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# Dietary patterns during high school and risk of colorectal adenoma in a cohort of middle-aged women

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Abbreviations: NHS II, Nurses' Health Study II; FFQ, food frequency questionnaire, HS-FFQ, high school food frequency questionnaire; YAQ, Youth Adolescent Questionnaire; BMI, body mass index.

**Novelty and Impact:** This is the first large-scale study on dietary patterns during adolescence and risk of colorectal adenoma later in life. In the Nurses' Health Study II, a large prospective female cohort, we used a validated and detailed 124-item high school food frequency questionnaire to assess dietary patterns. Our results suggest that overall eating patterns during high school may influence later risk of rectal and advanced adenoma, independent of adult diet, thus contributing to the growing evidence that early life exposures may have important consequences for later cancer development.

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## Abstract

Adolescent diet may be etiologically relevant for later risk of colorectal adenoma, a precursor of colorectal cancer. We aimed to examine associations between adolescent dietary patterns (derived using factor analysis) and risk of colorectal adenoma in middle adulthood. We analyzed data from 17,221 women participating in the Nurses' Health Study II, who had completed a validated high school (HS) food frequency questionnaire in 1998 when they were 34-51 years old, and had subsequently undergone at least one lower bowel endoscopy. Between 1998 and 2007, 1,299 women were diagnosed with at least one colorectal adenoma. In multivariable models adjusted for adult dietary patterns, a higher "prudent" pattern during HS, characterized by high consumption of vegetables, fruit, and fish was associated with a statistically significantly lower risk of rectal (odds ratio (OR) highest versus lowest quintile, 0.45, 95% CI 0.27-0.75, p-trend=0.005), but not colon adenomas. A higher "Western" pattern during HS, characterized by high consumption of desserts and sweets, snack foods, and red and processed meat, was significantly associated with rectal (OR 1.78, 95% CI 1.12-2.85, p-trend=0.005) and advanced (OR 1.58, 95% CI 1.07-2.33, p-trend=0.08), but not associated with colon or non-advanced adenomas. This study suggests that overall eating patterns during high school may influence later risk of rectal and advanced adenoma, independent of adult diet. Our results support the hypothesis that diet during early life may influence colorectal carcinogenesis.

## Introduction

Colorectal adenomas are established precursors of colorectal cancer, one of the major causes of cancer death in the US and other countries<sup>1,2</sup>. Among adults, dietary patterns correlating highly with intake of red meat, processed meat, refined grains and potatoes have been associated with higher risk of colorectal adenoma<sup>3-5</sup> and colon cancer<sup>6-9</sup>, while dietary patterns characterized by high intakes of fruit and vegetables have been associated with lower risk of colorectal adenoma<sup>3-5</sup> and colon cancer<sup>6-9</sup>. However, despite colorectal carcinogenesis being a long process that can take several decades<sup>10,11</sup>, few studies have examined whether diet during early life is associated with risk of colorectal adenoma or colorectal cancer later in life<sup>12,13</sup>. We hypothesized that overall eating patterns during adolescence may influence risk of colorectal adenomas later in life and therefore investigated the association between dietary patterns during high school and later risk of colorectal adenoma using data from the Nurses' Health Study II (NHS II), a large prospective US cohort.

## Subjects and Methods

### Study population

Details about the NHS II cohort have been reported previously<sup>14</sup>. In brief, the NHS II cohort included 116,671 female registered nurses who responded to a mailed questionnaire inquiring about lifestyle characteristics and medical history in 1989 when they were between 25 and 42 years old. After 1989, every two years questionnaires were mailed to participants to update lifestyle factors and to ascertain newly diagnosed diseases. In addition, every four years dietary intake was assessed by means of mailed food frequency questionnaires (FFQs). Follow-up response rates were approximately 90% in each two-year follow-up cycle<sup>15</sup>. On the 1997 follow-up questionnaire, participants were asked if they were willing to fill in an additional FFQ

about their diet during high school (HS-FFQ). Of the entire cohort, 64,380 women (55%) indicated willingness to do so and 47,355 women completed the HS-FFQ in 1998 (83% of women who were mailed the HS-FFQ). At the time of completion of the HS-FFQ, participating women were between 34 and 51 years old. Women who indicated willingness to fill out the HS-FFQ did not differ from women who did not in terms of baseline dietary intake or risk factors for colorectal cancer or adenoma<sup>16</sup>.

Only women who returned the HS-FFQ and underwent at least one lower bowel endoscopy between return of the HS-FFQ in 1998 and December 2007 were included in this study. After excluding women with a history of cancer or colorectal adenoma or hyperplastic polyps prior to return of the HS-FFQ, and women who reported implausible daily caloric intake for baseline intake levels (1991 FFQ,  $<600$  or  $\geq 3,500$  kcal/day;  $n=2,117$ ) or for high school intake levels (HS-FFQ,  $<600$  or  $\geq 5,000$ ;  $n=1243$ ) or had incomplete records (HS-FFQ,  $n=164$ ; 1991 FFQ,  $n=244$ ), 17,221 women formed the study population. This study was approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard School of Public Health.

#### Information on endoscopies

On each follow-up questionnaire, participants were asked whether they had had a lower bowel endoscopy (sigmoidoscopy or colonoscopy). Starting with the 2003 follow-up, sigmoidoscopies (which visualize only the rectum and distal colon) and colonoscopies (which visualize the entire colon and rectum) were inquired separately and on the 2005 follow-up questionnaires, participants were asked to indicate if lower bowel endoscopies in the past had been a sigmoidoscopy or a colonoscopy. As described in our previous NHS II study<sup>17</sup>, it is appropriate to include proximal adenomas as an outcome.

