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Obesity, type 2 diabetes and hormone replacement therapy vs. colorectal tumors in the elderly

Małgorzata Szamocka, Monika Ameryk, Agnieszka Meder, Alina Sokup, Maciej Świątkowski

Department of Gastroenterology and Nutrition Disorders, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland

Corresponding author:
Monika Ameryk, Department of Gastroenterology and Nutrition Disorders, the Jan Biziel University Hospital no. 2, ul. K. Ujejskiego 75, 85-168 Bydgoszcz, Poland; tel. +48 52 371 49 12; e-mail: monika.ameryk@gmail.com

Summary

Aims. A prophylaxis program for the early detection of colorectal cancer carried out by our department since the year 2000 has been extended to include people aged 65 and older. The subjects were asked additional questions regarding their dietary habits and possible coexistence of type 2 diabetes, and women were asked about the use of hormone replacement therapy. A physical examination, including measurements of nutritional status, was conducted. The aim of the study was to assess the effect of overweight, obesity, type 2 diabetes and hormone replacement therapy on the incidence of cancers and adenomas detected by colonoscopy screening in people aged 65 and older.

Methods. The study method was standard colonoscopy screening conducted in people aged 65 and older, in whom no clinical signs suggesting the presence of colorectal cancer were

observed. The subjects examined provided their answers to a number of questions related to coexisting conditions and medicines taken, and women were asked about their use of hormone replacement therapy in the past. Every subject underwent a thorough physical examination that included basic anthropometric measurements.

Results. Subjects with obesity, type 2 diabetes, and women who had used hormone replacement therapy had a greater risk of developing colorectal cancer.

Conclusions. The increased risk of colorectal cancer in people with obesity and type 2 diabetes, as well as women undergoing hormone replacement therapy, may be associated with insulin-like growth factor 1 (IGF-1). This polypeptide shows a similarity to insulin, is an active compound in the process of carcinogenesis and plays a role in the regulation of cell growth, proliferation, differentiation and apoptosis. Elucidating the molecular mechanism of action of IGF-1 is important for identifying the causes of tumorigenesis and can also be of significance for the future development of effective methods of treating malignancies.

Keywords: colorectal cancer, colonoscopy screening, obesity, type 2 diabetes, hormone replacement therapy, insulin-like growth factor (IGF-1)

Introduction

Colorectal cancer (CRC) is the world's third most common malignancy in men (600,000 people, 10%) and second most common malignancy in women (570,000, 9%) (1). It is assumed that 95% of CRC cases develop from adenomas. From the clinical point of view, the most significant colorectal adenomas are 'advanced adenomas', characterized by a high risk of developing CRC. A tumor can be referred to as an 'advanced adenoma' when it is an adenomatous polyp with one of the following characteristics: it is > 1 cm in size, has a villous component (villous and tubulovillous adenomas), exhibits a high degree of dysplasia or has a cancerous texture (2). Carcinogenesis is a continuous process that can be divided into three basic stages: initiation, promotion and progression. In the case of CRC, this process can take up to 10–20 years.

