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Intake of vegetables rich in carotenoids and risk of coronary heart disease in men: The Physicians' Health Study

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Background Previous studies of diet and coronary heart disease (CHD) have focused on intake of nutrients rather than whole foods. Because of the findings that dietary fibre, folate and antioxidants may be protective for CHD, increased intake of vegetables has been recommended. However, due to the chemical and physical complexity of vegetables, the effects of individual nutrients may differ if eaten as whole foods. Moreover, little is known about the direct association between vegetable intake and risk of CHD.

Methods We prospectively evaluated the relation between vegetable intake and CHD risk in the Physicians' Health Study, a randomized trial of aspirin and beta-carotene among 22 071 US male physicians aged 40–84 years in 1982. In this analysis, we included 15 220 men without heart disease, stroke or cancer at baseline who provided information on their vegetable intake at baseline, and in the 2nd, 4th and 6th years of follow-up using a simple semiquantitative food frequency questionnaire including eight vegetables. We confirmed 1148 incident cases of CHD (387 incident cases of myocardial infarction and 761 incident cases of coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) during 12 years of follow-up.

Results After adjusting for age, randomized treatment, body mass index (BMI), smoking, alcohol intake, physical activity, history of diabetes, history of hypertension, history of high cholesterol, and use of multivitamins, men who consumed at least 2.5 servings/day of vegetables had a relative risk (RR) of 0.77 (95% CI : 0.60–0.98) for CHD, compared with men in the lowest category (<1 serving/day). Adjusting for the same covariates in an analysis of the overall trend that considered intake of vegetables as a continuous variable, we found a RR of 0.83 (95% CI : 0.71–0.98) for risk of CHD for each additional serving/day of vegetables. The inverse relation between vegetable intake and CHD risk was more evident among men with a BMI ⩾25 (RR = 0.71, 95% CI : 0.51–0.99) or current smokers (RR = 0.40, 95% CI : 0.18–0.86) comparing highest to the lowest categories of intake.

Conclusions Our results suggest an inverse association between vegetable intake and risk of CHD. These prospective data support current dietary guidelines to increase vegetable intake for the prevention of CHD.

Keywords Vegetables, carotenoids, antioxidants, prospective study, coronary heart disease, men

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Much of our knowledge on the relation of diet to risk of coronary heart disease (CHD) comes from studies that focused primarily on nutrients rather than foods.[1,2] Dietary fibre, folate, and antioxidants have been related to lower risk of CHD.[3–6] Because of the high content of these nutrients in vegetables, increased vegetable intake has been recommended for the prevention of CHD.[7] However, due to the chemical and physical complexity of vegetables, the effects of individual nutrients may

differ if eaten as whole foods. Moreover, little is known about the direct association between vegetable intake and risk of CHD.[1] Confirmation of a vegetable-CHD relation is important because it can help elucidate the mechanisms for the overall diet-CHD relations and provide scientific rationale for formulating dietary guidelines. In the Physicians' Health Study, we were able to examine the direct relation of vegetable intake to subsequent occurrence of coronary events in a prospective setting.

Methods

Study design

The Physicians' Health Study was a randomized, double-blind, placebo-controlled trial in which a 2 × 2 factorial design was used to evaluate the roles of aspirin and beta-carotene in the primary prevention of cardiovascular disease and cancer. The study's methodology has been detailed previously.[8,9] Briefly, in 1982 at study entry, 22 071 male physicians aged 40–84 years were assigned randomly to receive aspirin alone, beta-carotene alone, aspirin plus beta-carotene, or both placebos. All men were free from a known history of cardiovascular disease or cancer (except for non-melanoma skin cancer). For the current analysis, we included 15 220 men (69%) who had complete information on their vegetable intakes at baseline, and in the 2nd, 4th and 6th years of follow-up. This analytical strategy increases internal validity because no assumptions are made regarding missing values and the sample units were used consistently for both time-dependent and time-independent analyses.

