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ORIGINAL PAPER

Inflammation and breast density among female Chinese immigrants: exploring variations across neighborhoods

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Abstract

Purpose We examined associations of inflammation with breast density, a marker of breast cancer risk, among female Chinese immigrants and explored whether associations varied by neighborhood environment.

Methods Assessments of serum C-reactive protein (CRP), soluble tumor necrosis factor receptor 2 (sTNFR2), and breast density were performed among 401 Chinese immigrants across the Philadelphia region. Participant addresses were geocoded, with the majority residing in areas representing traditional urban enclaves (i.e., Chinatown and South Philadelphia) or an emerging enclave with a smaller, but rapidly growing Chinese immigrant population (i.e., the Near Northeast). The remainder was classified as residing in non-enclaves.

Results In multivariable adjusted regression models, CRP was inversely associated with dense breast area ($p=0.01$). Levels of sTNFR2 were also inversely associated with dense breast area, but these associations varied by neighborhood (interaction $p=0.01$); specifically, inverse associations were observed among women residing in the emerging enclave ($p=0.03$), but not other neighborhoods.

Conclusions Among Chinese immigrant women, aggregate analyses that do not take neighborhood context into consideration can mask potential variations in association of inflammatory markers with breast density. Future studies should consider how neighborhood contextual factors may contribute to differential risk pathways.

Keywords Inflammation · Breast density · Neighborhood · Asian · Immigrant · Acculturation

Introduction

Approximately 13.4% of the U.S. population is foreign-born [1]. Asian immigrants comprise 26.9% of all immigrants [1], contributing to the rapid growth of the U.S. Asian population. As of 2015, 24% of Asian Americans were of Chinese origin, the largest single origin group. Studies of U.S. immigrants consistently report longer duration of U.S. residence to be associated with higher odds of poorer self-reported health [2, 3] and elevated risk for chronic disease [4], including breast cancer [5, 6]. Breast cancer is the most common cancer among Chinese American women [7]; and in contrast to reported declines in breast cancer incidence among U.S. non-Hispanic white women [8], Chinese American women experienced significant annual increases in breast cancer from 1990 to 2008 [7].

The factors contributing to increased risk in this population are varied, but may share a common biologic mechanism, such as inflammation. Studies have demonstrated positive associations between inflammatory markers in circulating blood and cancer risk in general [9], and breast cancer risk specifically [10, 11]. Inflammation may impact breast cancer risk via estrogen synthesis pathways [12], and it may also have a visible influence on breast density due to inflammatory effects on cell proliferation [9], insulin resistance [13], and insulin-like growth factor I, a risk factor for breast cancer [14]. Findings from several meta-analyses indicate that elevated levels of C-reactive protein (CRP), a sensitive marker of inflammation, are associated with a modest increase in breast cancer risk

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[15–17], an association that was observed to be stronger in Asian populations [16]. Notably, inflammatory markers such as CRP and those in the tumor necrosis factor-alpha (TNF-α) pathway appear to be associated with increased cancer risk in a linear dose–response fashion [18].

Among Chinese immigrants, post-migration changes in lifestyle behaviors [19] could have biologic consequences, such as increased inflammation. Changes in diet are commonly reported among Chinese American immigrants [19, 20] and include increased consumption of fats, sweets, and dairy products, decreased vegetable consumption, and the adoption of American-style meals (e.g., pizza, hamburgers, sandwiches) [21]. Meat-based or "Western-like" dietary patterns have been associated with elevated levels of inflammatory markers, including increases in CRP [22], whereas diets that are high in vegetables, fruits, nuts, whole grains, and fish have anti-inflammatory effects including lower concentrations of CRP and tumor necrosis factor (TNF) receptors in the blood [23].

Aside from behavioral changes, immigrants may also experience significant acculturative stress [24, 25], which has been associated with higher levels of inflammatory markers [26, 27]. In addition, immigrants may feel socially isolated due to language difficulties, separation from family and social networks, and feelings of "not belonging" [28, 29]. In both human and animal studies, social isolation has been associated with alterations in immune system regulation and greater inflammatory response [30, 31]. Directly relevant to breast cancer risk, mouse models have demonstrated that social isolation is associated with dysregulation of endocrine response to stress, altered mammary gland gene expression, and the development of larger mammary gland tumors [32, 33].

Among immigrants, data suggest that neighborhood factors may be associated with post-migration changes in health [34, 35]. For example, research suggests that residence in ethnic enclaves—areas with a higher concentration of co-ethnics (people of the same race/ethnicity)—may have health benefits for immigrants [36]. Ethnic enclaves not only encourage preservation of healthy, traditional behaviors such as diet [35–37], but also can provide essential social resources and networks that reduce social isolation and serve as a buffer against immigration-related stressors [28, 38–40]. Moreover, studies suggest that neighborhood-level factors such as ethnic density may be associated with breast cancer risk as well [41]. For example, breast cancer incidence rates were lower among Hispanic women residing in census tracts with more Hispanics (i.e., a high-density Hispanic neighborhood) compared to low-density Hispanic neighborhoods [42, 43]. To date, however, the potential biologic pathways underlying such observations have not been extensively investigated.

