

Is C-Reactive Protein Specific for Vascular Disease in Women?

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Background: C-reactive protein (CRP) predicts risk for future cardiovascular events in asymptomatic individuals. However, because CRP also predicts total mortality, its specificity for vascular disease is uncertain.

Objective: To compare the predictive value of CRP for cancer and cardiovascular disease, the major determinants of mortality.

Design: Prospective, nested case-control study.

Setting: The Women's Health Study, an ongoing prospective cohort study involving 28 345 U.S. women 45 years of age and older who were healthy at the time of enrollment.

Participants: 643 women who subsequently developed cancer or had cardiovascular events; 643 age- and smoking-matched women who remained free of either disease during 58-month follow-up.

Measurements: Baseline CRP levels.

Results: Little evidence showed that increasing quartiles of baseline CRP predicted incident cancer (adjusted relative risks, 1.0, 1.2, 1.1, and 1.3; *P* for trend > 0.2). In contrast, increasing quartiles of baseline CRP were a strong marker of risk for future cardiovascular disease (adjusted relative risks, 1.0, 2.9, 3.4, and 5.6; *P* for trend < 0.001).

Conclusion: C-reactive protein appears to independently predict cardiovascular events but not cancer.

Ann Intern Med. 2002;136:529-533.

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Recent evidence suggests that atherosclerosis is in part a chronic low-grade inflammatory condition (1), and prospective epidemiologic studies have demonstrated that plasma markers of inflammation, such as C-reactive protein (CRP), are strong independent predictors of future coronary events in apparently healthy persons (2-6). However, as an acute-phase reactant, CRP increases dramatically in various pathologic conditions. Moreover, CRP has been shown to predict all-cause mortality (7, 8), an observation that raises the possibility that CRP may not be specific for vascular disease. To evaluate this hypothesis, we directly compared the predictive value of CRP for incident cancer and cardiovascular disease, the two most important determinants of all-cause mortality in the western world.

METHODS

We performed a prospective, nested case-control analysis within the Women's Health Study, an ongoing randomized, double-blind, placebo-controlled trial of aspirin and vitamin E for primary prevention of heart disease and cancer, which involves 39 876 U.S. women 45 years of age and older. Of these study participants, 28 345 (71%) provided baseline blood samples, which were stored at -70 °C until the time of laboratory analysis. In the Women's Health Study, all participants are

followed prospectively for incident health events, including cancer and cardiovascular events. The methods used for cohort follow-up, end-point ascertainment, and adjudication for both cancer and cardiovascular events are described in detail elsewhere (5, 9).

For this study, we defined case-patients as apparently healthy women who provided an adequate baseline plasma sample and who subsequently developed cancer (*n* = 513) or an acute cardiovascular event (myocardial infarction, stroke, or cardiovascular death) (*n* = 130) over a mean follow-up period of 58 months. For each woman who had confirmed cancer or cardiovascular event during follow-up, one control of the same age (± 1 year) and smoking habit (former smoker, current smoker, or nonsmoker) was selected from among participants who provided baseline plasma samples and remained free of reported disease during the same follow-up period. Using these criteria, we evaluated 643 case-patients and an equal number of controls in two separate matched pairs, one for cancer (*n* = 513) and another for cardiovascular events (*n* = 130). The Institutional Review Board of the Brigham and Women's Hospital approved this study.

For each case-patient and control, plasma stored since the baseline examination was thawed and assayed for CRP levels by using a high-sensitivity assay (Dade Behring, Newark, Delaware) (10). Blood specimens

Context

Inflammatory markers, such as C-reactive protein (CRP), independently predict future coronary artery disease in patients without known disease at baseline.

However, an elevated CRP level also predicts all-cause mortality; therefore, it may not be specific for cardiovascular disease.

Contribution

This prospective case-control study showed that CRP level predicted the development of acute cardiovascular events but not cancer among 28 345 women followed for a mean of 58 months.

Clinical Implications

In women, CRP level appears specifically predictive of cardiovascular disease but not cancer.

This study adds further evidence that CRP levels may be useful in the clinical prediction of cardiovascular risk, at least in populations.

