Original Paper

Specific and Total Carotenoid Intakes Among Oral Contraceptive and Estrogen Hormone Users in the United States

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Objective: To compare carotenoid intakes between hormone users and nonusers in a nationally representative sample of US women by demographic and lifestyle characteristics and to identify those with potentially greater risk for disease.

Design: Data from the 1987 National Health Interview Survey's—Epidemiology Supplement food frequency questionnaire were linked to the USDA-NCI Carotenoid database to estimate mean total and specific carotenoid intakes.

Subjects: Women (n = 8,962) were grouped by menopausal status and classified by hormone use into premenopausal oral contraceptive users/nonusers (n = 5,918) and postmenopausal estrogen replacement hormone users/nonusers (n = 3,044).

Statistical Analyses Performed: Mean carotenoid intakes and standard errors were weighted using SUDAAN and adjusted for potential confounding factors using multiple linear regression analysis. Statistically significant differences were at p values <0.01.

Results: Compared to nonusers, oral contraceptive users had lower specific carotenoid intakes. Demographic and lifestyle characteristics differed between oral contraceptive users/nonusers and were examined in relation to carotenoid intakes. More oral contraceptive users than nonusers were married, highly educated, drank alcoholic beverages, and smoked. After adjustment for these factors in a multiple linear regression model, the associations between oral contraceptive use and carotenoid intake remained statistically significant. Mean carotenoid intakes were not significantly different among estrogen hormone replacement users versus nonusers.

Conclusions: Oral contraceptive users have lower dietary carotenoid intakes than nonusers. Since oral contraceptive users smoke and drink more than nonusers, and both factors are associated with lower carotenoid intakes, oral contraceptive users form a potential high risk group for disease.

INTRODUCTION

Epidemiologic evidence suggests that a diet rich in fruits and vegetables reduces risk of cancer and cardiovascular disease [1–4]. The antioxidant properties of some constituents of fruits and vegetables may contribute to this reduction. Provitamin A and non-provitamin A carotenoids can function as antioxidants by quenching singlet oxygen and neutralizing free radicals [5]. Normal cellular metabolism and oxidative stressors such as cigarette smoking or alcohol consumption are sources of free radical species [6]. Carotenoids interact with free radicals to produce more stable, less reactive, carbon-centered species [7]. Thus, carotenoids may prevent DNA damage directly induced by free radicals or may interfere with the normal metabolic activation of chemical carcinogens in the body [6]. In addition, the provitamin A activity of α-carotene, β-carotene, and β-cryptoxanathin, which convert to retinol in the intestine and liver, may reduce disease risk [3].

Given the frequent use of oral contraceptives and estrogen-progestogen hormones by women, the association between hormone use and risk of disease remains an important public health issue. Approximately 80% of all women by age 35 have

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used oral contraceptives at some point in their lives [8, 9], while 67% of women by age 40 to 59 have used estrogen-based hormone replacements [10]. Long-term oral contraceptive use may increase the risk of breast cancer [11] and may reduce the risk of ovarian and endometrial cancers [12]. Long-term use of hormone replacement therapies is associated with increased risk of endometrial, ovarian, and possibly breast cancers, and reduced risk of osteoporosis and coronary heart disease [13–15].

Epidemiologic studies suggest an inverse association between plasma carotenoid concentrations (primarily β-carotene) and subsequent cancer risk [16, 17]. Smoking and alcohol consumption are associated with lower plasma β-carotene levels [18, 19]. Plasma levels are lower in oral contraceptive users compared to nonusers, and after stratification by smoking status, the combined effect of smoking and oral contraceptive use may result in a "synergistic reduction of plasma β-carotene levels" [20]. Whether diet is associated with these differences in plasma β-carotene concentration remains to be determined.