## Identification of cases

If diagnosis of a colorectal adenoma was reported on one of the follow-up questionnaires, we requested the participant's permission to review medical records. Colorectal adenoma diagnoses were verified by study investigators using medical records who also extracted information on location, histological type, and adenoma size. We subdivided colorectal adenoma according to location into colon (proximal: cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure; distal: descending colon, sigmoid colon) and rectal (rectosigmoid junction, rectum) adenoma and according to neoplasia phase into advanced adenoma ( $\geq 1$  cm in size or any mention of villous features or high-grade dysplasia) and non-advanced adenoma ( $< 1$  cm in size and non-villous morphology without high-grade dysplasia).

## Assessment of high school and adulthood diet

As described in more detail in a previous publication<sup>18</sup>, the HS-FFQ is a 124-item FFQ specifically designed to ascertain dietary intake during high school (grades 9-12, ages 13-17 years). It includes certain foods, such as peanut butter, milkshakes, and French Fries, that were commonly consumed when NHS II participants were in high school, i.e. between 1960 and 1980. The HS-FFQ has been shown to be reproducible when HS-FFQs were administered a second time 4 years later to a subset of 333 NHS II participants (mean Spearman rank correlation for food intake 0.60, range 0.37-0.77)<sup>19</sup>. In a validation study among 80 young adults, i.e. children of randomly selected NHS II participants, who had completed three 24-hour dietary recalls and 2 FFQs (Youth Adolescent Questionnaire, YAQ) when they were between 13 and 18 years old, and then administered the HS-FFQ 10 years later, mean correlations for nutrient intake between HS-

FFQ and three 24-hour recalls was 0.69 (range 0.45-0.97) and between HS-FFQ and YAQ was 0.58 (range 0.40-0.88)<sup>20</sup>.

Adult dietary intake was assessed in 1991, 1995, 1999, 2003, and 2007 using ~131-item FFQs ascertaining habitual dietary intake during the past 12 months. Food items and response categories were similar to the HS-FFQ<sup>21</sup>.

### Dietary pattern analysis

FFQ items were grouped into 37 food groups for the HS-FFQ and 40 food groups for the NHS II adult FFQs<sup>18,22</sup>. Factor analysis was applied on the food groups to derive dietary patterns using the SAS procedure PROC FACTOR with the orthogonal rotation procedure varimax (for simpler structure and interpretability). The number of factors to retain was determined by eigenvalues (>1), inspection of Scree plots and interpretability. Factor analysis aggregates specific food groups on the basis of the degree to which food items in the dataset are correlated with one another<sup>23</sup>. Each resulting factor is a linear combination of all food groups weighted with their factor loadings. A dietary pattern score (factor score) for each pattern is computed for each participant by summing intakes of food groups weighted by their factor loadings. Dietary patterns were energy-adjusted using the residual method<sup>24</sup>.

### Statistical methods

Associations between quintiles of high school dietary pattern scores and risk of colorectal adenoma were analyzed using logistic regression. Covariates that were assessed repeatedly in follow-up questionnaires (e.g. smoking, aspirin use, physical activity) were updated to best represent the exposure in the 2-year interval before the most recent endoscopy. Cumulative updated average of adult dietary pattern scores was calculated using information from all



available adult FFQs up to the 2-year interval prior to the follow-up cycle of the most recent endoscopy. Test for trend was performed by modeling the quintile medians of the dietary pattern scores as continuous variable and deriving the p-value for trend employing the Wald test.

Two multivariable models were run to separately adjust for covariates in adolescence and adulthood. In the first multivariable model, in addition to age at baseline, height and family history of colorectal cancer, we also adjusted for confounders at young ages, i.e., physical activity during HS, packyears of smoking before age 20 years, and total energy intake in HS. In the second model, we additionally adjusted for risk factors occurring during adulthood, i.e., current BMI, packyears of smoking, current physical activity, aspirin use, time period of endoscopy, two or more endoscopies during the study period, endoscopy prior to 1998, reason for most recent endoscopy (screening vs. symptoms), current cumulative updated average alcohol intake, adult energy intake and the respective dietary pattern during adulthood. Because age-adjusted and multivariable results were similar, only multivariable results were shown. Associations between dietary patterns and risk of colorectal adenoma were also examined by location, neoplasia phase and number of colorectal polyps (single versus multiple). Using the variance-covariance matrix from polytomous logistic regression models, paired comparisons of the effect of dietary patterns on each of the subtypes of colorectal adenoma (p-difference) were computed.

We also examined joint effects of HS and adult dietary patterns (below and above median) and risk of colorectal adenoma. Furthermore, we performed analyses stratified by other risk factors including age, physical activity, body fatness and family history of colorectal cancer. Tests for interaction were performed by creating a cross-product term of the respective stratification variable and the median score of dietary pattern categories, adding this variable to the model including the main effects of these variables and evaluating its significance using the Wald test. All p-values are two sided. A p-value <0.05 was considered statistically significant.

All statistical analyses were performed using SAS software package, version 9.2 (SAS Institute, Cary, NC, USA).

## Results

Between return of the HS-FFQ in 1998 and December 2007, among the 17,221 women included in our study 1,299 women were diagnosed with a least one colorectal adenoma. Among these women, 1,116 adenomas were found in the colon and 215 adenomas in the rectum; 682 adenomas were non-advanced (early) and 329 were advanced.

We identified two major dietary patterns during high school, which were similar to adult dietary patterns observed in previous studies from our group<sup>25, 26</sup> (Supplementary Table S1). The first pattern, characterized by high intakes of vegetables, fruit, better quality grains, fish and poultry intake, was labeled prudent pattern and the second pattern characterized by high intakes of desserts and sweets, snack foods, red and processed meat, fries and refined grains was labeled Western pattern. Dietary patterns identified on 1991, 1995, 1999 and 2003 adult FFQs were consistent with a prudent and a Western pattern (Supplementary Table S2). Pearson correlation coefficient between high school and adult (cumulative updated average) prudent pattern was 0.48 and between high school and adult Western pattern was 0.39.

