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Vitamin A Intake and Risk of Incident, Sporadic Colorectal Adenoma

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Master of Public Health

Epidemiology

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Vitamin A Intake and Risk of Incident, Sporadic Colorectal Adenoma

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Bachelor of Science

Hope College

2014

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Abstract

Vitamin A Intake and Risk of Incident, Sporadic Colorectal Adenoma
By Matthew Thomas Ringel

Background: Colorectal cancer is the third leading cause of cancer incidence and mortality among both men and women in the United States. Colorectal cancer risk is modifiable, and dietary exposures are among the known risk factors for colorectal cancer. Vitamin A is an antioxidant, and has been shown to improve immune function. However, little is known about its association with colorectal adenoma, a precursor to colorectal carcinoma, in humans.

Methods: We examined the association between intakes of total and dietary vitamin A, including its two forms (retinol and carotene), with incident, sporadic colorectal adenoma in a case-control study of colorectal polyps conducted in Minnesota between 1991 and 1994). Individuals with no prior history of colorectal neoplasms completed comprehensive questionnaires prior to elective, outpatient endoscopy; of these patients, 564 colorectal adenoma cases, and 1,202 endoscopy-negative controls were identified. An additional group of 535 community controls frequency matched on age and sex was also included. The food frequency questionnaire (FFQ) was used to assess each participant's nutrient intakes. Logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CI) for associations of total and dietary intakes of vitamin A, and its major subtypes, retinol and carotene with colorectal adenoma.

Results: Dietary and total intakes of vitamin A, and total carotene intake were not statistically significantly associated with colorectal adenoma risk. The multivariable-adjusted ORs for incremental increases in total intake were OR = 0.97 (95% CI: 0.86-1.10) for total vitamin A (9561.56 IU/day), OR = 0.95 (95% CI: 0.87-1.05) for dietary vitamin A (7425.64 IU/day), OR = 1.03 (95% CI: 0.92-1.15) for total carotene (7425.64 IU/day), when comparing cases with all controls combined. There was, however, a significant inverse association, in the multivariable-adjusted model, with colorectal adenoma per 1 SD (SD = 3739.54 IU/day) increment in retinol (OR = 0.86, 95% CI: 0.75-0.98) when comparing cases with all controls combined. Associations did not vary substantially by sex, age, aspirin or NSAID use, or BMI.

Conclusion: These results suggest a possible inverse association between retinol, but not carotene, or total or dietary vitamin A, intakes and incident, sporadic colorectal adenoma.

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BACKGROUND

Colorectal Cancer as a Public Health Issue

Colorectal cancer contributes substantially to the burden of disease in the United States. It is the third leading cause of cancer incidence and of cancer mortality among both men and women (1). The American Cancer Society estimates that over 134,000 people will be diagnosed with colorectal cancer and over 49,000 people will die from colorectal cancer in the United States in 2016 (1).

The five-year relative survival is a common prognostic measurement in cancer epidemiology. It is calculated by taking the probability of surviving at least five years after the diagnosis divided by the probability of surviving at least five years for a person of that same age and sex in the underlying population (1).The relative five-year survival rate for colorectal cancer depends on the location and the stage of the cancer (1). The relative five-year survival rate for colorectal cancer ranges from 11%, for stage IV colon cancer, to 92% for stage I colon cancer (1).

Routine colorectal cancer screening is an important aspect of prevention. Colorectal cancer screening is estimated to reduce mortality by up to seventy percent because it allows the gastroenterologist to detect and remove colorectal adenomas (2). Colorectal adenomas are precancerous polyps from which the majority of colorectal carcinomas originate (3). Colorectal cancer screening is recommended for adults over the age of fifty, but only about two-thirds of adults between the ages of fifty and seventy-five are compliant (4).

Colorectal Carcinogenesis

The process of colorectal carcinogenesis occurs in four steps (5). The first is the formation of an aberrant crypt focus from normal mucosa, the second is the formation of an early adenoma from an aberrant crypt focus, the third is the formation of a late adenoma from an early adenoma, and the fourth is the formation of invasive cancer from a late adenoma (5). The three currently known molecular pathways that can account for this process are the chromosomal instability pathway, the microsatellite instability pathway, and the CpG Island Methylator Phenotype pathway (6).

The typical mutation rate of human cells is estimated to be one mutation per billion base pairs, and this is generally not rapid enough for colorectal cancer to occur (5). However, if one of these mutations occurs in a gene that is responsible for DNA repair, the mutation rate can increase and lead to chromosomal instability (5). Chromosomal instability accounts for an estimated 65% to 75% of sporadic colorectal cancer cases (5).

Microsatellites are regions of DNA that are prone to copying errors because they are short and repetitive (6). These errors are typically repaired by the DNA mismatch repair system, and highly abnormal microsatellites are indicative of a problem within that system (6). A problem with the DNA mismatch repair system can lead to colorectal cancer (7). Microsatellite instability can be detected in about 15% of sporadic colorectal cancer cases (6).

Tumor suppressor genes can be silenced by methylation of their promoter regions, otherwise known as CpG Islands (6). Environmental factors, such as age and smoking,

are correlated with higher rates of methylation (6). CpG Island methylations accounts for an estimated 15% to 20% of sporadic colorectal cancer cases (6).

Main Risk Factors for Colorectal Cancer

Several demographic, lifestyle, and dietary risk factors were previously shown to be associated with colorectal cancer incidence or mortality (1).

Demographic Factors

Age is strongly associated with almost all types of cancer, including colorectal cancer (2). The median age of a colorectal cancer diagnosis is 68 years (2).

