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Review

Hyperinsulinaemia and hyperglycaemia: possible risk factors of colorectal cancer among diabetic patients

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Abstract

Hyperinsulinaemia and hyperglycaemia are two possible risk factors for colorectal cancer, which constitutes the third leading cause of cancer death in Western countries. Molecular evidence as well as animal models provide support for these associations: Insulin has been shown to be an important growth factor for colonic carcinoma cells, and both insulin and insulin-like growth factor-1 receptors have been detected in colon cancer tissue. The insulin-signal transduction pathway is involved in the regulation of gene expression and apoptosis. The role of hyperglycaemia in carcinogenesis could include pathways via luminal factors (related to fecal bile acid concentrations, stool bulk, and prolonged transit time) or circulatory factors (via glucose as the only energy source for neoplastic cells). This review summarizes the epidemiologic literature with respect to hyperinsulinaemia and hyperglycaemia as risk factors for colorectal cancer, and aims to integrate the biological and epidemiological evidence. Epidemiologic findings to date indicate a slightly increased risk of colorectal cancer for diabetic patients; however, there are some inconsistencies. Possible explanations for these inconsistencies include inadequate information about patients' diabetic disease and treatment states. We suggest that future studies should take medical history, staging and treatment for hyperinsulinaemia and hyperglycaemia into account to further our understanding of the role of hyperglycaemia and hyperinsulinaemia in colorectal carcinogenesis. [Diabetologia (2003) 46:595–607]

Keywords Diabetes mellitus, colorectal cancer, carcinogenesis, hyperglycaemia, hyperinsulinaemia, insulin resistance, IGF-1, epidemiology, review.

Colorectal cancer is a major public health problem, being the fourth most common cancer and the second most common cause of cancer death in the USA [1]. On an international scale, colorectal carcinoma ranks second in cancer incidence in the majority of developed countries with high-risk areas being North America, Western Europe, and New Zealand [2]. Risk factors for colorectal cancer or polyps include meat consumption, smoking, alcohol consumption, and a positive family history. Inverse associations exist with physical activity, vegetable or folate intake, and use of nonsteroidal anti-inflammatory drugs (NSAIDs) or hormone replacement therapy [3].

The digestive system supports an individual's basic physical needs for nutrition and energy. Glucose is one of the prime biochemical entities used for transportation, storage, and generation of energy. The blood glucose concentration is kept in homeostasis through a complex network of energy output, dietary intake and hormonal regulation, involving insulin, glucagon, epinephrine, growth hormone, and cortisol. If this homeostasis is disturbed, a series of pathoglycaemic disorders

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Abbreviations: DCCT, Diabetes Control and Complications Trial; IGFBP-3, IGF binding protein-3; NSAIDs, Nonsteroidal anti-inflammatory drugs; OTC, Over the counter; UKPDS, United Kingdom Prospective Diabetes Study.

can develop [4]. Insulin plays a key role in this regulatory process, with a concentration in healthy subjects of 0.4 to 0.8 ng/ml after an overnight fast. Abnormalities of insulin concentrations can be caused by autoimmune-mediated beta cell failure in the pancreas (Type 1 diabetes) or by insulin resistance (Type 2 diabetes). Type 1 diabetes mellitus arises in the early stage of life, while Type 2 diabetes mellitus is a degenerative disorder among older people with complex causes [5]. In Type 1 diabetes mellitus patients, insulin secretion decreases continuously along with the development of diabetes, and then induces hyperglycaemia when insulin secretion is insufficient. At the early stage of Type 2 diabetes, hyperinsulinaemia exists because of a compensatory response to insulin resistance, whereas in the later stages, beta-cell malfunction contributes to a hypoinsulinaemic response as diabetes mellitus progresses [5, 6]. Without proper control of hyperglycaemia, diabetic patients are at risk of cardiovascular disease, hypertension, retinopathy, nephropathy, neuropathy, dyslipidemia, and ketoacidosis [7]. Diabetes mellitus has become a crucial health issue with major public health impact all over the world [8].

Previous reviews on the link between hyperglycaemia, hyperinsulinaemia and colorectal cancer risk have focused on the aspects of underlying biological models [9, 10, 11, 12, 13], animal models [11], and some epidemiologic evidence [9, 12, 13, 14, 15]. The current review centres on a comprehensive summary of the epidemiological literature on diabetes and colorectal cancer risk, thus describing one important line of evidence regarding the insulin-colorectal cancer hypothesis. Suggestions are made regarding study designs addressing limitations inherent in previous studies that could have obscured the associations between hyperinsulinaemia, hyperglycaemia, and colorectal cancer.

Evidence linking hyperinsulinaemia and hyperglycaemia to colorectal cancer

Several risk factors observed in epidemiologic studies provide a link to hyperinsulinaemia or hyperglycaemia. Those include a "Western Lifestyle" with diets low in fruits and vegetables or fibre, and high in fat and cooked meat, restricted physical activity, and an increased BMI [3]. In molecular and animal studies, hyperinsulinaemia [10] and hyperglycaemia [9] have been shown to be independent risk factors of colorectal carcinogenesis. In the following sections, we briefly describe the proposed biological mechanisms.

