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based cohort study with a two-year follow-up frequency provides a novel perception of the potential association between longitudinal CRP trajectory patterns and cancer risk. The results show that CRP trajectories play an important role in the occurrence of cancers, especially in the lung, breast, bladder, stomach, colorectal, liver, gallbladder or extrahepatic bile duct cancer and leukemia. The decreasing CRP trajectory pattern is associated with decreased esophageal and colorectal cancer risk.

1 | INTRODUCTION

Cancer is the first or second leading cause of premature death in 134 of 183 countries, and it ranks third or fourth in 45 of the remaining countries.[1] About one-third of deaths from non-communicable diseases are due to cancer.[1] The morbidity and mortality rates vary across countries due to different prevalence of key risk factors, as well as the impact of preventive methods, screening and therapeutic interventions.[2,3] Robust scientific evidence is essential for understanding its cause and prevention. In addition to some recognized factors like smoking,[4] drinking,[5] obesity,[6] nutrition,[7] family history of cancer, infectious disease[8] and environmental factors,[9] chronic inflammation has been demonstrated to be closely associated with cancers.[10,11] Cancer-associated inflammation is known as the seventh hallmark of cancer, associated with the six generally recognized hallmarks of cancer: self-sufficient growth signals, evasion of apoptosis, insensitivity to antigrowth signals, unlimited replicative potential, sustained angiogenesis and metastasis.[10]

C-reactive protein (CRP) is a classic acute-phase protein that responds to inflammation, infection and tissue damage, and is the most widely used biomarker of inflammation.[12,13] Recently, epidemiologic studies have demonstrated an association of elevated levels of circulating high sensitivity CRP (hs-CRP), CRP measured by a high-sensitivity assay which can accurately detect low-grade inflammatory state, with an increased risk of incident cancers.[14-16] However, results from previous studies were based on a single measurement of CRP level at baseline which may yield a certain degree of variability during the follow-up period and lead to misclassification of the participants.

No prospective study has used multiple CRP measurements to examine the association of long-term patterns of CRP concentration with subsequent cancer risk. Kailuan study is an ongoing, prospective, population-based cohort study with follow-up conducted every 2 years. Repeated CRP measurements can offer us a great opportunity to ascertain the association between CRP trajectory patterns and the risk of incident cancers.

2 | METHODS

2.1 | Study population

Data was taken from the Kailuan cohort study, which was designed to explore the risk factors for common chronic diseases. The detailed study design and procedures were described previously.[17] All 155 418 Kailuan Corporation employees (including retirees) were invited to participate in baseline physical examinations at Kailuan General Hospital and its 10 affiliated institutions between July 2006 and October 2007. A total of 101 510 individuals (65.3%) ranging in age from 18 to 98 years, with 81 110 males and 20 400 females, accepted and were enrolled after receiving written informed consent. All participants underwent health examinations including questionnaire assessments, clinical examinations and laboratory tests at baseline examination (2006-2007), and underwent follow-up examinations with the same examinations conducted every 2 years.

In the current study, CRP trajectories were developed from 2006 to 2010 to predict cancer risk from 2010 to 2019. In other words, the study was restricted to the population who participated in the examinations in 2006, 2008 and 2010 and had their plasma CRP measurements taken biennially. Participants were excluded if they: (1) failed to take 2008 and/or 2010 examinations; (2) had missing information of plasma CRP during 2006-2010; (3) lacked measurements of relevant confounders including age, sex, total cholesterol (TC, in mmol/L), triglyceride (TG, in mmol/L), body mass index (BMI, in kg/m^2), alanine aminotransferase (ALT, in u/L), total bilirubin (TBil, in umol/L), fasting blood glucose (FBG, in mmol/L), hepatitis B surface antigen (HBsAg), dietary salt intake, marital status, sedentary lifestyle, educational background, tobacco consumption, alcohol drinking, physical exercise, family history of cancer, liver cirrhosis, fatty liver, gallstone disease, gallbladder polyp, diabetes mellitus and hypertension; and (4) had a history of cancer at baseline or were diagnosed with cancer during 2006 to 2010 (trajectory patterns). A total of 52 276 individuals were left in the final analyses and scheduled a follow-up (Figure 1).

2.2 | Assessment of plasma CRP

After an overnight fasting period (at least 8 hours), blood samples were obtained from the antecubital vein in EDTA tubes for each individual. The blood was further centrifuged for 10 minutes at 3000 rotations per minute at 25 C. Plasma was separated and stored at 80 C until laboratory determinations were performed. CRP was measured using a high-sensitivity nephelometry assay (Cias Latex CRP-H, Kanto Chemical Co. Inc., Tokyo, Japan) and the lower limit of detection is 0.1 mg/L. The intra- and interassay coefficient of variation for CRP measurement were 6.53% and 4.78%, respectively. Plasma CRP and other blood variables were all analyzed at the central laboratory of the Kailuan Hospital using an autoanalyzer (Hitachi 747; Hitachi).

