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Specific metabolic biomarkers as risk and prognostic factors in colorectal cancer

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incidence and mortality in both men and women.

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Core tip: We describe the metabolic candidates of colorectal cancer: Dyslipidemias, adipokines and insulin/insulin-like growth factor axis as a potential risk and prognostic biomarkers.

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Abstract

Advances in genomics, molecular pathology and metabolism have generated many candidate biomarkers of colorectal cancer with potential clinical value. Epidemiological and biological studies suggest a role for adiposity, dyslipidaemia, hyperinsulinemia, altered glucose homeostasis, and elevated expression of insulin-like growth factor (IGF) axis members in the risk and prognosis of cancer. This review discusses some recent past and current approaches being taken by researches in obesity and metabolic disorders. The authors describe three main systems as the most studied metabolic candidates of carcinogenesis: dyslipidemias, adipokines and insulin/IGF axis. However, each of these components is unsuccessful in defining the diseases risk and progression, while their co-occurrence increases cancer

INTRODUCTION

The term “biomarkers” was first used in 1989 as a Medical Subject Heading (MeSH): “measurable and quantifiable biological parameters which serve as indices for health and physiology-related assessments, such as disease risk, psychiatric disorders, environmental exposure and its effects, disease diagnosis, metabolic processes, substance abuse, pregnancy, cell line development, epidemiologic studies, etc.”^[1-4]. Biomarkers aid in early diagnosis, disease prevention, drug target identification, drug response predictions, etc.^[5-9].

The National Cancer Institute defines a biomarker as: “a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process,

or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Also called molecular marker and signature molecule^[10]. According Tanaka *et al.*^[11], the ideal biomarkers for cancer have applications in determining predisposition, early detection, assessment of prognosis, and drug response. In cancer research and medicine, biomarkers are used^[6-12]: To help diagnose conditions (diagnostic); To indicate, before treatment, the long-term outcome for patients and to provide an estimate of the severity and likely outcome of the disease (prognostic); To predict how well a patient will respond to treatment (predictive).

Colorectal cancer (CRC) is the third most common malignant neoplasm worldwide; the global incidence of this cancer is estimated at 1 million people per year. According to the National Cancer Society, there will be 143460 new cases and 51690 deaths worldwide in 2013^[13-15]. In Poland, colorectal cancer ranks second in tumour incidence regardless of sex^[16]. Experimental, genetic, epidemiologic and socioeconomic studies^[17-20] have suggested that CRC is results from complex interactions between inherited susceptibility (Lynch syndrome I and II, familial polyposis), clinical conditions (ulcerative colitis, Crohn's disease) and environmental/lifestyle-related risk factors (physical inactivity, smoking, excessive alcohol consumption, high-fat/low-fibre diet, overweight/obesity). The hypothesis that diet and related metabolic, anthropometric and hormonal markers play a role in cancer aetiology was originally supported by a series of early case-control studies, epidemiological correlation studies and pioneering work on rodents in experimental laboratory studies carried out in the 1940s^[21].

Overweight/obesity and other metabolic disorders (hyperglycaemia, hyperinsulinemia, dyslipidaemia, type 2 diabetes, hypertension) are positively associated with the risk of CRC^[22-28].

Elevated body mass index (BMI), physical inactivity, and visceral adiposity were found to be consistent risk factors for colon cancer and adenoma^[25,27]. The European Prospective Investigation into Cancer and Nutrition (EPIC) study suggested that visceral adiposity and related metabolic abnormalities may play an important role in colon carcinogenesis^[29].

In the aetiopathogenesis of colorectal cancer in overweight/obese patients, fat tissue is said to be of high importance to the processes of neoplastic transformation^[30,31]. Fat tissue is treated like glandular tissue, performing endocrine, paracrine and autocrine functions, regulating triglyceride metabolism, influencing the coagulation system and inhibiting the anti-lipolytic effect of insulin^[16,32-35]. Previous reviews and studies of the metabolic biomarkers of CRC^[24,30-34] have indicated two hormonal systems, adipokines and the insulin/insulin-like growth factor (IGF) axis, as the most studied metabolic candidates of carcinogenesis.

In this review, we focus on the risk and prognostic effects of selected metabolic biomarkers in colorectal

cancer.

DYSLIPIDEMIA

Dyslipidaemia is a pathological alteration in the levels of serum lipids and lipoproteins. Generally, dyslipidaemia is defined as having levels of total cholesterol (TC), low-density lipoprotein (LDL), triglycerides (TG), apolipoprotein B (apoB) or lipoprotein above the 90th percentile or levels of high-density lipoprotein (HDL) and apolipoprotein A-1 (apoA-1) below the 10th percentile of the general population^[35]. Lipids and lipoproteins have been associated with neoplastic processes, such as inflammation, insulin resistance and oxidative stress^[36]. Abnormal levels of all lipid components studied are associated with an increased risk of obesity-related cancers. According to Gallagher *et al.*^[37] the cholesterol content of tumour cells is higher than that of normal cells, owing to the increased absorption of cholesterol from the circulation and the *de novo* lipogenesis of cancer cells.

