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Associations of serum CRP levels with demographics, health behaviors, and risk of cancer among the Mexican American Mano A Mano Cohort

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ABSTRACT

C-Reactive protein (CRP) is a well-known inflammatory marker, and elevated CRP levels has been reported to be associated with the risk of various cancers. To date, no study has investigated the association between elevated CRP and incidents of cancer among Mexican Americans. In the current prospective cohort study, we measured pre-diagnostic CRP levels in serum samples and evaluated their relationships with demographic characteristics and health behaviors associated with cancer risk among 2753 Mexican Americans selected from the Mano-A-Mano Mexican American Cohort Study. At baseline, median levels of serum CRP significantly differed by demographics (sex, age category, marital status, and education levels) and health behaviors (cigarette smoking status, alcohol drinking status, BMI category, and physical activity levels). In the multivariable analysis, the study participants who were women, older, never drinking alcohol, overweight or obese, and physically inactive had increased likelihood of having high CRP levels (≥ median levels among all study participants) compared to their counterparts. A total of 177 cancer cases were identified during the follow-up with a median follow-up time of 127 months. In the quartile analysis, study participants in the 4th quartile with highest CRP levels had significantly 1.88 fold increased risk of cancer (hazard ratio (HR) = 1.88, 95%CI: 1.12, 3.13) compared to those in the 1st quartile with lowest CRP levels. The association was further confirmed in analyses using clinical CRP levels. In summary, our findings suggested that serum CRP levels have potential to serve as a predictive marker of cancer risk in Mexican Americans.

1. Introduction

C-Reactive Protein (CRP), a 118 kDa non-glycosylated protein in the Pentraxin family, acts as a major acute-phase protein, and mediates the innate and adaptive immune response [1]. It is mainly produced by hepatocytes in response to a variety of inflammatory cytokines including interleukin (IL)-6 during infection, tissue injury and inflammation, and subsequently released into circulation [2]. After binding to the surface of damaged cells and platelets, CRP could activate the cascade of innate inflammation. CRP has been reported to be the independent predictor of cardiovascular events and diabetes, and is associated with different features of metabolic syndrome [3–6]. Due to its high sensitivity, CRP was identified by The American Heart Association and the Centers for Disease Control and Prevention as the best systematic marker of inflammation for clinical diagnosis [7].

Investigation of CRP is of particular interest to cancer since several health behaviors and chronic diseases are major risk factors of common types of cancer, such as tobacco use, alcohol use, radiation, high-calorie diet, obesity, chronic infections, etc., have been linked to inflammation [8]. As a matter of fact, epidemiologic studies in the past decade have provide accumulating evidence for the association of elevated CRP levels and the risk of a variety of cancers, including ovarian, breast, liver, lung, endometrial, and colorectal cancers [9–15]. However, most of the studies have been carried out in Caucasian populations.

Mexican immigrants are the fastest growing minority group. In the U.S., obesity/overweight is a major public health problem among those with Mexican origin. Unfortunately, to date, no prospective study has evaluated the association between elevated CRP and incidents of cancer among Mexican Americans. In the current study, we analyzed pre-diagnostic CRP levels in serum samples in relation to demographic characteristics and health behaviors at baseline among 2753 Mexican Americans without cancer identified from the Mano-A-Mano Mexican American Cohort study. In addition, we investigated the relationship between elevated CRP and cancer risk.

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Table 1
Median levels of CRP by demographics and health behaviors among MAC study participants.