Women with higher prudent pattern scores during high school tended to be leaner at baseline (1997), more physically active at ages 13-18 years, and had higher intakes of carbohydrates, fiber, calcium and total folate during high school, whereas women with higher Western pattern scores during high school tended to have a higher baseline body mass index (BMI), were more likely smokers, less physically active at ages 13-18 years and had lower intakes of protein, fiber, calcium and folate (Table 1). The number of endoscopies during the study period did not differ by high school prudent or Western pattern.

In multivariable logistic regression models adjusting for covariates in adolescence and adulthood, a higher prudent pattern score during high school appeared to be associated with lower risk of colorectal adenoma (odds ratio (OR) highest versus lowest quintile 0.82, 95% confidence interval (CI) 0.67, 1.02, p-trend 0.23), and was statistically significantly associated with a 55% lower risk of rectal adenoma (OR 0.45, 95% CI 0.27, 0.75, p-trend 0.005; table 2). A higher prudent pattern during high school was associated with statistically significantly lower risk of single colorectal adenoma (OR 0.75, 95% CI 0.60, 0.95, p-trend 0.05) but not with multiple colorectal adenomas. There was no association between prudent pattern during high school and either proximal or distal colon adenoma (data not shown), advanced or non-advanced adenoma.

A higher Western pattern during high school was statistically significantly associated with higher risk of rectal adenoma (OR highest versus lowest quintile 1.78, 95% CI 1.12, 2.85, p-trend 0.005), and borderline significantly associated with higher risk of advanced (OR 1.58, 95% CI 1.07, 2.33, p-trend 0.08), and single colorectal adenoma (OR 1.24, 95% CI 0.99, 1.56, p-trend 0.04) while the Western pattern was not associated with colon (neither proximal nor distal, data not shown), non-advanced, or multiple colorectal adenoma (table 3). A higher Western pattern during high school was also associated with higher risk of being diagnosed with advanced rectal adenoma (71 cases, OR highest vs. lowest tertile 2.24, 95% CI 1.18, 4.26), but not advanced colon adenoma (275 cases, OR 0.97, 95% CI 0.71, 1.34). Associations between HS dietary pattern and adenoma remained essentially unchanged when the pertinent adult dietary pattern was included in the model, suggesting that associations between dietary patterns during high school and risk of adenoma were independent of adult dietary patterns.

Joint analyses investigated combinations of dietary patterns during high school and adulthood in relation to risk of colorectal adenoma (Table 4). Women who had a high prudent pattern during both high school and adulthood had a significantly lower risk of rectal adenoma

(OR 0.64, 95% CI 0.45, 0.92) compared with women with low prudent pattern during both time periods. Women with a high prudent pattern during either high school or adulthood had no significantly lower risk of rectal adenoma. Women with a high prudent pattern in adulthood had a lower risk of advanced adenoma, regardless of low (OR 0.68, 95% CI 0.47, 0.99) or high (OR 0.78, 95% CI 0.59, 1.04) prudent pattern during high school.

Compared with women with a low Western pattern during both high school and adulthood, women with a high Western pattern during high school but low Western pattern during adulthood had a 59% higher risk of rectal adenoma (OR 1.59, 95% CI 1.04, 2.44), and women with a high Western pattern during both high school and adulthood had a 92% higher risk of rectal adenoma (OR 1.92, 95% CI 1.31, 2.81). Women with a high Western pattern during adulthood only had no significantly higher risk of rectal adenoma.

Associations were similar after stratification by family history of colorectal cancer, body fatness (body shape at age 10 years, BMI at age 18 years, current BMI, waist circumference) or physical activity between 13 and 18 years (all p-values for interaction >0.3). Associations were also similar when analyses were restricted to cases diagnosed at first endoscopy (data not shown).

Finally, we investigated whether the observed associations were attributable to major contributors to the dietary patterns: After adding intakes of fruit, vegetables, or better quality grains (for prudent pattern) or red meat, processed meat, snacks, fries, refined grains or desserts (for Western pattern) separately to the relevant multivariable models, associations between dietary patterns and adenoma were similar to those presented in Table 2 and 3.

## Discussion

In this study, a higher prudent pattern during high school was associated with lower risk of rectal adenoma, whereas a higher Western pattern during high school was associated with a higher risk of rectal and advanced adenoma later in life.

Our results suggest that overall eating patterns during adolescence may influence risk of colorectal adenoma later in life. Very few studies have investigated associations between diet during childhood or adolescence and risk of colorectal cancer later in life and we are not aware of any study relating dietary patterns during adolescence to adenoma later in life. In the British Boyd Orr cohort, a study of 4,999 children born in the 1920s or 1930s, with a follow-up of 65 years, dairy consumption during childhood assessed using data from household food inventories was significantly positively associated with risk of colorectal cancer later in life<sup>13</sup>, but results were based on a small number of cases (76 cases). Recently, in the prospective NIH-AARP Diet and Health Study which assessed participants' diet at ages 12-13 years using a 37-item FFQ, vegetable intake during adolescence was inversely associated with risk of colon but not rectal cancer, independent of adult vegetable intake<sup>12</sup>. In that study, results also suggested a positive association between red and processed meat intake at age 12-13 years and colorectal cancer. In a previous study in NHS II, total red meat intake during high school was not associated with later risk of colorectal adenoma<sup>16</sup>. However, assessment of high school diet (37 versus 124 HS-FFQ items), age of the study population as well as outcome (colorectal cancer vs. adenoma) were different between the NIH-AARP Diet and Health Study and NHS II.

