A Combined Healthy Lifestyle Score and Risk of Pancreatic Cancer in a Large Cohort Study

Li Jiao, MD; Panagiota N. Mitrou, PhD; Jill Reedy, PhD; Barry I. Graubard, PhD; Albert R. Hollenbeck, PhD; Arthur Schatzkin, MD; Rachael Stolzenberg-Solomon, PhD

Background: Smoking, alcohol use, diet, body mass index (calculated as weight in kilograms divided by height in meters squared), and physical activity have been studied independently in relation to pancreatic cancer. We generated a healthy lifestyle score to investigate their joint effect on risk of pancreatic cancer.

Methods: In the prospective National Institutes of Health–AARP Diet and Health Study, a total of 450 416 participants aged 50 to 71 years completed the baseline food frequency questionnaire (1995-1996) eliciting diet and lifestyle information and were followed up through December 31, 2003. We identified 1057 eligible incident pancreatic cancer cases. Participants were scored on 5 modifiable lifestyle factors as unhealthy (0 points) or healthy (1 point) on the basis of current epidemiologic evidence. Participants received 1 point for each respective lifestyle factor: nonsmoking, limited alcohol use, adherence to the Mediterranean dietary pattern, body mass index (≥18 and <25), or regular physical activity. A combined score (0-5 points) was calculated by summing the scores of the 5 factors. Cox proportional hazards regression models were used to estimate relative risk (95% confidence interval) for pancreatic cancer.

Results: Compared with the lowest combined score (0 points), the highest score (5 points) was associated with a 58% reduction in risk of developing pancreatic cancer in all participants (relative risk, 0.42; 95% confidence interval, 0.26-0.66; $P_{\text{trend}} < .001$). Scores of less than 5 points were associated with 27% of pancreatic cancer cases in our population.

Conclusion: Findings from this large study suggest that having a high score, as opposed to a low score, on an index combining 5 modifiable lifestyle factors substantially reduces the risk of developing pancreatic cancer.

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ACCORDING TO SURVEILLANCE Epidemiology and End Results (SEER) 2000-2003 statistics, the incidence of pancreatic cancer in the United States ranks 10th in men and 9th in women; however, mortality ranks 4th in both men and women. Because pancreatic cancer is difficult to detect at a potentially resectable stage and remains therapeutically intractable, prevention is the primary hope for reducing the burden of this disease. Cigarette smoking and obesity have been consistently associated with increased risk of pancreatic cancer. Findings on dietary intake and physical activity have been inconsistent.1,2 Typically, in epidemiologic studies of individual health behaviors or exposures, other factors are treated as covariates in statistical models. Several studies have identified patterns of health behavior in adults in the United States and suggested that a multidimensional lifestyle approach would be informative in exploring the cause of disease.3-4 Thus, we scored study participants according to their conformity to a healthy lifestyle using 5 potentially modifiable factors including cigarette smoking, alcohol use, dietary quality, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), and physical activity. We examined how the combined lifestyle score was associated with risk of pancreatic cancer in the National Institutes of Health–AARP (NIH-AARP) Diet and Health Study. We hypothesized that a higher healthy lifestyle score would be associated with a lower risk for pancreatic cancer.

STUDY POPULATION

The NIH-AARP Diet and Health Study is a large prospective cohort study of AARP members established in 1995-1996. Details of the study design and questionnaire have been described previously.5 In brief, a self-administered baseline Food Frequency Questionnaire (FFQ) was mailed to 3.5 million AARP members aged 50 to 71 years residing in 6 states (California,
Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia, and Detroit, Michigan). The questionnaire was returned by 617,119 members, and 567,169 completed the questionnaire satisfactorily. The study was approved by the National Cancer Institute Special Studies Institutional Review Board. Informed consent was obtained from all participants by virtue of completing the questionnaire.