The colorectal cancer incidence rate is higher among men that it is among women (4). This difference is not due to screening for precancerous polyps, as men are more likely than women to undergo routine colonoscopy (8). The difference is likely due to other risk factors, such as smoking or alcohol consumption, which are more common among men than women (9).

There may be an association between education level and colorectal cancer. One study found that people with an education from a college or university were more likely to develop colorectal cancer than those without one (10). The authors, however, could not explain the cause of this association (10).

Colorectal cancer incidence and mortality are higher among African Americans than among other races within the United States (1). The exact reason for this, however, is currently unknown, but lower screening rates among African Americans is likely a factor (11).

Lifestyle Factors

There is strong evidence indicating that a person's lifestyle contributes to his or her colorectal cancer risk (2). Lifestyle factors, such as physical activity and use of non-steroidal anti-inflammatory drugs, decrease a person's risk of colorectal cancer (2). Smoking and obesity, on the other hand, increase a person's risk of colorectal cancer (2).

Body Mass Index

Obesity is associated with many types of cancer, including colorectal cancer (2). A meta-analysis of thirty-one studies that included 70,000 events found a positive association between colorectal cancer and body mass index (obese vs. non-obese RR = 1.19, 95% CI: 1.11-1.29) (12).

Hormone Replacement Therapy

Hormone replacement therapy in women has been shown to affect the risk of certain types of cancer (2). A meta-analysis of twenty-seven studies found that hormone replacement therapy use was inversely associated with colorectal cancer incidence (RR = 0.67, 95% CI: 0.59-0.77) and fatal colorectal cancer incidence (RR = 0.72, 95% CI: 0.64-0.81) (13).

Aspirin and NSAID Use

Chronic inflammation has been shown to increase the risk of cancer, and having either ulcerative colitis or Crohn disease increases a person's risk of colorectal cancer (2).

It has, therefore, been hypothesized that regular use of aspirin or NSAIDs reduce a person's risk of colorectal cancer (2). A large cohort with 943,903 subjects and 2,002 cases found an inverse association between use of certain NSAIDs and colorectal cancer incidence (RR = 0.5, 95% CI: 0.4-0.7), as well as an inverse association between use of aspirin and colorectal cancer incidence (RR = 0.6, 95% CI: 0.5-0.9) (14).

Smoking

Smoking tobacco is associated with many types of cancer, including colorectal cancer (2). A meta-analysis of 106 studies found a positive association between smoking cigarettes and both colorectal cancer incidence (obese vs. non-obese RR = 1.19, 95% CI: 1.11-1.29) and mortality (obese vs. non-obese RR = 1.19, 95% CI: 1.11-1.29) (15).

Physical Activity

Some evidence suggests that physical activity can reduce the risk of certain types of cancer (2). A case-control study of 877 Chinese men and 608 Chinese women living in North America found a positive association between having a sedentary lifestyle, as opposed to a physically active lifestyle, and colon cancer among men (RR = 1.6, 95% CI: 1.1-2.4) and women (RR = 2.0, 95% CI: 1.2-3.3) (16). Having a physically active lifestyle was defined as spending at least five hours per day on moderate physical activity or spending at least one hour per day on vigorous physical activity (16). No significant associations were found with rectal cancer.

Dietary Factors

There is strong evidence indicating that a person's diet contributes to his or her colorectal cancer risk (17). Dietary exposures, such as vitamin C, vitamin E, calcium, and fiber decrease a person's risk of developing colorectal cancer (17). Red meat and alcohol, on the other hand, increase a person's risk of developing colorectal cancer (17).

Vitamin A Intake

A case-control study with 224 colorectal adenoma cases and 230 controls that were matched on age and sex, examined the association between colorectal adenoma risk and blood plasma concentration of retinol, α-carotene, β-carotene, lutein with zeaxanthin, and lycopene (18). The fully adjusted model found an inverse association among men, but not women, between colorectal adenoma risk and α-carotene blood plasma concentration (highest vs. lowest quartile OR = 0.38, 95% CI: 0.18-0.84) (18). Blood plasma concentration of carotenoids is a reliable biomarker that can be used to estimate dietary intake of carotenoids (19).

A case-control study with 73 colorectal adenoma cases and 63 controls that were matched on age and sex, examined the association between colorectal adenoma risk and blood plasma concentration of lycopene (20). The fully adjusted model found a positive association between colorectal adenoma risk and having a low lycopene concentration (<70 ug/L vs. >70 ug/L OR = 3.02, 95% CI: 1.46-6.25) (20).

A cohort study of 5477 women who were followed for twelve years, examined the association between colorectal cancer hazard and serum concentration of retinol, α-carotene, β-carotene, lutein with zeaxanthin, lycopene, β-cryptoxanthin, α-tocopherol, and γ-tocopherol (21). This study found no association between baseline concentrations

of any of these antioxidants and colorectal cancer hazard (21). It did, however, find an inverse association between serum β-carotene concentration and colorectal cancer incidence when taking an average of three measurements throughout the study (highest vs. lowest tertile OR = 0.54, 95% CI: 0.31-0.96) (21).

A clinical trial testing the effect of daily β-carotene supplementation on the risk of colorectal adenoma reoccurrence was conducted in 864 patients in the United States who had been diagnosed with at least one colorectal adenoma within the previous year (22). No effect was found (22).

A systematic review of eleven cohort studies was conducted in order to examine the association between the dietary intakes of various subtypes of vitamin A and colorectal cancer (23). The subtypes that were examined were α-carotene, β-carotene, lutein with zeaxanthin, lycopene, and β-cryptoxanthin (23). No meaningful associations were found (23).

