CANCER (MF LEITZMANN, SECTION EDITOR)

Influence of Obesity and Related Metabolic Alterations on Colorectal Cancer Risk

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Abstract Obesity and related metabolic alterations have been implicated to play a role in colorectal cancer risk. The metabolic syndrome, as assessed according to current international definitions by the key components, abdominal obesity, dyslipidemia, elevated blood pressure, and abnormal glucose metabolism, is associated with colorectal cancer. Recent studies suggest that abdominal obesity and abnormal glucose metabolism may primarily account for this association. Visceral adipose tissue is physiologically more active than subcutaneous adipose tissue and generates hormones and cytokines with inflammatory, metabolic, and direct carcinogenic potential, which may directly or indirectly increase colorectal cancer risk. Current evidence suggests that obesity acts as a risk factor for colorectal cancer by several mechanisms, including chronic low-grade inflammation, hyperinsulinemia, as well as alterations in insulin-like growth factor and adipokine concentrations. Metabolic biomarkers reflecting these processes may not only provide clues for etiological understanding of colorectal carcinogenesis but also might be an alternative way to define an "obesity phenotype" that is relevant for colorectal cancer development.

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Introduction

Colorectal cancer is the third most common type of cancer in men and the second most common type in women worldwide, accounting for approximately 10 % of cancer incidence in both men and women [1]. There is a pronounced gradient in incidence rates between developing and developed countries, with highest rates in Australia/New Zealand and Western Europe and lowest rates in Africa and South-Central Asia [1]. The high prevalence of obesity has been hypothesized to be among the factors responsible for the high incidence of colorectal cancer in most developed countries [2]. Obesity is associated with a number of metabolic abnormalities, such as elevated blood pressure, abnormal glucose metabolism, and dyslipidemia, which tend to cluster (referred to as metabolic syndrome) and increase the risk to develop cardiovascular disease and type 2 diabetes mellitus. Evidence accumulating during the past decade suggests that metabolic dysfunctions also may play a role for colorectal cancer risk. Given the high prevalence of obesity and colorectal cancer, a better understanding of the pathophysiology might have important preventive implications, because it may provide a more accurate and precise characterization of individuals at risk and it may point to targets for prevention. The current article reviews the influence of obesity and related metabolic alterations on

colorectal cancer risk with a particular emphasis on findings observed during the past year.

General Adiposity and Risk of Colorectal Cancer

According to the World Health Organization, obesity is "a condition of abnormal or excessive fat accumulation in adipose tissue, to the extent that health may be impaired" [3]. The globally accepted criteria for the definition of overweight and obesity in adults are based on body mass index (BMI), calculated as weight (in kilograms) divided by height (in meters) squared [4]. Based on the Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, general overweight is defined as BMI between 25 and 29.9 kg/m^2, and general obesity is defined as BMI ≥30 kg/m^2 [4]. The association between obesity as assessed by BMI and risk of colorectal cancer has been examined in a number of epidemiological studies, and several systematic reviews and meta-analyses have summarized the existing evidence. The most recent systematic review came from Ning et al., including 7,213,335 individuals from 56 populations with 93,812 colorectal cancer cases [5]. The authors found predominantly positive associations in the studies with an average relative risk (RR) for colorectal cancer of 1.18 (95 % confidence interval (CI), 1.14–1.21) per 5 unit higher BMI. The association was significantly (p=0.02) stronger for colon cancer (RR, 1.21; 95 % CI, 1.17-1.26) than for rectal cancer (RR, 1.11; 95 % CI, 1.06-1.16). This association was significantly (p=0.001) stronger in men (RR, 1.25; 95 % CI, 1.2-1.3) than in women (RR, 1.12; 95 % CI, 1.06-1.16).

Abdominal Obesity and Risk of Colorectal Cancer

Although BMI is correlated with fat mass and associated with morbidity and mortality, there are a number of limitations. An important drawback of BMI is the inability to distinguish between fat mass and lean body mass [6]. Furthermore, BMI does not take body fat distribution into account. Although fat distribution is to some extent gender-specific, with women usually having a greater amount of peripherally located subcutaneous fat and men having a greater amount of centrally located visceral fat, there also is substantial variation in sex-specific fat distribution for any given BMI. Importantly, viscerally deposited fat is metabolically more active and secretes greater amounts of cytokines and hormones compared with subcutaneous adipose tissue [7]. Furthermore, a higher influx of portal fatty acids, cytokines, and hormones into the liver from omental adipose tissue may specifically distort hepatic metabolism, including abnormal lipoprotein synthesis, hepatic

insulin resistance, and increased gluconeogenesis [8]. Body fat distribution most easily can be assessed by measurement of waist and hip circumferences. Current guidelines suggest a waist circumference of 102 cm in men and 88 cm in women, as being the cutoff points for abdominal obesity that is associated with an increased risk of morbidity [9, 10].

