Peripubertal dietary flavonol and lignan intake and age at menarche in a longitudinal cohort of girls

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BACKGROUND: Dietary phytoestrogens may alter hormonal activity in childhood. Flavonols and lignans are the most prevalent phytoestrogens in the Western diet. We examined whether higher intake of flavonols and lignans was associated with later age at menarche in a prospective study of young girls.

METHODS: In all, 1,044 girls aged 6–8 years (mean 7.3 years) with two to four 24-h dietary recalls during their baseline year were followed up for 11 years until the attainment of menarche in the Breast Cancer and Environment Research Project (BCERP). Associations of age at menarche with quintiles of phytoestrogens were assessed using hazard ratios (HR) and 95% confidence intervals (CIs) from Cox proportional hazards models, controlling for body mass index and other covariates.

RESULTS: The highest quintile of flavonol intake was associated with a later age at menarche, compared with the lowest quintile (adjusted HR: 0.80, 95% CI: (0.66–1.00). For lignans, there was a later age in overweight girls (HR: 0.56, 95% CI = 0.40–0.80).

CONCLUSION: These dietary bioactives may reflect a healthy diet, and foods high in phytoestrogens may influence the timing of menarche.

Early menarche has been associated with breast, endometrial, and ovarian cancer, possibly because it may lead to an increased lifetime estrogen exposure (1). Although timing of menarche is under genetic control (2), environmental factors may also have an important role. Childhood nutrition affects adolescent growth and pubertal development (3). In addition to the overall nutrition status, specific dietary components during childhood may influence the timing of puberty and menarche. Fiber (4,5) has mainly been associated with a later age at menarche, whereas animal fats (6) and protein (7) and dairy (8,9) are associated with earlier menarche, although not consistently across studies (10–13). Longitudinal studies of phytoestrogens, including soy

formula, dietary and urinary isoflavones, enterolactone, and flavonols, have shown later pubertal development (14–17). Reasons for differences may include prospective vs. cross-sectional study design and timing of diet collection. Understanding the relationship between diet and menarche can help identify modifiable risk factors for disease prevention later in life.

Phytoestrogens are naturally occurring plant-derived polyphenols found in many foods that have been postulated to have beneficial health effects (18). The main groups of phytoestrogens are lignans, isoflavones, and coumestans. Numerous epidemiologic studies have suggested that dietary intake of phytoestrogens, particularly isoflavones, have a role in preventing certain types of hormonally dependent cancers, including breast and prostate cancers (19,20). Mechanisms of the protective effect are not fully understood, although it may be explained by the competition of phytoestrogens with endogenous estradiol for hormone receptors or an inhibitory effect on aromatase activity and antioxidant properties (21). The intake of soy products that are the major contributors to isoflavone intake is low in Western societies, whereas the intake of Flavonols and lignans is higher in the Western diet. Flavonols and lignans have weak estrogenic activity (22) and they have been associated with estrogen-dependent outcomes, such as puberty, fecundity, menarche, and ovarian hormone profiles (19,23,24).

Identifying the major sources of foods eaten that contain high concentrations of these micronutrients in young girls may allow for targeted recommendations for health-care providers. Our previous work has shown these phytoestrogens to be associated with a delay in girls' breast development (14); therefore, we hypothesize that they also may be associated with later menarche. We examined whether increased intake of flavonols and lignans before puberty is associated with later age at menarche in a prospective study of young girls.