According to current knowledge, a protective effect against CRC is exerted by, for example, calcium, selenium, vitamins C, D and E, folates, polyunsaturated fatty acids, carotenoids, polyphenols, saponins, curcumin, sulfur compounds present in garlic, vegetable fibers, acetylsalicylic acid, sulindac, statins, bisphosphonates, hormone replacement therapy (HRT) in women, probiotics, prebiotics, and physical activity. The incidence of malignancies, including CRC, is increased by heterocyclic amines and polycyclic aromatic hydrocarbons, nitrates, nitrites, nitrosamines, nitrosamides, ethyl alcohol, tobacco smoking, overweight and obesity, type 2 diabetes and a low level of physical activity (3). Studies clearly confirm the correlation between excessive body weight (body mass index [BMI] > 25 kg/m^2) and higher morbidity and mortality of malignancies. BMI has a particularly strong effect on the incidence of CRC (4). There is also robust evidence regarding the role of the metabolic activity of adipose tissue, especially in the case of abdominal obesity, in hormone metabolism and the production of cytokines (5). A key phenomenon in these disorders is insulin resistance. Two factors associated with obesity, i.e. a high supply of energy and low physical activity, contribute to this phenomenon. Different mechanisms, including postprandial hyperinsulinemia, lead to an increase in the concentration of the biologically active insulin-like growth factor (IGF-1), which stimulates tumor development, intensifies their proliferation and metabolism, and inhibits the apoptosis of various cell types. This results in the generation of abnormal cells that are not eliminated from the body. Thus, insulin and IGF-1 increase the risk of CRC in the early stages of carcinogenesis. Hyperinsulinemia can also result from an excessive stimulation of pancreatic β cells in people consuming high quantities of red and fried meat, saturated fats and sweets (6, 7, 8). In the case of an increase in BMI from 23 to 30, the risk of developing CRC increases linearly. Compared to people with a BMI < 23, people with a BMI > 30 have this risk increased by 50% to 100%. This correlation is higher in men than in women. Obesity is also related to higher mortality due to CRC (9). A diet rich in animal fats and red meat, and poor in vegetables, fruit, calcium and selenium, adversely affects the bacterial flora of the gut, inducing the synthesis of precursors of carcinogenic compounds and extending the passage of food through the large intestine. The mechanism by which a diet rich in red and processed meat exerts its adverse effect is not yet clearly understood. However, most data indicate that the thermal processing of meat causes the release of polycyclic aromatic hydrocarbons, heterocyclic amines and nitrosamines, whose mutagenic action has been well documented (10).

Epidemiological studies indicate a protective effect of female sex hormones on the incidence of CRC (11). Studies in women have been conducted to answer the question of whether HRT after menopause reduces the risk of CRC. The observational data obtained show such an effect of estrogens in respect to CRC (12). One of the benefits of postmenopausal use of HRT is a significant reduction in the incidence of adenomas and the development of CRC in women. Researchers are not unanimous whether the use of estrogens with progesterone or estrogens alone is the optimal treatment in this respect (13). Although the positive effects of preventive postmenopausal hormone therapy have been confirmed in many studies, there are also observations that do not show such benefits. Moreover, the results of other observations indicate caution in recommending HRT in the prevention of CRC, e.g. due to the increased risk of developing breast cancer and cardiovascular diseases (14).

Aims of the study

The aim of the study was to assess the effect of obesity, type 2 diabetes and hormone replacement therapy on the incidence of colorectal adenomas and cancers during colonoscopy screening conducted in people aged 65 and older.

Material and methods

The study included 106 people aged > 65 years with a good health status who reported for gastroenterological consultation in 2010–2013 due to dyspeptic and intestinal ailments but without 'alarming' clinical signs suggesting the presence of CRC. The exclusion criteria were: a colonoscopy performed in the last 10 years and coexisting serious cardiovascular, respiratory, gastrointestinal, urinary, endocrine, nervous and locomotor system diseases and purpura. Along with undertaking a physical examination, each patient answered detailed questions regarding family history of CRC in the first degree of kinship, cigarette smoking currently and in the past, alcohol consumption, the use of acetylsalicylic acid, insulin, HRT or other medicines, as well as nutrition and the quality of food consumed. Anthropometric measurements, including body height and weight, were conducted along with laboratory tests, including those confirming previously diagnosed type 2 diabetes. The control group consisted of 100 randomly selected people aged 50–65 years, who reported to our center in 2010–2013 for colonoscopy screening performed under the state-funded prophylaxis program for the