Assuming that it is primarily visceral adipose tissue and not nonvisceral adipose tissue that is involved in tumorigenic processes, body weight and BMI may not accurately reflect the colon cancer risk that is associated with abdominal fat accumulation, particularly in women. This hypothesis has been supported by findings from the European Prospective Investigation into Cancer and Nutrition (EPIC) that have indicated that abdominal obesity (as defined by waist circumference or waist-to-hip ratio) is an equally strong risk factor for colon cancer in men and women, whereas body weight and BMI are associated with colon cancer risk in men but not in women [11]. Thus, men and women in the highest compared with the lowest gender-specific quintile of waist-to-hip ratio had a 50 % higher risk of developing colon cancer over a mean follow-up period of 6 years. This finding has largely been confirmed in a meta-analysis by Dai and colleagues [12], reporting a pooled estimate of 1.68 (95 % CI, 1.36, 2.08) for the highest vs. lowest quintile of waist circumference in men and 1.48 (95 % CI, 1.19, 1.84) in women. The respective estimates for rectal cancer were 1.26 (95 % CI, 0.9, 1.77) for men and 1.23 (95 % CI, 0.81, 1.86) for women. Furthermore, a meta-analysis of 21 observational studies on the association between abdominal obesity and the risk of colorectal adenoma reported summary relative risks (SRRs) of colorectal adenoma to be 1.39 (95 % CI, 1.24-1.56) for the highest versus the lowest level of waist circumference [13]. Summarizing the existing research findings, in 2011 the World Cancer Research Fund judged the existing evidence on body fatness and abdominal fatness as causes of colorectal cancer as convincing [14].

Metabolic Syndrome and Risk of Colorectal Cancer

Abdominal obesity is a key component of metabolic syndrome (MetS), which is characterized by clustering of metabolic abnormalities suggested to play a role in the development of cardiovascular diseases. According to recent international criteria, components include abdominal obesity (increased waist circumference), dyslipidemia (elevated triglycerides and low high-density lipoproteins (HDL)), elevated arterial blood pressure and abnormal glucose metabolism (elevated fasting glucose levels) [9, 10, 15]. The 2009 definition harmonizing the criteria proposed by several expert panels considers the MetS being present when any three of the following conditions are given: high

waist circumference (≥94 cm in men, ≥80 cm in women, for European population), elevated triglycerides (≥150 mg/dl), reduced HDL cholesterol (<40 mg/dL in men, >50 mg/dL in women), elevated blood pressure (systolic ≥130 mmHg, diastolic ≥85 mmHg), fasting glucose level ≥100 mg/dL [15]. Recently, other abnormalities, such as chronic proinflammatory and prothrombotic states, nonalcoholic fatty liver disease, and sleep apnea, have been proposed in addition to the entity of the syndrome [16], and there are still no universally accepted diagnostic criteria. Individual components of the metabolic syndrome have been related to colorectal cancer risk. In EPIC, high HDL concentrations were significantly associated with reduced risk of colorectal cancer, whereas no significant association was observed for triglycerides [17]. Furthermore, in EPIC, a high percentage of glycosylated hemoglobin (HbA1c), a marker for elevated blood glucose levels, was statistically significantly associated with higher colorectal cancer risk [18]. Fasting blood glucose has been found to be associated with higher risk of colorectal cancer in a study published last year [19], whereas no association was observed in another recent study [20]. A number of studies suggested that MetS is associated with risk of colorectal cancer. A recent meta-analysis summarizing the existing evidence from cohort studies reported that the presence of metabolic syndrome was associated with higher risk of colorectal cancer in both men (RR, 1.25; 95 % CI, 1.19-1.32) and women (RR, 1.34; 95 % CI, 1.09-1.64), despite the use of different definitions for MetS [21]. Importantly, it was shown recently in the EPIC study that among the five components of MetS, the association of MetS with colon cancer was largely accounted for by abdominal obesity and abnormal glucose metabolism, thus highlighting the role of the excess adipose tissue and associated hyperinsulinemia and hyperglycemia for risk of colon cancer [22•].