Assessment of vegetable intake and follow-up

Every 6 months for the first year and annually thereafter, participants were mailed monthly calendar packs that contained red capsules (beta-carotene or placebo) for even-numbered days and white pills (aspirin or placebo) for odd-numbered days. Along with the calendar packs, brief questionnaires were included asking about participants' compliance with the randomized treatment and about new medical diagnoses, including heart disease. At baseline, and in the 2nd, 4th and 6th years of follow-up, a simple semiquantitative food frequency questionnaire (SFFQ) including eight vegetable items was administered to all participants. On these dietary questionnaires, men reported their average intake of a specific portion size for these vegetables over the past year, including broccoli, brussels sprouts, carrots, spinach (cooked), spinach/dark green lettuce salad, yellow squash, tomatoes, and tomato juice. These vegetable items were selected from a validated SFFQ used in the Nurses' Health Study in 1980 to discriminate and rank intake of vegetables among participants.[10] For each food item on the questionnaire, seven responses regarding frequency of intake were possible, ranging from never to ⩾2 servings/day. These responses to individual food items were converted to average daily intake of each vegetable item for each participant. The average daily intakes of individual food items were summed to compute the total vegetable intake. A similar brief SFFQ was evaluated against more extensive methods of dietary assessment, and mean daily intake of vegetables was generally similar to those estimated by multiple diet records or 24-hour recalls.[11] The correlation coefficients between vegetable intake measured by the simple SFFQ and by more extensive SFFQ ranged from 0.47 to 0.57 across diverse populations.[11]

Ascertainment of coronary events

By the end of 1995, 99.2% of all participants were still providing questionnaire information on morbidity, including CHD. Follow-up for mortality was 99.9% complete. Incident cases of coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA) were self-reported. When a myocardial infarction (MI) endpoint was reported, we requested written consent to review the participant's medical records. Diagnoses of non-fatal MI were confirmed using World Health Organization criteria.[12] Fatal MI was confirmed by death certificates, hospital records, and (for death outside the hospital) observers' accounts.

Statistical analysis

For the current analysis, each participant accumulated follow-up time beginning at baseline and ending in the month of diagnosis of a relevant endpoint or censoring (death from causes other than MI, CABG/PTCA or 31 December 1995, whichever came first). We considered vegetable intake both as a continuous variable (servings/day) and a categorical variable. In initial descriptive analyses, we first examined the distribution of vegetable intake. Because the distribution of vegetable intake was not symmetrical (skewed to the high end) and somewhat truncated, we did not use quintiles to categorize intake. Rather, vegetable intake was categorized into <1 serving/day, 1–1.49 servings/day, 1.5–1.99 servings/day, 2–2.49 servings/day, and 2.5+ servings/day, based both on maintaining a natural gradient of exposure and including adequate person-years in each category. We calculated incidence rates of CHD for men in five categories of vegetable intake at baseline by dividing the number of incident cases by the person-years of follow-up. The relative risk (RR) was then estimated by dividing the rate among men in each specific baseline intake group by the rate among men in the lowest baseline intake group. We used Cox proportional-hazards models to estimate the relative risk of developing CHD adjusting for age (in years), randomized assignments, body mass index (BMI) (kg/m^2), smoking, alcohol intake, physical activity, history of high cholesterol or hypertension or diabetes, and use of multivitamins. We then conducted stratified analyses according to BMI (⩾25 or <25 kg/m^2), smoking status (past, current, never) and beta-carotene treatment status (yes or no) to evaluate whether the relation between vegetable intakes and CHD risk differs by these variables. Tests of linear trend across increasing categories of vegetable consumption were conducted by assigning the medians of intakes in categories (servings/day) treated as a continuous variable. All *P*-values were two-sided.

Finally, to reduce within-person variation and take into account changes in vegetable intakes over time, time-dependent Cox proportional hazards analyses were conducted using all measurements of vegetable intakes at baseline, and in the 2nd, 4th, and 6th years of follow-up and employing both the cumulative and simple updated methods.[13]

Results

Table 1 describes the associations between vegetable intake and potential risk factors for CHD. At baseline, men who had a greater intake of vegetables were slightly older and more physically active; they also had a lower prevalence of heavy

Table 1 Baseline characteristics according to intake of vegetables, Physicians' Health Study