early detection of colorectal cancer (15). The study method was standard colonoscopy screening conducted in people aged 65 and older. The study procedure started by providing the subjects with written information about the study and obtaining their consent for colonoscopy and the endoscopic removal of polyps encountered in the colon and rectum. Bowel cleansing before the examination was conducted using an isotonic solution of polyethylene glycol (PEG). During the examination, analgesics and sedatives were administered intravenously to the subjects to reduce potential pain. The examination was performed by the endoscopy team: an endoscopy nurse and a highly qualified gastroenterologist, with qualifications certified by the appropriate colonoscopy screening quality indices. During colonoscopy, biopsies of lesions found in the colon and rectum were taken and polyps were removed to be further assessed by an experienced pathomorphologist. After the examination, and once the medications had worn off, the patient received a detailed study report and information about further medical care, including the need to return after 14 days to collect the results of the histopathological examination of the excised polyp(s), to establish any further steps and, if needed, follow-up after polypectomy. Non-parametric statistical methods appropriate for two or more groups were used in the study. These methods include the Mann–Whitney U test for the comparison of two groups of variables and the Kruskal–Wallis analysis of variance for more than two compared groups of variables. In order to investigate the influence of some of the variables on others, non-parametric Spearman's rank correlation coefficient was used.

Results

The study group consisted of 74 women (69.8%) and 32 men (30.2%). Most of the subjects (57, 54.3%) were aged 66–70 years; 39 subjects (32.6%) were aged 71–75 years and the remaining subjects (10) were aged > 75 years. Half the subjects in the study group (53, 50%) were overweight. Obesity of the first degree was found in 17 subjects (16%), obesity of the second degree was found in one subject (0.94%), normal body weight was found in 27 subjects (25.5%), and underweight was found in two subjects (1.9%). BMI measurements were not conducted in six subjects. The control group consisted of 57 women (57%) and 43 men (43%). Thirty-six control subjects (36%) were aged 56–60 years; 35 subjects (35%) were aged 61–65 years; 27 subjects (27%) were aged 51–55 years; and the remaining subjects (2, 2%) were aged 40–50 years. Most subjects in the control group (60, 60%) were overweight. First-degree obesity and normal body weight (BMI 20–25) were each found to apply to 20 subjects (20%).

Figures 1 and 2 present the type and quantity of abnormalities observed in the histopathological examination of excised polyps and biopsies of lesions in the colon and rectum for the study and control groups, respectively. In the study group of 106 subjects aged > 65 years, six cancers and an additional eight "advanced adenomas" were detected, while in the control group of 100 subjects aged 40 to 65 years, one cancer and one "advanced adenoma" were found. The detection of adenomas in 42 out of the 100 subjects in the control group indicates that the quality of the colonoscopy screening performed was high.