In adult studies, hyperinsulinemia has been associated with higher risk of colorectal cancer<sup>27</sup> through an effect on cell proliferation and apoptosis<sup>28</sup> either directly through the insulin receptor or indirectly through pathways involving the insulin-like growth factor (IGF) axis<sup>29</sup>. During the growth period including adolescence, concentrations of growth factors such as IGF-1

are up to four times higher than during adulthood<sup>30</sup>. Therefore, childhood and adolescence may represent time periods with higher susceptibility to diets associated with hyperinsulemia or increase in IGF1 levels. Of note, findings from a previous study in the NHS II suggest that tallness—as a marker of IGF-1 exposure during the growth period- as well as higher body fatness during childhood may increase risk of colorectal adenoma, independent of adult adiposity<sup>17</sup>. Other pathways through which dietary patterns may influence colorectal carcinogenesis include inflammatory pathways, which may also overlap with energy-balance related pathways<sup>28,31</sup>. In previous studies involving two other cohorts, an adult Western dietary pattern, similar to the Western dietary pattern observed in our study, was positively correlated with plasma inflammatory markers<sup>32,33</sup>. Another possible mechanism through which adolescent diet may play a role in colorectal carcinogenesis is epigenetic programming. It has been shown that epigenetic modifications in young monozygotic twin pairs diverge as they become older, possibly due to differential exposure to environmental factors such as diet<sup>34</sup>. Another study found that severe energy restriction during adolescence and young adulthood may lower risk of colorectal cancer with a CpG methylator phenotype (CIMP+), suggesting that persistent epigenetic changes as a consequence of energy restriction during early stages of a life course may affect the risk of developing colorectal cancers later in life<sup>35</sup>.

In our study, significant associations between dietary pattern scores during high school and risk of adenoma were only observed for rectal and advanced (Western pattern only) but not for colon and non-advanced adenomas. In contrast, the majority of studies on adult dietary patterns and risk of colorectal cancers have observed inverse associations between a "healthy" and positive associations between a "less healthy" dietary pattern and risk of colon cancers, while results for rectal cancer were less consistent<sup>6,7,9</sup>. However, for some studies results were based on a limited number of rectal cancer cases<sup>36-38</sup>. Recent evidence suggests that positive

associations for adult red and processed meat intake, an established risk factor for colorectal cancer may be slightly stronger for rectal than colon cancers<sup>39-41</sup>. To our knowledge, only one small Japanese study in 1,331 middle aged men has examined associations between adult dietary patterns and adenoma separately for colon versus rectal adenoma<sup>42</sup>. In that study, a higher "high-dairy, high-fruit and-vegetable, high-starch, low-alcohol" dietary pattern was significantly associated with a lower risk of colon adenoma, but not rectal adenoma, possibly due to the small numbers of rectal adenoma cases (n=63). No associations were found between a higher "animal food" dietary pattern and risk of colon or rectal adenoma. The biological mechanisms that could explain our findings for rectal adenomas are unclear. Recent data suggests that the frequency of molecular characteristics of colorectal cancers (e.g. microsatellite instability, *BRAF* mutation) may differ by colorectal subsite<sup>43,44</sup>. Furthermore, there is data suggesting that lifestyle factors influencing inflammation and oxidative stress may particularly influence various rectal tumor markers<sup>45</sup>. However, we are not aware of any study that has investigated the association between adolescent dietary patterns and colorectal adenoma separately by molecular subtypes.

Our study has some limitations that need to be discussed. First, dietary intake during adolescence was retrospectively recalled when women were 34-51 years old and we had to rely on these women's memory and ability to recall diet during this time period. The HS-FFQ has been shown to be a dietary assessment instrument with reasonable reproducibility and validity<sup>19, 20</sup>. The HS-FFQ data were collected prior to diagnosis of colorectal adenoma, thereby reducing potential recall bias. In addition, misclassification of exposure is likely non-differential, which tends to bias associations towards the null association<sup>46</sup>. Because epidemiological studies on adolescent diet and risk of cancer later in life are extremely time consuming and expensive, the HS-FFQ is a useful instrument to apply in large cohorts in order to examine associations between adolescent diet and risks of adult cancers. Secondly, using factor analysis to derive dietary

patterns requires some subjective decisions such as how to group individual food items into food groups, decision on the number of dietary patterns to be retained<sup>23</sup>, as well as labeling of the dietary patterns. In our cohort, a Western pattern during adolescence has been positively associated with risk of type 2 diabetes in later life, underlining the ability of the HS-FFQ to capture adolescent dietary patterns and their relevance in relation to later risk of chronic disease<sup>18</sup>. Another limitation of our study is that some women had more than one lower bowel endoscopy during the study period, and thus had a higher probability of having a colorectal adenoma detected than women with only one endoscopy. However, results were similar after restricting analysis to cases diagnosed at their first endoscopy. In addition, the number of endoscopies during the study period did not differ by quintiles of high school dietary pattern scores.

Major strengths of our study include the large sample size, which made it possible to assess associations by location and neoplasia phase of adenomas as well as the ability to adjust for a variety of confounders during early life as well as confounders during adulthood including adult dietary patterns. Nevertheless, residual confounding by measured and unmeasured confounders cannot be excluded.

In conclusion, to our knowledge this is the first study to suggest that adherence to a prudent pattern during adolescence may lower risk of rectal adenoma in adulthood, whereas a Western pattern during high school may increase risk of rectal and advanced adenoma, independent of adult dietary patterns. Our results support the hypothesis that diet during early life may influence colorectal carcinogenesis.