Insulin Resistance, Hyperinsulinemia, and Elevated Insulin-Like Growth Factors

Hyperinsulinemia has been hypothesized as one of the major biological pathways to link obesity and colorectal cancer. Obesity and especially abdominal adiposity is associated with insulin resistance, a state when insulin is less effective in lowering blood glucose levels [23], resulting in elevated glucose levels (hyperglycemia), and subsequently compensatory elevated insulin levels (hyperinsulinemia). Insulin may influence colorectal carcinogenesis either directly or indirectly through the potent mitogen insulin-like growth factor 1 (IGF-1). Hyperinsulinemia enhances the bioactivity of IGF-1 by up-regulating hepatic IGF-1 synthesis, or by reducing hepatic secretion of two IGF binding proteins (IGFBP-1 and IGFBP-2), resulting in higher free or bioactive IGF-1 levels [23, 24]. The insulin and IGF responses

are mediated by insulin receptors (IR) and IGF-1 receptors (IGF1R), both of which are widely expressed in normal tissues as well as in epithelial colorectal cancer cells [25]. Binding of insulin or IGF-1 to their receptors is followed by a signal transduction cascade, which may stimulate cell proliferation and suppress apoptosis. A plausible support for the hypothesis that hyperinsulinemia may play a role in colorectal carcinogenesis comes from observational studies that found a higher risk of colorectal cancer in individuals with type 2 diabetes mellitus, which is usually associated with hyperinsulinemia, compared with individuals without diabetes. In a recent meta-analysis, comparing individuals with and without diabetes a significantly increased risk of colorectal cancer was observed (pooled RR, 1.26; 95 % CI, 1.2-1.31), which did not differ by sex or location of colorectal tumors [26]. There also is evidence that insulin therapy among diabetics is associated with higher risk of colorectal cancer [26]. Further evidence for a role of the insulin and IGF-axis in the etiology of colorectal cancer comes from the observation that patients with acromegaly, a rare disease of somatic growth accompanied by hyperinsulinemia and extraordinarily high IGF-1 concentrations are at increased risk of precancerous adenomatous polyps and colorectal cancer [27–30].

Higher circulating concentrations of insulin [31] or C-peptide (a marker of insulin secretion with a longer half-life than insulin) [32–34] were shown to be associated with a moderately increased risk of colorectal cancer in a number of epidemiological studies, whereas in two prospective studies published during the past year [19, 20] no association was observed.

The majority of prospective studies investigating circulating IGF-1 levels in relation to colorectal cancer risk showed positive albeit mostly nonsignificant associations [35•]. For example, in EPIC, which so far has the largest study investigating IGF-1 levels in relation to colorectal cancer risk, there was no significant association [35•]. A meta-analysis of 11 prospective studies, including the null-finding from EPIC, showed a moderately significantly increased risk of colorectal cancer, with a RR of 1.07 (95 % CI, 1.01-1.14) associated with one standard deviation higher IGF-1 levels [35•]. Taken together, serologic evidence from observational studies supports the hypothesis that the positive association between obesity and colorectal cancer is at least partly explained by hormonal changes related to hyperinsulinemia.

Chronic Inflammation

There is substantial evidence that inflammatory processes play an important role in colorectal carcinogenesis [36]. Thus, studies have shown that individuals with chronic

inflammatory bowel disease have a higher risk of colorectal cancer compared with individuals without such a condition [37, 38]. Furthermore, the use of aspirin and other anti-inflammatory drugs is associated with a lower risk of colorectal neoplasia [39, 40]. Obesity is associated with chronic low-grade inflammation due to the production of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6), which induce the hepatic secretion of acute phase proteins, such as C-reactive protein (CRP) [41]. It has been shown that weight loss reduces inflammatory processes not only systematically, as seen by reduced CRP-levels [42], but also locally in the colorectal mucosa [43]. Thus, inflammatory processes may account, in part, for the positive association between obesity and colorectal cancer risk.