Biological evidence supporting an association between hyperinsulinaemia and colorectal cancer

The biological mechanisms for insulin, insulin-like growth factors (IGF) and colon cancer have been extensively described [15]. Briefly, in vitro, insulin is an important growth factor for colonic mucosal cells and acts as a mitogen for colonic carcinoma cells [16, 17, 18]. Insulin-like growth factor-1 (IGF-1) inhibits apoptosis and is required for cell cycle progression [19]. Both normal colorectal epithelium and colon cancer tissue have insulin and IGF-1 receptors [20, 21]; upon activation by IGF-1, the receptor-ligand complex inhibits apoptosis with continuation of the cell cycle [16, 17, 18, 21]. Therefore, both pre-malignant and cancerous stages can be affected by IGF-1. IGF-1 could also enhance the production of vascular endothelial growth factor which is essential for angiogenesis and tumour growth [22]. IGF-2 can stimulate IGF-1 receptors, and colorectal tumours show increased concentrations of IGF-2 mRNA and secreted peptide [23, 24, 25]. The insulin-signal-transduction pathway can be mediated by activation of the PI3 kinases or by *ras* gene activation and is involved in the regulation of gene expression and mitogenicity [26, 27, 28]. Activating *ras* mutations occur in about half of colonic cancers [29]. Recently, positive associations between the plasma concentration of IGF-1 [30, 31] or concentrations of circulating C-peptide (a surrogate marker for insulin secretion) and colorectal cancer have been observed [30]. These findings were extended by showing that high concentrations of circulating IGF-1 and very low concentrations of insulin-like growth factor binding protein-3 (IGFBP-3) were associated independently with an increased risk of advanced colorectal adenomas and cancer [32].

The potential biological mechanisms linking insulin resistance to colorectal cancer by influencing cell growth and cell cycle control have been well described [11]. Nevertheless, it is possible that a particular factor could affect colon cancer risk both by influencing insulin concentrations and through other mechanisms [10, 11].

Biological evidence supporting an association between hyperglycaemia and colorectal cancer

There are at least two possible biological mechanisms linking hyperglycaemia to colorectal cancer. Among patients with diabetes, higher levels of fecal bile acid concentrations, greater stool bulk, and longer transit times have been observed [33]. It has been hypothesized that these luminal factors are involved in the carcinogenesis of the colorectal mucosa [34, 35]. In particular, fecal bile acids have been shown to promote colorectal neoplasia in animal models [36, 37, 38]. However, associations between stool transit time and colorectal cancer [39] or adenomatous polyps [40] were not observed in humans. This association warrants further investigation. Secondly, the energy supply to neoplastic cells might be important: In contrast to the normal colonic epithelium which is capable of

both aerobic and anaerobic metabolism, using short chain fatty acids, amino acids, and glucose as fuel [41], neoplastic cells switch from aerobic to anaerobic metabolism, requiring glucose rather than fatty acids for fuel [42]. Thus, plasma glucose might be associated with colorectal neoplasia by acting as a direct energy source to the tumour.

Animal studies investigating diets high in sucrose and low in dietary fibre support a positive association with colonic cell proliferation and growth rates of aberrant crypt foci [43, 44, 45, 46]. However, there is some, but insufficient, evidence regarding the relationship between colorectal cancer and plasma glucose [47, 48] or sugar intake [49] in humans.

Epidemiological studies investigating associations between hyperglycaemia or hyperinsulinaemia and colorectal cancer

Epidemiological studies of various designs have investigated associations between hyperglycaemia or hyperinsulinaemia and colorectal cancer risk. These studies include: (i) case-control and cross-sectional studies of patients with colorectal cancer or adenomas compared to appropriate control group(s) investigating exposures as a history of diabetes or impaired glucose tolerance; (ii) cohort studies of patients with diagnosed diabetes and subsequent risk of colorectal cancer; (iii) cohort studies using baseline measures for tracing insulin resistance or underlying diabetes and subsequent risk of colorectal cancer among general populations.

Case-control and cross-sectional studies

In the past two decades, several case-control or cross-sectional studies on the risk of colorectal cancer associated with diabetes have been conducted (Table 1), mostly reporting either no association or moderate positive associations: An approximately two-fold risk of overt diabetes has been reported in a comparison of colon/rectum cancer cases to lung cancer or hip fracture cases (hospital based) [50]. In a large multi-site cancer case-control study, prior history of diabetes was not found to be a risk factor for colorectal cancer compared to hospital controls [51]. Kune et al. examined several chronic illnesses as risk factors of colorectal cancer, without observing an increased risk associated with diabetes [52]. A series of case-control studies conducted in Northern Italy reported either no association, or a moderate positive association between Type 2 diabetes and risk of colorectal cancer [53, 54, 55]. However, a population-based case-control study conducted in Hawaii showed increased odds ratios (OR) for distal colorectal cancer among patients with diabetes (OR=1.9, 95% CI=1.1–3.5 for men; OR=3.0, 95% CI=1.2–7.1 for women) [56]. A recent report from Switzerland showed no substantial change in risk of colorectal cancer among men reporting a history of diabetes (OR=1.3, 95% CI=0.6–2.7), but a significantly increased risk among women (OR=3.6, 95% CI=1.1–12.1). The number of patients reporting a history of diabetes was small (21 cases and 18 controls), but the risk was substantially increased for individuals diagnosed with diabetes for five or more years (OR=4.1, 95% CI=1.6–10.8) [57].

Limitations of these studies were uncontrolled confounding factors [50], the use of hospital-based cases and controls [50, 51, 53, 54, 55, 57], and reliance on self-report for diabetes history [51, 52, 53, 54, 55, 57]. Lack of controlling for confounding factors could distort the associations between diabetes history and colorectal cancer. Hospital-based studies can result in a biased selection of control patients, in that they would not represent the general characteristics of the population where they come from. The United Kingdom European Prospective Investigation into Cancer was analyzed cross-sectionally for self-reported diabetes (Type 2 diabetes mellitus mostly) and prevalent colorectal cancer. The proportion of colorectal cancer cases with diabetes was 6.1%, whereas only 1.9% were observed among controls (OR=2.9, 95% CI=1.5–5.8) [58]. However, it is possible that a higher diagnosis rate for colorectal cancer among cases could have contributed to this increased risk.