Therefore, the objective of this study was to examine associations of inflammatory markers with breast density, a marker of breast cancer risk, among female Chinese immigrants and to explore whether associations varied by neighborhood environment. It was hypothesized that inflammatory markers would be positively associated with greater dense breast area and percent density, and that these associations would be more pronounced among women residing in non-enclaves (i.e., areas with few Chinese residents), but attenuated or not associated among women living in ethnic enclaves.

Methods

Participants

Participants were identified from a cohort of 433 healthy, premenopausal, foreign-born Chinese American women who were enrolled in a study of breast density. Inclusion criteria for the parent study included Chinese heritage, migration from Asia ≤ 20 years ago, and being of mammography screening age. Exclusion criteria included postmenopausal status; history of breast augmentation/reduction, prophylactic mastectomy, or any cancer except non-melanoma skin cancer; current pregnancy; and current breastfeeding or breastfeeding within the last 9 months. Of the 433 participants, 15 were missing data on breast density, 11 did not provide blood samples for analysis of inflammatory markers, and 1 participant was missing data on both breast density and inflammatory markers. Additional 4 participants were missing data on demographic or reproductive factors, and 1 participant was missing residential address, leaving a sample of 401 women for the present analysis. Characteristics of study participants are presented in Table 1. The study was approved by the Fox Chase Cancer Center Institutional Review Board, and written informed consent was obtained from all individual participants included in the study.

Procedures

Participants were recruited through Chinese community organizations, local medical practices, newspaper advertisements, and other contacts in the Chinese community in the Philadelphia region. Bilingual research staff administered interviews to obtain information on sociodemographic background, acculturation, and reproductive history.

All participants provided fasting blood samples in the morning. Trained personnel collected 1–2 tubes of blood in 10 mL red top tubes (containing no anticoagulant). Samples were labeled with a study ID number and transported to the Biosample Repository Core Facility (BRCF) at Fox Chase Cancer Center for processing and storage. Blood

Table 1 Distribution of participant characteristics by neighborhood

Variable	No. of participants (%)					*p* value
	All participants ($n=401$)	Chinatown ($n=52$)	South Phila. ($n=98$)	Near Northeast ($n=116$)	Non-enclave ($n=135$)	
Age (years; mean ± SD)	43.82 ± 4.54	43.81 ± 4.22	43.97 ± 4.51	43.69 ± 4.76	43.82 ± 4.53	0.98
U.S. residence (years, mean ± SD)	7.49 ± 4.79	6.81 ± 4.98	7.19 ± 4.30	7.83 ± 5.18	7.68 (4.71)	0.53
Married	371 (92.5)	49 (94.2)	94 (95.9)	105 (90.5)	123 (91.1)	0.41
Acculturation score (mean ± SD)	2.11 ± 0.72	2.02 ± 0.60	1.81 ± 0.61	2.16 ± 0.70	2.31 ± 0.77	**< 0.001**
Education level						**< 0.001**
< 8 years	193 (48.1)	29 (55.8)	62 (63.3)	62 (53.4)	40 (29.6)	
9–12 years	139 (34.7)	21 (40.4)	33 (33.7)	35 (30.2)	50 (37.0)	
Some college and above	69 (17.2)	2 (3.8)	3 (3.1)	19 (16.4)	45 (33.3)	
BMI (kg/m^2; mean ± SD)	23.41 ± 2.81	23.27 ± 2.73	23.51 ± 2.75	23.39 ± 2.88	23.43 ± 2.85	0.97
BMI (kg/m^2) categories						0.99
Normal (< 25.0)	293 (73.1)	37 (71.2)	73 (74.5)	85 (73.3)	98 (72.6)	
Overweight (25.0 to < 30.0)	97 (24.2)	14 (26.9)	23 (23.5)	27 (23.3)	33 (24.4)	
Obese (30.0 or more)	11 (2.7)	1 (1.9)	2 (2.0)	4 (3.4)	4 (3.0)	
Number of live births	1.96 ± 0.98	1.87 ± 0.89	2.36 ± 1.17	1.92 ± 0.92	1.75 ± 0.84	**< 0.001**
Age at first live birth (years; mean ± SD)	24.78 ± 4.60	23.92 ± 4.52	23.72 ± 4.40	25.67 ± 4.98	25.14 ± 4.25	**0.007**
Total duration of breastfeeding						0.35
None	67 (16.7)	9 (17.3)	12 (12.2)	27 (23.3)	19 (14.1)	
≤ 1 year	189 (47.1)	24 (46.2)	46 (46.9)	48 (41.4)	71 (52.6)	
> 1–2 years	92 (22.9)	15 (28.8)	26 (26.5)	24 (20.7)	27 (20.0)	
> 2 years	53 (13.2)	4 (7.7)	14 (14.3)	17 (14.7)	18 (13.3)	
Perimenopausal stage						0.97
Premenopausal	277 (69.1)	35 (67.3)	65 (66.3)	82 (70.7)	95 (70.4)	
Early perimenopausal	88 (21.9)	13 (25.0)	23 (23.5)	25 (21.6)	27 (20.0)	
Late perimenopausal	36 (9.0)	4 (7.7)	10 (10.2)	9 (7.8)	13 (9.6)	
Inflammatory markers						
CRP, mg/L [median (IQR)]	0.95 (0.43–1.96)	0.97 (0.49–1.80)	0.94 (0.52–1.95)	0.85 (0.37–2.05)	1.00 (0.38–1.97)	0.95
CRP categories [number (%)]						0.61
Low (< 1 mg/L)	207 (51.6)	28 (53.8)	50 (51.0)	62 (53.4)	67 (49.6)	
Average (1.0–3.0 mg/L)	137 (34.2)	19 (36.5)	37 (37.8)	33 (28.4)	48 (35.6)	
High (> 3.0 mg/L)	57 (14.2)	5 (10.0)	11 (11.2)	21 (18.1)	20 (14.8)	
Soluble TNF receptor 2, pg/mL [median (IQR)]	4044.67 (3499.11–4842.27)	3983.46 (3605.72–4647.94)	4307.13 (3682.48–4957.52)	3961.49 (3443.45–4882.78)	3992.00 (3443.31–4779.38)	0.36

