Diabetes, gestational diabetes and the risk of cancer in women: epidemiologic evidence and possible biologic mechanisms

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At present, more than 10% of adult American women are diagnosed with diabetes mellitus (DM). As the prevalence of the disease increases, there is greater interest in the relationship between DM and other major health issues, such as cancer – one of the leading causes of death in the western world. This paper reviews the literature on the relationship between Type 2 DM and different types of cancer among women. We discuss the possible biological mechanisms that may link diabetes and cancer, important confounders, shared risk factors and a short review of the epidemiologic literature on the association between Type 2 DM and cancer of specific organs (pancreas, liver, colorectal, bladder, endometrial, non-Hodgkin’s lymphoma and breast). We also examine the association between gestational diabetes, a closely related risk factor for DM in women, and subsequent risk of cancer. Cancer survival of diabetic women is also briefly discussed. The paper concludes with an agenda for future research targeting the relationship between diabetes and cancer.

With nearly 740,000 new cases in 2010 and 270,000 deaths, cancer is a major public health problem in the USA [1]. Even though progress has been made in reducing risk and improving survival, primary and secondary prevention of cancer remains an important challenge.

Although the pathogenesis of diabetes mellitus (DM) and cancer were only partially understood, speculations concerning relationships between the two diseases were not rare during the latter decades of the 19th century. The unexpectedly high prevalence of hyperglycemia among cancer patients led investigators to suggest the use of blood glucose measurements as a screening or diagnostic test for cancer [2]. In the past, the short survival of diabetic patients precluded the conduction of long-term studies. The introduction of glucose tests and hypoglycemic therapies including insulin, which revolutionized the treatment of diabetes, allowed much longer follow-up of patients and more valid studies [3]. Over the last four decades, much evidence has accumulated on the potential association between diabetes and cancer. High cancer morbidity and the rising prevalence of DM in the USA (currently estimated as 10% of all adult women) warrant a careful consideration of the potential effects of this preventable risk factor.

Certain types of malignancies are common in both sexes (e.g., lung and bronchus, colorectal), whilst others are sex specific (e.g., cervical, uterine, testicular or prostate cancer) or nearly so (breast cancer). Compared with women, men have a somewhat higher risk of both cancer and diabetes. However, several studies on the relationship between diabetes and cancer – including one of the earliest investigations that was published over 40 years ago [3] – have shown that among diabetics, women are at higher risk of cancer.

In December 2009, the American Diabetes Association and the American Cancer Society convened a consensus development conference that summarized the differences in cancer risk between diabetic men and women [4]. It was agreed that in both sexes, Type 2 diabetes is associated with an increased risk of digestive organ malignancies (liver, pancreas and colon), as well as bladder cancer. Of the sex-specific cancers, diabetic women are at higher risk of breast and endometrial cancer, whilst men have a reduced risk of prostate cancer. For some other cancer types, there appears to be no association or the evidence is inconclusive.

The biological link between diabetes and cancer can be explained by direct or indirect pathophysiological mechanisms, such as metabolic alterations that are present in diabetes, including hyperinsulinemia, hyperglycemia and chronic inflammation. In addition, several conditions and risk factors are often associated with both diabetes and cancer, such as aging, obesity, smoking and sedentary lifestyle. In this article we will describe possible biologic mechanisms, shared risk factors and the epidemiologic evidence of cancer risk in diabetic women. In the

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In the light of its growing prevalence, we also examine the association between gestational diabetes and subsequent risk of cancer.

Pathophysiological mechanisms

**Hyperinsulinemia**

Diabetes mellitus is a group of disorders characterized by hyperglycemia. In Type 2 DM, which accounts for 90–95% of DM cases, there is a state of insulin resistance with a resultant compensatory hyperinsulinemia [10]. Type 1 DM is defined by a deficiency of endogenous insulin due to pancreatic β-cell destruction and the requirement of exogenous insulin, which cannot mimic the pattern of physiologic secretion. Therefore, in both types of diabetes, most patients are continuously exposed to increased insulin concentrations. Insulin has a known mitogenic activity in cells, which can be mediated both directly and indirectly [5].

**Insulin/IGF1 axis**

Insulin binding to its transmembrane receptor leads to the activation of a cascade of cellular reactions through two main pathways: the inositol 1,4,5-triphosphate pathway, which regulates carbohydrate and lipid metabolism as well as cell proliferation and apoptosis, and the MAPK pathway, which affects cell growth, proliferation and survival [6].

