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Onion and Garlic Intake and Breast Cancer, a Case-Control Study in Puerto Rico

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ABSTRACT

Studies show an inverse association between onion and garlic intake and risk of cancers of the lung, prostate, and stomach. There is limited evidence on the association between onion and garlic intake and breast cancer. We assessed this association in a population-based, case-control study in Puerto Rico. Incident, primary breast cancer cases ($n = 314$) were identified among women aged 30–79 from hospital and clinic records. Controls ($n = 346$) were women with no history of cancer other than nonmelanoma skin cancer, residents of the same area. Dietary intake was estimated using a food frequency questionnaire. Total onion and garlic intake included sofrito (a popular garlic- and onion-based condiment) intake frequency. Unconditional logistic regression assessed the association between onion and garlic consumption and breast cancer adjusting for age, education, parity, family history, body mass index, age at menarche, total energy, and smoking. Inverse associations with breast cancer were observed for moderate (OR (odds ratio) = 0.59, 95% CI (confidence interval): 0.35, 1.01) and high consumption (OR = 0.51, 95% CI: 0.30, 0.87) compared to low consumption of onion and garlic (P_{trend} = 0.02). Results were similar when stratified by menopausal status. Study results suggest that high onion and garlic consumption is protective against breast cancer in this population.

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Introduction

Breast cancer is the leading cause of cancer-related deaths among women worldwide (1). Consistent with the global trend, breast cancer rates in Puerto Rico have steadily increased from 18 per 100, 000 in the 1960s to 50 per 100,000 in the 1990s (2). From 1987 to 2014, the incidence of invasive breast cancer among women increased by an average of 1.5% per year (3). Breast cancer accounted for 29.0% of all cancer cases and 18.4% of cancer deaths in Puerto Rico between 2008 and 2014 (3). Findings regarding the association of onion and garlic consumption with breast cancer have been inconsistent (Table 1). In studies in France, Mexico, Taiwan, and China, onion and garlic intake was inversely associated with breast cancer (4–7), but no association was seen in studies in the Netherlands, Italy, and China (8–11). In a study in Iran, there was decreased risk of breast cancer associated with garlic consumption, but increased risk with onion consumption (12). Garlic consumption has been shown to be inversely associated with risk of colon cancer in a cohort study (13), and with prostate (14), ovarian, esophageal, laryngeal, oral, as well as renal cancer (15) in case-control studies. Onion consumption has been found to be inversely associated with cancers of the bowel (16) and larynx (14) in case-control studies, and with stomach cancer in a cohort study (17). Consumption of onion and garlic at extremely high levels is associated with adverse effects in animal models; raw garlic juice (5 ml/kg) led to death in mice due to stomach injury after 21 days (18). This dose approximately equals the daily consumption of two cloves/kilogram. Similarly, oral administration of high

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Table 1. Literature review of epidemiologic studies on the relationship between onion and garlic consumption and breast cancer.