—The Editors

were analyzed in blinded pairs with the position of the patient's specimen varied at random to reduce the possibility of systematic bias and to decrease interassay variability. The day-to-day precision values, at CRP concentrations of 0.15 mg/L and 0.49 mg/L, were 4.9% and 6.4%, respectively.

Because CRP values are skewed rightward, median plasma concentrations were computed, and the significance of any difference in the distributions between the case-patients and controls was assessed by performing the Wilcoxon rank-sum test. We then used conditional logistic regression models to determine the risk for developing cancer or cardiovascular end points after dividing the study sample into quartiles on the basis of the distribution of the control group. Adjusted estimates of risk were obtained by use of similar models that accounted for the matching variables and that controlled for randomized treatment assignment (for vitamin E, aspirin, or both), body mass index, diabetes mellitus, history of hyperlipidemia, history of hypertension, and parental history of coronary heart disease.

All analyses were performed by using SAS software, release 8.2 (SAS Institute, Inc., Cary, North Carolina). All *P* values were two tailed, and CIs were computed at the 95% level.

The funding sources played no role in the design, conduct, or reporting of the study.

RESULTS

Table 1 shows the baseline characteristics of the study participants. We noted no significant differences at baseline between women who subsequently developed cancer and those who did not. As expected, women who

Table 1. Baseline Clinical Characteristics of the Study Participants

Characteristic	Incident Cancer		Incident Cardiovascular Events	
	Case-Patients (n = 513)	Controls (n = 513)	Case-Patients (n = 130)	Controls (n = 130)
Mean age, y*	56.7	56.7	60.4	60.3
Mean body mass index, kg/m ²	25.9	25.8	27.6	25.7
Hyperlipidemia, %	30.6	29.6	46.9	28.5
History of hypertension, %	27.3	25.0	56.9	34.9
History of diabetes mellitus, %	2.9	2.5	10.8	3.1
Parental history of myocardial infarction before age 60 y, %	12.4	14.9	22.7	10.7
Smoking status, %*				
Current smoker	15.2	15.2	26.9	26.9
Past smoker	39.4	39.4	31.5	31.5
Never smoker	45.4	45.4	41.5	41.5
Current use of hormone replacement therapy, %	42.9	47.4	44.6	40.0
Frequency of vigorous exercise, %				
Rarely or never	37.6	39.0	46.9	43.1
<1 time/wk	18.1	17.7	20.8	27.7
1–3 times/wk	34.3	30.2	25.4	21.5
>3 times/wk	9.9	13.1	6.9	7.7
Median C-reactive protein level, mg/L	2.6	2.5	5.1	2.8

* Case-patients and controls are matched for age and smoking status.

Table 2. Relative Risk for Future Cancer and Cardiovascular Events, according to Baseline Plasma C-Reactive Protein Level*

Variable	Quartiles of Baseline C-Reactive Protein Level				P Value for Trend
	1st (<1.0 mg/L)	2nd (1.0–2.4 mg/L)	3rd (2.5–5.6 mg/L)	4th (≥5.7 mg/L)	
Distribution of participants, <i>n</i> (%)					
Controls	164 (25.6)	159 (24.8)	160 (24.9)	159 (24.8)	
Incident cancer	123 (24.0)	131 (25.5)	116 (22.6)	143 (27.9)	
Incident CVD	7 (5.4)	25 (19.2)	35 (26.9)	63 (48.5)	
Crude relative risk (95% CI)†					
Incident cancer	1.0	1.1 (0.8–1.5)	1.0 (0.7–1.4)	1.2 (0.9–1.6)	>0.2
P value	–	>0.2	>0.2	>0.2	
Incident CVD	1.0	3.7 (1.6–8.8)	5.1 (2.2–11.9)	9.2 (4.1–20.8)	<0.001
P value	–	0.003	0.001	0.001	
Adjusted relative risk (95% CI)‡					
Incident cancer	1.0	1.2 (0.8–1.6)	1.1 (0.7–1.5)	1.3 (0.9–1.9)	>0.2
P value	–	>0.2	>0.2	0.2	
Incident CVD	1.0	2.9 (1.2–7.1)	3.4 (1.4–8.2)	5.6 (2.3–13.2)	<0.001
P value	–	0.02	0.007	0.001	

* Case-patients and controls were matched for age and smoking status. CVD = cardiovascular disease.

