Plasma C-Reactive Protein and Risk of Cancer: A Prospective Study from Greece

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Abstract

Background: Inflammation is an important component of carcinogenesis but little research has been conducted on whether inflammation markers can be predictive of cancer risk in humans.

Methods: We analyzed C-reactive protein (CRP), a marker of inflammation, in plasma samples of 496 cases of cancer and 996 controls selected among participants in a prospective study from Greece.

Results: Plasma CRP level was higher in cancer cases than controls (odds ratio for increase in CRP level of 3.2 mg/L, 1.20; 95% confidence interval, 1.10-1.32): The corresponding odds ratio after exclusion of the first year of follow-up and of individuals with CRP level above 20 mg/L was 1.32 (95% confidence interval, 1.15-1.52). Although based on small number of cases, the association between elevated plasma CRP level and risk was stronger for cancers of the liver, lung, skin, kidney, and bladder, as well as for lymphoma and leukemia than for other neoplasms.

Conclusions: Our results confirm the important role of inflammation in human cancer and suggest that plasma CRP level is a potential marker of increased cancer risk. (Cancer Epidemiol Biomarkers Prev 2006;15(2):381–4)

Introduction

There is growing evidence that chronic inflammation plays an important role in the development of human cancer (1). Several chronic inflammatory processes have been associated with specific cancers, such as Crohn’s disease and chronic ulcerative colitis with colorectal cancer, chronic bronchitis with lung cancer, and chronic pancreatitis with pancreatic cancer (2). The inflammatory component of chronic infections is a key element in the carcinogenic risk among carriers, e.g., of liver cancer among hepatitis B carriers (3) and cholangiocarcinoma among individuals with liver fluke infestation (4). The unspecific nature of the role of chronic inflammation in human carcinogenesis is substantiated by the observation of a reduced risk of several types of cancer with use of aspirin and anti-inflammatory agents (5).

C-reactive protein (CRP) is produced by the liver and other organs in response to release of interleukin-6 by monocytes and other immune cells (6) following infection and other conditions associated with tissue injury and inflammation (7). Elevated levels of this marker of infection have been associated with increased risk of cardiovascular disease (8, 9), as well as of increased overall mortality in the elderly (10). A few studies have recently been published on the association between prediagnostic CRP level and cancer risk, which suggest in particular an increased risk of cancers of colorectum (11) and ovary (12).

Given the unspecific nature of the role of chronic inflammation in carcinogenesis, and the potential importance of the ability of plasma CRP level to identify individuals at high risk of cancer, we studied the risk of cancer by site in relation to CRP levels in a prospective study from Greece.

Materials and Methods

The study base consisted of 28,572 volunteers, women and men 20 to 86 years old (mean, 53.3; SD, 12.6) recruited between 1994 and 1999 from all regions of Greece, to participate in the Greek component of the European Prospective Investigation into Cancer and Nutrition, a multicenter study of diet, nutrition, and cancer (13). All study procedures have been in accordance with the Helsinki declaration for human rights and all participants have provided written informed consent before enrollment; the study protocol has been approved by relevant ethics committees.

Study participants are actively followed-up through telephone interviews and then through visits to the respective hospitals or other health care institutions. By the end of 2004, 545 medically confirmed cases of cancer were identified among individuals who did not develop myocardial infarction. For 34 of them, however, there was evidence that cancer may have been present at enrollment, and these were excluded. For each of the remaining 511 cancer cases, two controls were chosen among those who did not have at enrollment and did not develop during follow-up cancer or myocardial infarction. The controls were individually matched to the respective cancer case by gender, age (plus or minus 1 year), and date of enrollment (plus or minus 6 months).

At enrollment, blood samples were collected from all study participants and plasma samples were stored at −80°C. Coded frozen plasma samples were retrieved from the identified cases and controls in January 2005. CRP levels were measured using an automatic latex agglutination photometric assay, the COBAS Integra 4000 from Roche Diagnostics (Meylan, France) (14). The laboratory staff was not aware of the case or control status of the blood samples under examination. A total of 102 duplicated samples were measured blindly: The correlation coefficient between the two measures was 0.98. For all but one of the duplicate samples, the difference was >1 mg/L.

