Commentary

C-reactive protein and colorectal cancer

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Introduction

There is no doubt that colorectal cancer poses a significant clinical burden. According to Cancer Research UK, there are around 35,000 new cases of large-bowel cancer in the UK annually, making it the second most common malignancy in women, and the third most common in men. In 2002, there were 16,220 deaths from the disease. Overall, around 40% of sufferers survive for 5 years. Early diagnosis leads to improved outcomes, and in October 2004 the government announced that a National Screening Programme using faecal occult blood testing will be introduced in April 2006.

There has been interest in identifying factors that could help predict colorectal cancer risk. Chronic inflammation has been linked to several solid malignancies, including cancers of the oesophagus, stomach, liver, pancreas, kidney and prostate. Possible mechanisms by which inflammation may contribute to carcinogenesis include: (i) the elaboration of cytokines and growth factors that favour tumour cell growth; (ii) the induction of cyclooxygenase-2 in macrophages and epithelial cells; and (iii) the generation of mutagenic reactive oxygen and nitrogen species. C-reactive protein (CRP) is a general marker for inflammation. The predictive value of CRP in colorectal cancer has provoked considerable interest, further fuelled by recent epidemiological data. Our review assesses the existing evidence for a relationship between CRP and colorectal cancer, and asks whether such enthusiasm is warranted.

C-reactive protein

C-reactive protein (CRP) is a general marker for inflammation. It is synthesized in hepatocytes and belongs to the family of acute-phase proteins, the concentration of which change in response to infection, injury and neoplasia. These changes are up-regulated by cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8) and tumour necrosis factor (TNF). Inappropriately prolonged elevation of this acute-phase protein may be detrimental, in that it results in reprioritization of nitrogen metabolism away from peripheral tissue towards the liver, which in turn may lead to accelerated wasting and shortened survival in disease. In paediatric and adult patients with Hodgkin’s disease, CRP levels correlated with stage, the presence of B symptoms and increased risk of relapse. Moreover, increased CRP was associated with shorter survival in patients with several cancers, including non-Hodgkin’s lymphoma, and lung, pancreatic and oesophageal malignancies. In prostate cancer, elevated CRP is a marker of poor prognosis, and is high in men with bone metastases. As well as this reported association with malignant potential of neoplasia and with cachexia, in recent years elevated levels of serum CRP have also been associated with cardiovascular events.

An increased risk for colorectal cancer has been demonstrated in patients with inflammatory bowel disease, particularly ulcerative colitis. In laboratory studies, inflammation promotes the conversion of colonic adenoma cells to adenocarcinoma cells. A reduced risk for colorectal adenomas...
and cancer is associated with long-term use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) in observational studies, and some clinical trials also support this hypothesis.\textsuperscript{17–19} Moreover, IL-6 stimulates the growth of primary and metastatic colon cancer cell lines.\textsuperscript{20} In observational studies, modest elevations in inflammatory markers, including total white blood cell count and fibrinogen, are associated with an increased risk of cancer mortality in patients free of cancer at baseline.\textsuperscript{21–23} However, inflammatory bowel disease accounts for only 1–2% of all cases of colorectal cancer in the general population.\textsuperscript{14} In addition, there is considerable debate over the mechanisms by which NSAIDs may reduce the risk for colorectal cancer, with evidence to suggest that pathways not associated with inflammatory processes may play a significant role.\textsuperscript{24}

CRP is one of the acute-phase proteins, which are components of the innate immune responses that increase after infections, trauma, burns, tissue infarction, inflammatory processes and tumours.\textsuperscript{25,26} Pre-operative CRP levels in patients with late-stage colorectal tumours are considerably and consistently higher than those in patients with early-stage disease.\textsuperscript{27–30} Moreover, elevated levels of CRP or IL-6 in patients with colorectal cancer have been associated with tumour stage and recurrence and reduced survival.\textsuperscript{30–32} However, in the study by Chung and Chang, although in one-third of 172 patients with colorectal cancer, the pre-resection CRP level was elevated and was associated with larger tumour size and lymph node or liver metastasis, under multivariate analysis, CRP level was not an independent factor predicting survival.\textsuperscript{33} In some studies, IL-6 levels in colorectal tumour tissue were substantially higher than those in normal tissue,\textsuperscript{34,35} and three small case–control studies reported higher CRP or IL-6 levels in patients with colorectal cancer than in controls.\textsuperscript{34,36,37} However, all of these data are consistent with the hypothesis that CRP levels increase after onset of colorectal cancer. Reverse causality (i.e. CRP increasing as a result of colorectal cancer) does not necessarily exclude a role for CRP or pro-inflammatory cytokines in the progression or aggressiveness of the disease. The issue of CRP acting as an independent prognostic factor in colorectal cancer cannot be adequately addressed by observational and retrospective studies alone.