Findings from epidemiological studies have shown positive associations between biomarkers of chronic inflammation (particularly CRP) and colorectal cancer risk. A meta-analysis from 2008 suggested that CRP concentrations are weakly positively associated with risk of colon cancer (RR, 1.13; 95 % CI, 1–1.27 per one unit increase in log CRP) and that this relationship is stronger in men than in women, whereas no association was found for rectal cancer [44]. CRP has been associated with increased colorectal cancer risk in 6 of 14 prospective studies published between 2003 and 2011 [45]. One of the more recent and so far the largest study, a prospective nested case–control study in EPIC showed significant positive associations between CRP and colon cancer risk in men and this association was independent of BMI and waist circumference, as well as of insulin resistance and dyslipidemia [46]. In the same study, the association between CRP and colon cancer in women was nonsignificant, and no association between CRP and rectal cancer in either men or women was observed. The three studies that have investigated the association between circulating CRP and risk of colorectal cancer in women only [47–49] did not observe positive associations, suggesting that inconsistency in studies published so far may be related to sex differences. Three studies that have investigated circulating IL-6 in relation to colorectal cancer risk observed no association [48, 50], and two studies on TNF-alpha and colorectal cancer risk did not observe an association [50, 51••]. In a case-cohort study within the Women's Health Initiative published during the past year, high levels of IL-6 were positively associated with risk of colorectal cancer, but the effect was likely to be mediated by insulin [51••]. To further elucidate the causal role of chronic inflammation as assessed by CRP, with colorectal cancer, a number of studies have investigated the association of CRP polymorphisms with disease risk [52]. Whereas two reports did not support such a causal hypothesis [53, 54], recent evidence suggests that certain CRP polymorphisms are associated with colorectal cancer risk [55, 56].

In conclusion, the overall evidence is supportive of obesity-related inflammatory processes as etiological factors for colon cancer, particularly in men, but more research is needed to clarify the extent to which these observations may be mediated by insulin resistance.

Alterations in Adipokine Concentrations

As stated earlier, the adipose tissue is an active endocrine organ that secretes a number of cytokines and hormones, which collectively are termed "adipokines" [57]. Among the large number of newly discovered adipokines, leptin, adiponectin, and resistin mostly have been considered to be potential mediators of the effects of obesity on cancer development [58].

Leptin

Leptin is a long-term regulator of food intake and energy balance acting in the hypothalamus, but it also exerts a number of effects purportedly relevant for carcinogenesis, such as inducing tumor angiogenesis, promoting cell proliferation and migration, interacting with metabolic and growth factors, and increasing estrogen biosynthesis [59]. Experimental studies have shown that leptin stimulates the proliferation and invasiveness of human colon cancer cells and may be directly related to risk of colorectal cancer [60]. In addition, energy balance, inflammation and insulin-signaling, which have been identified as contributors to the development of colon cancer, also are partly regulated by leptin. The association between leptin and colorectal cancer risk has been investigated in several observational studies [51••, 61–65]. Two Scandinavian studies [63, 64] reported that leptin was associated with risk for colon cancer in men but not in women, whereas an association in women was reported in the Japan Collaborative Cohort Study [65] and in the Women's Health Initiative [51••]. In the latter study, leptin was associated with colorectal cancer risk independent of insulin. The effects of leptin are mediated by membrane protein receptors, which also circulate in soluble form in plasma [66]. The major leptin binding protein, soluble leptin receptor (sOB-R), may act as a negative regulator of leptin's physiological functions or it may serve as a slow-release reservoir [67]. sOB-R is inversely associated with several important colorectal cancer risk factors, such as obesity [68], insulin resistance [69], and diabetes [70] and thus may be related to colorectal cancer risk [71]. The first evidence for an inverse association between sOB-R and colorectal cancer risk was found recently in the EPIC study [72]. In contrast, in EPIC, leptin levels were not related to colorectal cancer risk after adjustment for BMI and waist circumference. In this study, sOB-R concentrations were

strongly inversely associated with colorectal cancer risk, independent of adiposity measures, baseline leptin concentrations, and metabolic markers. Lower leptin binding to the leptin receptor has been shown for a SNP (rs1137101) of the leptin receptor (*LEPR*) gene, which also was related to obesity [73] and insulin sensitivity [74]. However, the evidence of the association between genetic variation in leptin and colorectal cancer risk is scarce; only one study has reported a positive association [75].