2.3 | Outcome ascertainment

Incident cancer cases were identified via (1) checking clinical examinations or questionnaires in the routine follow-up until 31 December 2019; (2) checking medical linkage with the provincial vital statistics data, the Tangshan medical insurance system and the Kailuan Social Security Information System annually; and (3) reviewing death certificates from the Provincial Vital Statistics Offices (PVSO) to prevent missed diagnosis. Trained medical staff further reviewed the hospitalization records including pathology and imaging results to i

TABLE 1 Baseline characteristics of the participants according to hs-CRP trajectory patterns

	Hs-CRP trajectory patterns				
Variables	**Low-stable**	**Moderate-increasing**	**Increasing-decreasing**	**Elevated-decreasing**	***P*-value**
n (%)	43 258	2591	2068	4359	
Age (year)	48.40 ± 11.62	49.99 ± 11.97	52.70 ± 12.15	55.17 ± 11.07	<.0001
Male (%)	32 915 (76.09)	2072 (79.97)	1509 (72.97)	3195 (73.30)	<.0001
Marital status (%)					<.0001
Never	734 (1.70)	36 (1.39)	24 (1.16)	28 (0.64)	
Married	40 637 (93.94)	2337 (90.20)	1871 (90.48)	3397 (77.95)	
Divorced	382 (0.88)	18 (0.69)	17 (0.82)	32 (0.73)	
Widowed	580 (1.34)	45 (1.74)	34 (1.64)	103 (2.36)	
Remarried	925 (2.14)	155 (5.98)	122 (5.90)	799 (18.32)	
Educational background (%)					<.0001
Never	276 (0.64)	19 (0.73)	19 (0.92)	40 (0.91)	
Primary school	2954 (6.83)	174 (6.72)	176 (8.51)	406 (9.30)	
Middle school	29 542 (68.29)	1823 (70.36)	1436 (69.43)	2781 (63.80)	
High school	6801 (15.72)	313 (12.08)	270 (13.06)	470 (10.80)	
College graduate or above	3685 (8.52)	262 (10.11)	167 (8.08)	662 (15.19)	
TC (%)					<.0001
<4.50 mmol/L	14 712 (34.01)	741 (28.60)	564 (27.28)	1473 (33.80)	
4.50-5.32 mmol/L	14 197 (32.82)	862 (33.27)	700 (33.85)	1451 (33.29)	
>5.32 mmol/L	14 349 (33.17)	988 (38.13)	804 (37.83)	1435 (32.91)	
TG (%)					<.0001
<1.02 mmol/L	14 970 (34.61)	703 (27.14)	546 (26.41)	1409 (32.33)	
1.02-1.65 mmol/L	14 302 (33.06)	773 (29.84)	640 (30.95)	1375 (31.55)	
>1.65 mmol/L	13 986 (33.58)	1115 (43.02)	882 (42.64)	1575 (36.12)	
ALT (%)					.0095
<15.00 u/L	15 538 (35.92)	908 (35.05)	729 (35.26)	1649 (37.83)	
15.00-22.00 u/L	13 193 (30.50)	735 (28.37)	627 (30.32)	1328 (30.47)	
>22.00 u/L	14 527 (33.07)	948 (36.58)	712 (34.42)	1382 (31.70)	
TBil (%)					<.0001
<10.70 umol/L	13 079 (30.23)	986 (38.06)	705 (34.09)	2320 (53.23)	
10.70-14.00 umol/L	14 757 (34.12)	756 (29.18)	647 (31.29)	1085 (24.90)	
>14.00 umol/L	15 422 (35.65)	849 (32.76)	716 (34.62)	954 (21.87)	
BMI (%)					<.0001
<24 kg/m^2	17 638 (40.77)	780 (30.10)	622 (30.08)	1509 (34.62)	
24-28 kg/m^2	17 902 (41.38)	1108 (42.76)	842 (41.72)	1930 (44.28)	
>28 kg/m^2	7718 (17.85)	703 (27.13)	604 (29.20)	920 (21.10)	
Physical exercise (%)					<.0001
Never	3924 (9.07)	181 (6.99)	143 (6.92)	224 (5.14)	
Occasionally	32 406 (74.91)	1945 (75.07)	1518 (73.40)	2834 (65.01)	
Regularly	6928 (16.00)	465 (17.94)	407 (19.68)	1301 (29.85)	
Smoking status (%)					<.0001
Never	25 299 (58.49)	1404 (54.19)	1243 (60.11)	2446 (56.11)	
Past	2314 (5.35)	102 (3.94)	109 (5.27)	207 (4.75)	
Moderate	1676 (3.87)	92 (3.55)	57 (2.76)	119 (2.73)	
Severe	13 969 (32.29)	993 (38.32)	659 (31.86)	1587 (36.41)	

