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Proportion of Colon Cancer Attributable to Lifestyle in a Cohort of US Women

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Abstract

Background—Many modifiable lifestyle factors have been associated with colon cancer risk, but less is known about their effect on disease when considered together. Estimating the proportion of colon cancer cases that could be prevented by the adoption of combined modifiable lifestyle behaviors will provide important insights into disease prevention.

Methods—In the Nurses' Health Study, we defined a low-risk group according to a combination of six factors: body-mass index < 25kg/m², physical activity of ≥ 21 metabolic equivalent of task per week, alcohol consumption ≤ 30g/day, cigarette smoking <10 pack years before the age of 30, current use of multivitamins for ≥ 15 years, and total calcium intake ≥ 700mg/day. A composite risk score index was created and the population attributable risk(PAR%) was calculated after accounting for other known risk or protective factors.

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Drs Erdrich and Zhang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Results—We documented 1,127 colon cancer cases among 81,092 over 24 years of follow-up. Compared to women in the lowest-risk category, the women at all other exposure levels had a hazard ratio of colon cancer of 1.81(95% confidence interval, 1.15-2.85). The score index was significantly and linearly related to an increasing risk of colon cancer (P -value for trend <0.0001). The PAR% of the six risk factors considered together in relation to colon cancer was 0.37(95%CI: 0.09-0.60). When regular aspirin use(two tablets/week for 6 or more years) was included with the other low-risk behaviors, the PAR% increased to 0.43(95%CI: 0.14-0.65).

Conclusions—Beyond the known benefit from colonoscopy/sigmoidoscopy, key behavior modifications and adherence to a healthy lifestyle could avoid approximately 37% of colon cancer cases among women.

Keywords

obesity; physical activity; smoking; calcium; multivitamin; alcohol; aspirin; screening; population attributable risk; colon cancer; prevention

INTRODUCTION

Colon cancer incidence is increasing worldwide and remains the third most commonly diagnosed cancer and the third greatest cause of cancer mortality in the United States. The American Cancer Society estimated there were 102,480 new cases of colon cancer diagnosed and 50,830 colon cancer deaths in the US alone in 2013.(1) Although genetic predisposition carries a significant risk, 75% of the cases in this country are sporadic, suggesting that environmental exposures play a pivotal and potentially modifiable role in disease etiology.(2) A large body of evidence implicates modifiable lifestyle factors in the etiology of colon cancer. (3-8) Body weight, physical activity, alcohol, smoking, and dietary factors consistently have been associated with the risk of colon cancer across populations, and the highest incidence rates are seen in affluent nations where obesity and sedentary lifestyles are common. Regular use of aspirin has been associated with lower risk of colorectal cancer in many prospective studies (8-13) and in a recent meta-analysis of randomized trials, aspirin use reduced the 20-year risk of colon cancer by 24%.(8)

Even modest differences in lifestyle practices may have substantial impact on colon cancer risk. In a previous analysis among men in the Health Professionals Follow-up Study, we estimated that approximately 71% of colon cancer cases could be avoided by adhering to a combination of healthy behaviors.(7) In this analysis, we examined a similar combination of beneficial lifestyle practices and estimated the percentage of colon cancer cases in the Nurses' Health Study that could be avoided by adoption of these behaviors and by regular aspirin use.

MATERIALS AND METHODS

Study Population

The Nurses' Health Study is a prospective cohort established in 1976 comprised of 121,701 registered female nurses aged 30-55 years of age at baseline completed a self-administered questionnaire regarding demographics, medical history, lifestyle, and other health

information. The participants live in the 11 most populous states. Geographical location is not associated with colon cancer risk in the cohort. The participants have completed biennial questionnaires since 1976 and have a 90% follow-up rate. (14, 15) For this analysis, women were followed from 1986 until the return of the last questionnaire in 2010, the development of any cancer or death, whichever event occurred first. The year 1986 was chosen as the start because physical activity was first assessed in detail that year. For this analysis, we excluded women with a history of cancer (except for non-melanoma skin cancer), ulcerative colitis, or extreme baseline total energy intake (<600 or >3500 kcal per day). After exclusions, 81,092 women were included for the analysis, providing a total of 1,724,234 person-years. This study was approved by the institutional review board of Brigham and Women's Hospital in Boston, Massachusetts. As approved by the committee, return of the questionnaires was considered to imply informed consent.