At enrollment, anthropometric measurements and demographic and lifestyle characteristics were recorded for all cohort participants with the use of standardized procedures (13). For the present study, the following variables were considered as potential confounders: sex, age, body mass...
index (BMI), tobacco smoking, consumption of ethanol from alcoholic beverages, duration of storage of frozen samples, and self-reported use of any type of non-steroid anti-inflammatory drug (NSAID) during the week before enrollment.

Cancers were classified on the basis of the International Classification of Diseases, 10th Revision (15), and International Classification of Diseases for Oncology, Second Revision (16). Of the 511 cancers, 15 were excluded because of missing information in one or more of the examined variables, or because plasma samples were inadequate or unsatisfactory. Of the 1,022 controls, 26 were excluded because of missing information in one or more variables.

Statistical analyses were done using the STATA statistical software (17). After exploratory cross-classification, CRP level was regressed on age (<45, 45-54, 55-64, and ≥65 years, categorically), sex, BMI (<25, 25 to <30, and ≥30 kg/m^2, categorically), tobacco smoking (never smoker, former smoker, and current smoker, categorically), ethanol consumption per day (<10 and ≥10 g, categorically), NSAIDs use (no, yes) and duration of storage in years (<7, 7 to <8, 8 to <9, and >9, categorically). This multiple regression was done among controls only and CRP values were log transformed (base 10) to accommodate the positive skewness of the distribution. For the main analysis, odds ratios (OR) for an increment of 1 SD of CRP among controls, for all cancers as well as for each site, were calculated.

### Table 1. Distribution of cases and controls by selected characteristics and association with CRP level (log 10–transformed values) among controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases, n (%)</th>
<th>Controls, n (%)</th>
<th>Coefficient (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age groups (y)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>58 (11.7)</td>
<td>106 (10.6)</td>
<td>Reference</td>
</tr>
<tr>
<td>45-54</td>
<td>95 (19.2)</td>
<td>183 (18.40)</td>
<td>0.08 (0.02 to 0.16)</td>
</tr>
<tr>
<td>55-64</td>
<td>142 (28.6)</td>
<td>300 (30.1)</td>
<td>0.12 (0.04 to 0.19)</td>
</tr>
<tr>
<td>≥65+</td>
<td>201 (40.3)</td>
<td>407 (40.9)</td>
<td>0.18 (0.10 to 0.26)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>243 (49.0)</td>
<td>484 (48.6)</td>
<td>Reference</td>
</tr>
<tr>
<td>Women</td>
<td>253 (51.0)</td>
<td>512 (51.4)</td>
<td>0.05 (−0.00 to 0.11)</td>
</tr>
<tr>
<td><strong>BMI (kg/m^2)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (&lt;25)</td>
<td>110 (22.2)</td>
<td>203 (20.4)</td>
<td>Reference</td>
</tr>
<tr>
<td>Overweight (25–&lt;30)</td>
<td>210 (42.5)</td>
<td>443 (44.5)</td>
<td>0.08 (0.03 to 0.14)</td>
</tr>
<tr>
<td>Obese (≥30)</td>
<td>176 (35.5)</td>
<td>350 (35.1)</td>
<td>0.23 (0.17 to 0.29)</td>
</tr>
<tr>
<td><strong>Tobacco smoking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>249 (50.2)</td>
<td>546 (54.8)</td>
<td>Reference</td>
</tr>
<tr>
<td>Former</td>
<td>119 (24.0)</td>
<td>226 (22.7)</td>
<td>−0.03 (−0.09 to 0.03)</td>
</tr>
<tr>
<td>Current</td>
<td>128 (25.8)</td>
<td>224 (22.5)</td>
<td>0.05 (−0.01 to 0.11)</td>
</tr>
<tr>
<td><strong>Ethanol consumption (g/d)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>376 (75.8)</td>
<td>721 (72.4)</td>
<td>Reference</td>
</tr>
<tr>
<td>≥10</td>
<td>120 (24.2)</td>
<td>275 (27.6)</td>
<td>−0.03 (−0.08 to 0.02)</td>
</tr>
<tr>
<td><em><em>NSAID</em> use</em>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>386 (77.8)</td>
<td>793 (79.6)</td>
<td>0.06 (0.01 to 0.11)</td>
</tr>
<tr>
<td>Yes</td>
<td>110 (22.2)</td>
<td>203 (20.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of storage (y)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7</td>
<td>121 (24.4)</td>
<td>257 (25.8)</td>
<td>Reference</td>
</tr>
<tr>
<td>7–&lt;8</td>
<td>76 (15.3)</td>
<td>147 (14.8)</td>
<td>−0.01 (−0.07 to 0.06)</td>
</tr>
<tr>
<td>8–&lt;9</td>
<td>129 (26.0)</td>
<td>283 (28.4)</td>
<td>−0.03 (−0.09 to 0.02)</td>
</tr>
<tr>
<td>&gt;9</td>
<td>170 (34.3)</td>
<td>309 (31.0)</td>
<td>−0.05 (−0.11 to 0.01)</td>
</tr>
<tr>
<td>Total</td>
<td>496 (100.0)</td>
<td>996 (100.0)</td>
<td>—</td>
</tr>
</tbody>
</table>