Author, year	Study design	Population	Type of *Allium* vegetables	Measure of consumption	Results
Dorant et al., 1995	Nested case control	469 cases and 1,713 controls, 1986–1989, the Netherlands	Garlic supplements, onions, leek	Garlic supplements: Daily intake Onions: #/day Leek: #/month	• Exclusive garlic supplements and BC: OR = 0.75 (0.58, 1.31) • Garlic + other supplements and BC: OR = 1.12 (0.63, 1.99) • Onion consumption and BC: ≥0.5/day vs. no intake OR = 0.95 (0.61, 1.47) • Leek consumption and BC: >2/month vs. no intake OR = 1.08 (0.79, 1.48)
Challier et al., 1998	Case control	345 cases and 345 controls, 1986–1989, France	Garlic and onions	Frequency/week	• Onion and garlic consumption >16 times/week vs. ≤6 times/week (ref): -OR = 0.30 (95%CI: 0.17, 0.52)*
Franceschi et al., 1998	Case control	2,569 cases, 5,155 controls, 1991–1996, Italy	Cooked garlic	Low, medium, high	• Cooked garlic-high vs. low (ref): OR = 0.90 (95%CI: 0.9, 1.0) • Cooked onions-high vs. low (ref): OR = 1.00 (95% CI: 0.9, 1.1)
Torres-Sánchez et al., 2000	Case control	198 cases and 198 controls, 1994–1995, Mexico	Onions	Slice/day	• Onion consumption ≥1 slice/day vs. <1 slice/day (ref): -Premenopausal women-OR = 0.18 (95%CI: 0.07, 0.42)* -Postmenopausal women-OR = 0.37 (95%CI: 0.18, 0.76)* -Combined-OR = 0.27 (95%CI: 0.16, 0.47)*
Lee et al., 2005	Case control	250 cases and 219 controls, 1996–1999, Taiwan	*Allium* vegetables	Grams/week	• *Allium* vegetables >52.2 g/week (Q_5) vs. <9.5 g/week (Q_1, ref): -≤40 years of age-OR = 1.0 (95%CI: 0.5, 2.1) ->40 years of age-OR = 0.4 (95%CI: 0.2, 0.9)* -Combined-OR = 0.6 (95%CI: 0.4, 1.0)
Zhang et al., 2009	Case control	438 cases and 438 controls, 2007–2008, China	*Allium* vegetables	Grams/day	• *Allium* vegetables and BC: (Q_5) vs. (Q_1, ref) OR = 0.92 (0.61, 1.38)
Bao et al., 2012	Case control	3,443 cases and 3,474 controls in 1996–1998, 2002–2005, China	*Allium* vegetables	Grams/day	• *Allium* vegetables and BC: ≥14.74 g/day (Q_5) vs. <3 g/day (Q_1, ref) -OR = 0.83 (95%CI: 0.71, 0.98)* for all cases -OR = 0.83 (95%CI: 0.67, 1.03) for ER+/PR + cases -OR = 0.91 (95%CI: 0.69, 1.21) for ER-/PR- cases -OR = 0.94 (95%CI: 0.63, 1.42) for ER+/PR- cases -OR = 0.89 (95%CI: 0.55, 1.42) for ER-/PR + cases
Yu et al., 2012	Cross-sectional	122,058 participants, 2008, China	Garlic	Frequent, infrequent	• Infrequent garlic consumption and BC: OR = 1.23 (95% CI: 0.97, 1.56)
Pourzand et al., 2016	Case control	285 cases, 297 controls, 2012–2013, Iran	*Allium* vegetables (cooked and raw)	Yes/no; grams/day	• Raw onion consumers vs. nonconsumers (ref): OR = 0.73 (95%CI: 0.48, 2.70) • Cooked onion consumers vs. nonconsumers (ref): OR = 1.54 (95% CI: 1.02, 2.32)* • Garlic consumers vs. nonconsumers (ref): OR = 1.39 (95%CI: 0.81, 2.37)

*Statistically significant.

BC: breast cancer; CI: confidence interval; ER: estrogen receptor; OR: odds ratio; PR: progesterone receptor.

doses of onion (500 mg/kg) led to tissue and lung damage in rats (19). Among humans, excessive garlic consumption on an empty stomach has been associated with gastrointestinal upset and changes in the microbiota of the intestine (20, 21). Overall, very few studies have focused on the adverse effects of excessive onion and garlic consumption in humans, none at levels comparable to the animal studies.

The genus *Allium* contains about 500 species including garlic, onions, leeks, and chives, foods which are commonly consumed worldwide. Onions (*Allium cepa*) and garlic (*Allium sativum*) are one of the world's oldest cultivated plants, and are popularly consumed in stews ("guisos"), beans, and rice dishes in Puerto Rican cuisine today (22). Garlic forms an important component of the Puerto Rican diet, and is mainly consumed in the cooked form in various sauces and seasonings, the most common being a condiment, "sofrito" (23).

Onions and garlic are rich in flavonols and organosulfur compounds (24, 25). Garlic has been used as a remedial agent for heart diseases, tumors, and headaches in ancient Chinese, Indian, and Egyptian traditions (26, 27). S-allylcysteine, diallyl sulfide, diallyl disulfide, diallyl trisulfide, organosulfur compounds found in garlic, have been found to be associated with anticarcinogenic properties in humans (27–29). Onions have been applied to wounds and to treat digestive ailments for thousands of years. They are rich in flavonoids and alk(en)yl cysteine sulphoxides (24, 30–32). A number of possible anticarcinogenic mechanisms have been proposed for these compounds including inhibition of cell proliferation, alteration of enzyme activities, and immune modulation (24, 33).

