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Dietary choline and betaine intakes and risk of total and lethal prostate cancer in the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Purpose: Two prior cohort studies suggested that choline, but not betaine intake is associated with an increased risk of advanced prostate cancer (PCa). Given that evidence remains limited, we evaluated whether intakes of choline and derivative betaine are associated with total and lethal PCa risk and PCa death in men with PCa.

Methods: We included 6,528 men (24.4% African American) without a cancer diagnosis at baseline (1987–1989) followed through 2012. Dietary intake was assessed using a food frequency questionnaire coupled with a nutrient database. We used Cox proportional hazards regression to estimate hazards ratios (HRs) and 95% confidence intervals (CIs) of total and lethal PCa risk overall and by race.

Results: Choline intake was not associated with total (N=811) or lethal (N=95) PCa risk overall or by race. Betaine intake was inversely associated with lethal (tertile 3 versus 1, HR: 0.59, 95% CI: 0.35–1.00, p-trend=0.04), but not total PCa risk; patterns for lethal PCa were similar by race. Neither nutrient was associated with PCa death in men with PCa.

Conclusions: Choline intake was not associated with total or lethal PCa or with PCa death in men with PCa. Betaine intake was inversely associated with lethal, but not total PCa risk or with

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PCa death in men with PCa. Our results do not support the hypothesis that higher choline intake increases lethal PCa risk, but do suggest that higher betaine intake may be associated with lower lethal PCa risk. Further investigation with a larger number of lethal cases is needed.

Keywords

choline; lethal prostate cancer; incidence; case-fatality; race

INTRODUCTION

Choline is an essential nutrient that is a precursor of phosphatidyl choline (a component of cell membranes) and acetylcholine (a neurotransmitter), and is a component of one-carbon metabolism. Choline deficiency may contribute to carcinogenesis: in an animal model, dietary deficiency caused the development of hepatocarcinoma without any known carcinogen [1]. Choline may affect cancer progression through one-carbon metabolism. Choline, via its derivative betaine, is a methyl donor to homocysteine. From homocysteine, methionine is generated, which is in turn converted into *S*-adenosylmethionine (SAM), the universal methyl donor. The availability of SAM may influence carcinogenesis via altering DNA methylation and disruption of DNA repair [2]. The availability of other nutrients involved in the one-carbon metabolism pathway and SAM production such as folate, vitamin B6, vitamin B12, and methionine may also influence the availability of choline and betaine and thus carcinogenesis [3]. Choline intake may have particular relevance to prostate cancer, especially lethal disease, because choline is more abundant in prostate cancer tissue compared with normal prostate tissue [4,5], and is higher in higher Gleason sum disease compared with lower [4]. Given its abundance, choline is used as a positron emission tomography (PET) scan agent for detecting bone metastases in men with prostate cancer [6,7].

The major food sources of choline are meat, milk, whole eggs, and poultry [8]. Two prospective studies have investigated the association between choline intake or circulating concentration and prostate cancer risk. The Health Professionals Follow-Up Study (HPFS) observed that compared to the bottom quintile, men in the highest quintile of dietary choline, but not betaine intake had a 70% increased risk of lethal prostate cancer [8]. Neither choline nor betaine intake was associated with progression to metastasis or death in men with prostate cancer that was not metastatic at diagnosis. A nested case-control study in Sweden found that higher blood concentration of choline was associated with increased prostate cancer risk; about 25% of cases were high-risk disease [3]. Concentrations of betaine was not associated with prostate cancer risk [3]. While these findings are compelling, the extent of evidence for choline and betaine intake influencing the development of prostate cancer with a total, lethal, and fatal phenotype or the progression of prostate cancer remains limited, and both studies evaluating the associations were conducted in majority white populations.

Thus, to fill knowledge gaps, we evaluated the associations of choline and betaine intake with risk of total, lethal (i.e., incident metastatic or a first primary that resulted in prostate cancer death), and fatal (i.e., prostate cancer death irrespective of whether the diagnosis was a first primary) prostate cancer and with case-fatality in the Atherosclerosis Risk in

Communities (ARIC) study overall and by race. ARIC has a different racial composition of participants compared to the two prior prospective studies [3,8]: in the whole cohort about 27% of men are African American. Based on the results of the two prior studies [3,8], we hypothesized that: 1) higher dietary intake of choline, but not betaine, is associated with an increased risk of lethal and fatal prostate cancer, and that neither is associated with total prostate cancer in men without prostate cancer at baseline; 2) higher intake of dietary choline, but not betaine, is associated with increased case-fatality in men with prostate cancer after taking into account prognostic factors. We also hypothesized that the associations of choline and betaine with these prostate cancer outcomes do not differ between white and African-American men when comparing the same ranges of intakes.