METHODS

This project was a part of the NIEHS/NCI Breast Cancer and the Environment Research Project (BCERP). BCERP is an observational

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longitudinal study of pubertal development of 1,239 girls enrolled at 6–8 years of age. Enrollment occurred between 2004 and 2007 at three sites as follows: Icahn School of Medicine at Mount Sinai (NYC), which recruited through clinics, schools, and neighborhood centers in East Harlem, NY, with girls seen annually; Cincinnati Children's Hospital/University of Cincinnati (Cincinnati, OH), which recruited through schools in the Cincinnati metropolitan area and through the Breast Cancer Registry of Greater Cincinnati, with girls seen semi-annually; and Kaiser Permanente Northern California (KPNC), which recruited KPNC Health Plan members in the San Francisco Bay Area, with girls seen annually. The study was approved by the institutional review board at each site. Eligible girls had no underlying conditions affecting metabolism or growth. All sites obtained informed consent from parent or guardian and assent from girls. Parents or guardians of the participants identified girls' race/ethnicity as Black, White, and Asian, and ethnicity as Hispanic or non-Hispanic. At enrollment (baseline), and approximately annually for 11 years, parents or guardians were interviewed in person or were made to answer a self-completed questionnaire, in either English or Spanish, about the children's environmental exposures, physical activity, medical history, and demographics. Anthropometry and pubertal staging were assessed at each visit. Questions about the presence and date of first menarche were asked after the first follow-up year in NYC and KPNC and ~5 years after baseline in Cincinnati. A complete description of the study design is available in Biro *et al* 2010 (ref. 25). We report on 1,044 girls with two to four diet recalls provided within their first year of enrollment, who were asked about menarche at least once during 2014 (mean years of follow-up=9).

Assessment of Age at Menarche

Age at menarche was assigned based on questionnaire information provided primarily by the parent or guardian ($N=795$, 76%) or based on the girl's self-reported information ($N=112$, 11%). Girls who did not reach menarche were censored for statistical purposes at their age at their last visit or response ($n=137$, 13%).

Dietary Data

Dietary recall interviews were performed by trained dietitians at the Cincinnati Center for Nutritional Research and Analysis using the NDSR, Minn, Minnesota. Multiple (two to four) 24-h recalls by telephone were conducted with caregivers during the first year to provide an average intake over a year's time, as previously described (14). Average intakes over 1 year account for daily and seasonal variation in food consumed. Three recalls have been shown to reliably rank individuals on energy and most nutrients (26). The majority of girls had a complete set of four recalls ($N=984$); the remainder had either two or three recalls ($N=148$ and 46, respectively). Recalls with either extremely low or high total energy consumption values (<400 and $>4,000$ k/cal per day) were excluded from analysis ($N=18$).

We developed a dietary database that captured flavonol and lignan contents of several hundred foods that were unavailable in standard dietary databases including NDSR (14). We assigned flavonol and lignan content (mg/100 g) for 2,319 individual foods and components reported, using published sources, including the United States Department of Agriculture (USDA). Flavonol and lignan intake was calculated for each reported food by multiplying the quantity consumed (g/day) and the phytoestrogen content (mg/g). Total daily flavonol and lignan intake (mg/day) was averaged over the two to four calls for each girl.

Statistical Analyses

Baseline characteristics of the study population were examined by quintiles of flavonol and lignan intake. Owing to skewed distributions, continuous variables are summarized as the medians and interquartile ranges. We tested for differences across quintiles of phytoestrogens by demographic characteristics using either χ^2 -test (categorical variables) or Kruskal–Wallis test (continuous variables).

We computed the amount of total flavonol and lignans in a standard serving size of foods selected as being high in these phytoestrogens, and then compiled the frequency of girls in our study who ate these foods (Tables 2 and 3).

Longitudinal analyses, examining associations between baseline flavonol and lignan intake and menarche, utilized reports of menarche over 11 years of annual follow-up visits. We used Cox proportional-hazards models to calculate the HRs and 95% CIs for associations between phytoestrogen levels and menarche. Proportional hazards' assumptions were met in all of our analyses. Censoring occurred at the age of first menstrual period or at the age at last visit if menarche had not been reported. We examined flavonol and lignan intake using quintiles unadjusted and calorie adjusted using the nutrient density method to remove variation caused by total energy intake (26). Associations were similar, and only calorie-adjusted values are reported. All analyses were performed using the Statistics Analysis System (SAS) statistical software, Version 9.3 (SAS Institute, Cary, NC).