We excluded 179 participants with duplicate responses, 321 who moved from the study areas before returning the baseline questionnaire, 261 who died before study enrollment, and 6 who withdrew. In the remaining 566,402 participants, we further excluded 15,760 whose questionnaires were completed by proxy participants by virtue of completing the questionnaire. We generated a healthy lifestyle score based on a priori knowledge of risk factors for pancreatic cancer and current public health recommendations.1,10,11 We used a binary score for each factor to produce an adequate sample size for the pattern analysis. The participants received 1 point for each factor if they were nonsmokers (never smoked or quit smoking ≥10 years ago), had limited daily alcohol use (≤1 drink for women or ≤2 drinks for men), and were of normal weight (BMI ≥18 and <25).11 or performed regular physical activity; otherwise they received 0 points for each corresponding factor (Table 1). We combined ever smokers who quit smoking 10 years or more previously with never smokers into a nonsmoking group because their risk of developing pancreatic cancer was similar to that in never smokers as observed.

### Exposure Assessment

A self-administered FFQ was used to elicit information on smoking, dietary intake, anthropometry, and physical activity, as well as demographic factors and medical history. The FFQ was a grid-based version of the National Cancer Institute Diet History Questionnaire that assessed the frequency of consumption and usual portion size of 124 food items and alcohol use during the last year.7 The Diet History Questionnaire was validated using two 24-hour dietary recalls that were administered to 2053 randomly chosen NIH-AARP participants.5 MyPyramid equivalents of all food items were generated by linking the FFQ data with the MyPyramid Equivalents Database (version 1.0; US Department of Agriculture, Washington, DC), which disaggregates all food mixtures into the appropriate food groups using standardized servings.13,14

Participants reported whether they smoked 100 cigarettes or more during their entire lifetime to define ever smokers and never smokers. Ever smokers were asked to report whether they currently smoked or whether they had stopped smoking within the last year or 1 to 4, 5 to 9, or 10 years or more previously. Body mass index was calculated from self-reported weight and height information. Participants reported how often (never, rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, or ≥5 times per week) they had engaged in physical activity at home or at work that lasted at least 20 minutes and caused increased breathing or heart rate or produced perspiration.

### Scores for Smoking, Alcohol Use, BMI, and Physical Activity

We generated a healthy lifestyle score based on a priori knowledge of risk factors for pancreatic cancer and current public health recommendations.1,10,11 We used a binary score for each factor to produce an adequate sample size for the pattern analysis. The participants received 1 point for each factor if they were nonsmokers (never smoked or quit smoking ≥10 years ago), had limited daily alcohol use (≤1 drink for women or ≤2 drinks for men), were of normal weight (BMI ≥18 and <25),11 or performed regular physical activity; otherwise they received 0 points for each corresponding factor (Table 1). We combined ever smokers who quit smoking 10 years or more previously with never smokers into a nonsmoking group because their risk of developing pancreatic cancer was similar to that in never smokers as observed.
in the present study and in previous studies.12 We generated a score for alcohol use based on the Dietary Guidelines for Americans 2005.16 We considered maintaining a BMI of 18 or more and less than 25 as a healthy behavior.11 Regular physical activity was defined as activity performed at least 3 or 4 times per week for at least 20 minutes and that caused increased breathing or heart rate or produced perspiration.

SCORE FOR DIETARY QUALITY

Dietary quality was evaluated on the basis of an alternate Mediterranean diet score (aMDS). The aMDS was derived from the traditional MDS and evaluated adherence to the Mediterranean dietary pattern in the US population.13-15 We further modified the aMDS by removing the alcohol component;16 we evaluated alcohol use as a separate factor. This modified score (no-alcohol aMDS) included 8 components (vegetables not including white potato, legumes, fruits, nuts, whole grains, red and processed meat, fish, and the ratio of monounsaturated to saturated fat) and assigned values from 0 to 8 points (minimum to maximum adherence; median, 4 points). Study participants who scored 5 to 8 points were categorized as having a healthy dietary quality and received 1 point for the dietary intake component on the combined healthy lifestyle score; those who scored 0 to 4 points received 0 points (Table 1).

SCORE FOR COMBINED HEALTHY LIFESTYLE

We assigned the healthy lifestyle score to each participant by summing the binary score for each of the 5 lifestyle factors described including smoking, alcohol use, dietary quality, BMI, and physical activity. The healthy lifestyle score ranges from 0 (least healthy) to 5 points (healthiest). Alternatively, we generated a weighted lifestyle score by using the percentage of the coefficient of each factor to the sum of the coefficients of each factor in the Cox proportional hazards regression model with all 5 factors included. This score ranges from 0 to 100 points and considers magnitudes of the adjusted relative risk (RR) for each factor in each lifestyle pattern as a combination of 5 factors. We categorized the weighted lifestyle score to 6 levels, where the distribution of the categories is similar with that of the 6 categories of the combined healthy lifestyle score.