† Adjusted for random assignment to vitamin E therapy and for random assignment to aspirin therapy.

‡ Adjusted for body mass index, hypertension, diabetes mellitus, hyperlipidemia, exercise, and parental history of coronary heart disease and for random assignment to vitamin E, aspirin, or both.

subsequently developed cardiovascular events had an increased baseline prevalence of hyperlipidemia, hypertension, diabetes, and obesity compared with controls who did not develop vascular events during follow-up.

Overall, median levels of CRP at baseline among women who subsequently developed cancer (2.6 mg/L [interquartile range, 1.1 to 5.9 mg/L]) were not significantly different from those of the control group (2.5 mg/L [interquartile range, 0.9 to 5.5 mg/L]) ($P > 0.2$). Furthermore, we observed no evidence of an association between baseline CRP level and the development of cancer in site-specific analyses evaluating carcinoma of the breast ($n = 223$), ovary or uterus ($n = 75$), colon ($n = 44$), lung ($n = 32$), hematopoietic system ($n = 31$), thyroid ($n = 14$), bladder ($n = 9$), brain ($n = 8$), or pancreas ($n = 8$); melanoma ($n = 31$); or other types of cancer ($n = 38$). In contrast, and consistent with previous work in this cohort for the end point of any vascular event (5), median CRP levels at baseline among women who subsequently developed cardiovascular disease (5.1 mg/L [interquartile range, 2.6 to 8.5 mg/L]) were significantly higher than those of the control group ($P < 0.001$).

Table 2 presents relative risks for developing either cancer or cardiovascular disease according to increasing quartiles of CRP levels obtained at study entry. As Table 2 shows, there was little evidence that baseline levels of

CRP predicted incident cancer in either crude or adjusted analyses. We found similar results after additional correction for alcohol use and age at menarche (data not shown). In contrast, increasing quartiles of baseline CRP level were a strong marker of risk for incident cardiovascular disease in crude and adjusted analyses. For example, the adjusted relative risks from the lowest to the highest quartiles of baseline CRP levels were 1.0, 2.9, 3.4, and 5.6, respectively (P for trend < 0.001).

DISCUSSION

In this prospective study of apparently healthy middle-aged and older women, baseline plasma CRP concentrations were not significantly related to the incidence of future cancer but were a strong independent predictor of future myocardial infarction, stroke, and cardiovascular death.

We believe these data have importance for general medical practice for several reasons. First, our data corroborate the findings in several previous reports (2–6) that baseline levels of CRP predict future vascular events among apparently healthy men and women (2–6) and that CRP level adds to the predictive value of total and high-density lipoprotein cholesterol levels (5, 11). As a result of these earlier findings, outpatient screening for CRP has recently become available. However, if CRP is

clinically nonspecific, as two recent studies evaluating all-cause mortality suggest (7, 8), then screening for this inflammatory marker might have reduced diagnostic utility. Thus, our finding that CRP appears to be specific for incident vascular disease but not for incident cancer has substantial clinical importance and suggests that data linking CRP level to overall death rates may have been due to the large contribution that vascular disorders make to all-cause mortality, particularly in the western world.

Second, the relative risks for future myocardial infarction or stroke observed among women in the top versus bottom quartile of baseline CRP in this analysis are somewhat greater than those previously reported from this cohort for the end point of any vascular event—an end point that included not only myocardial infarction, stroke, and cardiovascular disease mortality, but also coronary revascularization (5). Thus, these data also suggest that CRP level may be a stronger marker for events involving atherosclerotic plaque rupture and acute thrombosis than for events primarily involving progression of lesional stenosis. These epidemiologic data are thus consistent with the hypothesis that inflammation is an important determinant of plaque vulnerability (12).

Finally, we believe that our observation that CRP levels do not strongly predict future cancers is itself of pathophysiologic interest; this is of particular interest because levels of CRP and other inflammatory biomarkers are known to increase after development of certain malignancies (13, 14). As such, our data also suggest that the systemic inflammatory component of cancer previously reported in cross-sectional studies may be a late development in the genesis of that disease but is not likely to prove useful in determining risk among healthy persons.