	Intake of vegetables[a] (servings/day)				
Characteristics	<1 (N = 5826)	1–1.49 (N = 3964)	1.5–1.99 (N = 2478)	2–2.49 (N = 1525)	2.5+ (N = 1427)
Mean age (years)	51	52	53	53	54
Body mass index (kg/m^2)	24.9	24.9	24.8	24.9	24.9
BMI ⩾25 (%)	43	43	42	44	42
Physical activity (times/wk) (%)					
<1	31	27	24	24	20
1	20	19	17	18	17
2–4	35	39	42	41	39
5+	14	15	17	18	25
Cigarette smoking (%)					
Never	51	52	52	50	49
Past	37	37	39	41	41
Current, <20 per day	4	4	4	3	4
Current, 20+ per day	8	7	6	7	6
Alcohol consumption (%)					
Rarely	15	14	14	13	15
Monthly	14	11	10	10	9
Weekly	50	50	51	50	48
Daily	21	24	26	28	28
Current use of multivitamin supplement (%)	19	18	19	20	22
Family history of MI[b]	14	14	13	14	13
History of diabetes (%)	2	2	2	2	2
History of hypertension (%)	12	12	13	15	15
History of high cholesterol (%)	6	7	7	7	7
Randomized to:					
Aspirin (%)	50	50	51	52	48
Beta carotene (%)	50	50	51	51	50

[a] Included broccoli, brussels sprouts, carrots, spinach (cooked), spinach/dark green lettuce salad, yellow squash, tomatoes, and tomato juice.
[b] Myocardial infarction.

smoking, but higher prevalence of self-reported hypertension and multivitamin supplement use. Approximately equal proportions of men in each of the vegetable intake categories were randomized to taking active aspirin and active beta-carotene. Body mass index and history of parental MI before 60 years of age did not vary appreciably across categories of vegetable intake.

At baseline in 1982, about 9% of men reported on average at least 2.5 servings a day whereas 38% reported less than one serving a day. The mean daily intake of vegetables was 1.36 servings per day. During a 6-year period from 1982 to 1988, the reported mean intakes of vegetables remained fairly stable (1.36 servings/day in 1982, 1.34 servings/day in 1984, 1.36 servings/day in 1986 and 1.39 servings/day in 1988). The correlation coefficients between any two dietary assessments ranged from 0.47 to 0.55, depending on the closeness in the time of assessments.

During an average of 12 years of follow-up (185 366 person-years), we identified 1148 incident cases of CHD (387 MI and 761 CABG/PTCA). There was a graded inverse association between vegetable intake and risk of total CHD (Table 2). The age and treatment-adjusted RR of CHD was 0.71 (95% CI : 0.57–0.89; P = 0.001 for trend) comparing men in the highest (2.5+ serving/day) to the lowest categories (<1 serving/day). Higher intake of vegetables was also associated with lower risk of CABG/PTCA (RR = 0.67, 95% CI : 0.50–0.89; P trend = 0.002). In multivariate models additionally adjusted for cigarette smoking, alcohol intake, physical activity, BMI, history of diabetes mellitus, history of high cholesterol, history of hypertension, and use of multivitamins, the corresponding RR was 0.77 (95% CI : 0.60–0.98, P = 0.03) for CHD. Adjusting for the same covariates in an analysis of the overall trend, considering vegetable intake as a continuous variable, we found a RR of 0.83 (95% CI : 0.71–0.98) for risk of CHD for each additional serving/day of vegetables.

The inverse relation between vegetable intake and CHD risk appeared more evident among men with a BMI ⩾25 (RR = 0.71, 95% CI : 0.51–0.99) and among current smokers (RR = 0.40, 95% CI : 0.18–0.86) comparing highest to the lowest categories of intake (Table 3). The inverse relation did not differ according to beta-carotene treatment status. In addition, findings were similar regardless of whether we used simple or cumulative updated vegetable intakes in 1982, 1984, 1986, and 1988 (data not shown). To avoid biases from change in diet due to preclinical conditions, we examined the association between vegetable intake and CHD risk after excluding men who reported a history of diabetes, history of high cholesterol, or history of hypertension at baseline. The inverse relations

Table 2 Relative risks (95% CI) of myocardial infarction (MI) or coronary artery bypass grafting/percutaneous transluminal coronary angioplasty (CABG/PTCA) according to intake of vegetables, Physicians' Health Study