	Overall			Women (N = 2112)		Men (N = 641)	
Characteristics	N = 2753 (%)	CRP, median (range)	P-value*	CRP, median (range)	P-value*	CRP, median (range)	P-value*
Sex							
Men	641 (23.28)	2.00 (0.10, 42.00)	Reference				
Women	2112 (76.72)	3.75 (011, 48.00)	< 0.001				
Age group							
< 30	549 (19.94)	2.41 (0.11, 42.00)	Reference	2.80 (0.11, 30.00)	Reference	1.40 (0.15, 42.00)	Reference
30-39	734 (26.66)	3.20 (0.11, 44.11)	0.002	3.80 (0.11, 44.11)	0.004	1.40 (0.11, 39.50)	0.847
40-49	580 (21.07)	3.40 (0.12, 44.00)	< 0.001	3.96 (0.12, 44.00)	< 0.001	2.20 (0.12, 36.19)	0.014
50-59	443 (16.09)	3.61 (0.14, 44.00)	< 0.001	4.45 (0.10, 44.00)	< 0.001	2.20 (0.14, 16.00)	0.08
60+	447 (16.24)	3.74 (0.12, 48.00)	< 0.001	3.93 (0.12, 48.00)	< 0.001	3.31 (0.14, 39.00)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001	
Marital status							
Married	2,034 (73.96)	3.31 (0.11, 48.00)	Reference	3.89 (0.11, 48.00)	Reference	2.00 (0.12, 42.00)	Reference
Not married	716 (26.04)	3.01 (0.11, 44.00)	0.009	3.40 (0.11, 44.00)	0.003	1.93 (0.11, 39.50)	0.352
Education							
< High school	1659 (60.28)	3.40 (0.11, 48.00)	Reference	3.80 (0.11, 48.00)	Reference	2.20 (0.11, 42.00)	Reference
At least high school	1093 (39.72)	3.00 (0.12, 44.11)	0.018	3.60 (0.12, 44.11)	0.165	1.70 (0.12, 39.50)	0.349
Place of birth							
Mexico	1826 (66.33)	3.20 (0.11, 48.00)	Reference	3.60 (0.11, 48.00)	Reference	1.80 (0.12, 36.19)	Reference
US	927 (33.67)	3.40 (0.11, 44.11)	0.136	4.00 (0.12, 44.11)	0.076	2.25 (0.11, 42.00)	0.029
Language acculturation							
Low	1,601 (58.28)	3.20 (0.11, 44.11)	Reference	3.80 (0.11, 48.00)	Reference	1.80 (0.11, 32.00)	Reference
High	1,146 (41.72)	3.26 (0.11, 48.00)	0.361	3.60 (0.11, 44.11)	0.676	2.16 (0.12, 42.00)	0.108
Cigarette smoking status							
Never	1,893 (70.77)	3.49 (0.11, 48.00)	Reference	3.80 (0.11, 48.00)	Reference	1.80 (0.12, 36.19)	Reference
Former	410 (15.33)	3.00 (0.12, 44.00)	0.096	4.00 (0.12, 44.00)	0.302	2.40 (0.12, 39.50)	0.258
Current	372 (13.91)	2.93 (0.11, 44.11)	0.004	3.80 (0.12, 44.11)	0.838	1.80 (0.11, 42.00)	0.807
P for trend		0.002		0.565		0.926	
Alcohol drinking							
Never	1,708 (63.97)	3.74 (0.11, 48.00)	Reference	3.84 (0.11, 48.00)	Reference	1.90 (0.12, 39.50)	Reference
Former	333 (12.47)	3.25 (0.12, 44.00)	0.176	4.00 (0.10, 44.00)	0.138	2.60 (0.12, 42.00)	0.225
Current	629 (23.56)	2.40 (0.11, 44.11)	< 0.001	3.20 (0.12, 44.11)	0.007	1.73 (0.11, 36.59)	0.335
P for trend		< 0.001		0.052		0.14	
Body mass index							
Normal (< 25)	521 (19.09)	1.40 (0.11, 48.00)	Reference	1.60 (0.11, 48.00)	Reference	0.80 (0.11, 31.31)	Reference
Overweight (25-30)	925 (33.90)	2.45 (0.12, 36.59)	< 0.001	3.00 (0.12, 36.00)	< 0.001	1.67 (0.12, 36.59)	< 0.001
Class I obesity (30-35)	793 (29.06)	4.00 (0.11, 40.00)	< 0.001	4.20 (0.11, 40.00)	< 0.001	3.17 (0.12, 28.00)	< 0.001
Class II obesity (35-40)	307 (11.25)	5.70 (0.12, 44.00)	< 0.001	6.00 (0.20, 44.00)	< 0.001	4.36 (0.12, 39.50)	< 0.001
Class III obesity (40+)	183 (6.71)	7.00 (0.13, 44.11)	< 0.001	7.20 (0.60, 44.11)	< 0.001	3.95 (0.13, 42.00)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001	
Physical activity							
Low	2,054 (75.02)	3.60 (0.11, 48.00)	Reference	4.00 (0.11, 48.00)	Reference	2.27 (0.11, 42.00)	Reference
Medium	609 (22.24)	2.40 (0.12, 42.00)	< 0.001	2.87 (0.12, 42.00)	< 0.001	1.60 (0.12, 36.59)	0.018
High	75 (2.74)	1.85 (0.14, 14.12)	0.001	1.70 (0.14, 14.12)	0.035	2.20 (0.11, 12.10)	0.431
P for trend		< 0.001		< 0.001		0.046	

