	≤ 700	701-1,000	1,001-1250	1,251+
Adenoma				
Low phosphorus				
No. of Cases/ No. of Controls	323/4,904	491/7,760	215/3,698	167/3,115
Multivariable RR [§]	1.00	0.93(0.80-1.08)	0.83(0.69-1.01)	0.80(0.65-0.99)
High phosphorus				
No. of Cases/ No. of Controls	18/324	205/3,514	306/5,512	548/10,303
Multivariable RR [§]	0.93(0.57-1.53)	0.91(0.76-1.10)	0.85(0.72-1.01)	0.83(0.72-0.98)
Adenoma				
Low magnesium				
No. of Cases/ No. of Controls	307/4,595	447/7,421	245/4,223	172/3,247
Multivariable RR [§]	1.00	0.88(0.75-1.02)	0.83(0.69-1.00)	0.80(0.65-0.98)
High magnesium				
No. of Cases/ No. of Controls	34/633	249/3,853	276/4,987	543/10,171
Multivariable RR [§]	0.79(0.54-1.16)	0.96(0.79-1.15)	0.82(0.68-0.99)	0.81(0.68-0.97)

Adenoma found in proximal and/or distal colon and/or rectum

[†] Odds ratio and 95% confidence interval from logistic regression adjusted for variables mentioned in Table 2

[‡] Odds ratio and 95% confidence interval from logistic regression adjusted for variables mentioned in Table 2

[§] Odds ratio and 95% confidence interval from logistic regression adjusted for variables mentioned in Table 2