STATISTICAL ANALYSES

Cox proportional hazards regression models using age as the underlying time metric were used to calculate (sex-specific or sex-combined) RRs and 95% confidence intervals (CIs) for pancreatic cancer. Age (continuous), sex (in the sex-combined model), race/ethnicity (non-Hispanic white, non-Hispanic African American, Hispanic, and other), educational achievement (less than high school or unknown, high school, some college, and college graduate), marital status (married or living as married vs other), and total energy intake (log-transformed) were the variables included in the multivariate models. First, we evaluated the association of each binary lifestyle factor with pancreatic cancer risk, adjusting for the other factors including smoking, alcohol use, dietary quality, BMI, and physical activity. Participants with 0 points were the reference group. Second, we examined the agreement of the combined score and the weighted score in categorizing participants according to their health lifestyles. We evaluated the associations of 2 scores with pancreatic cancer risk separately. We calculated the P value for the linear trend using the Wald test, treating the lifestyle score as a continuous variable. Third, we investigated how risk differs by adding each factor to the combined score. We presented the risk estimate for the most common lifestyle pattern in each score category. In this case, the factors excluded from the pattern were adjusted in the models. Fourth, we evaluated whether the associations between the score and the risk varied significantly by age at enrollment (<62 vs ≥62 years) and sex by generating a cross-product term in the multivariate model and using the likelihood ratio test. Fifth, we performed a lag analysis excluding those who died or were censored within the second year of follow-up to reduce the influence of subclinical disease on the lifestyle score. We performed sensitivity analyses by excluding participants with self-reported history of cancer or including only individuals with pancreatic cancer identified from cancer registries.

We calculated the age- and energy-adjusted population-attributable risk (PAR) to estimate the percentage of cases that would have been eliminated had all participants adopted the healthiest lifestyle (5 points) or a healthier lifestyle (4-5 points), assuming a causal relationship between the score and risk of pancreatic cancer. The PAR of pancreatic cancer according to each of 3 factors was also calculated.

Statistical analyses were carried out using commercially available software (SAS version 9.0; SAS Institute, Inc, Cary, North Carolina). All P values were based on 2-sided tests, and P < .05 was considered statistically significant.

RESULTS

During a mean (range) of 7.2 (1.0-8.2) years of follow-up, 1057 individuals with pancreatic cancer (675 men and 382 women) were identified. We found no deviations from the proportional hazards assumption for our main exposures and covariates using the Grambsch-Therneau test. In the analyses using the combined lifestyle score and the weighted lifestyle score, we found that the 2 scoring algorithms had high agreement (88% overall) in categorizing participants into the respective score category. The distribution of participants by the combined lifestyle score (0-5 points) was 1.5%, 10.7%, 27.8%, 31.3%, 21.1%, and 7.6%, respectively, and the corresponding distribution for the weighted lifestyle score was 1.5%, 9.3%, 36.3%, 26.4%, 19.0%, and 7.6%. Because the risk estimates based on both algorithms were essentially the same (data not shown), we present the results based on the combined healthy lifestyle score only.

In our study population, 74.6% of participants were nonsmokers, 84.5% had limited alcohol use, 38.8% had healthy dietary quality, 36.9% had normal weight, and 47.5% engaged in regular physical activity (Table 1). Table 2 gives the baseline characteristics of the study participants according to the combined healthy lifestyle score in men and women. Women had a statistically significant higher mean score compared with men (2.86 vs 2.81 points; P < .001). Participants who received a higher score were older, less likely to be African American, and had achieved a higher educational level. A higher combined lifestyle score was related to a lower age-adjusted incident rate, less total energy intake, less total fat and red meat intake, more fruit and vegetable intake, and more folate intake. Family history of any cancer was unrelated to the score.