*Nonparametric Wilcoxon rank-sum test was applied.

2. Materials and methods

2.1. Study population

The study subjects were drawn from a large population-based ongoing prospective cohort of Mexican–American households initiated in 2001 by the Department of Epidemiology at the University of Texas MD Anderson Cancer Center, called the Mano-a-Mano Mexican American Cohort Study (MACS). To be eligible to participate in the MACS, participants had to self-identify as Mexican or Mexican–American. A detailed description of the recruitment strategy and the data collection procedures have been described previously [16]. Briefly, participants have been recruited through block walking through community centers and local health clinics in predominantly Mexican-American neighborhoods in Houston, Texas, and by networking through currently enrolled participants. Eighty eight percent of the identified eligible households agreed to participate in the study, and written informed consent was obtained from each participants. After that, trained bilingual research interviewers conducted a structured face-to-face interview using the participant's preferred language, either Spanish or English. A standardized and validated questionnaire was used in the interview, which included information on basic socio-demographic characteristics, residential history, lifestyle behaviors, physical activity, personal medical history, family history of chronic disease, acculturation, and occupational exposure. Physical activity were measured using 1) survey instruments from the 2007–2008 National Health and Nutrition Examination Survey (NHANES; CDCP, 2007) and supplemental items following the NHANES format that inquire about activities performed in and around the home. Anthropometric measures, including height, weight, and blood pressure, were obtained during the interview. Participants have been followed up via annual telephone re-contact to update BMI, selected exposures, and new diagnosis of selected chronic diseases, including cancer, type-2 diabetes, and hypertension. A total of 2800 participants were selected from CRP measurement. The main

selection criteria included the availability of serum samples, the completeness of questionnaire data, and no existing cancer at baseline. After initial quality check, we excluded 47 participants due to low quality in CRP measurement. Thus, serum CRP data were available for 2753 participants and they were included in the current study. Among them, 177 cancer cases were identified during the follow-up, and further confirmed with the Texas Cancer Registry. The study protocol was approved by the Institutional Review Board of the University of Texas MD Anderson Cancer Center.

2.2. Quantification of CRP level by ELISA assay

Blood draws were completed by trained interviewers. Forty ml of venous blood was collected per participant and stored in barcoded, prelabeled vacutainers (two 10 ml lavender tops, two 10 ml red tops). Once the blood is drawn, the tubes were inverted several times to completely dissolve their contents. The mixed tubes were then cooled to 4 °C by placing them in an ice bucket to transport to the MD Anderson laboratory. Serum, plasma and buffy coat were separated within 1 h of collection by centrifuging for 15 min at 2500 rpm. The biospecimens were stored in −80 °C freezer. Quantification of CRP level in serum was performed using the Human C-Reactive protein Quantikine ELISA (R&D systems) according to the manufacturer's instruction. All samples were analyzed in duplicate. A standard curve was created after the duplicate readings for each standard. Negative control, standards, positive control were included in each assay. The absorbance was measured at 450 nm using a microplate reader. Readings at 540 nm were subtracted from the readings at 450 nm, to correct for optical imperfections in the plate. Then CRP concentrations of samples were calculated from standard curve. Any result with an intra assay % CV > 20% were re-analyzed. The intra assay variance ranged from < 5% to 15%.

