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IS THERE A POTENTIAL USE FOR C-REACTIVE PROTEIN AS A DIAGNOSTIC AND PROGNOSTIC MARKER FOR COLORECTAL CANCER

Kharkiv National Medical University(KNMU) Ukraine

ZHUKOV V., Dr. Sci (Biology, Medicine), Professor, Chief of Department of Biochemistry
PEREPADYA S., oncologist doctor,
MOISEYENKO A. oncologist doctor,
ZAYTSEVA O., Dr. Sci (Biology), Professor
GRAMATIUK S., Associated Professor

C-reactive protein (CRP), named for its capacity to precipitate the somatic C-polysaccharide of Streptococcus pneumonia, is a member of the pentraxin family of plasma proteins [1]. Even though it was discovered as far back as 1929 [2] as the 'acute-phase protein' and was used for routine monitoring of acute rheumatic fever in the 1960s, it was not until the 1990s that its potential value as a diagnostic and prognostic marker of diseases, mainly cardiovascular diseases (CVD), was recognized [3]. One of the major driving forces was the development of immunoassays that could detect CRP with greater sensitivity than those used previously, which led to the realization that elevated CRP values even within the range previously considered normal were associated with future CVD events [3].

Like other acute-phase proteins, such as the protease inhibitors, coagulation, complement and transport proteins, CRP is a nonspecific marker of inflammation and tissue damage [4]. However, its high sensitivity, response speed, dynamic range synthesis starts within hours and peaks at approximately 48 h when its concentrations can increase 10000-fold [1]. After the stimulus has completely stopped, circulating CRP concentrations fall rapidly

at the rate of plasma clearance to reach prestimulus concentrations [1]. CRP has a plasma half-life of 19 h, which is and stability make it more clinically useful as a representative of the acute-phase response compared with other acute-phase proteins [1,5]. Similarly, immunoassays for CRP are well standardized, reproducible and readily available [1].

C-reactive protein is produced by the hepatocytes [6], and its plasma concentrations are usually low. CRP production is under transcriptional control by IL-6 [1]. There is a strong positive association between CRP, BMI [7] and many features of insulin resistance, which may reflect the fact that the adipocytes are a major source of IL-6 [8]. In healthy individuals CRP concentrations remain steady over time, unless there is an underlying pathological process, such as a short-term infection that stimulates its production. Over a 1-year period, CRP has a classification accuracy similar to cholesterol and an intraclass correlation of 0.66 (66% of variation explained by between-subject variation and 34% explained by within-subject variation) [9]. Following an inflammatory stimulus, de novo CRP constant under all conditions of health and disease, hence, the sole determinant of circulating CRP concentration is its rate of synthesis, which is an indication of the intensity of the pathological process stimulating its production [10]. CRP does not exhibit any diurnal or seasonal variation, is not affected by eating and apart from liver

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failure, no other concurrent pathology impairs CRP production unless they also affect the underlying acute-phase stimulus [1]. With the aforementioned attributes, CRP can be potentially useful not only in predicting and screening for inflammation-related diseases, but also in helping monitor disease progression and response to therapy in pathological conditions related to inflammation [1]. A recent meta-analysis of individual records of 160,309 people revealed that CRP is useful in predicting not only CVD (odds ratio [OR]: 1.32; 95% CI: 1.18–1.49 for ischemic stroke; and OR: 1.23; 95% CI: 1.07–1.42 for coronary heart diseases) and CVD mortality (OR: 1.34; 95% CI: 1.18–1.52) but also non-CVD mortality (OR: 1.34; 95% CI: 1.20–1.50) [11].

MATERIALS AND METHODS

239 patients at the age from 35 till 76 years with the established diagnosis of colorectal cancer (CRC) were examined and treated using clinical tools and clinical-morphological methods. According to localization of pathological process the rectum cancer (RC) was diagnosed in 54 patients (29 men, 25 women), cancer of the sigmoid colon (SC) – in 62 patients (37 men, 25 women), a cecum cancer (CeC) – in 27 patients (15 men, 12 women), cancer of the transverse colon (TCC) – in 66 patients (48 men, 18 women), a colon cancer (CoC) – in 30 patients (17 men, 13 women). The first (I) stage of cancer was detected in 6 patients, the second (II) – in 34, the third (III) – in 161 and the fourth (IV) – in 38 oncologic patients (inoperable forms of large intestine cancer). The comparison group included 43 conditionally healthy persons of similar age and sex (23 men, 20 women).

