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## Citation

Markt, Sarah C., Jennifer R. Rider, Kathryn L. Penney, Fredrick R. Schumacher, Mara M. Epstein, Katja Fall, Howard D. Sesso, Meir J. Stampfer, and Lorelei A. Mucci. 2014. "Genetic Variation across C-Reactive Protein and Risk of Prostate Cancer." *The Prostate* 74 (10): 1034–42. <https://doi.org/10.1002/pros.22820>.

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Published in final edited form as:

*Prostate*. 2014 July ; 74(10): 1034–1042. doi:10.1002/pros.22820.

## Genetic Variation across C-Reactive Protein and Risk of Prostate Cancer

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### Abstract

**Background**—Inflammation has been hypothesized to play an important etiological role in the initiation or progression of prostate cancer. Circulating levels of the systemic inflammation marker C-reactive protein (CRP) have been associated with increased risk of prostate cancer. We investigated the role of genetic variation in *CRP* and prostate cancer, under the hypothesis that variants may alter risk of disease.

**Methods**—We undertook a case-control study nested within the prospective Physicians' Health Study among 1,286 men with incident prostate cancer and 1,264 controls. Four single-nucleotide polymorphisms (SNPs) were selected to capture the common genetic variation across *CRP* ( $r^2 > 0.8$ ). We used unconditional logistic regression to assess the association between each SNP and risk of prostate cancer. Linear regression models explored associations between each genotype and plasma CRP levels.

**Results**—None of the *CRP* SNPs were associated with prostate cancer overall. Individuals with one copy of the minor allele (C) in rs1800947 had an increased risk of high-grade prostate cancer (OR: 1.7; 95% CI: 1.1–2.8), and significantly lower mean CRP levels (p-value < 0.001), however, we found no significant association with lethal disease. Mean CRP levels were significantly elevated in men with one or two copies of the minor allele in rs3093075 and rs1417939, but these were unrelated to prostate cancer risk.

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**Conflict of Interest Statement** None of the authors has a conflict of interest relevant to this study.

**Conclusion**—Our findings suggest that SNPs in the *CRP* gene are not associated with risk of overall or lethal prostate cancer. Polymorphisms in *CRP* rs1800947 may be associated with higher grade disease, but our results require replication in other cohorts.

### Keywords

*CRP* SNPs; prostate cancer; inflammation

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### Introduction

Several lines of evidence point to an infectious or inflammatory etiology as a possible mechanism for the initiation or progression of prostate cancer(1). Inflammatory infiltrates are commonly found near prostate cancer precursor lesions and tumor cells(2). In addition, several factors associated with chronic inflammation, including obesity, infectious agents, hormonal variations/exposures, and dietary factors, have been associated with the risk or progression of prostate cancer(3).

C-reactive protein (CRP) is a sensitive marker of nonspecific systemic inflammation. It is produced by hepatocytes and transcriptionally regulated primarily by IL-6(4). Circulating levels of CRP have been associated with an increased risk of several cancer outcomes(5,6); other studies have found no association with prostate cancer(7,8). In the Physicians' Health Study (PHS), we found that elevated CRP measured prior to cancer diagnosis was associated with an increased risk of total prostate cancer in healthy weight men and there was a suggestive trend of increasing risk with high grade disease(9). Among patients with metastatic prostate cancer, elevated plasma CRP levels were independent predictors of poor disease-specific survival(10). In tumor tissue, cytoplasmic CRP expression was positively associated with metastases at diagnosis and nuclear CRP presence was associated with increased metastases at relapse(11).

The genetic variation in immune and inflammatory pathways offers another potentially important linkage with prostate cancer pathogenesis and progression. Most previous studies have found no association between *CRP* single-nucleotide polymorphisms (SNPs) and overall risk of prostate cancer(12–14). A recent study found that compared to men with 2 copies of the major allele, men with at least 1 copy of the minor allele (C) in *CRP* rs1800947 had a lower risk of recurrence (OR = 0.53, 95% CI: 0.36–0.79)(15). Other studies have shown that genetic variation in the *CRP* gene and adiposity measures such as waist-hip ratio (WHR) and BMI interact to modify the risk of endometrial, colon and rectal cancer(16,17). Few studies have evaluated the association between CRP and prostate cancer for more aggressive disease or evaluated whether adiposity modifies this association.

