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Nut consumption and risk of pancreatic cancer in women

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Background: Increasing nut intake has been associated with reduced risk of diabetes mellitus, which is a risk factor for pancreatic cancer.

Methods: We prospectively followed 75680 women in the Nurses' Health Study, and examined the association between nut consumption and pancreatic cancer risk. Participants with a previous history of cancer were excluded. Nut consumption was assessed at baseline and updated every 2 to 4 years. Relative risks (RRs) and 95% confidence intervals (95% CIs) were estimated using Cox proportional hazards models.

Results: We documented 466 incident cases of pancreatic cancer. After adjusting for age, height, smoking, physical activity, and total energy intake, women who consumed a 28-g (1 oz) serving size of nuts ≥ 2 times per week experienced a significantly lower risk of pancreatic cancer (RR, 0.65; 95% CI, 0.47–0.92; *P* for trend = 0.007) when compared with those who largely abstained from nuts. The results did not appreciably change after further adjustment for body mass index (BMI) and history of diabetes mellitus (RR, 0.68; 95% CI, 0.48–0.95; *P* for trend = 0.01). The inverse association persisted within strata defined by BMI, physical activity, smoking, and intakes of red meat, fruits, and vegetables.

Conclusion: Frequent nut consumption is inversely associated with risk of pancreatic cancer in this large prospective cohort of women, independent of other potential risk factors for pancreatic cancer.

Pancreatic cancer is among the most fatal malignancies, representing the fourth most common cause for cancer-related mortality in the United States (Jemal *et al*, 2010). Primary prevention remains the most feasible approach to reducing the incidence of pancreatic cancer, which makes the identification of modifiable risk factors essential. Unfortunately, very few modifiable risk factors have been identified. The 2009 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report concluded that, beyond cigarette smoking, body fatness was the only convincing modifiable risk factor for pancreatic cancer (WCRF/AICR, 2009).

Extensive evidence suggests that common states of insulin resistance such as obesity (Larsson *et al*, 2007) are associated with

an increased risk of pancreatic cancer – possibly mediated through chronic hyperglycaemia and hyperinsulinaemia. Type II diabetes mellitus, a potential consequence of pancreatic cancer, is also a risk factor for this fatal disease (Everhart and Wright, 1995; Elena *et al*, 2013). Recent studies demonstrate that elevated baseline plasma insulin and C-peptide significantly increased subsequent pancreatic cancer risk (Stolzenberg-Solomon *et al*, 2005; Michaud *et al*, 2007). Nuts are a rich source of bioactive components such as unsaturated fatty acids, fibre, and magnesium (Brufau *et al*, 2006), which may improve insulin sensitivity (Anderson *et al*, 1987; Paolisso *et al*, 1989; Riserus *et al*, 2009). Data from the National Health and Nutrition Examination Survey (NHANES) found that nut consumption was associated with decreased insulin levels

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(O'Neil *et al*, 2012) and a lower prevalence of abdominal obesity and metabolic syndrome (O'Neil *et al*, 2011). Prospective epidemiologic data have further shown that regular nut consumption is associated with lower risk of type II diabetes (Jiang *et al*, 2002; Villegas *et al*, 2008). Because diabetes is a consistent risk factor for pancreatic cancer, and insulin resistance is an important underlying mechanism (Giovannucci and Michaud, 2007), we investigated prospectively the association between nut consumption and risk of pancreatic cancer in a large cohort of women in the Nurses' Health Study (NHS).

MATERIALS AND METHODS

Study population. The NHS began in 1976 when 121 700 US female nurses aged 30–55 years returned the initial questionnaire. In 1980, the questionnaire was expanded to include a validated semiquantitative food frequency questionnaire (Willett *et al*, 1985). Follow-up questionnaires were sent to participants every 2 years to update information on new disease diagnoses and potential risk factors for chronic diseases. The overall follow-up rate exceeded 90%.

For the present analysis, follow-up started in 1980 when dietary information was first assessed. At baseline, 92 468 women completed the dietary questionnaire. We excluded 3670 women who had a history of cancer, 1141 women who did not provide information on nut intake, and 11 977 women who did not provide information on anthropometric measures or physical activity, or reported implausible nutritional information (>9 missing food items or estimated daily energy intake <500 kcal or >3500 kcal). After these exclusions, 75 680 women were eligible for the analyses. This study was approved by the Human Research Committee at the Brigham and Women's Hospital.