Findings on the relationship between the levels of total cholesterol and triglycerides and the risk of CRC have been inconsistent. This increase in lipid accumulation has been shown to promote proliferation and protect cancer cells from apoptosis^[37]. Scientists have observed different associations between serum TC and CRC risk; a positive relation^[38,39], a positive association with the risk of rectal cancer only^[36,40], inverse^[41], and no significant association^[36,42]. For example, a positive association between the serum TC levels and the risk of colorectal carcinoma *in situ* after adjusting for age, sex, body mass index, smoking status and alcohol consumption was reported by Yamada *et al.*^[39], and high total cholesterol (≥ 240 mg/dL) was positively associated with the risk of colon cancer in men (HR, 1.12, 95%CI: 1.00-1.25, $P = 0.05$) in a large prospective study in South Korea^[43]. However, a case-control study by Chung *et al.*^[44] showed an inverse association between the lipid (TC and TG) levels and risk of CRC. In Notarnicola *et al.*^[45] studies, colorectal cancer patients with distant metastases have been significantly higher levels of TC, LDL-cholesterol (LDL-C) and the LDL-C/HDL cholesterol (HDL-C) ratio than patients without metastases ($P < 0.05$).

A few cohort studies have investigated the relationship between high serum TG concentrations in patients with metabolic disorders and the risk of colon cancer^[40]. In a large-scale cohort study performed by Ulmer *et al.*^[46] high serum TG concentrations were found to be correlated with a high risk of rectal cancer (HR = 1.56, 95%CI: 1.00-2.44) in men and women combined, whereas no association was found for colon cancer.

In the metabolic syndrome and cancer (Me-Can) project^[26,41], 2834 men and 1861 women were diagnosed with colorectal cancer. In men, a significant association was observed between the TG level and CRC (RR = 1.17, 95%CI: 1.06-1.28) and a modest positive association was observed for total cholesterol and CRC. However, no relationship between these factors was found in

women.

In the Swedish apolipoprotein mortality risk study^[40], 2472 colon and 1510 rectal cancer patients were selected, and baseline measurements of glucose, TC, TG, LDL-C, HDL-C, apoB, and apoA-I were recorded. The researchers observed a higher risk of colon cancer in patients with high levels of glucose and TG and an increased risk of rectal cancer in those with high TC levels. Stratification by glucose level showed that colon cancer risk was positively associated with the TG level primarily in those with a glucose level of $< 6.11 \mu\text{mol/L}$.

Melvin *et al.*^[38] summarised the results of 28 studies to quantify the link between the markers of lipid metabolism and the risk of obesity-related cancers. In this meta-analysis, the associations between four components of the serum lipid profile (TC, TG, HDL, and Apo-AI) and the risk of cancers that were previously shown to be linked with obesity were examined. To summarise the study, the authors concluded that “the modest relative risks suggest serum lipids to be associated with the risk of cancer, but indicate it is likely that other markers of the metabolism and/or lifestyle factors may also be involved”.

The EPIC study^[27,29,36,47], a multi-centre prospective cohort study, was designed to investigate the relationships between diet and other lifestyle factors and the incidence of different forms of cancer. The total cohort involved over 520000 subjects from ten Western European countries who joined the study between 1992 and 2000. In this group, there were 1238 colorectal cancer patients (779 colon cancer patients and 459 rectal cancer patients). The association between the serum concentrations of TC, HDL, LDL, TG, ApoA and ApoB and the incidence of CRC was examined. In this cohort study, the concentrations of HDL and apoA were found to be inversely associated with the risk of colon cancer [RR (1 SD increase of 16.6 mg/dL in HDL) 0.78, 95%CI: 0.68-0.89] [RR (1 SD increase of 32.0 mg/dL in apoA), 0.82, 95%CI: 0.72-0.94]. No association was observed with the risk of rectal cancer.

Similarly, researchers in the Department of Gastroenterology and Hepatology at the National Institute for Public Health and the Environment in the Netherlands found that high levels of HDL may prevent colon cancer^[36]. The mechanism behind this association requires further elucidation to gain an understanding of the involvement of HDL in the regulation of the levels of proinflammatory cytokines and the modulation of oxidative stress. Furthermore, HDL mimetics (constructed from a number of peptides and proteins with varying structures that possess anti-inflammatory and antioxidant properties reminiscent of HDL) have been shown to reduce the viability and proliferation of CT26 cells, a mouse colon adenocarcinoma cell line and to decrease CT26 cell-mediated tumour burden in BALB/c mice when administered subcutaneously or orally^[48].

Additional studies of HDL role in CRC will be useful for a more complete understanding of the circulating lipids-cancer relationship^[49].

ADIPOKINES

Adipose tissue consists of a variety of cells and structures, including adipocytes (30%-50%), preadipocytes, fibroblasts, collagen fibres, blood vessels and immune cells (monocytes, macrophages and lymphocytes). Since 1994, when the first adipokine, leptin, was discovered, a new era began in the investigation of the metabolic function of the white adipose tissue. Currently, there are a number of known adipose-derived peptides and proteins. These can be divided into two classes: adipocytokines or cytokines, adipokines, which are secreted by adipocytes (leptin, adiponectin, resistin, visfatin), and which are secreted from the stromavascular fraction of adipose tissue cells for example: interleukin 6 (IL6), plasminogen activator inhibitor-1, tumor necrosis factor α ^[16,50,51].

Adipokines affects a number of body processes, including appetite, energy balance, glucose and lipid metabolism, inflammation, thermogenesis, neuroendocrine function, reproduction, angiogenesis, cell proliferation, and atherosclerosis^[51].

Leptin

Leptin, the first discovered adipokine-derived hormone, contains 162 amino acids and is encoded by the OB gene^[52]. Initial interest on this adipokine was focused on its role in obesity, but the last decade brought attention to its association with the inflammatory response, insulin signalling, and carcinogenesis^[53-55].