METHODS

Study population

This analysis was conducted in ARIC, a prospective cohort study of 15,792 participants (7,032 men) aged 45 to 64 years old at enrollment between 1987 and 1989. Participants were recruited from Forsyth County, NC, Jackson, MS, Minneapolis, MN, and Washington County, MD [9]. Participants returned for follow-up study visits (1990–1992, 1993–1995, 1996–1998, 2011–2013, 2016–2017). Local institutional review boards approved the ARIC protocol. Informed consent was obtained; the majority (99.7%) of participants gave approval for follow-up for non-cardiovascular diseases.

For the analyses of men at risk for prostate cancer (total, lethal, and fatal), we excluded men who did not consent to non-cardiovascular disease studies (CVD studies; n=22) or who did not link to state cancer registry files (n=28). We excluded men who had prevalent cancer at baseline (n=325) or whose race was other than white or African-American (n=23). We also excluded men who did not sufficiently complete the semi-quantitative food frequency questionnaire (FFQ; missing ≥10 responses to food item questions; n=20) or had missing or extreme energy intake (men ≤600 or ≥4,200 kcal/day; n=136) as done previously [10]. After exclusions, 6,528 men (5,001 white, 1,527 African-American) comprised the analytic cohort.

For the analysis of men with prostate cancer (case-fatality), of the previous 6,528 men, we further restricted to those with a confirmed diagnosis of a prostate cancer during follow-up, irrespective of whether it was the first primary cancer (n=862). We then excluded men who had a diagnosis through death-certificate only (n=7), had missing stage (n=187), or had missing grade (n=27). 641 men (494 white, 147 African-American) comprised the final case-fatality analytic cohort.

Assessment of choline and betaine intake

Dietary intake was assessed by interview during Visits 1 (1987–1989) and 3 (1991–1993) using a modified 66-item Willett FFQ [11,12]. Nine responses for frequency of intake were specified for each food item ranging from “almost never” to “more than 6 times per day”, which were converted into daily intake. Energy and nutrient intakes, including choline and betaine, were calculated for each food using the Harvard University Food Composition

database for the FFQ coupled with data from the US Department of Agriculture [13,14] and daily intakes were summed across foods for each nutrient.

Bidulescu et al. [14] determined the reliability of the FFQ for choline and betaine intake over 3 years among a random sample (N=1,004) of ARIC participants. Similar to other nutrients, reliability coefficients were 0.50 for choline and for choline plus betaine.

Covariates assessment—Participant age, race, and attained education were assessed by interview and height was measured at Visit 1. Weight was measured and cigarette smoking status and physician-diagnosed diabetes status were assessed by interview at each visit. Participants self reported the frequency of routine physical examinations Visit 1, health insurance status at Visit 1, and type of health insurance at Visit 3. Body mass index (BMI, kg/m^2) was calculated from weight and height. For case fatality, all covariates were assessed and categorized in the same way except for age, which was assessed at prostate cancer diagnosis.

Outcomes assessment

Incident prostate cancers were ascertained from 1987 through 2012 by linkage with state cancer registries in Maryland, Minnesota, Mississippi, and North Carolina, and by additional active follow-up of the cohort, including cases diagnosed before these cancer registries were established [15]. Active follow-up included annual follow-up telephone calls, during which participants were asked whether they had been diagnosed with cancer since the last call, and review of hospital discharge summaries. Medical records and pathology reports were requested as appropriate to confirm these cases. All sources of data were adjudicated using standardized protocols. Date of diagnosis, pathologic and clinical TNM stage, and Gleason sum were abstracted from medical records. We adjudicated stage and grade across systems used for recording stage and grade in the multiple sources of cancer data we collected. Lethal prostate cancer was defined as cases with distant metastasis to any organ at diagnosis (pathologic TNM stage 4 or SEER summary stage 3, 4, or 7) or death from a first primary prostate cancer as the underlying cause. Fatal prostate cancer was defined as death from prostate cancer irrespective of whether the diagnosis was a first primary. Case-fatality was defined as death from prostate cancer in men with the diagnosis irrespective of whether prostate cancer was the first primary.

Statistical analysis

Analyses were conducted using SAS 9.4 (Cary, NC). All tests were 2-sided, and a P-value<0.05 was considered to be statistically significant. We used Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) of total, lethal, and fatal prostate cancer. For total and lethal prostate cancer, men contributed person-time at risk from Visit 1 until the outcome of interest, diagnosis of another cancer, death from any cause, or end of follow-up in 2012, whichever came first. For fatal prostate cancer, men contributed person-time at risk from Visit 1 until death from prostate cancer, death from other causes, or end of follow-up in 2012, whichever came first. We energy adjusted choline and betaine intake using the residual method [16]. Intake of energy-adjusted choline, betaine, and their sum were categorized into tertiles. In the main analysis, Visit 1 choline and

betaine intakes were the exposure variables. We also modeled time-varying choline and betaine intakes as well as the cumulative average of Visits 1 and 3 for each of choline and betaine intakes. Model 1 was adjusted for age (continuous), joint categories of race and field center (white from Minneapolis [reference]; white from Washington County; white from Forsyth County; African-American from Jackson; and African-American from Minneapolis or Washington County or Forsyth County), and education (less than high school graduate, high school graduate and vocational school, college graduate and some graduate school). Model 2 was adjusted for model 1 covariates plus purported risk factors for lethal prostate cancer – BMI (continuous; time-varying), height (continuous), cigarette smoking status (current/quit <10 years ago, quit ≥10 years ago, or never; time-varying), and diabetes status (yes, no; time-varying). We tested for trend by entering into the model a continuous term for choline, betaine, or their sum, and evaluated the coefficient using the Wald test. These analyses were repeated separately in African-American and white men.

