Chapter 10

Diabetes and Cancer

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Additional information is available at the end of the chapter

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1. Introduction

Diabetes and cancer are two common conditions. Many epidemiological studies suggest frequent co-occurrence of diabetes and cancer. Meta-analyses and the summary of recommendations from the American Diabetes Association (ADA) and American Cancer Society suggest association of cancer and diabetes including liver, pancreas, endometrial, colorectal, breast and bladder cancers.[1] Diabetes appears to protect against prostate cancer based on decreased incidence of prostate cancer in subjects with diabetes. Lung cancer appears not to be associated with diabetes, and data is inconclusive for renal cell cancer and lymphoma.[1] Most of the association data is on the relation of cancer to type 2 diabetes. The major concern is that type 2 diabetes is associated with three of the five leading causes of cancer mortality such as carcinoma of the colon [2], pancreas [3] and breast (postmenopausal) [4]. The excess risk for each cancer is ~30% (colon), ~50% (pancreas) and ~20% (breast). The majority of the epidemiological data on cancer incidence and mortality had been obtained in type 2 diabetic patients. A cohort study to examine cancer incidence among 29,187 patients in Sweden who were hospitalized for type 1 diabetes from 1965 through 1999, observed 355 incident cases of cancer and which corresponded to a 20% increase in overall cancer incidence among type 1 diabetes patients (RR:1.2; CI: 1.0 to 1.3) [5]. Patients with type 1 diabetes had elevated risks of cancers of the stomach (RR: 2.3; CI: 1.1 to 4.1), cervix (R: 1.6; CI: 1.1 to 2.2), and endometrium (RR: 2.7; CI: 1.4 to 4.7) [5]. Hyperinsulinemia most likely favors cancer in diabetic patients as insulin is a growth factor with pre-eminent metabolic as well as mitogenic effects. Insulin action in malignant cells is favored by mechanisms acting at both the receptor and post-receptor level. Obesity, hyperglycemia, and increased oxidative stress may also contribute to increased cancer risk in diabetes [6]. There are reports of concern of hypoglycemic therapies on cancer risk, especially with insulin analogue-Glargine. A growing body of evidence suggests that metformin potentially reduces the risk of cancer. Aspirin and non-aspirin non-steroidal anti-inflammatory drugs appear to reduce recurrence of adenomas and incidence of

advanced adenomas in individuals with an increased risk of colorectal adenomas and colorectal cancer, and calcium may reduce recurrence of adenomas [7, 8]. In this chapter we will include epidemiological evidence of association of diabetes and cancer, possible mechanisms and the effect of hypoglycemic agents in relation to cancer.

2. Epidemiology of diabetes and cancer risk

The Centers for Disease Control and Prevention (CDC) reports that 25.8 million people (8.3% of the U.S. population) have diabetes. Among them, 18.8 million people have diagnosed diabetes and 7.0 million people have undiagnosed diabetes. http://www.cdc.gov/diabetes/pubs/estimates11.htm#1. Three hundred and forty six million people worldwide have diabetes. Type 2 diabetes comprises 90% of people with diabetes around the world, and is largely the result of excess body weight and physical inactivity. http://www.who.int/mediacentre/factsheets/fs312/en/index.html. The incidence of diabetes is increasing globally. The estimated incidence of 12.7 million new cancer cases in 2008 will rise to 21.4 million by 2030, with nearly two thirds of all cancer diagnoses occurring in low- and middle-income countries. http://www.who.int/nmh/publications/ncd_report_chapter1.pdf. A series of recent studies and meta-analyses confirm that the risk for several solid and hematologic malignancies (including liver, pancreas, colorectal, kidney, bladder, endometrial and breast cancers, and non-Hodgkin's lymphoma) is increased in patients with diabetes [6]. Here the discussion follows on each malignancy with increased frequency in diabetes.