2.3. Statistical analysis

We used the statistical software package STATA version 14.0 (STATA, College Station, TX) for analysis. First, we performed univariate analysis to evaluate whether median levels of serum CRP differed according to selected characteristics (Table 1). Nonparametric Wilcoxon rank-sum test was applied. To further test for trend across ordered groups, nonparametric trend test was applied. Then, using median levels of serum CRP among all study participants as the cutoff point (CRP = 3.20), we stratified the study participants into two groups, low and high levels of CRP. We then conducted multivariable logistic regression analyses to assess the association between selected characteristics and high levels of CRP (Table 2). Age category, sex, marital status, education, place of birth, language acculturation, cigarette smoking status, alcohol drinking status, BMI category, and physical activity were included in the model. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. Then, among those born in the Mexico, we explored whether years of living in U.S. might affect median CRP levels and risk of high CRP levels (Table 3). Finally, the association between serum CRP levels and incidents of cancer was assessed using Cox proportional hazards regression models, controlling for variables significantly associated with CRP levels, including age group, sex, alcohol consumption status, BMI category, and physical activity levels (Table 4). Study participants were followed up from their initial enrollment to the end of 2016. The median follow-up time 127 months. Those who were still cancer-free at the end of 2016 were censored in the Cox regression analysis. For those without cancer diagnosed but died during the follow-up, they were censored at the time of their death. Death was identified during the annual follow-up and further confirmed with the death report. The proportional hazards assumption was tested using the Schoenfeld residuals. Serum CRP levels were analyzed as the categorical variable. The cutoff points were set at 1) the median and quartile values in the study participants and 2) clinical values. Adjusted hazard ratios (HRs) and 95% CIs were estimated. I further stratified analysis, we assess whether the cancer risk differed by the follow-up time, 1 to 5 years vs at least 5 years. All statistical tests were 2-sided, and P values of less than 0.05 were considered statistically significant.

3. Results

For basic demographic characteristics, serum CRP levels differed by sex, age category, marital status, and education levels, but not by place of birth and language acculturation (Table 1). Women had significantly higher median levels of CRP than men did (3.75 vs 2.00, P < 0.001). A trend of increasing median levels of serum CRP was observed with the increase of age category from < 30, 30 to 39, 40 to 49, 50 to 59, to ≥60 years old (P for trend < 0.001). Those who married had significantly higher median levels of CRP than their counterparts did (3.31 vs 3.01, P = 0.009). And those who had at least high school degree had significantly lower levels median levels of CRP than their counterparts did (3.00 vs 3.40, P = 0.018). However, when stratified by sex, the significant associations were only observed for age category for both women and men, and marital status for women only. Interestingly, men who were born in U.S. had significantly higher median levels of CRP than those born in Mexico (2.25 vs 1.80, P = 0.029). Similar difference was also observed for women, but the P value didn't reach statistical significance (P = 0.076).

For healthy behavior variables, serum median levels of CRP differed by cigarette smoking status, alcohol drinking status, BMI category, and physical activity level (Table 1). Specifically, with the increase of BMI category from normal weight (BMI < 25), overweight (BMI: 25 to 30), class I obesity (BMI: 30 to 35), class II obesity (BMI: 35 to 40), to class III obesity (BMI: ≥40), median levels of CRP increased steadily and significantly (P for trend < 0.001). On the other hand, a trend of decreasing median CRP levels was noted for cigarette smoking and alcohol drinking status from never, former, to current, and physical activity levels from low, medium, to high (P for trend = 0.002, < 0.001, < 0.001, respectively). However, in the stratified analysis by sex, the significant trend of decreasing median CRP levels was no longer existed for cigarette smoking and alcohol drinking status in both men and women. The significant trend was remained for BMI category and physical activity levels in both men and women.