Table 3 gives the main effect of each factor on pancreatic cancer risk. In all participants, after adjusting for the other risk factors, nonsmoking and normal BMI were associated with statistically significant reduced risk of pancreatic cancer, whereas healthy dietary quality, limited alcohol use, and regular physical activity were related to a nonsignificant re-
Table 2. Mean and Percentage of Baseline Characteristics of Participants According to the Combined Healthy Lifestyle Scorea

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Healthy Lifestyle Score</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No. of participants</td>
<td>263,398</td>
<td>4767</td>
<td>29,157</td>
</tr>
<tr>
<td>Age-adjusted incidence rate</td>
<td>41.8</td>
<td>294.3</td>
<td>59.8</td>
</tr>
<tr>
<td>Age at enrollment, mean, y</td>
<td>62.2</td>
<td>61.0</td>
<td>61.2</td>
</tr>
<tr>
<td>Race/ethnicity, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>93.4</td>
<td>95.0</td>
<td>94.4</td>
</tr>
<tr>
<td>African American</td>
<td>2.3</td>
<td>2.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Never smoker, %</td>
<td>30.8</td>
<td>0.0</td>
<td>7.1</td>
</tr>
<tr>
<td>Educational achievement level, college or postcollege, %</td>
<td>46.1</td>
<td>35.2</td>
<td>34.6</td>
</tr>
<tr>
<td>Married, %</td>
<td>85.4</td>
<td>78.7</td>
<td>81.6</td>
</tr>
<tr>
<td>Family history of any cancer, %</td>
<td>48.4</td>
<td>47.8</td>
<td>48.0</td>
</tr>
<tr>
<td>Dietary intake per day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol, g</td>
<td>17.4</td>
<td>94.5</td>
<td>44.2</td>
</tr>
<tr>
<td>Total energy intake, kcal</td>
<td>2020</td>
<td>2690</td>
<td>2307</td>
</tr>
<tr>
<td>Total fruits, cup/1000 kcal</td>
<td>1.1</td>
<td>0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Total vegetables, cup/1000 kcal</td>
<td>1.0</td>
<td>0.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Total fat, g/1000 kcal</td>
<td>33.5</td>
<td>30.1</td>
<td>34.3</td>
</tr>
<tr>
<td>Saturated fat, g/1000 kcal</td>
<td>10.5</td>
<td>9.9</td>
<td>11.3</td>
</tr>
<tr>
<td>Red meat, g/1000 kcal</td>
<td>37.2</td>
<td>42.5</td>
<td>45.3</td>
</tr>
<tr>
<td>Total folate, pg/1000 kcal</td>
<td>288</td>
<td>197</td>
<td>226</td>
</tr>
<tr>
<td>Fiber, g/1000 kcal</td>
<td>10.3</td>
<td>6.4</td>
<td>7.63</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; PAR, population attributable risk; RR, relative risk.

aAdjusted for age, race/ethnicity, educational achievement level, and marital status. For men and women combined model, adjusted also for sex.
bAdjusted for age, race/ethnicity, educational achievement level, marital status, total energy intake (log-transformed), and other lifestyle factors including smoking status, alcohol use, dietary quality, BMI, and physical activity (binary variable). For men and women combined model, adjusted also for sex.
cPopulation attributable risk of pancreatic cancer according to each single factor in all participants, adjusted for age, total energy intake (log-transformed), and other risk factors including smoking status, alcohol use, dietary quality, BMI, and physical activity (binary variable).

duced risk. We observed a 27% reduced risk with a high no-alcohol aMDS (7-8 points) compared with a low no-alcohol aMDS (0-1 points) (P = .06). The PAR for pancreatic cancer explained by smoking (ie, current smoking and smoking cessation for <10 years) was 14%, which was the largest PAR among the 5 single lifestyle factors.