The role of *CRP* SNPs in relation to prostate cancer risk and circulating levels of CRP has not been fully elucidated. The aims of the present study were to investigate whether common variants in *CRP* are associated with prostate cancer risk and circulating levels of CRP; to determine whether variants in CRP were more important for the development of aggressive tumors; and to assess the role of adiposity in modifying these associations.

## Materials and Methods

### Study Population

We undertook a case-control study nested within the prospective Physicians' Health Study I (PHS). As described in detail elsewhere, PHS I began in 1982 as a randomized, double-blind, placebo-controlled trial of aspirin and beta-carotene for the primary prevention of cardiovascular disease and cancer(18,19). The trial included 22,071 U.S. male physicians aged 40–84 years at randomization and free of cardiovascular disease and cancer at randomization(18,19). The study population was selected from 14,916 PHS participants who provided a blood sample at baseline (pre-randomization)(19).

Our analytic cohort included 1,286 incident and histologically confirmed prostate cancer cases diagnosed between 1982 to 2005. In a nested case-control design, cases were matched to 1,264 controls on age at randomization (within 1 year for cases  $\leq$  55 years old and within 5 years for cases  $>$  55 years), follow-up time, and smoking status (never, former, current). Although PHS is largely Caucasian (over 93%), we restricted this analysis to Caucasian men to decrease the likelihood of population stratification.

Each participant provided written informed consent, and The Physicians' Health Study receives ongoing approval from the Institutional Review Board at Partners Health Care.

### Outcome Ascertainment

Incident prostate cancer cases were first identified via self-report and confirmed by review of hospital medical records and pathology reports. Data on tumor stage and metastases were also abstracted from medical records. Stage was classified by the TNM staging system from pathology and clinical reports. Gleason score was obtained from original pathology records or from histopathological re-review of tumor specimens from biopsy or radical prostatectomy. Data on mortality (overall and prostate cancer specific) was available through March 20, 2012 and cause of death was determined by an Endpoints Committee of physicians through review of death certificates, medical records, and information from families. High-grade prostate cancer was defined as tumors with total Gleason scores 8–10. Advanced stage disease was defined as stage T3/T4 or N1 or M1 at cancer diagnosis and lethal was defined as death from prostate cancer or development of bony or organ metastases. Follow-up information on mortality is over 99% complete and follow-up for nonfatal outcomes is over 97% complete.

### Exposure Ascertainment

Genotyping and circulating CRP measures were undertaken on prediagnostic blood samples collected from August 1982 to December 1984, prior to randomization. The physician participants returned their drawn blood tubes to the laboratory via overnight mail on chill packs within 24 hours of being drawn. Once received the samples were aliquotted into separate tubes of whole blood and plasma and frozen for long-term storage. The median time between blood collection and cancer diagnosis among cases was 12.5 years (range: 0.2–21.9 years).

**Genotype**—Four SNPs were selected across the *CRP* gene using the 'Tagger' program in the HapMap Release 27 CEPH panel to capture the common (minor allele frequency >5%) genetic variation across the 2.3 kb gene and 5 kb upstream and downstream, with the coefficient of determination,  $r^2$ , >0.8. Genotyping was conducted blinded to case/control status using Sequenom GOLD iPLEX panels at the Harvard Medical School-Partners Healthcare Center for Genetics and Genomics. Genotyping of blind duplicate samples across genotyping batches was conducted for quality control, with concordance greater than 98% for duplicate samples.

**Biomarker**—Circulating levels of inflammatory biomarkers were measured from prospectively collected plasma stored in the laboratory of Dr. Nader Rifai (Boston, MA). CRP levels were measured using a high-sensitivity assay (Dade Behring). IL-6 and TNFR2 levels were determined by a commercially available enzyme-linked immunosorbent assay test (R and D Systems)(20). The median coefficients of variation (CV) for CRP, IL-6 and TNFR2 were 0.5%, 5.3%, and 6.8%, respectively(9,20). All laboratory personnel were blinded from case/control status. Case/control pairs were assayed in adjoining wells, and 10% of samples were randomly distributed across the plates as pooled quality controls.