2.1. Pancreatic cancer

Type 2 diabetes mellitus is considered to be the third modifiable risk factor for pancreatic cancer after cigarette smoking and obesity. Based on the meta-analysis of 36 case–control and cohort studies, Everhart and Wright reported that the age and sex adjusted odds ratio for the development of pancreatic cancer in people with diabetes was 1.8 (CI of 1.7–1.9) [9]. They also noted that increased frequency of pancreatic cancer occurs with long-standing diabetes, especially those with the duration of at least 5 years with a RR of 2.0 with CI of 1.2 to 3.2 [9]. Gallo *et al* [10] from Italy reported that 40.2% of patients with pancreatic cancer and diabetes were diagnosed concomitantly or 15.9% were diagnosed within two years prior to diagnosis of cancer. Based on the data, the authors concluded increased prevalence of diabetes is related to pancreatic cancer and the diabetes is caused by the tumor [10]. A causal relationship between diabetes and pancreatic cancer is also supported by findings from pre-diagnostic evaluations of glucose and insulin levels in prospective studies. Data show that up to 80% of patients with pancreatic cancer are either hyperglycemic or diabetic. Diabetes has been shown to improve after pancreatic-cancer resection, suggesting that diabetes is caused by the cancer [11]. Pannala *et al* suggest new-onset diabetes may indicate subclinical pancreatic cancer, and patients with new-onset diabetes may constitute a population in whom pancreatic cancer can be detected early [11]. A meta-analysis of three cohorts and six case-control studies revealed even a two-fold risk in type 1 diabetes patients [12]. A meta-analysis of 36 studies was carried out by Huxley and associates that included17 case-control and 19 cohort or nested case-control studies

with information on 9220 individuals with pancreatic cancer [3]. They noted that individuals with recent diagnosis of diabetes (< 4 years) had a 50% greater risk of the malignancy compared with individuals who had diabetes for ≥ 5 years (OR 2.1 vs. 1.5; $p = 0.005$).

2.2. Colorectal cancer

Increasing evidence suggests that a history of diabetes mellitus (DM) may be associated with an increased risk of colorectal cancer (CRC). In 2005, meta-analyses of 15 studies (six case-control and nine cohort studies) in the USA and Europe, including 2 593 935 participants, Larsson and associates found that diabetes was associated with an increased risk of colorectal cancer, compared with no diabetes (RR: 1.30; CI: 1.20–1.40] [2]. These results were said to be consistent between case-control and cohort studies and across the United States and Europe. The association did not differ significantly by sex, or by cancer sub-site. Diabetes was positively associated with colorectal cancer mortality. Results from a meta analysis of 41 cohorts was reported to support that diabetes was associated with an increased incidence of CRC (RR: 1.27;1.21-1.34) [13]. In a recent systematic review and meta-analysis, twenty-four studies including eight case-control and 16 cohort studies, with a total of 3,659,341 participants were included [14]. Meta-analysis of the 24 included studies indicated that diabetes was associated with an increased risk of colorectal cancer, compared with no diabetes (RR: 1.26; CI: 1.20-1.31), without heterogeneity between studies (p (heterogeneity) = 0.296). Sub-group analyses found that these results were consistent between case-control and cohort studies and among studies conducted in different areas. The association between diabetes and colorectal cancer incidence did not differ significantly by sex and sub-sites. Insulin therapy was also positively associated with risk of colorectal cancer (RR = 1.61; 1.18-1.35), with evidence of heterogeneity between studies (p (heterogeneity) = 0.014).

2.3. COX-2 and colon cancer

Although COX-2, the inducible isoform, is regularly expressed at low levels in colonic mucosa, its activity increases dramatically following mutation of the adenomatous polyposis coli (APC) gene, suggesting that β-catenin/T cell factor-mediated Wnt signaling activity may regulate COX-2 gene expression. In addition, hypoxic conditions and sodium butyrate exposure may also contribute to COX-2 gene transcription in human cancers [15]. Because of its role in carcinogenesis, apoptosis, and angiogenesis, it is an excellent target for developing new drugs with selectivity for prevention and/or treatment of human cancers [16].

2.4. Breast cancer

Meta-analyses of 20 studies (5 case-control and 15 cohort studies) by Larsson and associates found that women with diabetes had a statistically significant 20% increased risk of breast cancer (RR, 1.20; CI:1.12-1.28) compared with no diabetes [4]. The summary estimates were similar for case-control studies (RR, 1.18; CI: 1.05-1.32) and cohort studies (RR, 1.20; CI: 1.11-1.30). Meta-analysis of 5 cohort studies on diabetes and mortality from breast cancer yielded a summary RR of 1.24 and CI of 0.95-1.62 for women with versus without diabetes. Findings from this meta-analysis indicate that diabetes is associated with an increased risk of breast cancer [4]. In the

Nurses' Health Study, a total of 87,143 postmenopausal women, aged 30 to 55 years and free of cancer, were followed up for up to 26 years (1976-2002) and evaluated for the incidence of invasive breast cancer with increase in weight of at least 25.0 kg or more since age 18 years. Eliassen and associates noted an increased risk of breast cancer (RR: 1.45; CI: 1.27-1.66; $p <$ .001), with a stronger association among women who have never taken postmenopausal hormones (RR, 1.98; CI: 1.55-2.53). Data suggest that weight gain during adult life, specifically since menopause, increases the risk of breast cancer among postmenopausal women, whereas weight loss after menopause is associated with a decreased risk of breast cancer [17].