*NSAIDs (aspirin and other).

### Table 2. OR of cancer for 1 SD of CRP level (3.2 mg/L)

<table>
<thead>
<tr>
<th>Variables</th>
<th>All subjects*</th>
<th>Excluding first year of follow-up and CRP values, &gt;20 mg/L†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n cases</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>All cancers</td>
<td>496</td>
<td>1.20 (1.10-1.32)</td>
</tr>
<tr>
<td>Stomach</td>
<td>31</td>
<td>1.10 (0.82-1.47)</td>
</tr>
<tr>
<td>Colon-rectum</td>
<td>48</td>
<td>1.17 (0.93-1.46)</td>
</tr>
<tr>
<td>Liver</td>
<td>11</td>
<td>1.51 (1.20-1.90)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>14</td>
<td>1.29 (0.80-1.97)</td>
</tr>
<tr>
<td>Lung</td>
<td>72</td>
<td>1.31 (1.11-1.53)</td>
</tr>
<tr>
<td>Skin</td>
<td>30</td>
<td>1.24 (0.95-1.62)</td>
</tr>
<tr>
<td>Kidney</td>
<td>10</td>
<td>1.48 (1.11-1.96)</td>
</tr>
<tr>
<td>Bladder</td>
<td>17</td>
<td>1.21 (0.91-1.61)</td>
</tr>
<tr>
<td>Brain</td>
<td>11</td>
<td>1.00 (0.54-1.85)</td>
</tr>
<tr>
<td>Leukemia/lymphoma</td>
<td>27</td>
<td>1.26 (1.05-1.51)</td>
</tr>
<tr>
<td>Breast (women)</td>
<td>83</td>
<td>1.16 (0.95-1.41)</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>7</td>
<td>1.31 (0.72-2.35)</td>
</tr>
<tr>
<td>Corpus uteri</td>
<td>14</td>
<td>1.34 (1.03-1.74)</td>
</tr>
<tr>
<td>Ovary</td>
<td>29</td>
<td>1.00 (0.67-1.48)</td>
</tr>
<tr>
<td>Prostate</td>
<td>23</td>
<td>0.74 (0.37-1.47)</td>
</tr>
</tbody>
</table>

* Nine hundred ninety-six controls.
† Nine hundred eighty-seven controls.
‡ Adjusted for age (continuously, expressed in 10 years), sex, BMI (<25, 25 to <30, ≥30 kg/m^2, categorically), tobacco smoking (never, former, current, categorically), ethanol consumption per day (<10 and ≥10 g, categorically), NSAID use (no, yes) and duration of storage in years (continuously).
cancers and cancers of specific sites, were estimated through unconditional logistic regression, including the data from all controls from each comparison, while controlling for age (continuously, expressed per 10 years), sex, BMI, tobacco smoking, ethanol consumption, and NSAID use (all, as previously indicated) and duration of storage (in years, continuously). The main analysis was repeated after exclusion of cases that occurred within the first year of follow-up, as well as all subjects with CRP equal to or higher than 20 mg/L (who may have had a transient acute infection). All statistical tests were two tailed.