Several recent studies used biomarkers associated with hyperglycaemia or hyperinsulinaemia, rather than the rather imprecise exposure measure of self-reported diabetes mellitus history. Kono et al. measured glucose tolerance status in Japanese men aged 48 to 59 years who received colorectal cancer screening by sigmoidoscopy as part of a pre-retirement health examination [59]. Glucose-tolerance status was used to classify participants as “normal”, “having impaired glucose tolerance”, “newly diagnosed Type 2 diabetes”, and “diabetes under treatment”. Adenoma risk was significantly increased among participants with newly diagnosed Type 2 diabetes (OR=1.4, 95% CI=1.0–2.0, adjusted for possible confounders). Of twenty-one individuals in the “diabetes under treatment” category, all showed a non-significant risk of similar magnitude (adjusted OR=1.3, 95% CI=0.8–2.2). Nevertheless, the cross-sectional nature of this study limits the conclusions that can be drawn. Another screening study in a similar setting showed no increased risk of adenomas among those with impaired glucose tolerance, but an increased risk associated with Type 2 diabetes mellitus (OR=2.2, 95% CI=1.1–4.0, adjusted for age and BMI) [60]. Overall, the results from case-control and cross-sectional studies on diabetes history provide only modest support to the hypotheses of hyperinsulinaemia and hyperglycaemia as risk factors for colorectal cancer. Studies of biomarkers associated with hyperinsulinaemia or

Table 1. Case-control and cross-sectional studies relating diabetes history or glucose intolerance to colorectal cancer or adenomas

Study	Location	Exposure	Study Population	Major Outcomes: Odds Ratios (95% CI)
Case-control Studies:				
Williams et al. (1984) [50]	Mississippi, USA	Diabetes history	Cases: 696 colon cancer cases, and 252 rectal cancer cases from three medical centres Controls: 1916 admitted lung cancer and 1662 hip fracture inpatients from the same hospitals	Compared to lung cancer cases$^{(C)}$: Colon: 2.0 (1.5–2.8) Rectum: 1.8 (1.1–2.9) Compared to hip fracture cases$^{(C)}$: Colon: 2.3 (1.6–3.2) Rectum: 2.0 (1.2–3.3)
O'Mara et al. (1985) [51]	Buffalo, NY, USA	Diabetes history	Cases: 335/295 white females & 277/379 males with colon/rectal cancers Controls: 2475 white females & 2363 males admitted without neoplastic conditions	Males$^{(AS)}$: Colon: 1.2 Rectum: 1.1 Females$^{(AS)}$: Colon: 1.4 Rectum: 1.0 (95% CIs not provided; all non-significant)
Kune et al. (1988) [52]	Melbourne, Australia	Diabetes history	Cases: 715 colorectal cancers Control: 727 age/sex matched controls in community	Total$^{(AS)}$: 1.0 (0.6–1.7) Males$^{(AS)}$: 1.3 (0.7–2.5) Females$^{(AS)}$: 0.8 (0.4–1.6)
La Vecchia et al. (1991) [53]	Greater Milan area, Italy	Diabetes history	Cases: 673 colon cancers & 405 rectal cancers Controls: 1501 hospital controls admitted for acute, non-neoplastic, non-digestive tract conditions	Colon$^{(MV)}$: 1.7 (1.1–2.5)[a] Rectal$^{(MV)}$: 1.5 (1.0–2.5)[a]
La Vecchia et al. (1994) [54]	Greater Milan area, Italy	Diabetes history	Cases: 828 colon cancers & 498 rectal cancers Controls: 7834 hospital controls admitted for acute, non-neoplastic, non-metabolic, non-hormone-related conditions	Colon$^{(AS)}$: 1.1 (0.8–1.5) Rectal$^{(AS)}$: 0.9 (0.6–1.3)
La Vecchia et al. (1997) [55]	Six areas in northern, central, and southern Italy	Diabetes history	Cases: 1225 colon cancers & 728 rectal cancers Controls: 4154 hospital controls admitted for acute, non-neoplastic, non-digestive tract conditions and required no long-term modification of diet from the same surveillance areas	Total$^{(MV)}$: 1.3 (1.0–1.6)[b] Colon$^{(MV)}$: 1.2 (0.8–1.6)[b] Rectal$^{(MV)}$: 1.5 (1.1–2.2)[b] Colorectal cancer$^{(MV)}$: Males: 1.4 (1.0–1.9)[b] Female: 1.2 (0.8–1.8)[b]
Le Marchand et al. (1997) [56]	Hawaii, USA	Diabetes history	Cases: 698 male and 494 female colorectal cancers Controls: 1192 age/sex/ethnicity-matched community residents	Males$^{(MV)}$: Total: 1.2 (0.8–1.7) Proximal colon: 1.0 (0.4–1.8) Distal colon: 1.9 (1.1–3.5) Rectum: 0.7 (0.3–1.6) Females$^{(MV)}$: Total: 1.8 (1.1–2.8) Proximal colon: 1.3 (0.6–2.7) Distal colon: 3.0 (1.2–7.1) Rectum: 1.7 (0.7–4.4)
Levi et al. (2002) [57]	Canton of Vaud, Switzerland	Diabetes history	Cases: 174 male and 112 female colorectal cancer patients, University Hospital of Lausanne, Switzerland Controls: 550 (269 men, 281 women) residents admitted to the same hospital for acute non-neoplastic conditions	All$^{(MV)}$: 1.8 (0.95–3.2)[c] Men$^{(MV)}$: 1.3 (0.6–2.7)[c] Women$^{(MV)}$: 3.6 (1.1–12.1)[c]

Table 1. (continued)