Next, we performed multivariable logistic regression analysis to identify demographic characteristics and health behaviors associated with high levels of CRP, defined as ≥ median levels among all study participants (Table 2). The included variables were age category, sex, marital status, education, place of birth, language acculturation, cigarette smoking status, alcohol drinking status, BMI category, and physical activity. The variables significantly associated with high levels of CRP included sex, age group, alcohol drinking status, BMI category, and physical activity levels. Specifically, compared to men, women had 1.88-fold increased likelihood of having high levels of CRP (OR = 1.88, 95%CI: 1.48, 2.39). With the increasing of age, the likelihood of having high levels of CRP was significantly increased (P for trend = 0.018). Compared to those with normal weight, those with overweight, class I obesity, class II obesity, to class III obesity had significantly increased likelihood of having high levels of CRP. And a dose-response trend of increasing likelihoods was observed across the BMI category (P for trend < 0.001). On the other hand, compared to those who never consumed alcohol drinking, those who currently consumed had 21% decreased likelihood of having high levels of CRP (OR = 0.79, 95%CI: 0.60, 0.97). And compared to those with low levels of physical activity, those with medium levels of physical activity had 19% decreased risks of having high levels of CRP (OR = 0.81, 95%CI: 0.66, 0.99). When stratified by sex, BMI category was the only variable left significantly associated with high levels of CRP among women. In addition, a significant dose-response trend was observed between levels of physical activity and high levels of CRP (P = 0.045). Among men, both age category and BMI category were still significantly associated with high

Table 2
Multivariable logistic analysis to identify demographic and health behaviors associated with high CRP levels (N = 2753).

Characteristics	ORs (95%CI)*		
	Overall	Women	Men
Sex			
Men	Reference		
Women	1.88 (1.48, 2.39)		
Age group			
< 30	Reference	Reference	Reference
30-39	1.25 (0.96, 1.62)	1.33 (1.00, 1.77)	0.91 (0.48, 1.74)
40-49	1.41 (1.07, 1.86)	1.39 (1.02, 1.89)	1.62 (0.87, 3.02)
50-59	1.32 (0.99, 1.77)	1.47 (1.05, 2.06)	1.18 (0.61, 2.29)
60+	1.46 (1.08, 1.97)	1.17 (0.83, 1.65)	2.87 (1.50, 5.50)
P for trend	0.018	0.244	0.001
Marital Status			
Married	Reference	Reference	Reference
Not married	0.93 (0.76, 1.14)	0.89 (0.71, 1.12)	1.42 (0.88, 2.29)
Education			
< High school	Reference	Reference	Reference
At least high school	0.90 (0.74, 1.09)	0.93 (0.75, 1.16)	0.74 (0.49, 1.13)
Place of birth			
Mexico	Reference	Reference	Reference
US	1.15 (0.90, 1.47)	1.24 (0.92, 1.66)	0.92 (0.57, 1.47)
Language acculturation			
Low	Reference	Reference	Reference
High	1.15 (0.91, 1.45)	1.02 (0.77, 1.34)	1.78 (1.11, 2.86)
Cigarette smoking status			
Never	Reference	Reference	Reference
Former	0.93 (0.71, 1.20)	0.97 (0.69, 1.35)	0.75 (0.47, 1.20)
Current	1.10 (0.84, 1.44)	1.07 (0.76, 1.51)	1.12 (0.70, 1.78)
P for trend	0.630	0.772)	0.735
Alcohol drinking			
Never	Reference	Reference	Reference
Former	1.01 (0.75, 1.36)	0.95 (0.65, 1.40)	1.17 (0.68, 2.02)
Current	0.79 (0.60, 0.97)	0.81 (0.61, 1.08)	0.82 (0.51, 1.34)
P for trend	0.029	0.166	0.296
Body mass index			
Normal (< 25)	Reference	Reference	Reference
Overweight (25-30)	1.82 (1.42, 2.32)	2.00 (1.52, 2.64)	1.34 (1.78, 2.30)
Class I obesity (30-35)	3.71 (2.89, 4.78)	3.74 (2.82, 4.97)	3.59 (2.04, 6.33)
Class II obesity (35-40)	7.86 (5.58, 11.06)	8.08 (5.51, 11.85)	7.48 (3.40, 16.40)
Class III obesity (40+)	10.20 (6.58, 15.81)	12.10 (7.33, 19.97)	6.28 (2.29, 17.24)
P for trend	< 0.001	< 0.001	< 0.001
Physical activity			
Low	Reference	Reference	Reference
Medium	0.81 (0.66, 0.99)	0.79 (0.62, 1.01)	0.80 (0.54, 1.20)
High	0.71 (0.42, 1.20)	0.69 (0.33, 1.48)	0.76 (0.36, 1.62)
P for trend	0.023	0.045	0.256