Dietary assessment. Dietary intake was obtained from the NHS participants via validated semiquantitative food frequency questionnaires in 1980, 1984, 1986, and every 4 years thereafter. Participants were asked to report their average frequency of intake over the preceding year for a specified serving size of each food. Individual nutrient intakes (e.g., vitamin D intake) were calculated by multiplying the frequency of each food consumed by the nutrient content of the specified portion size and then summing the contributions from all foods.

In the 1980 and 1984 dietary questionnaires, we asked the participants how often, on average, they had consumed nuts (peanut butter not included; serving size, 28 g (1 oz)) over the preceding year: never/almost never, 1 to 3 times a month, once a week, 2 to 4 times a week, 5 to 6 times a week, once a day, 2 to 3 times a day, 4 to 6 times a day, or more than 6 times a day. In the 1986, 1990, 1994, 1998, 2002, and 2006 dietary questionnaires, the question for nuts was split into two items: peanuts and other nuts. Total nut consumption was the sum of peanuts and other nuts intake. A validation study of the food frequency questionnaires in the NHS indicated that nut intake was reported with reasonable accuracy; the correlation coefficient was 0.75 between nut intakes assessed by the 1980 questionnaire and by dietary records collected over 4 weeks (Salvini *et al*, 1989).

Identification of pancreatic cancer cases. Participants were asked to report specified medical conditions, including cancers, that were diagnosed in the 2-year period between each follow-up questionnaire. Whenever a participant (or next of kin for decedents) reported a diagnosis of pancreatic cancer, we asked for permission to obtain the participant's medical records. We also searched the National Death Index to identify deaths among nonrespondents. This method has been shown to capture >98% of deaths (Rich-Edwards *et al*, 1994). If the primary cause of death on the death certificate was a previously unreported pancreatic cancer

case, we contacted a family member to obtain permission to retrieve medical records. Study physicians who were blinded to participants' risk factor status reviewed medical records and assigned cancer diagnoses and causes of death. In the NHS cohort, all medical records had complete information on histology (hospitals were recontacted if the original information sent was incomplete). We were able to obtain pathology reports confirming the diagnosis of pancreatic cancer for 91% of cases. For the other 9% of cases, we obtained confirmation of the self-reported cancer from a secondary source (e.g., death certificate, physician, or telephone interview of a family member). In our analyses, associations were examined including and excluding cases confirmed by secondary sources; because no differences were observed between these two types of analyses, we included cases confirmed by secondary sources.

Assessment of nondietary factors. At baseline and in all subsequent questionnaires, women were asked about their history of active smoking, including smoking status, time since quitting, and average number of cigarettes smoked daily. Information on physical activity was assessed at baseline and updated every 2 to 4 years. Body mass index (BMI) was calculated from height self-reported at baseline and weight updated every 2 years. Because pancreatic cancer is frequently associated with profound weight loss, we added a 4-year lag period when we updated BMI during follow-up, that is, we used BMI data from the 1976 questionnaire for the follow-up period from 1980 to 1982, 1978 for the interval from 1982 to 1984, 1980 for the interval from 1984 to 1986, and so forth.

Statistical analysis. We computed person-time from the return date of the 1980 questionnaire to the date of pancreatic cancer diagnosis, death from any cause, or the end of follow-up (30 June 2010), whichever came first. We calculated the cumulative average of dietary factors from all dietary questionnaires, using methods for repeated measures described previously (Hu *et al*, 1997). Briefly, we used data from the 1980 questionnaire for the follow-up period from 1980 to 1984, the average of 1980 and 1984 for the interval from 1984 to 1986, and the average of 1980, 1984, and 1986 for the interval from 1986 to 1990, and so forth. For analysis of total nuts, we divided women into four categories according to their frequency of nut consumption: never/almost never (the reference group), 1 to 3 times a month, once a week, and at least 2 times a week. For separate analysis of peanuts and other nuts, we divided women into three categories: never/almost never (the reference group), 1 to 3 times a month, and at least once a week. Relative risks (RRs) and 95% confidence intervals (CIs) were estimated by Cox proportional hazards models.