Adiponectin

In contrast to other adipokines, adiponectin is inversely related to obesity and metabolic alterations [76]. Adiponectin is involved in the regulation of energy homeostasis, vascular reactivity, inflammation, cell proliferation, and tissue remodeling [77]. It also inhibits cancer cell growth [78] and induces apoptosis [79] and thus may be directly implicated in cancer development. The evidence on the association between adiponectin and colorectal cancer has been summarized by two recent meta-analyses [80, 81]. In the study by Xu et al. [81], a 2 % decreased risk of colorectal neoplasm for a 1 μg/mL increment in adiponectin levels was observed (odds ratio (OR), 0.98; 95 % CI, 0.96-0.99), whereas among women there was no evidence of such a trend (OR, 0.99; 95 % CI, 0.97-1.01). An et al. 2012 [80] suggested that adiponectin levels seemed to be related to colorectal cancer risk only in case–control studies or small sample size studies (n<100) but not in nested case–control studies or large sample size studies. Adiponectin circulates in plasma as a trimer, a hexamer, and a high-molecular-weight (HMW) form. HMW and non-HMW-adiponectin fractions possess different biological activities, with HMW form being more closely related to insulin sensitivity, whereas complexes with lower molecular weight (i.e., non-HMW-adiponectin) having stronger anti-inflammatory potential [82]. Different roles of adiponectin fractions in terms of colorectal cancer risk have been recently suggested in a report from the EPIC study [83]. In this study, circulating prediagnostic concentrations of total adiponectin and non-HMW-adiponectin were inversely associated with risk of colorectal cancer, independent of dietary and lifestyle factors. In contrast, HMW-adiponectin concentrations were not statistically significantly related to colorectal cancer. These data suggest that adiponectin is inversely associated with risk of colorectal cancer and that this association is largely accounted for by non-HMW-adiponectin. Studies that investigated the association between genetic variants at the adiponectin locus and the risk of colorectal cancer reported conflicting results; some studies showed significant associations [84, 85], whereas other studies did not observe any association [86].

Resistin

Resistin is a proinflammatory mediator belonging to the inflammatory zones (FIZZ) family also known as RELMs, resistin-like molecules [87]. It is mainly secreted by adipose tissue, but it has been found also in macrophages, neutrophils, and other cell types [88]. Resistin-like molecule beta (RELM beta) is overexpressed in human colon cancer cells [89]. Although resistin was proposed to be a hormone linking obesity to insulin resistance in rodents, in humans the role of resistin in metabolic deregulations was controversial [90]. However, some genetic studies have demonstrated an association between resistin and insulin resistance and obesity [91]. The proinflammatory potential of resistin, together with its association with obesity, suggest that it may be another potential mediator that links colorectal cancer with inflammation and obesity. The role of resistin in colorectal cancer has been proposed by several epidemiological studies [62, 92, 93]. More evidence from large, prospective studies would improve understanding these associations.

Other Factors

In addition to the metabolic pathways discussed earlier, other potential mechanisms for the association between body fatness and colorectal cancer risk have been proposed. Thus, obesity-related changes in sex hormone levels were suggested to be linked to colorectal cancer risk. For instance, high body fatness is associated with higher endogenous estrogen levels, and a prospective study among postmenopausal women observed a significant association between high endogenous estradiol levels and higher risk of colorectal cancer [94]. The positive association was unaffected by adjustment for waist circumference, insulin, and free IGF-1, which led the authors to the conclusion that a pathway involving endogenous estradiol may exist that is independent of the pathway broadly associated with obesity, hyperinsulinemia, and IGF-1. A second prospective study of postmenopausal women observed positive associations between endogenous estrone but not estradiol and colorectal cancer risk [95].

Alterations in the immune response, in the nuclear factor kappa B (NF-kappa B) system, in oxidative stress, and in peroxidation are alternative mechanisms that may link obesity to colorectal cancer risk [58]. For example, increased blood levels of oxidative stress markers have been observed in patients with familial adenomatous polyposis [96] and colorectal cancer [97, 98]. However, a recent nested case–control study in EPIC suggested that the association between oxidative stress indicators, such as reactive oxygen metabolites (ROM), and colorectal cancer risk is a result of reactive oxygen species (ROS) production by preclinical

tumors, rather than a causal factor in carcinogenesis (reverse causation) [99]. Studies with longer follow-up and combined measures of reactive oxygen exposure and antioxidant status are needed to further explore the association between oxidative stress and colorectal cancer risk.

Conclusions

The current body of evidence points to a causal role of obesity, and in particular abdominal obesity, in the development of colorectal cancer. Biomarker studies support the hypothesis that this association is mediated by obesity-related alterations, including hyperinsulinemia, chronic low-grade inflammation, and abnormal adipokine levels, such as adiponectin and leptin. The research pertaining to the biological factors explaining the positive association between body fatness and risk of colorectal cancer is not only relevant for understanding disease etiology but also for public health prevention activities. For risk prediction of colorectal cancer, a more precise characterization of the risk-defining obesity phenotype is necessary, which may be achieved in a simple way by measuring WC in addition to BMI but also by using biomarkers as predictive measurements. It has been estimated that in Europe 10.9 % of colon cancer cases in men and 2.6 % in women are attributable to excess BMI ($\geq$25 kg/m^2) [100]. Considering that abdominal obesity is more closely associated with colorectal cancer risk than general obesity as represented by BMI, it is likely that the proportion of colorectal cancer disease burden attributable to excess body fatness is even higher.

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