*Age category, sex, marital status, education, place of birth, language acculturation, cigarette smoking status, alcohol drinking status, BMI category, and physical activity were adjusted in the logistic regression as appropriate.

levels of CRP. In addition, men with high language acculturation had 1.78-fold increased likelihood of having high levels of CRP (OR = 1.78, 95%CI: 1.11, 2.86).

Then, among those born in the Mexico, we explored whether years of living in U.S. and age of immigration in U.S. might affect CRP levels. With years of living in U.S. increased, median levels of CRP was gradually increased from 3.00 to 3.77 (Table 3). Such increase was particularly evident among men (P for trend < 0.001). In further multivariable analysis, compared to those living in U.S. for less than 10 years, those living in U.S. for 10 to 20, 20 to 30, 30 to 40, and at least 40 years had increased likelihoods of having high levels of CRP. And a dose-response trend of increasing likelihoods was observed across the BMI category (P for trend = 0.018). Such relationship was observed in both men and women, but the trend was more evident among men (P for trend = 0.040). No similar association was observed for age of immigration in U.S.

Finally, we investigated whether serum CRP levels were associated with incidents of cancer using multivariable Cox regression analysis and the results are summarized in Table 4. Among the 2753 study participants, a total of 177 cases were identified during the follow-up as having experienced cancer. The major cancers included cancers in breast (N = 53), colorectal (N = 18), uterine (N = 15), cervical (N = 14), prostate (N = 12) and lung (N = 11). When CRP levels were dichotomized into two groups (high or low) using median CRP levels (3.20), high CRP levels were not significantly associated with cancer risk. However, in further quartile analysis using 25%, 50%, and 75% values of CRP levels as cutoff points, those in the highest quartile (≥ 6.40) had an increased cancer risk when compared to those in the lowest quartile of CRP levels (< 1.32) (HR = 1.88, 95%CI = 1.12, 3.13). In addition, a statistically significant dose–response trend was observed (P = 0.035). Similarly, when CRP levels were separated into 4 groups using clinical CRP levels [17], those with highest CRP levels

Table 3
Median levels of CRP and risk of high CRP by years of living in U.S. among MAC study participants born in Mexico.

	All (N = 1826)		Women (N = 1461)		Men (N = 365)	
Characteristics	CRP, median (range)	P-value	CRP, median (range)	P-value	CRP, median (range)	P-value
< 10 years	3.00 (0.11, 44.00)	Reference	3.58 (0.11, 44.00)	Reference	1.30 (0.12, 24.39)	Reference
10-20 years	3.20 (0.12, 42.00)	0.459	3.60 (0.12, 42.00)	0.582	1.52 (0.12, 15.50)	0.459
20-30 years	3.20 (0.13, 33.50)	0.478	3.54 (0.13, 33.50)	0.528	1.75 (0.14, 23.00)	0.478
30-40 years	3.23 (0.12, 48.00)	0.512	3.76 (0.12, 48.00)	0.630	2.37 (0.16, 36.19)	0.512
40+ years	3.77 (0.20, 18.00)	0.280	3.88 (0.20, 18.00)	0.469	3.20 (0.20, 9.80)	0.280
P for trend	0.294		0.435		< 0.001	
Risk of high CRP levels						
	OR (95%CI)*		OR (95%CI)*		OR (95%CI)*	
< 10 years	Reference		Reference		Reference	
10-20 years	0.89 (0.65, 1.21)		0.79 (0.56, 1.11)		1.34 (0.66, 2.72)	
20-30 years	1.08 (0.76, 1.52)		1.00 (0.67, 1.50)		1.35 (0.66, 2.78)	
30-40 years	1.47 (0.95, 2.28)		1.16 (0.67, 2.02)		2.28 (1.05, 4.97)	
40+ years	1.98 (1.01, 3.87)		2.10 (0.88, 4.97)		2.18 (0.68, 6.95)	
P for trend	0.018		0.184		0.040	