Confounding by potential covariates was assessed for the following variables: self-declared race/ethnicity, parent or guardian education, total daily average calories, fiber intake, and BMI percentile (BMI%) dichotomized at the 85th percentile, which defines overweight (specific for age and gender) according to the CDC (27). We examined BMI% separately at two time points—at baseline and at visit closest to menarche. These variables were chosen because they have been associated with both menarche and diet in the literature and because they were based on a conceptual model of diet and pubertal development. We included covariates that altered the estimate by more than 10%. We did not include site because of its collinearity with race and BMI%. Final models were adjusted for self-declared race/ethnicity and baseline BMI%. Tests for trend across phytoestrogen quintiles were performed by including flavonol and lignan quintile ordinals as continuous variables. P-constrasts were obtained from the contrast statement comparing the HR of the first quintile to the fifth quintile. We obtained adjusted median pubertal ages for flavonol and lignan intake using survival function estimates from the baseline survivor function of multivariable-adjusted Cox models with quintiles as a strata statement. We evaluated race and baseline BMI% as effect modifiers by adding interaction terms to the model (flavonol or lignan quintile $\times$ BMI% dichotomized at the 85th percentile and flavonol or lignan quintile $\times$ race). If there was a significant interaction with either race or BMI% we examined stratum-specific models.

RESULTS

Table 1 presents the demographic characteristics of the study population at baseline. All girls consumed at least one food with flavonol and lignan content. The median intake of flavonols was 6.0 mg/day and that of lignans was 0.40 mg/day. Flavonols and lignans are found in lower concentrations in more frequently consumed foods such as potatoes, grains, cereals, tomato products, and coffee (Tables 2 and 3) compared with those in foods like kale and arugula. The average intake consumed in our population for both flavonol and lignans was a full serving per day for some of the foods (e.g., grapefruit juice, pears, and strawberries).

Tables 4 and 5 show the baseline characteristics of 1,044 participants according to quintiles of flavonol and lignan intake. Girls with higher flavonol and lignan intake were more likely to be white, have more educated parents/guardians, and consume more calories. On their last visit, 907 (87%) of the girls had reported a first menstrual period. The unadjusted median age at menarche in our sample was 12.2 years (interquartile range: 11.4–13.1 years). This was the same as

the median of the total cohort of 1,089 reporting age at menarche (median age 12.3 years (interquartile range: 11.4–13.2 years), which included girls without diet data.

The highest quintile of flavonol intake was associated with a later age at menarche, compared with the lowest quintile

(adjusted hazard ratio (HR): 0.80, 95% confidence interval (CI): (0.66–1.00; [Table 6](#)). Compared with the lowest lignan intake (median 0.14 mg/day), highest intake (median 0.88 mg/day) was also suggestive of an association with later menarche (adjusted HR: 0.84, 95% CI: (0.66–1.04; [Table 6](#)). We additionally adjusted for average fiber intake and estimates were unchanged (data not shown). The BMI–lignan interaction was significant in the test for effect modification (P for interaction = 0.02). As shown in [Table 7](#), the association with later menarche was restricted to girls with higher BMI (HR: 0.56, 95% CI = 0.40–0.80). There was no evidence of interaction by BMI with flavonols nor was there interaction of the association of lignans or flavonols and menarche by race (data not shown).

DISCUSSION

Our findings suggest that specific childhood dietary factors may influence the pubertal trajectory. In this longitudinal cohort, flavonol consumption was associated with later age at menarche, in keeping with our hypothesis. Similar relationships were observed in this cohort between increased intake of these phytoestrogens and later age at breast development, which typically precedes menarche by 2–3 years. Association of lignans was restricted to overweight and obese girls, whereas flavonol associations were not modified by BMI. There was a 6-month delay in menarche among overweight girls with high lignan consumption compared with those with low lignan intake. To put this age difference in perspective, a time period of 6 months is the difference seen in black and

Table 1. Baseline characteristics of 1,044 BCERP participants, 2004–2014

Characteristic	Mean (Std)	
Baseline age (years)	7.3 (0.68)	
Child race/ethnicity	<i>N</i>	%
Black	316	30
Hispanic	316	30
White	357	34
Asian	55	5
Parent or guardian education ^b		
≤ High school	296	29
> High school	725	71
Baseline BMI percentile ^c		
< 50th	349	33
50–85th	359	34
≥ 85th	336	32

BCERP, Breast Cancer and Environment Research Project; Std, standard.