Table 1 (continued)

Variable	No. of participants (%)					*p* value
	All participants ($n=401$)	Chinatown ($n=52$)	South Phila. ($n=98$)	Near Northeast ($n=116$)	Non-enclave ($n=135$)	
Breast density						
Dense area (cm^2; mean ± SD)	36.65 ± 16.58	36.98 ± 14.71	36.67 ± 17.14	34.81 ± 14.37	38.09 ± 18.53	0.48
Non-dense area (cm^2; mean ± SD)	45.07 ± 26.18	40.03 ± 19.05	50.66 ± 30.63	42.97 ± 24.03	44.77 ± 26.39	0.07
Percent density (mean ± SD)	46.64 ± 15.88	49.11 ± 15.26	43.81 ± 14.95	46.81 ± 17.09	47.61 ± 15.55	0.18

Note: Significant differences across neighborhoods are designated in bold

samples were centrifuged, and aliquots of serum were stored at −80 °C until analysis. At the time of blood draw, participant weight and standing height were measured using standard protocols [44] as previously reported [45]. All measurements were taken and recorded in duplicate, with the mean value used in analyses. Participants also underwent mammographic screening either at Fox Chase Cancer Center or on its mobile mammography unit, which enabled the study team to capture measures of breast density (see Measures below).

Measures

Demographic and health history

Demographic characteristics including participant age, education, length of U.S. residence, and marital status were assessed. Participants also provided information on reproductive factors including pregnancy history, age at first live birth, and duration of breastfeeding (in months).

With regard to premenopausal stage, women who reported regular menses in the prior 3 months with no decrease in predictability were classified as premenopausal. Those who reported menses in the prior 3 months but with decreased predictability were classified as early perimenopausal, and women who reported 3–11 months of amenorrhea were classified as late perimenopausal.

Acculturation level was measured using an adapted 11-item measure of the General Ethnicity Questionnaire-American (GEQ-A) version [46], which has demonstrated high validity and reliability in prior studies of Chinese Americans [26, 47, 48]. The GEQ-A assesses acculturation in various life domains (including language use and proficiency, social affiliation, cultural activities, and cultural pride) and provides an overall score of identification with American culture. All items on the scale are scored on a five-point Likert type scale, with higher scores representing greater endorsement of American culture [46]. The mean of all items is used to quantify overall acculturation to American culture. In the present sample, internal reliability was high with an alpha coefficient of 0.91.

Anthropometric assessments of weight and height were used to compute body mass index (BMI), which is defined as an individual's weight (in kilograms) divided by the square of their height (in meters).

Inflammatory markers

Inflammatory markers assessed in this study included C-reactive protein (CRP) and soluble tumor necrosis factor receptor 2 (sTNFR2). CRP is a widely utilized marker of systemic inflammation [49] that has been associated with breast cancer risk [15, 16]. TNF-α may also be associated with breast cancer risk [50–52], but due to its sensitivity to sample processing conditions [53], we assessed sTNFR2, one of the receptors through which TNF-α signals and whose expression is induced by TNF-α. Studies report that sTNFR2 is a more stable protein than TNF-α in circulation, has excellent reliability over time (ICCs = 0.85) that is not degraded by long-term storage of samples [54], and is an informative marker in studies of breast cancer [55].

Procedures for the assessment of serum CRP and sTNFR2 have been previously described [26]. In brief, the inflammatory markers were assessed using fluorescent bead-based immunoassays with a Bio-Plex 200 Luminex system and commercially available kits following manufacturer's protocol (Millipore, Billerica, MA). None of the samples tested were below the lower limit of quantification (LoQ) for either marker. A randomly selected 10% of samples were re-assayed in both the same and separate batches to evaluate within and between-batch reproducibility of all assays. The intra-batch coefficient of variance (CV) based on the blinded duplicate samples was 6.1% for CRP and 6.6% for sTNFR2.

