DIET, OBESITY AND COLORECTAL CANCER - CURRENT ACKNOWLEDGED FACTS

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The prevalence of colorectal cancer is increasing worldwide mostly due to a series of risk factors associated with Western life style. Among those modifiable risk factors obesity plays a crucial role and may be responsible for a 33% increase of colorectal cancer risk. A 5 kg weight gain augments the risk by 3%, the relevance being higher in men than in women. The frequently cited mechanisms involved are related to: insulin, insulin growth factor 1, adiponectin, leptin, chronic inflammation. Gut microbiota as well as tissue microbiota may play a role, the details of which are subject to current research studies. A diet being hypercaloric, rich in animal fat, rich in red meat, poor in vegetal fibers inconsistently have been associated with colorectal cancer; a large pool of data is revealed by EPIC study. A better acknowledgement of those modifiable risk factors may be the starting point for measures to effectively reduce the prevalence of colorectal cancer.

Key words: colorectal cancer, obesity, western diet

INTRODUCTION

The prevalence of cancer worldwide is increasing despite the overwhelming evidence that a main proportion of cases may be preventable. In 2008 there were almost 12.7million people worldwide suffering from any type of cancer and 7.6million people were dying of this ailment. The recognized modifiable risk factors, mainly related to lifestyle and environmental exposure, may serve as a pillar for effective prevention strategies. It is estimated that 50% of cancer cases is highly preventable. Nine modifiable risk factors were indicated to cause 35% of all cancer globally: excess weight, inactivity, smoking, alcohol use, low vegetable diets, unsafe sex, air pollution, use of solid fuels, contaminated injections in hospital care. There are also studies to show that if you never smoked, BMI is less than 30, physical activity exceeds 3 hours per week and your diet is prudent than the risk of cancer is decreased by a third. All those data may indicate a huge armamentarium reserve for prevention strategies.

Lifestyle issues as risk factor is also implicated and extensively studied in heart disease, diabetes and stroke. The term is very complex as it implies behavioral patterns, constant environmental exposures and diet habits. Among these an unhealthy diet (commonly known as western type diet) seems to have the utmost importance as risk factor. The main features of this diet are: hyper caloric, rich in animal fats, rich in red meat, low vegetable fibers.

Colorectal cancer (CRC) has an increasing prevalence all over the world. It is the second leading cause of cancer death in USA and in Western Europe. It is a third cause of cancer in men and a second cause of cancer in women. Every year there are diagnosed 1,2million new cases in the world. The highest incidence is encountered in Australia (75/100000), New Zeeland, North America and Europe. In Romania the incidence has doubled from 1994 (13/100000) to 2005 (23/100000). The lifetime risk of CRC is 5%. 90% of cases appear after the age of 50; beneath this age threshold is rare encountered but the current trend indicates an increasing prevalence in young. Among the risk factors most frequently cited obesity has been estimated to be the cause of 20% of cases.

The worldwide prevalence of obesity has doubled from 1980 to 2008. 10% of men and 14% of women were obese (BMI>30kg/m2) in 2008. An estimated 205 million men and 297 million women over the age of 20 were obese-almost half a billion adults worldwide. If it is taken into consideration the overweight (BMI>25kg/m2), then 35% of adults over the age of 20 were suffering from this ailment of epidemic proportions. Hypercaloric diet habits and lack of physical activity justifies this data but a large pool of evidence favors the idea that alteration of gut microbiota may be responsible for increasing prevalence of obesity worldwide.

Studies of CRC risk factors
20% of CRC suffering patients have a genetic factor accountable for the disease, in spite of the fact that only 2% of CRC is related to a defined genetic disease that may trigger cancer (familial adenomatous polyposis syndrome, .

Lynch syndrome, Peutz Jegers syndrome). 80% of CRC suffering patients have a sporadic form of cancer triggered by modifiable risk factors\textsuperscript{10}. Among those factors, western diet and obesity play a major role.

Dietary fats have been extensively studied as a possible explanation of high variation in prevalence of cancer in the world. There have been not clear conclusions about a link between dietary fats and colon or breast cancer; the data are more convincing for prostate cancer\textsuperscript{11}. Epidemiologic studies that have been controlled for caloric intake, didn’t conclude that there is a close association between total fat intake and CRC. The prospective Women’s Health Initiative Dietary Modification Trial included 48835 women that have been randomly assigned to dietary intervention in order to decrease the quantity of fats in their daily meal as compared to a usual diet control group. The targeted group, compared to control, reduced the percentage of calories consumed as fat (by 10.7% in year one, 8% in year six). The conclusion: there was no difference in incidence of CRC at the end of 8 years of follow up\textsuperscript{12}.

While total fat does not appear to impact CRC risk the question that remains is whether particular types of fat (saturated, unsaturated) affect risk differently. It is utterly acknowledged that red meat is associated with increased risk of CRC. In one large population study that included 617,119 individuals, high red meat intake has been associated with cancer-specific mortality while comparing highest and lowest quintiles of consumption (HR 1.2, 95% CI 1.1-1.3)\textsuperscript{13}. Current evidence supports the idea that there is a 15% to 20% increased risk of CRC per 100g of red meat consumed per day\textsuperscript{14}. The mechanisms involved may include: hem content in the red meat, animal fat and carcinogens produced by cooking at high temperature. A cohort study of almost 500,000 individuals (EPIC) followed for nine years found only a weak association between increasing fruits and vegetables intake and decreasing the overall risk of CRC (HR 0.97, 95% CI 0.96-0.99)\textsuperscript{15}. A pooled analysis of 14 cohort studies (including EPIC) that gathered more than 750,000 subjects, concluded that the daily consumption of more than 800g of fruits and vegetables comparing to less than 200g may decrease the risk of CRC (RR 0.74) at proximal colonic location but not for distal location\textsuperscript{16}. A meta-analysis of 19 cohort studies showed an even weaker protective effect of fruit and vegetables intake\textsuperscript{17}.

