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INNOVATIVE TOOLS AND METHODS

C-reactive protein trajectories and the risk of all cancer types: A prospective cohort study

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Abstract

A single CRP measurement is insufficient to examine the association of long-term patterns of CRP concentration with cancer risk. We prospectively examined the relationship between CRP trajectory patterns and new-onset cancers among 52 276 participants. Latent mixture modeling was used to identify CRP trajectories. Cox proportional hazards regression models were used to evaluate the association between CRP trajectory patterns and the risk of overall and specific-site cancer. Four CRP trajectories patterns were identified: low-stable pattern (n = 43 258), moderate-increasing pattern (n = 2591), increasing-decreasing pattern (n = 2068) and elevated-decreasing pattern (n = 4359). Relative to the low-stable pattern, the moderate-increasing trajectory pattern was associated with an elevated risk of overall, lung, breast, leukemia, bladder, stomach, colorectal, liver, gallbladder or extrahepatic bile duct cancer and leukemia. Participants in the increasing-decreasing trajectory pattern were associated with an elevated risk of overall, lung, breast, bladder, pancreatic and liver cancer. The increasing-decreasing trajectory pattern was also associated with decreased risk of colorectal cancer in the multivariate analyses. Elevated-decreasing trajectory pattern was associated with increased risk of leukemia and decreased risk of esophageal and colorectal cancer. CRP trajectories play an important role in the occurrence of cancers, especially in the lung, breast, bladder, stomach, colorectal, liver, gallbladder and extrahepatic bile duct cancer and leukemia.

KEYWORDS
cancer, C-reactive protein, prospective, risk, trajectory

What's new?

Chronic inflammation is closely associated with cancers. However, most previous studies used a single measurement of C-reactive protein (CRP) level at baseline. This prospective, population-

Abbreviations: ALT, alanine aminotransferase; ANOVA, one-way analysis of variance; BIC, Bayesian information criterion; BMI, body mass index; CRC, colorectal cancer; CRP, C-reactive protein; FBG, fasting blood glucose; HBsAg, hepatitis B surface antigen; hs-CRP, high sensitivity CRP; TBil, total bilirubin; TC, total cholesterol; TG, triglyceride.

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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 identified the incident cancer cases and coded cases according to the International Classification of Diseases, Tenth Revision (ICD-10) as the following: head and neck cancer (00-14, 30-32, 71, 73), esophageal cancer (15), stomach cancer (16), small intestine cancer (17), colorectal cancer (18-21), liver cancer (22), gallbladder or extrahepatic bile duct cancer (23-24), pancreatic cancer (25), lung cancer (34), bone and soft tissue cancer (40-41, 49), skin cancer (43-44), breast cancer (50), cervix cancer (53), uterus cancer (54-55), ovarian cancer (56), prostate cancer (61), kidney cancer (64-65), bladder cancer (67), lymphoma (81-89), leukemia and multiple myeloma (90-96).

2.4 | Potential confounders

Information on age, sex, socioeconomic status, educational background, lifestyle behaviors, medical histories of personal and family members were collected through a questionnaire which was done via trained medical staff. Drinking and smoking status was classified into three categories: never, past or current. Physical exercise was evaluated from responses regarding the frequency of physical activity and classified as: never, occasionally or regularly (≥3 times/week, ≥30 minutes/time). Information on perceived salt intake was determined via a questionnaire survey about regular salt consumption and classified into three categories: low (<6 g/day), intermediate (6-9 g/day) or high (≥10 g/day). In 2012, a validation study was conducted by collecting random spot urine samples from 231 hypertensive participants who did not use any antihypertensive drugs from the Kailuan Study.[18] A sedentary lifestyle was categorized into three groups according to the responses about daily sedentary time.

Trained medical staff performed physical examinations for each participant. BMI was classified into normal (<24 kg/m^2), overweight (24.00-27.99 kg/m^2) or obese (≥28 kg/m^2). Hypertension was defined as having a SBP ≥140 mm Hg, and/or a DPB ≥90 mm Hg, and/or a previous diagnosis of hypertension. The abdominal region, including liver, gallbladder, pancreas and spleen of each participant was examined by specialists after fasting for at least 8 hours using the real-time ultrasound sonography (PHILIPS HD-15). The diagnoses of liver cirrhosis, fatty liver, gallstone disease and gallbladder polyp were based on the results of abdominal ultrasonography or through medical records from the Tangshan medical insurance system. Diabetes mellitus was defined as having a FBG level ≥ |

the PROC TRAJ procedure in SAS. We initiated a model with five trajectory patterns and then compared the pattern with 4, 3, 2 and 1 trajectories, respectively. The Bayesian information criterion (BIC) with the smallest negative number was used to choose the best-fit trajectory patterns. In addition, the models with different functional forms were compared via the significance level of cubic, quadratic and linear terms, starting with the highest polynomial.