In multivariate analyses, we adjusted for potential confounding variables including age, height (quintiles), physical activity (quintiles), smoking (never; past; current 1–14 pack-years; current 15–24 pack-years; current ≥ 25 pack-years), and total energy intake. We then adjusted for BMI (quintiles) and diabetes (yes/no), to see if the observed association was independent of these potential mediators or confounding factors for the association between nut intake and pancreatic cancer risk. We further adjusted for dietary factors including alcohol (never, 0.1–4.9, 5–14.9, and ≥ 15 g day⁻¹), multivitamin use (yes/no), and intakes of red meat, fruits, and vegetables, and vitamin D (quintiles). As nut is often considered a component of the Mediterranean dietary pattern and a recent study showed an inverse association between the Mediterranean diet and pancreatic cancer risk (Bosetti *et al*, 2013), we additionally adjusted for a Mediterranean diet score (Trichopoulou *et al*, 2003) in a sensitivity analysis to examine whether the association with nuts is independent of the Mediterranean dietary pattern. The *P*-values for trend were calculated by the Wald test of a score variable that contained median values of intake categories.

To test the robustness of our results, we conducted a sensitivity analysis excluding individuals with diabetes. To rule out any effect of subclinical pancreatic cancer on nut intake, we performed an additional analysis in which we added a 4-year lag period between nut intake assessment and each follow-up period (follow-up started in 1984 for this analysis), that is, we used nut intake from the 1980 questionnaire for the follow-up period from 1984 to 1988, the cumulative average of nut intake in 1980–1984 for the interval from 1988 to 1992, and so forth.

To examine whether the association between nut intake and risk of pancreatic cancer was modified by other factors, we examined the association in subgroups defined by BMI, physical activity, smoking status, and intakes of red meat, fruits, and vegetables. Tests for interaction were performed by the Wald test of cross-product terms. All statistical analyses were performed with the SAS 9.1 statistical package (SAS Institute, Cary, NC., USA) and all *P*-values are two sided.

RESULTS

During study follow-up, nut consumption remained relatively constant. Women with more frequent nut consumption were generally leaner, more likely to exercise, and less likely to smoke (Table 1). They also tended to consume more alcohol, multivitamin supplements, and fruits and vegetables.

During 2 112 234 person-years of follow up from 1980 to 2010, we documented 466 confirmed incident cases of pancreatic cancer. Frequency of nut consumption was inversely associated with risk of pancreatic cancer (Table 2). Compared with women who largely abstained, participants who consumed a 28-g (1 oz) serving size of nuts ≥ 2 times per week experienced an age-adjusted RR of pancreatic cancer of 0.65 (95% CI, 0.47–0.90; *P* for trend = 0.005) and a multivariate RR of 0.65 (95% CI, 0.47–0.92; *P* for trend = 0.007). The RR did not appreciably change after controlling for BMI and history of diabetes (RR, 0.68; 95% CI, 0.48–0.95; *P* for trend = 0.01). Further controlling for dietary variables, including alcohol, multivitamin use, and intakes of red meat, fruits, and vegetables, and vitamin D, yielded similar results (multivariate RR, 0.68; 95% CI, 0.48–0.96; *P* for trend = 0.01). The results also remained the same when we adjusted for the Mediterranean diet score (multivariate RR, 0.65; 95% CI, 0.46–0.92; *P* for trend = 0.008).

We considered the possibility that occult pancreatic cancer in the years that preceded diagnosis may have influenced dietary patterns. However, our findings remained essentially unchanged after we added a 4-year lag period between nut intake assessment and each follow-up period (multivariate RR, 0.73; 95% CI, 0.52–1.03, comparing ≥ 2 times/week with never/almost never; *P* for trend = 0.03). Moreover, our results remained consistent after excluding women with a history of diabetes mellitus (multivariate RR, 0.67; 95% CI, 0.46–0.96, comparing ≥ 2 times/week with never/almost never; *P* for trend = 0.02).

To examine further the independent association with nut consumption, we repeated the multivariate analyses within subgroups of BMI, physical activity, smoking, and intakes of red meat, fruits, and vegetables (Table 3). An inverse association persisted in all subgroups, and we found no apparent modification of the relation between nut consumption and pancreatic cancer risk by these factors.

In analyses of peanuts and other nuts (assessed in 1986) separately, peanuts and other nuts were both inversely associated with risk of pancreatic cancer, although the associations were not statistically significant. The multivariate RRs comparing ≥ 2 times/week with never/almost never are 0.89 (95% CI, 0.57–1.39; 27 cases) for peanuts and 0.63 (95% CI, 0.39–1.03; 20 cases) for other nuts ($P_{\text{heterogeneity}} = 0.30$).