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Table 1. Characteristics of the study population by quintiles of energy-adjusted dietary pattern scores, Nurses' Health Study II, 1998-2007

	Quintile of prudent pattern during high school			Quintile of western pattern during high school		
	1 (lowest) (n=3423)	3 (n=3458)	5 (n=3424)	1 (lowest) (n=3426)	3 (n=3461)	5 (n=3426)
Age at 1997 questionnaire return <sup>1</sup>	43.6(4.0)	44.1(4.0)	44.1(4.0)	43.5(4.0)	44.2(4.0)	44.1(4.0)
Age at most recent endoscopy <sup>1</sup>	51.0(4.3)	51.5(4.4)	51.5(4.3)	50.9(4.3)	51.5(4.3)	51.4(4.3)
BMI (baseline, kg/m <sup>2</sup> )	26.1(5.7)	25.7(5.5)	25.6(5.5)	25.1(5.2)	25.7(5.2)	26.9(6.3)
BMI at age 18 years (kg/m <sup>2</sup> )	21.0(3.3)	21.1(3.2)	21.3(3.3)	21.0(3.1)	21.0(3.1)	21.5(3.6)
Physical activity 13-18 years (METs/week)	45.8(33.1)	47.4(31.3)	54.8(34.8)	53.5(34.3)	47.4(31.9)	47.8(33.8)
Current physical activity (METs/week)	18.6(23.8)	21.8(25.2)	27.8 (30.7)	27.4(29.7)	21.4(24.8)	18.3(23.1)
Smoking before age 20 years, %	26	22	22	18	22	29
Current smokers (baseline), %	9	8	7	5	8	11
Premenopausal (baseline), %	86	86	86	87	86	84
Family history of colorectal cancer (baseline), %	13	12	13	13	13	12
Number of endoscopies during the study period	2.0(1.3)	2.0(1.2)	2.0(1.3)	2.0(1.3)	2.0(1.3)	2.0(1.3)
Reason for most recent endoscopy is screening, %	66	69	69	70	69	64
Aspirin use (baseline) 2 or more times/week, %	13	12	11	11	12	13
Dietary intake during high school						
Alcohol gm/day	0.4(2.1)	0.2(1.3)	0.2(1.4)	0.2(1.8)	0.2(1.4)	0.3(1.7)
Total fat gm/day <sup>2</sup>	131(13)	126(12)	117(14)	115(13)	127(11)	133(12)
Protein gm/day <sup>2</sup>	101(14)	107(14)	112(15)	112(16)	107(14)	102(14)
Carbohydrates gm <sup>2</sup>	299(39)	306(35)	324(40)	327(39)	305(35)	295(37)
Fiber gm/day <sup>2</sup>	16.3(3.0)	19.9(3.1)	26.4(5.6)	24.7(6.4)	19.7(4.0)	18.3(3.7)
Calcium mg/day <sup>2</sup>	1037(337)	1099(346)	1111(339)	1258(372)	1085(326)	913(274)
Total Folate mcg/day <sup>2</sup>	246(59)	309(66)	400(91)	381(100)	305(70)	268(60)
Adult dietary intake (baseline) <sup>3</sup>						
Total Calories kcal/day	1786(484)	1754(479)	1872(485)	1871(478)	1743(467)	1793(489)
Alcohol gm/day	3.1(5.7)	3.5(6.2)	3.7(5.8)	3.4(5.2)	3.5(6.0)	3.5(6.5)
Total fat gm/day <sup>2</sup>	63.4(10.7)	60.5(10.2)	57.2(10.3)	56.7(10.2)	60.7(10.1)	63.7(11.0)
Protein gm/day <sup>2</sup>	84.6(12.9)	86.2(12.5)	87.2(13.6)	86.9(13.3)	85.9(12.3)	85.6(13.3)
Carbohydrates gm/day <sup>2</sup>	225(31)	230(30)	237(32)	240(31)	230(30)	222(32)
Fiber gm/day <sup>2</sup>	16.7(4.8)	18.8(4.7)	22.0(5.5)	21.3(5.6)	18.8(5.0)	17.6(4.8)
Calcium mg/day <sup>2</sup>	1013(416)	1068(414)	1103(413)	1144(406)	1060(410)	976(395)
Total Folate mcg/day <sup>2</sup>	427(217)	472(226)	523(229)	523(229)	464(220)	427(212)

Values are mean (standard deviation) or percentages and are standardized to the age distribution

of the study population.



<sup>1</sup> Value is not age adjusted

<sup>2</sup> Energy-adjusted by residual method

<sup>3</sup> cumulative updated average of 1991 and 1995 food frequency questionnaires

Table 2. Association between prudent pattern during high school and risk of colorectal adenoma, Nurses' Health Study II, 1998-2007