The characteristics of the subjects with normal distribution were expressed as mean ± SD and compared using one-way analysis of variance (ANOVA). Categorical variables were represented as absolute value with percentage and the χ^2 test was used for comparison among groups. The calculation of person-year was based on the time from the established CRP trajectory patterns until the date of cancer diagnosis, death or end of follow-up (31 December 2019), whichever event came first. Cox proportional hazards analysis was used to explore the hazard ratios (HRs) and their 95% confidence intervals (CIs) for determining the association between CRP trajectories from 2006 to 2010 and the subsequent risk of cancers. Adjustments for confounders were made when fitting three models as follows: model 1 was a univariate analysis; model 2 was adjusted for age and sex; model 3 was further adjusted for BMI, concentrations of TC, TG, ALT and TBil, smoking and drinking status, levels of education, marital status, dietary salt intake, diabetes mellitus, hypertension, sedentary lifestyle, physical exercise and family history of cancer. The selection of the confounders was based on the results from previous studies.[19-21]

In the analyses of pooled cancers, only the first reported cancer type was included. However, for patients with multiple cancers, site-specific analyses were conducted for each cancer type. In the site-specific analyses, HBV infection, liver cirrhosis and fatty liver were additionally adjusted in the multivariate model of liver cancer. Meanwhile, gallstone disease and gallbladder polyp were further adjusted the model of the gallbladder or extrahepatic bile duct cancer.

As a sensitivity analysis, we first excluded participants levels greater than 10 mg/L from 2006 to 2010, which an acute inflammatory response. We further exc who received oral aspirin therapy or statins the the CRP concentration. Although reverse c here because of the clear temporal seq tory patterns and the occurrence of pants who had less than 1 year o

A two-sided P value <.0 Statistical analyses were software program (SA

3 | R

3.

jectories with cubic order terms 2). A total of 43 258 participants aintained a low CRP concentration (mean ed from 1.00 mg/L in 2006 to 1.30 mg/L in

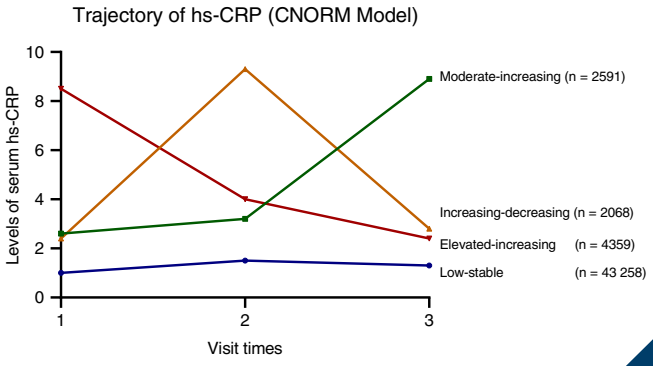

FIG E 2 CRP trajectory patterns during 2006 to 2010 in Kailuan cohort [Color figure can be viewed at wileyonlinelib

2010) were referred to as the low-stable pattern; 2 (4.96%) who initially had moderate CRP levels a an increase of CRP (mean FBG concentration in 2006 to 8.96 mg/L in 2010) were re increasing pattern; 2068 (3.96%) parti ing CRP concentrations and the (mean CRP concentrations 9.43 mg/L in 2008 and 2 increasing-decreasing had elevated conc ean CRP concentra mg/L in 2010) were

ne study

691 men and 12 585 women) were the mean age was 49.29 ± 11.80 years. e found in age, levels of TC, TG, ALT, TBil ce of chronic HBV infection, physical exercise, nking status, dietary salt intake, marital status, sed- e, hypertension, diabetes mellitus, gallstone disease, and family history of cancer among four groups. However, erences in the prevalence of gallbladder polyp and liver cirrho- were observed among groups (Table 1).

3.3 | Association of CRP trajectory patterns with overall cancer risk

During a median of 8.51 years of follow-up, a total of 2510 cancer cases were identified. The absolute count of specific-site cancers is presented in Table S1. For all cancers combined, the age- and sex-standardized incidence rates per 100 000 population per year are higher in our study than the results reported previously in Northern China[22] (234.9 vs 213.2 per 100 000). Table 2 shows the association of CRP trajectory patterns with overall cancer risk. Compared to the low-stable pattern, the moderate-increasing trajectory pattern and

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)

ABLE 1 (Continued)