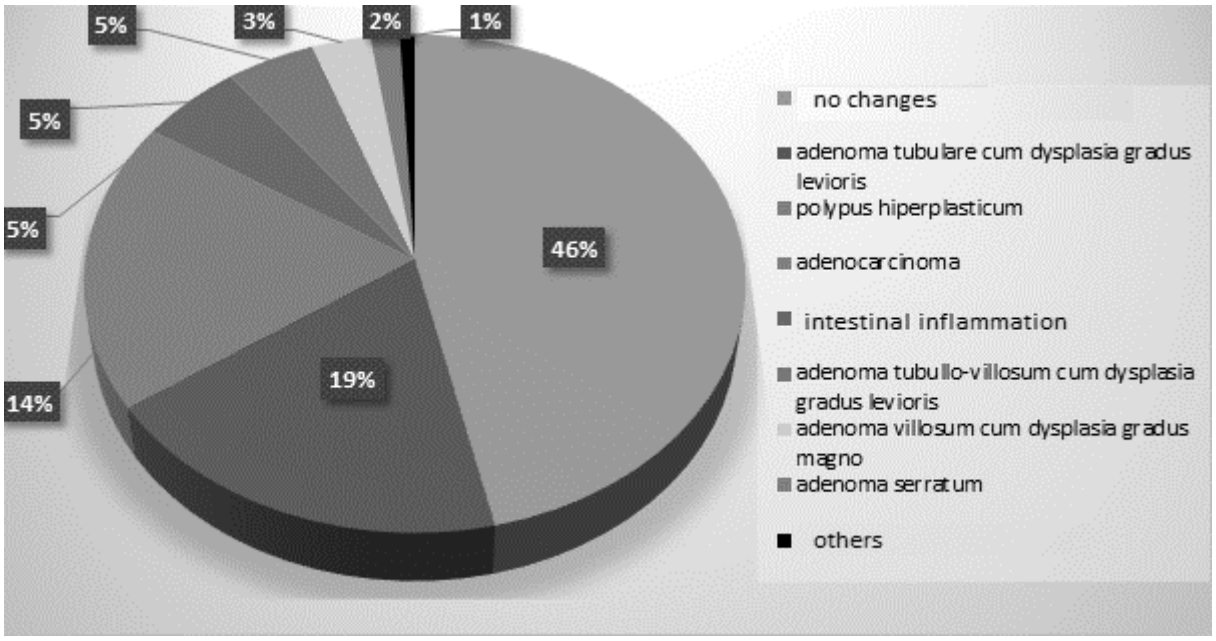

Figure 1. Study group: type and quantity of histopathological lesions detected in the colon and rectum

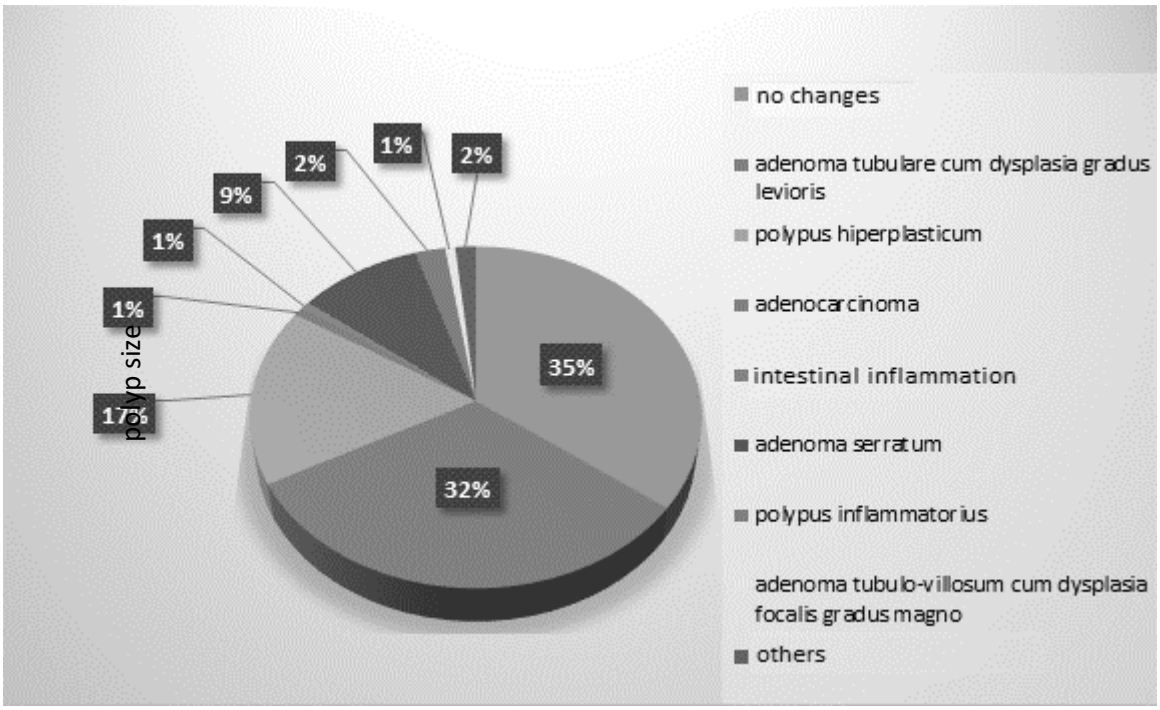

Figure 2. Control group: type and quantity of histopathological lesions detected in the colon and rectum

