

## CLINICAL STUDY

## The risk of cancer in relationship to diet

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**Abstract:** Globally, colorectal cancer is the leading cause of mortality due to malignant diseases. Probiotics are live microbial food supplements or functional foods containing specific nonpathogenic organisms that beneficially affect the host by improving the intestinal microbial balance. Therefore they can be used as an innovative tools to alleviate intestinal inflammation, normalize gut mucosal dysfunction, and down-regulate hypersensitivity reactions. In the past decade, there has been a dramatic increase of experiments and studies documenting prophylactic and therapeutic benefits of probiotics and prebiotics in order to reduce the risk of chronic civilization diseases. The current knowledges on probiotics qualify them as the pivotal components of self-care and complementary medicine (Ref. 27). Full Text (Free, PDF) [www.bmj.sk](http://www.bmj.sk).

**Key words:** colon cancer, probiotics, prebiotics, synbiotics, nutritional supplements.

The interest in the role of probiotics for human health dates back to the beginning of the 20th century (1908) when the Nobel Prize winner, the Russian scientist Elie Metchnikoff, linked the long, healthy life of Bulgarian peasants to their high intake of fermented milk products containing lactic acid producing microorganisms (Sanders, 2000, 2003). He theorized that the lactic acid bacteria in fermented milk displace bacteria normally present in the intestine, resulting in a healthier life. In recent years, scientific studies have been published examining the health attributes of probiotics, especially those related to gastrointestinal health and immune system modulation.

The human gastrointestinal tract contains an extremely complex and diverse microbial population of more than 400 different species of bacteria. While the majority of these bacteria are non-pathogenic, some may cause disease. In healthy individuals, there is a bacterial balance. Disrupting this balance in the gastrointestinal tract (e.g. by stress, infection, antibiotic therapy) can lead to proliferation of undesirable or pathogenic microbes and increased risk of clinical disorders such as inflammatory diseases, infectious illnesses, and others (Brown and Valiere, 2004). Increasing scientific evidence indicates that consumption of probiotics can help to maintain a healthy microbial population, resulting in several therapeutic benefits (Goossens et al, 2003; Reid et al, 2003a).

**Probiotics** are biopreparations containing living cells or metabolites of stabilised autochthonous microorganisms that

optimise the colonisation and gut microflora in both animals and humans, and have a stimulatory effect on digestive processes and the immunity of the host (Fuller, 1992). The majority of probiotics are strains of different species of *Lactobacillus* and *Bifidobacterium* – *Lactobacillus bulgaricus*, *L. acidophilus*, *L. casei*, *L. helveticus*, *L. lactis*, *L. salivarius*, *L. plantarum*, *Bifidobacterium* spp., *Streptococcus thermophilus*, *Enterococcus faecium*, *Enterococcus faecalis*, and particular strains of *E.coli*. All the above-mentioned microorganisms, except for *L. bulgaricus* and *Streptococcus thermophilus*, which are starter cultures of yoghurt, form natural components of the gut microflora (Fuller, 1989; Reid et al, 2003b; Brown and Valiere, 2004).

Probiotics should not be confused with prebiotics or synbiotics. Prebiotics are non-digestible food carbohydrates such as inulin, oligofructose and oligosaccharides that stimulate the growth or activity of health-promoting lactobacilli and bifidobacteria. A synbiotic is a combination of prebiotics and probiotics. This combination can have an additive or synergic effect on the host by improving the survival and/or persistence of the probiotic in the intestinal tract.

Recently, the probiotic preparations with a higher efficacy have been developed, so called potentiated probiotics. Potentiated probiotics are defined as biopreparations containing production strains of microorganisms and synergistically acting components of natural origin which exert their potentiated effect through effects on probiotic and gut microorganisms, gut mucosa and intestinal environment or immune system (Bomba et al, 2002, Bomba et al, 2006).

**Potential health benefits of probiotics**

The quantitative and qualitative composition of the gastrointestinal microbial flora of a healthy human being is relatively stable, with the domination of beneficial bacteria (espe-

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cially of the protective *Lactobacillus* and *Bifidobacterium* types). They create a natural protective barrier against pathogens. The quantitative participation of the colonic bacteria fluctuates and depends on age, physiological status, diet, medications, the host's immune system effectiveness and other environmental factors. It can be modulated via probiotic flora taken with food, thus creating in the gastrointestinal tract conditions conducive to the development of health-protecting bacterial strains, with the simultaneous inhibition of pathogenic flora, the improvement of intestinal epithelium functions and the modulation of immune system parameters (Isolauri, 2001; Kaenhammer, 2000; Sanders, 2000).

