Editorial Commentary

Systemic and intestinal chronic inflammation, diet and cancer: an unbreakable bond

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Idiopathic intestinal inflammatory diseases (IID) include two types of chronic intestinal disorders: Crohn's disease and ulcerative rectocolitis. Evidence suggests that the IID is derived from the loss of immune tolerance in normal enteric bacteria diners in a genetically susceptible host. In humans, the initial intestinal immune response to intestinal microbiota is closely regulated; this regulation determines if there is a condition of immune tolerance or an inflammatory defensive response. The alteration of the balance of this immune response can lead to IID. In healthy people, the intestinal lamina contains a complex population of cells of the immune system that secrete cytokines with the function of modulating the immune response, both in anti-inflammatory direction that reduce immune response [transforming growth factor β (TGF-β) and interleukin-10] and pro-inflammatory direction. All these mediators are produced by innate and adaptive immune cells, which limit the excessive entry of intestinal microbiota and defend themselves from pathogens. The balance of the immune response is maintained between regulatory T cells and effector T cells (Th1, Th2 and Th17). In IID, innate cells increase the production of tumor necrosis factor alpha (TNF-α), interleukin-1β, interleukin-6, interleukin-12, interleukin-23 and chemokines. There is a marked increase in the thickness of the lamina propria, with an increase in the number of CD4+ T cells, in particular proinflammatory subgroups of T cells, which also produce cytokines and chemokines in high quantities. This increase in the production of cytokines determines the recruitment of further leukocytes, thus determining a vicious circle that maintains the state of inflammation (1).

Evidence suggests that antigens of the microbial flora normally present in the intestinal lumen guide the intestinal inflammation. Furthermore, when compared to control subjects, patients with Crohn's disease and those with ulcerative recto-colitis have depletion and reduction of diversity of the phyla Firmicutes members associated with mucosa, and Bacteroidetes. Changes in diet, excessive or improper use of antibiotics and, paradoxically, intestinal decolonization (for example the eradication of intestinal helminths), have also likely contributed to the increase in the prevalence of inflammatory intestinal disease (2-4).

It is known that life expectancy is reduced in patients with Crohn's disease and in patients with ulcerative recto-colitis. Patients with IID have excess mortality due to infections, cardiovascular diseases and tumours, especially colon-rectal cancer (CRC) (5-8).

Although the precise etiology of IID remains incompletely understood, the evidence suggests that environmental factors, including eating habits, contribute to its pathogenesis. It is known that dietary components directly regulate the immunomodulatory function of immune cells in bowel residents. Similarly, food nutrients shape the composition of the intestinal microbiota. On the contrary, nutrient metabolism in host cells and intestinal microbiota can be altered by intestinal inflammation, thereby increasing or decreasing the amount of nutrients needed to maintain homeostasis and immune microbial (9).

Nutritional interventions or specific diets, such as diet based on carbohydrates, oligosaccharides bottom-fermented, disaccharides, monosaccharides and polyol diet, have shown to have strong anti-inflammatory properties and promise to improve disease symptoms. It has been suggested that the Mediterranean diet (MD) exerts strong

Table 1 The basic components of the Mediterranean diet

High monounsaturated:saturated fat ratio (extra-virgin olive oil)
Moderate intake of alcohol
High intake of vegetable proteins
Daily intake of cereals and derived products (bread, pasta, rice, cous cous and other cereals, preferably low refined)
Daily intake of fruits and vegetables
Moderate intake of fish and occasional intake of red and processed meat
Daily intake of low-fat dairy products and occasional intake of high-fat dairy products

immunomodulatory effects and shows a potential to modulate epigenetic mechanisms by methylation of genes related to inflammation (10,11).

Therefore, a balanced diet with low fat and low sugar content, and prepared with fresh ingredients, such as the Mediterranean diet, is essential for good health. This dietary model inspired by the Mediterranean diet has shown both to act on the microbiome and to have anti-inflammatory properties on intestinal activity (12). It has been shown that subjects with greater food diversity, i.e., taking different foods (potatoes, vegetables, legumes, fruits, dairy products, cereals, meat, fish, eggs and lipids) in a well-balanced way, experience a longer and healthier life. The food diversity may reflect healthy eating habits, which in turn can promote the prevention and the maintenance of health and longevity (13).

It is known that IID is an important risk factor for the occurrence of malignancies of the colon and extra-intestinal organs. It is also known that elderly patients with IID have a higher risk than the younger IID patients, of developing malignancies. This increased risk seemed to be associated with corticosteroid use, but not with immunomodulators or biologics use (14).