Type 2 diabetes

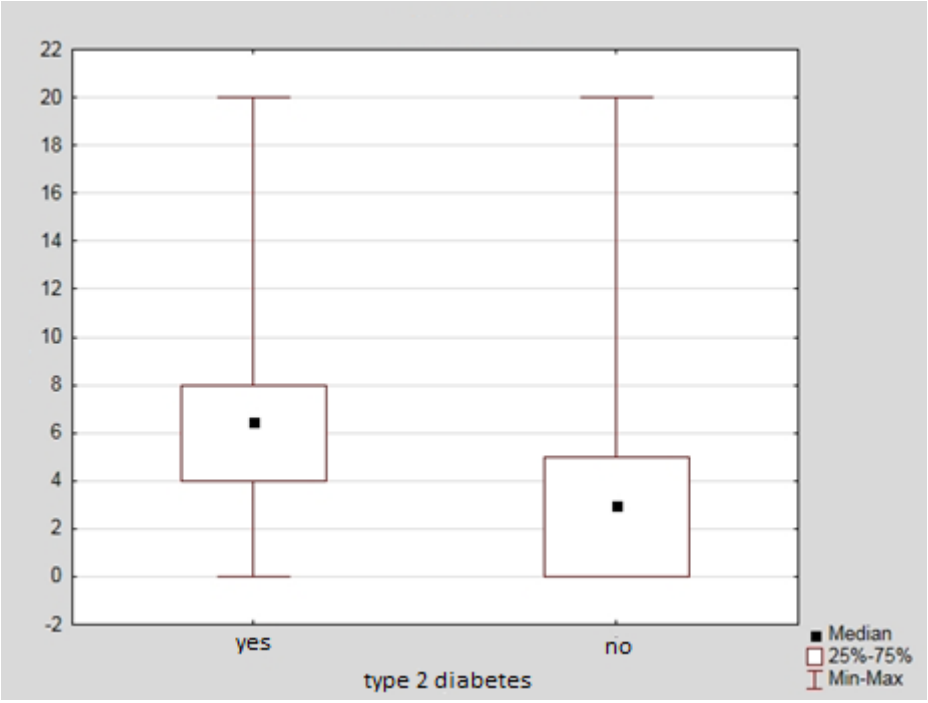

Figure 3. Type 2 diabetes and polyp size in the control group

In the control group, larger polyps were detected more frequently in subjects with type 2 diabetes than in subjects not suffering from diabetes. The average difference in the size of detected polyps was 4 mm (Figure 3).

Obesity

Table 1. Mann–Whitney U test for obesity and colonoscopy-related variables in the study group

	No obesity	Obesity	U	Z	p	Inv. Z	P
Cancers	1346.0	3505.0	804.0	0.880	0.379	1.973	0.048
Polyps > 10 mm	1462.5	4102.5	862.5	1.031	0.303	2.027	0.043
Polyps 5–10 mm	1430.5	3420.5	719.50	1.569	0.1167	2.231	0.0257

As shown in Table 1, the results of the Mann–Whitney U test indicate that people with obesity are more often at risk of developing CRC and polyps > 10 mm and 5–10 mm.