The importance of these pathways for cancer promotion is illustrated by the high expression of insulin receptors and downstream mediating molecules that are found in various cancer types, including breast and colon. Moreover, the predominant receptor found in cancer cells is isoform A which, unlike the B isoform, elicits more mitogenic activity than metabolic activity [7]. Imbalance between these activities also occurs in the setting of insulin resistance, which selectively affects the metabolic pathway with relative sparing of the mitogenic pathways, leading to overactivation, secondary to hyperinsulinemia [6]. As described in the next section, the strongest association between Type 2 DM and cancer was found in regard to pancreatic and liver cancers [8]. Both of these organs are highly exposed to endogenous insulin, which supports a role for hyperinsulinemia in tumor progression.

The insulin signaling pathway can be activated by another set of ligand receptors: IGF1 and IGF1 receptor (IGF1R), which share high homology to insulin and insulin receptor accordingly [9]. Activation of IGF1R has a stronger effect on cell proliferation and survival than insulin, and accumulating evidence suggests it plays a critical role in tumor development [10]. First, high circulating levels of IGF1 were linked to breast, colon and prostate cancers [10]. Second, IGF1R expression was found to be regulated by the action of various suppressor genes [11]. Finally, genetic studies in breast cancer found that breast cancer risk in carriers of mutations in BRCA1 and BRCA2 is affected by alterations in IGF1 signaling [12]. In the presence of hyperinsulinemia, IGF1R can be activated directly, by the high circulating levels of insulin, as well as indirectly, since insulin upregulates IGF1 liver production and inhibits the synthesis of IGF1-binding protein with a net effect of increasing IGF1 bioavailability [10]. Additionally, insulin can augment the cellular reaction to growth factors by upregulating and activating intermediate molecules involved in the growth factor signal transduction pathway [13].

**Indirect effect of insulin: insulin & female sex hormones**

The relationship between insulin and sex hormones is complex and gender-specific. Type 2 DM is associated with high levels of testosterone and low levels of sex hormone-binding globulin (SHBG) in women, while in men it is associated with low levels of testosterone and low–normal levels of SHBG [14]. The temporal direction of the association is not clear. On the one hand testosterone is suspected to increase adiposity and insulin resistance in women, with the opposite effect in men. On the other hand, insulin reduces liver synthesis of SHBG and increases the production of estradiol and androgens [15]. The resulting net effect is a higher bioavailability of androgens in diabetic women. Hyperandrogenemia is linked to a higher risk for endometrial cancer and breast cancer, possibly by local tissue transformation of androgens to estrogens, as well as direct interaction with androgen receptors [16]. In women, diabetes is often associated with postmenopausal breast and endometrial cancers, which are associated with high estrogen exposure [5]. Insulin was found to increase the production of estradiol and androgens, independent of obesity [15]. As most Type 2 DM patients are obese, this can be further augmented by high estrone and estradiol production through aromatase activity in adipose tissue. Involvement of insulin and estradiol in breast carcinogenesis is suggested by demonstration of reciprocal interactions between estradiol and insulin signaling pathways in breast cancer cell lines. In a cohort of postmenopausal women, fasting insulin levels were associated with increased breast cancer risk among women who...
did not use hormonal therapy, independently of the effect of estradiol and obesity levels [17]. Insulin resistance was found to be associated with polycystic ovary syndrome (PCOS), which is characterized by high levels of both estrogen and androgen [18]. According to a recent meta-analysis, women with PCOS are at an increased risk of developing endometrial and ovarian cancer [19]. One suggested mechanism included the hormonal imbalance between estrogen and progesterone [18]. Given the link between insulin resistance and PCOS, hyperinsulinemia can contribute to cancer risk in these patients.

**Hyperglycemia**

The hallmark of DM is hyperglycemia, and a strong association between high glucose level and cancer risk has been demonstrated [20]. However, since in most patients both hyperglycemia and hyperinsulinemia are present simultaneously, it is not clear whether the hyperglycemia itself functions as an independent risk factor or if it is merely a marker for hyperinsulinemia. Since many tumors use mainly anaerobic metabolism which relies on a high supply of glucose for energy, it was suggested that hyperglycemia can facilitate tumor growth. Yet, tumors often have effective glucose-uptake pathways independent of insulin. Thus, the significance of this mechanism may be limited [21]. Another pathway relates to increased production of reactive oxygen species (ROS) induced by hyperglycemia [21]. ROS can lead to carcinogenesis by damaging cellular DNA through oxidation, as well as causing gene mutations, which was recently demonstrated in lymphoblastoid cell lines exposed to hyperglycemia [22].

**Oxidative stress**

The metabolic abnormalities typical of DM, including hyperglycemia and increased fatty acid oxidation, lead to high oxidative stress and accumulation of ROS [22]. High levels of ROS can damage the DNA directly, as well as indirectly through inhibition of its repair mechanisms. Both these effects increase the occurrence of somatic mutations that form the basis of tumorigenesis.