1. Non-modifiable risk factors:
a. Age
b. Sex
c. Ethnicity
2. Modifiable risk factors:
a. Overweight/obesity
b. Physical activity
c. Diet
3. Biological links:
a. Hyperglycemia
b. Insulin
c. IGF-1
d. Estrogen and androgen bioavailability
e. Cytokines

Table 1. Risk factors common to both diabetes and cancer

3. Pathophysiology

3.1. Hyperinsulinemia and cancer

Hyperinsulinemia most likely favors cancer in diabetic patients as insulin is a growth factor with pre-eminent metabolic but also mitogenic effects, and its action in malignant cells is favored by mechanisms acting at both the receptor and post-receptor level. Obesity, hyperglycemia, and increased oxidative stress may also contribute to increased cancer risk in diabetes [6].

3.2. Insulin

Insulin resistance and hyperinsulinemia are important factors in the development of type 2 diabetes. Insulin is known to stimulate cell proliferation and injection of insulin in rats

promoted carcinogen-induced colon cancer [18]. Insulin/insulin-like growth factor 1(IGF-1) receptors and G protein-coupled receptors (GPCR) signaling systems are implicated in autocrine-paracrine stimulation of a variety of malignancies, including ductal adenocarcinoma of the pancreas. Metformin, the most widely used drug in the treatment of type 2 diabetes, activates AMP kinase (AMPK), which negatively regulates mammalian target of rapamycin (mTOR) complex 1 (mTORC1) [19]. Metformin was shown to significantly decrease the growth of pancreatic cancer cells xenografted into the flank of nude mice by interrupting the G protein-coupled receptor (GPCR), insulin receptor signaling by down-regulating the mTOR pathway [20]. The GPCR and insulin receptor pathways are associated with increased DNA synthesis and pancreatic cancer cell growth. By negatively regulating GPCR and insulin receptor signally, and interrupting their cross talk, metformin is shown to decrease pancreatic cancer cell growth in mice. In a meta-analysis of epidemiological studies on markers of hyperinsulinemia and cancer, Pisani reported that subjects who develop colorectal and pancreatic cancers have increased pre-diagnostic blood levels of insulin and glucose [21]. High insulin levels have also been shown to be associated with risk of endometrial cancer independent of estradiol [22]. A link between breast cancer risk and hyperinsulinemia (measured by fasting C-peptide levels) has been shown mainly in postmenopausal breast cancer. Insulin levels were positively associated with endometrial carcinoma [HR: 2.33, CI: 1.13-4.82] among women not using hormone therapy [23].

3.3. Insulin resistance

The term insulin resistance denotes that action of insulin is impaired in peripheral target tissues that include skeletal muscle, liver, and adipose tissue. Recent literature supports the hypothesis that insulin resistance is a high risk for cancers. The molecular mechanisms for this association and the role in the neoplastic transformation process are being explored. Insulin is a major anabolic hormone that can stimulate cell proliferation. Adiposity induces adverse local and systemic effects that include adipocyte intracellular lipid accumulation, endoplasmic reticulum and mitochondrial stress, and insulin resistance, with associated changes in circulating adipokines, free fatty acids, and inflammatory mediators. Insulin resistance and associated hyperglycemia, hyperinsulinemia, and inflammation have been suggested to be the underlying mechanisms contributing to development of diabetes-associated pancreatic cancer. Hyperinsulinemia, insulin resistance and proinflammatory cytokines have been linked to neoplastic proliferation of various organ cells (Fig. 1).

In a study of the Polyp Prevention Trial of insulin and fasting glucose and risk of recurrent colorectal adenomas, Flood et al. noted the association of increased risk of adenoma recurrence and risk for recurrence of advanced adenomas with increased insulin [24].

3.4. Insulin-like Growth Factor-1 (IGF-1) and cancer

The IGF (insulin-like growth factor) system is essential for physiological growth. The IGF complex includes IGF-1 and IGF-2, their corresponding receptors (IGFR-1 and IGFR-2), IGF binding proteins 1–6 (IGFBPs), insulin receptor substrate (IRS). The signaling pathway of IGF plays a critical role in cellular proliferation and inhibition of apoptosis. Though growth