Breast density

For the majority of participants ($n=358$), breast density was assessed using cranio-caudal mammographic views that

were digitized with a Kodak LS-85 laser film scanner at a resolution of 100 pixels/cm. However, toward the end of data collection, Fox Chase Cancer Center transitioned to digital mammography equipment; thus, for 43 participants, digital images were directly available, eliminating the need to scan and digitize images. Breast density was assessed using a highly reproducible computer-assisted method previously described [45, 56, 57]. In this method, the dense and non-dense tissue area can be quantified (in cm^2), and the number of pixels in the digitized image of the breast that are radio-dense can be calculated. The percentage of dense tissue (percent density) is estimated as the number of dense area pixels divided by the number of pixels in the total breast area [57]. Breast density assessed using this method has been strongly associated with breast cancer risk [58]. To assess reproducibility, 10% of images were re-submitted for analysis. Intra-batch and inter-batch intraclass correlation coefficients were all > 0.94, indicating excellent reproducibility.

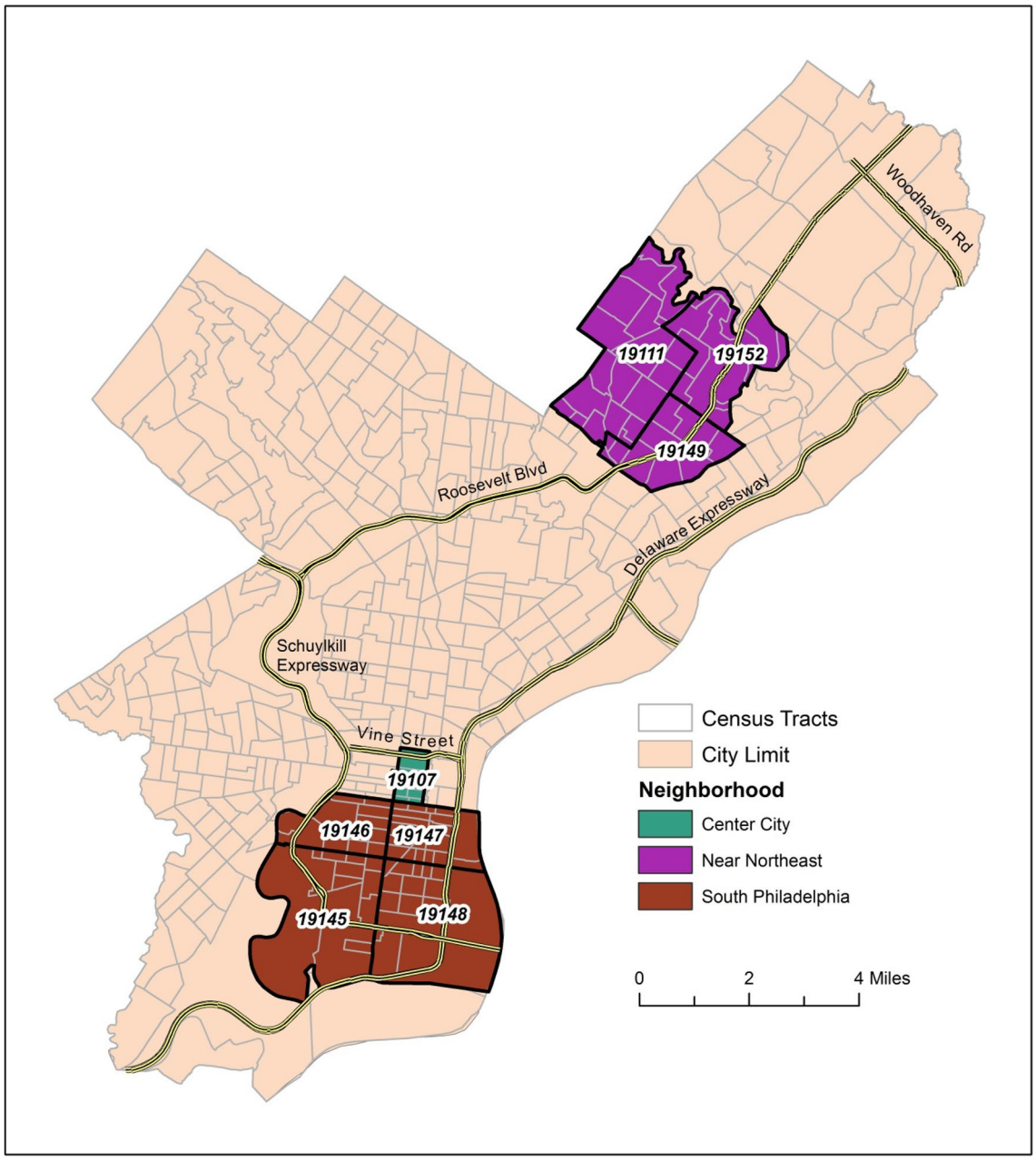

Fig. 1 Map of study neighborhoods in Philadelphia, PA

Neighborhood residence

Participant addresses were geocoded (ESRI, Inc., Redlands, CA) and linked to census tracts. The majority of participants ($n = 266$) resided in three defined sections of Philadelphia, PA (Fig. 1) represented by eight zip code areas. These areas fall within three geographically distinct 'planning analysis sections' generated by the Philadelphia City Planning Commission: Center City (19107), South Philadelphia (19145, 19146, 19147, 19148), and the Near Northeast (19111, 19149, 19152). These areas also correspond with local knowledge of regional immigrant neighborhoods and the academic [59–61] and lay [62, 63] literature. In Philadelphia, the Chinese immigrant population is heavily concentrated in Chinatown (which is located in Center City) and South Philadelphia [62]. These areas represent entry points for new immigrants [64], with well-established institutions that offer social, cultural, or economic support and services for recent immigrants, and are characteristic of traditional urban enclaves [65]. However, immigrant growth outside of these densely populated areas has significantly increased in recent years [61, 64]. This area, locally known as the Near Northeast, has become home to an increasing number of Chinese immigrants and represents an "emerging" ethnic enclave [62, 64] with a growing density of co-ethnic residents, but fewer established resources and institutions. In the present study, 52 participants resided in Chinatown, 98 resided in South Philadelphia, and 116 in the Near Northeast. The remaining participants ($n = 135$) resided in scattered areas throughout the greater Philadelphia region and surrounding areas and were categorized as residing in a "non-enclave" neighborhood.

We linked Census tract information to data from the 2010 American Community Survey (ACS) 5-year estimates summary file to characterize these neighborhoods in relation to percent reporting Asian race and percent of residents living in poverty. Chinatown had the highest median proportion reporting Asian race (63.2%) compared to South Philadelphia (19.4%), the Near Northeast (21.0%), and non-enclave areas (5.5%). The median poverty rate was similar across neighborhoods, ranging between 25 and 31%.

Statistical analyses

Descriptive analyses were used to characterize the study measures. Analysis of variance (ANOVA) or χ^2 tests were conducted to examine potential unadjusted differences in participant characteristics across neighborhoods (Chinatown, South Philadelphia, Near Northeast, and non-enclave areas).