^b $n = 1,021$ girls with all variables.

^cBMI (kg/mg2) specific for age and sex according to CDC growth data.

Table 2. Food items containing high flavonol content and frequency of consumption at baseline in 1,044 BCERP participants, 2004–2014

Food	Serving size ^a	Total flavonol (mg) serving ^b	<i>N</i> (%) any reported intake	Average BCERP intake (mg) of flavonol per day ^c
Arugula	1 Cup	158.8	0	
Kale	1 Cup	68.9	0	
Cranberries, raw	1/2 Cup	21.96	19 (2)	3.5
Onions	1/2 Cup	19.51	913 (87)	4.2
Spinach	1 Cup	18.02	114 (11)	1.5
Blueberries	1/2 Cup	10.59	90 (8)	4.2
Pears	1 Medium fruit	4.81	113 (10)	5.8
Plums	1 Medium fruit	4.01	58 (5)	4.6
Apple w/ skin	1 Medium fruit	3.38	836 (80)	3.5
Cherries	1/2 Cup	2.92	36 (3)	1.5
Tomato/tomato products	1/2 Cup	2.88	939 (90)	1.7
Cocoa dry powder, unsweetened	1 Tablespoon	2.88	204 (20)	1.2
Tea	8 fl oz	0.22	194 (19)	5.4
Grapes	1/2 Cup	2.10	296 (28)	2.3
Strawberries	1/2 Cup	1.69	251 (24)	2.8

The major contribution of foods to total flavonol intake: apples 28%, onions 19%, tea 11%, tomato products 11%, strawberries 7%, grapes 7%, pears 7%, broccoli 5%, and blueberries 4%.

^aServing Sizes based on the USDA guidelines.

^bTotal flavonol values were derived from the nutrient database described in Methods.

^cAverage flavonol intake includes only girls eating that food.

Table 3. Food items containing high lignan content and frequency of consumption at baseline in 1,044 BCERP participants, 2004–2014

Food	Serving size ^a	Total lignan (mg)/serving ^b	N(%) any reported intake	Average BCERP intake (mg) of lignan per day ^c
Spinach	1 Cup	0.76	114 (11)	0.05
Orange juice	3/4 Cup	0.52	592 (57)	0.53
Grapefruit juice	3/4 Cup	0.52	17 (2)	1.80
Eggplant	1/2 Cup	0.40	5	0.12
Squash	1/2 Cup	0.38	69 (6)	0.21
Carrots	1/2 Cup	0.35	688 (66)	0.14
Yams/sweet potatoes	1/2 Cup	0.30	41 (4)	0.43
Broccoli	1/2 Cup	0.23	314 (30)	0.09
Hamburgers/tacos	2–3 Ounces	0.21	563 (54)	0.16
Cauliflower	1/2 Cup	0.10	66 (5)	0.07
Strawberries	1/2 Cup	0.08	251 (24)	0.51
French fries/potatoes	1/2 Cup	0.08	702 (67)	0.11
Banana	1 Medium fruit	0.07	395 (38)	0.07
Tomato/tomato products	1/2 Cup	0.06	939 (90)	0.1
Peanut butter	2 Tablespoons	0.05	375 (36)	0.06
Apples/applesauce	1 Medium fruit	0.05	836 (80)	0.05
Pears, raw	1 Medium fruit	0.05	113 (10)	0.24

BCERP, Breast Cancer and Environment Research Project.