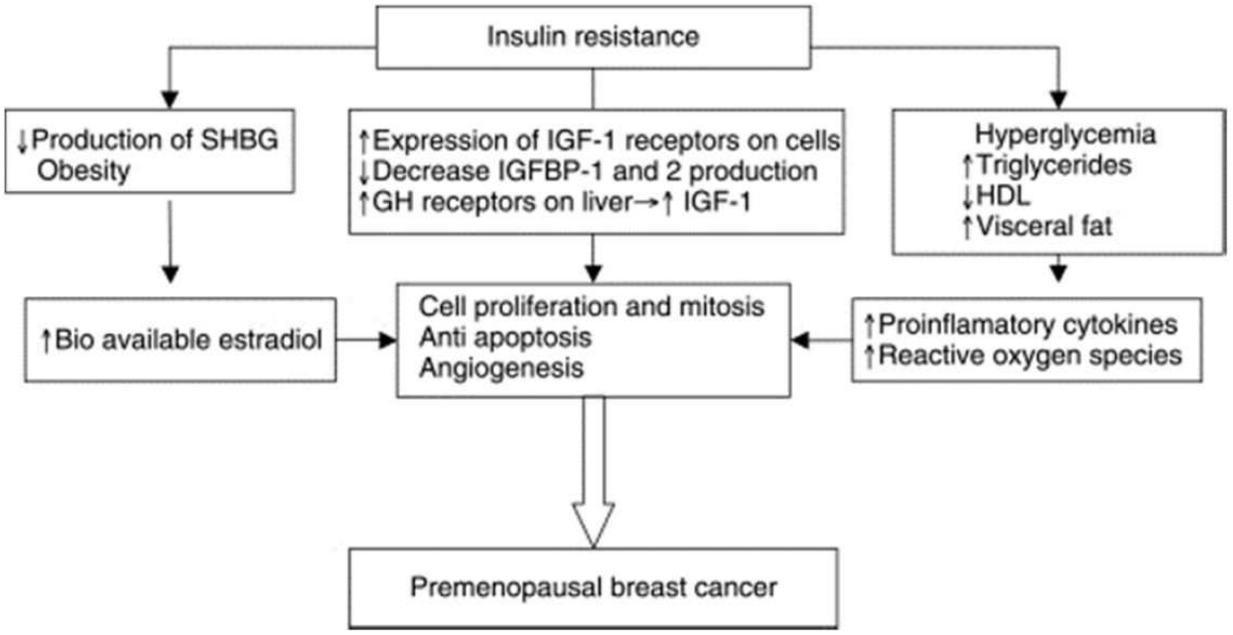

Figure 1. Insulin resistance and premenopausal breast cancer. Abbreviations: SHBG, sex hormone-binding globulin; IGF, insulin-like growth factor; GH, growth hormone; HDL, high-density lipoprotein cholesterol.

hormone is the primary stimulus for IGF-1 production in the liver and insulin can increase the IGF-1 production by up-regulating growth hormone receptors in the liver, hyperinsulinemia can also increase IGF-1 bioavailability by decreasing hepatic secretion of IGF-binding protein (IGFBP)-1 and −2 [25]. IGF-R, a tyrosine kinase receptor for IGF-I and IGF-II is said to play a role in malignant transformation, progression, protection from apoptosis, and metastasis as documented in cell culture, animal and human studies [26]. Since the expression of IGF-1 receptors occurs in several cancers, the effects of insulin on cancer cell proliferation *in vivo* may involve IGF-1 stimulation and indirectly stimulate cancers. The IGF signaling pathway is involved in cell proliferation and differentiation and inhibits apoptosis. Increased expression of IGF-1, IGF-2, IGF-1R, or combinations have been documented in various malignancies including glioblastomas, neuroblastomas, meningiomas, medulloblastomas, carcinomas of the breast, malignancies of the gastrointestinal tract, such as colorectal and pancreatic carcinomas, and ovarian cancer [27]. Higher IGF-1 levels were reported to be associated with increased colorectal adenoma risk (ORs = 1.58; 1.16-2.16),[28] and inversely associated with endometrial carcinoma (HR: 0.53; 0.31-0.90) [23].