### Statistical Analysis

Each *CRP* SNP was evaluated for deviation from Hardy-Weinberg Equilibrium (HWE) in controls using an exact test with 10,000 permutations, setting  $p < 0.05$  to indicate deviation from HWE.

To evaluate the association between *CRP* SNPs and overall prostate cancer, we conducted unconditional logistic regression controlling for the matching factors (age at randomization, follow-up time, and smoking status), conducting the analysis separately for each SNP. Odds ratios (OR) and 95% confidence intervals (CI) were calculated modeling each genotype as an ordinal or dichotomous variable with homozygous common genotype as the reference group. We used dominant models for those SNPs with rare homozygotes (<5% of individuals homozygous for the variant allele), combining rare homozygous and heterozygous individuals into one category; co-dominant models were used for SNPs with 5% of individuals homozygous for the minor allele. Statistical significance was determined using a likelihood ratio test (LRT) with 1 d.f. for dominant models and 2 d.f. for co-dominant models. To evaluate whether *CRP* SNPs were associated with the development of aggressive prostate cancer, we conducted analyses modeling several different outcomes of interest, including high grade disease (defined as Gleason 8–10), advanced stage (defined as stage T3/T4 or N1 or M1 at cancer diagnosis), lethal (defined as death from prostate cancer or development of bony or organ metastases), and a combination of advanced stage or lethal disease.

We also assessed the association between *CRP* SNPs and survival after prostate cancer diagnosis among the cases. We followed the men from date of prostate cancer diagnosis until death from prostate cancer or progression to bony or organ metastases, or until censoring (death from other causes or end of follow-up, March 20, 2012). We conducted

Cox proportional hazards models and calculated hazard ratios adjusted for age at diagnosis, separately modeling each *CRP* SNP as the exposure of interest.

We also evaluated whether there was a differential effect of BMI on the association between each SNP and prostate cancer. Because there were few men with BMI  $\geq 30$  kg/m<sup>2</sup>, we combined 'overweight' (BMI 25–30 kg/m<sup>2</sup>) and 'obese' (BMI  $\geq 30$  kg/m<sup>2</sup>) men and compared them to 'normal' (BMI  $<25$  kg/m<sup>2</sup>) weight men. We evaluated interaction terms and conducted stratified analyses using each of the outcomes defined above. We also conducted each analysis stratified by PSA-era, which was defined as cases diagnosed before (pre-PSA) and after (post-PSA) January 1, 1992.

For a subset of the men (n=1,171) we had *CRP* SNP data and circulating levels of CRP. We excluded men with greater than a six day delay in returning the blood sample to our laboratory (n=24), and cases diagnosed less than 5 years after the blood draw (n=70) to reduce the likelihood of pre-clinical disease affecting CRP levels; however, results were similar when these men were included (data not shown). We conducted linear regression analysis separately modeling log<sub>10</sub>-transformed CRP as the outcome of interest and each *CRP* SNP as the ordinal or dichotomous exposure of interest, adjusting for dichotomous BMI, age at randomization, and smoking status. We conducted the same analyses stratified by BMI, adjusting for age at randomization and smoking.

We tested the global association across the 4 SNPs in the *CRP* gene using a kernel machine method. This approach groups SNPs together into 'SNP-sets' based on biological significance (i.e. genes) and allows one to perform tests for SNP-sets rather than evaluating SNPs individually(21). The logistic kernel machine test was used to test the global association of the *CRP* gene with each of the prostate cancer outcomes listed above; we conducted a linear kernel machine test the global association of the *CRP* gene with CRP levels.