The major contribution of foods to total lignan intake—orange juice 35%, strawberries 17%, broccoli 8%, carrots 8%, potatoes 6%, and meat 5%.

^aServing sizes based on the USDA guidelines.

^bTotal lignan values were derived from the nutrient database described in Methods.

^cAverage lignan intake includes only girls eating that food.

Table 4. Baseline characteristics of participants by flavonol intake in BCERP, 2004–2014

Characteristic	Median (IQR)					P-value ^a
	Quintile of Flavonol Intake					
	1 (n = 204)	2 (n = 204)	3 (n = 203)	4 (n = 206)	5 (n = 202)	
Flavonols (mg/day)	2.7 (1.9–3.1)	4.4 (3.9–4.8)	6.0 (5.6–6.4)	7.9 (7.4–8.4)	11.1 (10.0–13.4)	
Baseline age (years)	7.2 (6.6–7.8)	7.2 (6.7–7.8)	7.4 (6.9–7.8)	7.5 (6.9–7.8)	7.4 (6.9–7.8)	0.06
Calories (kcal/day)	1,413 (1,209–1,650)	1,495 (1,290–1,730)	1,533 (1,386–1,790)	1,601 (1,453–1,860)	1,674 (1,453–1,860)	0.001
Child race/ethnicity (%)						
Black	30	35	28	25	31	0.09
Hispanic	32	32	32	32	25	
White	33	28	34	35	42	
Asian	5	4	6	8	3	
Parent or guardian education ^b						
≤ High school	32	32	25	25	25	0.16
> High school	68	68	75	75	75	
Baseline BMI Percentile ^c						
< 50th	35	33	32	31	36	0.41
50-85th	29	31	39	34	36	
≥ 85th	36	35	29	36	28	

BCERP, Breast Cancer and Environment Research Project; IQR, interquartile range.

^a χ^2 -test for categorical variables and Kruskal–Wallis test for continuous variables.

^bn = 1,021 girls with all variables.

^cBMI (kg/mg²) specific for age and sex according to CDC growth data.

white girls in a number of studies (28). This present study is the only one that has examined the association between these two phytoestrogens, which are widespread in the Western

diet, and age at menarche. Previous longitudinal and cross-sectional studies have looked at soy and other dietary components and age at menarche with mixed results, possibly

Table 5. Baseline characteristics of participants by lignan intake in BCERP 2004–2014

Characteristic	Median (IQR)					<i>P</i> -value ^a
	Quintile of lignan intake					
	1 (<i>n</i> = 202)	2 (<i>n</i> = 201)	3 (<i>n</i> = 208)	4 (<i>n</i> = 205)	5 (<i>n</i> = 204)	
Lignans (mg/day)	0.14 (0.10–0.17)	0.26 (0.23–0.28)	0.39 (0.35–0.42)	0.56 (0.50–0.62)	0.88 (0.77–1.06)	
Baseline age (years)	7.3 (6.6–7.8)	7.2 (6.7–7.7)	7.4 (6.9–7.9)	7.3 (6.7–7.7)	7.4 (7.0–7.9)	0.01
Calories (kcal/day)	1,458 (1,278–1,678)	1,534 (1,293–1,728)	1,544 (1,327–1,826)	1,599 (1,379–1,792)	1,598 (1,432–1,792)	0.001
Child race/ethnicity (%)						
Black	30	31	32	33	23	0.31
Hispanic	35	26	29	29	36	
White	31	36	35	33	37	
Asian	5	7	5	6	5	
Parent or guardian education ^b						
≤ High school	33	24	31	30	26	0.24
> High school	67	76	69	70	74	
Baseline BMI percentile ^c						
< 50th	30	37	37	35	28	0.41
50–85th	35	31	34	34	36	
≥ 85th	35	32	29	31	36	

BCERP, Breast Cancer and Environment Research Project; IQR, interquartile range.