Fiber intake is a subject of great interest in preventive medicine. It is associated with reduction of heart disease and diabetes risk; there is a significant pool of evidence that fiber intake may decrease the risk of CRC. A large European study on 519,978 patients concluded that there is an inverse relationship between dietary fiber intake and CRC incidence (RR 0.58, 95% CI 0.41-0.85)\textsuperscript{18}. A meta-analysis of 16 studies found that the decreased risk was associated with fiber intake of cereal origin but not of fruit and vegetable origin\textsuperscript{19}. There are studies that do not concur with the above mentioned conclusions. A pooled analysis of 13 prospective cohort studies (725,628 subjects followed 20 years) found that decrease of risk of CRC is not significant after accounting for other dietary factors\textsuperscript{20}.

Dietary supplementation with omega 3 fatty acids does not seem to be effective to decrease CRC incidence but fish consumption does. There are an inverse relationship between fish intake and CRC risk (OR 0.96, 95% CI 0.81-1.14)\textsuperscript{21}.

Dietary patterns, instead of component of diet in isolation, may offer a closer answer to the question of how nutrition interventions are able to influence the risk of CRC. An expanding body of evidence favor the Mediterranean diet as a protective factor. In a larger analysis of EPIC cohort, a greater adherence to this type of diet resulted in a decreased risk of cancer\textsuperscript{22}. A large cohort study in Europe also found a decreased risk of CRC in association with the Mediterranean diet\textsuperscript{23}. Conversely, a Western diet was associated with a 30% increase of CRC.

Difficulties of studies of lifestyle and diet impact as risk factors

Inconsistencies in results of nutritional studies related to alleged role of diet as a risk factor for CRC are frequently encountered and may be attributable to a complex of multiple factors. Observational studies are subject to error due to imprecision of diet recall and to the presence of confounding risk factors that occur unequally in target population. Randomized controlled trials may yield flawed results because of insufficient follow up time, poor adherence to studied diet, wrong dose or form of the nutrient. Inaccurate results may also be due to the tendency to study a certain risk nutrient in isolation from the general diet, when whole foods or the full composition of a diet may correlate better with cancer risk than any single component.

Obesity and cancer

Obesity and overweight are definitely associated with the increasing prevalence of several cancers such as: breast in menopausal women, colon and rectum, endometrium, kidney, adenocarcinoma of the esophagus and pancreas, liver, gallbladder, cervix, ovary, non-Hodgkin lymphoma, prostate\textsuperscript{24}. Obesity is an important risk factor for CRC, with a 33% increased risk of CRC for obese individuals compared with normal weight individuals\textsuperscript{25}. A 5kg weight gain increases 3% the risk of CRC, the association being slightly stronger for men than for women\textsuperscript{26}. The distribution of fat tissue plays a crucial role. Abdominal fatness, as opposed to distribution of the fat on hips and thighs, increases by 50% the risk of CRC in the highest category of waist circumference\textsuperscript{26}. A current
explanation of this phenomenon is not available. In addition to current obesity, there is pertinent proof that adult weight gain is associated with increasing the CRC risk. Weight gain from early adulthood to midlife is more risky than weight gain from midlife to older age. There is a 16% increased risk of CRC with the highest category of weight gain compared to the reference category. It’s interesting to notice that the association between physical activity and decreasing the risk of CRC has been demonstrated across levels of obesity, raising the suggestion that this protective effect is independent of the impact on body weight. The optimal duration and intensity of physical activity to achieve cancer protection is unknown. A meta-analysis of 21 studies indicated that the risk of CRC is reduced by 27%, comparing the sedentary and the most physically active subjects. Physical activity reduces, also, by 15% the risk of colonic polyps.

Mechanisms to relate obesity with CCR
The postulated mechanisms that explain the link between obesity and CRC are suggested to be: hyperinsulinemia associated with peripheral resistance to insulin, a state of chronic inflammation, an altered level of various adipokines. Among those adipokines, adiponectin level seems to be in inverse relation with the risk of CRC, especially its non-HMW (high molecular weight) fraction). Adiponectin is, also, in inverse relationship with body weight, insulin resistance and type II diabetes. Adiponectin inhibits cancer cell growth and induces cell apoptosis. Hyperinsulinemia goes along with increased level of IGF-1 (insulin growth factor) which is a major growth factor in adulthood and is involved in tumorigenesis. Its role in CRC in obese patients is demonstrated in an experimental study publish recently in 2015.

An intracellular molecular mechanism that connects in a common pathway obesity, physical inactivity, poor diet and CRC may be represented by 5′-adenosine monophosphate activated protein kinase (AMPK) pathways. AMPK is a cellular energy and nutrient sensor that inhibits cell proliferation. AMPK is suppressed by obesity, physical inactivity and western diet.

Some mechanisms have been proposed for the protective effect of physical activity: reduction in circulating levels of insulin and other growth factors, impact on prostaglandin levels; improved immune function.

CONCLUSIONS
The prevalence of overweight and obesity is increasing worldwide in part because of a poor diet, generally associated with western type diet, in part, as it is suggested by an expanding pool of evidence, by a certain poorly defined change in gut microbiota. The prevalence of colorectal cancer is, also, increasing probably as a direct consequence of those modifiable risk factors responsible for majority of cases. Among those modifiable risk factors obesity and poor diet play major role. In the present and in the near future all those data may serve as a rationale for health politics to develop strategies that may translate the preventability of CRC into practice of a better world.

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REFERENCES
7. Romanian Ministry of Health 2015