	Intake of vegetables (servings/day)					
	<1	1–1.49	1.5–1.99	2–2.49	2.5+	*P* trend
CHD (MI + CABG/PTCA)[a]						
Cases (N = 1148)	451	308	185	111	93	
Person-years	70 898	48 366	30 208	18 541	17 354	
Model 1: Age and treatment adjusted	1.00	0.93	0.88	0.82	0.71	0.001
	(referent)	(0.81–1.08)	(0.74–1.04)	(0.67–1.01)	(0.57–0.89)	0.001
Model 2: Multivariate[b]	1.00	0.99	0.93	0.89	0.77	0.03
	(referent)	(0.85–1.15)	(0.78–1.12)	(0.71–1.10)	(0.60–0.98)	
MI						
Cases (N = 387)	145	109	57	41	35	
Person-years	70 899	48 366	30 209	18 541	17 354	
Model 1: Age and treatment adjusted	1.00	1.01	0.82	0.92	0.79	0.16
	(referent)	(0.79–1.30)	(0.61–1.12)	(0.65–1.30)	(0.55–1.16)	
Model 2: Multivariate[b]	1.00	1.05	0.90	0.98	0.81	0.24
	(referent)	(0.84–1.31)	(0.59–1.16)	(0.67–1.43)	(0.59–1.31)	
CABG/PTCA						
Cases (N = 761)	306	199	128	70	58	
Person-years	70 905	48 368	30 211	18 543	17 356	
Model 1: Age and treatment adjusted	1.00	0.90	0.90	0.77	0.67	0.002
	(referent)	(0.75–1.08)	(0.73–1.11)	(0.60–1.00)	(0.50–0.89)	
Model 2: Multivariate[b]	1.00	0.94	0.99	0.88	0.70	0.03
	(referent)	(0.78–1.14)	(0.79–1.23)	(0.67–1.16)	(0.51–0.95)	

[a] Coronary heart disease was defined as either MI or CABG/PTCA.

[b] Additionally adjusted for cigarette smoking, alcohol intake, physical activity, BMI, history of diabetes mellitus, history of high cholesterol, history of hypertension, and use of multivitamins.

Table 3 Relative risks (95% CI) of coronary heart disease (CHD) according to intake of vegetables among men with body mass index (BMI) ⩾25 or current smokers, Physicians' Health Study

	Intake of vegetables (servings/day)					
	<1	1–1.49	1.5–1.99	2–2.49	2.5+	*P* trend
CHD (MI + CABG/PTCA)[a]						
Current smokers						
Model 1: Age and treatment adjusted	1.00	0.95	1.00	0.84	0.40	0.04
	(referent)	(0.66–1.39)	(0.65–1.57)	(0.47–1.48)	(0.18–0.86)	
Model 2: Multivariate[a]	1.00	1.03	1.06	0.75	0.41	0.06
	(referent)	(0.69–1.55)	(0.65–1.73)	(0.39–1.44)	(0.18–0.97)	
BMI ⩾25						
Model 1: Age and treatment adjusted	1.00	1.03	0.88	0.80	0.73	0.01
	(referent)	(0.84–1.25)	(0.70–1.11)	(0.60–1.06)	(0.54–0.99)	
Model 2: Multivariate[a]	1.00	1.07	0.93	0.91	0.74	0.07
	(referent)	(0.86–1.32)	(0.72–1.20)	(0.67–1.23)	(0.53–1.03)	

[a] Additionally adjusted for cigarette smoking, alcohol intake, physical activity, history of diabetes mellitus, history of high cholesterol, history of hypertension, and use of multivitamins.

between vegetable intake and CHD risk remained evident (RR = 0.82 comparing two extreme categories of intake, $P = 0.02$ for trend).

To determine which individual vegetables were responsible for the reduction in CHD risk in our cohort, we further examined the relations of CHD with specific types of vegetable—including cruciferous vegetables (broccoli and brussels sprouts), dark yellow vegetables (carrots, yellow squash), green leafy vegetables (spinach cooked or uncooked), and tomatoes or tomato juices—that contributed to total vegetable consumption in this cohort. The reduction in CHD risk associated with higher intake was found for all types of vegetables, albeit with smaller magnitude, because of the narrow range of variation for most types of vegetable intake in this cohort (data not shown).