^a χ^2 -test for categorical variables and Kruskal–Wallis for continuous variables.

^bn = 1,021 girls with all variables.

^cBMI (kg/mg²) specific for age and gender according to CDC growth data.

Table 6. HRs and 95% CI from Cox proportional models for two dietary phytoestrogens in relation to menarche BCERP, 2004–2014

Quintile		HR (95% CI) for menarche lignan and flavonol intake				
		1	2	3	4	5
Flavonols	Median (mg/day)	2.7	4.4	6	7.9	11.1
	Range(mg/day)	0.035–3.6	3.6–5.19	5.19–6.87	6.88–9.11	9.12–28.12
	N per quartile	208	209	209	209	208
	HR ^a (CI)	1 (Ref)	1.04 (0.84–1.28)	1.09 (0.88–1.34)	1.02 (0.82–1.25)	0.83 (0.66–1.03)
	HR ^b (CI)	1 (Ref)	0.86 (0.70–1.06)	0.92 (0.75–1.12)	0.95 (0.78–1.17)	0.80 (0.66–1.00)*
	Median menarche (months) ^c	144	146	144	142	147
Lignans	Median (mg/day)	0.14	0.26	0.39	0.56	0.88
	Range (mg/day)	0.01–0.196	0.197–0.314	0.316–0.45	0.45–0.69	0.69–2.76
	N per quartile	208	209	209	209	209
	HR ^a (CI)	1 (Ref)	0.80 (0.65–0.99)*	0.88 (0.71–1.09)	0.84 (0.69–1.04)	0.85 (0.69–1.05)
	HR ^b (CI)	1 (Ref)	0.81 (0.66–1.00)*	0.81 (0.66–1.00)	0.86 (0.70–1.06)	0.84 (0.68–1.04)
	Median menarche (months) ^c	142	147	143	146	145

CI, confidence interval; BCERP, Breast Cancer and Environment Research Project; HR, hazard ratio.

*P < 0.05.

^aHR (CI): nutrient density calorie intake; unadjusted model.

^bHR (CI): nutrient density calorie intake; adjusted for race, baseline BMI% dichotomized > or < 85%.

^cPredicted from survivor function of adjusted Cox models.

Table 7. Interaction* of lignan intake and BMI with age at menarche

Lignan intake Quintiles	All	HR (95% CI) adjusted for race/ethnicity				Median age at menarche (months)
		N	Normal weight, BMI < 85%	Median age at menarche (months)	N	Overweight, obese BMI ≥ 85%
1	1.00 (ref)	135	1.00 (ref)	148	73	1.00 (ref)
2	0.81 (0.66–1.00)	148	0.93 (0.72–1.2)	153	62	0.66 (0.45–0.95)
3	0.91 (0.74–1.12)	147	1.1 (0.78–1.4)	149	62	0.66 (0.45–0.94)
4	0.86 (0.70–1.06)	144	1.0 (0.78–1.3)	151	65	0.63 (0.44–0.91)
5	0.84 (0.68–1.04)	134	1.1 (0.84–1.4)	148	75	0.56 (0.40–0.80)

CI, confidence interval; HR, hazard ratio.

* $P < 0.01$.

due to the time when diet was assessed during childhood and the type of database used (10,11,13,16).

Our findings are particularly noteworthy, given that flavonol and lignan intake in this cohort is relatively low compared with a few studies reporting these phytoestrogens in US adults (29,30). Intake of phytoestrogens is usually lower in children, especially in an urban low socioeconomic status population (14). Flaxseeds are rich sources of lignans (80 mg per 1 oz serving size), although they were not consumed in our cohort. In contrast, flavonols and lignans are found in much lower concentrations in many more frequently consumed foods such as potatoes, grains, cereals, strawberries, coffee, tea, and wine. Girls in this cohort consumed a serving size per day of some of the foods with the highest content of flavonol and lignan (Tables 2 and 3). Isoflavones, important phytoestrogens associated with reduced risk of breast cancer, and a later onset of puberty come from different types of foods compared with flavonols and lignans. Isoflavones are found in soy foods (soybeans, tofu, soy milk, and soy nuts) that are infrequently consumed in the United States compared with the foods high in flavonols and lignans. We did not examine these in our study. Although some foods high in lignans, flaxseeds, and spinach also contain isoflavones, the concentration of isoflavones in these foods is extremely low when compared with that in soybeans.