To test if there was an interaction between the purported risk factors and choline or betaine in association with prostate cancer, we entered into the model main effects terms for choline, betaine, or their sum and for BMI (time-varying), height, smoking (recent, quit ≥10 years ago, or never, time-varying), and diabetes status (yes, no, time-varying) along with a term for their cross-product. The statistical significance of the coefficient for the cross-product term was evaluated by the Wald test. Because of the inter-relation of components in the one-carbon metabolism pathway [10], interaction was tested by entering into statistical models two main effects terms for choline, betaine, or their sum and for folate, methionine, vitamin B6, or B12 along with a term for their cross-product, the coefficient for which was evaluated by the Wald test. Unless otherwise noted, in these interaction models, variables were entered as continuous terms using the median of the tertiles as possible values.

Because dietary intake (Visits 1 and 3) was assessed months to decades before diagnosis of prostate cancer, statistical models were stratified by median follow-up time to assess the influence of possible increasing nondifferential error in the measurement of choline and betaine intake with time since FFQ completion. We expected that if an association were present, it would be stronger in early than in later follow-up.

Finally, to address the possibility of differences in the likelihood of receipt of prostate cancer screening by diet, for total prostate cancer, we a) stratified the analyses by frequency of routine physical examinations (at least every 5 years vs. less frequently), b) restricted to men with health insurance at Visit 1, and c) additionally restricted to men with private health insurance and/or Medicare at Visit 3 (74% of the study population; excluded men without health insurance or on Medicaid only).

For the analysis among men with prostate cancer (case-fatality), a similar approach was used as for the analysis among men at risk for prostate cancer except that we used time since diagnosis as the time scale. Men contributed person-time at risk from date of diagnosis of prostate cancer until death from prostate cancer, death due to other causes, or end of follow-up in 2012, whichever came first. We additionally adjusted for the prognostic factors such as stage and grade and for time from FFQ completion to prostate cancer diagnosis

(continuous). We confirmed that associations did not differ by median time between FFQ completion and diagnosis via stratified analysis.

RESULTS

Total, lethal, and fatal prostate cancer in men at risk for prostate cancer

Mean baseline intake of choline was 313.0 mg/day and of betaine was 85.2 mg/day; intake was similar in white and African-American men. Men in the highest tertile of choline intake had a higher education level and BMI, and were more likely to have diabetes compared with men in the lowest tertile (Table 1); these patterns were similar among white and African-American men. At baseline, the Spearman correlation between choline and betaine was 0.07.

The top ten foods contributing to choline intake were whole and scrambled eggs, red meat, chicken without skin, low fat milk, chicken with skin, fish such as cod, perch, catfish, whole milk, fried food eaten away from home (e.g., fish, chicken, chicken nuggets, etc.), and liver (Table 2). These contributors were similar in white and African-American men, with the exception of mashed potatoes consumption, which was the 7th highest contributor to choline intake in African-American men, but was not among the top 10 contributors for white men. The top ten foods contributing to betaine intake were spaghetti or other pasta, cooked cereals such as oatmeal, grits, cream of wheat, cold cereal, dark or whole grain bread, biscuits or cornbread, white bread, spinach, collards or other greens, butter, sweet potatoes, and coffee. These contributors were similar in white and African-American men, with the exception of sweet potatoes, which was 8th highest contributor to betaine intake in white, and hamburgers, which was the 10th highest contributor to betaine intake in African-American men respectively, but were not among the top 10 contributors overall.

Over a mean follow-up of 18 years, we observed 811 total first primary prostate cancer cases during 118,211 person-years, 95 lethal prostate cancer cases during 118,433 person-years, and 88 fatal prostate cancer cases during 132,309 person-years. Overall, baseline choline intake was not associated with incidence of total, lethal or fatal prostate cancer overall (model 1; Table 3), although compared to the first tertile, the second tertile of baseline choline intake was associated with increased total prostate cancer risk (HR: 1.22 [95% CI: 1.03–1.44]) . These HRs were similar in white men, although in African-American men, the HRs for lethal and fatal disease appeared inverse, albeit not statistically significant. After additionally adjusting for purported prostate cancer risk factors (model 2), baseline choline intake was not associated with incidence of total, lethal or fatal prostate cancer overall or in white or African-American men.