*Adjusted by age category, gender, marital status, education level, language acculturation, cigarette smoking status, alcohol drinking status, BMI category, age of immigration, and physical activity levels as appropriate.

(> 10) had 1.86 fold increased risk of cancer (HR = 1.96, 95%CI = 1.01, 3.41) when compared with those with lowest CRP level (< 1). We also examined the impact of the time between cancer diagnosis and CRP measures at baseline and incidents of cancer, using 5 years as the cutoff point. The significant association between CRP and cancer risk was only evident among participants whose cancer was diagnosed beyond 5 years of blood collection, but not among those whose cancer was diagnosed earlier.

4. Discussion

The current study assessed the associations between serum CRP levels with demographic characteristics and health behaviors, as well as for the first time prospectively examined the relationship between pre-diagnostic serum CRP levels and all cancer risk among Mexican Americans. We found that median levels of serum CRP significantly differed by demographic characteristics and health behaviors. In quartile analysis, a significant dose response trend was observed between increasing CRP levels and overall cancer risk (P < 0.05). We further found that the risk was more evident among those whose cancer was diagnosed beyond 5 years of blood collection.

We found that women had higher median levels of serum CRP than men did. Such observation is in consensus with the findings from previous studies [18,19]. For example, in the Multiethnic Study of Atherosclerosis (MESA) cohort, CRP levels were higher in women compared with men despite accounting for BMI and other common confounding variables [18]. Our observation that median CRP levels increased with age group is consistent with the literature reports too [20,21]. Interestingly, in a recent publication, CRP could promote ageing via a Smad3-dependent p21/p27 mechanism and through impairing cell regeneration by causing the G1 cell cycle arrest [22]. In the National Social Life, health, and Aging Project (NSHAP), education levels were inversely associated with CRP levels [23], which is consistent with our findings. However, in the multivariable analysis, the education was not associated with high CRP levels. In NSHAP, marriage was found a protective factor against elevated CRP for men [24]. In our study, similar but non-significant association was observed for men. In the multivariable analysis, men or married or living together had 1.42 fold increased likelihood of having high CRP levels (OR = 1.42, 95%CI: 0.88, 2.29).

Table 4
Multivariable adjusted hazard ratios for incidents of cancer (n = 177).

	All cancer cases (n = 177)			Follow-up time between 1-5 year (n = 55)			Follow-up time > 5 year (n = 109)		
	Cases	HR (95%CI)*	P value	Cases	HR (95%CI)*	P value	Cases	HR (95%CI)*	P value
CRP									
Median									
< 3.20	71	Reference		20	Reference		40	Reference	
≥ 3.20	106	1.18 (0.85-1.62)	0.317	35	1.15 (0.56-2.80)	0.745	69	1.29 (0.79-2.40)	0.301
Quartile									
< 1.32	22	Reference		10	Reference		10	Reference	
1.18 < 3.20	43	1.54 (0.91-2.58)	0.105	10	0.99 (0.39-2.48)	0.975	30	2.46 (1.19-5.08)	0.015
3.20 < 6.40	44	1.25 (0.72-2.09)	0.452	12	1.11 (0.41-2.73)	0.873	29	1.87 (0.89-3.95)	0.100
≥ 6.40	67	1.88 (1.12-3.13)	0.016	23	1.26 (0.49-2.94)	0.765	40	2.66 (1.28-5.55)	0.009
P for trend			0.035			0.597			0.040
Clinical									
< 1	20	Reference		8	Reference		10	Reference	
1-3	51	1.39 (0.82-2.35)	0.226	14	1.04 (0.42-2.56)	0.937	34	1.88 (0.92-3.88)	0.084
3-10	76	1.33 (0.80-2.23)	0.276	24	1.36 (0.59-3.14)	0.935	48	1.82 (0.89-3.71)	0.099
> 10	29	1.86 (1.01-3.41)	0.046	9	1.43 (0.46-4.78)	0.759	17	2.29 (1.03-5.08)	0.042
P for trend			0.098			0.761			0.100

*Adjusted by age category, gender, alcohol drinking status, BMI category, and physical activity levels as appropriate.