	Ca/Co	Adj. OR <sup>1</sup>	95% CI	Adj. OR <sup>2</sup>	95% CI
Colorectal adenoma					
Quintile 1	293/3130	1.00		1.00	
Quintile 2	252/3211	0.83	(0.69,0.99)	0.82	(0.68,0.99)
Quintile 3	256/3202	0.84	(0.71,1.01)	0.85	(0.70,1.03)
Quintile 4	267/3186	0.88	(0.74,1.05)	0.93	(0.77,1.13)
Quintile 5	231/3193	0.76	(0.64,0.92)	0.82	(0.67,1.02)
p-trend			0.02		0.23
Colon adenoma					
Quintile 1	243/3130	1.00		1.00	
Quintile 2	215/3211	0.84	(0.69,1.02)	0.83	(0.68,1.02)
Quintile 3	223/3202	0.88	(0.73,1.06)	0.88	(0.72,1.08)
Quintile 4	228/3186	0.90	(0.75,1.09)	0.94	(0.77,1.16)
Quintile 5	207/3193	0.82	(0.68,1.00)	0.89	(0.71,1.11)
p-trend			0.13		0.59
Rectal adenoma					
Quintile 1	61/3130	1.00		1.00	
Quintile 2	46/3211	0.75	(0.51,1.11)	0.74	(0.49,1.11)
Quintile 3	38/3202	0.62	(0.41,0.93)	0.63	(0.41,0.98)
Quintile 4	43/3186	0.69	(0.47,1.03)	0.74	(0.48,1.14)
Quintile 5	27/3193	0.42	(0.27,0.67)	0.45	(0.27,0.75)
p-trend			0.0003		0.005
P-difference (colon versus rectal adenoma)			0.02		0.03
Non-advanced adenoma					
Quintile 1	146/3130	1.00		1.00	
Quintile 2	126/3211	0.84	(0.66,1.07)	0.83	(0.64,1.07)
Quintile 3	146/3202	0.98	(0.77,1.24)	0.98	(0.76,1.26)
Quintile 4	136/3186	0.91	(0.71,1.16)	0.95	(0.73,1.23)
Quintile 5	128/3193	0.85	(0.67,1.09)	0.92	(0.70,1.22)
p-trend			0.34		0.85
Advanced adenoma					
Quintile 1	68/3130	1.00		1.00	
Quintile 2	61/3211	0.86	(0.60,1.22)	0.88	(0.61,1.27)
Quintile 3	69/3202	0.98	(0.69,1.38)	1.06	(0.74,1.52)
Quintile 4	76/3186	1.08	(0.78,1.52)	1.23	(0.86,1.78)
Quintile 5	55/3193	0.78	(0.55,1.13)	0.90	(0.60,1.36)
p-trend			0.42		0.94
P-difference (non-advanced versus advanced adenoma)			0.92		0.96
Single colorectal adenoma					

Quintile 1	235/3130	1.00		1.00	
Quintile 2	199/3211	0.82	(0.67,0.99)	0.81	(0.66,1.00)
Quintile 3	199/3202	0.82	(0.67,1.00)	0.82	(0.67,1.02)
Quintile 4	201/3186	0.83	(0.68,1.01)	0.86	(0.69,1.07)
Quintile 5	175/3193	0.72	(0.59,0.88)	0.75	(0.60,0.95)
p-trend			0.005		0.05
Multiple colorectal adenoma (2 or more)					
Quintile 1	55/3130	1.00		1.00	
Quintile 2	50/3211	0.86	(0.58,1.27)	0.83	(0.56,1.24)
Quintile 3	55/3202	0.95	(0.65,1.39)	0.97	(0.65,1.45)
Quintile 4	61/3186	1.06	(0.73,1.54)	1.15	(0.77,1.72)
Quintile 5	52/3193	0.92	(0.62,1.35)	1.08	(0.70,1.67)
p-trend			0.99		0.38
P-difference (single versus multiple adenoma)			0.17		0.06

<sup>1</sup> adjusted for age, height, family history of colorectal cancer, physical activity during 9th-12th grade (quintiles), packyears of smoking before age 20 years (0, >0-2.5, >2.5), and high school total calories (quintiles)

<sup>2</sup> additionally adjusted for current body mass index (<25, 25-<30, ≥30 kg/m<sup>2</sup>), packyears of smoking (0, 0-10,>10-20, >20-40,>40), current physical activity (quintiles), aspirin use (never, past, current 1 day/week, 2-3 days/week, 4-5 days/week, ≥6 days/week), time period of endoscopy, at least 2 endoscopies during the study period (yes/no), endoscopy prior to 1998 (yes/no), reason for most recent endoscopy (screening vs. symptoms), current cumulative average alcohol intake (quintiles), adult total calories and adult cumulative updated average prudent pattern (quintiles)

Ca/Co=Number of cases/number of controls

OR=Odds ratio

Table 3. Association between Western pattern during high school and risk of colorectal adenoma, Nurses' Health Study II, 1998-2007

	Ca/Co	Adj. OR <sup>1</sup>	95% CI	Adj. OR <sup>2</sup>	95% CI
Colorectal adenoma					
Quintile 1	240/3186	1.00		1.00	
Quintile 2	244/3220	0.99	(0.82,1.19)	1.02	(0.84,1.24)
Quintile 3	248/3213	1.00	(0.83,1.20)	1.00	(0.82,1.22)
Quintile 4	272/3172	1.11	(0.92,1.33)	1.07	(0.88,1.31)
Quintile 5	295/3131	1.22	(1.02,1.46)	1.13	(0.93,1.38)
p-trend			0.01		0.19
Colon adenoma					
Quintile 1	212/3186	1.00		1.00	
Quintile 2	217/3220	0.99	(0.81,1.20)	1.01	(0.82,1.25)
Quintile 3	213/3213	0.96	(0.79,1.17)	0.96	(0.78,1.19)
Quintile 4	232/3172	1.06	(0.87,1.29)	1.03	(0.83,1.27)
Quintile 5	242/3131	1.13	(0.93,1.37)	1.05	(0.85,1.30)
p-trend			0.16		0.66
Rectal adenoma					
Quintile 1	33/3186	1.00		1.00	
Quintile 2	31/3220	0.94	(0.57,1.54)	0.99	(0.60,1.65)
Quintile 3	39/3213	1.17	(0.73,1.88)	1.22	(0.75,2.01)
Quintile 4	48/3172	1.47	(0.93,2.30)	1.43	(0.88,2.31)
Quintile 5	64/3131	1.94	(1.27,2.97)	1.78	(1.12,2.85)
p-trend			0.0003		0.005
P-difference, colon versus rectal adenoma)			0.01		0.01
Non-advanced adenoma					
Quintile 1	137/3186	1.00		1.00	
Quintile 2	123/3220	0.88	(0.68,1.12)	0.89	(0.68,1.15)
Quintile 3	138/3213	0.98	(0.77,1.26)	0.95	(0.74,1.24)
Quintile 4	149/3172	1.07	(0.84,1.36)	1.01	(0.78,1.31)
Quintile 5	135/3131	0.98	(0.77,1.25)	0.89	(0.68,1.16)
p-trend			0.69		0.62
Advanced adenoma					
Quintile 1	50/3186	1.00		1.00	
Quintile 2	75/3220	1.46	(1.01,2.09)	1.51	(1.04,2.20)
Quintile 3	56/3213	1.08	(0.73,1.59)	1.16	(0.77,1.73)
Quintile 4	64/3172	1.26	(0.86,1.84)	1.25	(0.84,1.87)
Quintile 5	84/3131	1.67	(1.17,2.39)	1.58	(1.07,2.33)
p-trend			0.02		0.08
P-difference, non-advanced versus advanced adenoma)			0.08		0.07