In 1987, the National Health Interview Survey (NHIS) was administered to a nationally representative sample of the US population to collect data on dietary intake and cancer risk factors such as smoking and hormone use. Specific and total carotenoid intakes were calculated by linking the United States Department of Agriculture—National Cancer Institute (USDA-NCI) carotenoid food composition database to the 1987 NHIS food frequency questionnaire (FFQ). The objectives of this paper are to evaluate differences in mean specific and total carotenoid intakes between pre- and postmenopausal hormone users and nonusers, after adjustment for demographic and lifestyle characteristics and to identify those with greater risk for disease.

MATERIALS AND METHODS

NHIS Methods

The 1987 National Health Interview Survey included a 'Cancer Epidemiology Study Supplement' sponsored and designed by the NCI [21]. This supplemental questionnaire included basic health and demographic information such as diet, smoking, drinking, occupational status, and cancer history. A representative sample of households within the 48 contiguous United States was selected from geographically defined primary sampling units using a stratified multistage cluster sampling frame. This sampling procedure was designed to ensure the representativeness of the target population to the civilian, non-institutionalized US population. Experienced interviewers from the Census Bureau administered in-home interviews to one randomly selected adult age ≥18 years in each household. The overall response rate to this supplemental questionnaire was 82% [21].

The semi-quantitative, 60-item version of a Block food frequency questionnaire (FFQ), part of the Cancer Epidemiology Study Supplement, asked about an individual's reported usual frequency of intake (and portion size) of each item for the past year [22]. The questionnaire was validated against multiple dietary records in middle aged women [23], and in younger Black and White men and women age 25 to 50 years [24]. Further details describing the administration, collection, and validation methods are reported elsewhere [22, 25]. In this paper, data analysis focused on Black and White (n = 8,962; 83% White, 17% Black) women aged 18 to 69 years, and excluded Hispanics and other minorities due to small sample sizes and the difficulty in reporting ethnic-specific foods in the FFQ.

Estimation of dietary carotenoid intakes. All carotenoid-rich food items in the FFQ (fruits, vegetables, and mixed dishes containing them) were linked to the USDA-NCI carotenoid food composition database to determine their specific carotenoid content (α-carotene, β-carotene, β-cryptoxanthin, lutein plus zeaxanthin, and lycopene) [26]. For each carotenoid-rich questionnaire item in the FFQ (e.g., tomatoes, tomato juice), a set of foods representing that questionnaire item was identified from 24-hour recalls in National Health and Nutrition Examination Survey (NHANES) II [27]. The frequency of intakes of these grouped foods from NHANES II was calculated and weighted to reflect the total US population by age and gender. The specific carotenoid value for each food in the questionnaire item was then multiplied by this weighted frequency from NHANES II. Then, the respondent's reported item-specific frequency of intake during the past year and reported portion size were multiplied by the weighted individual carotenoid values for all questionnaire items. The sum of the respondent's item specific carotenoid intakes over the year was averaged to estimate daily dietary intakes (mg/day). Finally, a total carotenoid intake was estimated from the sum of the five specific carotenoid intakes [28, 29].

Variable Definition

All women (n = 8,962) were grouped by menopausal status based on their response to specific questions and classified as premenopausal (n = 5,918) or postmenopausal (n = 3,044). Postmenopausal women had stopped their menses from natural causes. Premenopausal women were classified as oral contraceptive users if they reported ever using them for > 30 days. Postmenopausal women were classified as estrogen hormone users if they reported ever using estrogen replacement pills > 30 days. Past use of any oral contraceptives was noted. Specific brands of hormone preparations were not identified in the 1987 NHIS. Subjects with a reported body mass index < 17 or > 50 kg/m^2 were below the 1st or above the 99th percentile and were excluded.

Statistical Analysis

This survey was a complex design involving multistage stratified sampling. All analyses were computed with observations weighted by their sample weights and with standard errors and tests of significance estimated by accounting for stratification, clustering and weighting of the sample selection in NHIS. The sample weights were derived from a probability sampling procedure and adjusted for non-response and standardization to US population. The software package SUDAAN, (SUDAAN, ver 6.0, Research Triangle Park, NC) was used in all data analyses to account for the complex survey design.