Biological Plausibility of Vitamin A Reducing Colorectal Cancer Risk

Vitamin A plays an important role in allowing the immune system to function properly. Specifically, retinoic acid gives immune cells the capacity to target the intestines (24). Insufficient vitamin A consumption is associated with poor immune function in the intestines (24). Poor immune function in the intestines would likely contribute to the development of cancerous cells in the intestines.

Vitamin A is an antioxidant (17). Antioxidants are associated with a decrease in the risk of many types of cancer, including colorectal cancer (25). The likely mechanism for this association is that antioxidants reduce oxidative damage done to DNA (25).

There is also *in vitro* evidence that supports the biological plausibility of an inverse association between vitamin A intake and colorectal cancer risk (26). Both natural and synthetic retinoid, in high concentrations *in vitro*, were found to reduce proliferation of colorectal carcinoma cells and to induce their apoptosis (26). The effect of the synthetic retinoid was stronger than the effect of the natural retinoid, but both relationships were dose-dependent (26).

Research Question

Despite biological plausibility, there is very little evidence at this time of an association between vitamin A intake and colorectal neoplasms. Most previous studies, however, have not focused on early stages of carcinogenesis, such as adenoma formation or emphasized the potential for effect modification. The purpose of this thesis is to examine the associations of total vitamin A intake, retinol intake, carotene intake, and dietary vitamin A intake with the risk of incident, sporadic colorectal adenoma and to assess whether these associations vary by biologically plausible factors such as age, sex, body mass index, and aspirin or NSAID use.

METHODS

Study Population

The University of Minnesota Cancer Prevention Research Unit, a collaborative initiative between the University of Minnesota and a private gastroenterology practice, conducted a case-control study from April of 1991 to April of 1994 (27). The gastroenterology practice performed the colonoscopies and sigmoidoscopies, collectively referred to as endoscopies, and recruited study participants while scheduling those endoscopies (27). In order to be initially included in the study, patients had to be between the ages of 30 and 74, Minneapolis-St. Paul metropolitan area residents, able to speak English, Patients were initially excluded if they were known to have ever had a genetic syndrome associated with the development of a colonic neoplasia, inflammatory bowel disease, an adenomatous polyp, or a cancer other than non-melanoma skin cancer (27). Each study participant gave informed consent in writing, and the study was approved by the institutional review boards of the University of Minnesota as well as each endoscopy site (27).

Outcome Assessment

The endoscopy results were used to classify participants as either a case or an endoscopy control (27). If at least one adenoma was detected during endoscopy, the participant was classified as a case (27). Otherwise, the participant was classified as a control (27). Participants were excluded if they did not undergo a complete endoscopy or have all polyps removed (27). They were also excluded if they were diagnosed with

inflammatory bowel disease or invasive carcinoma (27). A separate group of community controls was randomly selected from the 1991 Minnesota State Driver's License Registry and matched to the cases on age within five years, sex, and zip code (27). The community controls were required to meet the inclusion criteria that the other subjects were required to meet (27). It was unknown, however, whether or not the community controls had a colorectal adenoma because they did not undergo an endoscopy as part of the study (27). The final study population consisted of 564 cases, 1,202 endoscopy controls, and 535 community controls (27).

Exposure Assessment

The participants were assessed on demographic, lifestyle, and dietary exposures (27). The demographic and lifestyle exposures of each participant were provided directly, and the dietary exposures were assessed via a food frequency questionnaire (27). In order to assess their food and nutritional supplement intakes over the previous 12 months, subjects were given information about a standard portion size and offered nine responses regarding the frequency with which they consumed these items (27). These ranged from "never or less than once per month" to "6 or more times per day" (27). The exposures of interest in this study were total and dietary intakes of vitamin A, and its major subtypes, retinol and carotene (27). Dietary vitamin A intake was calculated by subtracting supplemental vitamin A intake from total vitamin A intake (27).

Statistical Analysis

Logistic regression models were used to calculate odds ratios and 95% confidence intervals for associations of total and dietary intakes of vitamin A, and its major subtypes, retinol and carotene with colorectal adenoma. The analyses were performed for comparisons of cases with the endoscopy controls, the community controls, and all the controls combined. The exposure intakes were analyzed as both continuous variables, per increase of one standard deviation among the community controls, and categorical variables. These standard deviations were 9561.56 IU/day for total vitamin A intake, 3739.54 IU/day for retinol intake, 8231.67 IU/day for carotene intake, and 7425.64 IU/day for dietary vitamin A intake. The categorical variables were created based on the quintiles of the intakes among the community controls, which represent the general population. The median value of each quintile was included in the model as a continuous variable to test for trend.

A literature review was performed to determine which confounders should be included in the logistic regression models. Three multivariable models were created. The confounders included in the first model were age (years; continuous), sex (men / women), and total daily energy intake (kcal/day; continuous). The second model included all of the confounders in the first model, as well as education (bachelor's degree or higher / less than a bachelor's degree), race (White / other), body mass index (kg/m^2; continuous), hormone replacement therapy use among females (yes / no), having a first degree relative with a history of colorectal cancer (yes / no), aspirin or non-steroidal anti-inflammatory drug use (yes / no), smoking status (current / former / never), and physical activity (MET-hours/week). The third model included all of the confounders in the first multivariable model as well as daily intakes of vitamin C (mg/day; continuous), vitamin E (mg/day;

continuous), calcium (mg/day; continuous), dietary fiber (g/day; continuous), saturated fat (g/day; continuous), alcohol (g/day; continuous). This was chosen as the final model after performing stepwise addition of these variables and checking for meaningful changes in the odds ratio estimates or the precision of those estimates. Age, sex, BMI, and aspirin or NSAID use were also examined as possible effect modifiers, and a test for interaction was performed. All analyses were conducted with $\alpha = 0.05$, and SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, North Carolina) was used.