We then created a 'genetic score' combining the *CRP* SNPs to determine if having multiple variant alleles was associated with increased CRP levels. The  $r^2$  between each tag SNP pair was  $<0.30$ . Any SNP not significantly associated with mean CRP levels was excluded from the score. Alleles associated with higher mean CRP received a score of 1 and those associated with lower mean CRP received a score of 0; each allele score within each SNP was summed. The SNP scores were then summed together into a 'genetic score' and evaluated as the exposure of interest, with log<sub>10</sub>-transformed plasma CRP and prostate cancer (overall, high grade, advanced stage, and lethal) as the outcomes of interest.

Finally, using linear regression analysis and adjusting for dichotomous BMI, age at randomization, and smoking status, we assessed whether circulating levels of log<sub>10</sub>-transformed IL-6, TNFR2, or baseline PSA levels were associated with any of the four *CRP* SNPs, the genetic score, or circulating levels of CRP.

All analyses were conducted using SAS v.9.2 (SAS Institute, Cary, NC) and all p-values were 2-tailed with statistical significance at  $\alpha < 0.05$ .

## Results

The study population consisted of 1,286 incident histologically confirmed prostate cancer cases and 1,264 controls. The distribution of BMI was similar between cases and controls, as was the mean plasma CRP level at baseline (Table 1). There were 142 cases with advanced stage and 172 cases with high grade disease. Of the 618 cases who died, 30% (n=183) died from prostate cancer; 25 additional men developed bony or organ metastases over follow-up. 70% of the cases (n=899) were identified during the PSA era.

We evaluated 4 *CRP* SNPs (rs3093075, rs2808630, rs1800947, rs1417938) on chromosome 1 in the locations listed in Table 2. All 4 *CRP* SNPs conformed to Hardy-Weinberg equilibrium among controls and the frequency of each SNP in this population was similar to those from the HapMap CEPH set (data not shown).

None of the four *CRP* SNPs evaluated were significantly associated with overall prostate cancer risk (Table 2). The association between each SNP and overall prostate cancer risk did not differ substantially when stratified by BMI or PSA-era (data not shown).

To evaluate whether *CRP* SNPs were associated with more aggressive prostate cancer, we assessed 172 men with high grade disease, 142 men with advanced stage, 195 men with lethal, and 262 men with advanced stage or lethal disease. As shown in Table 3, men with one copy of the variant allele (C) in rs1800947 and men with two copies of the variant allele (C) in rs2808630 had 1.7 times the odds of high grade disease compared to men with no copies of the variant allele (GG genotype and TT genotype, respectively; OR: 1.7; 95% CI: 1.1–2.8 and OR: 1.7; 95% CI: 1.0–3.0, respectively). Although the multiplicative interaction term was not statistically significant (p-value 0.25), the association between rs1800947 and high grade disease appeared stronger in healthy weight men (OR: 2.2; 95% CI: 1.2–4.0) than overweight men (OR: 1.2; 95% CI: 0.6–2.7). Results were not significantly altered for the other SNPs when stratified by BMI (data not shown).

None of the four *CRP* SNPs were associated with the combined endpoint of advanced stage and lethal prostate cancer (data not shown). Restricted to lethal prostate cancer alone (Table 3), men who had at least one copy of the variant allele (A) in rs3093075 had a borderline statistically significant 1.5 fold higher odds of lethal prostate cancer compared to men with no copies of the variant allele (OR: 1.5; 95% CI: 1.0–2.3). The association was significant when restricted to overweight men (OR: 1.9; 95% CI: 1.1–3.4; p-value 0.03). Men with two copies of the variant allele (C) in rs2808630 had a borderline statistically significant 1.7 fold higher odds of lethal prostate cancer compared to men with no copies of the variant allele (OR: 1.7; 95% CI: 0.9–3.0). There were no significant associations between any of the four *CRP* SNPs and advanced stage disease alone or survival following prostate cancer diagnosis (data not shown).

*CRP* SNPs rs3093075, rs1800947, and rs1417938 were significantly associated with mean plasma CRP levels after adjusting for BMI, smoking status and age at randomization (Figure 1). Mean CRP levels were significantly elevated in men with one copy of the variant allele in rs3093075 compared to those with no copies (p-value 0.009). Men with one or two copies of the variant allele in rs1417938 had significantly elevated mean CRP levels compared to

those men with no copies of the variant allele (trend  $p$ -value  $<0.001$ ). Conversely, men with one copy of the variant allele of rs1800947 had significantly lower mean CRP levels than those men with no copies ( $p$ -value  $<0.0001$ ). Variation in rs2808630 was not associated with circulating CRP ( $p$ -value 0.52).