Statistical analyses

Cox regression models were used to estimate the association between dietary antioxidant vitamins and carotenoids, and serum concentrations of -tocopherol, -carotene and retinol and the risk for colorectal cancer. Our analysis used follow-up time starting from randomisation and ending at diagnosis of colorectal cancer, at death, or at the end of follow-up (30 April 1995). Dietary variables were log-transformed and energy-adjusted according to the Willett residual method (Willett & Stampfer, 1986). Dietary and serum variables were entered into the models as indicator variables defined by the second through fourth quartiles among the entire cohort, with the lowest quartile as the reference group. An ordinal score variable was also created to test for dose-response relationships across levels of dietary and serum variables.

RESULTS OF RESEARCHES AND THEIR DISCUSSION

C-reactive protein's sensitivity as a predictor for colorectal cancer risk seems to be somewhat stronger than for adenoma. Several prospective studies [20–34] have evaluated the association of CRP with colorectal cancer risk, however, the results are not consistent, especially among women. Of 14 studies, only six [20,23–25,28,33] have reported significantly positive associations between CRP and colorectal cancer risk with the strongest OR being 2.9 (95% CI: 1.4–6.0) in a case–control study nested among a cohort of smokers from Finland [24]. So far, three studies have explored the association of CRP with colorectal cancer risk among women only and the three studies have all reported inverse associations [21,29,32] (OR: 0.66; 95% CI: 0.43–1.03 in the Women's Health Study [21] and OR: 0.65; 95% CI: 0.40–1.05 in the Nurses' Health Study) [32]. A systematic review of eight studies published in 2008 reported a significant, albeit weak, positive association between CRP and colorectal cancer risk among men (OR: 1.18; 95% CI: 1.04–1.34) but not among women (OR: 1.09; 95% CI: 0.93–1.27) [35]. A total of eight studies have explored the associations of CRP and colorectal

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cancer by tumor site [20,22,24,25,31,33,34,36]. Of these, four studies reported a significant positive association between CRP and colon cancer [20,25,33,36] and only one study so far has reported a positive association with rectal cancer [24]. The largest study to date, which has investigated the association of CRP with colorectal cancer by tumor site is the European Prospective Investigation into Cancer and Nutrition (EPIC) study (1096 cases of which 545 were women) [31]. The authors reported a significant 74% (95% CI: 1.11–2.73) increased risk of colon cancer among men with the highest CRP concentrations but a nonsignificant 6% increase among women (95% CI: 0.67–1.68). Thus, apart from the seemingly weak association between CRP and colorectal cancer, there appears to be a sex-based difference. It has been speculated that the use of exogenous hormones could explain some of the sex-based differences as the use of exogenous hormones may be associated with a reduced risk of colon cancer in postmenopausal women [37]. However, in the EPIC study, the associations between CRP and colon cancer in women did not become stronger when the analysis was restricted to women who were not using hormone replacement therapy [31], which does not support the notion that the sex-based differences could be owing to the use of exogenous hormones.

While it is clear that CRP is a sensitive marker for inflammation, it has not demonstrated a consistent association with colorectal cancer in studies available to date and its ability to predict colorectal cancer is too weak for it to be considered a good marker for the diagnosis of colorectal cancer at the moment. However, we do not discard the possibility that CRP could be potentially useful in the diagnosis of colorectal cancer in the future, either alone or in conjunction with other biomarkers. However, before then, larger studies are required to tease out not only the sex-based differences but also the differences in risk according to tumor site because with the exception of the EPIC study, most previous studies were relatively small and their power to detect differences in subgroup analyses may be limited. Prospective studies where CRP concentrations are measured repeatedly before cancer diagnosis are required as this will increase the predictive value of CRP and such studies can relate changes in CRP concentrations before cancer diagnosis to cancer risk (one such study within the Women's Health Initiative Observational Study [WHI-OS] is currently underway). Lastly, polymorphisms in the CRP gene are associated with differences in blood CRP concentrations [38], and may modify associations with cancer risk [39]. The interplay between genetic variation, inflammatory pathways, NSAID use and cancer risk has been insufficiently studied [12]. Until these interactions as well as the clinical value of repeat measurements in predicting cancer risk have been established, CRP is not ready for primetime in the diagnosis of colorectal cancer.

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