Leptin acts predominantly through the plasma membrane receptor Ob-R, which is encoded by the OB gene. As a result of alternative splicing, it has at least six isoforms, from OB-Ra to OB-Rf, with OB-Rb being the predominant isoform responsible for the biological actions of leptin. This adipokine stimulates colorectal cancer cells by activating multiple signalling pathways. It induces the trans-phosphorylation of a variety of kinases, including cytoplasmic Janus kinase, tyrosine kinase, phosphoinositide kinase, mammalian target of rapamycin kinase (mTOR), and protein kinase C to promote cellular proliferation, stimulate the invasive capacity of early neoplastic cells, increase the formation of lamellipodial structures that are important for cell motility and regulate malignant cell migration^[56,57]. Leptin also inhibits apoptosis, induces angiogenesis, and promotes cellular proliferation in these cell lines similar to the effects of IGF-1. Of particular importance for colorectal cancer is the influence of leptin on suppressors of cytokine signalling, which blocks Ob-R-mediated signal transduction^[58,59].

Leptin was found to be overexpressed in colorectal cancer, and its expression increases gradually from normal mucosa, simple adenoma with low-grade dysplasia, adenoma with high-grade dysplasia to adenocarcinoma^[60].

Interestingly, it has also been reported that peroxisome proliferator-activated receptor- γ (PPAR- γ) activation in leukaemia inhibits the cytokine-induced activation of the JAK/STAT pathway. Hence, PPAR- γ agonists are functional antagonists of leptin signalling with respect

to tumourigenesis^[61-64]. However, increased leptin and PPAR- γ expression in colorectal cancer are both associated with favourable outcomes and longer disease-free survival. The STAT3 protein acts as a transcription factor to increase the expression of the anti-apoptotic protein Mc1-1. It is postulated that elevated expression of STAT3 and its target genes in colorectal carcinoma may be markers of malignancy. Bartucci *et al*^[65] suggested that leptin activation of the extra cellular signal-regulated kinases 1/2 (ERK1/2) and AKT signalling pathways enhances cell growth in soft agar and improves sphere formation associated with E-cadherin overexpression. Hoda *et al*^[66] proved that leptin serves as a mitogenic agent and has an anti-apoptotic effect on the cells of the large intestine. The connection between cancer and leptin and its receptors should be considered as a dynamic system in relation to the external and internal environment^[16,54,55]. Considering the therapeutic aspect, researchers have asked whether receptors on the surface of cancer cells can be therapeutic targets for newly developed drugs, such as monoclonal antibodies or low-molecular-weight tyrosine kinase inhibitors.

A number of epidemiological studies^[55,67-69], with different results have examined the association of the levels of leptin and its soluble receptors with CRC. In a large Scandinavian case-control study, leptin was found to be associated with increased risk for CRC in men but not in women. In studies of the Japanese population, leptin was suggested to increase the risk of female colorectal cancer in the Japan Collaborative Cohort Study and the Women's Health Initiative cohort of postmenopausal women^[68-70]. Cong *et al*^[71] summarised their research, stating that the serum leptin concentrations were significantly higher in the CRC group than in the control group for both males and females; however, these concentrations were significantly lower in males than in females. The authors observed a statistically significant relationship between leptin expression and tumour differentiation but not tumour location or TNM stage.

In a previous study from our laboratory in which a total of 146 colorectal cancer patients in various stages of clinical progression of CRC were enrolled^[72], we did not observe statistically significant differences in the levels of leptin or its receptors (OB-Ra and OB-Rb) between the groups of colorectal cancer patients in different stages of clinical and pathological progression. A statistically significant difference was observed in OB-Ra expression between patients with a normal body weight and obese patients with respect to TNM stage. Similar results were obtained by Arpacı *et al*^[73], who found that serum leptin does not correlate with the stage of CRC progression.

However, the results of a study by Wang *et al*^[61] (108 patients with CRC) showed that leptin/OB-R expression is significantly associated with T stage, TNM stage, lymph node metastasis and distant metastasis. The authors suggested that leptin regulates proliferation and apoptosis of colorectal carcinoma cells through the PI3K/Akt/mTOR signalling pathway.

The EPIC study examined the association of serum leptin and sOR-R with CRC risk and lifestyle and dietary factors (BMI, WH and circulating metabolic biomarkers). This study concluded that sOB-R is strongly inversely associated with the risk of CRC, independent of BMI and the levels of leptin and circulating metabolic biomarkers. Leptin was not related to CRC risk^[70].

In conjunction with adiponectin, leptin may be used as a predictor for adverse outcome (leptin to adiponectin ratio). Most of the studies in this area have indicated that leptin may potentiate the growth of cancer cells *in vitro*, while adiponectin has an opposite effect^[74,75].

Adiponectin

Adiponectin (ADN) is a 244-amino acid protein belonging to the collagen superfamily. It is an insulin-sensitising hormone with anti-diabetic, anti-inflammatory, anti-atherogenic and anti-proliferative properties^[76]. Levels of this hormone are inversely correlated with body fat percentage. Full-length ADN exists in three forms in human serum: a low molecular weight trimer, a middle molecular weight hexamer that forms through the self-association of two trimers, and a high molecular weight (HMW) multimer^[77]. This adipokine exerts its action by binding to two main receptors, AdipoR1 and AdipoR2 (which show homology to G protein coupled receptor), and one minor receptor, T-cadherin (Cdh13)^[78]. AdipoR1 is expressed abundantly in muscle tissue, whereas AdipoR2 is expressed at high levels in the liver^[79]. T-cadherin is located on the cellular surface of endothelial, epithelial, and smooth muscle cells^[80]. ADN has been shown to suppress the secretion of proinflammatory cytokines by macrophages and to increase glucose uptake and decrease the proliferation of obesity-associated cancer cell lines^[81,82]. According to Williams *et al*^[80], the anti-tumour effects of ADN may be either indirect, through improving insulin resistance and hyperinsulinemia or modulating neovascularisation and inflammation, and/or direct, through anti-proliferative and/or pro-apoptotic actions on cancer cells. ADN has been shown to act indirectly on colorectal cancer cells by regulating whole body insulin sensitivity and contributing to the inflammatory state through mutations of the K-ras proto-oncogene. Sugiyama *et al*^[83] showed that adiponectin suppresses colon cancer cells through its receptor-mediated AMPK activity.