We then assessed the global test for association between common genetic variation in *CRP* and each of the outcomes. We found a significant association of common variation in *CRP* and CRP levels ( $p = 0.009$ ); however, we found no association for any of the prostate cancer outcomes (data not shown). Increasing genetic score was significantly associated with increasing mean CRP ( $p$ -value  $<0.0001$ ). Men with 3 or 4 “risk” alleles had a mean CRP level of 1.2 mg/L compared to a mean CRP level of 0.6 mg/L among men with no risk alleles (Figure 2). Genetic score was not associated with prostate cancer, overall ( $p$ -value 0.78) or among high grade ( $p$ -value 0.19), advanced stage ( $p$ -value 0.55), or lethal cancers ( $p$ -value 0.26)

In general, obese men had higher mean levels of plasma CRP than normal weight men ( $\mu$ : 1.04 mg/L vs. 0.65 mg/L, respectively). Although interactions between BMI and each *CRP* SNP were not significant ( $p$ -interaction  $>0.05$ ), the association between mean CRP level and rs1800947 was significant among healthy weight men ( $p$ -value 0.008), but not among overweight men ( $p$ -value 0.09). Similarly for rs1417938, mean plasma CRP was significantly associated with variation in rs1417938 in healthy weight ( $p$ -value  $<0.001$ ), but not overweight men ( $p$ -value 0.06). In contrast, the association between rs3093075 and mean plasma CRP was significant in overweight men, but not healthy weight ( $p$ -value 0.04 and 0.08, respectively). There remained no significant association between rs2808630 and mean CRP levels stratified by BMI.

There were no significant associations between any of the four *CRP* SNPs or genetic score and circulating levels of IL-6 or TNFR2 (data not shown). There was also no association between baseline PSA levels and the SNPs or circulating CRP levels (data not shown).

## Discussion

We evaluated the association between four SNPs in the *CRP* gene in a case-control study nested within the large prospective Physicians' Health Study. Similar to previous reports, none of the *CRP* SNPs we evaluated were associated with overall risk of prostate cancer(13,14,22). It has been hypothesized that CRP plays a role in the progression of prostate cancer and is therefore thought to be associated with more aggressive forms of the disease. Our findings of a borderline significant association between the variant allele in rs1800947 and increased risk of high Gleason grade disease, and between rs3093075 and lethal prostate cancer support this hypothesis and warrant further investigation. In addition, our study adds to accumulating evidence supporting the hypothesis that aggressive and indolent prostate cancer may have distinct etiologies(23).

Most previous studies on the association between polymorphisms in the *CRP* gene and prostate-specific disease endpoints found no association overall and did not present findings by grade or stage(12–14,22). In addition, each study had fewer than 300 incident prostate



cancer cases. Dluzniewski et al. recently reported an inverse association between *CRP* rs1800947 and risk of recurrence(15); we found men with one copy of the minor allele (C) in *CRP* rs1800947 had an increased risk of high grade prostate cancer compared with men with 2 copies of the major allele (G). A study by Pierce et al. on 215 men in the Cardiovascular Health Study found no association between rs1800947, rs1417938, and rs2808630 and plasma CRP levels or risk of prostate cancer(22). In contrast, we found having two copies of the variant allele (CC) in rs2808630 was associated with an increased risk of high grade prostate cancer, as was having at least one copy of the variant allele in rs1800947 (C). At least one copy of the variant allele in rs3093075 (A) was associated with a borderline statistically significant increased risk of lethal prostate cancer, and increasing variant alleles in rs3093075 and rs1417938 were significantly associated with elevated plasma CRP. We found no association between rs2808630 and plasma CRP, and found carriers of the C allele in rs1800947 had lower plasma CRP, similar to previously published reports(5,24).