Dietary modulations of the human gut microflora can be of great benefit. The most frequently used dietary method of influencing of gut flora composition is the consumption of probiotic food (Isolauri, 2001; Saavedra, 2000).

The diet and nutrition play an extraordinary role in the aetiology and prevention of civilizing diseases, that represent the most serious health, economic, and social problem. Synthetic therapeutics have many side-effects unfavourable influencing the human health and at the same time inducing new ones. For these reasons, worldwide, the interest in using an ecological methods of prevention and therapy by substances of biotechnological and natural origin has been increasing (Bengmark, 1998). The optimization of nutrition requires the completion of diet by suitable dietetic supplements. Nutritional supplements of natural and biotechnological origin represent a natural and effective way of civilizing diseases prevention. Within the frame of referenced substances, probiotics, oligosaccharides, plant and their extracts and poly-unsaturated fatty acids can be effectively used in prevention. It will be important to search for ways to improve the efficacy of nutritional supplements by an adequate combination of substances of biotechnological and natural origin.

The principal effect of probiotics is characterized by stabilization of the gut microflora. The clinical benefit of probiotics was shown when treating conditions in which the gut microbiology is disturbed by changes in the environment (traveller's diarrhoea) or by adding antimicrobial therapy (antibiotic-associated diarrhoea). The best documented clinical application of probiotics is in the treatment of the acute diarrhoea caused by rotavirus infection especially in infants. The beneficial role of probiotics in secondary lactose intolerance in adults is also well known (Vanderhoof and Young, 2001; Vanderhoof et al, 1999; Cremonini et al, 2002; Guandalini et al, 2000).

The ingestion of probiotic bacteria can potentially stabilize the immunologic barrier in the gut mucosa by reducing the generation of local proinflammatory cytokines, which can be observed in inflammatory bowel diseases, food allergy and atopic eczema (Vanderhoof and Young, 2001; Kalliomäki et al, 2001; Kirjavainen et al, 1999; Sartor, 1997).

Functional dairy products may be used not only to enhance a certain physiological function, but also to reduce the risk of disease. These food products have a significant role in reducing the risk of chronic civilization diseases, e.g. cancer, cardiovascular diseases, osteoporosis and osteopenia, glucose intolerance and diabetes mellitus.

## Cancer

Colorectal cancer is the fourth most common cause of cancer-related mortality in the world. Epidemiological evidence suggests a negative correlation between the incidence of certain cancers, including colon cancer, and the intake of fermented dairy products. The mechanisms by which lactic acid bacteria may have an effect on colon carcinogenesis is unknown. Some of the possible mechanisms include an enhancement of the host's gut immune response, suppression of harmful intestinal bacteria, reduction of pH concentration in the colon, reduction of faecal enzymes converting procarcinogens to carcinogens, production of antimutagenic compounds or sequestration of potential mutagens. Indigestible dietary residues and endogenous materials form the pool of substrates metabolizable by the enzymatic bacterial activity in the large intestine. The production of bacterial enzymes with toxicological importance such as  $\beta$ -glucuronidase, nitroreductase and azoreductase could be influenced by feeding with different kinds of nondigestible compounds. Bacterial  $\beta$ -glucuronidase in the colon is able to release carcinogens from hepatically derived glucuronic acid.  $\beta$ -glucosidase releases aglycones, many of which are mutagenic, although some exert an anticarcinogenic activity. Azo- and nitroreductase reduce their substrates to amines, which are usually more toxic than the parent compound, and nitrate reductase generates the highly reactive and toxic anion nitrite.

Probiotics may stimulate both the non-specific and specific immune systems, e.g. by increasing IgA secretion or induction of various cytokines. They may also enhance the post-immune response.