Baseline betaine intake was inversely associated with incidence of lethal and fatal prostate cancer, but not total prostate cancer overall. Such inverse associations were also seen for lethal and fatal prostate cancer in white and African-American men (Table 4). Betaine intake was also inversely associated with total prostate cancer in white, but not African-American men. These patterns were not appreciably changed after further multivariable adjustment (model 2). Statistical interaction between betaine and race was not detected (all p-interaction>0.05). The sum of choline and betaine was also not associated with total, lethal,

or fatal prostate cancer overall or in white or African-American men including after multivariable adjustment (Table 5).

When stratified by median person-time contributed by total (12.7 years), lethal (9.5 years), and fatal (18.0 years) cases, results (null) for choline intake and the sum of choline and betaine intake were not appreciably different in early follow-up (less than or equal to the median) and in later follow-up (greater than the median) for each outcome overall or by race. For betaine intake, associations were null in later follow-up for each outcome overall or by race, although we could not rule out inverse associations in early follow-up (lethal: p-trend=0.03, fatal: p-trend=0.04) overall, but not by race.

We repeated the analyses for choline and betaine using time-varying and cumulative average intake (Visits 1 and 3 FFQs). Associations were similar to that of baseline intake, therefore, we only present the results for baseline intake.

Statistical interaction was not detected between BMI, height, smoking, diabetes, or intake of components of one carbon metabolism (methionine, vitamin B6, and vitamin B12) and intake of choline, betaine, or their sum in association with risk of total, lethal, or fatal prostate cancer (Supplement Table 3), with two exceptions. We noted statistical interaction between folate and choline (p=0.03) and sum of choline and betaine (p=0.02). When stratifying by folate tertile, choline and sum of choline and betaine appeared to be inversely associated with total prostate cancer risk among men in the highest tertile of folate intake (choline: p-trend=0.06; sum of choline and betaine: p-trend=0.02), but not associated among men in the middle and lowest tertile of folate intake.

Associations for choline and betaine did not notably differ from overall by frequency of routine physical examinations, when restricted to men with health insurance at Visit 1, or when additionally restricted to men with private health insurance and/or Medicare at Visit 3 (data not shown).

Death from prostate cancer in men with prostate cancer (case-fatality)

Mean pre-diagnostic (Visit 1) choline intake was 324.2 mg/day overall and was similar in white and African-American men. Mean pre-diagnostic betaine intake was 84.6 mg/day overall, and was similar in white and African-American men.

Men in the highest tertile of choline intake had higher BMI and were more likely to have diabetes compared with men in the lowest tertile, patterns that were generally similar by race (Supplement Table 1). In 5,374 person-years, we observed 52 deaths from prostate cancer as the underlying cause in men with the diagnosis, of which 41 deaths were in white and 11 were in African-American men. Due to the small numbers in African-American men, we report only on overall and in white men.

Pre-diagnostic intakes of choline, betaine, and the sum of choline and betaine were not associated with case-fatality overall or in white men (models 1 and 2; Supplement Table 2). Results were comparable in those with longer and shorter times between FFQ completion and prostate cancer diagnosis (stratified at median of 14.5 years) in all men and in white men.

DISCUSSION

In this prospective study, choline intake was not consistently associated with risk of total, lethal, or fatal prostate cancer overall or in white or African-American men. However, betaine intake was statistically significantly inversely associated with risk of lethal prostate cancer and fatal prostate cancer overall, and suggestively inversely associated in both white and African-American men. Betaine was also modestly inversely associated with total prostate cancer in white, but not African-American men. No interactions between components of one carbon metabolism and choline or betaine were observed aside from an interaction between folate and choline and sum of choline and betaine with total prostate cancer only. Neither pre-diagnostic choline nor betaine intake was associated with case-fatality. Given the small number of cases that were lethal and fatal, further investigation in studies with larger numbers is needed.

We studied choline and betaine intake in the context of carcinogenesis because these can serve as methyl donors in one-carbon metabolism, which can affect DNA methylation in vivo [17]. Adequate intake for choline for men aged over 19 years as established by the Institute of Medicine is 550 mg/day [18]. In HPFS study, median intake of choline was about 385 mg/day (using the Willett FFQ with ~140 items) [8]. Median intake in the current study was about 313 mg/day (using the Willett 66-item FFQ). Intakes may not be comparable between the two studies because of differences in number of FFQ items. In the nationally representative National Health and Nutrition Examination Survey 2009–2012, using data from dietary recall interviews, median choline intake in men aged 50–70 years old was 395 mg/day (inter-quartile range 324–476 mg/day) [19]. Inadequate intake of dietary choline and betaine could increase the probability of DNA global hypomethylation as well as regional hypomethylation of oncogenes and prometastatic genes [20], which could further raise cancer risk. On the other hand, excessive choline intake could induce regional hypermethylation of tumor suppressor genes [20], which predisposes an individual to neoplasm development. Furthermore, due to the inter-relation of choline and other components of one carbon metabolism, the associations between dietary choline intake, DNA methylation and cancer outcomes are complicated [21,22].