The association between common variation across *CRP* and between individual *CRP* SNPs rs3093075, rs1800947, and rs1417938, and circulating levels of CRP, perhaps suggest these SNPs, or others in linkage disequilibrium (LD), alter the expression or ability to produce an inflammatory response in the blood. Interestingly, we found one polymorphism (rs3093075) was associated with elevated mean plasma CRP and borderline increased risk of lethal disease, while another (rs1800947) was associated with lower plasma CRP levels and an increased risk of high Gleason grade. Thus, our findings may point to a different pathway acting to influence tumor progression.

We hypothesized that the association between *CRP* SNPs and prostate cancer and between *CRP* SNPs and circulating CRP would vary according to BMI (BMI < 25 kg/m<sup>2</sup> vs. BMI ≥ 25 kg/m<sup>2</sup>). Circulating levels of CRP have been associated with adipose tissue and a previous report on 2,300 participants in the AGES-Reykjavik study found an interaction between adiposity and CRP genotypes on circulating CRP(25). Slattery et al. reported a significant interaction between *CRP* rs1800947 and BMI in modifying the risk of both rectal and colon cancer(16). Our previous analysis in PHS showed elevated plasma CRP levels were associated with an increased risk of overall prostate cancer only among healthy weight men(9). Similarly, we found the association between *CRP* rs1800947 and risk of high Gleason grade disease and CRP levels was stronger among healthy weight than overweight men. Conversely, we found the association between *CRP* rs3093075 and risk of lethal prostate cancer and CRP levels was significant only among overweight men. Thus, our findings suggest that BMI and *CRP* genotypes may interact to affect circulating CRP levels and the risk of aggressive prostate cancer.

The functional significance of rs1800947, rs2808630 and rs3093075 is unknown at this time. SNP rs3093075 and rs2808630 are polymorphisms located in the 3' flanking region. The A allele in rs3093075 has been previously associated with a reduced risk of rectal cancer(16) and showed a significant association with microangiopathic stroke(26). SNP rs1800947 is a synonymous base polymorphism in the coding region of exon 2, an evolutionarily conserved coding region(27) and was previously found associated with

reduced risk of prostate cancer recurrence(15). Thus, it remains unclear what functional role, if any, these SNPs play in relation to progression of prostate cancer.

One potential limitation of our study is that CRP is a systemic inflammation marker and is not a specific marker for inflammation in the prostate, nor is it a cause of inflammation. In addition, we only had one measure of plasma CRP and although the four-year ICC was estimated to be 0.66 in another cohort(28), multiple measurements may be a more accurate representation of true CRP level over time. We also cannot rule out false-positive findings in this analysis, especially the paradoxical result that rs1800947 was associated with an increased risk of high grade disease, but decreased levels of CRP. Finally, over half the men were missing plasma CRP data and thus our stratified analysis of circulating levels may have been underpowered.

The main strengths of our study are the prospective nature of our nested case/control design, detailed information on clinical and physical characteristics, and high follow-up rates. Moreover, this nested study included 1,286 cases matched to 1,264 controls and thus, permitted analyses stratified by BMI, and allowed us to evaluate the associations restricted to more aggressive prostate cancer endpoints.

In summary, our findings suggest that SNPs in the *CRP* gene are not associated with overall prostate cancer risk. Polymorphisms in *CRP* SNPs rs1800947, rs2808630, and rs3093075 may be associated with more aggressive forms of prostate cancer, but our results require replication in other cohorts. In addition, the functional significance of these SNPs in prostate carcinogenesis remains unknown and warrants further study.