**Prospective studies**

Whether CRP levels are elevated before biological onset of colorectal cancer, or indeed whether CRP is a risk factor for the de novo development of colorectal cancer, are questions that relatively few prospective studies have tried to address. The studies published to-date demonstrate inconsistent results and the analysis of causal link has been limited by considerable differences in study design. One study examined the risk of incident colon cancer associated with higher concentrations of CRP.\textsuperscript{38} The association was not statistically significant, but the study was aimed at risk of any cancer, had few colon cancer cases (n = 44), and had limited follow-up (58 months). In another study, lower serum concentrations of albumin were associated with an increased risk of incident colon cancer.\textsuperscript{39} Because serum albumin is reduced in the presence of inflammation, an inverse association between serum albumin levels and risk of colon cancer supports the hypothesis that inflammation increases the risk of colon cancer.

Erlinger et al. conducted a prospective, nested case-control study of a cohort of 22,887 adult residents of Washington County, Maryland, USA, with an 11-year follow-up (the CLUE II study).\textsuperscript{40} A total of 172 colorectal cancer cases were identified. Up to two controls (n = 342) were selected from the cohort for each case, matched by age, sex, ethnicity, and date of blood draw. Plasma CRP concentrations were higher among all colorectal cases combined than in controls (median CRP 2.44 vs. 1.94 mg/l, respectively; p = 0.01). The highest concentration was found in those who subsequently developed colon cancer vs. matched controls (median CRP 2.69 vs. 1.97 mg/l; p = 0.001). Among rectal cancer cases, CRP concentrations were not significantly different from controls (median CRP 1.79 vs. 1.81 mg/l; p = 0.32). The risk of colon cancer was higher in people who were in the highest (vs. the lowest) quartile of CRP concentrations (OR 2.55; 95%CI 1.34–4.88; p for trend = 0.002). In non-smokers, the corresponding association was stronger (OR 3.51; 95%CI 1.64–7.51; p for trend = 0.001). A potential limitation of this study was its lack of adjustment for physical activity, alcohol intake, and colorectal cancer screening. There may have also been inadequate control for use of aspirin and postmenopausal hormones, because these variables were assessed only within the last 48 h before blood collection. CRP was measured only at one point, as in many other studies, thereby allowing the potential for intra-individual variation, which may have further affected the analysis.

Ito and co-investigators conducted a nested case-control analysis in the Japan Collaborative Cohort Study, investigating the relationship between the risk for colorectal cancer and serum CRP levels determined by a high-sensitivity CRP
enzyme immunoassay. The subjects recruited were 141 patients with colorectal cancer (63 males, 78 females) and 327 controls with no history of cancer (148 males, 179 females). Each case of colorectal cancer was matched for sex, age and participating institution to two or three controls. Serum CRP levels were not significantly associated with the risk of colorectal cancer. The OR for the highest serum CRP levels was 0.9 (95% CI 0.68–1.20) for colorectal cancer and 1.42 (95% CI 0.73–2.74) for colon cancer, compared to subjects with lowest serum levels. The OR for incidence of colorectal cancer showed a similar trend, but again the difference was not significant.

Zhang et al. carried out a prospective cohort study of participants in the Women’s Health Study. Over 27,000 apparently healthy women aged ≥45 years had CRP measured at entry into a trial of low-dose aspirin and vitamin E. Maximum length of intervention and follow-up was 10.8 years. A total of 169 women developed colorectal adenocarcinomas during follow-up. Baseline CRP levels were not significantly associated with colorectal cancer risk. The multivariate hazard ratios according to cut-off points for CRP proposed in clinical guidelines were 0.79 (95% CI 0.53–1.17) for the category of 1–3 mg/l and 0.66 (95% CI 0.43–1.03) for the category of >3 mg/l (p for trend = 0.09), compared with the category of <1 mg/l. High CRP levels were also not associated with increased risk in analyses done according to tumour location and stage at diagnosis, according to alternative cut-off points for CRP, or in any of the subgroups evaluated. A potential difference between the Women’s Health Study and the investigation described by Erlinger et al. is that the former did not include patients with inflammatory bowel disease. Some of the observed risk in the CLUE II cohort may have resulted from inclusion of such patients. Also, the participants in the CLUE II study were on average 10 years older, and approximately 40% were male. The incidence rate of colorectal cancer increases with age, and is 30% lower in women than men. It is also possible that the analysis may have been complicated by the use of hormone replacement therapy (HRT), which was higher than in the general population. The authors however pointed out that there was no positive association between CRP and colorectal cancer amongst women who had never used HRT.