RESULTS

Characteristics of Cases and Controls

Selected characteristics of the cases and controls are presented in Table 1. Compared with the endoscopy controls, the cases were older, more likely to be male, more likely to be current smokers, and less likely to use aspirin or an NSAID. They also had lower intakes of vitamin C and vitamin E and higher intakes of alcohol. The female cases were less likely to use hormone replacement therapy than the endoscopy controls. Compared with the community controls, the cases were more likely to be male, more likely to be smokers, and more likely to have a first degree relative with colorectal cancer. They also had lower intakes of vitamin C and vitamin E and higher intakes of alcohol.

Total Vitamin A Intake and Colorectal Adenoma

In the comparisons involving all controls combined, higher levels of total vitamin A intake were associated with a statistically non-significant lower risk of colorectal adenoma after multivariable adjustment (highest vs. lowest quintile OR = 0.91, 95% CI: 0.61-1.37, p-trend = 0.50). There was a suggestion that the dose-risk association might be non-linear, with the fourth quintile of total vitamin A intake being statistically significantly associated with lower risk of colorectal adenoma in the same model (OR = 0.69, 95% CI: 0.48-0.98). We also analyzed total vitamin A intake as a continuous variable in the multivariable model and found a statistically non-significant inverse association with colorectal adenoma per 1 SD (SD = 9561.56 IU/day) increment in total

vitamin A (OR = 0.97, 95% CI: 0.86, 1.10). Similar associations were observed in the comparisons involving either the endoscopy or community controls (Table 2). Sex, age, aspirin or NSAID use, and BMI were examined as potential modifiers of the association between total vitamin A intake and incident, sporadic colorectal adenoma, but no statistically significant interactions were found (Table 6).

Retinol Intake and Colorectal Adenoma

In the comparisons involving all controls combined, higher levels of retinol intake were associated with a statistically non-significant lower risk of colorectal adenoma after multivariable adjustment (highest vs. lowest quintile OR = 0.88, 95% CI: 0.61-1.27, p-trend = 0.04). There was a suggestion that the dose-risk association might be non-linear, with the fourth quintile of retinol intake being statistically significantly associated with lower risk of colorectal adenoma in the same model (OR = 0.67, 95% CI: 0.48-0.95). We also analyzed retinol intake as a continuous variable in the multivariable model and found a statistically significant inverse association with colorectal adenoma per 1 SD (SD = 3739.54 IU/day) increment in retinol (OR = 0.86, 95% CI: 0.75-0.98). This result did not change when adjusting for carotene intake. Similar associations were observed in the comparisons involving either the endoscopy or community controls (Table 3). Sex, age, aspirin or NSAID use, and BMI were examined as potential modifiers of the association between retinol intake and incident, sporadic colorectal adenoma, but no statistically significant interactions were found (Table 6). Effect modification due to aspirin or NSAID use, though not significant (p-interaction = 0.01), shows that there may be an inverse association between retinol intake and colorectal adenoma among aspirin or

NSAID non-users (OR = 0.79, 95% CI: 0.66-0.94) but not among users (OR = 0.98, 95% CI: 0.81-1.19).

Carotene Intake and Colorectal Adenoma

In the comparisons involving all controls combined, higher levels of carotene were not associated with a lower risk of colorectal adenoma after multivariable adjustment (highest vs. lowest quintile OR = 1.13, 95% CI: 0.76-1.69, p trend = 0.69). We also analyzed carotene intake as a continuous variable in the multivariable model and found a statistically non-significant positive association with colorectal adenoma per 1 SD (SD = 8231.67 IU/day) increment in carotene (OR = 1.03, 95% CI: 0.92, 1.15). Similar associations were observed in the comparisons involving either the endoscopy or community controls (Table 4). Sex, age, aspirin or NSAID use, and BMI were examined as potential modifiers of the association between carotene intake and incident, sporadic colorectal adenoma, but no statistically significant interactions were found (Table 6).

Dietary Vitamin A Intake and Colorectal Adenoma

In the comparisons involving all controls combined, higher levels of dietary vitamin A intake were associated with a statistically non-significant lower risk of colorectal adenoma after multivariable adjustment (highest vs. lowest quintile OR = 0.89, 95% CI: 0.58-1.34, p trend = 0.41). We also analyzed dietary vitamin A intake as a continuous variable in the multivariable model and found a statistically non-significant inverse association with colorectal adenoma per 1 SD (SD = 7425.64 IU/day) increment in dietary vitamin A (OR = 0.99, 95% CI: 0.88, 1.10). Similar associations were

observed in the comparisons involving either the endoscopy or community controls (Table 5). Sex, age, aspirin or NSAID use, and BMI were examined as potential modifiers of the association between dietary vitamin A intake and incident, sporadic colorectal adenoma, but no statistically significant interactions were found (Table 6).

DISCUSSION

Summary of Results

Our results suggest that total vitamin A intake, dietary vitamin A intake, and carotene intake are not associated with incident, sporadic colorectal adenoma. Our results do suggest, however, that retinol intake may be inversely associated with colorectal adenoma. The association between retinol and colorectal adenoma was not altered when adjusting for carotene. These results were similar when dividing the controls into endoscopy controls and community controls. No significant effect modifiers of the associations were found, but non-significant effect modification due to aspirin or NSAID use shows that the association between retinol and colorectal adenoma may be limited to non-users.