Hypoadiponectinaemia is inversely linked to the risk of obesity-associated neoplasms and insulin resistance *in vivo*^[74].

Most retrospective case-control studies have confirmed that lower adiponectin levels are associated with an increased risk for CRC. The adiponectin level is inversely correlated with the number of adenomas ($P = 0.02$) but is not correlated with the tumour size. This finding suggests that ADN plays a protective role in cancer progression^[84-86].

In the Health Professionals Follow-up Study, Wei *et al*^[87] evaluated the association between adiponectin and colorectal cancer among 18225 men. CRC patients had statistically

significantly lower ADN levels and higher BMIs, waist circumferences, and waist-to-hip ratios than the control subjects. Men in the highest quintile of adiponectin presented a 58% lower risk of CRC than those in the lowest quintile, even after adjustment for body size, physical activity, and waist circumference.

Conversely, Fukumoto *et al.*^[88] revealed that there is no measurable association between the circulating level of adiponectin and the incidence of colorectal adenoma.

In the European Prospective Investigation into Cancer and Nutrition Study, Aleksandrova *et al.*^[70] explored HMW and non-HMW adiponectin fractions in relation to CRC risk. Non-HMW adiponectin was associated with CRC risk, even after adjustment for body mass index and waist circumference (RR = 0.39, 95%CI: 0.26-0.60, $P < 0.0001$), whereas the association with total ADN was not significant (RR = 0.81, 95%CI: 0.60-1.09, $P = 0.23$)^[89]. Adiponectin receptors are expressed on the cell surface in both colorectal cancer and healthy tissue. According to Dalamaga *et al.*^[74], an upregulation of adiponectin receptors in colorectal cancer tissues induced by hypoadiponectinaemia may compensate and maintain the adiponectin signalling pathways. The results from several case-control colorectal cancer studies have demonstrated the important role of a variety of adiponectin genes (ADIPOQ) with regard to increasing or reducing the risk for colorectal cancer^[90]. The cross-sectional study of a cohort of hospital-based patients in Japan (47 with adenoma, 34 with early cancer, 17 with advanced cancer, and 26 without tumours as controls) showed that a decreased level of ADN is as a strong risk factor for both colorectal adenoma and early stage of cancer^[91].

The level of ADN and the tissue expression of its receptors was shown to be associated with CRC and with the clinico-pathological characteristics of CRC, notably stage and grade, by Gialamas *et al.*^[92] at Harvard University.

He *et al.*^[93] measured the incidence of five polymorphisms in the ADIPOQ gene and two polymorphisms in the ADIPOR1 gene and analysed their association with CRC risk in 420 CRC patients and 555 age- and gender-matched healthy individuals. The rs12733285C/T genotype and the presence of the A allele of rs1342387 (A/G or A/A) in ADIPOR1 are protective factors for CRC, while the rs266729G/C genotype and the presence of the G allele of ADIPOQ are risk factors for colon cancer, after excluding the rectal cancer cases. Liu *et al.*^[94] suggested that mutations in ADIPOQ may contribute to increased colorectal cancer risk in the Chinese population and that their contribution may be modified by environmental factors, such as smoking status, family history of cancer and BMI.

Song *et al.*^[95] prospectively evaluated the association of plasma adiponectin and soluble leptin receptor (sOB-R) with CRC risk in the Nurses' Health Study (1990-2008) and the Health Professionals Follow-up Study (1994-2008) among 616 incident CRC cases and 1205 controls that were selected using risk-set sampling

and matched by age and date of blood draw. Plasma adiponectin was determined to be significantly associated with reduced risk of CRC among men but not among women, and plasma sOB-R was not associated with overall CRC risk in either men or women^[96].

Resistin

Resistin, an adipocyte-specific hormone, is a 12.5-kDa cysteine-rich protein that is abundantly secreted by macrophages. Human resistin may interfere with insulin signalling by stimulating the expression of phosphatase and tensin homolog deleted on chromosome ten, which dephosphorylates 3-phosphorylated phosphoinositide (PIP3)^[97,98]. According to Benomar *et al.*^[99], the resistin receptors are still unknown, while Daquinag *et al.*^[100] has stated that an isoform of decorin (Δ DCN) is a functional receptor of resistin in adipocyte progenitors and may regulate white adipose tissue expansion. Other studies^[101] have identified adenylyl cyclase-associated protein 1 as a novel functional receptor for human resistin and clarified its intracellular signalling pathway in the modulation of the inflammatory action of monocytes.

Resistin upregulates proinflammatory cytokines in human peripheral blood mononuclear cells through the NF- κ B pathway. In addition, it promotes endothelial cell activation, including the stimulation of endothelin-1 release and the upregulation of cellular adhesion molecules, such as vascular and intercellular adhesion molecule-1 and intercellular adhesion molecule-1. The resistin concentration is increased in obesity, and overexpression of this peptide is associated with insulin resistance and dyslipidaemia^[102].