Variables	Hs-CRP trajectory patterns				
	Low-stable	Moderate-increasing	Increasing-decreasing	Elevated-decreasing	*P*-value
Drinking status (%)					<.0001
Never	24 149 (55.83)	1479 (57.08)	1259 (60.88)	2558 (58.68)	
Past	1377 (3.18)	88 (3.40)	63 (3.05)	119 (2.73)	
Moderate	9606 (22.21)	458 (17.68)	321 (15.52)	598 (13.72)	
Severe	8126 (18.78)	566 (21.84)	425 (20.55)	1084 (24.87)	
Salt intake (%)					<.0001
Low (<6 g/day)	4198 (9.70)	202 (7.80)	156 (7.54)	269 (6.17)	
Intermediate (6-10 g/day)	33 879 (78.32)	1985 (76.61)	1589 (76.84)	2949 (67.65)	
High (>10 g/day)	5181 (11.98)	404 (15.59)	323 (15.62)	1141 (26.18)	
Sedentary lifestyle (%)					<.0001
<4 hours/day	31 346 (72.46)	1904 (73.49)	1490 (72.05)	2838 (65.11)	
4-8 hours/day	9981 (23.08)	443 (17.10)	393 (19.00)	574 (13.17)	
>8 hours/day	1931 (4.46)	244 (9.42)	185 (8.95)	947 (21.72)	
Hypertension (%)	15 917 (36.80)	1179 (45.50)	997 (48.21)	2124 (48.73)	<.0001
Diabetes mellitus (%)	2918 (6.75)	216 (8.34)	206 (9.96)	441 (10.12)	<.0001
Gallbladder polyp (%)	365 (0.84)	15 (0.58)	18 (0.87)	19 (0.44)	.1428
Gallstone disease (%)	851 (1.97)	73 (2.82)	59 (2.85)	100 (2.29)	<.0001
Fatty liver (%)	12 843 (29.69)	1056 (40.76)	848 (41.01)	1535 (35.21)	<.0001
Liver cirrhosis (%)	38 (0.09)	5 (0.19)	3 (0.15)	4 (0.09)	.2806
HBsAg seropositive (%)	1259 (2.91)	68 (2.62)	50 (2.42)	82 (1.88)	.0006
Family history of cancer (%)	1779 (4.11)	73 (2.82)	65 (3.14)	137 (3.14)	<.0001

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; HBsAg, hepatitis B surface antigen; hs-CRP: high-sensitivity C-reactive protein; TBil, total bilirubin; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

ABLE 2 Hazard ratios (HRs) for the association between hs-CRP trajectory patterns and overall cancer risk

Hs-CRP trajectory patterns	Cases/person-years	Crude models		Adjusted models	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Low-stable pattern	1948/365 006	Ref.		Ref.	
Moderate-increasing pattern	210/21 527	1.65 (1.21-2.09)	<.0001	1.44 (1.19-1.69)	.0004
Increasing-decreasing pattern	154/17 422	1.53 (1.31-1.76)	<.0001	1.22 (1.04-1.41)	.0154
Elevated-decreasing pattern	198/35 924	1.11 (0.87-1.40)	.5301	1.07 (0.71-1.44)	.3172

Note: Adjusted 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.

increasing-decreasing trajectory pattern were associated with an elevated risk of pooled caners with the corresponding multivariate HR (95%) CI of 1.44 (1.19-1.69), 1.22 (1.04-1.41), respectively. However, no significant association between elevated-decreasing pattern and overall cancer risk after adjusting for potential confounders.

3.4 | Association of CRP trajectory patterns with the risk of specific-site cancer

Table 3 demonstrates the effect of CRP trajectories from 2006 to 2010 on the risk of specific-site cancer. In the site-specific analyses, compared to the low-stable pattern of CRP, individuals in moderate-increasing trajectory pattern exhibited an increased risk of lung cancer (HR = 1.21, 95% CI: 1.04-1.42), breast cancer (HR = 1.30, 95% CI: 1.09-1.59), leukemia (HR = 9.54, 95% CI: 6.35-14.34), bladder cancer (HR = 1.31, 95% CI: 1.11-1.54), stomach cancer (HR = 1.22, 95% CI: 1.03-1.49), colorectal cancer (HR = 1.13, 95% CI: 1.01-1.23), liver cancer (HR = 1.07, 95% CI: 1.02-1.11) and gallbladder or extrahepatic bile duct cancer (HR = 1.33, 95% CI: 1.12-1.53) in the fully-adjusted analyses.

After adjusting for the aforementioned confounders, participants in the increasing-decreasing trajectory pattern were associated with an elevated risk of lung cancer (HR = 1.09, 95% CI: 1.02-1.15), breast

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

		Hs-CRP trajectory patterns			
Specific cancer site	**Cases**	**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

		Adjusted models	
Group	**Cases/person-years**	**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

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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 (HBC) infection for liver3.3(u)rf7.6(ce)24oC1.5(ng)],4(edi)26.1(on)2n.8(n)6(8344.6(r)0(e)280(f7.6(ce)24.2(f)17(.622-7.8(u0(t)26at)-216(.)-76(c)14.)-28s)16(tx)11.3(

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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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