In the initial analysis, demographic and lifestyle characteristics of oral contraceptive users and nonusers, and of estrogen hormone replacement users and nonusers, were compared using the Chi-square test for independence. The following variables were categorized: education (0–8, 9–12, 13+ years), income (<$20,000, ≥$20,000), body mass index (17–21, 22–26, 27–32, 33–50 kg/m^2), alcohol consumption (0, 1–6, 7+ drinks/week), cigarette smoking (never, former, current), race (Black, White) and parity (ever/never delivering a live born infant). Next, the unadjusted mean carotenoid intakes were calculated for both oral contraceptive and estrogen replacement hormone users and nonusers.

Using multiple linear regression analysis, demographic and lifestyle factors that varied by hormone use were entered into a model with mean carotenoid intakes as the dependent variable. Age remained as a continuous variable in the model. Tests for interactions between hormone use and smoking, as well as hormone use and drinking were performed. Adjusted means were calculated by taking a weighted average over the predicted values of the observations derived from the regression model, where each observation was assigned to the category for which the mean was being computed. These adjusted means were analogous to the least square means in SAS, except the sample weights were used in the computation.

The standard errors for the adjusted means were computed by appropriately combining the variances and covariances of the coefficients in the fitted regression model. All reported differences were considered statistically significant with a two sided p value < 0.01. This p value was chosen to protect against inflated Type I errors due to multiple comparisons. Since the food frequency questionnaire provided a relative measure of intake, not an individual's absolute quantitative intake, the reported estimated mean carotenoid intakes were used only for comparison between subgroups and not used to estimate absolute values of consumption.

RESULTS

Among the premenopausal women (Table 1), oral contraceptive users were more frequently married, were better educated, and had a higher income compared to nonusers. More oral contraceptive users than nonusers delivered live births, were former or current smokers, and consumed alcohol. Among the postmenopausal women, (Table 2) more estrogen hormone users than nonusers were White, better educated, and had a higher income. Estrogen hormone users had lower BMI and consumed alcohol more frequently compared to nonusers. For the premenopausal group, the mean age for oral contraceptive users was 32 years and 33 years for nonusers. In the postmenopausal group, the mean age for estrogen hormone users was 61 years and 60 years for nonusers. Among postmenopausal women taking estrogen replacement hormone pills (n = 1,176), 35% reported taking oral contraceptive pills when they were premenopausal. Among postmenopausal women who did not use estrogen hormone pills (n = 1,868), 41% reported taking oral contraceptive pills earlier in life.

Mean carotenoid intakes (± standard error) among hormone users and nonusers, after adjustment for age, hormone use, race, education, income, alcohol, smoking, and BMI in the multiple linear regression model, are reported in Table 3. The unadjusted and adjusted means were very close, thus only adjusted means are reported. Compared to nonusers, women taking oral contraceptives reportedly consumed significantly

Table 1. Weighted Percent (Sample Size) of Premenopausal Oral Contraceptive Users/Nonusers by Demographic and Lifestyle Characteristics (n = 5,608)

Oral contraceptive	User	Nonuser	Chi-square p value
Race			NS
Black	13% (765)	13% (254)	
White	87% (3460)	87% (1129)	
Marital status			0.0001
Married	70% (2467)	46% (568)	
Widow/divorced/single	30% (1757)	54% (587)	
Education			0.001
0–8 years	2% (74)	4% (57)	
9–12	51% (2172)	53% (701)	
13+	47% (1979)	43% (625)	
Income			0.0001
<$20,000	31% (1651)	38% (636)	
≥$20,000	69% (2525)	62% (725)	
Body mass index			NS
17–21 kg/m^2	48% (1948)	43% (574)	
22–26	31% (1330)	33% (451)	
27–32	17% (729)	19% (284)	
33–50	4% (218)	5% (74)	
Birth to liveborn			0.0001
Yes	71% (3002)	52% (740)	
No	29% (1221)	48% (641)	
Smoking			0.0001
Former	17% (679)	12% (175)	
Current	33% (1441)	25% (359)	
Never	50% (2105)	63% (849)	
Drinking			0.0001
7+/week	12% (544)	10% (145)	
1–6/week	66% (277)	56% (787)	
Never	22% (910)	34% (451)	

NS = not significant.