## Acknowledgments

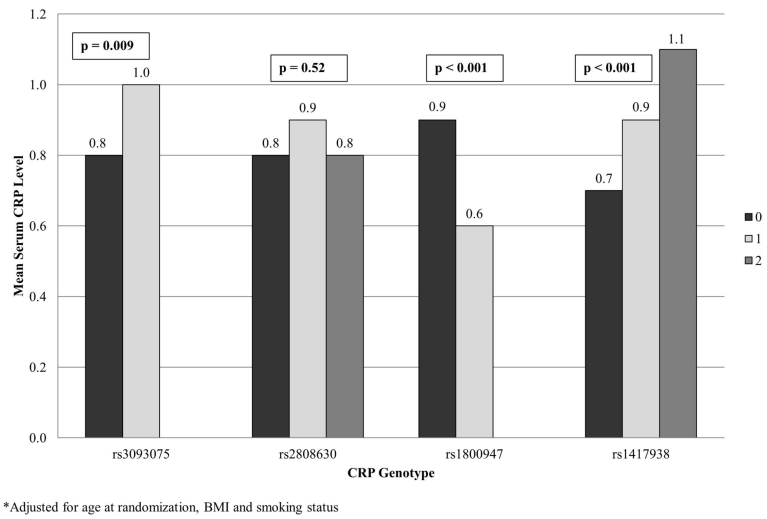
**Funding** National Institutes of Health research training grant (NIH, R25 CA098566 to S.C.M. and M.M.E. T32 CA09001-35 to S.C.M.). L.A.M., K.L.P., and J.R.R. are supported by the Prostate Cancer Foundation. The Physicians' Health Study is supported by the National Cancer Institute (CA42182, CA34944, CA40360, CA141298, and CA097193); the National Heart, Lung, and Blood Institute (HL26490, HL34595), Bethesda, MD.

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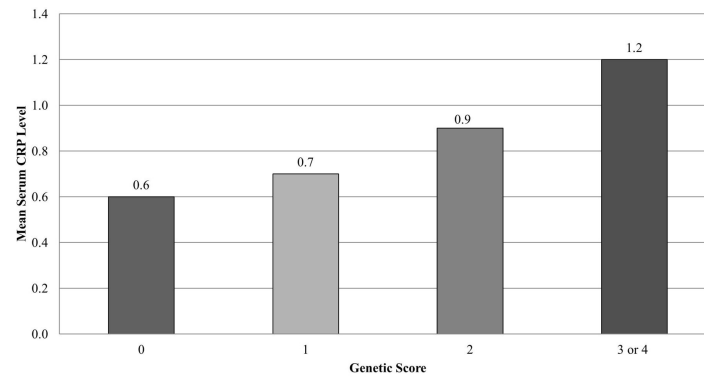
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**Figure 1.**  
Mean Plasma CRP Levels by *CRP* SNP Genotype



\*Adjusted for age at randomization, BMI and smoking status

\*\*The genetic score was calculated by summing the alleles associated with increasing CRP level. For example, a person with two copies of the variant allele in rs1417938 (score of 2) and no copies of the variant allele in rs1800947 (score of 1) receive a total genetic score of 3; whereas those with two copies of the variant allele in rs1417938 (score of 2) and one copy of the variant allele in rs1800947 (score of 0) receive a total genetic score of 2. A person with one copy of the variant allele in rs3093075 (score of 1), no copies of the variant allele in rs1800947 (score of 1) and two copies of the variant allele in rs1417938 (score of 2) receive the maximum total genetic score of 4.

**Figure 2.**  
Mean Plasma CRP Levels by Genetic Score

**Table 1**

Characteristics of study population, Physicians' Health Study (1982–2012)

	Cases (n= 1,286)	Controls (n=1,264)
Age at enrollment, years		
Mean ( $\pm$ SD)	57.9 (8.4)	57.5 (8.4)
Follow-up time, years		
Mean ( $\pm$ SD)	12.2 (5.1)	12.1 (5.0)
Smoking Status, N (%)		
Never	625 (49%)	634 (50%)
Past	553 (43%)	531 (42%)
Current	106 (8%)	99 (8%)
BMI, N (%)		
< 25 kg/m <sup>2</sup>	746 (58%)	759 (60%)
25 to < 30 kg/m <sup>2</sup>	499 (39%)	465 (37%)
30 kg/m <sup>2</sup>	41 (3%)	40 (3%)
Randomized to Aspirin Treatment, N (%)		
Yes	650 (51%)	630 (50%)
No	636 (49%)	634 (50%)
Plasma CRP, mg/L		
Mean ( $\pm$ SD)	1.6 (3.3)	1.7 (3.8)
Among cases only (n= 1,286)		
Age at diagnosis, years		
Mean ( $\pm$ SD)	70.0 (7.4)	
Stage, N (%)		
T1/T2	1079 (84%)	
T3	63 (5%)	
T4/N1/M1	79 (6%)	
Missing	65 (5%)	
Gleason score *, N (%)		
2–6	753 (59%)	
7	300 (23%)	
8–10	172 (13%)	
Missing	61 (5%)	
Outcomes, N		
Bony Metastases	23	
Organ Metastases	2	