The role of resistin in colorectal cancer is "far from being elucidated"^[103].

In a case-control study in which 40 CRC patients and 40 controls were enrolled, the association between circulating resistin and the risk of CRC was examined^[103]. Markedly higher resistin levels were observed in the CRC patients than in the controls^[104], and these levels were also higher in women than in men. The concentrations of leptin, adiponectin, and resistin in patients with adenomatous polyps and colorectal cancer were examined by Kumor *et al.*^[105]. The serum concentrations of leptin and adiponectin were lower in the patients with adenomas compared to the control group. The serum resistin level was not significantly different in the adenoma group ($P > 0.05$) but was higher than in the controls ($P < 0.05$). There was a correlation between adiponectin and leptin serum concentration ($r = 0.61$). The authors concluded that the serum levels of adiponectin and resistin may play an important role in colon carcinogenesis. Leptin may possibly have prognostic value, independent of BMI.

Visfatin

Visfatin (pre-B cell colony-enhancing factor) is 52-kDa peptide that was discovered by Fukuhara *et al.*^[106] in 2005. It possesses NAD biosynthetic activity and regulates growth, apoptosis, and angiogenesis in mammals^[107]. Visfatin is

Table 1 Features of the insulin-like growth factors genes^[117]

Gene	Molecular weight (kDa)	Mature protein (number of amino acids)	Chromosomal localization	Gene size (kb)	Exons (n)
IGF1	7.7	70	12q22-12q24	100	6
IGF2	7.5	67	11p15	30	9
IGF1R	225	α 706 β 626	15q25-15q26	100	21
IGF2R	270	2450	6q25-6q27	140	48
IGFBP1	25.3	234	7p12-7p14	5.2	4
IGFBP2	31.4	289	2q31-2q34	32	4
IGFBP3	28.7	264	7p12-7p14	8.9	5
IGFBP4	26	237	17q12-17q21	12	4
IGFBP5	28.6	252	2q31-2q24	33	4
IGFBP6	22.8	216	12q13	4.7	4
IGFBP7	29.130	282	4q12		

IGF: Insulin-like growth factor; IGFBP: Insulin-like growth factor binding proteins.

a newly identified insulin mimetic adipocytokine that directly interacts with the insulin receptor but not the insulin-like growth factor receptor and can subsequently promote cancer cell proliferation. It is more highly expressed in primary colorectal cancer than in non-neoplastic mucosa^[85,108,109]. A study performed by Huang *et al.*^[110] revealed that visfatin induces the expression of stromal cell-derived factor-1, a chemokine that plays a role in CRC progression, *via* β 1 integrin signalling in colorectal cancer cells.

Nakajima *et al.*^[85,109] observed that the visfatin and resistin levels in colorectal cancer patients were significantly higher than those of controls in a multivariate analysis ($P < 0.01$ and $P = 0.03$, respectively). In case-control studies, an increased level of visfatin was found to be a strong risk factor for both early and advanced CRC^[111,112] and to correlate with stage progression^[109].

INSULIN-LIKE GROWTH FACTOR SYSTEM

The insulin-like growth factor system includes the IGF ligands (insulin, IGF1, and IGF2), IGF receptors (IGF1R and IGF2R) and IGF binding proteins (IGFBPs) (Table 1). The association between the IGF system and cancer has been a topic of investigation for many years^[24,34,113-117]. Insulin-like growth factors exert their biological functions through their specific receptors. Insulin (INS) signal transduction occurs through its receptor (IR), which has two isoforms (IRA and IRB). IRA recognises INS, IGF1 and IGF2 but has the highest affinity for IGF2. The INS signal that is transduced through the IRB isoform is associated with glucose homeostasis. IGF signals that are passed through IGF1R, which induce the kinase activity of the receptor, activate the phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), mTOR, PI3K/Akt/forkhead box O (FoxO) and Ras/MAPK/ERK1/2 pathways^[118,119], which play a role in cancer growth. Many studies have indicated an association between type 2 diabetes and an increased risk of developing colorectal cancer^[118-120]. IGF1R recognises IGF1 and IGF2 and INS

as well^[115,121]. IR and IGF1R are members of the tyrosine kinase class of membrane receptors. IGF2R recognises IGF2 and attenuates IGF2 signalling *via* IGF1R^[34,115,118].

Epidemiologic studies have demonstrated an association between obesity and the risk of colorectal cancer^[122,123]. Obesity and lifestyle factors influence the levels of circulating IGFs^[124,125] and, thus, increase colorectal cancer incidence, as a one of many mechanisms of carcinogenesis. Insulin resistance in addition to type 2 diabetes mellitus, adipokine inflammation and others, which provides risk for cancer.

The most important colorectal cancer risk factors among metabolic disorders are insulin resistance, hyperinsulinemia and hyperglycaemia^[16,22,24,26,27,113,115,120,122,123,126-129]. There is a significantly elevated risk for proximal colorectal cancer in men suffering from type 2 diabetes mellitus and no significant increase in risk in women with this condition^[129]. Other studies have indicated that diabetes mellitus type 2 is a risk factor for distal CRC^[130] and both proximal and distal CRC^[131].

