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C-reactive protein levels and subsequent cancer outcomes: Results from a prospective cohort study

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ABSTRACT

Chronic inflammation has been implicated in the pathogenesis of many common chronic diseases, including cancer. C-reactive protein (CRP) concentration is a non-specific serum marker of inflammation, and higher levels have been observed among individuals who go on to develop cardiovascular disease. Nested case-control studies were conducted within the CLUE II study, a community-based cohort, to examine the association between CRP concentrations and subsequent development of colorectal or prostate cancer. CRP concentrations were higher among individuals who went on to develop colon cancer, but not rectal or prostate cancer, compared with controls. The association between CRP concentrations and development of colon cancer is consistent with other evidence suggesting a role of inflammation and cancer. Preventive interventions that decrease systemic chronic inflammation have the potential to reduce certain types of cancer as well as cardiovascular disease. However, the potential benefits of anti-inflammatory chemopreventive agents must be weighed against their adverse effects before widespread use is recommended.

1. Introduction

Inflammation has been invoked as a potential contributory factor in the development of a variety of cancers and other chronic diseases, and anti-inflammatory agents such as aspirin have been investigated as potential chemopreventive agents. C-reactive protein (CRP) is a serological marker of inflammation that can be used to investigate the association between inflammation and risk of cancer.

C-reactive protein (CRP) is an acute-phase reactant produced in the liver in response to interleukin-6 (IL-6), an inflammatory cytokine and is a serological marker of inflammation. The development of a high-sensitivity assay method[1] has allowed the investigation of the associations of inflammation with disease risks across a wide spectrum of CRP levels, especially in the range of concentrations previously considered 'normal'; ranges <10 mg/l. For example, an increased risk of heart disease has been observed with CRP levels as low as 2–3 mg/l.[2,3] Because of the association of inflammation with cell injury, repair and proliferation, factors favourable to accumulation of cell mutations, it has been hypothesised that inflammation may play a role in initiation or progression to cancer.

Long-term prospective cohort studies with associated specimen repositories provide a tremendous resource for investigating prospectively the association between factors such as systemic inflammation and risk of cancer. In the cohort design, the exposure information has been collected

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years prior to the onset of disease, thus minimising the possibility that the disease itself alters the biomarker of interest, in this case measures of systemic inflammation. This overcomes a major limitation of case-control studies, where the presence of cancer may cause an inflammatory response and influence measured biomarker levels.

Nested case-control studies were conducted within the ongoing CLUE II Cohort to examine the association between pre-diagnostic levels of CRP, a measure of chronic low-grade systemic inflammation, and the risk of colon, rectal and prostate cancer.[4,5] Ongoing studies are also examining the association with other cancers. The CLUE II study is a community-based cohort study established in Washington County, MD, United States of America (USA) in 1989.

2. Methods

The CLUE studies were named after the campaign slogan 'Give us a clue to cancer and heart disease'. In 1989, CLUE II was conducted, with about one-third of the county population donating a blood specimen and completing a baseline questionnaire. Blood specimens were processed within 6–24 h of collection and stored at −70 °C. Follow-up for cancer outcomes occurs through linking of participants to the Washington County and Maryland Cancer Registries.

Two nested case-control studies were conducted to examine the association between CRP and colorectal and prostate cancer, the results of which have been published.[4,5] The studies followed the same basic design: 172 cases of colorectal cancer and 264 cases of prostate cancer occurred among cohort participants. Cancer cases were matched to controls by age, sex, race, date of blood sampling and time since last meal. Controls were cancer-free until the date of diagnosis of the case and were not known to be deceased.

CRP concentrations were measured using a high-sensitivity assay (Dade Behring, Newark Del, USA).[1] Cases and controls were measured together in sets with laboratory personnel masked as to their status. Pooled quality control samples demonstrated intra-pair coefficients of variation of less than 4%.

Conditional logistic regression analysis was used to examine the association between CRP levels and the risk of cancer. CRP concentrations were examined both as continuous variables (log-transformed) and by fourths, according to the distribution among controls.