Probiotics may alter the metabolism of intestinal flora, and may produce antitumour factors. There have been studies on several lactic acid bacteria of the human colon, especially *Bifidobacterium longum*, showing that this organism may reduce tumour ornithine decarboxylase activity and have a strong antitumour activity (Wollowski et al, 1999). Elevated activity of several bacterial faecal enzymes, some of which are involved in the metabolism of genotoxic nitrates, is associated with an increased risk of colon cancer. Activity of these enzymes can be altered by diet or antibiotic intake. *Lactobacillus acidophilus* and *Lactobacillus gasseri* were shown to reduce the activity of the faecal enzymes nitroreductase, azoreductase and  $\beta$ -glucuronidase in humans, with a reduction by 50 % or 75 % during a period of *Lactobacilli* feeding.

Wollowski et al (2001) studied the protective effect of several strains of lactic acid bacteria against 1,2-dimethylhydrazine (DMH)-induced colon carcinogenesis in rats. Oral treatment with *Lactobacillus bulgaricus* protected against DMH-induced DNA damage in the colon. It is speculated that products of the proteolytic activity of *Lactobacillus* may have produced the effect.

Not only probiotics but also prebiotics may have potential health implications against cancer. Experimental data showed that the incidence of the so-called aberrant crypt foci induced by colon carcinogens such as azoxymethane and dimethylhydrazine was reduced significantly in rats fed by inulin-type fructans.

A synbiotic approach combining inulin and bifidobacteria was shown to be more effective than either the probiotic or the prebiotic alone (Femia et al, 2002). It may be caused by the possible anticarcinogenic activity of butyrate. Butyrate, along with other short-chain fatty acids, is produced by bacterial fermentation of the various oligosaccharides in the colon (Hijová and Chmelárová, 2007).

Singh et al (1997) showed that butyrate can act as a growth stimulator or apoptosis inducer in human colonic epithelial cell lines depending on the presence of alternative energy sources. In vivo, butyrate is a major source for the colonic epithelium and is thought to stimulate proliferation. In contrast, in vitro butyrate has been shown to inhibit proliferation and induce differentiation and apoptosis in colonic epithelial cells. Most colon cell cultures are grown in medium containing high concentration of glucose, whereas in vivo, the main energy source used by the colon cells is butyrate. The sensitivity of two human colorectal tumour cell lines, one adenoma (S/FG/C2) and one carcinoma (HT29) to butyrate-induced growth inhibition and apoptosis was studied to determine whether these cellular effects were altered under glucose depleted culture conditions. Glucose depletion resulted in an increased apoptosis in both cell lines in the absence of butyrate. Butyrate in the standard culture conditions inhibited growth and induced apoptosis in both cell lines. The results showed that in glucose depleted culture conditions, butyrate at low concentrations was found to be a growth stimulator whereas in the presence of glucose, these same concentrations of butyrate induced apoptosis. Thus, whether butyrate is a growth stimulator or growth inhibitor may depend on the availability of other energy sources. These observations may, in part, provide an explanation for the apparent opposite effects of butyrate on proliferation reported in vivo and in vitro. Some studies confirmed that butyrate may induce growth arrest and cell differentiation and may also upregulate apoptosis (Bolognani et al, 2001; Rowland et al, 1998).

The prebiotic oligosaccharides may also aid in increasing concentrations of calcium and magnesium in the colon. Elevated concentrations of these cations may help to control the rate of cell turnover and to control the formations of insoluble bile salts of fatty acids, which might reduce the potential damaging effects of bile or fatty acids on colonocytes (Wollowski et al, 2001; Greger, 1999).

In human medicine, colorectal cancer represents the most serious health, economic, and social problem. Many factors have been found to be associated with colorectal cancer, such as polluted environment, life style (low levels of physical activity, smoking, alcohol consumption, low intake of fruits and vegetables and high meat consumption). The concept of colonic health has become a target for the development of functional foods and other dietary components that target the colon and affects its environment, composition of the microflora, as well as the physiology of the colon, and display distinct health benefit. Regular intake of food containing pro- and prebiotics as an everyday part of the diet is safe and can be recommended for healthy humans, but many clinical studies are needed to confirm this. Future research

should be aimed at the enhancement of the effectiveness of cancer diseases prevention using nutritional supplements. It will be important to find the way to improve the efficacy of nutritional supplements by an adequate combination of substances of biotechnological and natural origin.

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