Study	Location	Exposure	Study Population	Major Outcomes: Odds Ratios (95% CI)
Cross-sectional studies:				
Kono et al. (1998) [59]	Japan	Glucose tolerance status	Screening Study Cases: 821 male self-defense officials with sigmoid colon adenomas Controls: 4372 men from the same civil servant population	Impaired glucose tolerance$^{(MV)}$: 1.1 (0.9–1.4)[d] New diagnosed Type 2 DM$^{(MV)}$: 1.4 (1.0–2.0)[d] DM under treatment$^{(MV)}$: 1.3 (0.8–2.2)[d]
Nishii et al. (2001) [60]	Japan	Glucose tolerance status	Screening Study Cases: 233 men from Japan Self Defence Forces Fukuoka Hospital with colon adenomas Controls: 497 men from the same hospital with normal colonoscopy	Impaired glucose tolerance$^{(MV)}$: 1.0 (0.6–1.5)[e] Type 2 DM$^{(MV)}$: 2.2 (1.1–4.0)[e]
Sandhu et al. (2001) [58]	East Anglian, UK	Self-reported diabetes history	European Prospective Investigation into Cancer Cases: 126 prevalent cases of colorectal cancer Controls: 28,644 participants without prevalent cancer	All$^{(MV)}$: 2.9 (1.5–5.8)[f] Men$^{(MV)}$: 3.1 (1.3–7.3)[f] Women$^{(MV)}$: 2.5 (0.8–8.3)[f]

( ): Methods of adjustment; C: crude odds ratio, AS: age- or age/sex-adjusted odds ratio, and MV: Multivariate adjusted odds ratio

[a] Adjusted for age, sex, area of residence, education, BMI, and selected indicator foods (pasta or rice, meat, green vegetables, fresh fruits and coffee)

[b] Adjusted for age, sex, centre, education, body mass index, family history of colorectal cancer, physical activity, fat, total energy and fiber and alcohol intake

[c] Adjusted for age, smoking status, BMI, education, and alcohol consumption

[d] Adjusted for body mass index, cigarette smoking, alcohol use, rank of the Self Defence Forces, and hospital

[e] Adjusted for age and BMI

[f] Adjust for age, smoking status, BMI, education, and alcohol consumption

hyperglycaemia show increased risks, ranging from moderate to strong associations.

Prospective studies

In the past two decades, fifteen cohort studies, usually among diabetic patients, addressed the association between diabetes, hyperinsulinaemia, hyperglycaemia and colorectal cancer. Several of these studies were conducted in Nordic countries (Table 2).

Studies using cohorts of diabetic patients. The approach of using cohorts of diabetic patients and comparing the incidence in this group to the general population ensures a sufficient number of exposed individuals. A weakness of this design is the limited amount of data that can be collected from the comparison group (usually the general population), thus reducing the possibility to adjust for confounding factors beyond sex and age.

Most cohort studies of patients with diabetes reported moderately increased risks of colorectal cancer compared to the general population, with standardized incidence ratios (SIR, the standardized incidence ratio, is the ratio of total observed case number in the exposed group to the sum of expected case numbers, calculated by exposed persons in each specific age group multiplied by its compared age-specific incidence rate.) ranging from 1.0 to 1.4 (Table 2). The first cohort study was carried out in Rochester, Minnesota, USA among 1135 diabetic cases followed up for 25 years (SIR=1.2, 95% CI=0.7–1.8) [61]. However, the increased risk was only found among men. Several Nordic cohort studies reported similar findings [62, 63, 64, 65, 66]. For example, one study observed a significantly increased incidence of colon cancer (SIR=1.4, 95% CI=1.3–1.5) and rectal cancer (SIR=1.2, 95% CI=1.1–1.4) among more than 150 000 population-based diabetic patients compared to the Swedish population, with a slightly higher excess risk for proximal and sigmoid colon cancers [65]. Wideroff et. al. followed more than 100 000 subjects diagnosed with diabetes and observed a similarly increased risk for colon cancer among men (SIR=1.3, 95% CI=1.1–1.4), and a very slightly increased risk among women (SIR=1.1, 95% CI=1.0–1.2) [66].

As discussed previously, possible uncontrolled confounding was a limitation for these studies [61, 62, 63, 64, 65, 66, 67]. Another restriction was the utilization of hospital-discharged diabetic patients as the exposed group [63, 65, 66], which could have led to falsely

Table 2. Prospective studies investigating associations between diabetes, hyperinsulinaemia, hyperglycaemia, and colorectal cancer (SIR, standardized incidence ratio; SMR, standardized mortality ratio; RR, relative risk)