Table 1. Characteristics of person-years by nut consumption^a

	Frequency of nut consumption (28 g serving)			
	Never/ almost never	1–3 Times per month	Once per week	≥ 2 Times per week
Nut intake, servings per day	0	0.01–0.09	0.10–0.19	≥ 0.20
Person-years	364 282	971 411	388 832	387 709
Age, years, mean (s.d.)	55.8 (10.9)	59.6 (10.9)	60.3 (10.8)	60.9 (10.8)
Height, inches, mean (s.d.)	64.4 (2.4)	64.5 (2.4)	64.6 (2.4)	64.6 (2.4)
Body mass index, kg m ⁻² , mean (s.d.)	25.8 (5.2)	25.8 (5.1)	25.5 (4.9)	24.9 (4.6)
Physical activity, metabolic equivalents per week, mean (s.d.)	13.8(20.4)	15.7(21.0)	17.4(22.1)	19.5(25.1)
Current smoking, %	20.7	15.3	13.8	13.5
History of diabetes mellitus, %	7.8	7.1	6.6	6.0
Multivitamin use, %	32.5	42.6	46.5	49.9
Alcohol intake, g day ⁻¹ , mean (s.d.)	5.2 (9.4)	5.6 (9.0)	6.6 (9.4)	7.4 (10.2)
Red meat, servings per day, mean (s.d.)	1.1 (0.7)	1.1 (0.6)	1.1 (0.6)	1.1 (0.6)
Vegetables, servings per day, mean (s.d.)	2.3 (1.2)	2.6 (1.2)	2.8 (1.2)	3.0 (1.3)
Fruits, servings per day, mean (s.d.)	2.0 (1.2)	2.1 (1.1)	2.3 (1.2)	2.5 (1.3)

^aAll variables (except age) are age standardised.

DISCUSSION

In this large prospective cohort of women, frequent nut consumption was associated with a significantly reduced risk of pancreatic cancer, independent of established or suspected risk factors for pancreatic cancer including age, height, obesity, physical activity, smoking, diabetes, and dietary factors. Women who consumed a 28-g (1 oz) serving size of nuts ≥ 2 times per week had a significantly lower risk of pancreatic cancer, and the inverse association persisted in all subgroup analyses.

To our knowledge, this represents the first study to prospectively assess the association between nut consumption and pancreatic cancer risk. Although a previous case-control study found no association between combined intake of 'nut and tasty snacks' and risk of pancreatic cancer, the analysis was limited by its retrospective design, use of proxy next-of-kin respondents, assessment of diet within 1 year of diagnosis, and lack of data on nut intake exclusive of other snack foods (Bueno de Mesquita *et al*, 1991).

To date, no specific dietary factor or nutrient has been conclusively associated with the risk of pancreatic cancer (WCRF/AICR, 2009). Nut consumption could influence pancreatic cancer risk through several potential mechanisms, most notably

Table 2. Relative risks (RRs) and 95% confidence intervals (CIs) for pancreatic cancer according to nut consumption

	Frequency of nut consumption (28 g serving)				<i>P</i> _{trend}
	Never/almost never	1–3 Times per month	Once per week	≥2 Times per week	
Nut intake, servings per day	0	0.01–0.09	0.10–0.19	≥0.20	
Cases	75	236	78	77	
Person-years	364 282	971 411	388 832	387 709	
Age adjusted	1.00	0.85 (0.65–1.10)	0.67 (0.49–0.93)	0.65 (0.47–0.90)	0.005
Multivariate I ^a	1.00	0.86 (0.66–1.13)	0.68 (0.49–0.94)	0.65 (0.47–0.92)	0.007
Multivariate II ^b	1.00	0.87 (0.67–1.14)	0.70 (0.50–0.97)	0.68 (0.48–0.95)	0.01
Multivariate III ^c	1.00	0.90 (0.69–1.18)	0.71 (0.51–0.99)	0.68 (0.48–0.96)	0.01

^aAdjusted for age, height (quintiles), physical activity (quintiles), smoking (never; past; current 1–14 pack-years; current 15–24 pack-years; current ≥25 pack-years), and total energy intake.
^bMultivariate I + body mass index (BMI; quintiles) and history of diabetes mellitus (yes/no).
^cMultivariate II + dietary variables including alcohol (never, 0.1–4.9, 5–14.9, and ≥15 g day⁻¹), multivitamin use (yes/no), and intakes of red meat, fruits and vegetables, and vitamin D (quintiles).