Because of skewed distributions, inflammatory markers were categorized into empirical tertiles based on the sample distribution, with each woman assigned a tertile value. We adjusted for potentially confounding demographic and clinical characteristics using propensity score-based methods [66]. The exposures for consideration in the propensity score models were the twelve categories formed by the four neighborhoods and three marker tertiles ($4 \times 3 = 12$ for each inflammatory marker). Propensity scores were estimated by a multinomial logistic regression of the 12 categories, and included age, education level, acculturation, BMI, number of live births, age at first live birth, total lifetime duration of breast feeding (categorized as: none; ≤ 1 year; > 1 year to 2 years; > 2 years), perimenopausal stage, mammogram image modality, and census tract poverty. For reporting descriptive-adjusted biomarker levels in tables by tertile within neighborhood, we used propensity score-based weighting [67]. For hypothesis testing, we used multiple linear regression with generalized propensity score adjustment [68]. Eleven of the 12 generalized propensity scores from the multinomial model were included as covariates in the multiple linear regression analyses of dense breast area, non-dense breast area, and percent density. The 12th generalized propensity score term was left out as it was a collinear with the other 11 (i.e., the twelfth is a linear combination of 1 minus the sum of the first 11). Also included in the multiple linear regressions were neighborhood indicators (binary yes/no variables) and the interaction [69] of the neighborhood indicators with the ordinal biomarker tertile variable. The interaction terms were used to assess whether associations between inflammatory markers and measures of breast density tertile varied by neighborhood. Separate models were run for each inflammatory marker. The unadjusted models controlled for neighborhood-level effects, but not for the other confounding demographic and clinical characteristics listed above.

Analyses were conducted using STATA 13 (StataCorp, College Station, Texas) and reported p values correspond to two-tailed tests. p values of less than 0.05 were used as the criteria for statistical significance.

Results

Participant characteristics

Participants ($n = 401$) were on average 43.8 years of age and had lived in the U.S. for a mean of 7.5 years. The majority was married (92.5%), and nearly one-half (48.1%) had less than a high school education. The average body mass index (BMI) was 23.4 kg/m^2. Other characteristics of the sample are reported in Table 1.

No differences in participant age, length of U.S. residence, marital status, BMI, duration of breastfeeding, perimenopausal status, or levels of inflammatory markers were

observed by neighborhood. Breast density also did not differ across women as a function of neighborhood. However, differences were observed in acculturation score, education level, number of live births, and average age at first live birth. Specifically, women in Chinatown and South Philadelphia reported significantly lower levels of acculturation compared with women residing in non-enclaves (both p values < 0.01).

With respect to education, a greater proportion of women in the Near Northeast and in non-enclave settings had obtained some college education or beyond compared with women in Chinatown and South Philadelphia. Reproductive factors also differed across neighborhoods. Women residing in South Philadelphia had a significantly greater number of live births ($M = 2.36$, SD = 1.17) compared to each of the other neighborhoods (all p values < 0.01). Average age at first live birth was also significantly younger among women in Chinatown ($M = 23.92$, SD = 4.52) and South Philadelphia ($M = 23.72$, SD = 4.40) compared with women in the Near Northeast ($M = 25.67$, SD = 4.98), both p values < 0.04.

CRP, neighborhood, and breast density

We examined associations of inflammatory markers and neighborhood with measures of breast density in regression models adjusted for relevant sociodemographic and reproductive history variables. In regression analyses, CRP was negatively associated with dense breast area in unadjusted ($\beta = -2.33$, 95% CI −4.31 to −0.35, $p = 0.02$) and adjusted models ($\beta = -2.79$, 95% CI −4.95 to −0.63, $p = 0.01$; Table 2a). This inverse association was most pronounced among women residing in non-enclaves, whereby increasing tertile of CRP was negatively associated with dense breast area (adjusted model trend p value = 0.01; Table 2b), although the p value for the interaction was not statistically significant ($p = 0.44$).