Relation to Previous Research

Since there is very little evidence suggesting an association between vitamin A intake and colorectal cancer, it is possible that the significant result we found between retinol intake and colorectal adenoma was due to a type 1 error. This association was not particularly strong and was not observed with total vitamin A.

Blood plasma or serum concentration of carotenoids is a reliable biomarker that can be used to reflect a person's usual dietary intake of carotenoids (19). Measuring blood plasma concentration is not subject to the same amount of information bias as issuing food frequency questionnaires is. A cohort study of 5477 women found an inverse association between serum β-carotene concentration and colorectal cancer incidence (20).

A case-control study of 73 colorectal adenoma cases and 63 controls found an inverse association between colorectal adenoma risk and plasma lycopene concentration (21). These studies suggest that carotenes may be inversely associated with colorectal adenoma risk, in contract to our findings.

Natural and synthetic retinoid, in high concentrations *in vitro*, have been shown to reduce proliferation of colorectal carcinoma cells and to induce their apoptosis (26). If natural retinoid could also have this effect of on colorectal adenoma cells *in vitro*, an inverse association between retinol intake and colorectal adenoma risk would be expected, as supported by our findings.

Since a case-control study with 224 colorectal adenoma cases and 230 controls found an association between α-carotene blood plasma concentration and colorectal adenoma risk among men, but not women, sex was expected to modify the association between carotene intake and colorectal adenoma risk (19). However, no statistically significant interaction was observed in our data.

Strengths and Limitations

This study has several strengths. One is that the colorectal adenomas were pathologically verified (27). This likely resulted in very little, if any, misclassification of the outcome among the cases and endoscopy controls. Another is the use of two different control groups as well as an analysis with all controls combined. The endoscopy controls were useful for comparing cases to subjects who are known to not be cases. The community controls are useful for comparing cases to subjects who reflect the underlying population. One other strength of this study is that three different models were used. This

design allowed us to determine if the association between vitamin A intake and colorectal adenoma is independent of lifestyle and dietary exposures.

This study also has several limitations. One of these is that the outcome of interest was colorectal adenoma instead of colorectal cancer. Sine colorectal adenomas are precursors to colorectal carcinomas, and colorectal carcinomas are rarer than colorectal adenomas, this was a reasonable outcome to choose (3). It would have, however, been more informative to use colorectal carcinoma as the outcome instead. Another limitation is the potential for misclassification of the community controls since their case status was not assessed.

FUTURE DIRECTIONS

Future studies could be conducted to further explore the association between vitamin A intake and incident, sporadic colorectal adenoma. This could be done by assessing adenomas by size or severity instead of as a dichotomous variable to determine if vitamin A intake is associated with prognosis, as opposed to development, of adenomas. This could also be done by considering other subtypes of vitamin A, such as lutein and lycopene, or by separating carotene into α-carotene and β-carotene.

Future studies could also be conducted to explore the association between other dietary intakes and incident, sporadic colorectal adenoma. It seemed likely in this study that other dietary exposures were associated with incident, sporadic colorectal adenoma. It would be interesting to examine the association between incident, sporadic colorectal adenoma and the other vitamins.

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Table 1. Selected characteristics of incident, sporadic colorectal adenoma cases and controls, CPRU study, 1991-1992.

[a] Characteristics	Cases (N = 564)	All Controls (N = 1737)	Endoscopy Controls (N = 1202)	Community Controls (N = 535)
Demographic				
Age (yrs.)	58.1 (9.6)	54.3 (11.1)	52.8 (11.1)	57.7 (10.4)
Male (%)	61.7	43.8	38.8	55.1
Bachelor's Degree or Higher Education Level (%)	30.5	32.6	34.1	29.2
[b] White Race (%)	97.9	97.2	97.3	97.2
Lifestyle				
[c] BMI (kg/m^2)	27.4 (4.7)	26.7 (4.8)	26.6 (4.9)	26.8 (4.5)
HRT Use among Females (%)	27.3	34.6	36.3	29.6
First Degree Relative with Colorectal Cancer (%)	16.1	16.0	20.0	6.9
Aspirin or NSAID Use (%)	29.3	38.7	42.3	30.8
[d] Current Smoker (%)	20.7	13.8	13.1	15.5
[d] Former Smoker (%)	46.8	40.5	40.6	40.4
Physical Activity (MET-hours/week)	37.4 (39.4)	35.9 (34.9)	34.8 (32.8)	38.2 (39.2)

Daily Dietary Intakes				
Total Energy Intake (kcal)	2090.7 (775.7)	2018.5 (718.8)	2002.5 (718.3)	2054.5 (719.2)
Total Vitamin A (IU)	12827.6 (10071.1)	14168.2 (11597.2)	14399.3 (12393.0)	13649.0 (9561.6)
Dietary Vitamin A (IU)	10937.5 (8392.6)	11604.5 (9186.1)	11717.3 (9870.0)	11350.9 (7425.6)
Retinol (IU)	3042.1 (3009.2)	3542.3 (3974.7)	3538.8 (4076.5)	3550.2 (3739.5)
Carotene (IU)	9785.4 (9262.5)	10625.9 (10051.6)	10860.5 (10758.0)	100.98.7 (8231.7)
Vitamin C (mg)	247.5 (296.1)	288.0 (311.5)	299.1 (317.9)	263.0 (295.4)
Vitamin E (mg)	62.7 (142.5)	81.0 (170.5)	83.4 (170.9)	75.8 (169.9)
Calcium (mg)	988.4 (543.8)	996.1 (538.7)	999.9 (526.9)	987.6 (564.6)
Dietary Fiber (g)	21.8 (9.6)	22.3 (10.1)	22.3 (10.2)	22.2 (9.7)
Saturated Fat (g)	25.3 (13.0)	23.4 (11.4)	23.1 (11.4)	24.0 (11.5)
Alcohol (g)	10.1 (16.6)	6.9 (13.8)	6.4 (12.9)	8.1 (15.5)

[a] categorical variables displayed as percentages and continuous variables displayed as mean (SD)

[b] information missing for one case and one community control

[c] information missing for ten cases, twenty endoscopy controls, and four community controls

[d] information missing for one community control

Table 2. Associations between total vitamin A intake and incident, sporadic colorectal adenoma, CPRU study, 1991-1994.