Discussion

In this large prospective study of US male physicians followed for 12 years, we found a graded association between higher vegetable intake and lower risk of CHD that was independent of known coronary risk factors. It is possible that this observed inverse association between vegetable intake and CHD risk could be at least partially explained by confounding because other heart-healthy lifestyle factors were associated with higher vegetable intake. However, some reassurance is afforded by the homogeneity in education and occupation of our study population, which should have safeguarded the internal validity by minimizing confounding by socioeconomic variables. Additionally, the apparent protective effect of vegetable intake persisted in multivariate models accounting for known coronary risk factors. It could be argued that such a homogeneous population may not have enough variation in diet and and this may have dampened the sensitivity to detect a diet-disease association. However, we were still able to detect about a 25% reduction in CHD risk comparing the two extreme categories of intake (at least two and a half servings versus less than one serving per day) as well as an inverse trend across the range of vegetable intake documented in this population. Another major concern was that some intermediary events including hypercholesterolaemia, diabetes, and hypertension could lead to changes in diet and may therefore confound the association between vegetable intake and CHD risk. However, any biases from these indications would tend to attenuate the protective effect of vegetable intake because the tendency would be for men to increase vegetable intake if they perceived themselves to be at elevated risk of CHD. Further, the inverse association persisted when men with those conditions at baseline in 1982 were excluded from the main analysis.

Misclassification of vegetable intake also needs to be considered when interpreting these findings because vegetable intake was reported through a brief SFFQ. This simple SFFQ was designed to discriminate and rank long-term average intake of vegetables rich in carotenoids among participants. Such a simple SFFQ was evaluated against more extensive methods of dietary assessment, and mean daily intake of vegetables was generally similar to those estimated by multiple diet records or 24-hour recalls.[11] The correlation coefficients between vegetable intake measured by the simple SFFQ and by more extensive SFFQ ranged from 0.47 to 0.57 across diverse populations,[11] suggesting a reasonable precision of this measurement. Unfortunately, we did not assess intake of many fruit items at baseline. Although intakes of orange juice and cantaloupe were also reported, we did not examine the association between intake of fruits and CHD risk because of the small variation in items and no documented validity of such an assessment. In addition, although the total intake of vegetables may have been underestimated by this simple SFFQ, this underestimation was likely to be unrelated to CHD endpoints in a prospective setting, and would thus tend to weaken any association between vegetable intake and CHD risk. Therefore, the approximately 25% reduction in risk associated with higher intake of vegetables observed in our study may be a conservative estimate.

Two previous prospective studies have directly related vegetable intake to mortality from cardiovascular diseases.[1] In a 5-year study of 1273 Massachusetts residents aged ⩾65, Gaziano *et al.* used a 43-item SFFQ to assess participants' average dietary intake in the previous year and related vegetable intake to subsequent cardiovascular death. The authors found that those residents in the highest quartile of carotene-containing fruits or vegetables had a 46% lower risk of cardiovascular death compared with those who reported intake in the lowest quartile.[14] Similar findings were also observed in a 14-year study of 5133 Finnish adults.[8] Assessing vegetable intake with a diet history method, Knekt *et al.* reported an RR of 0.66 (P = 0.02) for CHD mortality comparing the highest to the lowest tertiles of vegetable intake. Among studies relating markers of vegetable intake to CHD risk, most have found reduced CHD risk associated with higher intakes of dietary fibre, folate or antioxidants.[2–6] Our data further extended the assessment of the relation of vegetable intake to CHD to include non-fatal CHD outcomes. Also, the magnitude was in general agreement with these previous findings. In stratified analyses, we found that those who were overweight (BMI ⩾25) or current smokers appeared to have the largest risk reduction associated with higher vegetable intake. However, due to the small sample size, these findings among subgroups of the cohort should be interpreted cautiously and need to be confirmed by future studies.

Current understanding of the antioxidant, potassium, fibre, and folate content of vegetables can at least partially explain our findings.[2–6] Other compounds such as flavonoids, phytates, lycopenes, other carotenoids, and many unknown phytochemicals in vegetables may also have significant protective effects in reducing CHD risk. The Year 2000 Objective for the US advocates increasing intake of fruits and vegetables to five or more servings per day, but a recent survey of 28 286 adults in 16 US states[9] suggests that the average daily intake of all fruits and vegetables was only about 3.5 servings. In our cohort, men in the top category consumed a median of only three servings of vegetables per day, yet had approximately 25% lower risk of CHD compared with those in the lowest category (a median of 0.6 servings per day). Because the observed inverse relation between vegetable intake and CHD risk in this cohort appeared to be continuous and without an apparent threshold, increasing the frequency of vegetable intake is likely to be associated with significant reduction in CHD risk.

In conclusion, in this large population of men, higher intake of vegetables was associated with lower risk of CHD, independent of known coronary risk factors. These prospective data support current dietary guidelines to increase vegetable consumption for the prevention of CHD.

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