Assessment of Diet

Dietary information has been collected from participants using a validated, semi-quantitative food-frequency questionnaire (FFQ) starting in 1980 and repeated every 4 years afterward to elicit data on the long-term average diets of the participants. (14) Respondents answer how frequently they consume a standard serving of each specific food item according to 9 categorical choices. The nutrient intake is calculated by multiplying the frequency of consumption by the nutrient content. Beer, wine, and liquor are included in the food-frequency questionnaire to allow computation of alcohol consumption. The food-frequency questionnaire additionally inquires about use of multivitamins and selected single supplements. Most nutritional variables measured by the FFQ has been developed, tested and refined by our group over the past 30 years. The validity of the FFQ has been extensively evaluated. The Pearson correlation coefficients comparing the FFQ and the average of multiple 1-week diet records were 0.63 for total calcium intake (16, 17) and 0.84 for alcohol intake (18). Details of the dietary assessment and validation are described in detail elsewhere.(19)

Assessment of nondietary factors

Participant height was collected in 1976, and in each follow-up questionnaire we asked for current weight to update BMI (weight in kilograms divided by the square of the height in meters). Detailed information on physical activity (MET-hours/week) was first obtained in 1986 and updated every two years thereafter. (20) We calculated MET hours expended per week performing moderate-to-vigorous activity, including brisk walking. Information on cigarette smoking has been collected on all questionnaires since 1976. Specifically, smoking as measured by pack years in early adulthood, assessed at baseline was most relevant for this analysis.(21) Information on other nondietary factors related to colon cancer risk included family history of colorectal cancer in a parent or sibling (yes/no), personal history of previous colonoscopy/sigmoidoscopy (yes/no), regular aspirin use (yes/no, defined as 2 standard dose tablets per week for 6 or more years), and postmenopausal hormone use (never, past, or current user).

Definition of the Low-Risk Group

The aim of this study was to estimate the relation of modifiable diet and lifestyle factors to the risk of colon cancer, emphasizing the combination of modifiable behaviors. Therefore, we did not consider pharmacologic agents or predisposing medical conditions as exposures, but we did adjust for them or study them in secondary analyses. While multiple variables have been studied, only the following six factors were included because of strong supportive evidence from many sources for having an effect on colon cancer risk: BMI, physical activity, alcohol consumption, smoking, multivitamin use, and calcium intake. (3, 8, 21-28) If the definition of low-risk was met for that factor, then zero risk points were assigned. Any level of exposure outside of the low-risk definition was assigned 1 risk point. The range of total risk points was 0 (lowest risk) to 6 (highest risk). All definitions of low risk for each factor were established *a priori*. Please see **Online Data Supplements**.

Ascertainment of Cases of Colon Cancer

Participants reported cancer and other disease conditions on the biennial questionnaires. When a woman reported a diagnosis of colon cancer, permission was sought and granted for researchers to obtain medical records and pathological reports. These documents were reviewed by study physicians blinded to exposure information. Colon cancer was defined according to the International Classification of Diseases, Ninth Revision (ICD-9).(54) Deaths were identified through the National Death Index or reported by family members. During the follow-up period a total of 1127 incident colon cancer cases were documented. We chose colon cancer as our endpoint rather than colon and rectal cancer combined because the risk factors associated with colon vs. rectal cancer differ.(26)

Statistical Analysis

Person-time for each participant was calculated from the date of the baseline questionnaire to the date of death, colorectal cancer diagnosis, or the end of follow-up (June 2010), whichever occurred first. Cox proportional hazards regression models were used to calculate relative risks and 95% confidence intervals for each of the six lifestyle factors.(55) We adjusted for other factors that were significantly associated with colon cancer risk in this study, which include: age, family history of colorectal cancer, history of previous colonoscopy or sigmoidoscopy, postmenopausal hormone use and regular aspirin use. (9, 10, 26, 56-61) When we adjusted for red and processed meat consumption, which have shown association with colon cancer elsewhere, the results were essentially the same (data not shown); therefore it was not adjusted in final analysis. In a recent publication from the cohort (62), shift work was not associated with colorectal cancer risk and therefore not included.

A risk score system with 0-1 points assigned per factor (0 for those categorized as low risk, 1 for everyone else) was established, leading to a total composite point value ranging 0-6 points. Cox proportional hazards analyses were conducted using the composite score as the independent variable. Because so few cases occurred in the group with zero points, we used the 0-1 composite point category as the referent to which all other score categories for the component variables were compared.