Hormone replacement therapy and presence of lesions in the colon and rectum

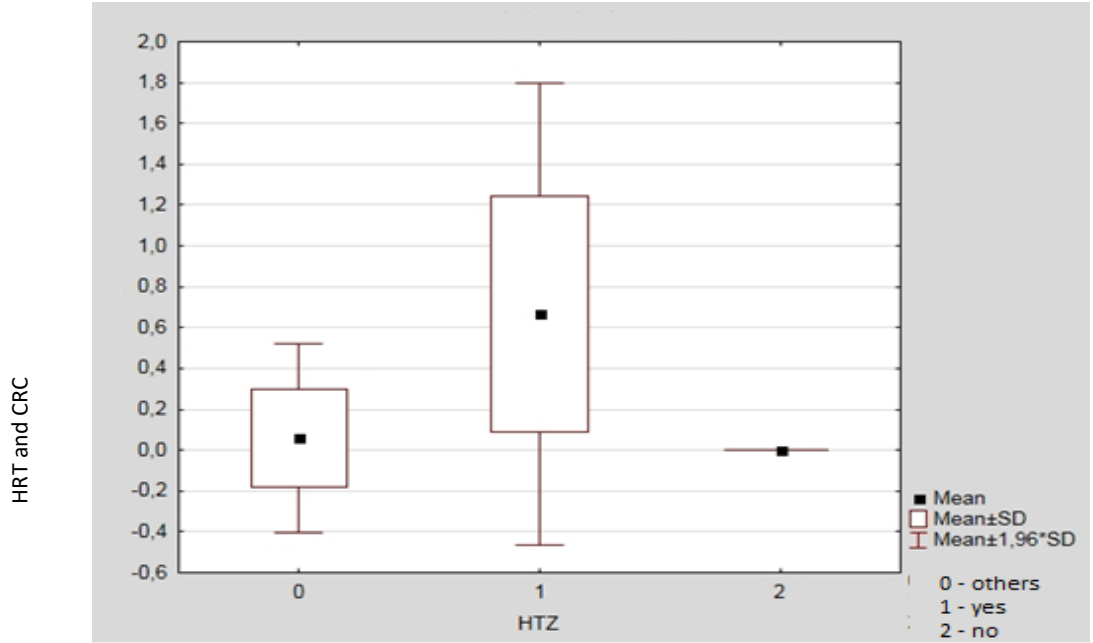

Figure 4. HRT and CRC detected by colonoscopy in the study group

As can be seen in Figure 4, CRC is more frequently detected in women using hormone replacement therapy than in women not using HRT.

Discussion

Obesity and overweight have, due to their rapidly increasing epidemiological indicators, become a major public health concern in developed countries. In most countries in the world, the number of adults having the problem of obesity increased by 40–50% between the mid-1990s and mid-2010s. Currently, more than half the global population is overweight or obese, and prognostic data developed in the UK as part of the government "Foresight" program suggest that, by 2050, 60% of all men, 50% of women and approximately 25% of all children under the age of 16 will be obese (16). This has significant implications for health, since excessive fat accumulation results in an increased risk of diabetes, ischemic heart disease and certain types of malignancies. Studies carried out among the US population have shown that in people aged 51–70 years with a BMI above 30 kg/m^2, the risk of death from any cause increases by 170%. In European studies, it has been shown that nearly 8% of all deaths are associated with obesity, 20% of which have a malignancy-related background, while 70% have a cardiovascular background (17, 18). Observational cohort studies have shown that CRC occurs more frequently in people with metabolic disorders, such as obesity or type 2 diabetes, accompanied by a high-calorie diet and sedentary lifestyle (19). A meta-analysis including 56 research projects conducted among more than 7 million people and covering 93,812 CRC cases has shown that the occurrence of CRC and advanced adenomas in both men and women increases directly proportionally to the degree of obesity expressed as BMI (20). Another meta-analysis of prospective studies has shown that the risk of developing CRC increases by 33% in men and 16% in women for every 10 cm of increment in waist circumference (21). In our study group, which included 106 subjects aged 65 or older, the risk of developing CRC and polyps > 10 mm was higher in a statistically significant manner in patients with obesity compared to those who were not obese. Among the mechanisms that contribute to the higher risk of developing colorectal cancer in patients with obesity are: hyperinsulinemia, increase in the concentration of bioactive IGF-1, decrease in the level of IGF-1-binding protein, increase in the concentration of C-peptide in blood serum, low level of adiponectin, and higher consumption of red and processed meat and saturated fatty acids, iron and heterocyclic amines (22). The increased incidence of CRC among people with type 2 diabetes can be partly associated with the gradual reduction in insulin sensitivity and the consequent chronic hyperinsulinemia to counteract insulin resistance in these patients.