3.5. Adiponectin and cancer

Adiponectin, which is also referred to as ACP30 (Acrp30), is secreted predominantly by white adipose tissue [29]. Circulating concentrations of adiponectin are reduced in obesity and type 2 diabetes [30-32]. Adiponectin is considered to have beneficial antineoplastic effects, which are believed to be due to anti-proliferative, anti-inflammatory effects, along with antagonizing insulin resistance [33]. Adiponectin has been found to be an important negative regulator of

hematopoiesis and the immune system as adiponectin was shown to suppress the growth of myelomonocyte cell lines *in vitro* by inducing apoptosis in myelomonocytic progenitor cells (leukaemia lines) and modulating expression of apoptosis-related genes and down regulating Bcl-2 gene expression [34]. Epidemilogical data have also shown a link between low adiponectin levels and renal cell cancer [35, 36]; especially large tumor size [37, 38]. Adiponectin was inversely associated with non-Hodgkin lymphoma and acute myeloblastic leukaemia (OR: 0.56; 0.34-0.94), but not with acute lymphoblastic leukaemia of B or T cell [39]. In a number of epidemiological studies, adiponectin levels have been linked to breast cancer and are believed to inhibit breast cancer cell proliferation *in vivo.* This effect may be due to adiponectin-triggered cellular apoptosis in MDA-MB-231 breast cancer cells in the presence of 17β-estradiol. These findings may suggest that a cross-talk between adiponectin and estrogen receptor signaling exists in breast cancer cells and that adiponectin effects on the growth and apoptosis of breast cancer cells *in vitro* are dependent on the presence of 17β-estradiol [40]. Low serum adiponectin is associated with colon, prostate and breast cancer [41]. In a recent study, plasma adiponectin level was associated with decreased colorectal cancer risk [42].

Adiponectin and colorectal cancer: Adiponectin was shown to act on preneoplastic colon epithelial cells to regulate cell growth by inducing autocrine IL-6 production and trans-IL-6 signaling. In a prospective case control study, men with low plasma adiponectin levels were said to have a higher risk of colorectal cancer than men with higher levels [43]. Meta analysis of 13 studies in patients with colorectal cancer and adenoma, though there was significant heterogeneity among studies, noted that there was a negative dose response relationship between levels of adiponectin and the risk of colorectal neoplasm in men [44].

Adiponectin and Endometrial cancer: Circulating adiponectin concentrations are inversely correlated with the incidence of endometrial carcinoma in epidemiological studies. In a study that investigated the direct effects of adiponectin on two endometrial carcinoma cell lines, HEC-1-A and RL95–2, adiponectin treatment led to suppression of cell proliferation in both cell types, which was primarily believed to be due to the significant increase of cell populations at G_1/G_0 phase and secondary to the induction of apoptosis [45].

3.6. Obesity and cancer

Accumulating epidemiologic evidence shows that obesity is associated with an increased risk of several common adult cancers. The risk of diabetes increases linearly with BMI; the prevalence of diabetes increased from 2% in those with a BMI of 25 to 29.9 kg/m2, to 8% in those with a BMI of 30 to 34.9 kg/m2, and finally to 13% in those with a BMI greater than 35 kg/m2 [46]. Similarly, an association between obesity or an incremental increase in body mass index (BMI) and an increased cancer risk have been reported for colon cancer (men and women) and rectal cancer (men only),[47] colon cancer,[48] liver cancer,[49] gall bladder cancer,[50] multiple myeloma, non-Hodgkin's lymphoma,[51] pancreatic cancer,[52] leukemia,[53] ovarian cancer,[54] breast cancer,[55] and endometrial cancer [56, 57]. In a population based prospective study of more than 900,000 U.S. adults, the reported relative risk of cancers in overweight and obesity was 1.52 for men and 1.62 for women [18]. A study from the United

Kingdom showed that increasing BMI was associated with an increased incidence of endometrial cancer (RR:2.89, CI: 2.62–3.18), adenocarcinoma of the esophagus (RR:2.38;CI: 1.59–3.56), kidney cancer (RR:1.53, CI: 1.27–1.84), leukemia (RR:1.50, CI:1.23–1.83), multiple myeloma (RR:1.31;CI: 1.04–1.65), pancreatic cancer (RR:1.24;CI: 1.03–1.48), non-Hodgkin's lymphoma (RR:1.17; CI: 1.03–1.34), ovarian cancer (RR: 1.14; CI: 1.03–1.27), all cancers combined (RR:1.12; CI:1.09–1.14), breast cancer in postmenopausal women (RR: 1.40; CI: 1.31–1.49), and colorectal cancer in premenopausal women (RR:1.61; CI: 1.05–2.48) [58]. It is not surprising to note that increased adiposity may have a negative effect on treatment outcome and ultimate survival, because obesity has been found to be a negative prognostic factor for breast cancer[59] and colon cancer [60, 61].

3.7. Cyclooxygenase and cancers

Cyclooxygenase-2 (COX-2) over expression has been found in several types of human cancers, such as colon, breast, prostate, and pancreas, and appears to control many cellular processes. The contribution of COX-2 to carcinogenesis and the malignant phenotype of tumor cells have been thought to be related to its abilities to: (1) increase production of prostaglandins, (2) convert procarcinogens to carcinogens, (3) inhibit apoptosis, (4) promote angiogenesis, (5) modulate inflammation and immune function, and (6) increase tumor cell invasiveness [62].

