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REVIEWS: CURRENT TOPICS

Obesity and colorectal cancer: epidemiology, mechanisms and candidate genes

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Abstract

There is increasing evidence that dysregulation of energy homeostasis is associated with colorectal carcinogenesis. Epidemiological data have consistently demonstrated a positive relation between increased body size and colorectal malignancy, whereas mechanistic studies have sought to uncover obesity-related carcinogenic pathways. The phenomenon of "insulin resistance" or the impaired ability to normalize plasma glucose levels has formed the core of these pathways, but other mechanisms have also been advanced. Obesity-induced insulin resistance leads to elevated levels of plasma insulin, glucose and fatty acids. Exposure of the colonocyte to heightened concentrations of insulin may induce a mitogenic effect within these cells, whereas exposure to glucose and fatty acids may induce metabolic perturbations, alterations in cell signaling pathways and oxidative stress. The importance of chronic inflammation in the pathogenesis of obesity has recently been highlighted and may represent an additional mechanism linking increased adiposity to colorectal carcinogenesis. This review provides an overview of the epidemiology of body size and colorectal neoplasia and outlines current knowledge of putative mechanisms advanced to explain this relation.

Family-based studies have shown that the propensity to become obese is heritable, but this is only manifest in conditions of excess energy intake over expenditure. Inheritance of a genetic profile that predisposes to increased body size may also be predictive of colorectal cancer. Genomewide scans, linkage studies and candidate gene investigations have highlighted more than 400 chromosomal regions that may harbor variants that predispose to increased body size. The genetics underlying the pathogenesis of obesity are likely to be complex, but variants in a range of different genes have already been associated with increased body size and insulin resistance. These include genes encoding elements of insulin signaling, adipocyte metabolism and differentiation, and regulation of energy expenditure. A number of investigators have begun to study genetic variants within these pathways in relation to colorectal neoplasia, but at present data remain limited to a handful of studies. These pathways will be discussed with particular reference to genetic polymorphisms that have been associated with obesity and insulin resistance.

Keywords: Body size; Obesity; Colorectal cancer; Insulin resistance; Genetics

1. Introduction

Obesity is a result of positive "energy balance" and prevails in conditions of energy excess. As a consequence of major economic, social and technological changes, many populations find themselves in environments characterized by abundant calorie-rich food and low physical activity requirements. As a result, obesity is rapidly approaching epidemic proportions in many parts of the world and has become a major public health concern. At present, more than 1 billion people are overweight, whereas more than 300 million people worldwide can be classified as obese [with body mass index (BMI) of 30 kg/m^2 or higher] [1]. Over the past 40 years, the prevalence of obesity in the United States has increased from around 13% to 30% [2]. Two thirds of the American population is overweight, and this trend is mirrored in most other western populations. A

Abbreviations: ATP, adenosine triphosphate; BMI, body mass index; HbA1c, glycated hemoglobin; IGF, insulin-like growth factor; IL-6, interleukin 6; SNP, single nucleotide polymorphism; TNF-α, tumor necrosis factor α; T2DM, diabetes mellitus Type 2; VNTR, variable number of tandem repeats.

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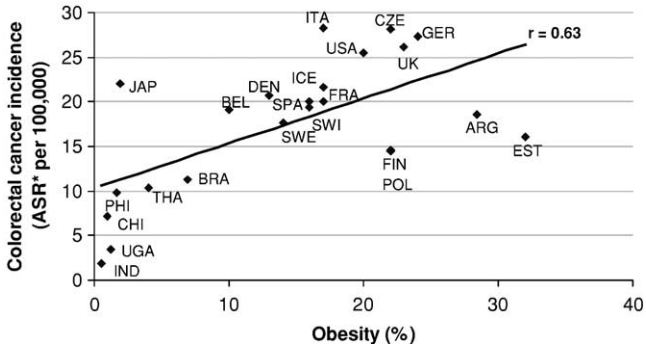

Fig. 1. A plot of age standardized colorectal cancer incidence vs. obesity prevalence (%) for 23 countries. *ASR, age standardized rates. Colorectal cancer ASR (2002) and obesity prevalence (percentage of the population with a BMI 30 kg/m^2 or more) data were obtained from IARC [4,5] .

global comparison reveals the highest obesity rates in the United States, Europe and the Middle East and the lowest in sub-Saharan Africa and East Asia [3].