Puerto Rico lends itself to the study of health effects of garlic and onion consumption because of the variability in intake, with many consuming larger amounts than in many other cuisines such as those in Europe or much of the US. There are, to our knowledge, no previous population-based studies on the association between onion and garlic intake and breast cancer among women in Puerto Rico; we report here on findings from a population-based case-control study in Puerto Rico.

Methods

Participant Recruitment

The Atabey Study of Breast Cancer, a population-based case-control study named after the Puerto Rican goddess of fertility, was conducted in Puerto Rico between November 2008 and June 2014. Cases were women aged 30–79, and residents of the San Juan Metropolitan Area, including San Juan, Bayamón, Guaynabo, and Carolina municipalities. All breast cancer cases were eligible for inclusion if they had primary, incident, and histologically confirmed breast cancer with no previous history of cancer (other than nonmelanoma skin cancer). Breast cancer cases were identified from the hospitals and breast surgeons serving the San Juan area; completeness of case ascertainment was confirmed through the Puerto Rico Central Cancer Registry ($n = 315$). Controls were population based, and consisted of women residing in the same geographical area, who did not have a history of cancer (except nonmelanoma skin cancer). The sampling frame list was provided by Dr. Gilberto Ramos, biostatistician and director of the Puerto Rico Health Interview Survey, a national cross-sectional health survey based on a multistage sampling procedure of geopolitical conglomerates (municipalities) as defined by the US Bureau of the Census (34). The selection of potential controls for the Atabey study was similarly based on a multistage cluster sampling stratified by targeted municipalities (counties). The sampling frame consisted of census blocks that were the primary sampling units. Census blocks were randomly selected and a household within the block was then randomly selected. A community outreach worker (CO) visited that household and if an eligible woman resided there, she was invited to enroll in the study. If there was no eligible woman or the woman did not agree to participate, the next neighbor was approached, until all households in the block were approached, if necessary. If there was no answer at a house, the CO repeated the visit at least three times. There was no substitution of households. Controls were frequency matched to cases on age and broad geographical residential area. Informed consent was obtained from all study participants. The study protocol was approved by the Institutional Review Boards of the University of Puerto Rico, University at Buffalo, and the Human Subjects Protection Scientist of the Congressionally Directed Medical Research Program. Participants received a small monetary compensation to cover the costs of participation (parking, other travel-related costs).

Data Collection

Interviewer-administered questionnaires were used to collect data regarding demographic factors, personal medical history, family history of cancer, and reproductive history. Usual diet was assessed with a food

frequency questionnaire previously calibrated in this population, adapted to include foods frequently consumed by this population. It included a question about consumption of "sofrito," a garlic- and onion-based condiment widely used in Puerto Rican cuisine that could also contain tomatoes, bell peppers, cilantro, black pepper, and lard or oil. The specific question was "How many times did you cook or consume commercial and homemade sofrito 12 months ago?". Onion and garlic consumption was additionally measured by a question regarding onion and garlic intake, excluding sofrito, as follows: "How many times did you cook or consume garlic and onions (not in sofrito) 12 months ago?". Possible responses were never/rarely, number of times per month, number of times per week, or number of times daily.

Statistical Analysis

The variables for onion and garlic intake frequency, as well as sofrito intake frequency were categorized as follows: never, >0 – <twice/week, ≥twice/week – <once/day, once/day, and > once/day. These categories were given scores from 0 to 4 in an ordinal manner and summed for the two questions related to onion and garlic and for sofrito intake; the sum of scores ranged from 0 to 8. Scores from 0 to 2 were defined as "low" exposure, 3 to 4 as "moderate" exposure, and 5 to 8 as "high" exposure. The low category was the referent.