		[a] Model 1		[b] Model 2		[c] Model 3	
Quintile	**Ca / Co**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
All Controls Combined							
[d] **Q1**	138 / 376	1.00	ref.	1.00	ref.	1.00	ref.
[e] **Q2**	114 / 305	0.89	0.66, 1.20	0.92	0.68, 1.25	0.93	0.68, 1.27
[f] **Q3**	130 / 353	0.89	0.66, 1.19	0.95	0.70, 1.29	1.00	0.73, 1.37
[g] **Q4**	82 / 344	0.57	0.41, 0.79	0.65	0.46, 0.91	0.69	0.48, 0.98
[h] **Q5**	100 / 359	0.66	0.47, 0.91	0.79	0.56, 1.11	0.91	0.61, 1.37
p – trend			0.003		0.094		0.496
[i] **1 SD**	564 / 1737	0.87	0.79, 0.97	0.92	0.84, 1.02	0.97	0.86, 1.10
Endoscopy Controls							
[d] **Q1**	138 / 269	1.00	ref.	1.00	ref.	1.00	ref.
[e] **Q2**	114 / 198	0.91	0.65, 1.26	0.97	0.69, 1.37	0.98	0.69, 1.38
[f] **Q3**	130 / 246	0.87	0.64, 1.20	1.00	0.72, 1.39	1.05	0.75, 1.49
[g] **Q4**	82 / 237	0.55	0.39, 0.79	0.67	0.46, 0.98	0.72	0.49, 1.07

[h] **Q5**	100 / 252	0.61	0.43, 0.87	0.78	0.54, 1.14	0.93	0.60, 1.45
p – trend			0.001		0.090		0.573
[i] **1 SD**	564 / 1202	0.85	0.77, 0.95	0.91	0.82, 1.01	0.96	0.84, 1.09
Community Controls							
[d] **Q1**	138 / 107	1.00	ref.	1.00	ref.	1.00	ref.
[e] **Q2**	114 / 107	0.79	0.55, 1.15	0.82	0.56, 1.20	0.83	0.56, 1.22
[f] **Q3**	130 / 107	0.89	0.62, 1.30	0.89	0.60, 1.31	0.89	0.60, 1.33
[g] **Q4**	82 / 107	0.56	0.38, 0.84	0.57	0.37, 0.86	0.56	0.36, 0.88
[h] **Q5**	100 / 107	0.69	0.46, 1.04	0.73	0.48, 1.12	0.75	0.45, 1.25
p – trend			0.046		0.098		0.183
[i] **1 SD**	564 / 535	0.92	0.81, 1.04	0.95	0.84, 1.08	0.98	0.83, 1.16

[a] adjusted for age, sex, and energy intake

[b] adjusted for covariates in Model 1, hormone replacement therapy in women, history of colorectal cancer in a first degree relative, education, race, BMI, aspirin or NSAID use, smoking status, and physical activity

[c] adjusted for covariates in Model 2, vitamin C intake, vitamin E intake, alcohol intake, dietary fiber intake, saturated fat intake, and calcium intake

[d] 0.00 IU/day – 6548.99 IU/day

[e] 6548.99 IU/day – 9411.25 IU/day

[f] 9411.25 IU/day – 13272.80 IU/day

[g] 13272.80 IU/day – 19121.75 IU/day

[h] 19121.75 IU/day or higher

[i] linear effect of 9561.56 IU/day change

Table 3. Associations between retinol intake and incident, sporadic colorectal adenoma, CPRU study, 1991-1994.

		[a] Model 1		[b] Model 2		[c] Model 3	
Quintile	**Ca / Co**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
All Controls Combined							
[d] **Q1**	116 / 355	1.00	ref.	1.00	ref.	1.00	ref.
[e] **Q2**	150 / 360	1.17	0.87, 1.57	1.27	0.94, 1.71	1.26	0.93, 1.71
[f] **Q3**	119 / 344	0.91	0.67, 1.25	0.97	0.70, 1.34	0.95	0.68, 1.32
[g] **Q4**	88 / 355	0.63	0.46, 0.88	0.67	0.48, 0.94	0.67	0.48, 0.95
[h] **Q5**	91 / 323	0.75	0.54, 1.04	0.85	0.60, 1.19	0.88	0.61, 1.27
p – trend			0.002		0.012		0.039
[i] **1 SD**	564 / 1737	0.82	0.73, 0.93	0.85	0.75, 0.95	0.86	0.75, 0.98
Endoscopy Controls							
[d] **Q1**	116 / 248	1.00	ref.	1.00	ref.	1.00	ref.
[e] **Q2**	150 / 253	1.16	0.85, 1.60	1.31	0.94, 1.82	1.29	0.92, 1.80
[f] **Q3**	119 / 237	0.88	0.62, 1.23	0.96	0.68, 1.37	0.93	0.64, 1.35
[g] **Q4**	88 / 248	0.58	0.41, 0.83	0.63	0.43, 0.90	0.63	0.43, 0.91