3. Results

Pre-diagnostic measures of CRP were associated with the development of colon cancer, but not rectal or prostate cancer.[4,5] Geometric means at baseline were significantly higher among individuals who went on to develop colon cancer compared with matched controls.[4] No statistically significant differences were observed between rectal cancer cases or prostate cancer cases and their matched controls.

Table 1 shows the dose–response analysis for colon and prostate cancer cases according to fourths of the distribution among controls. A statistically significant trend in risk of colon cancer was observed increased to a 2.5-fold increased risk among individuals in the highest fourth of the distribution of CRP level. No trend in risk was observed for prostate cancer risk. The association for colon cancer was observed among men and women and among smokers and non-smokers. The association was also observed regardless of reported use of non-steroidal anti-inflammatory drugs (NSAIDs) at the time of blood sampling. Those in the highest fourth of the distribution in both studies had CRP levels in the range of ~3 mg/l or higher, similar to the levels associated with an increased risk of cardiovascular disease.

4. Discussion

The results of the colon cancer nested-case control study examining the association between CRP levels and risk of colon cancer add to the accumulating evidence supporting a role of inflammation in the aetiology of colon cancer, and suggest that interference with inflammatory pathways may provide an opportunity for the primary prevention of cancer. Following the initial report from the CLUE studies, several other studies have examined the association with mixed results among very diverse cohorts. Similar to the results in the CLUE study, a case-control study of colorectal cancer nested within the Alpha Tocopherol Beta-Carotene (ATBC) Intervention Trial participant cohort observed an increased risk with increasing baseline CRP levels.[6] Also consistent with our findings, a study nested within the Health Aging and Body Composition study observed an increased risk of colorectal cancer, but not of prostate cancer.[7] A meta-analysis of fibrinogen levels, a serological factor correlated with CRP levels, observed a statistically significant increased risk of colorectal cancer associated with fibrinogen levels.[8] However, not all

Table 1 – Relative risk of colon and prostate cancers by fourth of baseline C-reactive protein

	Matched odds ratio and 95% confidence interval				
	Lowest fourth	Second fourth	Third fourth	Highest fourth	*p* Trend
Colon cancer					
Number of cases/controls	20/59	27/68	34/71	50/62	
Odds ratio of colon cancer	1.00	1.25	1.44	2.55	0.002
95% Confidence interval	Reference	0.63–2.47	0.76–2.73	1.34–4.88	
Prostate cancer					
Number of cases/controls	61/64	83/69	60/65	60/66	
Odds ratio of prostate cancer	1.00	1.29	0.98	0.95	0.66
95% Confidence interval	Reference	0.8–2.08	061–1.58	0.57–1.58	

studies have consistent results. Among female participants in the Women's Health Study, an intervention trial of aspirin and vitamin E, no association was observed between baseline levels of CRP and colorectal cancer.[9] A nested case-control study conducted within the Japan Collaborative Cohort Study also did not observe a statistically significant increased risk with increasing CRP levels.[10]

Additional evidence supports the role of inflammation in the aetiology of colon cancer and the potential role of anti-inflammatory agents for the prevention of cancer, but like the association with CRP, the evidence is mixed. Prospective cohort studies have observed a reduced mortality and incidence of colorectal cancer associated with long-term use of NSAIDS, such as aspirin.[11,12] However, randomised clinical trials suggest only a moderate protective effect against colorectal adenomas,[13,14] and clinical trials of 5–10 years duration with low-dose aspirin have not shown a protective effect against colorectal cancer.[15,16]

The evidence for a possible role of systemic inflammation and the development of cancer is strongest for colon cancer. The CLUE study did not find an association between systemic CRP levels and prostate cancer, but an inflammatory process more localised to the prostate cannot be ruled out.[5]

Despite conflicting evidence, the totality from human, animal and in vitro studies suggest that interfering with inflammatory pathways may reduce the risk of colon cancer. Chemoprevention trials were launched, investigating the potential of NSAIDs, especially the COX-2 inhibitors, with their more focused action and promise of less gastrointestinal toxicity to reduce the incidence of colon polyps, an intermediate surrogate marker for colon cancer.[17] These studies were halted abruptly when excess cardiovascular toxicity was observed with the COX-2 inhibitors in these and other trials.[18–21] The serious adverse events observed have brought to the forefront the question of the appropriate balance of risks versus potential benefits to individuals participating in prevention trials.