Characteristics of cases and controls were compared with *t*-tests and analysis of variance (ANOVA) for continuous covariates, and chi-square tests for categorical covariates. Unconditional logistic regression analyses were performed to assess the association between onion and garlic consumption and breast cancer. Separate analyses were conducted for the onion and garlic intake frequency variable, the sofrito intake frequency variable, and also for the combined total exposure variable with breast cancer. In all these analyses, model 1 was an unadjusted model. Model 2 was adjusted for age (years) and education (<12 yr, 12 yr, technical or vocational or associates degree, bachelor's degree, graduate school), and model 3 was further adjusted for parity, family history of breast cancer (yes/no), body mass index (kg/m^2), age at menarche (years), total energy (kilocalories), and smoking status (never/ever). The details about finer categories of smoking (never/former/current) were available; however, the former and current smoking categories were collapsed because of the small cell sizes. Furthermore, upon adding this variable (never/former/current smokers) to our models, the results changed by <1% (results not shown), and hence the binary smoking variable was kept in the models. Information regarding second-hand smoking was available as well, particularly whether the participants had ever worked/lived with a smoker. However, adding this variable to the final model changed the result by <1%, and hence it was excluded. Model 4 was included in the analyses of the separate exposure variables, wherein, the model for the association between sofrito intake and breast cancer was further adjusted for onion and garlic intake frequency, and the model for the association between onion and garlic intake and breast cancer was adjusted for sofrito intake frequency. The *P* value for an analysis with the exposure as an ordinal variable was used to examine trend. The association between total exposure to onion and garlic and breast cancer was assessed among all participants, as well as in strata defined by menopausal status. All the analyses were conducted among the complete case sample consisting of 314 cases and 346 controls.

Results

Characteristics of the 314 cases and 346 controls are presented in Table 2. Cases were on average somewhat older than controls (mean age 58.7 ± 11.0 yr vs. 54.1 ± 13.4 yr), and had higher education. Additionally, cases and controls were different based on BMI, physical activity, parity, and family history of breast cancer. Distribution of participants' characteristics by their total onion/garlic consumption is presented in Table 3. There were differences in education and parity by consumption.

The associations between onion and garlic intake frequency, and sofrito intake frequency with breast cancer are shown in Table 4. In the fully adjusted model, there was a trend toward lower breast cancer risk associated with increased onion and garlic consumption, although confidence intervals included the null and the *P* for trend did not reach statistical significance (P_{trend} = 0.18). Sofrito intake, when examined alone, was inversely associated with breast cancer; for those consuming sofrito more than once/day, there was a 67% decrease in risk compared to never consumers in the adjusted model (OR (odds ratio) = 0.33, 95% CI (confidence interval): 0.11, 0.99, P_{trend} = 0.02). With further adjustment for onion and garlic intake frequency, these inverse associations with sofrito consumption persisted (OR = 0.36, 95% CI: 0.12, 1.10; P_{trend} = 0.05), however, did not reach statistical significance.

Table 2. Demographic characteristics of cases and controls among total population, and stratified by menopausal status.

	Total population			Premenopausal women			Postmenopausal women		
Variables	Cases	Controls	*P* value*	Cases	Controls	*P* value*	Cases	Controls	*P* value*
Total *N* (%)	314 (47.6)	346 (52.4)		83 (38.4)	133 (61.6)		231 (52.0)	213 (48.0)	
Age, years	58.7 (11.0)	54.1 (13.4)	<0.01	45.5 (5.4)	40.2 (6.4)	<0.01	63.5 (8.2)	62.7 (8.5)	0.33
Mean (SD)									
Education									
<12 yr, *n* (%)	48 (15.3)	83 (24.0)		10 (12.1)	30 (22.6)		38 (16.5)	53 (24.9)	
12 yr, *n* (%)	54 (17.2)	69 (19.9)	<0.01	7 (8.4)	25 (18.8)	0.01	47 (20.4)	44 (20.7)	0.02
Technical[a], *n* (%)	84 (26.8)	95 (27.5)		24 (28.9)	38 (28.6)		60 (26.0)	57 (26.8)	
Bachelor's degree, *n* (%)	82 (26.1)	77 (22.3)		26 (31.3)	28 (21.1)		56 (24.2)	49 (23.0)	
Graduate school, *n* (%)	46 (14.7)	22 (6.4)		16 (19.3)	12 (9.0)		30 (13.0)	10 (4.7)	
BMI (kg/m^2)	30.0	31.3	<0.01	30.3	31.9	0.15	29.9 (5.5)	31.0 (6.3)	0.04
Mean (SD)	(5.8)	(7.3)		(6.6)	(8.6)				
Smoking									
Never, *n* (%)	221 (70.4)	220 (63.6)	0.06	58 (69.9)	81 (60.9)	0.18	163 (70.6)	139 (65.3)	0.23
Ever, *n* (%)	93 (29.6)	126 (36.4)		25 (30.1)	52 (39.1)		68 (29.4)	74 (34.7)	
Physical activity, MET-mins/wk									
Mean (SD)	2475.6 (1401)	2855.5 (1480)	<0.01	2995.5 (1535)	3163.4 (1487)	0.43	2290.3 (1304)	2662.5 (1445)	<0.01
HT	NA	NA		NA	NA		86	61	0.06
Ever, *n* (%)							(38.2)	(29.8)	
Age at menarche	12.2	12.5	0.11	12.0	12.5	0.06	12.3	12.5	0.44
Mean (SD)	(1.6)	(1.8)		(1.6)	(1.9)		(1.7)	(1.8)	
Pregnancy	260	298	0.03	64	115	<0.01	196	183	0.03
Ever pregnant, *n* (%)	(82.8)	(86.1)		(77.1)	(86.5)		(84.9)	(85.9)	
Number of children	2.6 (1.3)	2.9 (1.4)	<0.01	2.2	2.7	0.02	2.7	3.1	<0.01
Mean (SD)				(1.1)	(1.3)		(1.3)	(1.5)	
Family history of breast cancer[b]									
Yes, *n* (%)	66 (21.0)	30 (8.7)	<0.01	11 (13.3)	7 (5.3)	0.04	55 (23.8)	23 (10.8)	<0.01