**Important confounders & shared risk factors for DM & cancer**

The association between diabetes and some cancers may be due, in part, to shared risk factors between the two diseases. The question remains whether the association between diabetes and cancer is mostly due to the presence of shared risk factors or due to the DM pathophysiology. Some risk factors are nonmodifiable (e.g., aging), whilst others are modifiable (obesity, diet and physical inactivity). The importance of these risk factors is supported by data from randomized trials showing that nutritional or physical activity interventions can prevent diabetes [23].

**Aging**

Both cancer and Type 2 DM become increasingly common with age. Approximately 78% of all newly diagnosed cancer cases in developed countries occur among individuals aged 55 years or older [102]. In parallel, nearly 23.8% of adults older than 60 years are diagnosed with Type 2 DM. However, the increased long-term risk of all-site cancer was also observed in large age-matched cohorts [24].

**Body mass**

In women, overweight and obesity are important risk factors for Type 2 DM and cancer. Obesity is tightly linked to Type 2 DM: over 80% of patients with Type 2 DM are obese and the increase in the global prevalence of obesity is closely followed by an increase in DM prevalence [24]. Obese individuals have a higher risk of cancer and the tumor types most commonly associated with obesity are very similar to those associated with diabetes; postmenopausal breast cancer and adenocarcinoma of the colorectum, endometrium, pancreas, kidney, esophagus, gallbladder and liver [4].

The suggested mechanism linking obesity to DM and cancer is the induction of subclinical inflammation through secretion of various cytokines by adipose tissue including IL-6, TNF-α, leptin and adiponectin [10]. These cytokines can induce insulin resistance via multiple pathways leading to DM, and be involved in tumorigenesis and tumor progression. For instance, TNF-α and IL-6, which are pro-inflammatory cytokines secreted by adipose tissue and involved in insulin resistance, were found to be involved in tumor progression and survival [5]. Once insulin resistance progresses to overt diabetes, the resultant hyperglycemia can further stimulate the secretion of IL-6 and TNF-α, thus augmenting the inflammatory process [25]. Another mechanism linking obesity, cancer and DM with a possible synergism relates to sex hormone levels and postmenopausal breast cancer risk, as discussed above.

**Physical inactivity**

Independent of body mass, physical inactivity is well known to increase the risk of Type 2 DM [26], as well as the risk of colon, postmenopausal breast cancer and endometrial cancer [27].
and endometrial cancer [27]. A small number of studies, however, provide evidence suggesting that physical inactivity may also be associated with a higher occurrence of pancreatic and liver cancers.

Diet
Food intake is another modifiable risk factor for both cancer and Type 2 DM. For example, a large body of evidence suggests that diets rich in red meat (beef, pork, lamb and goat from domesticated animals) or processed meats are associated with higher risk of many types of cancer [105], as well as Type 2 DM [28]. By contrast, dietary fibers and vegetables were associated with lower rates of both diabetes [29] and cancer [103].

One example of the effect of lifestyle and diet on cancer occurrence is gastric cancer in Japan. Over the last decades, a remarkable decline (of approximately 50%) was observed among Japanese women in some areas of Japan and in Hawaii. This reduction was explained by an ongoing decrement in consumption of salty food and an increase in green or yellow vegetables, as well as fresh fruits [30].

In addition to these factors, there are certain conditions that occur more commonly in diabetic patients and act as risk factors for specific tumors that are associated with DM; these include hepatitis B and C infections or hepatic steatosis and liver cancer, hypertension and kidney cancer and suppression of cellular immunity and non-Hodgkin lymphoma (NHL) [5,31].

Cancer and diabetes are therefore both heterogeneous and complex processes, and the apparent link between them can be explained by various interconnected mechanisms; some of them are part of the DM pathophysiology, while others are commonly associated with diabetes. Further studies are required to elucidate the relative contribution of each mechanism, which probably differ in each individual and tumor type.

Type 2 DM & specific cancer sites in women: epidemiologic evidence
Pancreatic cancer
It is estimated that over 40,000 people are diagnosed with pancreatic cancer annually in the USA, half of whom are women. The annual risk of pancreatic cancer among men and women is 13.3 and 10.5 per 100,000, respectively [104]. The association between diabetes and pancreatic cancer has attracted most interest so far. However, since many pancreatic cancer patients (up to 80%) are diagnosed with hyperglycemia or Type 2 DM shortly prior to cancer diagnosis, and which often improves or remits after resection of cancer, it was suggested that pancreatic tumors are most likely the cause and not the result of the recent onset of diabetes [32]. These mutual associations raised a long-standing controversy on reversed causality between Type 2 DM and pancreatic cancer. Nonetheless, there is increasing evidence to support the notion that pancreatic cancer may also be a consequence of long-standing Type 2 diabetes.