To analyze the combination and interaction of multiple factors in a way that accounts for the strength of the variable associations and distribution of exposures in the population, we calculated the population attributable risk percent (PAR%). (63, 64) This provides an estimate of the percentage of cases of colon cancer in this cohort that theoretically would not have occurred if all women had been in the low-risk group.(63-65) We further calculated the PAR% by age below and above 65 years. In addition, we ran a model restricted to never-smokers in order to evaluate how much colon cancer can be prevented in this particular group.

Given the well documented effect of aspirin use in preventing colorectal cancer, we conducted an additional analysis with aspirin included as a seventh modifiable factor. The low-risk group was defined as women with 6 or more years of current, regular aspirin use. In this definition, regular use reflected two or more standard dose tablets per week, consistent with the definition published in other studies specifically focused on aspirin and colorectal cancer. (8-10, 61) We also stratified the analysis by regular aspirin users and non-regular aspirin users, the latter of which included those who took any non-zero amount of aspirin for less than six years. The PAR was calculated for both of these groups. There were too few cases with absolutely no aspirin exposure to examine this as a separate stratum.

To obtain the best estimate of long-term exposure, the cumulative average of each factor was compiled and updated through biennial questionnaires. Smoking was the only exception as the early adulthood exposure reported at baseline was most relevant for the study outcome. All statistical tests were 2-sided and $p < 0.05$ was considered significant. The analyses were conducted in SAS 9.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

During 24 years of follow-up, we documented 1127 cases of colon cancer. Over the entire follow-up period, the mean age (range) was: 63 year (40-89).Table 1 shows the relative risk of colon cancer for each of the six factors considered as dichotomies: low risk as the reference category vs. all-other levels. After adjusting for family history of colorectal cancer, history of endoscopy, regular aspirin use, and postmenopausal hormone use, women who had a BMI greater or equal to 25 had a relative risk for colon cancer of 1.09 (95% CI: 0.97, 1.23). Women who exercised less than 21 MET hours per week had a relative risk of 1.17 (1.02-1.35). Participants who consumed alcohol at a level of 30g or greater per day had a relative risk of 1.15 (0.84-1.56). Those who smoked 10 pack years or more before the age of 30 had a relative risk of 1.15 (0.96-1.38). Regarding multivitamins, compared to those who used multivitamins for 15 years or more, women who were never-users, past users, or current users with less than 15 years of exposure had a relative risk of 1.32 (1.11-1.55). The women who consumed less than 700mg of calcium per day had a relative risk of 1.28 (1.11-1.46). Table 2 provides the composite score in relation to risk of colon cancer. Overall, the score index was significantly and linearly related to the risk of colon cancer with a p-value for trend < 0.0001 . Compared to the reference group (0-1 risk factor), the multivariable hazard ratio was 1.81 (1.15-2.85) for five-six factors and 1.76 (1.44-2.17) for at least four factors.

The proportion of colon cancer cases attributable to the six risk factors considered together was 0.37 (0.09-0.60), suggesting that 37% of the colon cancer cases in this cohort might have been prevented if all women had been like the 20% of the cohort in the lowest risk group (0-1 risk point) (Table 3). In an analysis stratified by age, the proportion of colon cancer cases attributable to the combined factors for those less than 65 years of age was 0.44 (-0.10-0.78) while for the cohort members 65 years or older the PAR was 0.31 (-0.02-0.58).

We repeated the multivariable regression and the PAR analysis for the women in the cohort who were never smokers. Compared to the reference group (0-1 risk factor), the multivariable hazard ratios was 1.53 (1.01-2.33) for the remaining 4-5 factors. The proportion of colon cancer cases attributable to the remaining combined factors with smoking excluded was 0.35 (-0.12-0.69). This suggests that among the never-smokers, 35% of the colon cancer cases in this cohort might have been prevented by adhering to the low-risk practice in the remaining five factors (Table 3). We conducted an additional analysis without multivitamin use since there is no existing recommendation for its use in cancer prevention. The PAR% of the five remaining risk factors in relation to colon cancer was 0.23 (95% CI: 0.02-0.41). When regular aspirin use was included with the other low-risk behaviors, the PAR% increased to 0.29 (95% CI: 0.07-0.49).