Similarly, to IID, it has been shown that nutritional interventions or specific diets, such as MD, exert a strong protective effect for incidence and progression of CRC. Since 1996, Trichopoulou *et al.* (15) showed that high adherence to the traditional MD exerted a strong protective effect versus the cancer. They reported a 25% reduction of CRC and 15% reduction of the breast cancer. Furthermore, the authors have defined what are the fundamental elements that constitute the MD (*Table 1*).

Successive reviews and meta-analyses have confirmed the role of diet in reducing the incidence of colorectal cancer. In their meta-analysis aimed at investigating the association between the inflammatory potential of the diet, as estimated by the Dietary Inflammatory Index (DII) score, and incidence of CRC, Shivappa *et al.* (16) showed that subjects in the highest category versus the lowest DII category of exposure had an 40% augmented risk of developing CRC (RR =1.40; 95% CI, 1.26–1.55; P<0.0001), where a high DII score defines a diet rich in red and processed meat, refined grains, sugar and fatty acids, while a low DII score defines a diet rich in anti-inflammatory components, like fruits and vegetables. Subsequently, in their review from both cohort and case-control studies, Garcia-Larsen *et al.* (17) showed that a "Western" dietary pattern, which is rich in red and processed meat, refined grains and sugar, was associated to a 25% increased risk of developing CRC (RR =1.25; 95% CI, 1.11–1.40; P<0.0001), while a "prudent" dietary pattern, as the MD which is rich in fruits, vegetables, legumes, fibers and flavonoids, was associated to a 24% reduced risk of developing CRC (RR =0.76; 95% CI, 0.68–0.86; P<0.0001). Donovan *et al.* (18) in their narrative review confirmed the protective role of MD. They first reiterated that the MD's ability to protect from CRC is due to the sum of the anti-inflammatory effects exercised by the various food components that are present in this diet (fruit, vegetables, legumes, olive oil, fish), which contribute with a significant load of phenolic compounds. Secondly, analysing results from preclinical and clinical studies, they reiterated that consumption of foods commonly found in the MD eating pattern attenuates biomarkers (i.e., high sensitivity CRP) and symptoms associated with IID. But above all, they further confirmed that only high and lifetime adherence to a MD pattern may exert beneficial and protective effects against the development of IID and CRC, likely acting against DNA methylation and on the host microbiome.

Previous retrospective and cohort studies have shown that IID represents a significant risk factor for the onset of prostate cancer, especially in patients older than 65 years (19,20). However, the interpretation of the association

between IID and prostate cancer is lacking. The authors proposed various hypotheses, from the use of corticosteroids among elderly patients, instead of immunomodulators or biological therapies (19), to the use of tobacco or even to continuous exposure to radiation during the computed tomographic scan, or more realistically to concomitant environmental risk factors (20).

In their retrospective cohort study Burns *et al.* (21) showed that men with IID were at higher risk than the general population for prostate cancer (hazard ratio: 4.84; 95% CI, 3.34–7.02; P<0.001), and even for clinically significant prostate cancer (hazard ratio: 4.04; 95% CI, 2.52–6.48; P<0.001). Risk was even higher for men older than 70 years, both for prostate cancer (hazard ratio: 8.56; 95% CI, 3.30–22.18; P<0.001), and for clinically significant prostate cancer (hazard ratio: 8.96; 95% CI, 2.61–30.75; P<0.001). The strength of their study includes the large size of the cohort (1,033 patients and 9,036 controls), the distribution of the cohort on an age group represented by subjects under 40 years to subjects over 70 years old, the longitudinal follow-up of all patients for a period almost 21 years. The authors attribute the development of prostate cancer to the state of chronic inflammation of the prostate induced by IID, with the consequent reduction of immunosurveillance.

Several evidences strongly support the association between nutritional factors and the development and progression of cancer, including prostate cancer. Similarly, many dietary components have been implicated as protective or to promote the development of cancer (19). On the other hand, also for prostate cancer, the concept is strengthened by the fact that a high adhesion to a protective dietary pattern based on the traditional model of the MD plays a protective role on the development and progression of cancer (22). The protective effect of the MD is exercised by the intake of its main components and above all by the myriad of micronutrients that have an important antioxidant function, such as vitamin E, alpha-tocopherol, carotenoids and various other phenyl compounds, such as tyrosol and hydroxytyrosol, present in olive oil. An important protective factor to the incidence of prostate cancer is represented by lycopene, which is found in tomatoes and red fruits and vegetables such as red carrots, watermelons, strawberries, cherries, pomegranate and blood orange. In particular, the bioavailability of lycopene is improved by cooking in the tomato sauce in olive oil. This last statement, together with the very interesting results of retrospective cohort study by Burns *et al.* (21), makes it desirable to start future studies which, considering the environmental and behavioural factors of individuals, with particular attention to eating habits, clarify the relationship between chronic systemic and intestinal inflammation and the onset of prostate cancer.

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Footnote

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