Our findings differ notably from the two prospective studies that found positive associations between dietary intake (positive dose-response) [8] or blood concentrations (highest versus lowest categories) [3] of choline and (advanced) prostate cancer. While in ARIC, we did observe that men in the middle versus bottom tertile had a higher risk of total prostate cancer, we did not observe this for the top tertile or for lethal or fatal prostate cancer. Our findings also differ from both of the prior studies, which reported no association for betaine overall [3], although in the study on blood concentrations, a positive association was noted for betaine among men 55 years and older, but not younger [3]. We cannot rule out differences in intake or sufficiency of intake of choline, betaine, and other components of the one-carbon metabolism pathway, both from diet and supplements, at baseline or during follow-up as explanatory. Due to the complexity of one-carbon metabolism, more research is needed to identify differences in association among studies.

We did not expect to observe an inverse association between betaine and lethal prostate cancer given the prior findings[8,3]. A few studies have reported that higher plasma betaine concentration was associated with a lower risk of colorectal cancer (CRC) among those with low plasma folate concentration (<11.3 nmol/L) [23], and that higher dietary betaine intake was associated with a decreased lung cancer risk [24]. Our findings are consistent in the direction of the association between betaine and other cancers. However, we cannot rule out the possibility that the inverse association for betaine is due to bias or due to chance related to a small number or lethal and fatal cases.

Strengths of this study include the prospective analysis; inclusion of white and African-American men; and confirmed prostate cancer outcomes. The study also has some limitations. First, while we adjusted for confirmed and purported prostate cancer risk factors, including those specific to lethal disease, we cannot rule out residual confounding. Second, we were not able to account for variations in cooking methods, which may influence choline and betaine content. Third, the FFQ was administered at two ARIC visits; it is unclear whether these time points in middle and older may relate to the etiologically relevant time points for the development and progression of prostate cancer. Fourth, although in ARIC the reliability coefficients were 0.50 for choline and for choline plus betaine, we did not determine the validity of the method we used to estimate choline and betaine intake and we cannot rule out the possibility of participants' inaccurate recall of food intake substantially attenuated the association. Fifth, we included only dietary intake of choline and betaine as use of choline and betaine supplements at Visits 1 and 3 was not collected. Sixth, we did not have the power to detect moderate to small associations. For example, with 80% power for a 2-sided test with alpha=0.05, we could detect as statistically significant an HR of lethal prostate cancer of 2.23 or higher. However, the HR reported in HPFS was 1.70, thus we did not have sufficient power to detect that effect size. Power was also limited to detect effect modification by purported risk factors and one-carbon metabolism components. While we did observe statistically significant interactions between folate and choline and the sum of choline and betaine with total prostate cancer, given the number of tests we performed we cannot rule out chance as an explanation. Finally, although information on PSA screening history was not collected, we observed little differences in the associations for choline and betaine with total prostate cancer by frequent versus infrequent routine physical examinations (which are the usual time when prostate cancer screenings are done) or when restricting to those with health insurance. However, we cannot rule out differences in screening intensity by intake of these nutrients.

With respect to the analysis among men with prostate cancer (case-fatality), we could not study post-diagnosis intake of choline and betaine because the majority of cases were diagnosed after Visit 4 and the FFQs were administered earlier. Relatedly, it is possible that participants changed their diet after their diagnosis, and if so, it is possible that we did not capture the etiologically relevant diet. It is possible that participants changed their diet between when we assessed diet and the date of diagnosis and given median time of 14.7 years, and if so, non-differential measurement error could be an explanation for the null association for these nutrients for those with shorter and longer times between assessment and diagnosis. Finally, the number of men with prostate cancer and the number of prostate

cancer deaths was small, so that we cannot rule out chance as an explanation for these null results.

In summary, in this prospective study, dietary choline intake was not associated with prostate cancer risk, while intake of betaine, a choline derivative, was inversely associated with risk of lethal and fatal prostate cancer, possibly in both white and African-American men. Neither pre-diagnostic choline or betaine intakes were associated with case-fatality. More research is needed with a larger number of lethal and fatal cases to elucidate the role of these two important nutrients in clinically important prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Age-adjusted baseline characteristics by tertile of energy-adjusted choline intake (mg/day),[a] 6,528 men in ARIC, 1987–1989