BMI: body mass index; HT: hormone therapy; MET: metabolic equivalents; NA: not applicable.
[a]Also includes vocational/associate.

[b]First degree relatives.

*t-tests for continuous variables and chi square test/Fisher's exact test for categorical variables.

Table 3. Comparison of participants' demographic characteristics by total onion and garlic consumption.

	Total onion and garlic consumption			
Variable	Low	Medium	High	*P* value*
Total *N* (%)	93, 14.1	279, 42.3	288, 43.6	
Age, years	56.9 (12.9)	57.4 (12.4)	55.1 (12.5)	0.09
Mean (SD)				
Education				
<12 yr, *n* (%)	9 (9.7)	60 (21.5)	62 (21.5)	
12 yr, *n* (%)	14 (15.1)	51 (18.3)	58 (20.1)	0.01
Technical/vocational/associate, *n* (%)	22 (23.7)	77 (27.6)	80 (27.8)	
Bachelor's degree, *n* (%)	29 (31.2)	61 (21.9)	69 (24.0)	
Graduate school, *n* (%)	19 (20.4)	30 (10.8)	19 (6.6)	
BMI (kg/m^2)	29.6	30.6	31.1	0.15
Mean (SD)	(6.5)	(6.4)	(7.0)	
Smoking				
Never, *n* (%)	55 (59.1)	196 (70.3)	190 (66.0)	0.13
Ever, *n* (%)	38 (40.9)	83 (29.8)	98 (34.0)	
Physical activity, MET-mins/wk	2743.1	2700.5	2625.6	0.74
Mean (SD)	(1424)	(1497)	(1424)	
Age at menarche	12.2	12.5	12.3	0.23
Mean (SD)	(1.6)	(1.7)	(1.8)	
Menopausal status				
Premenopausal, *n* (%)	29 (31.2)	87 (31.2)	100 (34.7)	0.63
Postmenopausal, *n* (%)	64 (68.8)	192 (68.8)	188 (65.3)	
Hormone therapy[a]	28 (39.4)	62 (31.3)	57 (28.5)	0.23
Ever				
Pregnancy	71 (76.3)	236 (84.6)	251 (87.2)	0.07
Ever pregnant, *n* (%)				
Number of children	2.3 (1.0)	2.9 (1.5)	2.8 (1.3)	0.01
Mean (SD)				
Family history of breast cancer, first degree relatives				
Yes, *n* (%)	15 (16.1)	45 (16.1)	36 (12.5)	0.42

BMI: body mass index; MET: metabolic equivalents.
[a]Postmenopausal women only.

*ANOVA test for continuous variables and chi square test/Fisher's exact test for categorical variables.

Table 4. Association between onion and garlic intake (excluding sofrito) and breast cancer, and sofrito intake (alone) and breast cancer in the total population.