We confirmed that aspirin had an important inverse association with colon cancer in this cohort. The use of two or more standard tablets of aspirin per week, taken for a minimum duration of six years had a relative risk of 0.79 (0.71-0.89). The partial PAR for regular aspirin use was 0.09 (0.04-0.14), indicating that 9% of colon cancer cases in the cohort could be prevented by regular use of aspirin alone (Table 3). When aspirin was moved from an adjusted variable to an exposure along with the original six factors, the population attributable risk of these seven factors combined then became 0.43 (0.14-0.65). This suggests that 43% of colon cancer cases in the cohort could be prevented if all women had been in the low risk group for the combination of risk factors and took aspirin regularly. In additional analyses, we calculated the PAR using the original six exposures among regular aspirin users, and then again among non-regular aspirin users, which yielded estimates of 0.35 (-0.03- 0.64) and 0.40 (-0.02-0.70) respectively.

DISCUSSION

In this large, prospective cohort study, women who fell outside the low risk categories for all exposure variables combined had 1.81 times the risk of colon cancer compared to those in the lowest risk category. We estimated that 37% of the colon cancer cases that occurred in the cohort could have been avoided by behavior modification. Given that the women in this cohort likely have lower risk behavior compared to the broader population of US women, we suspect this underestimates the percentage of cases that could be prevented nationally. Using incidence rates from Cancer Statistics 2013,⁽¹⁾ at least 19,384 colon cancers could be prevented per year among women in the United States if they were to practice the described combination of lifestyle factors.

The individual factors that were independently and significantly associated with colon cancer were physical activity, multivitamins, and calcium. Overweight, smoking, and heavy

alcohol consumption were associated with higher risk, although nonsignificant. We still included them in the model because we have seen these reach significance in the full cohort and elsewhere(3, 8, 25, 26)and we maintained our *a priori* definitions because we wanted to preserve thresholds consistent with common health guidelines.

The lower risks seen with use of multivitamins and calcium are noteworthy as they are relatively simple and inexpensive measures to adopt. Many individual micronutrients contained in multivitamins, including folate, vitamin B-6, and vitamin D, have been postulated as influencing colon cancer risk, (28, 39, 41-49, 66, 67) but not all have been studied extensively or found to be consistently significant, and there may be other constituents that contribute to lower risk. In the Physicians' Health Study II (PHS-II), a randomized trial, long-term multivitamin supplementation for a median usage of 11.2 years had a modest but significant reduction in risk of total cancer with a relative risk of 0.92, and nonsignificant reduction for colorectal cancer of 0.89.(40) Our results are consistent with the protective benefit seen in the PHS-II trial, but show a stronger and significant reduction of colon cancer risk associated with longer duration of use. Although calcium is included in many multivitamin preparations, women in the cohort and the general population frequently take a separate supplement with a higher dose.(50) We found that a total daily calcium intake of 700mg or more, whether from dietary and/or supplementary sources, was associated with a significantly lower risk of colon cancer. Support that this is potentially causal has come from randomized trials in which calcium supplements reduce recurrence of colorectal adenomas.(50-53)

When stratifying by age, we found that among members under the age of 65 years who had 5-6 high risk factors, the multivariate relative risk of colon cancer was 2.34 (1.21-4.51) and the associated PAR% for this age group was 0.44 (-0.10-0.78). This subgroup analysis is relevant because approximately two-thirds of the US population is <65 years of age. Exposure prevalence of these six factors among this subgroup of women under the age of 65 was roughly comparable to those in the overall population (as shown in table 1) except for slightly higher prevalence of <700 mg/d of calcium intake (27%), and none, past, or current multivitamin use <15 years (87%). These findings suggest that 44% of colon cancer cases might be preventable in the majority of the US population age range. Although adopting these lifestyle modifications is important across a broad age range for colon cancer prevention, it seems particularly important to adopt early in life.

Long-term aspirin use has been associated with lower risk of colon cancer in this cohort and elsewhere, including a recent summary of randomized trials.(8-13, 61) We adjusted for this factor rather than include it as one of the main exposures in the primary lifestyle index because of the potential side effects, such as gastrointestinal bleeding, that make it difficult to recommend on a population level. However, with the ongoing interest in aspirin as a chemopreventive agent, we performed a secondary PAR calculation with regular aspirin use considered as one of the main exposures in the lifestyle index. Under this new combination of seven factors, we estimated that 43% of colon cancer cases might be prevented, suggesting there may be modest benefit in adding regular aspirin use to a healthy lifestyle. Further studies are warranted to determine which populations are the best targets for aspirin chemoprevention.