Table 3. Multivariate relative risks (RRs) and 95% confidence intervals (CIs) for pancreatic cancer according to nut consumption, stratified by risk factors^a

	Frequency of nut consumption (28 g serving)						<i>P</i> _{trend}	<i>P</i> _{interaction}
	Cases	Person-years	Never/almost never	1–3 Times per month	Once per week	≥2 Times per week		
Nut intake, servings per day			0	0.01–0.09	0.10–0.19	≥0.20		
Body mass index								0.26
<25 kg m ⁻²	201	1 160 296	1.00	0.93 (0.61–1.42)	0.75 (0.45–1.24)	0.86 (0.53–1.41)	0.50	
≥25 kg m ⁻²	265	951 938	1.00	0.88 (0.62–1.25)	0.68 (0.44–1.04)	0.57 (0.36–0.91)	0.01	
Physical activity								0.97
≤9.5 Metabolic equivalents per week	236	1 148 936	1.00	1.17 (0.76–1.80)	1.03 (0.63–1.70)	0.80 (0.47–1.34)	0.09	
>9.5 Metabolic equivalents per week	230	963 298	1.00	0.70 (0.50–0.99)	0.49 (0.31–0.78)	0.61 (0.39–0.96)	0.05	
Smoking								0.76
Never	188	960 486	1.00	0.76 (0.50–1.15)	0.65 (0.39–1.08)	0.54 (0.32–0.93)	0.03	
Ever	278	1 151 748	1.00	0.93 (0.66–1.32)	0.71 (0.46–1.09)	0.77 (0.49–1.19)	0.14	
Red meat consumption								0.26
≤1.0 Servings per day	294	1 058 710	1.00	1.00 (0.71–1.41)	0.65 (0.42–1.01)	0.70 (0.45–1.08)	0.02	
>1.0 Servings per day	172	1 053 524	1.00	0.71 (0.46–1.11)	0.75 (0.45–1.24)	0.64 (0.37–1.09)	0.22	
Vegetable consumption								0.30
≤2.5 Servings per day	195	1 066 486	1.00	0.78 (0.89–1.75)	0.51 (0.75–1.79)	0.58 (0.50–1.25)	0.02	
>2.5 Servings per day	271	1 045 748	1.00	1.02 (0.67–1.55)	0.88 (0.55–1.40)	0.82 (0.51–1.31)	0.18	
Fruit consumption								0.33
≤2.0 Servings per day	211	1 058 444	1.00	0.85 (0.59–1.24)	0.78 (0.48–1.25)	0.78 (0.47–1.29)	0.36	
>2.0 Servings per day	255	1 053 790	1.00	0.91 (0.61–1.34)	0.65 (0.41–1.03)	0.62 (0.39–0.98)	0.01	

^aAdjusted for the same covariates as multivariate II in Table 2.

insulin resistance and hyperinsulinaemia. Prospective observational studies have reported increased risk of pancreatic cancer among subjects with higher circulating insulin (Stolzenberg-Solomon *et al*, 2005) or C-peptide (Michaud *et al*, 2007) and among those with a history of type II diabetes (Everhart and Wright, 1995; Elena *et al*, 2013). Concurrently, studies have found that increasing nut intake was associated with decreased insulin levels (Estruch *et al*, 2006; Jenkins *et al*, 2006; Tapsell *et al*, 2009; Casas-Agustench *et al*, 2011b; O'Neil *et al*, 2012) and lower risk of

developing metabolic syndrome (Salas-Salvado *et al*, 2008; Fernandez-Montero *et al*, 2013). Furthermore, some (Jiang *et al*, 2002; Villegas *et al*, 2008), though not all (Parker *et al*, 2003), prospective studies have shown that regular nut consumption was inversely associated with the risk of type II diabetes mellitus. In a previous analysis of this same cohort, higher nut consumption was associated with lower risk of type II diabetes (multivariate RR comparing ≥5 times per week with almost never = 0.73; 95% CI, 0.60–0.89; *P* for trend <0.001) (Jiang *et al*, 2002). Similarly, a

