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ASSOCIATIONS OF SOLUBLE FIBER, WHOLE FRUITS/ VEGETABLES, AND JUICE WITH PLASMA BETA-CAROTENE CONCENTRATIONS IN A FREE-LIVING POPULATION OF BREAST CANCER SURVIVORS

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Abstract

Objective—Soluble fiber and the physical state of fruits/vegetables affect plasma ß-carotene concentrations; however, most of this research was conducted in laboratory-based settings. These analyses investigated the relationship between soluble fiber and juiced vs. whole fruits/vegetables to plasma ß-carotene concentrations in a free-living population.

Method—This cross-sectional analysis used 12-month follow-up data from the Women's Healthy Eating & Living Study (WHEL) (1995-2006), a study to improve diet in breast cancer survivors in the Western United States. The dietary nutrients considered in this analysis included intake of soluble fiber (g), ß-carotene from fruit/vegetable juice (mg), and ß-carotene from whole fruits/ vegetables (mg). A linear regression model was used to assess the relationship of the variables to plasma ß-carotene concentrations.

Results—Out of 3,088 women enrolled in WHEL 2,397 women had complete data (mean age=54). The final model accounted for approximately 49% of the explained variance in plasma ß-carotene concentrations. Fruit/vegetable juice had the largest, positive relation to plasma ß-carotene concentrations (standardized parameter estimate=0.23, $p < 0.01$) followed by whole fruits/vegetables (standardized parameter estimate=0.09, $p < 0.01$). Conclusion: Soluble fiber may inhibit ß-carotene absorption; therefore, consumption of juice may increase plasma ß-carotene concentrations more than whole fruits/vegetables in free-living populations.

Keywords

Dietary fiber; carotenoids; antioxidants; diet; food

Introduction

Epidemiologic studies have shown that fruit and vegetable intake is associated with a reduced risk for many chronic diseases, including breast cancer (Joshipura et al. 2001; Toniolo et al. 2001; Steinmetz and Potter 1993). Researchers have posed a number of hypotheses regarding the underlying mechanisms for this observed association. In particular, fruits and vegetables contain a variety of antioxidants, which may protect cells from the damage caused by free radicals (Chatterjee and Janarthan 2011; Sies 1997). Although there

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are approximately 600 known carotenoids, ß-carotene is the most abundant carotenoid in plants, and a number of studies have shown that higher plasma concentrations of ß-carotene predict reduced cancer risk (Kirsh et al. 2006; Johnson 2002; Rock et al. 1998).

While most studies of plasma ß-carotene concentrations have found an inverse association with cancer risk, some studies have shown ß-carotene to have a null or negative association with cancer risk. Specifically, randomized trials using high dose ß-carotene supplements have shown an increase in lung cancer risk among smokers in the supplement user arm (Omenn et al. 1996; Heinonen and Albanes 1994). However, it is difficult to extrapolate from studies of supplements in smokers to the consumption of food sources of ß-carotene in the general population. It is also notable that a trial testing increased consumption of fruits and vegetables among breast cancer survivors showed no effect on recurrence or breast cancer mortality (Pierce et al. 2007). However, in a follow-up analysis, the authors concluded that higher biological exposure to carotenoids was associated with greater likelihood of breast cancer-free survival regardless of the study group assignment (Rock et al. 2009).

Other dietary constituents, particularly fiber, affect the absorption of ß-carotene. Most studies indicate that enriching meals with fiber decrease carotenoid absorption and plasma concentrations(Rock and Swendseid 1992; Riedl et al. 1999; Hoffmann et al. 1999). However, other research has shown that the addition of sugar beet fiber, which is a combination of soluble and insoluble fibers, had no effect on ß-carotene absorption (Castenmiller et al. 1999). In the studies showing that fiber inhibited ß-carotene absorption, soluble fiber had the strongest effect. When researchers added soluble fibers pectin, guar, and alginate to meals, they found decreased blood plasma concentrations of ß-carotene by 30% to 50% (Riedl et al. 1999).