3.8. Proinflammatory cytokines

Adipocytes secrete a number of proinflammatory cytokines. These cytokines are known to promote insulin resistance and increase circulating TG, features of the metabolic syndrome. Several cytokines, reactive oxygen species (ROS), and mediators of the inflammatory pathway, such as activation of nuclear factor-κB (NF-κB) and COX-2, lead to an increase in cell proliferation, survival, and inhibition of the proapoptotic pathway, ultimately resulting in tumor angiogenesis, invasion, and metastasis [16]. Proinflammatory cytokines implicated in carcinogenesis include IL-1, IL-6, IL-15, colony-stimulating factors, TNF-α, and the macrophage migration inhibitory factor.

Macrophage inhibitory cytokine-1 (MIC-1), also known as prostate-derived factor (PDF), is a molecule of the TGF-β super family and has been associated with the progression of various types of diseases including prostate cancer [63]. Collectively, cytokines are considered as a linker between inflammation and cancer. Cytokines, ROS, and mediators of the inflammatory pathway (e.g., NF-κB and COX-2) have been shown to increase cell cycling, cause loss of tumor suppressor function, and stimulate oncogene expression and lead to cancers. Positive feedback mechanisms between estrogens and inflammatory factors may exist in the breast and contribute to hormone-dependent breast cancer growth and progression [64]. Prostaglandin E synthase (PTGES) is also up-regulated by the proinflammatory cytokines TNF-α or IL-1β. Cytokines can enhance estrogen receptor (ER) activity and PTGES expression through the NF-κB pathway and cytokines can act to up-regulate aromatase expression as well as 17β-hydroxysteroid dehydrogenase activity in breast tissue, thereby leading to a further increase in E2 production [64].

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4. Diabetes therapies and cancer

Diabetes is associated with increased risks of bladder, breast, colorectal, endometrial, kidney, liver and pancreatic cancer and a lower risk of prostate cancer. Diabetes treatments may influence the risk of cancer independently of their effect on glycemia. This may complicate the issues in investigation of the association between diabetes and cancer. Epidemiologic studies have suggested a protective role for metformin. On the other hand, Glargine, the most widely used long-acting insulin analogue, may confer a greater risk than other insulin preparations, particularly for breast cancer. In general, diabetes therapies that are said to be associated with increased risk of cancer include, use of insulin, sulfonyl urea and DPP4 inhibitors. Diabetes therapies that are shown benefit by decreasing the cancer risk include use of metformin and thiazolidinediones. Here we will discuss association of cancer risk with each of the diabetes therapeutic agents.

4.1. Thiazolidinedione (TZD) and cancer risk in type 2 diabetes

TZDs are reported to decrease in cancer both in clinical data series and in vitro studies. In addition pioglitazone, one of the TZDs, was shown to increase the risk of bladder cancer in those with the use for more than 24 months. Based on the randomized clinical trials of rosiglitazone with duration of >24 weeks that includes eighty trials enrolling 16,332 and 12,522 patients in the rosiglitazone and comparator groups, Monami and associates reported that the incidence of malignancies was significantly lower with the use of rosiglitazone than in control groups (RR: 0.23; CI: 0.19–0.26) vs. RR of 0.44(CI:0.34–0.58) cases/100 patient-years; $p < 0.05$) [65]. In a study using the diabetes registry of Hong Kong, Yang and associates reported that TZD usage was associated with 83% reduction in cancer risk in Chinese patients with type 2 diabetes in a dose–response manner [66]. Using the Taiwan National Health Insurance claims database, significantly lower risk of liver cancer incidence was found for any use of rosiglitazone or pioglitazone; use of rosiglitazone but not pioglitazone was associated with decreased incidence of colorectal cancer [67].

4.2. Pioglitazone and bladder cancer

Using the Kaiser Permanente Northern California diabetes registry with 193,099 patients who were ≥40 years of age between 1997 and 2002, excluding those with prior bladder cancer, 30,173 patients treated with pioglitazone were identified. In this cohort of patients with diabetes, short-term use of pioglitazone was not associated with an increased incidence of bladder cancer, but use for more than 2 years was weakly associated with increased risk [68].

Using the general practice research database in the United Kingdom, use of pioglitazone more than 24 months was reported to be associated with an increased risk of incident bladder cancer among people with type 2 diabetes [69. Using data from the French national health insurance information system, in a population based study, pioglitazone use of more than 24 months was reported significantly associated with increased risk of bladder cancer [70].