Study	Location	Exposure	Study Population	Major Outcomes (95%CI)
Cohorts of patients with diabetes				
Ragozzino et al. (1982) [61]	Rochester, Minnesota, USA	Initial diagnosis of diabetes mellitus* (25-year follow-up)	Exposed group: 1135 initially diagnosed diabetic patients (120 cases) Comparison group: Rochester population	Total: SIR=1.2 (0.7–1.8) for colorectal cancer Male: SIR=1.3 (0.6–2.4) for colorectal cancer Female: SIR=1.0 (0.4–2.0) for colorectal cancer
Green et al. (1985) [62]	Fyn County, Denmark	Insulin-treated diabetes* (8.5-year follow-up)	Exposed group: 783 male and 716 female insulin-treated diabetic subjects (17 cases for stomach, colon, and rectal cancer) Comparison group: Danish population	SIR=1.3 (0.8–2.1) for stomach, colon, and rectal cancer combined
Adami et al. (1991) [63]	Uppsala, Sweden	Discharge diagnosis of diabetes* (18-year follow-up)	Exposed group: 23,146 male & 27,862 female population-based diabetic patients (325 cases) Comparison group: six-county Uppsala Healthy Care Region population	Male: SIR=1.2 (0.9–1.4) for colon; 1.3 (1.1–1.7) for rectum Female: SIR=1.0 (0.8–1.2) for colon; 0.9 (0.7–1.2) for rectum
Smith et al. (1992) [67]	London, England	Previously diagnosed diabetes* (19-year follow-up)	Whitehall Study Exposed group: 224 male civil servants with a plasma glucose level of ≥ 200 mg/100 ml or with previously diagnosed diabetes (1 death from colon cancer) Comparison group: 17,051 male normoglycaemic civil servants	Diabetic men: SMR=0.6 (0.1–4.5) for colon cancer
Hjalgrim et al. (1997) [64]	Funen County, Denmark	Insulin treated diabetes* (19,511 person-years of follow-up)	Danish National Conscript Registry Exposed group: 1499 insulin treated diabetic patients (37 cases for cancers for digestive organs and peritoneum combined) Comparison group: Danish population	Cancers for digestive organs and peritoneum combined: SIR=1.3 (0.6–2.6) for those diagnosed with diabetes before 30 years old; SIR=1.1 (0.7–1.5) for those diagnosed with diabetes after age of 30
Weiderpass et al. (1997) [65]	Sweden	Discharge diagnosis of diabetes* (6 to 24-year follow-up)	Exposed group: 153,852 population-based diabetic patients (1,435 cases) Comparison group: Swedish population	Male: SIR=1.4 (1.2–1.5) for colon cancer; 1.4 (1.2–1.5) for rectal cancer Female: SIR=1.4 (1.3–1.6) for colon cancer; 1.1 (0.9–1.3) for rectal cancer
Wideroff et al. (1997) [66]	Denmark	Discharge diagnosis of diabetes* (628,129 person-years of follow-up)	Danish Central Hospital Discharge Register Exposed group: 109,581 nationwide subjects diagnosed with diabetes (1257 cases) Comparison group: Danish population	Males: SIR=1.3 (1.1–1.4) for colon cancer; 1.1 (0.9–1.2) for rectal cancer Females: SIR=1.1 (1.0–1.2) for colon cancer; 1.0 (0.9–1.2) for rectal cancer
Cohorts of the general population, evaluating diabetes history as exposure				
Steenland et al. (1995) [68]	USA	Self-reported diabetes history* (15-year follow-up)	National Health and Nutrition Survey I (NHANES1) Exposed group: 522 self-reported diabetes at baseline (176 cases for colorectal cancer) Comparison group: 12,532 nondiabetes reported NHANES1 subjects matching on race and follow-up time	Men: Adjusted RR=1.4 (0.6–3.3) for colorectal cancer[a] Women: Adjusted RR=1.4 (0.6–3.1) for colorectal cancer[a]

Table 2. (continued)

Study	Location	Exposure	Study Population	Major Outcomes (95%CI)
Will et al. (1998) [69]	USA	Self-reported diabetes history* (13-year follow-up)	First Cancer Prevention Study of the American Cancer Society Exposed group: 7229 male and 8258 female volunteers diagnosed with diabetes (7224 cases) Comparison group: 848,212 recruited volunteers without diabetes	Men: Adjusted RR=1.3 (1.0–1.7) for colorectal cancer[b] Women: Adjusted RR=1.2 (0.9–1.5) for colorectal cancer[b]
Hu et al. (1999) [70]	USA	Self-reported diabetes history** (18-year follow-up)	Nurses' Health Study Exposed group: 7069 women with history of diabetes (62 cases) Comparison group: 111,003 women without history of diabetes	Adjusted RR=1.4 (1.1–1.9)[c]
Nilsen et al. (2001) [71]	Nord-Trondelag county, Norway	Diabetes history* (follow-up for medium of 10.8 years)	Nord-Trondelag Health Survey Exposed group: 6510 person-years for men and 8202 person-years for women with history of diabetes (37 cases) Comparison group: all residents in Nord-Trondelag county aged 20 years or older (357,986 and 376,715 person-years, respectively)	Men: SIR=0.7 (0.4–1.2) for colorectal cancer Women: SIR=1.6 (1.0–2.3) for colorectal cancer
Cohorts evaluating biomarkers of insulin-resistance				
Smith et al. (1992) [67]	London, England	Impaired glucose tolerance (19-year follow-up)	Whitehall Study Exposed group: 999 male nondiabetic civil servants with glucose concentrations above the 95thcentile (6 deaths from colon cancer) Comparison group: 17,051 male normoglycaemic civil servants	Men with impaired glucose tolerance: SMR=0.8 (0.4–1.8) for colon cancer
Schoen et al. (1999) [72]	USA	Fasting glucose, 2-hr glucose, Fasting insulin, and 2-hr insulin at baseline (follow-up for medium of 77 months)	Cardiovascular Health Study Population-based cohort with 5888 subjects aged 65 years old or more (mostly minority groups, excluding treated diabetic subjects) (102 cases)	Q4/Q1 of fasting glucose: RR=1.8 (1.0–3.1) for colorectal cancer; Q4/Q1 of 2-hr glucose: RR=2.4 (1.2–4.7) for colorectal cancer; Q4/Q1 of fasting insulin: RR=1.2 (0.7–2.1) for colorectal cancer; Q4/Q1 of 2-hr insulin: RR=2.0 (1.0–3.8) for colorectal cancer.
Platz et al. (1999) [73]	USA	Glycosylated haemoglobin (HbA_{1c}) (follow-up for about 4 years)	Nurses' Health Study Cases: 79 women with colorectal cancer Controls: 156 controls matched on year of birth, month of blood draw, and fasting state	Tertile3/tertile1 of HbA_{1c}: OR=1.2 (0.6–2.7) for colorectal cancer OR=4.6 (1.2–17.1) for advanced colorectal cancer
Nilsen et al. (2001) [71]	Nord-Trondelag county, Norway	Non-fasting blood glucose level (follow-up for medium of 10.8 years)	Nord-Trondelag Health Survey Exposed group: 11,302 person-years for men and 6502 person-years for women with non-fasting blood glucose level ≥ 8.0 mmol/l (46 cases) Comparison group: all residents in Nord-Trondelag county aged 20 years or older	Men: SIR=0.9 (0.6–1.4) for colorectal cancer Women: SIR=2.0 (1.3–3.0) for colorectal cancer