	Cases (n= 1,286)	Controls (n=1,264)
Death from Prostate Cancer	183	
Death from other causes	435	

\* For those missing Gleason data, Gleason 8–10 includes “poorly differentiated” and Gleason 2–6 includes “well differentiated” tumors



**Table 2**  
Association between CRP SNPs and overall incident prostate cancer, Physicians' Health Study (1982–2012)

SNP	Genotype	Location	Population Frequency*	Overall Prostate Cancer Risk <sup>*,‡</sup>			P <sup>***</sup>
				Cases n (%)	Controls n (%)	OR <sup>**</sup>	
rs3093075	CC	3' Flanking	87%	1077 (87%)	1065 (88%)	Referent	0.55
	AC		12%	167 (13%)	1.1	0.9–1.4	
	AA		0.5%				
rs2808630	AA	3' Flanking	52%	622 (53%)	600 (52%)	Referent	0.11
	AG		40%	455 (39%)	0.9	0.8–1.1	
	GG		8%	100 (8%)	1.3	0.9–1.7	
rs1800947	GG	Exon 2	88%	1007 (88%)	1010 (89%)	Referent	0.23
	CG		12%	140 (12%)	1.2	0.9–1.5	
	CC		0%				
rs1417938	AA	Intron 1	50%	616 (50%)	603 (50%)	Referent	0.89
	AT		41%	496 (40%)	1.0	0.8–1.2	
	TT		9%	118 (10%)	1.0	0.8–1.4	

\* Excluded missing genotype data; missing genotype data ranged from 3–11% per SNP

‡ Dominant Model where MAF <5%: rs3093075 (AA/AC vs. CC) and rs1800947 (GG/GC vs. CC) Codominant Model where MAF >5%: rs2808630 and rs1417938

\*\* OR adjusted for matching factors: age at randomization, follow-up time, and smoking status

\*\*\* p-value from LRT

**Table 3**  
 Association between CRP SNPs and high grade or lethal prostate cancer, Physicians' Health Study (1982–2012)

SNP	Genotype	High grade disease* (n=172 cases; n=1,264 controls)			Lethal** (n=195 cases; n=1,264 controls)				
		Cases (n)	OR	95% CI	P***	Cases (n)	OR	95% CI	P***
rs3093075	CC	146	Referent	Referent	0.95	158	Referent	Referent	0.06
	AC/AA	21	1.0	0.6–1.7		33	1.5	1.0–2.3	
rs2808630	TT	87	Referent	Referent	0.03	87	Referent	Referent	0.16
	CT	51	0.7	0.5–1.1		64	0.9	0.7–1.4	
	CC	19	1.7	1.0–3.0		19	1.7	0.9–3.0	
rs1800947	GG	126	Referent	Referent	0.03	153	Referent	Referent	0.56
	CG/CC	25	1.7	1.1–2.8		20	1.2	0.7–2.0	
rs1417938	TT	87	Referent	Referent	0.80	87	Referent	Referent	0.65
	AT	64	0.9	0.6–1.3		82	1.2	0.8–1.6	
	AA	15	0.9	0.5–1.7		19	1.2	0.7–2.0	

\* High grade: Gleason 8–10 and if missing Gleason data, “poorly” differentiated tumors

\*\* Lethal Prostate cancer (n=195); n=170 prostate cancer deaths, n=12 developed bone or organ metastases, and n=13 developed bone or organ metastases and died from prostate cancer

\*\*\* P-value from LRT