Several limitations of our study deserve attention. Plasma CRP levels increase acutely in a wide variety of pathologic conditions, including febrile illness, various inflammatory states, and trauma (15). In our study, however, baseline levels of CRP were well below the standard thresholds associated with these acute-phase effects. Furthermore, participants in our study were free of known vascular disease, cancer, and other major inflammatory disorders at the time of study enrollment and blood collection. Thus, we believe that the presence of any of these conditions on an acute basis probably does

not explain our observations. On the other hand, smoking, obesity, and older age are all positively associated with CRP levels (4). Nonetheless, in our study the relationships between baseline CRP levels and subsequent vascular risk were independent of these potential confounding factors. Although our decision to match case-patients and controls on smoking status limits our ability to evaluate the contribution of this variable to overall risk, it does not reduce the internal validity of these data with regard to CRP levels.

In conclusion, in this prospective, nested, case-control study of apparently healthy women, plasma CRP levels were not associated with incident cancer. In contrast, the relative risk for future cardiovascular events increased significantly with each increasing quartile of baseline CRP level.

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Disclosure: Dr. Ridker is named as a co-inventor on patents related to the use of inflammatory biomarkers in cardiovascular disease.

Grant Support: By the National Heart, Lung, and Blood Institute (HL 58755); an Established Investigator Award from the American Heart Association (Dr. Ridker); and a Distinguished Clinical Scientist Award from the Doris Duke Charitable Foundation (Dr. Ridker).

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References

1. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med.* 1999;340:115-26. [PMID: 9887164]
2. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med.* 1997;336:973-9. [PMID: 9077376]
3. Tracy RP, Lemaitre RN, Psaty BM, Ives DG, Evans RW, Cushman M, et al. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. *Arterioscler Thromb Vasc Biol.* 1997;17:1121-7. [PMID: 9194763]
4. Koenig W, Sund M, Fröhlich M, Fischer HG, Löwel H, Döring A, et al. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation.* 1999;99:237-42. [PMID: 9892589]
5. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med.* 2000;342:836-43. [PMID: 10733371]
6. Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ.* 2000;321:199-204. [PMID: 10903648]
7. Harris TB, Ferrucci L, Tracy RP, Corti MC, Wacholder S, Ettinger WH Jr, et al. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *Am J Med.* 1999;106:506-12. [PMID: 10335721]
8. Gusssekloo J, Schaap MC, Fröhlich M, Blauw GJ, Westendorp RG. C-reactive protein is a strong but nonspecific risk factor of fatal stroke in elderly persons. *Arterioscler Thromb Vasc Biol.* 2000;20:1047-51. [PMID: 10764671]
9. Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. Beta-carotene supplementation and incidence of cancer and cardiovascular disease: the Women's Health Study. *J Natl Cancer Inst.* 1999;91:2102-6. [PMID: 10601381]
10. Rifai N, Tracy RP, Ridker PM. Clinical efficacy of an automated high-sensitivity C-reactive protein assay. *Clin Chem.* 1999;45:2136-41. [PMID: 10585345]
11. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation.* 1998;97:2007-11. [PMID: 9610529]
12. Maseri A. Inflammation, atherosclerosis, and ischemic events—exploring the hidden side of the moon [Editorial]. *N Engl J Med.* 1997;336:1014-6. [PMID: 9077383]
13. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet.* 2001;357:539-45. [PMID: 11229684]
14. Kodama J, Miyagi Y, Seki N, Tokumo K, Yoshinouchi M, Kobashi Y, et al. Serum C-reactive protein as a prognostic factor in patients with epithelial ovarian cancer. *Eur J Obstet Gynecol Reprod Biol.* 1999;82:107-10. [PMID: 10192497]
15. Pepys MB. C-reactive protein fifty years on. *Lancet.* 1981;1:653-7. [PMID: 6110874]

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Bones can break, muscles can atrophy, glands can loaf, even the brain can go to sleep, and endanger our survival; but should the kidneys fail in their task neither bone, muscle, gland nor brain could carry on.

Homer W. Smith
From Fish to Philosopher
Boston: Little, Brown; 1959

Submitted by:
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