Table 2. (continued)

Study	Location	Exposure	Study Population	Major Outcomes (95%CI)
Trevisan et al. (2001) [74]	Italy	Insulin resistance (7-year follow-up)	Risk Factor and Life Expectancy Project Exposed group: 1185 persons with insulin resistance syndrome (6 cases) Comparison group: 36,116 persons without insulin resistance syndrome (48 cases)	Total: RR=3.0 (1.3–7.0) for colorectal mortality Male: RR=3.0 (1.1–8.3) for colorectal mortality Female: RR=2.7 (0.6–12.5) for colorectal mortality
Colangelo et al. (2002) [75]	Chicago, USA	Post-load plasma glucose (PLG) level (866,926 person-years of follow-up)	Chicago Heart Association Detection Project in Industry Population-based cohort with 20,433 men and 15,149 women without diabetes at baseline; follow-up since 1967 (317 colorectal cancer deaths)	Men (PLG, mg/dl): ≤119: RR=1 (reference) 1 20–159: RR=1.1 (0.8–1.6)[d] 160–199: RR=0.8 (0.5-1.3)[d] ≥200: RR=1.5 (0.9–2.4)[d] Women (PLG, mg/dl): ≤119: RR=1 (reference) 120–159: RR=1.8 (1.1–2.8)[d] 160–199: RR=1.4 (0.8–2.4)[d] ≥200: RR=1.9 (1.04–3.6)[d]

[*] Not discriminating between Type 1 and Type 2 diabetes mellitus (DM)
[**] Type 2 DM only
[a] Adjusted for age, BMI, smoking, alcohol, income, and recreational physical activity
[b] Exact controlling factors were not specified
[c] Adjusted for age, time period, BMI, smoking before age 30, menopausal status, multivitamin supplement use, alcohol consumption, average hours per week of moderate or vigorous activity, aspirin use, parental history of colorectal cancer, and red meat consumption
[d] Adjusted for age, race, education, and height

low associations by including diabetic patients in the comparison group. Most of these studies did not distinguish between Type 1 and Type 2 diabetes, although the vast preponderance of patients would be Type 2 diabetes [61, 62, 63, 64, 65, 66, 67]. Types of diabetes could differ in etiology and exposure to internal or environmental factors of importance for initiation or promotion of colorectal cancer. The number of colon cancer cases in the exposed group was small in several studies [62, 64, 67]. However, most studies with at least 100 exposed cases reported consistently increased SIRs, ranging between 1.1–1.4 [61, 65, 66].

Cohort studies among the general population. Several prospective studies evaluated diabetes history as a risk factor among the general population, or included baseline measures for evidence of insulin resistance or diabetes (Table 2). Major strengths of this design are the ability to control for confounding factors and elimination of selection bias. Studies investigating the risk of colorectal cancer associated with a history of diabetes reported slightly increased relative risks (ranging from 1.2 to 1.4) [68, 69, 70]. These included NHANES1, the First Cancer Prevention Study of the American Cancer Society, and the Nurses' Health Study, in which a significantly elevated relative risk was observed (adjusted RR=1.4, 95% CI=1.1–1.9). A Norwegian study reported an increased risk only among women, but not for men (women: SIR=1.6, 95% CI=1.0–2.3; men: SIR=0.7, 95% CI=0.4–1.2) [71]. Overall, these well-designed cohort studies provide support for a slightly increased risk of colorectal cancer associated with a history of diabetes.

Cohorts evaluating biomarkers of insulin-resistance. Several prospective studies used surrogate indicators for hyperinsulinaemia or hyperglycaemia and assessed future colorectal cancer incidence or mortality (Table 2). Impaired glucose tolerance (the sub-clinical stage of Type 2 diabetes) was found to be a negative (but not significant) predictor of colon cancer deaths among men (Standardized mortality ratio: SMR=0.8, 95% CI=0.4–1.8) [67]. (The standardized mortality ratio (SMR) is equivalent to the SIR, but replaces the age-specific incidence rate by the age-specific mortality rate.) However, assessing colon cancer mortality rather than incidence can result in biased findings for etiology. Diabetes is not only a possible risk factor, but also an important determinant of survival for colorectal cancer cases.

The Cardiovascular Health Study provided the first direct evidence of the association between glucose/insulin concentration and colorectal cancer in the elderly (65 years old or more) [72]. 2-h post-challenge glucose concentration was shown to be a significant risk factor of colorectal cancer (Q4/Q1 RR=2.4, 95% CI=1.2–4.7, Q: quartile, i.e. 25%), whereas fasting glucose (Q4/Q1 RR=1.8, 95% CI=1.0–3.1) and 2 h post-challenge insulin concentrations (Q4/Q1 RR=2.0, 95% CI=1.0–3.8) were positively associated, with borderline statistical significance [72]. These findings were replicated by Nilsen et al. for women (SIR=2.0,