**Results**

A total of 496 cases of cancer and 996 controls were included in the analysis. Their distribution by age, sex, BMI, tobacco smoking, alcohol drinking, and use of aspirin and other NSAIDs is shown in Table 1. Because of matching, the distribution of the two groups by age and sex was very similar. The distributions of the other variables presented in the table were not significantly different between cases and controls. The association among controls between CRP level and these covariates is also presented in Table 1. Although no significant differences were noticed according to sex, tobacco smoking, alcohol drinking, and duration of follow-up, CRP level increased with age, BMI, and use of NSAID (the latter, probably as an indication of the condition that required medication).

The mean CRP level was 4.1 mg/L among cases (SD, 10.3) and 2.6 among controls (SD, 3.2). Table 2 shows the OR of cancer for an increase of 1 SD in CRP level (3.2 mg/L). The OR of all cancers was 1.20 [95% confidence interval (95% CI), 1.10, 1.32]; an increased OR was found for cancers of the liver, lung, kidney, and endometrium, as well as for lympho-haematopoietic neoplasms. In the case of cancers of colorectum, pancreas, skin (nonmelanoma), bladder, and breast, there was a small, nonsignificantly increased OR. Exclusion of 70 cases occurring during the first year of follow-up, and of an additional seven cases and nine controls with CRP levels above 20 mg/L, resulted in a further increase in the OR of all cancers (OR, 1.32; 95% CI, 1.15-1.52) and in that of cancers of the lung, skin, and kidney, whereas the OR of endometrial cancer decreased to 1.06. Exclusion of cases who occurred within either 2 or 5 years of follow-up resulted in very similar OR. Figure 1 shows the mean and 95% CI of log-transformed plasma CRP values among cases and controls.

There was a stronger association between elevated CRP level and overall cancer risk in subjects below 55 years than among older subjects, among smokers than among non-smokers, and among users of NSAID than among nonusers (Table 3). These differences, which, however, were not statistically significant, were also suggested in the analysis of colorectal cancer, lung cancer, and of lymphoma and leukemia (not reported in detail). No differences were noticed in the association between CRP level and cancer risk (either overall or for the main types of cancer) according to alcohol drinking and BMI.

**Discussion**

Our findings indicate that elevated plasma CRP level is a marker of cancer risk in healthy individuals and are consistent with the growing evidence of an important role of inflammation in many types of human cancer. The results are internally consistent and, with the exception of endometrial cancer, are not dependent on the inclusion of cases of cancer occurring early during the follow-up, among whom elevated CRP level might reflect the presence of a subclinical cancer or a complicating inflammation.

Plasma CRP level is influenced by diseases associated with chronic inflammation, such as myocardial infarction, chronic hepatitis, chronic bronchitis, and arthritis. We have excluded individuals who experienced myocardial infarction. We have no information on occurrence of other inflammatory-related conditions. However, this would result in confounding only if these conditions are strongly associated with cancer, and this is likely to be only the case for chronic hepatitis and liver cancer, as discussed below. We expected to observe an increased risk of colorectal cancer among individuals with elevated plasma CRP level based on the results of a previous prospective study (11) and the evidence that chronic inflammatory conditions of the bowel entail such a risk (18). In line with our results, however, a recent prospective study in women failed to replicate the earlier reported positive association (11, 19), suggesting that low-grade inflammation might not increase the risk of colorectal cancer. Similarly, we were not able to confirm the association between increased CRP level and liver cancer, which has been found in a combined analysis of four cohorts from United States and United Kingdom (12). For prostate and breast cancer, we confirmed the lack of a predictive role of CRP as also reported by other authors (20, 21).