Table 2. Weighted Percent (Sample Size) of Postmenopausal Estrogen Replacement Therapy Users/Nonusers by Demographic and Lifestyle Characteristics (n = 1,440)

Estrogen replacement	User	Nonuser	Chi-square p value
Race			0.0001
Black	3% (16)	12% (166)	
White	97% (331)	88% (927)	
Marital status			NS
Married	72% (201)	66% (549)	
Widow/divorced/single	28% (145)	34% (537)	
Education			0.001
0–8 years	7% (28)	14% (164)	
9–12	63% (216)	62% (664)	
13+	30% (103)	24% (265)	
Income			0.01
<$20,000	38% (150)	48% (606)	
≥$20,000	62% (189)	52% (464)	
Body mass index			0.0001
17–21 kg/m^2	27% (97)	22% (246)	
22–26	44% (148)	38% (409)	
27–32	26% (93)	29% (319)	
33–50	3% (9)	11% (119)	
Birth to liveborn			NS
Yes	86% (293)	88% (946)	
No	14% (52)	12% (147)	
Smoking			NS
Former	23% (84)	19% (215)	
Current	24% (87)	28% (306)	
Never	53% (176)	53% (572)	
Drinking			0.0001
7+/week	15% (44)	9% (94)	
1–6/week	50% (172)	43% (463)	
Never	35% (131)	48% (536)	

NS = not significant.

lower amounts of α-carotene (14%), β-carotene (10%), β-cryptoxanthin (21%), lutein (9%), lycopene (9%), and total carotenoids (9%). No significant differences in adjusted carotenoid intakes by estrogen replacement hormone use were seen. All tests for interactions between smoking, alcohol use, and hormone use within each pre- or postmenopausal group were not statistically significant.

DISCUSSION

Compared to nonusers, oral contraceptive users reported lower specific and total dietary carotenoid intakes, both before and after adjustment for confounding variables. Education, alcohol use, and smoking status were associated with oral contraceptive use and dietary carotenoid intakes.

It is unclear why carotenoid intake differences remained between oral contraceptive users and nonusers after adjustment for recognized confounders. The characteristic profiles of oral contraceptive users and nonusers in this study were similar to the profiles reported in earlier research [30–32]. Earlier reports indicated that oral contraceptive users were more likely to be thinner, better educated, have a higher income level, to be married, have a greater number of children, and drink alcohol more frequently than nonusers [30–32].

In this study, estrogen hormone replacement use among postmenopausal women was not associated with differences in carotenoid intakes after adjustment for potential confounders. Estrogen users are reported to be thinner, younger, to exercise more regularly, to have a higher income and level of education, to smoke and consume alcohol less frequently, and have lower serum cholesterol levels compared to nonusers [33, 35]. In a study of 179 women with naturally occurring menopause, 40% of the estrogen users reported past use of oral contraceptive products during their reproductive years compared to 18% of the nonusers of estrogen [31]. The postmenopausal women in our study were slightly different from the above mentioned studies. Estrogen users and nonusers in the NHIS population sample did not significantly differ by age, marital status, number of liveborn children, or smoking status. Moreover, 35% of women who reported using estrogen replacement hormones had used birth control pills previously, compared to 41% of the nonusers of estrogen hormones. Perhaps these demographic and lifestyle similarities of the estrogen replacement hormone users and nonusers in the NHIS partially account for the absence of differences in carotenoid intakes.