95% CI=1.3–3.0), but not for men (RR=0.9, 95% CI=0.6–1.4) (Nord-Trondelag Health Survey) [71]. Subjects with abnormal insulin/glucose measurements could have been potentially Type 2 diabetic patients. A limitation of these studies was that they did not collect information about anti-diabetic treatment regimens during the follow-up period. A case-control study nested in the Nurses' Health Study with a follow-up period of about 4 years used measurements of HbA_{1c} as an indicator of previous 2-month glycaemia concentration (direct) and blood insulin concentration (indirect). Although the risk associated with overall colorectal cancer or adenomas was not significantly increased, they observed a substantially increased risk for advanced colorectal cancer (OR=4.6, 95% CI=1.2–17.1), which indicates that hyperinsulinaemia might foster the progression of colorectal cancer [73]. As discussed by the authors, a weakness of this study was that blood samples were not collected substantially prior to diagnoses of cases (1989–90 vs 1989–94); thus, HbA_{1c} might not have reflected glycaemia status prior to the incidence of colorectal cancer, and measures could have been affected in some cases by subclinical colorectal cancer. Besides, HbA_{1c} could be a problematic marker of the average blood insulin concentration because different antidiabetic agent interventions would result in different insulin concentrations with similar HbA_{1c} percentage.

"X syndrome" (a cluster of metabolic abnormalities associated to insulin resistance—serum triglycerides, HDL cholesterol, glucose, and blood pressure) was treated as the main risk factor for colorectal cancer mortality in a combined cohort. An approximate three-fold increased risk was observed with RRs of 3.0 (95% CI=1.1–8.3), 2.7 (95% CI=0.6–12.5), and 3.0 (95% CI=1.3–7.0) for men, women, and both sexes combined respectively [74]. A recent large cohort study utilized 1-h post-load plasma glucose concentrations as an indicator of hyperinsulinaemia [75]. Both men and women with the highest post-load plasma glucose concentrations (>200 mg/dl) were found at risk of somewhat greater colorectal cancer mortality (men: RR=1.5, 95% CI=0.9–2.4, women: RR=1.9, 95% CI=1.04–3.6) than those with the lowest concentrations (<120 mg/dl). Major limitations in these two studies were the use of mortality rather than incidence as the end point and regardless of medicine interventions, but the findings provide evidence for a modest association between insulin resistance syndrome and colorectal cancer mortality.

Results among specific sub-groups

Considering a slightly increased risk associated with a history of diabetes, hyperinsulinaemia, or hyperglycaemia, the question arises whether there are any subgroups of patients that are at particular risk. Are the associations consistent across men and women or do they differ for different sites of the colorectal tract? Several studies explored stratification by sex, colorectal cancer site, exposure time period, age at diagnosis of cancer or diabetes, and type of diabetes mellitus.

Sex differences. Six studies reported an increased risk of colorectal cancer among male diabetic patients but not in women [52, 58, 61, 63, 66, 74], in contrast to five others showing higher risks of colorectal or colon cancer for women, rather than men [53, 56, 57, 71, 75]. Several other studies did not report sex differences [51, 54, 55, 65, 68, 69, 74, 75]. Therefore, there is currently no consistent evidence for a differential association between diabetes and colorectal cancer among men and women.

Site-specific associations. Among the studies investigating site-specific associations, no consistent patterns were observed. However, the case numbers were often small, limiting statistical power. For colon cancer, an increased risk was detected in four studies [50, 53, 65, 66], and similarly for rectal cancer [50, 53, 55, 63, 65]. Some studies suggest that proximal and distal colon tumours differ in their histopathologic characteristics, precursor lesions, and patterns of associated molecular alterations and could be considered different entities [71, 76], and some studies have reported risk estimates stratified by tumour site [56, 60, 65, 70]. In two cohort studies [65, 70] and one cross-sectional study [60], higher relative risks were detected for proximal colon tumours than those of the distal colon. However, a case-control study in Hawaii reported a higher risk of cancers in the distal colon in both men and women [56]. Thus, the current evidence regarding differences by tumour location is inconsistent, but indicates possibly a stronger association for the proximal colon.

Timing and duration of exposure. Studies investigating the temporal effects of an association between diabetes mellitus and colorectal cancer can provide clues to the underlying molecular mechanisms about the effect of hyperinsulinaemia/hyperglycaemia to different stages of colonic carcinogenesis. Some studies reported stronger associations with a longer time period between diagnosis of diabetes and colorectal cancer. La Vecchia et al. observed significantly increased odds ratios for rectal cancer, but not colon cancer, in patients with diabetes for ≥10 years compared to those diagnosed less than 10 years previously [55]. The risk for colorectal cancer was substantially increased for individuals diagnosed with diabetes for five or more years (OR=4.1, 95% CI=1.6–10.8) in Levi et al.'s study [57]. In the Nurses' Health Study, an increased risk of colorectal cancer was observed for patients with 11 to 15 years of diabetes history, but not for those with ≤10 years [70]. The authors suggested as a possible explanation that patients with long-term Type 2 diabetes

could be more likely to be hypoinsulinaemic over longer periods due to pancreatic beta-cell decay [15]. Nevertheless, a Swedish study reported significantly increased risks of colon cancer among diabetic patients, with SIRs ranging from 1.3 to 1.5, independent from the time of follow-up (1–4 years, 5–9 years, and 10–24 years), but the risks decreased by time length of follow-up for rectal cancer (SIRs=1.29, 1.25, 1.10, respectively) [65].

Age at diagnoses of diabetes mellitus or colorectal cancer. The age of onset of diabetes mellitus provides information regarding the relative importance of Type 1 (early onset in life) versus Type 2 (generally late onset) diabetes in colon carcinogenesis. Differences in findings between these two subtypes of diabetes mellitus could provide evidence for the underlying biological mechanisms and timing of diabetes progression. Although the data are scarce, there is some indication that a diagnosis of diabetes at an older age is more likely to be a risk factor for colon or rectal cancer [55, 66]. In the series of studies from Italy, only patients diagnosed with colon or colorectal cancer >60 years old show an increased risk associated with diabetes [53, 55]. Thus, one could hypothesize, that Type 2 diabetes (and insulin resistance) is of greater relevance in colorectal carcinogenesis. Overall, no patterns with respect to the temporal sequence emerged, which might be attributable to small sample sizes, or the inherent difficulty of measuring the "onset" of the exposures of hyperinsulinaemia and hyperglycaemia.