Although based on relatively few cases, we found an association between increased CRP level and liver cancer risk, which can be explained by chronic infection with hepatitis B and hepatitis C viruses. The results on lung cancer show a strong association with CRP level, which is not explained by confounding by tobacco smoking. They support the notion of a role of inflammatory pathways in tobacco-related lung cancer, in addition to a direct genotoxic effect of tobacco carcinogens. Chronic inflammation is central in other respiratory effects of

![Figure 1](https://example.com/figure1.png)

**Table 3. OR of all cancers for 1 SD of CRP level (3.2 mg/L), by selected characteristics**

<table>
<thead>
<tr>
<th>OR (95% CI)</th>
<th>$P_{\text{heterogeneity}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>1.54 (1.12-2.10)</td>
</tr>
<tr>
<td>55+</td>
<td>1.28 (1.09-1.50)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>1.34 (0.93-1.92)</td>
</tr>
<tr>
<td>25+</td>
<td>1.35 (1.14-1.54)</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1.17 (0.96-1.42)</td>
</tr>
<tr>
<td>Ever</td>
<td>1.50 (1.22-1.84)</td>
</tr>
<tr>
<td>Ethanol consumption (g/d)</td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>1.31 (1.11-1.54)</td>
</tr>
<tr>
<td>10+</td>
<td>1.34 (1.02-1.77)</td>
</tr>
<tr>
<td>NSAID* use</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.22 (1.03-1.45)</td>
</tr>
<tr>
<td>Yes</td>
<td>1.52 (1.18-1.95)</td>
</tr>
</tbody>
</table>

*NOTE: Data exclude first year of follow-up and CRP values ≥20 mg/L.*

*NSAIDs (aspirin and other).*
tobacco smoking, such as chronic obstructive pulmonary diseases (22). Although based on small numbers, our results suggest that inflammation may be a relevant mechanism for lung carcinogenesis also in nonsmokers.

For a number of cancers, including skin (nonmelanoma), kidney, and bladder cancer, as well as lymphoma and leukemia, our study provides the first suggestion of an association with elevated CRP level. At least in the case of bladder cancer, chronic inflammation is a recognized mechanism of carcinogenesis (23). However, caution is needed in the interpretation of the results for these four types of cancer because of the small number of observed cases and the possibility of false-positive results generated by chance. The positive association between elevated CRP level and endometrial cancer was not confirmed after exclusion of the first year of follow-up and of subjects with high CRP level, suggesting that CRP might mark an acute inflammatory process associated with an existing subclinical cancer.

We did not collect information on acute inflammatory diseases at enrollment. These conditions would have caused a transient increase in CRP level, but, as long as they are not predictors of cancer, the bias would have been toward an underestimation of the association between CRP level and cancer. Similar considerations apply to other conditions linked to CRP level, such as depression and fatigue. We have addressed this problem by excluding individuals with CRP level $\geq 20 \text{ mg/L}$; our results are robust to the choice of the cutoff: For example, the OR of all cancers after excluding individuals with CRP level $\geq 10 \text{ mg/L}$ was 1.34 (95% CI, 1.09-1.66).

Our investigation has some other limitations. We had no information on use of drugs other than anti-inflammatory, such as antihistamine, possibly linked to CRP level. The number of cases of several types of cancers was too small to provide a precise estimate of the association with CRP level. The availability of only one plasma sample for most subjects introduced regression dilution, which likely biased risk estimates toward the null (24). The lack of data on interleukin-6 and other cytokines hampers a more complete understanding of the role of CRP in human carcinogenesis: We plan to expand the study by measuring additional markers of inflammation in this population. It should be noticed, however, that the prospective nature of the study and the random and blind measurement of the plasma marker prevent the occurrence of biases resulting in false-positive results. The robustness of most results after exclusion of the first year of follow-up and of cases with very elevated CRP level, the medical confirmation of cases, and the reliability of CRP measurements are all aspects that strengthen the validity of our findings.

In conclusion, our study detected an association between plasma CRP level and cancer risk that might be of clinical significance. Although the analysis of more rare cancers was hampered by small numbers, our results suggest that the risk of several cancers, and notably those of lung, liver, and possibly skin, kidney, bladder as well as lymphoma and leukemia (but not colorectum, breast, or ovary), is predicted by elevated CRP.

Acknowledgments

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References

17. STATA Corporation. Intercooled Stata 7.0 for Windows 98/95/NT. College Station (Texas): STATA Corp.; 2002.
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