In addition to the effect of soluble fiber, ß-carotene absorption may be related to the physical state of the food (i.e. liquefied/juiced vs. whole food). The mechanical and chemical processing that liquefies fruits/vegetables may break down the cellular matrixes of the food, which releases the antioxidant from its cellular compartment making it more available for absorption (Castenmiller et al. 1999; Cohn et al. 2004; Edwards et al. 2002). Homogenized canned tomatoes (Cohn et al. 2004), enzymatically liquefied spinach (Castenmiller et al. 1999), and pureed carrots (Edwards et al. 2002) increased ß-carotene absorption compared to the whole food version. Juicing is another way to liquefy food mechanically; however, some research has shown no difference in plasma ß-carotene concentrations with consumption of the juiced versus the whole foods version of plant foods (McEligot et al. 1999; Torronen et al. 1996)

Most of the previous research on plasma ß-carotene concentrations in laboratory settings that used meals enriched with fiber and/or ß-carotene supplements. Therefore, the results of these studies do not reflect dietary constituents or eating behavior in free-living populations. The objective of these analyses was to determine the relation of soluble fiber and the physical state of food, whole or juiced, to plasma ß-carotene concentrations in a large sample of free-living breast cancer survivors from the Women's Healthy Eating and Living Study (WHEL)(Pierce et al. 2002; Pierce et al. 2004). Fruit/vegetable juice was hypothesized to have a stronger, positive relation to plasma ß-carotene concentrations than the whole fruits/vegetables variable.

Materials and Methods

Study Design and Sample

These analyses used data from women enrolled in the intervention and comparison arms of the Women's Healthy Eating and Living (WHEL) study. Briefly, the WHEL study was a multi-site randomized dietary intervention trial for women with early-stage invasive breast cancer who were enrolled within four years of the initial diagnosis of cancer(Pierce et al. 2002). The WHEL study assessed whether a major increase in vegetable, fruit, and fiber intake and a decrease in dietary fat intake reduced the risk of recurrent and new primary breast cancer and all-cause mortality among women with previously treated early stage breast cancer. Women aged 18 – 70 years at cancer diagnosis were recruited between 1995 and 2000 by letters of invitation from tumor registries, community outreach, and physician records from seven sites in the Western United States. The WHEL staff screened 7572 women for potential enrollment, confirmed 3479 women (46%) as eligible, and enrolled 3,088 women (88% of those confirmed as eligible) in the study. These analyses used data from 2397 women that had complete plasma beta-carotene data. The WHEL study was approved by the Institutional Review Board (IRB) of the University of California, San Diego (UCSD) and IRBs from all participating sites. All participants signed an informed consent form.

The WHEL staff randomized the women to either a dietary intervention arm or a comparison arm after stratification by age, stage of tumor, and clinical site. The intervention group (1537 women) received telephone counseling, cooking classes, and printed materials that encouraged women to eat five vegetable servings, 16 ounces of vegetable juice, three fruit servings, 30grams of fiber and 15–20% energy from fat. At 12 months, participants in the intervention group markedly improved their diet compared to the control group (Pierce et al. 2004). On average the intervention group consumed 3.9 servings/d of fruit, 7.1 servings/d of vegetables (including an average of 7.8 ounces/d of vegetable juice), 27.7 grams/d of fiber, and 23.7% fat (Pierce et al. 2004).

Measures

With the exception of demographic information, all measurements used in these analyses were taken at 12-month follow-up because by this follow-up the participants in the intervention group had significantly increased their intake of the dietary constituents that were considered in these analyses (i.e., fiber, juice, and whole fruit/vegetable intake). Therefore, by using the 12-month data greater statistical power was available to see the association of these foods with plasma ß-carotene concentrations because the12-month data had more variance compared to the baseline measures. Personal and medical history questionnaires were used to assess covariate information, and body mass index (BMI) was calculated as kg/m^2using measured height and weight.

Assessment of Dietary Intake

Trained dietary assessors collected four 24-hour dietary recalls on randomly selected prescheduled days stratified for weekend versus weekdays over a 2-week period (with an allowable extension to three weeks). They used multipass software-driven recall protocol to maximize completeness of recalled intake (Conway et al. 2003). They taught participants how to describe the foods they consumed, including how to estimate food portions accurately. The dietary assessors used the Minnesota Nutritional Data System for Research (NDS-R) software to collect data on intake of foods and beverages and derive estimates of intakes of soluble fiber, ß-carotene, fat, and alcohol (Nutritional Data System version 4.01, 2001 University of Minnesota, Minneapolis, MN). NDS-R quantifies dietary intake on four recall days, which were averaged to derive estimates of customary daily dietary intake.

Dietary intake computation included all fortified foods that were reported by participants and included in the nutrient database of NDS-R.

The WHEL staff also ascertained comprehensive information about dietary supplement use. The procedure for supplement use has been described in detail previously (Pierce et al. 2002). Briefly, participants were asked to bring all the dietary supplements that they used to each clinic visit. Whenever possible, interviewers viewed the actual supplement labels so that complete and accurate information about the products could be recorded if the product was not already entered in the USCD Dietary Supplement Database (Newman et al. 1998). The interviewers recorded the product name, manufacturer, usual dosage, and frequency of use during the previous three months for each product.