(Continues)

TABLE 3 Hazard ratios (HRs) for the association between hs-CRP trajectory patterns and specific site cancer risk

Specific cancer site	Cases	Hs-CRP trajectory patterns			
		Low-stable	Moderate-increasing	Increasing-decreasing	Elevated-decreasing
Lung cancer	664	Ref.	**1.21 (1.04-1.42)**	**1.09 (1.02-1.15)**	0.79 (0.61-1.02)
Breast cancer	202	Ref.	**1.30 (1.09-1.59)**	**2.47 (1.16-2.51)**	0.89 (0.51-1.56)
Leukemia	137	Ref.	**9.54 (6.35-14.34)**	0.93 (0.37-2.34)	**4.87 (3.27-7.26)**
Kidney cancer	141	Ref.	0.57 (0.23-1.39)	0.44 (0.15-1.72)	0.34 (0.15-1.77)
Bladder cancer	103	Ref.	**1.31 (1.11-1.54)**	**6.71 (4.30-10.48)**	0.72 (0.33-1.59)
Prostate cancer	80	Ref.	0.77 (0.28-2.11)	0.79 (0.29-2.19)	1.10 (0.30-1.45)
Pancreatic cancer	61	Ref.	0.86 (0.21-3.58)	**1.92 (1.10-2.88)**	0.43 (0.10-1.80)
Head and neck cancer	113	Ref.	0.84 (0.26-2.68)	0.37 (0.05-2.65)	1.04 (0.44-2.45)
Esophageal cancer	83	Ref.	0.62 (0.20-1.96)	1.30 (0.52-3.23)	**0.23 (0.05-0.95)**
Stomach cancer	161	Ref.	**1.22 (1.03-1.49)**	1.08 (0.52-2.21)	0.82 (0.46-1.47)
Colorectal cancer	348	Ref.	**1.13 (1.01-1.23)**	**0.33 (0.15-0.73)**	**0.54 (0.35-0.85)**
Liver cancer[a]	138	Ref.	**1.07 (1.02-1.11)**	**1.29 (1.15-1.44)**	0.88 (0.48-1.61)
Gallbladder or extrahepatic bile duct cancer[b]	63	Ref.	**1.33 (1.12-1.53)**	0.34 (0.05-2.44)	0.29 (0.07-1.23)

Note: Models were adjusted for age (every 10 years), gender, BMI, TG, TC, TBil, ALT, diabetes, family income, educational background, marital status, salt consumption, current smoker, drinking status, physical activity, sedentary lifestyle and family history of cancer.
Results presented with bold valued were statistically significant with all p value < 0.05.
[a]Further adjusted for HBV infection, liver cirrhosis and fatty liver disease.
[b]Further adjusted for gallstone disease and gallbladder polyp.

TABLE 4 Hazard ratios (HRs) for the association between hs-CRP trajectory patterns and specific site cancer risk in the sensitivity analysis

Group	Cases/person-years	Adjusted models	
		HR (95% CI)	*P*-value
Exclude participants hs-CRP >10 mg/L			
Low-stable pattern	1948/365 006	Ref.	
Moderate-increasing pattern	178/14 999	1.86 (1.54-2.24)	<.0001
Increasing-decreasing pattern	131/11 627	1.84 (1.53-2.22)	<.0001
Elevated-decreasing pattern	156/27 284	1.02 (0.87-1.20)	.0532
Exclude participants who took aspirin			
Low-stable pattern	1927/363 222	Ref.	
Moderate-increasing pattern	210/21 423	1.44 (1.21-1.70)	<.0001
Increasing-decreasing pattern	154/17 310	1.42 (1.19-1.68)	.0001
Elevated-decreasing pattern	195/35 668	1.03 (0.70-1.42)	.2129
Exclude participants who took statins			
Low-stable pattern	1929/361 654	Ref.	
Moderate-increasing pattern	207/21 367	1.40 (1.17-1.65)	.0001
Increasing-decreasing pattern	151/17 214	1.38 (1.16-1.65)	.0003
Elevated-decreasing pattern	178/35 350	0.90 (0.77-1.04)	.1555
Exclude participants with follow-up <1 year			
Low-stable pattern	1773/363 832	Ref.	
Moderate-increasing pattern	179/21 345	1.41 (1.16-1.64)	<.0001
Increasing-decreasing pattern	129/17 271	1.34 (1.11-1.58)	.0001
Elevated-decreasing pattern	150/35 662	0.94 (0.80-1.10)	.2331

Note: Models were adjusted for age (every 10 years), gender, BMI, TG, TC, TBiL, ALT, diabetes, family income, educational background, marital status, salt consumption, current smoker, drinking status, physical activity, sedentary lifestyle and family history of cancer.

cancer (HR = 2.47, 95% CI: 1.16-2.51), bladder cancer (HR = 6.71, 95% CI: 4.30-10.48), pancreatic cancer (HR = 1.92, 95% CI: 1.10-2.88) and liver cancer (HR = 1.29, 95% CI: 1.15-1.44). Remarkably, the increasing-decreasing trajectory pattern was also associated with the decreased risk of colorectal cancer in the multivariate analyses (HR = 0.33, 95% CI: 0.15-0.73).