However, several studies have revealed a decrease in cancer risk in diabetic patients treated with metformin, an anti-diabetic agent^[132,133]. Metformin reduces insulin resistance and improves glycaemic control, and many studies have shown that it inhibits the growth of cancer cells^[134]. Its pleiotropic effects on multiple pathways against the growth of cancer cell are associated with the activation of AMPK by proteins, including the enzymes LKB1 serine-threonine kinase, calcium/calmodulin-dependent protein kinase and TGF- β -activated protein kinase^[135] and by the tumour suppressor gene ATM, which has been implicated in DNA repair and cell cycle arrest^[136,137]. Metformin inhibits the mTOR signalling pathway by decreasing the levels of INS and IGF1, independent of AMPK^[138].

A relationship between type 2 diabetes mellitus and CRC has been proposed in many studies. As far as we know, the treatment modalities for diabetes can modify the insulin and glucose levels, therefore increasing CRC incidence. Not only drugs, but life style factors, such as diet therapy, weight control, exercise and smoking, may

Table 2 Insulin-like growth factor system/prognostic factors in colorectal cancer

IGF system	Researches
Insulin	There were no statistical significance relative to insulin serum level in groups independently of clinical stage of CRC and tumor localization, Nowakowska-Zajdel <i>et al</i> ^[127] , Kaczka <i>et al</i> ^[147] , Nowakowska-Zajdel ^[148]
IGF1	Hyperinsulinemia and hyperglycaemia has been associated with higher mortality from CRC, Yang <i>et al</i> ^[131] , Deng <i>et al</i> ^[149] High IGF1 levels is associated with increased risk of CRC, Ma <i>et al</i> ^[156] IGF1 serum levels are increased in patients with locally advanced CRC (pT ₃ , pT ₄) in comparison to less advanced cancer. Higher serum level of IGF1 is observed in patients with G3 (histopathological malignancy), in male patients older than 60 yr and in mucinogenous cancer, Kukliński <i>et al</i> ^[157] EPIC cohort and meta-analysis of prospective studies pointed a relatively modest association of CRC risk with IGF1 levels, Rinaldi <i>et al</i> ^[160]
IGF2	The serum levels is significantly elevated in patient with CRC <i>vs</i> control group and without difference between metastatic and local CRC, Matuschek <i>et al</i> ^[158] Higher IGF2 levels were associated with better overall survival in CRC patients, Liou <i>et al</i> ^[166] IGF2 serum levels were higher in patients with more advanced CRC, Zhao <i>et al</i> ^[164] The IGF2 overexpression in tumor cells was associated with more advanced CRC and poor survival, Wang <i>et al</i> ^[162] , Kukliński <i>et al</i> ^[163]
IGF1R	IGF1R is overexpressed in CRC cells, Pollak <i>et al</i> ^[168]
IGF2R	IGF2R imprinting is observed in CRC, Ouyang <i>et al</i> ^[170] , Kuhlmann <i>et al</i> ^[171]
IGF1/IGFBP3 ratio	Higher IGF1/IGFBP-3 ratio is associated with CRC risk, Rowlands <i>et al</i> ^[179]
IGFBPs	Total IGFBP-3 levels is significantly related with risk of CRC, Rinaldi <i>et al</i> ^[160] Lower IGFBP-3 levels correlate with the CRC risk, Wolpin <i>et al</i> ^[128] High levels of IGFBP-3 has been associated with reduced risk of CRC, Ma <i>et al</i> ^[181] No correlation between circulating IGFBP-3 and mortality, Kaplan <i>et al</i> ^[178] IGFBP-7 is overexpressed in CRC cells, Ruan <i>et al</i> ^[177]

IGF: Insulin-like growth factor; IGFBP: Insulin-like growth factor binding proteins; CRC: Colorectal cancer.

similarly impact cancer risk^[122,132-134,139].

Insulin

Insulin signal transduction occurs through its receptors (IRA, IRB) and IGF1R as well as hybrid receptors (IGF1R/IR). The cellular signalling of IR and hybrid receptors is similar but not identical because different cell types use this control system to regulate different processes. In the liver, gluconeogenesis is inhibited and glycogen storage is activated, while in epithelial cells, the consequences of pathway activation is stimulation of proliferation and inhibition of apoptosis^[121]. Most cancers express both IR and IGF1R genes. It is important to recognise that receptors perform their functions in signal transduction in both cancer cells and normal tissues. The expression levels of IGF receptors in cancer are sometimes higher than those observed in normal cells^[115].

Abnormal autocrine production of insulin in cancer is uncommon, but many cancers show a high level of insulin-independent glucose uptake. In cancers in diabetic patients with insulin resistance, the transformed cells are more insulin sensitive than the liver, muscle or adipose tissue. In addition, hyperinsulinemia stimulates the growth of cancer cells and influences cancer risk and prognosis^[140,141]. Higher circulating insulin levels that are directly or indirectly caused by IGF1 (circulating levels of IGF1 are dependent on GH secretion and weakly affected by insulin) may modulate carcinogenesis^[126,129,142,143]. Hyperinsulinemia may influence cancer cell growth through IRA/IGF1R by increasing signalling, and increasing the expression of IRA on cancer cells can mediate the effects of metabolism in cancer^[144].

One prognostic factor in CRC that is connected

with diabetes is the level of glycated haemoglobin A1C (HbA1C). HbA1c has been proven to be an independent predictor of aggressive clinical behaviour in CRC patients, leading to more right-sided and advanced cancers that present at a younger age and show poor 5-year survival^[145]. However, in their recent study involving 25476 patients with type 2 diabetes mellitus, Miao Jonasson *et al*^[146] did not find any association between HbA1C and risk for all cancers or specific types of cancer.