4.3. Metformin

Studies of patients with T2DM on metformin have demonstrated a lower risk of cancer [71-74]. In a recent study of the influence of treatment with metformin on survival after cancer diagnosis by Currie and associates, metformin was shown to be associated with survival benefit both in comparison with other treatments for diabetes and in comparison with a non-diabetic population [75]. An observational cohort study from the United Kingdom suggested that metformin use may be associated with a reduced risk of cancer (HR:0.63 (0.53-0.75) [72]. The study noted that the reduced risk was after adjusting for sex, age, BMI, A1C, smoking, and other drug use [72]. In a different database study from UK general practices, metformin use was reported to be associated with lower risk of cancer of the colon or pancreas, but did not affect the risk of breast or prostate cancer [71]. Metformin use was associated with survival benefit in comparison with other treatments for diabetes and also in comparison with a non-diabetic population [75]. Metformin has been associated with reduced risk of pancreatic cancer in diabetics and recognized as an antitumor agent with the potential to prevent and treat this cancer [76]. A retrospective cohort study to investigate the survival benefit of metformin in patients with diabetes and pancreatic malignancy, from the MD Anderson Cancer Center from 2000 to 2009, reported that metformin users have a significant survival benefit compared to non-users (the median survival 16.6 *vs*. 11.5 months; $p = 0.0044$) [77]. They also report a 33% decrease risk of death in patients who used metformin (HR: 0.67; $p = 0.005$) [77]. This implies that metformin may have some beneficial effects on slowing the progression of pancreatic malignancy. However, specific pathogenesis is unclear and would have to be further explored. In an interesting finding from a data base study from Hong Kong, nonusers of metformin with low HDL cholesterol had an adjusted hazard ratio of 5.75 (CI: 3.03-10.90) compared with HDL cholesterol ≥ 1.0 mmol/L plus use of metformin [78]. The reduction in cancer risk with the use of metformin in patients with type 2 diabetes is said to be dose related [74]. In a Canadian population-based cohort study, Bowker and associates noted that patients with type 2 diabetes exposed to sulfonylureas and exogenous insulin had a significantly increased risk of cancer-related mortality compared with patients exposed to metformin [79]. In addition they also noted that, the sulfonylurea cohort had greater cancer-related mortality compared with the metformin cohort after multivariate adjustment [79]. There are several *in vitro* and *in vivo studies* from cell lines and animal models support the benefit of metformin against cancer. There are several ongoing trials to examine the clinical outcomes.

4.3.1. Metformin and individual cancers

Long term use of metformin was shown to decrease risk of breast cancer in female patients with type 2 diabetes [80]. In a case-control study using the U.K.-based General Practice Research Database, metformin use was associated with an adjusted odds ratio of 0.44 (CI: 0.24-0.82) for developing breast cancer compared with no use of metformin [81]. In a similar study from the UK, long-term use of ≥ 40 prescriptions (>5 years) of metformin, based on 17 exposed case patients and 120 exposed control patients, was associated with an adjusted odds ratio of 0.44 (95% CI 0.24-0.82) for developing breast cancer compared with no use of metformin [80]. A meta-analysis of 17 case-control studies and 32 cohort studies of diabetes and hepato-

cellular carcinoma, metformin treatment was potentially protective [82]. In a meta- analysis of five studies comprising 108,161 patients with type 2 diabetes, metformin therapy appears to be associated with a significantly lower risk of colorectal cancer in patients with type 2 diabetes [82].

4.3.2. Mechanism of metformin in reducing cancer

It has been postulated that the effect of metformin on cancer development and progression may be a result of decreased levels of insulin [83] and insulin resistance. However, the possible anticancer effect of metformin is believed to be mediated by the inhibition of mitochondrial oxidative phosphorylation leading to activated AMPK pathway or independent of non-AMPK pathway. Human breast cancer cells treated with metformin demonstrate inhibited proliferation and colony formation and increased cell cycle arrest [84]. Studies have shown that metformin also has a direct effect on tumor cell proliferation [85]. As stated previously, metformin activates AMPK. The AMPK/mTOR axis is modulated by liver kinase B1 (LKB1). LKB1 is a tumor suppressor that activates AMPK, leading to mTOR inhibition, resulting in inhibited cell growth [85]. In vitro studies have shown that treatment with metformin inhibits cancer cell lines such as breast cancer breast cancer cells,[86] prostate cancer cell lines,[87, 88] glioma,[89] and fibro sarcoma cell lines [90].