Intake frequency	Ca/Co	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[c]	OR (95% CI)[d]
		Onion and garlic intake, total population ($n = 660$)			
Never	54/58	1.00	1.00	1.00	1.00
>0 – <twice/week	43/39	1.18 (0.67, 2.10)	0.91 (0.50, 1.65)	0.92 (0.49, 1.72)	0.82 (0.40, 1.67)
≥twice/week – <once/day	102/87	1.26 (0.79, 2.01)	1.07 (0.66, 1.74)	0.96 (0.58, 1.60)	0.96 (0.53, 1.73)
Once/day	107/150	0.77 (0.49, 1.20)	0.78 (0.49, 1.24)	0.76 (0.47, 1.23)	0.80 (0.48, 1.34)
>Once/day	8/12	0.72 (0.27, 1.89)	0.64 (0.23, 1.74)	0.56 (0.19, 1.61)	0.69 (0.22, 2.15)
P_{trend}		0.11	0.22	0.18	0.43
		Sofrito intake, total population ($n = 660$)			
Never	22/13	1.00	1.00	1.00	1.00
>0 – <Twice/week	31/22	0.83 (0.35, 2.00)	0.71 (0.29, 1.77)	0.72 (0.28, 1.89)	0.76 (0.27, 2.14)
≥twice/week – <once/day	119/101	0.70 (0.33, 1.45)	0.63 (0.29, 1.35)	0.60 (0.27, 1.34)	0.57 (0.24, 1.36)
Once/day	132/186	**0.42 (0.20, 0.86)**	**0.46 (0.22, 0.98)**	0.49 (0.22, 1.10)	0.53 (0.23, 1.19)
>Once/day	10/24	**0.25 (0.09, 0.67)**	**0.28 (0.10, 0.80)**	**0.33 (0.11, 0.99)**	0.36 (0.12, 1.10)
P_{trend}		**<0.0001**	**<0.01**	**0.02**	0.05

Ca/Co: cases/controls; CI: confidence interval; OR: odds ratio.
Estimates in bold represent statistical significance at an alpha of 0.05.
[a]Crude.
[b]Adjusted for age, education.
[c]Further adjusted for parity, family history of breast cancer, BMI, age at menarche, smoking, total energy.
[d]Further adjusted for sofrito intake if main exposure was onion and garlic, and adjusted for onion and garlic intake if main exposure was sofrito intake.

Table 5. Association between total onion and garlic intake (including sofrito) and breast cancer in the total population, and by menopausal status.

Intake frequency*	Ca/Co	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[c]
		Total population ($n = 660$)		
Low	59/34	1.00	1.00	1.00
Medium	136/143	**0.55 (0.34, 0.89)**	0.61 (0.37, 1.02)	0.59 (0.35, 1.01)
High	119/169	**0.41 (0.25, 0.66)**	**0.50 (0.30, 0.83)**	**0.51 (0.30, 0.87)**
P_{trend}		**<0.001**	**<0.01**	**0.02**
		Premenopausal women ($n = 216$)		
Low	16/13	1.00	1.00	1.00
Medium	37/50	0.60 (0.26, 1.40)	0.59 (0.23, 1.52)	0.74 (0.28, 1.95)
High	30/70	**0.35 (0.15, 0.81)**	**0.38 (0.15, 0.99)**	0.52 (0.19, 1.40)
P_{trend}		**<0.01**	**0.04**	0.17
		Postmenopausal women ($n = 444$)		
Low	43/21	1.00	1.00	1.00
Medium	99/93	**0.52 (0.29, 0.94)**	0.58 (0.32, 1.07)	**0.49 (0.25, 0.94)**
High	89/99	**0.44 (0.24, 0.80)**	**0.52 (0.28, 0.96)**	**0.47 (0.24, 0.91)**
P_{trend}		**0.01**	0.06	0.07

Ca/Co: cases/controls; CI: confidence interval; OR: odds ratio.
Estimates in bold represent statistical significance at an alpha of 0.05.
[a]Crude.
[b]Adjusted for age, education.
[c]Further adjusted for parity, family history of breast cancer, BMI, age at menarche, smoking, total energy.
*The variables for onion and garlic, and sofrito intake frequency were categorized as never, >0 – <twice/week, ≥twice/week – <once/day, once/day, and > once/day. These categories were given scores from 0 to 4 in an ordinal manner and summed for the two questions related to onion and garlic and for sofrito intake; the sum of scores ranged from 0 to 8. Scores from 0 to 2 were defined as "low" exposure, 3 to 4 as "moderate" exposure, and 5 to 8 as "high" exposure.