A meta-analysis of 17 case-control and 19 cohort (or nested case-control) studies published by Huxley et al. in 2005 found that diabetic women are at a 57% (95% CI: 30–89%) higher risk of pancreatic cancer (Table 1) [33]. Adjustments to smoking, method of DM diagnosis (self-report, medical records or laboratory tests) and study design did not materially change these results. To address the possibility of reversed causation, that is, the appearance of DM as an early symptom of latent malignancy, the investigators stratified the analysis according to duration of diabetes. The association between DM status and pancreatic cancer remained high (RR: 1.51; 95% CI: 1.16–1.96) even in patients with more than 10 years of diagnosed diabetes.

The relationship between Type 2 DM and the long-term risk of pancreatic cancer was further supported by more recent studies, such as a US cohort of 1.3 million middle-aged women, who were followed for 9.2 million person-years (with a total of 1338 documented incident pancreatic cancer cases) [34]. After adjustments for major confounders such as smoking, height, BMI, alcohol consumption and physical activity, history of diabetes was associated with a 58% (95% CI: 22–103%) higher risk of pancreatic cancer, a nearly identical estimate to the one calculated in Huxley’s meta-analysis. A similar increment in risk was calculated when the first 4 years of follow-up were excluded from analysis, which corroborates a causal relationship between diabetes and pancreatic cancer.

The association between Type 2 DM and pancreatic cancer potentially provides an important opportunity for early detection of pancreatic cancer by testing for hyperglycemia. However, to be clinically useful in secondary prevention efforts, screening should aim at detecting asymptomatic individuals with hyperglycemia. However, Type 2 DM is common in the adult population and pancreatic cancer is relatively rare. Only one in 125 patients aged 50 years or older with new-onset diabetes will be diagnosed with pancreatic cancer within 3 years [32]. Thus, for effective screening programs, we should first be able to differentiate pancreatic cancer-induced diabetes by diagnostic methods that are currently unavailable.
**Hepatocellular cancer**

The annual incidence rates of hepatocellular cancer (HCC) among US women (3.7 per 100,000) are substantially lower compared with men (10.7 per 100,000) [104]. Nonetheless, liver cancer is among the ten leading causes of cancer death in females. The association between diabetes and HCC has been summarized in a systematic review, showing that diabetics have a 2.5-fold risk of liver cancer [35]. Most studies, particularly the earlier ones, did not account for important confounding factors, such as alcohol consumption, smoking habits, or the presence of serum markers of hepatitis C or B virus. These factors may have inflated the calculated RR. In one cohort study, the RR of HCC declined from 2.90 (95% CI: 1.13–7.41) to 1.35 (95% CI: 0.41–4.43) after adjustments to hepatitis and cirrhosis status [36]. This is further complicated by a potential synergy between DM and several important risk factors involved in HCC, such as alcohol consumption and chronic hepatitis virus infection. For example, in a hospital-based, case–control study at the University of Texas MD Anderson Cancer Center (TX, USA), which included 115 HCC patients and 230 non-liver cancer controls, Hassan et al. found synergistic interactions between heavy alcohol consumption and chronic hepatitis virus infection (odds ratio [OR]: 53.9; 95% CI: 7.0–415.7) and diabetes (OR: 9.9; 95% CI: 2.5–39.3), whereas the OR for DM alone was 4.3 [37].

Nevertheless, studies that carefully accounted for these important confounders confirmed the association between diabetes and HCC. In a large population-based HCC case (n = 2061) control (n = 6183) study conducted among US Medicare enrollees, diabetes was associated with a 2.87 (95% CI: 2.49–3.30) increase in the risk of HCC, even after the exclusion from the sample of individuals with chronic viral liver infections, alcoholic liver diseases or hemochromatosis [38]. The study also showed that women are at a 70% lower risk of HCC compared with men after adjusting for age, race, Surveillance, Epidemiology and End Results (SEER) registry and Medicare/Medicaid dual enrollment.