Table 4 gives the combined healthy lifestyle score in relation to pancreatic cancer risk. Compared with the least healthy score (0 points), the combination of the 5 healthy lifestyle factors (5 points) was statistically significantly associated with a 59% risk reduction (RR [95% CI]) in men (0.41 [0.24-0.71], P_{trend} < .001), a nonsignificant 53% risk reduction in women (0.47 [0.19-1.15], P_{trend} < .001), and a 58% risk reduction in all participants (0.42 [0.26-0.66], P_{trend} < .001). The PAR for pancreatic cancer was 27% for having a combined lifestyle score of less than 5 points. Because there was a relatively smaller number of participants with the lowest and highest scores, we combined the lower (0-1 points) and higher (4-5 points) scores. The RR for having a higher score compared with a lower score was 0.64 (95% CI, 0.45-0.91; P_{trend} = .003) in women. The PAR for pancreatic cancer was 29% for having a combined lifestyle score of fewer than 4 points. The associations between the score and risk of pancreatic cancer did not vary significantly by sex (P_{interaction} = .49) or age (P_{interaction} = .89).

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We identified 32 healthy lifestyle patterns derived from various combinations of the lifestyle score factors. For simplicity, we present the most common pattern in each score category (Table 5). The risk decreased with the addition of each lifestyle factor in the following order: limited alcohol use, nonsmoking, regular physical activity, healthy dietary quality, and normal BMI, when the other factors in the pattern were adjusted in the respective models. The addition of normal BMI to the most common 4-factor pattern (nonsmoking, limited alcohol use, healthy diet quality, and regular physical activity) reduced the risk in women but not in men. However, the association between the lifestyle pattern and risk of pancreatic cancer did not differ by sex (P = .09 - .72, Wald test).

In sensitivity analyses, when 5-point scores were compared with 0-point scores, the RR (95% CI) was 0.39 (0.24-0.62) in a 2-year lag analysis based on 925 cases, 0.40 (0.24-0.64) in an analysis based on 922 cases identified from cancer registries only, and 0.41 (0.25-0.66) in participants without a self-reported history of cancer based on 947 cases.

In this large prospective study in older individuals in the United States, we found that the risk of pancreatic cancer was significantly lower in participants who had the highest combined lifestyle score compared with participants who had the lowest score. Approximately 14% of cases may have been prevented if all participants were nonsmokers, whereas 27% of cases may have been pre-
vented if all participants were nonsmokers and had li-
limited alcohol use, healthy dietary quality, normal weight,
and regular physical activity. There was a significant trend
of risk reduction with increment in the number of healthy
lifestyle factors.

In the analyses of single lifestyle factors, consistent with
findings of previous studies,1,11 nonsmoking and nor-
mal BMI had inverse associations with pancreatic can-
cer. Although nonsmoking showed the strongest effect,
the combination with other factors rendered a further risk
reduction. We found that the lack of further risk reduc-
tion by adding normal BMI to the most common 4-fac-
tor pattern was solely driven by the risk estimate in men
aged 62 years or older. For example, we did not observe
a risk reduction in older men when normal BMI was added
to the less common 3-factor pattern (including nonsmok-
ing, limited alcohol use, and healthy dietary quality),
whereas the risk reduction was observed in younger men
and women regardless of age. We examined alcohol use
as a separate factor because we found that limited alco-
hol use was a significant protective factor for pancreatic
cancer in men. Most epidemiologic studies have not
shown an association between physical activity and pan-
creatic cancer.5 We found that the addition of regular
physical activity to the most common 2-factor pattern
(nonsmoking and limited alcohol use) further reduced
the risk. If these observations are true, it may reflect the
interactions among these lifestyle factors.

Two studies have examined the association between risk
of pancreatic cancer and dietary patterns as determined by
data-driven factor analysis. A population-based study in-
cluding 585 patients and 4779 control individuals showed
a significant inverse association with a high fruit and ve-
getable dietary pattern in men but not in women.18 A pooled
prospective analysis including 366 cases found no asso-
ciation of either a western (high fat and meat intake) or
prudent (high fruit and vegetable intake) dietary pattern
with incident pancreatic cancer.19 We used adherence to
the no-alcohol aMDS to evaluate the diet quality because
in 3 US studies, the Mediterranean dietary pattern has been
associated with reduced risk of colorectal adenoma in
men20,21 and reduced all-cause and cancer mortality.14 We
also observed a reduced risk associated with a high no-
alcohol aMDS. Among the food groups in the Mediterra-
nean diet, fruits and vegetables have been associated with
reduced risk of pancreatic cancer,2 whereas red meat in-
take22 has been associated with increased risk.

