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Original article

Dietary flavonoid intake and Barrett's esophagus in western Washington State

Jessica L. Petrick PhD, MPH [a,*], Susan E. Steck PhD, MPH, RD [b], Patrick T. Bradshaw PhD, MS [c], Wong-Ho Chow PhD [d], Lawrence S. Engel PhD, MS [a], Ka He ScD, MD, MPH [e], Harvey A. Risch MD, PhD [f], Thomas L. Vaughan MD, MPH [g], Marilie D. Gammon PhD [a]

[a] Department of Epidemiology, University of North Carolina, Chapel Hill
[b] Department of Epidemiology and Biostatistics, University of South Carolina, Columbia
[c] Department of Nutrition, University of North Carolina, Chapel Hill
[d] Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston
[e] Department of Epidemiology and Biostatistics, Indiana University, Bloomington
[f] Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT
[g] Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA

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ABSTRACT

Purpose: Flavonoids, concentrated in fruits and vegetables, demonstrate in experimental studies chemopreventive properties in relation to Barrett's esophagus (BE), a precursor lesion for esophageal adenocarcinoma. One case-control investigation reported an inverse association between isoflavone intake and odds of BE, yet no epidemiologic study has considered other flavonoid classes, which are more commonly consumed by Americans.
Methods: We examined intake of total flavonoids, six flavonoid classes, and lignans among case-control study participants in western Washington State. Food frequency questionnaires were self-completed by BE cases with specialized intestinal metaplasia ($n = 170$) and matched controls ($n = 183$).
Results: In logistic regression models adjusted for age, sex, body mass index, and energy intake, the odds ratio (OR) for specialized intestinal metaplasia BE associated with anthocyanidin intake was 0.49 (95% confidence interval: 0.30–0.80, for quartiles 2–4 combined vs. quartile 1), for which wine and fruit juice were major dietary sources. More moderate decreased ORs were noted for flavanones, flavonols, isoflavones, and lignans. A modest increased OR was observed for flavones, for which pizza was the main dietary source in our population.
Conclusions: Our findings of an inverse association between anthocyanidins and odds of BE suggest that adequate dietary intake of these compounds may lower risk of this cancer precursor lesion.

Introduction

Over the last 2 decades, the incidence rate for esophageal adenocarcinoma has been among the most rapidly increasing of any cancer type in the United States (U.S.) [1,2]. Esophageal adenocarcinoma is thought to arise in Barrett's esophagus (BE), specialized intestinal metaplasia (SIM) of the lower esophageal epithelium [3]. Studying precursor lesions may provide insight into the etiology of cancer by elucidating risk factors that act early in disease initiation. Epidemiologic studies have shown that diets high in fruit and vegetable intake are inversely associated with odds of BE [4]. Flavonoids, a group of bioactive polyphenolic compounds naturally occurring in fruits, vegetables, and beverages of plant origin, may partially account for the inverse dietary association of fruits and vegetables with BE [5,6].

Experimental studies support the hypothesis of an inverse association between flavonoid exposure and BE. For example, flavan-3-ol inhibited BE cell growth through downregulation of cyclin D1 protein expression [7]. Lignans are other polyphenolic compounds that have antioxidant properties, anti-inflammatory and proapoptosis effects, and promote cell cycle arrest [8]. One epidemiologic investigation to date has examined the association between dietary flavonoid intake and odds of BE. This Texas case-control study of 151 BE cases considered one class of flavonoids,

* Corresponding author. Department of Epidemiology, University of North Carolina, CB# 7435, Chapel Hill, NC 27599-7435.
E-mail address: jessica.petrick@unc.edu (J.L. Petrick).

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isoflavones and found an inverse association [9]. However, intake of isoflavone-containing foods in the U.S. is limited, whereas the other five flavonoid classes are found in foods more commonly consumed by Americans [10], yet their associations with BE have not been considered.

To determine whether intakes of total flavonoids or specific flavonoid classes are associated with odds of BE, we compared flavonoid intake between patients newly diagnosed with BE and general population controls who participated in a community-based case-control study.

Materials and methods

To conduct this ancillary study, we built on resources collected for the Study of Reflux Disease, a case-control investigation conducted in western Washington State [11,12]. This study was approved by the institutional review boards of the participating institutions.

Study population

Eligible case participants were men and women, aged 20–80 years without previously diagnosed BE who underwent upper endoscopy for gastroesophageal reflux disease (GERD) symptoms between 1997 and 2000 at community gastroenterology clinics. Consenting participants had four-quadrant biopsy specimens collected. Specimens were evaluated by one of the three university-based pathologists, who were blinded to the endoscopy findings. BE was considered present if at least one biopsy specimen had SIM. Case participants were classified into one, two, or three diagnostic categories indicating disease progression, based on the presence (and length) or absence of visible columnar epithelium (visible BE [VBE]) during endoscopy: (1) SIM (i.e., all cases), (2) SIM and VBE (VBE cases), and (3) SIM and VBE greater than 2 cm (long-segment BE [LSBE] cases). The first and most inclusive category (SIM cases) adheres to the concept of "ultra-short segment BE" [13]. The latter two categories were selected because they are consistent with the American College of Gastroenterology definition of BE [14], enhancing the clinical relevance of our study results.