Challenges for investigating the association between diabetes, hyperinsulinaemia, hyperglycaemia, and colorectal cancer

Treatment modalities for diabetes can modify the relationship between insulin and glucose concentration, and thus need to be considered when evaluating the association between diabetic status and colorectal cancer. Diabetic treatment strategies have been continuously improved over the past decades. For the majority of Type 1 diabetic treatments, subcutaneous insulin injections are necessary, usually in combination with a controlled diet, exercise, self-monitoring of blood glucose, and routine monitoring of glycosylated haemoglobin (HbA_{1c}), urine glucose and urine ketones [77]. Potential alternative treatments, (e.g. islet cell transplantation or gene therapy) are still under experimental investigation [78, 79]. Among Type 2 patients, diet therapy, behavioural weight control, exercise, oral medications, and, eventually, insulin replacement are utilized to control blood glucose concentrations [77]. Furthermore, a combination therapy of insulin and oral antidiabetic agents is becoming increasingly used [80]. One category of antidiabetic agents increase insulin secretion by enhancing exocytosis of insulin-containing secretory granules (sulfonylureas) or by increasing calcium influx on beta-cell membranes (meglitinides). The other increases the peripheral glucose uptake and utilization (biguanides), influences insulin receptor activities and hepatic glucose uptake (thiazolidinediones), or delays glucose absorption and lower postprandial hyperglycaemia (alpha-glucosidase inhibitors) [81]. Thus, the first category raises insulin concentrations, while the latter one could possibly decrease insulin concentrations.

Few studies to date have investigated the association between Type 1 diabetes and colon cancer risk. Researching the association between Type 1 diabetic patients and colorectal cancer is challenging, and statistical power is usually limited: the exposure is rare and occurs at an early age, thus requiring a long follow-up period in cohort studies. Among patients with Type 1 diabetes undergoing adequate treatment, insulin concentrations usually stay within a similar range as in healthy individuals, while glucose concentrations are increased [7, 82]. Therefore, using a study population of Type 1 diabetic patients will not provide an adequate setting for testing the hypothesis of hyperinsulinaemia as a risk factor of colorectal cancer. However, comparing these patients to healthy individuals can provide information regarding the hypothesis on hyperglycaemia and colorectal cancer.

In contrast, among Type 2 diabetic patients, insulin concentrations depend on their stage of diabetes and the antidiabetic medications used. At the early stage of (untreated) Type 2 diabetes, fasting insulin concentrations are increased, representing insulin resistance. An increase in exercise, use of oral antidiabetic agents, and body weight loss would delay or even prevent the need for insulin injections [7, 83]. One can infer that insulin concentrations must be higher in Type 2 patients who are untreated or treated conservatively only by diet control or increased physical activity. Among patients taking oral antidiabetics, they would be higher in those treated with sulfonylureas or meglitinides (drugs with the mechanism of increasing blood insulin concentration) than in those treated with biguanides, thiazolidinediones, or alpha-glucosidase inhibitors (drugs with the mechanism of increasing sensitivity to insulin). Thus, treatment modalities might be important factors that could obscure associations, and need to be taken into account when addressing the research question of hyperinsulinaemia, hyperglycaemia, and colorectal cancer.

Future research directions

As illustrated above, the diagnosis of diabetes by itself is only a crude surrogate measure of hyperinsulinaemia because insulin concentrations mostly depend on the severity of diabetes and treatment modalities (es-

pecially for Type 2 diabetic patients). Future studies should aim to obtain specific information on these modifying factors, and ideally use records of blood glucose tests obtained during routine outpatient visits of diabetic patients. These measures could be obtained either prospectively in a cohort of Type 2 diabetic patients (comparing patients with poor glucose control to the ones with appropriate controls), or retrospectively for patients enrolled in large health plans (comparing cases/controls about their diabetes history, treatments carried out, and results of glucose control) like the Baltimore Longitudinal Study of Aging (BLSA) [84]. HbA_{1c} measurements would provide additional information regarding treatment efficacy and thus the endogenous exposure to insulin and glucose [77, 85]. We suggest using insight in the natural history of diabetes, its clinical course, and the management with oral agents with different mechanisms to refine current research methods. Meanwhile, there is emerging evidence that the long-term use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) can prevent colorectal neoplasia. In addition to several well-designed retrospective and prospective studies [86, 87, 88, 89, 90] and intervention studies among patients with familial adenomatous polyposis [91, 92], two recent secondary prevention trials of colorectal adenomas showed a reduction in polyp risk among aspirin users [93, 94]. Since many diabetic patients may use aspirin or NSAIDs for pain relief or cardiovascular disease prevention, this factor needs to be taken into account in future studies. If the proportion of aspirin/NSAID users among diabetic patients was larger than in the general population, potential confounding could be introduced that would mask a truly higher risk of colon cancer associated with diabetes mellitus.

In conclusion, most epidemiological studies summarized in this review support a slightly increased risk of colorectal cancer associated with diabetes or indicators of insulin resistance. However, limitations inherent in the studies undertaken to date could have restricted our ability to understand the true association between diabetes and colorectal cancer, as well as the underlying molecular mechanisms. Misclassification due to crude exposure measurements may have biased the observed associations towards the null. We suggest utilizing information on the natural course of diabetes mellitus, its specific treatment modalities, and biomarkers of endogenous exposure to further elucidate the relationship between diabetes, hyperinsulinaemia, hyperglycaemia, and colorectal cancer.

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