Gunter et al. recently reported their examination of serum CRP levels with colorectal cancer incidence in a nested case-control study within the Alpha Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study, a cohort of 29,133 Finnish males enrolled from 1985 to 1988, with follow-up through to April 2002. Colorectal cancer cases were ascertained by the Finnish Cancer Registry. This analysis included 130 cases of colorectal cancer and 260 matched controls. Baseline median CRP levels were approximately 25% higher among colorectal cancer cases (3.4 mg/l) than controls (2.6 mg/l; p = 0.04). Relative to men in the lowest quartile of CRP concentration, men in the highest quartile had an odds ratio of 2.9 (95% CI 1.4–6.0) for developing colorectal cancer, with a dose-response relationship supported. The relation between CRP and incident colorectal cancer was modified by body mass index, such that the association was stronger among lean individuals than in heavier individuals.

Il’yasova et al. reported the relationships between circulating levels of IL-6, CRP and TNF, with total as well as site-specific cancer incidence, in 24,388 adults aged 70–79 years participating in the Health Aging and Body Composition study over an average follow-up of 5.5 years. Inflammatory markers were measured in stored baseline fasting blood samples. IL-6 and CRP were associated with colorectal cancer risk, and even more so with risk of colorectal cancer mortality. All three markers were associated with lung cancer risk, and CRP only with breast cancer. Prostate cancer was not associated with any of the markers. The site-specific differences observed suggest different roles for inflammation in organ-specific carcinogenesis, and perhaps different functions of specific cytokines. In part of a large meta-analysis of prospective studies examining the association of plasma fibrinogen level and risk of major cardiovascular events and nonvascular mortality, fibrinogen predicted colorectal cancer mortality in previously healthy persons.

Conclusions

There are clearly advantages in the identification of surrogate markers for disease and risk of disease in colorectal cancer. There is interest in the hypothesis that inflammation plays a role in colorectal carcinogenesis, and in the notion that CRP may predict colorectal cancer risk. However, the precise mechanisms involved remain unclear. CRP is a non-specific marker of inflammation, and additional studies of specific cytokines or factors that regulate the acute-phase response are necessary to elucidate the mechanisms by which inflammation may increase risk of colorectal cancer.

There has been a great deal of interest in the value of CRP in colorectal cancer. It is our opinion, however, that much of this enthusiasm is premature. While to a large extent, observational data support an association between CRP and colorectal cancer,
the epidemiological evidence is relatively sparse and far from consistent, with at least two large prospective studies suggesting no link. Further studies are needed. In particular, the lack of large prospective studies specifically designed to examine the notion of CRP as an independent predictive parameter of colorectal cancer specifically (as opposed to cancer in general, or even ‘diseases’ as a whole), hampers the analysis. One of the problems in interpreting the available data is the considerable potential for confounding even in the larger studies. For example, studies have demonstrated that CRP levels can be reduced with smoking cessation and weight loss, factors often ignored in analyses. The inconsistency of the results may also reflect differences in study design.

Many issues remain essentially unexplored. The effect of anti-inflammatory medication on the suggested relationship between CRP and colorectal cancer has yet to be addressed. The balance of the epidemiological evidence available to date does favour a link between NSAID and selective cyclooxygenase inhibitor-2 use and reduced risk of colorectal cancer and colorectal adenomatous polyps. The correlation between CRP, anti-inflammatory use, and colorectal risk in the context of a prospective study would be desirable. There are, however, pending questions of how much drug should be taken and for how long, as well as concerns over the long-term use of such agents. Another important issue if CRP is to be used to predict colorectal risk is the implication this may have for colorectal cancer screening and therapy. What ultimately is the point in evaluating CRP levels in patients? Such information should lead to an improvement in patient outcome. What action should be taken in individuals considered to be ‘at risk’ of developing colorectal cancer on the basis of their CRP? Could measuring pre-operative serum CRP level help in selecting patients who would benefit from neoadjuvant or adjuvant therapy? Could CRP be included in a scoring system that is predictive of primary treatment failure in colorectal cancer? Also, given that CRP has been associated with tumour size and disease stage, can it be used as a ‘tumour marker’ in the determining of disease activity, much as carcinoembryonic antigen and CA19-9 are currently used? On the face of it, there appear to be more questions than answers. While its measurement is accessible and convenient, further evaluation through carefully designed studies is needed to determine whether CRP has a role as a diagnostic and prognostic index in colorectal cancer.

References