Compared to non-users, oral contraceptive users have lower plasma β-carotene levels; while smokers who take oral contra-

Table 3. Adjusted[1] Mean ± SE (mg/day). Carotenoid intake by Hormone User Group: Premenopausal Oral Contraceptive Group (n = 5,608) and Postmenopausal Estrogen Hormone Replacement Group (n = 1,440)

Hormone users	Carotenoids					
	α-carotene	β-carotene	β-cryptoxanthin	lutein	lycopene	total carotenoids
Oral contraceptive						
Non-user	.32 ± .01	2.65 ± .01	.03 ± .001	2.18 ± .06	2.15 ± .06	7.33 ± .18
User	.28 ± .01‡	2.39 ± .01†	.02 ± .006‡	1.98 ± .09‡	1.97 ± .02†	6.66 ± .18†
Estrogen hormone						
Non-user	.32 ± .01	3.14 ± .09	.03 ± .002	2.43 ± .08	2.21 ± .08	8.21 ± .21
User	.34 ± .02	3.37 ± .13	.03 ± .003	2.51 ± .10	2.16 ± .09	8.34 ± .29

P value ‡ = <0.0001; † = <0.001.

[1] Adjustment variables include: age, hormone use, race, education, alcohol, smoking, income, and BMI.

ceptives have synergistically lower plasma levels than nonsmoking, nonusers [20]. Because dietary data were not collected in the above study, the association between oral contraceptive use and plasma carotenoid levels could be confounded by dietary carotenoid intake as well as intake of fat, fiber, and alcohol, all of which are recognized factors influencing plasma carotenoid levels [18–20, 35–39].

Plasma lycopene, α- and β-carotene are transported predominantly by low-density lipoproteins (LDL), while lutein is transported more equally by LDL and high-density lipoprotein (HDL) fractions [37]. Estrogen and progestogen components of oral contraceptive agents alter plasma lipoprotein levels [39, 40]. Progestin decreases HDL and increases LDL plasma levels, while estrogens have the opposite effect [39, 40]. Thus, hormone use may possibly affect plasma carotenoid concentrations through its direct effect on circulating lipoprotein fractions. Plasma samples were not collected in the 1987 NHIS sample in order to test this hypothesis. Further research is needed to clarify the association between diet, oral contraceptive use, and plasma carotenoid levels.

Finally, there are several limitations to our analysis. Any multi-purpose food frequency questionnaire (FFQ) that is part of a large scale population survey may not capture all foods eaten by a specific population group compared to 24-hour dietary food records [41]. All foods that contribute to the total carotenoid intake in the US are not included in any FFQ, which also limits the interpretation of these findings [28]. The Block-designed FFQ used in the 1987 NHIS was carefully pretested in a pilot study for validity and was administered by professionally trained census bureau staff to improve the accuracy of data collection and help reduce potential bias [22–25]. Therefore, this paper represents the only currently available national survey data that includes data on diet and historical and current use of oral contraceptives and estrogen hormones in US women.

For the first time we report differences in carotenoid intake between oral contraceptive users and nonusers after adjustment for confounding factors. This finding has implications for the possible confounding role of dietary carotenoid intakes in the oral contraceptive-plasma carotenoid association.

CONCLUSIONS

In a nationally representative sample, premenopausal women who use oral contraceptives reportedly smoke and drink more frequently and also have lower dietary carotenoid intakes than nonusers. The combination of these factors may compromise plasma carotenoid levels, but further research is needed to clarify these associations. While oral contraceptive users appear to be different from nonusers in lifestyle characteristics, health status, and dietary carotenoid intakes, such differences were not evident in postmenopausal estrogen hormone replacement users. Should future research identify that diet is a true confounder of the oral contraceptive-plasma carotenoid association, then dietary intervention programs to enhance carotenoid-rich food intake could be considered for this population subgroup.

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