Several studies have shown the beneficial effects of
adopting a healthy lifestyle on total mortality23 and coro-
nary heart disease.23 To our knowledge, no study has
evaluated the combined lifestyle factors in relation to can-
cer incidence. The mechanism by which the combined
factors reduce risk of pancreatic cancer likely involves
multiple pathways. For example, lifestyle with nonsmok-
ing would mean less exposure to tobacco carcinogens.24
Inflammation may be a common etiologic factor for
chronic diseases, which may create a microenvironment
that fosters pancreatic tumor growth.25 Alternati-
vatively, the combined healthy lifestyle could influence
pancreatic cancer risk via energy balance.26,27

The strengths of the present study include the large
sample size, the prospective study design, and a wide range
of dietary intake and detailed exposure information. Health
behaviors are complex and consist of multiple di-
mensions; thus, using a lifestyle pattern analysis may cap-
ture the influence of multiple health behaviors better than
an analysis based on single health behaviors. We ob-
served a stronger risk reduction in the lifestyle pattern-
based analysis than that observed in a single risk factor–
based analysis, which would support the use of lifestyle
pattern in risk assessment. The use of the simple score
algorithm facilitated study interpretation and provided
equivalent risk estimates compared with the weighted life-
style score, which considers the unequal contribution of
each factor in risk reduction in various lifestyle pat-
terns. Our study findings may be generalizable to other
study settings and could have implications for the pre-
vention of other lifestyle-related cancers.

The present study has some limitations. First, to pro-
duce an adequate number of participants in each of 32
lifestyle patterns, we dichotomized 5 factors to main-
tain a lower data dimension. However, the dichotomi-
zation could result in loss of study power. The cutoff
points we used were based on public health recommenda-
tions rather than pancreatic cancer–specific cutoff
points. This could further reduce the magnitude of as-
sociations and result in loss of study power. Second, we
had only 1 baseline measure of the factors that contrib-
uted to our healthy lifestyle score, which did not take into
account lifestyle changes before or after assessment. Third,
the combined score did not include all possible life-
styles, occupational exposure, or medical history that
could be risk factors for pancreatic cancer. With these
additional factors, the PAR might be larger and the pre-
diction of pancreatic cancer might be stronger. Our study
findings should be confirmed in other studies with re-
fined exposure information to give a comprehensive eval-
uation of lifestyle patterns and pancreatic cancer risk.

In conclusion, the combined healthy lifestyle factors
including nonsmoking, adherence to US alcohol use
recommendation, healthy dietary quality as defined by
adherence to the Mediterranean diet pattern excluding
alcohol consumption, normal weight, and regular
physical activity may have direct implications for pan-
creatic cancer prevention in older individuals in the
United States. Although further searching for cancer-
causing factors or mechanisms may contribute to inno-
vative preventive strategies, the examination of
combined known modifiable factors in cancer risk
assessment is an appropriate way to translate analytic
epidemiologic findings to primary cancer prevention,
especially for the prevention of pancreatic cancer for
which both early diagnosis and effective treatment
remain challenging.

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the data in the study and takes full responsibility for the
integrity of the data and the accuracy of the data analysis. Drs Mitrou and Reedy contributed equally to this study. **Study concept and design:** Jiao, Mitrou, Reedy, Hollenbeck, Schatzkin, and Stolzenberg-Solomon. **Acquisition of data:** Jiao, Hollenbeck, Schatzkin, and Stolzenberg-Solomon. **Analysis and interpretation of data:** Jiao, Mitrou, Reedy, Graubard, Schatzkin, and Stolzenberg-Solomon. **Drafting of manuscript:** Jiao, Mitrou, Reedy, and Stolzenberg-Solomon. **Critical revision of the manuscript for important intellectual content:** Jiao, Mitrou, Reedy, Graubard, Hollenbeck, Schatzkin, and Stolzenberg-Solomon. **Obtained funding:** Hollenbeck and Schatzkin. **Administrative, technical, and material support:** Hollenbeck, Schatzkin, and Stolzenberg-Solomon. **Study supervision:** Schatzkin and Stolzenberg-Solomon.

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