Community-based control participants were identified using a modified Waksberg random digit dialing technique [15], which identifies individuals living in the same geographic area as case participants [16]. Controls were matched to cases on age (±3 years) and sex.

In the parent study, SIM was identified in 208 individuals providing biopsy specimens. However, only 193 of these cases successfully completed interviews. Thus, study participants included 193 cases (92.8% of eligible) and 211 community controls (68.7% of eligible) [11]. Of those, 87.4% (170 cases, 183 controls) provided adequate dietary intake information (see Exposure assessment section in the following) and are the focus of the current report. Their demographic characteristics are summarized in Supplementary Table 1.

Exposure assessment

Information on potential risk factors was obtained by a 45-minute structured questionnaire administered face to face by trained interviewers. The time between endoscopy and interview for case participants was 1–2 months. Written informed consent was obtained from each participant before interview.

Dietary intake for the 1 year before interview was assessed by a validated self-administered, 131-item food frequency questionnaire (FFQ) [17]. In total, 177 cases (91.7%) and 192 controls (91.0%) completed FFQs. Individuals with estimated total energy intake of less than 500 or more than 4000 kcal/d for women or less than 800 or more than 5000 kcal/d for men were excluded based on implausible energy intake (seven cases, nine controls) [12,18].

Assessment of dietary flavonoid intake

Intakes of total flavonoids, six classes of flavonoids (anthocyanidins, flavan-3-ols, flavanones, flavones, flavonols, and isoflavones), and lignans were estimated from 91 food and beverage FFQ items that contained measurable amounts of flavonoids [19–21]. A study-specific flavonoid database was developed by linking the FFQ data with the 2011 U.S. Department of Agriculture (USDA) database for the flavonoid content of selected foods [19] and the 2008 USDA-Iowa State University database on the isoflavone content of selected foods [20]. To assess lignan content, specifically secoisolariciresinol and matairesinol, we used data from foods consumed by a North American population [21].

Some FFQ items represented groups of foods or beverages. For flavonoid intake calculations, the individual foods and beverages represented in a single item were weighted, based on the relative frequency of consumption in the general American population [17]. For example, the FFQ item of "apples and pears" was assigned a weight of 0.75 for "apples" and 0.25 for "pears." To calculate the flavonoid intake, the weight assigned to each food in the FFQ item was multiplied by the flavonoid content of that food, summed across all foods in the FFQ item, and then multiplied by the number of times consumed per day and by the serving size [10].

Statistical analysis

Unconditional logistic regression was used to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the association between flavonoid intakes and odds of BE. Conditional logistic regression was also performed on matched pairs of cases and controls [22]. Results were similar; therefore, only unconditional logistic regression results are reported. All analyses were conducted using SAS, version 9.2 (SAS Institute, Cary, NC).

Flavonoid intakes were categorized in quartiles, based on the distributions of intakes among the control participants [18]. To examine linear trend, we also used restricted quadratic spline coding (Supplementary Fig. 1). Tests for linear trends were based on continuous flavonoid values in milligrams per day.

Effect measure modification by cigarette smoking (evaluated as continuous pack-years and as dichotomous, ever or never) and body mass index (BMI, kilogram per square meter) at interview (evaluated as continuous and as dichotomous, <25 or ≥ 25 kg/m^2) was assessed using likelihood ratio tests to compare regression models with and without a multiplicative term [22]; there was no evidence of effect measure modification by either covariate ($P \geq .05$) on the association between total flavonoid intake and BE in any of the models.

Potential confounders included BMI (evaluated as continuous and as dichotomous, <25 or ≥ 25 kg/m^2), race (white or other), income ($<$\$45,000, $\geq$\$45,000–\$74,999, or $\geq$\$75,000), education ($\leq$high school, technical school, or $\geq$college), and cigarette smoking (evaluated as ever or never and continuous pack-years). If variable elimination changed the log OR by 10% or more, the variable was considered a confounder and included in the model [22]; only BMI met this criterion. Total energy intake was included for adjustment on an *a priori* basis [23]. Thus, the final models included BMI (continuous), total energy intake (kilocalories, continuous), and the matching factors age (continuous) and sex.

To determine whether associations with flavonoids varied by diagnostic category, BE patients were categorized into progressively more exclusive groups by segment length [13], and then, each case