Many studies have indicated no significant difference in the insulin levels of CRC patients compared with controls and no correlation between insulin levels and advanced stage or malignancy^[127,147,148]. It was observed that insulin levels are higher in obese CRC patients group in comparison with CRC patients with a proper BMI^[15]. Hyperinsulinemia and hyperglycaemia have been associated with higher mortality from CRC and more advanced tumours compared to non-diabetic patients. However, the insulin and glucose levels of CRC patients do not seem to be prognostic factors^[131,149] (Table 2). Future studies should further examine the possibility of insulin levels and hyperglycaemia as risk factors of cancer.

IGF1

IGF1 shows approximately 50% structural homology to insulin. IGF1 is produced by many cell types, including cancer cells. The liver is its main site of IGF1 production, which is stimulated by GH^[114,115]. The GH/IGF1 axis is the regulator of postnatal growth. The production of IGF1 by cancer cells might be sufficient for both autocrine and paracrine effects on tumour growth. IGF1 and IGF2 function as hormones and tissue growth factors.

A large case-control study showed that higher IGF1

levels are associated with increased risk of advanced colorectal adenoma^[150,151]; this finding is supported by other studies^[152-155]. Ma *et al.*^[156] observed that high IGF1 levels are associated with increased risk of CRC (RR, 2.51; 95%CI: 1.15-5.46), but there are some studies that do not report a statistically significant association between IGF1 and colorectal adenoma^[153,154]. It is theoretically possible that adenomas could progress to cancer independently of IGF1 or the autocrine or paracrine mechanism of IGF1 signalling. Further prospective research is needed.

In addition, the IGF1 levels in the serum are increased in patients with locally advanced colorectal cancer (pT3, pT4) in comparison to less advanced cancer, and higher serum levels of IGF1 are observed in patients with G3 cancer (histopathological malignancy), in male cancer patients older than 60 years and in mucinogenous cancer^[157]. This study highlighted IGF1 as a putative prognostic factor, but it was observed that there were no significant differences in the IGF1 levels in colorectal cancer patients when compared to the control group^[157,158]. Thus, IGF1 does not seem to be a marker of existing colorectal cancer^[157].

The biological activity of IGF is regulated by the insulin-like growth factor binding proteins (IGFBP) family. Some research has indicated that high circulating IGF1 levels and an increased IGF1/IGFBP3 ratio disturbs GH/IGF1 homeostasis, which could be an indicator of risk for cancer development^[159]. Rinaldi *et al.*^[160] studied the EPIC cohort and performed a meta-analysis of prospective study results. They indicated a relatively modest association of CRC risk with serum IGF1 (1121 cases of CRC and 1121 matched controls). In this study, the IGF1 and IGFBP3 levels were analysed, and it was examined whether the relative risk associated with the IGF1 level was modified by anthropometric and dietary factors related to IGF1 and CRC risk. The serum IGF1 levels were not significantly associated with CRC risk, but total IGFBP3 showed a significant relationship with risk of CRC. No significant interaction was found between IGF1 and IGFBP3 (total and intact). The same data obtained in relation to gender and separately for right and colon cancer. When IGF1 was adjusted for total IGFBP3, its association with right-sided colon cancer was stronger than for overall colon cancer -[RR (top *vs* bottom quintile), 1.98, 95%CI: 1.01-3.89]. Analysis of the BMI and WHR revealed a significant positive association of the IGF1 level and risk of rectal cancer among participants whose BMI was in the lowest tertile of the distribution (BMI of < 25 kg/m², RR = 1.06, 95%CI: 1.01-1.12)^[160]. The authors stated that a limitation of their study and other studies in their meta-analysis was that only a single blood sample had been collected from each patient (Table 2).

IGF2

IGF2 is produced by the liver, but many tissues have the ability to synthesise this peptide. The hepatic synthesis of IGF2 is independent on GH. IGF2 plays a role during foetal development^[161].

Overexpression of IGF2 can modulate carcinogenic effects through IRA^[162], but the lower affinity of IGF2 for this receptor results in a less powerful activation in comparison with INS. It protects the receptor from downregulation.

IGF2 overexpression in tumour cells is associated with more advanced colorectal cancer and poor survival^[162,163]. Zhao *et al.*^[164] stated that the IGF2 serum levels are higher in patients with more advanced cancer. Other studies have shown that higher levels of circulating IGF2 are associated with better overall survival in CRC patients^[165]. Liou *et al.*^[166] indicated that higher plasma IGF2 levels are associated with better overall survival in colorectal cancer patients. The presence of loss of imprinting (LOI) of IGF2 is associated with the overexpression of IGF2 in tumours and with worse overall survival in metastatic patients. The authors concluded that the overexpression of IGF2 in tumours might not correlate with the circulating IGF2 levels. The bioavailability of IGF ligands might be higher in tumour tissues.

Matuschek *et al.*^[158] showed significantly elevated serum levels of IGF2 in a group of colorectal cancer patients (*n* = 21) compared to a healthy control group (*n* = 13) (*P* < 0.01), but sensitivity and specificity were only approximately 70%. There was no difference in the serum IGF2 levels between metastatic and local colorectal cancer patients, suggesting that IGF2 is not a tumour or prognostic marker. However, this study examined only very small groups. Thus, these results are preliminary, and more research should be conducted in this area in the future (Table 2).