Characteristic	Tertile of energy-adjusted choline intake		
	1 (59.7–281.1)	2 (281.1–345.1)	3 (345.2–887.5)
N	2,176	2,176	2,176
Age, mean (y)	54.1	54.7	54.8
African American (%)	20.2	21.0	29.0
Education (%)			
Less than high school graduate	26.4	22.8	23.1
High school graduate, vocational school, some college	38.9	34.9	35.1
College graduate or beyond	34.7	42.3	41.8
BMI, mean (kg/m^2)	27.1	27.5	27.9
Height, mean (cm)	175.8	176.1	176.2
History of diabetes (%)	3.6	6.1	12.1
Cigarette smoking status (%)			
Recent (current or quit <10 yrs ago)	46.9	42.1	42.0
Quit ≥10 years ago	27.5	29.6	28.0
Never	25.6	28.3	30.0
Physical activities (%)			
Meet recommendation	41.6	47.6	44.9
Not meet recommendation	58.4	52.4	55.1
Routine physical exam performed (%)			
Frequent	55.8	62.8	64.4
Not frequent	44.2	37.2	35.6
Baseline insurance status (%)			
Yes	90.7	91.6	90.7
No and missing	9.3	8.4	9.3
Visit 3 insurance status (%)			
Yes (Prepaid health insurance or health plan, Medicare)	75.4	77.1	73.8
No (no insurance or Medicaid only) and missing	24.6	22.9	26.2

Characteristic	Tertile of energy-adjusted choline intake		
Energy-adjusted intake, mean			
Choline (mg/day)	235.3	313.0	406.3
Betaine (mg/day)	78.2	85.2	91.0
Choline + betaine (mg/day)	304.9	388.7	487.3
Methionine (g/day)	1.3	1.7	2.0
Vitamin B6 (mg/day)	1.5	1.7	1.8
Vitamin B12 (μg/day)	6.2	7.7	9.3
Folate (μg/day)	207.8	231.7	240.9
Calcium (mg/day)	560.5	651.1	724.2

[a] All variables (except age and choline) were age adjusted.

Table 2.

Top 10 food contributors to dietary intake of choline and betaine, 6,528 men in ARIC, 1987–1989

Choline		
Rank	**Food group**	**% of nutrient**
1	Egg	12.2
2	Beef, pork, lamb at side dish	9.7
3	Beef, pork, lamb at main dish	9.2
4	Chicken or turkey, without skin	7.8
5	Low fat milk	5.9
6	Consumed chicken with the skin	4.5
7	Fish such as cod, perch, catfish	3.8
8	Consumed whole milk	3.3
9	Consumed food fried away from home, such as fish/chicken/chicken nuggets	2.9
10	Consumed liver	2.5
Betaine		
Rank	**Food group**	**% of nutrient**
1	Consumed spaghetti or other pasta	12.1
2	Consumed cooked cereals such as oatmeal, grits, cream of wheat	11.0
3	Consumed cold breakfast cereals	9.0
4	Consumed dark or whole grain bread	7.6
5	Consumed biscuits or cornbread	7.3
6	Consumed white bread	6.8
7	Consumed spinach, collards or other greens	4.2
8	Consumed butter	4.2
9	Consumed sweet potatoes	3.9
10	Consumed coffee	3.3

Table 3.

Association between tertiles of baseline energy-adjusted choline intake (mg/day) and total, lethal, and fatal prostate cancer in all men and by race, 6,528 men in ARIC, 1987–2012

Outcome	Group		Tertile of energy-adjusted choline intake			p-trend[a]
			1 (59.7–281.1)	2 (281.1–345.1)	3 (345.2–887.5)	
Total prostate cancer	All	Events	238	309	264	
		Person-years	39970	39770	38472	
		Model 1, (HR)[b]	1.00	1.22 (1.03–1.44)	1.01 (0.84–1.21)	1.0
		Model 2, (HR)[c]	1.00	1.22 (1.03–1.45)	1.02 (0.85–1.22)	0.8
	White	Events	172	215	164	
		Person-years	32414	32092	28519	
		Model 3, (HR)[d]	1.00	1.18 (0.96–1.44)	1.02 (0.82–1.27)	0.9
		Model 4, (HR)[e]	1.00	1.17 (0.96–1.43)	1.01 (0.81–1.26)	0.9
	African American	Events	66	94	100	
		Person-years	7555	7678	9953	
		Model 3, (HR)	1.00	1.33 (0.97–1.83)	1.01 (0.73–1.39)	0.8
		Model 4, (HR)	1.00	1.37 (0.99–1.88)	1.07 (0.77–1.47)	0.5
Lethal prostate cancer	All	Events	29	34	32	
		Person-years	40027	39816	38590	
		Model 1, (HR)	1.00	1.02 (0.62–1.69)	0.86 (0.51–1.44)	0.3
		Model 2, (HR)	1.00	1.05 (0.64–1.73)	0.89 (0.53–1.50)	0.4
	White	Events	18	21	18	
		Person-years	32468	32138	28635	
		Model 3, (HR)	1.00	1.03 (0.55–1.95)	0.99 (0.50–1.93)	0.6
		Model 4, (HR)	1.00	1.03 (0.54–1.94)	0.94 (0.48–1.86)	0.5
	African American	Events	11	13	14	
		Person-years	7559	7678	9955	
		Model 3, (HR)	1.00	1.03 (0.46–2.31)	0.71 (0.31–1.59)	0.4
		Model 4, (HR)	1.00	1.09 (0.48–2.46)	0.80 (0.35–1.85)	0.6