Compared to the low-stable pattern of CRP, individuals in the elevated-decreasing trajectory pattern had a 4.8-fold increased risk of leukemia in the adjusted models (HR = 4.87, 95% CI: 3.27 to 7.26). However, the elevated-decreasing trajectory pattern is also associated with decreased risk of esophageal cancer (HR = 0.23, 95% CI: 0.05 to 0.95) and colorectal cancer (HR = 0.54, 95% CI: 0.35 to 0.85).

3.5 | Sensitivity analysis

In the sensitivity analysis, after excluding individuals with CRP levels greater than 10 mg/L during 2006 to 2010 (n = 2601), or who had received oral aspirin therapy (n = 282), or who took statins (n = 535) at baseline examination, or with follow-up less than 1 year (n = 879), the association between CRP trajectory patterns and the risk of pooled cancers remained significant in the multivariate analysis (Table 4).

4 | DISCUSSION

In this large, prospective cohort study, compared to the low-stable CRP trajectory pattern within 4 years, we found (i) a positive association of the moderate-increasing CRP and increasing-decreasing CRP trajectory pattern with overall cancer risk; (ii) participants in the moderate-increasing CRP trajectory pattern exhibited elevated risk of lung, breast, bladder, stomach, colorectal, liver, gallbladder or extrahepatic bile duct cancer and leukemia; (iii) the increasing-decreasing CRP trajectory pattern was associated with increased risk of lung, breast, bladder, pancreatic, liver cancer and decreased risk of colorectal cancer. (iv) elevated-decreasing CRP trajectory pattern was associated with increased leukemia risk and decreased esophageal and colorectal cancer risk. As far as we are aware, this is the first study to comprehensively evaluate the impact of heterogeneous CRP trajectories on the risk of overall and specific-site cancers worldwide.

Participants in the moderate-increasing and increasing-decreasing CRP trajectory patterns were at a higher risk of developing cancer in the future. This should be a matter of concern for loctontrjectory54((HR)]TJme(the4679.5(ri45.4(p-30trol(indiv43.4(individua)(ind174.8(mo8-1.6ctio1.4l0.5(of2

driver of lowering CRP concentration, regardless of diet composition.[35] In this current study, the reversed association between the decreased trajectory of CRP and cancer risk is independent of BMI. Taken together, the antiinflammatory effect produced by changing a healthy lifestyle and weight loss may partially clarify the anticancer effect of the decreasing trajectory of CRP in our study. Future studies should be conducted to better assess the potential mechanism of decline in serum CRP levels for the anticarcinogenesis effect.

Although the exact mechanisms surrounding the association of elevated CRP levels with increased risk of cancer remain unsolved, several possible mechanisms may help to elucidate this matter. Long-term low degree inflammation can promote tumor development and progression by leading to oxidation of protein and DNA.[36] Crucial pathways that maintain normal cellular homeostasis can be altered by genetic and epigenetic variations, due to mediators of the inflammatory response such as cytokines, free radicals, prostaglandins and growth factors. These variations include point mutations in tumor suppressor genes, DNA methylation and posttranslational variations, all of which can lead to the eventual presence and growth of cancer.[36] The association between inflammation and cancer has also been further fortified after observing the interaction of microRNAs and innate immunity during inflammation.[37] Previous research suggested that CRP was not just a marker of inflammation but has numerous critical proinflammatory properties.[38,39] Specifically, CRP can cause the initiation of endothelial cells, monocytes and smooth muscle cells, prompt expression of adhesion molecules, chemoattractant, tissue factors and activation of the NF-κB pathway.[40] Adhesion molecule expression is essential for the invasion of cancer, whereas NF-κB pathway activation has been linked to crucial oncogenic effects.

The major strength of this current study is that it provides a novel perception of the potential association between longitudinal CRP trajectory patterns and cancer risk. Furthermore, the broad evaluation of potential confounders has been well addressed in our study, including lifestyle behaviors and history of cancer-associated diseases. Finally, cancer cases were obtained through inspection of the Tangshan medical insurance system and the Kailuan social security system which record all the health information of participants. Using this method, the follow-up rate was almost 100% in the current study.

Limitations should also be noticed in our study when interpreting the results. First, the Kailuan study does not contain detailed information on other cancer-associated causal factors including hepatitis C virus

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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