The association between overall consumption of onion and garlic and breast cancer is shown in Table 5. Among all participants, onion and garlic consumption was inversely associated with breast cancer (OR = 0.59, 95% CI: 0.35, 1.01; OR = 0.51, 95% CI: 0.30, 0.87) for moderate and high consumption, respectively, and there was evidence of significant dose-response (P_{trend} = 0.02). In analyses stratified on menopausal status, associations were similar. Some of the CIs included the null, likely related to smaller sample size.

Discussion

We found inverse associations between total intake frequency of onion and garlic in moderate (OR = 0.59, 95% CI: 0.35, 1.01) and high (OR = 0.51, 95% CI: 0.30, 0.87) amounts with breast cancer. Similar protective associations were seen among both pre- and postmenopausal women.

Our results are consistent with the results of some of the previous studies of onion and garlic

consumption and breast cancer. In a case-control study in France, there was a 70% decrease in risk for consumption of garlic and onion; in that study, the categories were different from ours, >16 times/week compared to ≤6 times/week (5). In a study in Mexico, consumption of ≥1 slice of onion/day compared to <1 slice/day was also associated with about a 70% decrease in risk (7). Consistent with our findings, results were similar for pre- and postmenopausal women (7). In an analysis of intake of *Allium* vegetables as a whole in China, participants consuming ≥14.75 g/day of *Allium* vegetables were at significantly lower risk of breast cancer compared to those consuming <3.00 g/day (OR = 0.83, 95% CI: 0.71, 0.98) (4). However, results of other studies on intakes of these foods have not been consistent. In case-control studies in Italy, China, and the Netherlands, while there was evidence of a trend toward lower breast cancer risk with increasing consumption of *Allium* vegetables, particularly garlic and garlic supplements, associations did not reach statistical significance (8, 9, 11). In contrast, a study in Iran showed increased risk of breast cancer associated with cooked onion consumption (OR = 1.54, 95% CI: 1.02, 2.32) (12). It may be that another food in the Iranian diet eaten with the onion was associated with increased risk, or the observed result could be due to chance. The Iranian study was the only one that showed increased risk associated with onion consumption. Differences in the diets in various populations, the ways of consuming onions and garlic, for example, cooked vs. raw, and differences in the amount of consumption might explain the observed inconsistencies of the results.

Anticancer properties of garlic and onions have been studied in cell and animal models. Exposure to dialyl disulfide and S-allylmercaptocysteine, compounds found in garlic and onions, respectively, inhibits in vitro cell proliferation through the induction of a gap 2/mitosis phase arrest (33, 35). Quercetin, a constituent of onions, downregulates the expression of mutant p53 protein in breast cancer cell lines (36). Allicin, a component of garlic, has the ability to inhibit of proliferation of the Michigan Cancer Foundation-7 human breast cancer cell lines (37). Similar results have been seen in Michigan Cancer Foundation-7 cell lines in response to quercetin (38). Compounds from onions and garlic can also restrict DNA adduct formation with carcinogens in animal models (39). Diallyl sulfide has been shown to induce production of glutathione S-transferase and enhance glutathione peroxidase activity in vitro, thereby affecting the regulation of the cell cycle (24, 40, 41). Both onions and garlic have radical scavenging activities, another proposed anticancer mechanism (27, 42). Both aqueous and ethanolic extract of garlic powder stimulate the proliferation of rat spleen lymphocytes, which indicates immune modulation, a suggested anticancer mechanism (27, 43).

There is some evidence that cooking may reduce the anticancer activity of onions and garlic (44, 45). The antioxidant content of onions and garlic is substantially reduced upon heating them at 100 °C for about 40–60 min, and quercetin glycosides from onions are degraded when heated at 180 °C (45). One minute of microwave heating of garlic is shown to block its ability to inhibit the in vivo binding of the metabolites of 7, 12-dimethylbenzene(a)anthracene, a known carcinogen, to rat mammary epithelial cell DNA (44). The query regarding consumption of onions and garlic, not including sofrito, included both raw and cooked onions and garlic. The inclusion of cooked onions and garlic and a small number of participants with high consumption (>once/day), could have led to weaker associations between the consumption of onions and garlic alone, excluding sofrito, and breast cancer. In this study, sofrito consumption was high; approximately 53% of the participants reported consuming it once/day or more.