Are individuals with polyps at high enough risk of colon cancer, especially when under regular screening with colonoscopy, a preventive as well as a screening intervention, to justify the use of chemopreventive agents associated with adverse events? Colon polyps are one of the few well-documented intermediate markers for the development of cancer, but most colon polyps do not progress to cancer.[22–24] In addition, among individuals with documented polyps, regular screening with colonoscopy is a preventive intervention as well as an early detection tool. One would need to have an exceedingly effective preventive agent to observe a benefit in preventing colon cancer incidence, over and above that expected due to regular colonoscopy screening and removal of polyps. On the other hand, the majority of individuals do not comply with recommended colon cancer screening guidelines.[25] Thus, an intervention that could reduce polyp formation and decrease the risk of colon cancer would benefit those who do not undergo regular screening. However, assuming a benefit for COX-2 inhibitors for polyp prevention (efficacy results from the terminated trials have not yet been reported), at least similar to that observed for aspirin and prevention of adenomatous polyps, what are the risks? And are these risks acceptable?

The enormous challenge of prevention interventions is to maintain the appropriate balance of benefit to harm. The large samples sizes required for cancer prevention trials demonstrate that, for prevention, many individuals are treated but relatively few ultimately benefit. For example, among the participants in the Breast Cancer Prevention Trial (BCPT P-1), selected on the basis of an increased risk of breast cancer, of the more than 13,000 women enrolled, 264 cases of breast cancer occurred: 175 among women on placebo and 89 among women on tamoxifen.[26] For colon cancer prevention, especially among those with a history of colon polyps who are already undergoing colonoscopy screening with removal of polyps, the benefit of a preventive agent has to exceed the preventive benefit of polyp removal – therefore risks must be minimal.

One way to evaluate risks and benefits of interventions is to calculate the number needed to be treated (NNT) in order to prevent one event, or alternatively, to cause a harmful event: the number needed to harm (NNH).[27] In the case of COX-2 inhibitors, the trials have not reported the benefit in terms of polyp prevention, but the NNH for adverse cardiovascular events can be calculated from the published reports.[20,21] The NNH for the composite cardiovascular events over the 3-year period of the trials ranged from 43 to 78 depending on the dose and agent. The highest risk (lowest NNH) was associated with celecoxib at a dose of 400 mg twice daily.[20] To put these risks into perspective, aspirin therapy for the prevention of myocardial infarction will cause 1 haemorrhagic stroke and three major gastrointestinal bleeding events (NNH ~330) among 1000 individuals treated for 5 years.[28] Among participants of the BCPT P-1 trial, the NNH associated with 5 years of treatment with tamoxifen was 335 for endometrial cancer and about 500 for deep vein thrombosis.[26,29]

The association between inflammatory pathways and the risk of developing cancer presents a potential modifiable risk factor. Interventions that interfere with this pathway may reduce the risk of cancer. The evidence is most compelling for the role of inflammation in the aetiology of colon cancer. However, the risks associated with chemoprevention interventions, such as the use of COX-2 inhibitors, are significant. Whether chemoprevention interventions can offer significant benefit over and above the benefits of early detection of preneoplastic lesions with screening interventions such as colonoscopy and without significant harm is uncertain. Lifestyle interventions with high benefit to risk ratios that may also interfere with the inflammatory pathway should also be investigated, as should the role of inflammation in other cancers.

Conflict of interest statement

None declared.

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