[h] **Q5**	91 / 216	0.74	0.52, 1.06	0.88	0.61, 1.27	0.93	0.62, 1.39
p – trend			0.003		0.021		0.080
[i] **1 SD**	564 / 1202	0.81	0.72, 0.92	0.84	0.74, 0.95	0.86	0.75, 0.98
Community Controls							
[d] **Q1**	116 / 107	1.00	ref.	1.00	ref.	1.00	ref.
[e] **Q2**	150 / 107	1.22	0.85, 1.77	1.38	0.94, 2.02	1.36	0.92, 2.00
[f] **Q3**	119 / 107	0.96	0.65, 1.41	1.03	0.69, 1.53	1.01	0.66, 1.54
[g] **Q4**	88 / 107	0.71	0.47, 1.06	0.77	0.51, 1.17	0.75	0.49, 1.16
[h] **Q5**	91 / 107	0.75	0.50, 1.12	0.82	0.54, 1.24	0.79	0.50, 1.23
p – trend			0.010		0.021		0.021
[i] **1 SD**	564 / 535	0.84	0.73, 0.96	0.84	0.73, 0.97	0.83	0.71, 0.97

[a] adjusted for age, sex, and energy intake

[b] adjusted for covariates in Model 1, hormone replacement therapy in women, history of colorectal cancer in a first degree relative, education, race, BMI, aspirin or NSAID use, smoking status, and physical activity

[c] adjusted for covariates in Model 2, vitamin C intake, vitamin E intake, alcohol intake, dietary fiber intake, saturated fat intake, and calcium intake

[d] 0.00 IU/day – 900.37 IU/day

[e] 900.37 IU/day – 1784.64 IU/day

[f] 1784.64 IU/day – 3262.60 IU/day

[g] 3262.60 IU/day – 5803.04 IU/day

[h] 5803.04 IU/day or higher

[i] linear effect of 3739.54 IU/day change

Table 4. Associations between carotene intake and incident, sporadic colorectal adenoma, CPRU study, 1991-1994.

		[a] Model 1		[b] Model 2		[c] Model 3	
	Ca / Co	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
All Controls Combined							
[d] **Q1**	129 / 378	1.00	ref.	1.00	ref.	1.00	ref.
[e] **Q2**	118 / 314	0.99	0.73, 1.34	1.06	0.78, 1.44	1.09	0.80, 1.48
[f] **Q3**	124 / 374	0.90	0.67, 1.21	0.99	0.73, 1.35	1.05	0.76, 1.44
[g] **Q4**	95 / 321	0.80	0.58, 1.11	0.92	0.66, 1.29	1.01	0.71, 1.43
[h] **Q5**	98 / 350	0.77	0.55, 1.07	0.94	0.67, 1.33	1.13	0.76, 1.69
p – trend			0.059		0.522		0.694
[i] **1 SD**	564 / 1737	0.92	0.84, 1.01	0.97	0.88, 1.07	1.03	0.92, 1.15
Endoscopy Controls							
[d] **Q1**	129 / 271	1.00	ref.	1.00	ref.	1.00	ref.
[e] **Q2**	118 / 207	1.07	0.77, 1.49	1.16	0.83, 1.63	1.22	0.87, 1.71
[f] **Q3**	124 / 267	0.89	0.64, 1.23	1.06	0.76, 1.49	1.16	0.82, 1.64
[g] **Q4**	95 / 214	0.84	0.59, 1.20	1.07	0.74, 1.53	1.21	0.82, 1.79

[h] **Q5**	98 / 243	0.78	0.54, 1.11	1.01	0.69, 1.48	1.31	0.84, 2.05
p – trend			0.081		0.785		0.339
[i] **1 SD**	564 / 1202	0.90	0.82, 0.99	0.95	0.86, 1.05	1.01	0.90, 1.13
Community Controls							
[d] **Q1**	129 / 107	1.00	ref.	1.00	ref.	1.00	ref.
[e] **Q2**	118 / 107	0.88	0.60, 1.27	0.91	0.62, 1.34	0.93	0.63, 1.38
[f] **Q3**	124 / 107	0.93	0.64, 1.36	0.94	0.64, 1.39	0.94	0.63, 1.41
[g] **Q4**	95 / 107	0.72	0.48, 1.07	0.71	0.47, 1.07	0.72	0.46, 1.12
[h] **Q5**	98 / 107	0.74	0.49, 1.11	0.80	0.52, 1.22	0.82	0.50, 1.37
p – trend			0.103		0.186		0.325
[i] **1 SD**	564 / 535	0.98	0.87, 1.10	1.01	0.89, 1.14	1.07	0.92, 1.24

[a] adjusted for age, sex, and energy intake

[b] adjusted for covariates in Model 1, hormone replacement therapy in women, history of colorectal cancer in a first degree relative, education, race, BMI, aspirin or NSAID use, smoking status, and physical activity

[c] adjusted for covariates in Model 2, vitamin C intake, vitamin E intake, alcohol intake, dietary fiber intake, saturated fat intake, and calcium intake

[d] 0.00 IU/day – 4342.34 IU/day

[e] 4342.34 IU/day – 6418.25 IU/day

[f] 6418.25 IU/day – 9752.78 IU/day

[g] 9752.78 IU/day – 14503.20 IU/day

[h] 14503.20 IU/day or higher

[i] linear effect of 8231.67 IU/day change

Table 5. Associations between dietary vitamin A intake and incident, sporadic colorectal adenoma, CPRU study, 1991-1994.