In interpretation of these findings, it is important to recognize the limitations of this study. The size of the study was small, particularly for analyses stratified on menopausal status. This study included only 12 participants who reported never consuming onion, garlic, and sofrito. As a result, the reference group that we chose for our analysis, the low exposure group, included participants who had some exposure to onions and garlic. As a result, we may have underestimated the true association between garlic and onion intake and breast cancer. Because the question regarding the consumption of onions and garlic focused on the intake of both these vegetables, we cannot separate the effect of onions and garlic while interpreting our study findings. Furthermore, there is not a standardized recipe for sofrito, a condiment which is frequently homemade and therefore varies at least somewhat in recipe from person to person. Hence, we were also not able to estimate the amount of onion and garlic in sofrito. Furthermore, our estimates of the consumption of onions and garlic were based on the use intake frequencies alone, potentially resulting in exposure misclassification. Likely such misclassification would be nondifferential, resulting in bias toward the null. Participants filled out a food

frequency questionnaire and a lifestyle/behavior-related questionnaire as part of data collection. At that time, onion and garlic intake was not mentioned as the main exposure of interest. Furthermore, there still is limited evidence that onion and garlic intake is inversely associated with the risk of breast cancer. As a result, it is unlikely that participants recalled their onion and garlic intake differentially based on their case status. Thus, the likelihood of recall bias is low. Although the recipe for sofrito varies to some extent, other ingredients such as bell peppers, tomatoes, cilantro, and black pepper are usually added. Since we did not adjust our models for these ingredients, we cannot be sure that our results were due to the sole effect of onions and garlic. Cases in this study were significantly older than controls (58.7 ± 11.0 yr vs. 54.1 ± 13.4 yr; $P < 0.01$). However, the difference in their ages was within 5 yr, the criterion that was used to frequency match the cases and controls.

Strengths of our study include high participation rates for both cases and controls; of the eligible participants, 72% cases and 65% controls participated in the study. We extensively examined and adjusted our models for several confounding factors, including total energy intake, which has not been done in several previous studies. We also assessed the independent associations of onion and garlic consumption, and sofrito consumption with breast cancer, which is vital in a population where sofrito forms an important component of the diet. Among women in Puerto Rico, we found variability in intake of onions and garlic, with 11.3% of controls reporting consuming them < twice/week. Others have also reported on onions and garlic as significant part in the Puerto Rican diet, and not just in the form of supplements (22, 23). Sofrito, a commonly used condiment in the Puerto Rican diet, contains raw onions and garlic as important constituents. We found a decrease in risk of breast cancer associated with increased consumption of onions and garlic, particularly sofrito. The associations were similar for pre- and postmenopausal women. To our knowledge, this is the first study to assess the relationship between onion and garlic consumption and breast cancer in Puerto Rico. Further studies in other populations with variable intake of these foods is warranted.

Conclusion

Our study provides evidence that the consumption of onions and garlic is associated with reduced risk of breast cancer. Further prospective studies and clinical trials are necessary to evaluate the use of onions and garlic in breast cancer prevention.

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Author Contributions

Ms. Desai analyzed the data and wrote the manuscript. Drs. Schelske-Santos, Mansilla-Rivera, Ramírez-Marrero designed the questionnaire used in the study, reviewed and edited the manuscript. Dr. Rosario-Rosado developed the methodology for the case ascertainment and the sample selection of the controls, reviewed and edited the manuscript. Dr. Nazario acquired funding, designed the study, designed the questionnaire used in the study, developed the methodology for the case ascertainment and the sample selection of the controls, supervised data collection, reviewed and edited the manuscript. Dr. Freudenheim acquired funding, designed the study, designed the questionnaire used in the study, supervised data collection, reviewed and edited the manuscript. Dr. Nie cleaned the data and calculated variables including the nutrient intakes from the questionnaire, reviewed and edited the manuscript. Drs. Myneni and Zhang contributed to data analysis, reviewed and edited the manuscript. Dr. Mu supervised and contributed to data analysis, reviewed and edited the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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