Single adenoma					
Quintile 1	180/3186	1.00		1.00	
Quintile 2	187/3220	1.01	(0.82,1.25)	1.06	(0.85,1.32)
Quintile 3	197/3213	1.06	(0.86,1.31)	1.10	(0.88,1.38)
Quintile 4	213/3172	1.17	(0.95,1.43)	1.17	(0.93,1.46)
Quintile 5	232/3131	1.29	(1.05,1.57)	1.24	(0.99,1.56)
p-trend			0.01		0.04
Multiple adenoma (2 or more)					
Quintile 1	58/3186	1		1.00	
Quintile 2	54/3220	0.88	(0.60,1.28)	0.87	(0.59,1.28)
Quintile 3	46/3213	0.74	(0.50,1.10)	0.67	(0.45,1.02)
Quintile 4	55/3172	0.89	(0.61,1.30)	0.77	(0.52,1.16)
Quintile 5	60/3131	1.00	(0.70,1.45)	0.82	(0.55,1.22)
p-trend			1.00		0.28
P-difference (single versus multiple polyps)			0.18		0.04

<sup>1</sup> adjusted for age, height, family history of colorectal cancer, physical activity during 9th-12th grade (quintiles), packyears of smoking before age 20 years (0, >0-2.5, >2.5), and high school total calories (quintiles)

<sup>2</sup> additionally adjusted for current body mass index (<25, 25-<30, ≥30 kg/m<sup>2</sup>), packyears of smoking (0, 0-10,>10-20, >20-40,>40), current physical activity (quintiles), aspirin use (never, past, current 1 day/week, 2-3 days/week, 4-5 days/week, ≥6 days/week), time period of endoscopy, at least 2 endoscopies during the study period (yes/no), endoscopy prior to 1998 (yes/no), reason for most recent endoscopy (screening vs. symptoms), current cumulative average alcohol intake (quintiles), adult total calories and adult cumulative updated average Western pattern (quintiles)

Ca/Co=Number of cases/number of controls

OR=Odds ratio

Table 4 Joint analysis of dietary patterns during high school and adulthood and risk of colorectal adenoma, Nurses' Health Study II, 1998-2007

Ca/Co OR <sup>1</sup> (95% CI)	Colon adenoma		Rectal adenoma		Non-advanced adenoma		Advanced adenoma	
Adult Prudent Pattern	HS Prudent Pattern		HS Prudent Pattern		HS Prudent Pattern		HS Prudent Pattern	
Low	Low	High	Low	High	Low	High	Low	High
	390/5362	195/2698	88/5362	31/2698	223/5362	122/2698	127/5362	63/2698
	1.00	1.00	1.00	0.71	1.00	1.08	1.00	1.00
	(Ref.)	(0.83,1.20)	(Ref.)	(0.46,1.08)	(Ref.)	(0.86,1.37)	(Ref.)	(0.73,1.37)
High	187/2573	344/5289	40/2573	56/5289	122/2573	215/5289	43/2573	96/5289
	0.98	0.90	0.93	0.64	1.13	0.97	0.68	0.78
	(0.81,1.19)	(0.77,1.06)	(0.62,1.39)	(0.45,0.92)	(0.89,1.43)	(0.79,1.19)	(0.47,0.99)	(0.59,1.04)
Adult Western Pattern	HS Western Pattern		HS Western Pattern		HS Western Pattern		HS Western Pattern	
Low	Low	High	Low	High	Low	High	Low	High
	328/5077	200/2891	46/5077	44/2891	198/5077	120/2891	86/5077	63/2891
	1.00	1.03	1.00	1.59	1.00	1.02	1.00	1.25
	(Ref.)	(0.85,1.24)	(Ref.)	(1.04,2.44)	(Ref.)	(0.81,1.30)	(Ref.)	(0.89,1.75)
High	221/2932	367/5022	37/2932	88/5022	135/2932	229/5022	69/2932	111/5022

1.17	1.10	1.45	1.92	1.20	1.16	1.36	1.29
(0.97,1.41)	(0.93,1.31)	(0.92,2.27)	(1.31,2.81)	(0.95,1.51)	(0.95,1.43)	(0.98,1.90)	(0.95,1.74)

<sup>1</sup> Models adjusted for adjusted for age, height, family history of colorectal cancer, physical activity during 9th-12th grade (quintiles), packyears of smoking before age 20 years (0, >0-2.5, >2.5), current body mass index (<25, 25-<30,  $\geq 30$  kg/m<sup>2</sup>), packyears of smoking (0, 0-10, >10-20, >20-40, >40), current physical activity (quintiles), aspirin use (never, past, current 1 day/week, 2-3 days/week, 4-5 days/week,  $\geq 6$  days/week), time period of endoscopy, at least 2 endoscopies during the study period (yes/no), endoscopy prior to 1998 (yes/no), reason for most recent endoscopy (screening vs. symptoms), current cumulative average alcohol intake (quintiles), and high school and adult total calories (quintiles)