Plasma Concentration Measurements

The main outcome measure in these analyses was plasma ß-carotene concentrations at the 12-month follow-up. Staff collected fasting blood samples by venipuncture using a standardized protocol that included protection of the samples from light at clinic visits and recorded theclinical site of the blood draw. They stored plasma aliquots at −80°C until analysis, and they measured baseline and 12-month samples for each participant in the same laboratory batch run. Researchers quantified ß-carotene using high-performance liquid chromatography assay with a Varian Star 9010, 9050 system as previously described(Rock 1997; Rock et al. 2005). The day-to-day coefficient of variation was 4%. Throughout the WHEL study, quality assurance procedures included the concurrent analysis of a pooled plasma reference sample. Also, the laboratory participated in the National Institute of Standards and Technology round robin quality assurance program to monitor precision and reliability of carotenoid measurements. .

Total plasma cholesterol was determined using the Kodak Ektachem Analyser kit (Johnson & Johnson, Rochester, NY;(Shirey 1983)) using reference materials from the manufacturer for quality assurance. The laboratory also participated in the American College of Pathologists quality assurance program to monitor precision and reliability for these lipid measures.

Statistical Analysis

The main dietary nutrients considered in these analyses included soluble fiber (g), estimated ß-carotene intake from whole fruits/vegetables (mg), and estimated ß-carotene from fruit/vegetable juice (mg). The following variables were specified *a priori* as covariates, based on research findings suggesting that they might be related to plasma ß-carotene concentrations and/or health status. The covariates included treatment group, age(Arab et al. 2011), ß-carotene from supplements (mg) (Willett et al. 1983), race/ethnicity (Caucasian, African American, Hispanic, or other) (Arab et al. 2011), body mass index (BMI) (kg/m^2) (Switzer et al. 2005),current smoking status (smoker or non-smoker), dietary fat (g) (Unlu et al. 2005), alcohol consumption (g) (Leo et al. 1992),total plasma cholesterol (mg/dl) (Richelle et al. 2004), clinical site of blood draw (7 sites) (Pierce et al. 2006), education level (High School Graduate or Less, Post High School Training, College/University Graduate, and Post College/University Education) (Patterson et al. 2010), and employment status (employed or unemployed) (Patterson et al. 2010). Current use of antiestrogens (Tamoxifen/Nolvadex, none, or other) was also included as a covariate because antiestrogens have the potential to interact with antioxidants (Kucuk 2002). Plasma ß-carotene concentrations were tested as a function of each covariate with linear regression models.

Bivariate analyses were used to determine appropriate variables to include in the multivariate models (i.e., Pearson correlations for normally distributed data, Spearman

correlations for non-normally distributed data, and ANOVA tests for categorical variables). Variables significantly related to the outcome measure at the $p < 0.10$ level were included in all multivariate models. These dietary nutrients were assessed for co-linearity using correlations. The variance inflation factor (VIF) was assessed for variables correlated at $r > 0.50$. Any variable with a VIF of > 10 was excluded from all multivariate models (Hair et al. 1995). Chi-square tests were used to check for potential confounders among the categorical variables.

Linear regression models were used to examine the association of the independent variables with plasma ß-carotene concentrations. Plasma ß-carotene data were log transformed to improve their fit to the Gaussian distributions assumed by standard statistical tests. Index variables were added first, followed by the covariates. General linear model (GLM) testing was used to assess the simultaneous relation of the categorical variables to the outcome, removing categorical variables that did not relate to the outcome. GLM testing was used to assess the appropriate number of levels for the categorical variables. If a significant difference was not observed between each level, the categories were collapsed to simplify the model. The relative contributions of the explained variance were reported to estimate the degree to which each variable contributed to 12-month plasma ß-carotene concentrations. Model fit was assessed using adjusted R^2 values. As these analyses were exploratory, adjustments were not made for multiple comparisons. The means and standard deviations were computed for normally distributed data, median and range for non-normally distributed data, and number and percentage for categorical variables. Data analyses were performed using SAS software, Version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 2397 women (mean age = 54 years)had complete 12-month diet and plasma follow-up data, 85% of whom were Caucasian (with approximately equal distributions of other racial/ethnic groups).Most participants were overweight, non-smokers, married, educated, employed, and using antiestrogens (Table 1).