Outcome	Group		Tertile of energy-adjusted choline intake			p-trend[a]
Fatal prostate cancer	All	Events	27	29	32	
		Person-years	44673	44727	42909	
		Model 1, (HR)	1.00	0.89 (0.53–1.51)	0.88 (0.52–1.49)	0.5
		Model 2, (HR)	1.00	0.90 (0.52–1.52)	0.88 (0.52–1.51)	0.5
	White	Events	17	19	19	
		Person-years	36238	35893	31632	
		Model 3, (HR)	1.00	0.97 (0.50–1.88)	1.08 (0.55–2.13)	1.0
		Model 4, (HR)	1.00	0.95 (0.49–1.84)	1.01 (0.51–2.00)	0.8
	African American	Events	10	10	13	
		Person-years	8435	8834	11277	
		Model 3, (HR)	1.00	0.82 (0.34–1.97)	0.66 (0.28–1.56)	0.4
		Model 4, (HR)	1.00	0.84 (0.35–2.05)	0.74 (0.31–1.77)	0.4

[a] P-value calculated by modeling energy-adjusted choline intake as a continuous term.

[b] Cox proportional hazards regression model adjusted for age (year, continuous), education level, joint categories of race and ARIC field center, and energy intake (kcal/day).

[c] Cox proportional hazards regression model adjusted for variables in model 1 plus height, BMI, smoking and diabetes status.

[d] Cox proportional hazards regression model adjusted for age (year, continuous), education level and energy intake (kcal/day).

[e] Cox proportional hazards regression model adjusted for variables in model 3 plus height, BMI, smoking and diabetes status.

Table 4.

Association between tertiles of baseline energy-adjusted betaine intake (mg/day) and total, lethal, and fatal prostate cancer in all men and by race, 6,528 men in ARIC, 1987–2012

Outcome	Group		Tertile of energy-adjusted betaine intake			p-trend[a]
			1 (12.4–71.6)	2 (71.6–92.7)	3 (92.7–488.6)	
Total prostate cancer	Whole	Events	265	267	279	
		Person-years	39345	39728	39138	
		Model 1, (HR)[b]	1.00	0.96 (0.81–1.14)	0.94 (0.79–1.12)	0.2
		Model 2, (HR)[c]	1.00	0.95 (0.81–1.13)	0.93 (0.78–1.11)	0.1
	White	Events	201	182	168	
		Person-years	32127	32282	28616	
		Model 3, (HR)[d]	1.00	0.88 (0.72–1.07)	0.92 (0.75–1.13)	0.05
		Model 4, (HR)[e]	1.00	0.87 (0.71–1.06)	0.91 (0.74–1.12)	0.04
	African American	Events	64	85	111	
		Person-years	7217	7446	10522	
		Model 3, (HR)	1.00	1.23 (0.89–1.71)	1.02 (0.74–1.41)	0.6
		Model 4, (HR)	1.00	1.26 (0.91–1.75)	1.03 (0.75–1.42)	0.6
Lethal prostate cancer	Whole	Events	34	34	27	
		Person-years	39421	39797	39215	
		Model 1, (HR)	1.00	0.90 (0.56–1.46)	0.59 (0.35–0.99)	0.03
		Model 2, (HR)	1.00	0.91 (0.56–1.47)	0.59 (0.35–1.00)	0.04
	White	Events	24	20	13	
		Person-years	32201	32347	28693	
		Model 3, (HR)	1.00	0.79 (0.44–1.44)	0.57 (0.29–1.13)	0.07
		Model 4, (HR)	1.00	0.81 (0.45–1.48)	0.57 (0.29–1.13)	0.08
	African American	Events	10	14	14	
		Person-years	7220	7449	10522	
		Model 3, (HR)	1.00	1.20 (0.53–2.71)	0.65 (0.28–1.50)	0.3
		Model 4, (HR)	1.00	1.24 (0.55–2.81)	0.64 (0.27–1.49)	0.2

Outcome	Group		Tertile of energy-adjusted betaine intake			p-trend[a]
Fatal prostate cancer	Whole	Events	32	31	25	
		Person-years	44143	44352	43815	
		Model 1, (HR)	1.00	0.87 (0.53–1.43)	0.58 (0.34–1.00)	0.03
		Model 2, (HR)	1.00	0.88 (0.53–1.44)	0.59 (0.35–1.02)	0.04
	White	Events	23	19	13	
		Person-years	36048	35808	31907	
		Model 3, (HR)	1.00	0.75 (0.41–1.38)	0.56 (0.28–1.12)	0.06
		Model 4, (HR)	1.00	0.78 (0.42–1.44)	0.57 (0.29–1.15)	0.07
	African American	Events	9	12	12	
		Person-years	8095	8544	11908	
		Model 3, (HR)	1.00	1.20 (0.50–2.86)	0.63 (0.26–1.56)	0.3
		Model 4, (HR)	1.00	1.22 (0.51–2.92)	0.60 (0.24–1.49)	0.2

[a] Calculated by modeling energy – adjusted betaine intake as a continuous term.