This analysis has important limitations. Although the exposures in the lifestyle index are well-substantiated in their relation to risk of colon cancer, they represent a limited set of the numerous factors that have been studied with this disease outcome. It is possible that including additional potential preventive factors could lead to even further risk reduction. Our dichotomization of components of the risk score limited our ability to observe dose-response relationships, but Wacholder et al have shown that calculating the PAR% based on dichotomized data yields similar results to a more complex integration across dose-responses.(64) Previous investigations also enabled us to consider duration and timing of exposure in relation to the period of colon carcinogenesis, but not for all factors. The critical windows during which BMI, physical activity, and calcium intake most matter is yet to be defined. Given that the women in the cohort are health care professionals, they may not be the best group for generalizability. However, they provide one of the largest and longest running data sets available to initiate the query. Because some of these risk factors may be more prevalent in other populations, our results are probably a conservative estimate and flag the protective benefit that could arise from complying with the behavioral modifications we describe.

A strength of the analysis is that it took into account a combination of factors. To date, the majority of studies have focused on individual factors, which does not account for the impact of multiple factors considered together. Our model provides a more realistic reflection of the way an individual practices behaviors simultaneously. Furthermore, our lifestyle index overlaps with guidelines and indices for prevention of diabetes and coronary artery disease, and are consistent with an overall pattern of healthy living.(33-36) Strengths of the study also include a prospective design with long follow-up and a high response rate, which minimizes potential selection and information bias. Additionally, the long and detailed follow-up allowed us to consider cumulative exposure rather than simple baseline assessment, which captures the impact of changed behaviors over time and minimizes measurement error. Finally, the data is based on validated questionnaires, which should minimize any misclassification.

To our knowledge, ours is the first paper to examine the population attributable risk of colon cancer in US women. There are few PAR papers available for comparison, and direct comparisons are difficult in all cases because the combination of factors utilized and the cut-off points vary; however, themes in the benefit of a healthy diet, regular exercise, and minimal alcohol and smoking exposure recur as critical preventive measures. From an Italian case-control study based on five factors in relation to colorectal cancer, the PAR was reported to be 63% while the PAR from the Health Professionals Follow-up Study based on six factors was 71% for men. (7, 68) The lower estimate we found may be an indicator of true sex differences, or a reflection of the lower prevalence of some of the risk factors, such as smoking, alcohol consumption and red meat consumption, as well as decreased consumption of red meat with time, in women in our cohort. Also, our lower PAR% is partly a function of the lower relative risks for some factors, namely BMI and physical activity, which have had weaker associations for women compared to men in our studies and others. (7, 69) Furthermore, it may be that the common use of postmenopausal hormones among women confers protection that attenuates the benefits of the other factors. In our analysis, 72% of the women had used postmenopausal hormones, which in this analysis and a meta-

analysis of 18 studies were associated with an approximately 20% lower risk of colorectal cancer.(57) We did adjust for this important factor. Lastly, in a prospective Danish cohort where men and women were combined, the PAR based on five factors was 23%, an estimate closer to our results for an all-female analysis.(30) Again, this study showed the associations to be weaker for women than men in their analyses stratified by gender. While women in our study have comparable physical activity level as those in the US general population (i.e., physical activity 21+ MET hrs/week: 32% vs. 30%(70)), women in our study tend to have lower prevalence of overweight (defined by BMI>25 kg/m²: 45% vs. 60%) and alcohol consumption (>30 g/d: 3% vs. ~4%(71)). Among studies identified, we do not get prevalence data on other factors examined in the US general population. Nevertheless, additional studies in different racial/ethnic groups or in populations with different characteristics would provide more insights into how a constellation of modifiable risk factors influences colon cancer risk.