		[a] Model 1		[b] Model 2		[c] Model 3	
	Ca / Co	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
All Controls Combined							
[d] **Q1**	127 / 365	1.00	ref.	1.00	ref.	1.00	ref.
[e] **Q2**	134 / 357	0.97	0.72, 1.29	1.04	0.77, 1.40	1.06	0.78, 1.43
[f] **Q3**	115 / 369	0.78	0.57, 1.06	0.86	0.63, 1.18	0.88	0.63, 1.22
[g] **Q4**	92 / 306	0.74	0.53, 1.03	0.83	0.59, 1.17	0.86	0.60, 1.23
[h] **Q5**	96 / 340	0.69	0.49, 0.98	0.82	0.57, 1.17	0.89	0.58, 1.34
p – trend			0.020		0.159		0.407
[i] **1 SD**	564 / 1737	0.91	0.83, 1.01	0.95	0.87, 1.05	0.99	0.88, 1.10
Endoscopy Controls							
[d] **Q1**	127 / 258	1.00	ref.	1.00	ref.	1.00	ref.
[e] **Q2**	134 / 250	0.91	0.66, 1.25	0.99	0.71, 1.37	1.01	0.72, 1.42
[f] **Q3**	115 / 262	0.73	0.52, 1.02	0.84	0.59, 1.18	0.87	0.61, 1.25
[g] **Q4**	92 / 199	0.78	0.54, 1.11	0.93	0.64, 1.35	0.98	0.66, 1.47

[h] **Q5**	96 / 233	0.68	0.47, 0.99	0.83	0.56, 1.22	0.94	0.60, 1.49
p – trend			0.048		0.344		0.836
[i] **1 SD**	564 / 1202	0.90	0.81, 0.99	0.94	0.85, 1.04	0.97	0.87, 1.09
Community Controls							
[d] **Q1**	127 / 107	1.00	ref.	1.00	ref.	1.00	ref.
[e] **Q2**	134 / 107	1.00	0.69, 1.45	1.09	0.75, 1.60	1.11	0.75, 1.63
[f] **Q3**	115 / 107	0.85	0.58, 1.25	0.86	0.58, 1.28	0.86	0.57, 1.31
[g] **Q4**	92 / 107	0.67	0.45, 1.00	0.67	0.44, 1.02	0.67	0.43, 1.04
[h] **Q5**	96 / 107	0.70	0.46, 1.06	0.77	0.50, 1.19	0.76	0.45, 1.29
p – trend			0.029		0.067		0.092
[i] **1 SD**	564 / 535	0.95	0.85, 1.08	0.98	0.87, 1.11	1.02	0.88, 1.18

[a] adjusted for age, sex, and energy intake

[b] adjusted for covariates in Model 1, hormone replacement therapy in women, history of colorectal cancer in a first degree relative, education, race, BMI, aspirin or NSAID use, smoking status, and physical activity

[c] adjusted for covariates in Model 2, vitamin C intake, vitamin E intake, alcohol intake, dietary fiber intake, saturated fat intake, and calcium intake

[d] 0.00 IU/day – 5652.40 IU/day

[e] 5652.40 IU/day – 8337.78 IU/day

[f] 8337.78 IU/day – 11380.54 IU/day

[g] 11380.54 IU/day – 15839.75 IU/day

[h] 15839.75 IU/day or higher

[i] linear effect of 7425.64 IU/day change

Table 6. Effect modification of the association of continuous vitamin A intakes and incident, sporadic colorectal adenoma, CPRU study, 1991-1994, all controls combined.

		Vitamin A per 1 SD		Retinol per 1 SD		Carotene per 1 SD		Dietary Vitamin A per 1 SD	
	Ca / Co	[a] OR	95% CI	[a] OR	95% CI	[a] OR	95% CI	[a] OR	95% CI
Sex									
Men	348 / 761	0.93	0.77, 1.12	0.84	0.70, 1.01	1.01	0.85, 1.19	0.98	0.82, 1.15
Women	216 / 976	0.99	0.84, 1.16	0.89	0.74, 1.07	1.02	0.89, 1.19	0.99	0.85, 1.14
p – interaction			0.720		0.849		0.865		0.988
Age (yrs.)									
< 56	205 / 889	0.80	0.62, 1.02	0.74	0.58, 0.95	0.91	0.74, 1.12	0.83	0.65, 1.05
≥ 56	359 / 848	1.05	0.92, 1.21	0.92	0.79, 1.08	1.08	0.95, 1.24	1.06	0.94, 1.21
p – interaction			0.204		0.359		0.313		0.164
Aspirin or NSAID Use									
Yes	165 / 673	0.94	0.78, 1.15	0.98	0.81, 1.19	0.95	0.79, 1.14	0.95	0.79, 1.14
No	399 /1064	0.99	0.85, 1.17	0.79	0.66, 0.94	1.08	0.94, 1.25	1.01	0.88, 1.17
p – interaction			0.871		0.095		0.403		0.660

BMI (kg/m^2)									
< 25	182 / 718	0.99	0.80, 1.22	0.79	0.62, 1.00	1.07	0.89, 1.28	1.04	0.88, 1.24
≥ 25	382 / 1019	0.98	0.84, 1.15	0.88	0.76, 1.03	1.03	0.90, 1.19	0.97	0.84, 1.13
p – interaction			0.192		0.971		0.158		0.121

[a] adjusted for age, sex, and energy intake, hormone replacement therapy in women, history of colorectal cancer in a first degree relative, education, race, BMI, aspirin or NSAID use, smoking status, and physical activity, vitamin C intake, vitamin E intake, alcohol intake, dietary fiber intake, saturated fat intake, and calcium intake