BMI has been shown to be a strong predictor of early menarche and early pubertal development (31). We saw that overweight/obesity modified the relationship between lignan intake and age at menarche. This finding is consistent with evidence of possible mechanisms that lignans regulate adipogenesis through the modulation of the estrogen receptor-signaling pathway in both animal and human studies (21), and that phytoestrogens activate the PPAR γ receptor that controls many genes associated with fat and energy metabolism (32). Lignans are metabolized to enterolactone and enterodiol by gut microbiota in the colon, and a few human studies have shown that higher consumption of lignans was associated with lower overall fat mass (33). Enterolactone is also an aromatase inhibitor, which could reduce estrogen levels essential for pubertal changes.

Studies of menarche have measured diet at different time points of childhood, ranging from 1–3 years (34) to mid

childhood (9 years; (ref. 8)) and later (9–14 years; (10)). Evidence is mixed as to when the critical period may be for diet to have an impact on the occurrence of menarche. Studies have shown associations between early-childhood diet and growth and pubertal development (35,36). Birth may be a critical window for environmental exposures related to pubertal development, as it is a time when the reproductive tract is susceptible to changes in the developmental process. Soy intake during infancy altered the timing of menarche (17). Rapid weight gain in infancy and early childhood is a determinant of timing of pubertal development, and this reflects the importance of early “windows” during which nutrition can have long-term consequences for growth and development (37). However, later “windows of susceptibility” may have a different influence. For example, a protective effect of dietary phytoestrogen intake on breast cancer risk was observed for relatively high isoflavone consumption before puberty (18) and during adolescence (38). Phytoestrogen exposure may need to occur in a critical window long before the outcome to have an influence.

Strengths of this study are its prospective nature, comprehensive diet assessment, and reliable outcome. We measured diet when girls were 6–8 years of age, several years before menarche, strengthening conclusions of the observed relationship. Diet was assessed using an average of multiple 24-h dietary recalls, and we utilized an extensive database created to assess flavonol and lignan intake. The idea that dietary intake may change over time has been studied in children aged 9–18 years; dietary intake patterns that were assessed 5 years apart were stable over time (39). A main limitation is the method of assessing flavonol and lignan intake. Our database was developed using the currently known information of foods with flavonol and lignan content, which may not have had flavonol and lignan content of every food item reported in the Nutrition Data System for Research (NDSR, Minn, Minnesota) questionnaire. Another method of lignan exposure assessment is using urine biomarkers; however, biomarkers have temporality concerns. In our previous report of this cohort for diet and breast development, we showed low-moderate correlations between urine enterolactone and lignan intake assessed through dietary records, and urinary enterolactone was associated with pubertal development (14,25).

We report an association between higher childhood consumption of flavonols and lignans and later age at menarche. These agents have known anti-hormonal and anti-obesogenic properties. It is possible that flavonols and lignans reflect a healthy diet, as they are derived mainly from fruits, vegetables, and fiber in our cohort. However, the associations remain after adjusting for fiber, which may be another surrogate for a healthy diet. Although it is difficult to disentangle the individual effects of these phytoestrogens from fruits, vegetables, and fiber, nonetheless they all may have a role in the observed pubertal delay. Our findings suggest that specific dietary bioactives in certain fruits and vegetables may have additional long-term benefits, and dietary modifications are of continued importance to young girls.

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DISCLAIMER

Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIEHS or NCI, the National Institutes of Health, the Centers for Disease Control and Prevention, Atlanta, Georgia, or the California Department of Public Health.

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