Mounting epidemiological evidence suggests that obesity is associated with cancer, particularly cancer of the colorectum. Indeed, consensus panels have cited "convincing" evidence for obesity as a cause of colorectal cancer [4]. In parallel to the geographic variation seen in obesity rates worldwide, colorectal cancer incidence is highest in affluent industrialized countries such as the United States, Australia and Western Europe and lowest in India and sub-Saharan Africa [5]. In concordance with ecological data that have demonstrated rapid increases in colorectal cancer in populations with positive energy balance (Fig. 1), experimental data have indicated that energy intake contributes to colorectal cancer etiology. Data from animal models suggests that overnutrition augments colorectal carcinogenesis, whereas caloric restriction reduces colorectal tumor incidence [6,7].

In recent years, several hypotheses have emerged to explain this relationship. The notion of "insulin resistance" or the impaired ability to normalize plasma glucose levels has formed the core of these hypotheses, but other related mechanisms have also been advanced (Fig. 2). As we move forward into an era of greater understanding of the human genome, there is a strong impetus to identify susceptibility genes for body size. Family-based studies suggest that the heritability of body size is substantial: up to 80% of the variability in BMI can be accounted for by genetic factors [8]. The identification of genetic variants that confer susceptibility to obesity may not only enhance knowledge of the biology that underlies its development, but may also lead to the discovery of genes that predispose to colorectal malignancy in the general population. This review will focus on the putative mechanisms that link increased body size to colorectal cancer. In addition, the paper will provide an overview of candidate genes for obesity and colorectal neoplasia.

2. Epidemiological studies of body size and colorectal cancer

Cohort and case-control studies have consistently demonstrated a positive relation between body size and colorectal cancer. A report published in 2002 by IARC evaluated all available studies on obesity and colorectal cancer risk and found elevated risks in men and women with risks being stronger for men than women [4]. Of the eight case-control studies on BMI and colorectal cancer published to date, all reported relative risks greater than one for overweight (BMI>25 kg/m^2) or obese individuals (BMI>30 kg/m^2) compared with normal weight individuals (BMI 18.5–25 kg/m^2) apart from one study that found an inverse association between BMI and colorectal cancer risk among females [9–15] and one that reported no association [16]. Similarly, for the 10 prospective cohort investigations, all reported a positive association between BMI and colorectal cancer, with relative risks in the range of 1.2 to 3.4 [17–26]. In general, the association has proven stronger for cancer of the colon than the rectum and for the distal than the proximal colon. Body size also seems to influence early stages of colorectal carcinogenesis: BMI has been associated with colorectal adenoma and, in particular, large adenomas of the distal colorectum in seven epidemiological studies [16,27–32].

There is evidence to suggest that abdominal or visceral adiposity is a risk factor for colorectal cancer independent of BMI. Indeed, waist to hip ratio (WHR) or waist circumference appear to be superior indicators of obesity than BMI, particularly in older individuals. One recent study conducted among men reported a 2.1-fold increased risk of colon cancer for men comparing a high WHR to those with a low WHR, whereas a high BMI (>29.2 kg/m^2) conferred a 1.7-fold increased risk of colon cancer compared to a BMI<24.8 kg/m^2 [33]. Following adjustment for BMI, a large prospective study found a twofold elevated risk for colorectal cancer among men and women

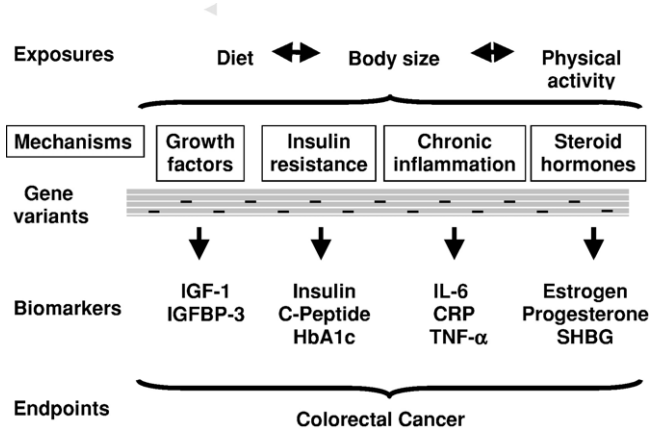

Fig. 2. Proposed mechanisms that link energy balance and colorectal cancer (HbA1c, glycated hemoglobin).