prospective, Chinese cohort of 64 227 women found an inverse association between peanut consumption and risk of type II diabetes (multivariate RR comparing extreme quintiles = 0.80; 95% CI, 0.68–0.93; *P* for trend < 0.0001) (Villegas *et al*, 2008). Although the underlying mechanisms remain uncertain, nuts are rich in several nutrients associated with improved insulin sensitivity and decreased insulin demand and resistance, including unsaturated fatty acids, fibre, and magnesium (Anderson *et al*, 1987; Paolisso *et al*, 1989; Riserus *et al*, 2009). It is noteworthy that intakes of unsaturated fat, fibre, and magnesium were not associated with pancreatic cancer risk in this (Michaud *et al*, 2003) or other cohorts (Stolzenberg-Solomon *et al*, 2002; Kesavan *et al*, 2010; Molina-Montes *et al*, 2012).

Alternatively, other nutrients and bioactive compounds in nuts, such as vitamins (e.g., folate, niacin, vitamin E) and phytochemicals (e.g., carotenoids, flavonoids, and phytosterols), may confer antioxidant, anti-inflammatory, or anticancer properties (Gonzalez and Salas-Salvado, 2006). Indeed, observational studies and clinical trials have demonstrated beneficial effects of nuts on oxidative stress (Jenkins *et al*, 2006; Torabian *et al*, 2009) and inflammatory markers (Jiang *et al*, 2006). In addition, some studies reported that high serum α -tocopherol, the biologically active form of vitamin E, was associated with a reduced risk of pancreatic cancer (Stolzenberg-Solomon *et al*, 2009). This evidence supports a role of nuts in pancreatic cancer prevention.

There may be a concern that frequent nut consumption may result in weight gain and therefore increase the risk of developing pancreatic cancer. However, in our cohort, women reporting greater nut intake tended to weigh less (Table 1). In fact, nut consumption has been shown to be associated with less weight gain (Bes-Rastrollo *et al*, 2007; Bes-Rastrollo *et al*, 2009; Casas-Agustench *et al*, 2011a). A recent analysis of this same cohort found that higher nut consumption was associated with a slightly lower risk of weight gain and obesity (Bes-Rastrollo *et al*, 2009).

The strengths of this study include its prospective design, large sample size, and > 30 years of follow-up. Our validation data indicate that nut intake was measured reasonably accurately (Salvini *et al*, 1989); in addition, we updated nut consumption repeatedly during follow-up, thereby accounting for true changes in diet and reducing measurement error. Moreover, as dietary data were collected prospectively, any misclassification of exposure should be random, thereby biasing the association towards the null. Although participants with subclinical pancreatic cancer may have decreased their nut consumption, the inverse association persisted when we added a 4-year lag period between nut intake and each follow-up period.

Our study also has limitations. Although we cannot exclude residual confounding by other potential risk factors for pancreatic cancer, our study provided detailed information on the lifestyle and diet of the participants. In our analysis, we adjusted for BMI, physical activity, smoking, diabetes history, and other relevant dietary factors, and the results were virtually unchanged. In addition, the inverse association persisted across all subgroups (e.g., subgroups defined by BMI, physical activity, smoking, red meat, fruits, and vegetables), further suggesting an independent inverse association. Because our study population is relatively homogeneous in education and occupation, confounding by socioeconomic status was minimised. Although we cannot rule out the possibility of confounding by unknown risk factors, it is unlikely that it can fully explain the observed modest association (Flanders and Khoury, 1990).

In conclusion, frequent nut consumption was associated with a reduced risk of pancreatic cancer in this large prospective cohort study of women. Although additional confirmatory studies are warranted, our findings offer potential insights into both the prevention and biology of this highly fatal and poorly understood malignancy.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Dr Bao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Bao and Fuchs; acquisition of data: Hu, Giovannucci, Stampfer, Willett, and Fuchs; analysis and interpretation of data: Bao, Hu, Giovannucci, Wolpin, Stampfer, Willett, and Fuchs; drafting of the manuscript: Bao and Fuchs; critical revision of the manuscript for important intellectual content: Bao, Hu, Giovannucci, Wolpin, Stampfer, Willett, and Fuchs; statistical analysis: Bao and Fuchs; obtained funding: Bao and Fuchs; administrative, technical, or material support: Hu, Giovannucci, Stampfer, Willett, and Fuchs; study supervision: Fuchs.

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