In conclusion, we have estimated that a substantial proportion of colon cancer cases in US women might be prevented by more widespread adoption of healthy lifestyle practices. Colon cancer diagnosis and treatment carries immense individual and societal burden. Primary prevention efforts to decrease colon cancer incidence and cost are crucial, and our study offers a set of behaviors that can be recommended to individuals. Our findings also support a likely benefit of more widespread use of aspirin, but the benefit of this in isolation would be modest and must be weighed against side effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Associations between individual factors and risk of colon cancer in the Nurses' Health Study

Factors (score)	% of Cohort	Multivariable adjusted hazard ratio (95% CI) ^a
BMI (kg/m ²)		
<25 (0)	55%	1 (reference)
25+ (1)	45%	1.09 (0.97, 1.23)
Physical Activity (MET hrs/ week)		
21+ (0)	27%	1 (reference)
<21 (1)	73%	1.17 (1.02-1.35)
Alcohol Consumption (g/day)		
30g/day (0)	97%	1 (reference)
30+ g/day (1)	3%	1.15 (0.84-1.56)
Smoking (pack years before age 30)		
<10 pack years (0)	89%	1 (reference)
10+ pack years (1)	11%	1.15 (0.96-1.38)
Multivitamin Use		
Current use for 15+ years (0)	18%	1 (reference)
None, past, or current use <15 years (1)	82%	1.32 (1.11-1.55)
Calcium Intake (mg/day)		
700mg+/day (0)	78%	1 (reference)
<700 mg/day (1)	22%	1.28 (1.11-1.46)

^a MV-HR: Although individual factors were not adjusted for each other, we have adjusted for age(continuous), history of colorectal cancer in a parent or sibling (yes, no), history of colonoscopy/sigmoidoscopy (yes, no), regular aspirin use (yes, no), postmenopausal hormone use (never, past, or current user).

Table 2Multivariate^a hazard ratios of colon cancer in relation to risk score in the Nurses' Health Study

Risk score	% of cohort	# of cases	Multivariable adjusted hazard ratio (95% CI) ^a
0, 1	20	181	1 (reference)
2	34	352	1.20 (0.99-1.43)
3	33	399	1.43 (1.19-1.70)
4	12	174	1.76 (1.42-2.17)
5	1	21	1.81 (1.15-2.85)
<i>p</i> -value for trend			<.0001

^aMV-HR: adjusted for age (continuous), history of colorectal cancer in a parent or sibling (yes, no), history of colonoscopy/sigmoidoscopy (yes, no), regular aspirin use (yes, no), postmenopausal hormone use (never, past, or current user).

Table 3

Summary of Population Attributable Risk (PAR%) Estimates

<i>Primary Analysis</i>	PAR% (95% CI)	Multivariate RR (95% CI) for having all risk factors (5-6 points)
PAR for the original lifestyle index ^{a,b}	0.37 (0.09-0.60)	1.81 (1.15-2.85)
<i>Secondary Analyses</i>		
PAR for the original lifestyle index stratified by age ^{a,b}		
Age <65 years		0.44 (−0.10-0.78) 2.34 (1.21-4.51)
Age 65+ years		0.31 (−0.02-0.58) 1.40 (0.73-2.66)
PAR for the original lifestyle index stratified by aspirin use ^a		
Regular aspirin users ^c		0.35 (−0.03-0.64) 1.96 (1.08-3.58)
Non-regular aspirin users ^d		0.40 (−0.02-0.70) 1.65 (0.82-3.28)
PAR for a modified lifestyle index that includes regular aspirin use ^e		0.43 (0.14-0.65) 2.18 (1.62-2.92)
Partial PAR for regular aspirin use ^f		0.09 (0.04-0.14) --
PAR for a modified lifestyle index among never-smokers ^g		0.35 (−0.12-0.69) 1.53 (1.01-2.33)

^a BMI <25 kg/m², physical activity ≥ 21 MET hrs/week, alcohol consumption ≤ 30g/day, cigarette smoking ≤ 10 pack years before age 30, current use of multivitamins for ≥ 15 years, and total daily calcium intake ≥ 700mg.

^b adjusted for age, history of colorectal cancer in a parent or sibling, history of endoscopy, regular aspirin use, postmenopausal hormone use

^c regular aspirin user defined as consumption of ≥ 2 standard tablets of aspirin per week for ≥ 6 years

^d non-regular aspirin user group includes any amount or duration of aspirin use less than 2 standard weekly tablets and less than 6 years duration.

^e regular aspirin use was run as an exposure alongside the other six modifiable variables for this analysis instead of being a covariate

^f calculated with the original lifestyle index and regular aspirin usage run as a covariate

^g the same lifestyle index listed in "^a" minus the category "cigarette smoking ≥ 10 pack years before age 30"