[b] Cox proportional hazards regression model adjusted for age (year, continuous), education level, joint categories of race and ARIC field center, and energy (kcal/day).

[c] Cox proportional hazards regression model adjusted for variables in model 1 plus height, BMI, smoking and diabetes status.

[d] Cox proportional hazards regression model adjusted for age (year, continuous), education level and energy (kcal/day).

[e] Cox proportional hazards regression model adjusted for variables in model 3 plus height, BMI, smoking and diabetes status.

Table 5.

Association between tertiles of baseline energy-adjusted sum of choline and betaine intake (mg/day) and total, lethal, and fatal prostate cancer in all men and by race, 6,528 men in ARIC, 1987–2012

Outcome	Group		Tertile of energy-adjusted sum of choline and betaine intake			p-trend[a]
			1 (77.1–353.6)	2 (353.7–424.3)	3 (424.7–1070.8)	
Total prostate cancer	Whole	Event	244	306	261	
		Person-years	40127	39526	38559	
		Model 1, (HR)[b]	1.00	1.17 (0.99–1.39)	0.95 (0.79–1.14)	0.7
		Model 2, (HR)[c]	1.00	1.17 (0.98–1.38)	0.95 (0.79–1.45)	0.8
	White	Event	179	217	155	
		Person-years	32887	31792	28347	
		Model 3, (HR)[d]	1.00	1.16 (0.95–1.42)	0.94 (0.75–1.17)	0.5
		Model 4, (HR)[e]	1.00	1.14 (0.94–1.40)	0.93 (0.74–1.16)	0.7
	African American	Event	65	89	106	
		Person-years	7241	7733	10212	
		Model 3, (HR)	1.00	1.19 (0.86–1.65)	0.99 (0.72–1.36)	0.7
		Model 4, (HR)	1.00	1.21 (0.87–1.67)	1.03 (0.75–1.43)	0.5
Lethal prostate cancer	Whole	Event	30	33	32	
		Person-years	40186	39586	38661	
		Model 1, (HR)	1.00	0.93 (0.56–1.53)	0.77 (0.46–1.30)	0.1
		Model 2, (HR)	1.00	0.95 (0.58–1.57)	0.80 (0.47–1.35)	0.2
	White	Event	20	17	20	
		Person-years	32945	31849	28447	
		Model 3, (HR)	1.00	0.80 (0.39–1.44)	1.00 (0.51–1.86)	0.3
		Model 4, (HR)	1.00	0.75 (0.39–1.43)	0.93 (0.49–1.79)	0.3
	African American	Event	10	16	12	
		Person-years	7241	7737	10214	
		Model 3, (HR)	1.00	1.31 (0.59–2.91)	0.57 (0.24–1.36)	0.3
		Model 4, (HR)	1.00	1.32 (0.59–2.96)	0.63 (0.26–1.53)	0.4

Outcome	Group		Tertile of energy-adjusted sum of choline and betaine intake			p-trend[a]
Fatal prostate cancer	Whole	Event	28	28	32	
		Person-years	44972	44436	42901	
		Model 1, (HR)	1.00	0.82 (0.49–1.40)	0.81 (0.48–1.40)	0.3
		Model 2, (HR)	1.00	0.82 (0.49–1.47)	0.82 (0.48–1.40)	0.2
	White	Event	19	15	21	
		Person-years	36869	35584	31310	
		Model 3, (HR)	1.00	0.70 (0.35–1.39)	1.08 (0.56–2.05)	0.6
		Model 4, (HR)	1.00	0.70 (0.35–1.36)	1.01 (0.52–1.94)	0.5
	African American	Event	9	13	11	
		Person-years	8103	8853	11591	
		Model 3, (HR)	1.00	1.17 (0.49–2.78)	0.54 (0.22–1.37)	0.3
		Model 4, (HR)	1.00	1.12 (0.47–2.69)	0.58 (0.23–1.47)	0.3

[a] Calculated by modeling energy – adjusted choline + betaine intake as a continuous term.

[b] Cox proportional hazards regression model adjusted for age (year, continuous), education level, joint categories of race and ARIC field center, and energy (kcal/day).

[c] Cox proportional hazards regression model adjusted for variables in model 1 plus height, BMI, smoking and diabetes status.

[d] Cox proportional hazards regression model adjusted for age (year, continuous), education level and energy (kcal/day).

[e] Cox proportional hazards regression model adjusted for variables in model 3 plus height, BMI, smoking and diabetes status.