The bivariate analyses revealed that BMI, alcohol intake, dietary fat, ß-carotene from supplements, ß-carotene intake from whole fruits/vegetables, and ß-carotene from juice were significantly related to the plasma ß-carotene concentrations (Table 2). Employment status and age were not related to the outcome, and therefore were not included in the multiple regression analyses. Even though plasma cholesterol was not significantly related to the outcome in the bivariate analyses, this variable was included in the multiple regression because previous research suggested it is associated with plasma ß-carotene concentrations(Pierce et al. 2006). Soluble fiber was moderately to strongly correlated with ß-carotene intake from whole fruits/vegetables $\rho = 0.63$ ($p < .0001$) and estimated ß-carotene from fruit/vegetable juice $\rho = 0.51$ ($p < .0001$). However, co-linearity was not an issue because the variance inflation factor was low (1.52 – 1.83).

The final model explained approximately 49% of the explained variance in the data (Table 3). As hypothesized, fruit/vegetable juice was more strongly positive associated with plasma ß-carotene concentrations than whole fruits/vegetables. Dietary fat, site of blood draw, race/ethnicity, marital status, and alcohol were not statistically significantly related to plasma ß-carotene and were omitted from the final model. None of the omitted categorical variables were confounders or simultaneously affected the outcome.

Discussion

These analyses revealed that in a free-living population fruit/vegetable juice had a stronger, positive relation to plasma ß-carotene concentrations than whole fruits/vegetables. These results suggest that fiber may have inhibited ß-carotene absorption, which is congruent with most previous research, which in laboratory-based settings, have demonstrated that meals enriched with soluble fiber decrease plasma ß-carotene concentrations (Rock and Swendseid 1992; Riedl et al. 1999; Hoffmann et al. 1999).

As juiced fruits/vegetables generally contain less fiber than in corresponding amounts of whole food, consuming juice may have increased plasma ß-carotene concentrations more than whole fruits/vegetables. This conclusion is consistent with most previous research. Many studies have found that the juiced version of fruits/vegetables increase ß-carotene absorption more than the whole food version (Castenmiller et al. 1999; Cohn et al. 2004; Edwards et al. 2002). However, fiber content may not be the only explanation for this observation. Processing fruits/vegetables may break down the cellular matrixes of the food, which makes antioxidants more available for absorption (Castenmiller et al. 1999; Cohn et al. 2004; Edwards et al. 2002). On the other hand, some trials have demonstrated that juice did not increase plasma concentrations more than whole fruits/vegetables (Pierce et al. 2002; Pierce et al. 2004). This discrepancy in the research may be because plasma ß-carotene concentrations are a result of both the availability of the antioxidants in the cellular matrixes and fiber content.

The major limitation of this study was that it was not possible to determine from these data whether individuals actually consumed fiber at the same meal as the carotenoids. In addition, dietary fat increases carotenoid absorption (Unlu et al. 2005),and alcohol decreases it (Leo et al. 1992)when consumed at the same time as the carotenoid source, but it was not possible to assess when these dietary constituents were consumed. A second limitation was that findings in this population might not be generalizable to all breast cancer survivors, due to antiestrogen medication use and use of the 12-month data point of the intervention. A third limitation was the use of self-reported dietary intake measures to estimate ß-carotene consumption. Considerable random and systematic errors are associated with self-reported dietary intake measuring instruments(Black and Cole 2001). Nonetheless, this analysis used multiple 24-hour recalls, which appeared to provide more precise nutrient estimates than food frequency questionnaires (Natarajan et al. 2006). A fourth limitation was that the food content database was also limited for carotenoids. The food content database did not contain information regarding the variability in carotenoid concentrations in foods due to factors such as plant genotype, maturity, and climate(Beecher and Khachik 1989). Database limitations result in measurement errors between actual carotenoid intake and estimated levels. However, ß-carotene has higher quality food content data than other carotenoids (Michaud et al. 1998). Finally, the cross-sectional design prohibited the ability to assess the temporal relations of variables.

To the authors' knowledge, the current analysis is one of the first studies to investigate the association of soluble fiber and ß-carotene intake from whole versus juiced fruits/vegetables in a large sample of free-living individuals with prior breast cancer. Previous studies on the association of fiber with ß-carotene plasma concentrations had smaller sample sizes and studied meals enriched with soluble fiber and/or ß-carotene supplements instead of whole fruits/vegetables(Rock and Swendseid 1992; Riedl et al. 1999; Hoffmann et al. 1999). The results of the present analyses suggested that fiber was positively associated with plasma ß-carotene concentrations and thus may inhibit ß-carotene absorption; therefore, consumption of juiced fruits/vegetables may increase plasma ß-carotene concentrations more than whole fruits/vegetables. In conclusion, incorporating fruit/vegetable juice into one's diet may

increase ß-carotene concentrations, which in turn may provide health benefits. Similar associations maybe seen in non-breast cancer, free-living populations.