Hyperinsulinemia has been found to be strongly correlated with increased body weight, especially with abdominal adipose tissue (23). Our results showed that, in the control group, subjects with type 2 diabetes had an average polyp size a few millimeters greater than that in subjects without diabetes. Insulin promotes the carcinogenesis of CRC by, for example, 'cross-talk' with IGF-1 and the insulin-like receptor, leading to the stimulation of the proliferation and increased survival of colorectal epithelial cells, dysplastic cells and CRC cells. The study showed that type 2 diabetes is associated with a moderate increase in the risk of developing colorectal cancer. However, among patients with diabetes, this risk was increased in those who also had obesity and in whom both conditions had been coexisting for at least four years. Obesity is considered to be the main cause of insulin resistance and is strongly correlated with hyperinsulinemia (24, 25). Therefore, in accordance with current knowledge, medical procedures aimed at reducing the risk of CRC in type 2 diabetes patients should be focused on the treatment of obesity (26, 27).

HRT was introduced 70 years ago, mainly as monotherapy using estrogens. An increase in the incidence of uterine cancer was observed in women using HRT in this form. The introduction of HRT based on tablets containing estrogen and progesterone in 1995 not only enabled its safe use by women with a preserved uterus, but also apparently reduced the risk of CRC (28). Since that time, clinical follow-up studies, cohort studies and numerous meta-analyses have demonstrated the protective effect of HRT against CRC. Depending on the HRT product used, the age of the woman at the start of treatment and the duration of the treatment, the reduction in the incidence of CRC is between 15% and 46% (29, 30). There are also, however, results from certain studies in which no significant difference in the incidence of CRC was found in women receiving estrogens compared to those receiving a placebo (31). In other observational studies, a statistically insignificant increase has been found in the risk of developing CRC by patients using estrogen-based HRT (32). Our results indicate that among women aged 65 and older who had used HRT in the past, colorectal cancers were detected more frequently than in women who had not used hormone therapy. Concurrently, the use of HRT reduced the incidence of colorectal diverticula in the group of women studied. In younger subjects in the control group who had not used HRT, abnormalities were detected within the sigmoid and cecum, while in patients who had used HRT, abnormalities were detected in the entire colon, and particularly within the rectum. Reduction of the risk of developing CRC in women using HRT may be due to the reduced production of bile acids by exogenous estrogens and progestogens (33). Epidemiological studies suggest a relationship between colorectal cancer and the concentration of IGF-1 in blood serum and the level of

IGF-3-binding protein. The use of HRT reduces both IGF-1 and IGF-3 in the blood plasma of women. Moreover, studies have indicated the protective action against CRC exerted by estrogen receptors, whose presence has been detected in colorectal epithelial cells (34).

Conclusions

Balanced nutrition in terms of energy supply and individual nutrients, as well as physical activity, are not only the foundations of a healthy lifestyle and health promotion, but also a means to reduce the morbidity of chronic non-infectious diseases, such as colorectal carcinoma, one of the most common malignancies in people from developed countries. The increased risk of colorectal cancer in people with obesity and type 2 diabetes, as well as the protective effect of hormone replacement therapy against this malignancy in women, may be associated with IGF-1. This polypeptide, showing similarity to insulin, is an active compound in the process of carcinogenesis and plays a role in the regulation of cell growth, proliferation, differentiation and apoptosis. Elucidating the molecular mechanism of action of IGF-1 is important for identifying the causes of tumorigenesis and can also be of significance for the future development of effective methods of treating malignancies.

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