CRP was associated with non-dense breast area in unadjusted analyses ($\beta = 4.05$, 95% CI 0.94 to 7.16, $p = 0.01$), but the association was not statistically significant in the adjusted model ($p = 0.16$; Table 2a). Similarly, CRP was negatively associated with percent density in unadjusted analyses ($\beta = -4.05$, 95% CI −5.91 to −2.19, $p < 0.001$), particularly in the Near Northeast (unadjusted model trend p value = 0.01) and non-enclave neighborhoods (unadjusted model trend p value = 0.01; Table 2b). However, these associations were no longer statistically significant in the adjusted models. The interaction of CRP with neighborhood was not statistically significant for any measure of breast density.

sTNFR2, neighborhood, and breast density

No main effects of sTNFR2 on dense breast area emerged (Table 3a). However, a statistically significant interaction of sTNFR2 with neighborhood was observed for dense breast area (interaction $p = 0.01$; Table 3b). Specifically, sTNFR2 was negatively associated with dense breast area among women residing in the emerging enclave of the Near Northeast (adjusted model trend p value = 0.03; Table 3b), whereas the opposite pattern was detected among women in Chinatown and South Philadelphia. Interaction analyses indicated that the association of sTNFR2 tertile and dense breast area did not differ between women in Chinatown and South Philadelphia, but did significantly differ from the associations observed in the Near Northeast (adjusted $\beta = -8.06$, $p = 0.015$) and in non-enclaves ($\beta = -6.45$, $p = 0.049$).

In the adjusted model, sTNFR2 was positively associated with non-dense breast area ($\beta = 3.36$, 95% CI 0.32 to 6.40, $p = 0.03$; Table 3a). Further examination suggests that the association between sTNFR2 and non-dense breast area was most pronounced among women in South Philadelphia (adjusted model trend p value = 0.01; Table 3b). The interaction of sTNFR2 with neighborhood, however, was not statistically significant.

sTNFR2 was negatively associated with percent density in the unadjusted model ($\beta = -1.91$, 95% CI −3.80 to −0.02, $p = 0.05$; Table 3a), but not the adjusted model. The negative association was primarily observed among women residing in the Near Northeast (adjusted model trend p value = 0.01; Table 3b), and not in the other neighborhoods. The interaction of sTNFR2 with neighborhood was not statistically significant (interaction $p = 0.23$; Table 3b).

Discussion

In the present study, we examined associations of inflammatory markers (CRP, sTNFR2) with breast density in a sample of Chinese immigrant women. Overall, CRP was inversely associated with dense breast area, whereas sTNFR2 was positively associated with non-dense breast area. An inverse association of sTNFR2 with dense breast area was also noted, but only among women residing in emerging enclaves. Further, an inverse association of sTNFR2 with percent density was also observed among women in emerging enclaves; however, the interaction term was not statistically significant.

The finding that CRP and sTNFR2 are inversely associated with dense breast area is contrary to our initial hypothesis, but mirrors prior findings reported in the broader population of U.S. women [70–72]. In a study of 653 pre- or perimenopausal participants in the Study of Women's Health Across the Nation [72], CRP was inversely associated