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Table 1

Demographic characteristics of the WHEL study participants: Breast cancer survivors who participated in a dietary intervention to increase intake of fruits, vegetables, and fiber and reduce fat intake (N = 2397)

Characteristics	Overall Sample[1]
Age at Study Entry in years, mean (SD)	53.88 (8.79)
BMI (kg/m^2), mean (SD)	27.31 (5.88)
Smoking Status, N (%)	
Non-smoker	2231 (96)
Race/Ethnicity, N (%)	
Caucasian	2000 (86)
African American	73 (3)
Hispanic	111 (5)
Other	135 (6)
Married, N (%)	1649 (71)
Education, N (%)	
High School Graduate or Less	266 (11)
Post High School Training	767 (33)
College/University Graduate	685 (30)
Post College/University Education	601 (26)
Currently Employed, N (%)	1623 (70)
Antiestrogen Use, N (%)	
Tamoxifen/Nolvadex	1601 (69)
Other	74 (3)
None	644 (28)
Dietary Variables	
ß-carotene from Whole Fruits/Vegetables (mg),Median (range)	4,852.03 (3.08 – 40, 465.56)
ß-carotene from Juice (mg),Median (range)	0.01 (0.01 – 93, 285.23)
Soluble Fiber (g), Mean (SD)	8.18 (3.14)
ß-carotene from Supplements (□g), Median (range)	533.28 (0.01 – 50,000.00)
Dietary Fat (g), Mean (SD)	46.74 (19.59)
Alcohol Intake (g), Median (range)	0.12 (0.00 – 145.60)
Blood Draw Variables	
Log Transformed Plasma β-carotene (mol/L), Mean (SD)	−0.23 (0.98)
Cholesterol (mg/dl), Mean (SD)	194.05 (39.15)
Blood Draw Site, N (%)	
University of California, San Diego	393 (17)

Characteristics	Overall Sample[1]
Kaiser, Oakland	368 (16)
University of California, Davis	371 (16)
University of Arizona	337 (14)
Stanford University/ University of California, San Francisco	392 (17)
MD Anderson Cancer Center	252 (11)
Kaiser Portland	206 (9)

SD = standard deviation

[1]The mean and standard deviation are reported for normally distributed continuous data; the median and range are reported for non-normally distributed continuous data; the number of participants and percentages are reported for categorical data

Table 2

Bivariate associations between log transformed plasma ß-carotene concentrations (mol/L) and the continuous independent variables (N = 2412)

Variable	Correlation [a]
Age at Study Entry	−0.01
BMI (kg/m^2)	−0.44**
Plasma Cholesterol (mg/dl)	0.03
Alcohol Intake (g)[b]	0.09**
Dietary Fat (g)	−0.20**
ß-carotene from Whole Fruits/Vegetables (mg)[b]	0.40**
ß-carotene from Juice (mg)[b]	0.42**
ß-carotene from Supplements (□g)[b]	0.25**

*p<0.10;

**p<0.05

[a]All correlations used Pearson r for normally distributed data unless otherwise noted

[b]Spearman rho was used for non-normally distributed data

Table 3

Final linear regression model for the cross-sectional analysis of the association of dietary nutrients with plasma ß-carotene concentrations (mol/L) in breast cancer survivors from the WHEL study (N = 2397)

Variables	Standardized Parameter Estimates
Intercept	0.00**
ß- Carotene from Whole Fruits/Vegetables (mg)	0.09**
ß- Carotene from Juice (mg)	0.23**
Soluble Fiber (g)	0.18**
Covariates	
BMI (kg/m^2)	−0.37**
Plasma Cholesterol (mg/dl)	0.11**
β-Carotene from Supplements (mg)	0.21**
Education	0.09**
Treatment Group	
Intervention	0.06**
Control	Reference
Anti-estrogen Use	
Tamoxifen/Nolvadex	−0.16**
None	−0.01
Other	Reference
Smoking Status	
Non-smoker	0.08**
Current Smoker	Reference
Goodness of Fit Statistics	
Adjusted R^2	0.49
Sum of Squares Error	1159.08
Degrees of Freedom Error	2385

* p<0.05;

** p<0.01

All dummy codes were1 and 0 for each level of the categorical variables. Education was considered ordinal data.