4.4. Therapeutic consideration

4.4.1. Therapeutic considerations in general

Therapeutic considerations need to focus on reduction of the risk factors. Various therapeutic interventions for weight reduction and healthy life style have been linked to a reduced cancer risk in the general population. Therapeutic strategies to decrease chronic hyperinsulinemia and insulin resistance may offer a general approach to prevention of cancer. Metformin is the insulin sensitizer used primarily in the treatment of type 2 diabetes mellitus.

In a retrospective study of long term benefits of bariatric surgery, a significant decrease in mortality from cancer-related deaths in the bariatric surgery group compared both with all subjects and matched subjects with a decrease of 60% for cancer at mean follow-up of 7.1 years. Anticytokine vaccines, inhibitors of proinflammatory NF-κB and COX-2 pathways, thiazolidinediones, and antioxidants are potentially useful for the prevention or treatment of pancreatic cancer. Similarly epidemiologic studies have documented a 40–50% reduction in the incidence of colorectal cancer in individuals taking nonsteroidal anti-inflammatory drugs (NSAIDs). The long-term use of COX-2-selective inhibitors has, unfortunately, demonstrated cardiovascular toxicity, so their use in cancer prevention and therapy is currently questionable. However, there is evidence suggesting that further development of novel COX-2-selective agents is needed for the prevention and/or treatment of human cancers, especially pancreatic cancer. Targeting PGE_2 signaling by EP receptor antagonists holds promise for the development of targeted therapy for the treatment of cancer [91]. PPARs also play a role in the regulation of cancer cell growth. Recent evidence suggests that PPAR modulators may have beneficial effects as chemopreventive agents [92].

Recent clinical studies with IGF-1R inhibitors have revealed several obstacles to successful use in cancer therapy. Strategies to inhibit IGF-1R signaling such as tyrosine kinase inhibitors also disrupt IR signaling, resulting in hyperglycemia and hyperinsulinemia. Several strategies being considered are based on biomarkers that could identify subpopulations most likely to be responsive to IGF targeting. The combination therapies with other targeted drugs could maximize the therapeutic effects of IGF inhibitors [93].

4.4.2. Chemoprevention of colorectal cancer

Of cancers affecting both men and women, colorectal cancer (cancer of the colon and rectum) is the second leading cancer killer in the United States and the incidence increases with age. The U.S. Preventive Services Task Force report on the effectiveness of aspirin (ASA), non-aspirin non steroidal anti-inflammatory drugs (non-ASA NSAIDs), and cyclooxygenase-2 inhibitors (COX-2 inhibitors) for the chemoprevention of colorectal cancer indicate that aspirin and non-ASA NSAIDs appear to be effective at reducing the incidence of CRAs and CRC [7]. The report also stated that more information is required to clarify the optimal dose, starting age, and duration of use of ASA since observational studies suggest that higher doses and prolonged use improve chemo-preventative efficacy. In a recent systematic review and meta-analysis for randomized controlled trials (RCTs) from United Kingdom, Cooper and associates identified 44 relevant RCTs and six ongoing studies [8]. They reported that there was a statistically significant 21% reduction in risk of adenoma recurrence (RR: 0.79; CI: 0.68 to 0.92) in an analysis of aspirin versus no aspirin in individuals with a history of adenomas or CRC. In the general population, a significant 26% reduction in CRC incidence was demonstrated in studies with a 23-year follow-up (RR: 0.74; CI: 0.57 to 0.97). In individuals with a history of adenomas there was a statistically significant 34% reduction in adenoma recurrence risk (RR: 0.66; CI: 0.60 to 0.72) and a statistically significant 55% reduction in advanced adenoma incidence (RR 0.45; CI: 0.35 to 0.58). No studies assessed the effect of non-aspirin NSAIDs in the general population. There was said to be no significant effect of folic acid versus placebo on adenoma recurrence (RR: 1.16; CI: 0.97 to 1.39) or advanced adenoma incidence in individuals with a history of adenomas. In the general population there was said to be no significant effect of folic acid on risk of colorectal cancer (RR: 1.13; CI: CI: 0.77 to 1.64), although studies were of relatively short duration. Calcium use by familial adenomatous polyposis (FAP) patients was reported to have no significant reduction in polyp number or disease progression. In individuals with a history of adenomas there was said to be a statistically significant 18% reduction in risk of adenoma recurrence (RR: 0.82; CI: 0.69 to 0.98) and a non-significant reduction in risk of advanced adenomas (RR: 0.77; CI: 0.50 to 1.17). Though these studies are not selective for subjects with diabetes, prevention of colorectal cancer in subjects with diabetes is important and relevant.

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