Table 2 Associations of breast density with tertile of CRP

(a) Overall model						
	Dense area		Non-dense area		Percent density	
	Mean (SD)	*p* value	Mean (SD)	*p* value	Mean (SD)	*p* value
Unadjusted		**0.02**		**0.01**		**0.001**
T1	**39.2 (19.0)**		**42.1 (30.2)**		**50.4 (14.6)**	
T2	**36.2 (14.4)**		**42.8 (21.4)**		**47.2 (16.0)**	
T3	**34.6 (15.8)**		**50.2 (25.6)**		**42.3 (16.1)**	
Adjusted		**0.01**		0.16		0.29
T1	**36.6 (20.2)**		42.7 (27.0)		47.5 (15.8)	
T2	**35.8 (12.9)**		41.5 (20.2)		47.9 (15.3)	
T3	**34.4 (14.4)**		41.8 (21.4)		46.6 (15.3)	
(b) Interaction models						
	Mean (SD)	Trend *p*	Mean (SD)	Trend *p*	Mean (SD)	Trend *p*
Chinatown						
Unadjusted		0.82		0.36		0.19
T1	35.7 (12.8)		32.2 (14.8)		53.5 (12.4)	
T2	40.2 (17.1)		45.2 (22.3)		48.3 (15.8)	
T3	34.7 (13.6)		41.1 (17.2)		46.3 (16.8)	
Adjusted		0.72		0.72		0.85
T1	38.9 (14.6)		31.0 (16.1)		57.0 (13.8)	
T2	39.6 (17.0)		47.5 (23.6)		47.1 (17.1)	
T3	32.0 (14.5)		39.5 (16.9)		45.0 (18.1)	
South Phila						
Unadjusted		0.76		0.17		0.13
T1	39.7 (20.6)		45.2 (37.5)		49.0 (14.5)	
T2	32.8 (13.1)		52.1 (24.7)		40.3 (15.1)	
T3	38.2 (17.3)		54.2 (29.8)		42.9 (14.2)	
Adjusted		0.76		0.15		0.46
T1	39.6 (22.0)		43.8 (34.4)		49.3 (13.4)	
T2	33.0 (11.1)		47.8 (19.3)		42.0 (12.4)	
T3	41.9 (14.9)		47.1 (18.4)		47.4 (11.0)	
Near NE						
Unadjusted		0.21		0.27		**0.01**
T1	36.2 (14.5)		42.8 (30.0)		**49.4 (16.9)**	
T2	36.8 (12.7)		36.3 (18.2)		**51.7 (15.9)**	
T3	31.5 (15.5)		49.3 (20.3)		**39.5 (16.4)**	
Adjusted		0.14		0.73		0.07
T1	34.7 (15.5)		45.7 (25.4)		45.2 (18.5)	
T2	37.6 (12.7)		36.7 (18.8)		52.0 (15.2)	
T3	31.7 (13.6)		45.6 (20.3)		42.3 (16.5)	
Non-enclave						
Unadjusted		**0.02**		0.10		**0.01**
T1	**42.7 (22.6)**		42.8 (29.1)		**51.2 (13.3)**	
T2	**36.8 (15.3)**		39.4 (17.9)		**48.9 (15.5)**	
T3	**34.6 (15.8)**		51.7 (28.9)		**42.8 (16.8)**	
Adjusted		**0.01**		0.39		0.55
T1	**37.2 (23.8)**		41.6 (26.1)		46.9 (14.2)	
T2	**35.3 (12.9)**		38.8 (19.8)		49.4 (16.0)	
T3	**33.4 (13.9)**		37.2 (23.7)		49.6 (14.9)	
Interaction *p*	0.44		0.83		0.34	

a. Overall model—presents the overall relationship of CRP with each breast density measure; and b. Interaction models—presents the relationships by neighborhood. Significant associations are designated in bold.

We used generalized propensity score adjustment that accounted for participant age, BMI, acculturation score, education level, census tract

Table 2 (continued)

poverty, mammogram image modality (digital vs. non-digital), perimenopausal stage, number of live births and age at first live birth, and total months of breastfeeding

with percent density at baseline, but also with lower age-related decline in percent density in longitudinal analyses. In studies among postmenopausal women, one study noted inverse associations of CRP with dense breast area and percent density among 302 women in the U.S. [71]; in another study of 397 postmenopausal women, the inverse association between CRP and TNF-α with percent density was attenuated to non-significance after adjustment for BMI [70]. Some experimental studies of non-steroidal anti-inflammatory drugs (NSAIDs) and mammographic density are consistent with these findings, whereby longer duration of NSAID use was associated with greater percent density among postmenopausal women [73]. As a result, it has been suggested that inflammation may not directly impact breast cancer risk via pathways involving mammographic density [70, 74]. What contributes to an apparent *inverse* association between inflammatory markers and breast density observed in previous studies and ours, however, is unclear.

Similar to Reeves et al. [70], we found a positive association between sTNFR2 and non-dense breast area. This finding is not entirely surprising given that TNF-α is positively associated with BMI and total body fat [75], both of which in turn are positively associated with non-dense breast area [45, 76]. Studies consistently report positive associations between measures of body fatness and abdominal fat distribution with non-dense breast area [77]. However, given meta-analytic findings that non-dense breast area is inversely associated with breast cancer risk [78], raises questions about the interrelations among adiposity (a risk factor for breast cancer), non-dense breast area, and breast cancer risk. Some researchers have proposed that weight change in adulthood may be a critical factor driving cancer risk, as studies have reported that weight gain during adulthood was negatively associated with absolute non-dense area [77], a finding that is consistent with current evidence on breast cancer risk factors.

Importantly, the interaction of neighborhood and sTNFR2 suggests that associations may vary across residential areas. It is interesting to note that women in the emerging enclave were more similar in terms of demographic and reproductive characteristics to women residing in non-enclaves than those in traditional, urban enclave settings. Women in traditional enclaves were less acculturated, had lower levels of education, and were of younger age at first full-term pregnancy than their more acculturated counterparts in emerging enclave and non-enclave neighborhoods. It is possible that other differences in lifestyle behaviors, social dynamics, and individual economic factors also exist, but were not captured in the present study.

A key strength of the present study is the focus on geographically distinct immigrant neighborhoods, combined with detailed individual-level risk factors and biologic markers. However, we also acknowledge several limitations to the present study. First, due to the cross-sectional nature of this analysis, we cannot make any inferences about the causal nature of the inflammation–breast density associations. Longitudinal assessments are needed to establish the direction of the observed associations. Second, the study did not include assessments of neighborhood-level factors (e.g., urban factors, mixed-land use) that may partially contribute to breast cancer risk [79]. Such assessments could help capture key differences across neighborhoods and clarify which elements of enclave residence are uniquely advantageous for immigrant health. Third, similar to prior research in other Asian American communities [80], we found that the median percent poverty rate did not differ greatly across the neighborhoods studied; however, it is possible that variations in individual-level poverty status or income (which were not assessed in the present study) could have altered study findings. Future studies that take into account both neighborhood-level and individual-level socioeconomic characteristics will help provide a richer context for interpreting how these factors intersect in relation to breast cancer risk. Fourth, the use of breast density as an intermediate marker of breast cancer risk, rather than cancer incidence rate itself, limits the conclusions that can be drawn. However, breast density is one of the strongest risk factors and has consistently been shown to be associated with breast cancer risk [81]. Finally, we acknowledge that the focus on a Chinese immigrant population may limit generalizability of study findings to other immigrant groups. Yet despite these limitations, the present study represents one of the first efforts to examine potential mechanisms by which local neighborhood environment may modify breast cancer risk in Chinese immigrants.