Among all variables associated with CRP levels, BMI is the most significant and consistent one. Our results are in line with the previous literature reports in several different populations, including Mexican American [25–29]. We also found a significant trend of decreasing median CRP levels with the increase of physical activity levels even after adjustment of BMI and other co-variants, indicating that being physical active may reduce inflammation directly. In fact, our results are supported by the findings from other studies [30–34]. In the multivariable analysis, we also found a protective association of alcohol drinking. Compared to never drinkers, current drinkers had lower median CRP levels in the univariate analysis ($P < 0.001$). The difference was only evident among women. In the multivariable analysis, current drinkers had 21% decreased likelihood of having high CRP levels than neve drinkers did (OR = 0.79, 95%CI: 0.60, 0.97). Moderate alcohol drinkers is known to have lower CRP compared to never drinkers and heavy drinkers [35,36]. Overall, Hispanics are less likely to drink alcohol at all than are non-Hispanic Whites. In fact, Mexican Americans have the lowest rate of binge drinking among all Hispanics. Although the current study doesn't have the data on the amount and type of alcohol consumed, it is still reasonable to assume that most of the current drinkers in our study only drink lightly or moderately.

Among those born in Mexico, median levels of CRP were gradually increased with years of living in U.S, particularly among men. Such association was further confirmed in the multivariable analysis. Coupled with the observation that median CRP levels were higher among those born in U.S. than their counterpart in both men ($P = 0.029$) and women ($P = 0.076$), we can assume that the adoption of American culture and behaviors, such as being overweight or obese, leading a sedentary lifestyle, being lack of sleep, and eating fast or processed foods, during the immigration and acculturation may influence CRP levels. With more accustomed to American lifestyle, the prevalence of such unhealthy behaviors is likely to increase. As shown in this study, both being over-weight or obese and physically inactive are correlated with increased CRP levels. Although we already included BMI, physical activity, cigarette smoking, and alcohol drinking in the analysis, there are still a few potential confounding factors left out, such as sleep and diet. The impact of sleep loss on CRP levels has been reported previously [37]. And dietary fatty acid intake has been shown to affect serum CRP levels [38].

In addition, this study examined the relationship between elevated CRP and incidents of cancer among Mexican Americans who experienced cancer at follow-up. We found a significant dose-response trend between increased CRP levels and increased risk of all cancer. Our results are consistent with literature reports from several prospective cohort studies that have shown that elevated serum CRP levels are associated with increased risk of cancer [9–14]. Since our study is a prospective cohort study, we have the ability to determine temporal exposure in relation to disease and evaluate the possibility of reverse causation. As the associations we observe are only evident among cases occurring more than 5 years of follow-up, our results suggest increased levels of serum CRP may be a cancer risk factor, not a biomarker of subclinical cancer in Mexican Americans. Our observations are also consistent with the notion that CRP is a marker for systemic inflammation.

The major strengths of this study include its large sample size, detailed epidemiologic questionnaire data, and unique Mexican American study population. One weakness of our study is that we were unable to obtain repeated measures of CRP over time because one time quantification may not echo CRP over a long period. Nevertheless, our results provide the first evidence in Mexican Americans that higher CRP levels were significantly associated with increased overall cancer risk. Future large-scale and well design prospective studies are required to further validate the observed association of our study.

Authorship contribution

JS has performed the assays and drafted the manuscript.

DH, LHM, and WHC have participated in the study design and manuscript drafting.

HZ has participated in study design, data analysis, and manuscript drafting.

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Declaration of interest

All authors have declared no conflict of interest.

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