IGF1R

The IGF1R is a transmembrane heterotetramer that consists of two α subunits and two β subunits. The α subunits are responsible for binding IGF1, and the β subunits are involved in the phosphorylation and synthesis of intracellular proteins. There is approximately 60% sequence homology between IGF1R and IR. IGF1R possesses tyrosine kinase activity. The postreceptor signal transduction includes the phosphorylation of IRS1 and the activation of PI3K and mitogen-activated protein kinases (MAPKs)^[115,167]. IGF2 and INS bind to IGF1R but with lower affinity than IGF1 (2- to 15- and 1000-fold, respectively)^[115]. IGF1R regulates cell proliferation through its signalling pathway, protecting cells against apoptosis or inducing cell growth. IGF1R is frequently overexpressed in human colorectal cells as well as in ovary, breast, endometrial, thyroid and glioma cells^[168]. IGF1R blockage results in the inhibition of tumour growth. IGF1R expression is significantly downregulated in adults but is still present in most tissues. The increased expression of IGF1R that is observed in some tumours may respond to paracrine, autocrine or circulating IGFs. Binding of IGF1 and IGF2 ligands to IGF1R promotes receptor autophosphorylation and activates various signalling pathways, including the MAPK and PI3-K/Akt1 pathways^[115].

IGF2R

The mammalian mannose 6-phosphate/IGF2 receptor (M6P/IGF2R) is a monomeric receptor that binds IGF2 with a 500-fold increased affinity over IGF1. IGF2R does not bind INS^[117]. Four classes of ligands bind to the extracytoplasmic receptor domain of IGF2R, lysosomal enzymes, IGF2, retinoic acid and urokinase-type plasminogen activator receptor^[169]. IGF2R is a tumour suppressor that regulates the internalisation and degradation of extracellular IGF2, thus mediating the circulating levels of IGF2. Another main function of the receptor is to regulate the intracellular trafficking of lysosomal enzymes^[169].

Recent data have indicated that IGF2R plays a crucial role in cancer prevention. Ouyang *et al.*^[170] observed loss of function mutations in the IGF2R gene in colorectal cancer. LOI of IGF2 leads to the overexpression of IGF2, and LOI of IGF2 is associated with increased susceptibility to colorectal cancer and more advanced disease in other several cancer types^[170,171].

IGFBP

Six IGF binding proteins (IGFBP-1-6) have a high affinity for IGFs, and four IGFBPs, also known as IGFBP-related proteins (IGFBP-rp-1-4), have a low affinity for IGFs. IGFBPs are tumour suppressors, and their increased expression attenuates the proliferative and anti-apoptotic effects of IGFs.

The majority of circulating IGFBPs are synthesised in the liver, but many organs are capable of producing these proteins. IGFBP-3 is the most abundant binding protein in the serum. IGFs are regulated by the IGFBP family. Some of these binding proteins have IGF-independent actions (IGFBP1, IGFBP3, IGFBP5 and IGFBP7)^[117]. IGFBP7 is representative of the IGFBP-rps. IGFBP-3 binds and sequesters the majority of the IGF1 ligands. It has been shown to inhibit proliferation and induce apoptosis in human colon cancer cells *in vitro* and in an experimental CRC animal model^[172-174]. Epidemiological studies showed that higher circulating IGF1 levels and lower IGFBP-3 levels independently correlate with increased CRC risk^[128]. However, such data has not been confirmed in all studies^[175]. *IGFBP3* and *IGFBP7* genes seem to be multifunctional genes, and their deregulation is related to metastatic CRC. In CRC patients, a significant correlation between the expression levels of these genes was noted, but no relation to overall survival was confirmed^[176]. IGFBP7 exhibits low affinity for the IGFBP ligands IGF1 and IGF2. IGFBP7 is expressed in many tumour types and is overexpressed in CRC tissue^[177]. Its expression is associated with a favourable prognosis in CRC patients. However, future research should explore the molecular role of IGFBP7.

Recently, Kaplan *et al.*^[178] demonstrated that there is no significant correlation between overall cancer mortality and circulating IGF1 or IGFBP3 levels. Another study indicated that the IGF1 and IGFBP3 levels show potential as prognostic markers, but in prostate cancer^[179]. In CRC, the risk of cancer may be associated with a higher IGF1/

IGFBP3 ratio and higher C-peptide levels^[180]. IGFBP3 modulates the activity of IGF1^[172]. Furthermore, high levels of IGFBP3 have been associated with reduced risk of CRC (RR, 0.28, 95%CI: 0.12-0.660)^[181]. The differences in these studies indicate that there is variability in the IGF1 levels and that many others factors, such as life style factors, influence the IGF system.

IGFBP-2 is another binding protein that modulates the interaction of IGFs with IGF1R. Some of studies have shown significant inverse associations between IGFBP1 and CRC^[182,183], but others have shown no association^[142].

CONCLUSION

The list of metabolic biomarkers with potential diagnostic and prognostic users in colorectal cancer patients is continuously growing. Results on the relationship between the levels of TC and TG and the risk of CRC have been inconsistent. High concentrations of serum HDL are associated with a decreased risk of colon cancer. The serum adiponectin, leptin, resistin and visfatin levels and/or the expression of its receptors may be good metabolic biomarkers of CRC. Hyperinsulinemia and hyperglycaemia could be biomarkers of the higher mortality from CRC, but the high IGF2 levels seemed to be connected with better overall survival in the patients. The high HbA1C as an independent predictor of aggressive clinical behaviour may be a prognostic biomarker in CRC patients. Additionally the risk factors of CRC are the IGF1 circulating levels and increased IGF1/IGFBP3 ratio as well.

In the future, technological advances will likely facilitate the use of biomarker profiling to individualize treatment of colorectal cancer. To validate the metabolic biomarkers as prognostic and predictive factors seemed to be evaluated as clinical trials proceed. More evidence from a large, epidemiological studies could improve understanding the CRC risk and prognosis as well.

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