In conclusion, inflammation was negatively associated with dense breast area and not associated with percent density in aggregate analyses, but variable associations were observed across different neighborhoods. Future studies that explore the links between neighborhood typologies and biomarkers of health and disease can lead to a greater understanding of how neighborhood contextual factors may modify risk pathways.

Table 3 Associations of breast density with tertile of sTNFR2

(a) Overall model						
	Dense area		Non-dense area		Percent density	
	Mean (SD)	*p* value	Mean (SD)	*p* value	Mean (SD)	*p* value
Unadjusted		0.49		**0.01**		**0.05**
T1	38.3 (19.0)		**40.9 (22.3)**		49.0 (15.4)	
T2	34.7 (14.5)		**44.4 (25.2)**		46.0 (15.4)	
T3	36.9 (15.9)		**49.8 (29.8)**		45.0 (16.6)	
Adjusted		0.42		**0.03**		0.16
T1	37.6 (19.8)		**43.6 (24.7)**		47.4 (16.5)	
T2	34.9 (14.7)		**43.6 (22.8)**		45.9 (15.4)	
T3	36.0 (14.8)		**47.2 (30.6)**		46.2 (16.2)	
(b) Interaction models						
	Mean (SD)	Trend *p*	Mean (SD)	Trend *p*	Mean (SD)	Trend *p*
Chinatown						
Unadjusted		0.10		0.20		0.92
T1	32.7 (15.3)		33.6 (15.3)		49.5 (17.5)	
T2	36.9 (12.7)		42.1 (18.1)		47.8 (13.0)	
T3	41.9 (15.5)		44.8 (22.8)		50.1 (15.8)	
Adjusted		0.15		0.28		0.77
T1	30.1 (13.2)		33.1 (17.6)		49.6 (18.6)	
T2	39.0 (11.9)		41.6 (18.0)		49.7 (14.2)	
T3	38.0 (10.2)		37.2 (17.0)		52.0 (11.9)	
South Phila						
Unadjusted		0.18		**0.01**		0.79
T1	35.7 (16.3)		**44.0 (18.1)**		44.7 (15.8)	
T2	33.1 (14.0)		**45.5 (23.1)**		43.3 (13.5)	
T3	40.7 (19.8)		**60.2 (40.6)**		43.6 (16.0)	
Adjusted		0.13		**0.01**		0.99
T1	36.1 (17.3)		**42.4 (16.3)**		45.3 (14.6)	
T2	37.2 (15.7)		**43.9 (16.9)**		45.6 (12.9)	
T3	40.5 (19.4)		**55.4 (40.8)**		45.7 (14.2)	
Near NE						
Unadjusted		**0.04**		0.18		**0.01**
T1	**38.9 (15.8)**		39.7 (22.6)		**50.9 (15.6)**	
T2	**33.5 (11.9)**		42.2 (24.7)		**47.4 (15.9)**	
T3	**31.3 (13.8)**		47.5 (25.0)		**41.6 (18.8)**	
Adjusted		**0.03**		0.30		**0.01**
T1	**39.0 (16.2)**		40.2 (21.3)		**50.2 (16.4)**	
T2	**34.8 (12.1)**		44.5 (25.8)		**47.3 (16.7)**	
T3	**32.5 (12.7)**		43.3 (23.3)		**44.9 (18.7)**	
Non-enclave						
Unadjusted		0.20		0.74		0.44
T1	41.3 (23.7)		43.2 (25.9)		49.5 (14.1)	
T2	36.0 (17.4)		46.1 (30.1)		46.2 (17.5)	
T3	36.9 (12.8)		45.1 (23.6)		47.0 (15.2)	
Adjusted		0.17		0.96		0.81
T1	39.4 (24.9)		50.4 (30.8)		45.3 (16.8)	
T2	31.7 (16.1)		43.4 (26.4)		44.1 (16.9)	
T3	35.1 (13.2)		48.2 (30.6)		45.6 (16.7)	
Interaction *p*	**0.01**		0.23		0.23	

a. Overall model—presents the overall relationship of sTNFR2 with each breast density measure; and b. Interaction models—presents the relationships by neighborhood. Significant associations are designated in bold.

We used generalized propensity score adjustment that accounted for participant age, BMI, acculturation score, education level, census tract

Table 3 (continued)

poverty, mammogram image modality (digital vs. non-digital), perimenopausal stage, number of live births and age at first live birth, and total months of breastfeeding

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Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest. The views expressed are those of the authors and do not necessarily reflect the official views of the Uniformed Services University of the Health Sciences or the U.S. Department of Defense.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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