HS=High school

Ca/Co=Number of cases/number of controls

Low=Below median dietary pattern score

High=Above median dietary pattern score

Supplementary Table S1. Factor loadings for the two dietary patterns identified from the Nurses' Health Study II high school food frequency questionnaire

Food Groups	High School FFQ (1998) n=47,355	
	Prudent	Western
Other vegetables	0.77	.
Leafy green vegetables	0.71	.
Cruciferous vegetables	0.68	.
Yellow vegetables	0.67	.
Fruit	0.65	.
Tomatoes	0.56	.
Legumes	0.52	0.16
Salad dressing	0.44	0.23
Garlic	0.42	.
Fruit juice	0.41	.
Better quality grains	0.39	.
Fish	0.38	0.18
Poultry	0.31	0.18
Potato salad	0.28	0.26
Low-fat dairy	0.26	.
Organ meat	0.20	.
Diet soda	.	.
Tea	.	.
Coffee	.	.
Desserts and sweets	.	0.62
Condiments	.	0.61
Snack foods	0.19	0.58
Processed meat	.	0.56
Fries	.	0.55
Refined grain	.	0.53
Red meat	.	0.52
Mayonnaise	0.19	0.44
Nuts/peanut butter	0.26	0.42
High-fat dairy	.	0.41
Soda	-0.16	0.40
Pizza	.	0.37
Potato (mashed boiled)	.	0.33
Eggs	.	0.31
Margarine	.	0.26
Butter	.	0.22
Cream soup (Chowder)	0.16	0.18
Iced tea	.	0.17
Cereals	.	.

Factor loadings are equivalent to Person Correlation coefficients. Factor loadings <0.15 are not displayed for simplicity.



Supplementary Table S2. Factor loadings for the two identified dietary patterns derived from food frequency questionnaires in 1991, 1995, 1999, and 2003 in the Nurses' Health Study II

Food Groups	1991 n=97,813		1995 n=87,448		1999 n=87,676		2003 n=101,495	
	Prudent	Western	Prudent	Western	Prudent	Western	Prudent	Western
Leafy green vegetables	0.70	.	0.68	.	0.62	.	0.69	0.21
Other vegetables	0.70	0.20	0.71	0.17	0.69	0.17	0.73	0.25
Yellow vegetables	0.66	.	0.61	.	0.56	.	0.60	0.17
Fruit	0.63	.	0.61	.	0.61	.	0.67	0.22
Cruciferous vegetables	0.60	.	0.60	.	0.59	.	0.65	0.16
Tomatoes	0.55	0.19	0.55	0.18	0.45	0.36	0.57	0.43
Legumes	0.53	0.20	0.55	.	0.50	.	0.59	.
Fish	0.48	.	0.42	0.16	0.45	.	0.62	0.18
Poultry	0.44	.	0.27	0.25	0.30	0.28	0.46	0.43
Salad dressing	0.37	.	0.41	.	0.38	0.17	0.52	0.24
Water	0.36	.	0.36	.	0.38	.	0.58	0.28
Olive oil	0.36	.	0.35	.	0.48	.	0.59	.
Garlic	0.35	.	0.42	.	0.45	.	0.55	.
Whole grains	0.31	.	0.29	.	0.27	.	0.47	0.33
Low-fat dairy	0.28	.	0.24	.	0.27	.	0.37	0.36
Juice	0.26	.	0.25	.	0.21	.	0.20	0.28
Wine	.	.	0.17	.	0.19	.	0.22	.
Coffee	.	.	.	.	.	.	0.34	0.29
Red meat	.	0.65	.	0.64	.	0.63	0.23	0.69
Processed meat	.	0.60	.	0.59	.	0.55	.	0.52
Fries	-0.16	0.57	-0.19	0.56	-0.20	0.53	.	0.63
Dessert	.	0.50	.	0.45	.	0.41	.	0.59
Pizza	.	0.45	.	0.44	.	0.43	.	0.58
Potato	0.17	0.44	0.19	0.40	.	0.44	0.19	0.61
Refined grain	.	0.42	.	0.37	.	0.43	0.26	0.67
Snack foods	.	0.41	.	0.39	.	0.39	.	0.58
Eggs	.	0.40	.	0.40	.	0.32	0.32	0.31
High-fat dairy	.	0.37	.	0.35	.	0.34	0.29	0.43
Condiments	.	0.35	.	0.41	.	0.44	0.27	0.50
High calorie Soda	.	0.35	.	0.35	-0.16	0.32	.	0.42
Mayonnaise	.	0.34	0.16	0.36	0.20	0.35	0.31	0.37
Margarine	.	0.34	.	0.37	.	0.32	.	0.44
Nuts	0.19	0.29	.	0.25	0.25	0.18	0.45	0.19
Cream soup	.	0.26	.	0.32	.	0.31	.	0.43
Butter	.	0.23	.	0.22	.	0.21	0.19	0.28
Tea	.	.	.	.	0.17	.	0.34	0.17
Diet soda	.	.	.	0.15	.	0.23	.	0.36
Beer	.	.	.	.	.	.	.	.
Organ meat	.	.	.	.	.	.	.	.
Liquor	.	.	.	.	.	.	.	.
Egg Whites	.	.	.	.	0.18	.	0.27	.

Factor loadings are equivalent to Person Correlation coefficients. Factor loadings  $<0.15$  are not displayed for simplicity.