**Colorectal cancer**

With an annual incidence of 41.7 per 100,000, colorectal cancer (CRC) is the third most common cancer in US women [104]. Based on the biological models mentioned above, a unifying hypothesis has been proposed in which insulin and insulin-like growth factors play a central role in colorectal carcinogenesis. In support of this hypothesis, a 2005 meta-analysis of epidemiologic studies reported that DM was associated with a moderate increased risk of CRC overall, with almost identical associations in men (summary relative risk [RR]: 1.52; 95% CI: 1.23–1.80) and women (summary RR: 1.33; 95% CI: 1.23–1.44) [39]. Possible explanations for the lack of association between diabetes and CRC in women could relate to gender differences in the use of metformin, an oral antidiabetic that reduces insulin resistance pre-eminently at the hepatic level and has been associated with a significantly lower risk of CRC [40]. Metformin has become more frequently used since the mid-1990s and according to one study, women are somewhat more likely to be prescribed metformin [41]. It has also been suggested that the attenuated risk among women may also relate to their better glucose control as reported by the National Health and Nutrition Examination Survey [42].

**Bladder cancer**

In the USA, bladder cancer incidence is less frequent in women (9.2 per 100,000) compared with men (37.2 per 100,000) [104]. However, it represents the ninth most common malignancy in US women. The findings from epidemiologic studies on the relationship between diabetes and bladder cancer are inconsistent. In a meta-analysis of 16 studies, the summary
estimates for case–control (seven studies) and cohort studies (three studies), but not from studies of hospitalized DM patients (six studies), indicated that individuals with diabetes may have an approximately 40% increased risk of bladder cancer [47]. The authors did not stratify their analyses by sex. Among the three investigated cohort studies, two were limited for cancer death and only one, the Iowa Women's Health Study, collected data on cancer incidence [48]. The Iowa Women's Health study, which included a total of 37,459 women who were followed for 13 years, indicated that post-menopausal women with self-reported diabetes had a 2.46-fold (95% CI: 1.32–4.59) increase in bladder carcinoma risk versus controls, after controlling for major confounders such as smoking, physical activity and BMI. Risk of bladder carcinoma remained significantly elevated in women with diabetes, even after excluding women who had developed bladder carcinoma within the first year of follow-up. Although not supported by subsequent smaller cohort studies with cancer incidence data, the results of the Iowa Women’s Health Study warrant further investigation [24,49].

Endometrial cancer

The incidence of endometrial cancer in the USA is 23.5 per 100,000 women [104]. Nearly all studies, mostly case–controls, of Type 2 diabetes in relation to the incidence of endometrial cancer reported a positive association. A meta-analysis of 16 studies, for a total of 96,000 participants and 7596 cases of endometrial cancer, showed that diabetes was associated with a doubling of the risk of endometrial cancer (RR: 2.10; 95% CI: 1.75–2.53) [50]. Similar risk ratios have been reported by more recently published cohorts [24,51,52]. As mentioned above, obesity is a common risk factor both for diabetes and endometrial cancer. However, most studies have shown that diabetes was independently associated with endometrial cancer with risk ratios ranging from 1.3 to 3.6 [52].

As described in the biological mechanisms section, several possible mechanisms may operate in linking diabetes and elevated insulin to endometrial cancer development. These include growth-enhancing properties of insulin, increased levels of IGF-1 receptors in the cancer tissue and suppressed gene expression of endometrial IGF-binding protein 1 (IGFBP-1), leading to increased biological activity of IGF-1, a known endometrial growth factor [53]. Increment in insulin and IGF-1 may also explain the strong association between obesity and endometrial cancer. There is also mounting evidence that DM is associated with increased proinflammatory cytokine production, especially IL-1, IL-6 and TNF-α. Inflammation can subsequently induce rapid cell division, increasing the possibility for replication error, ineffective DNA repair and subsequent mutations, increasing the likelihood of endometrial cancer [54]. A recent study found an association between endometrial cancer and polymorphism in the insulin receptor substrate-2 (IRS-2) gene, which is also involved in insulin resistance, thus providing a biological link between these two diseases.

NHL

The annual risk of NHL among US men and women is 23.6 and 16.5 per 100,000, respectively [104]. The potential relationship between NHL and diabetes was first suggested in the mid 1960s [55]. In their comprehensive meta-analysis on the association between NHL and DM, Mitri and colleagues summarized ten case–control reports and five prospective cohorts, which included more than 160,000 diabetic patients and 337 histologically confirmed incident cases of NHL over a mean follow-up period of 7–24 years [56]. This meta-analysis indicated that women with DM had a pooled RR of 1.38 (95% CI: 1.06–1.80) to develop NHL. Similar results were calculated in a second meta-analysis of five studies in which the pooled RR of NHL in female DM patients was 1.60 (95% CI: 1.15–2.22) [31]. Moreover, several studies suggested that the risk of NHL is particularly high among women at the earlier stages of diabetes. For example, Cerhan et al. reported a significantly elevated risk of NHL (RR: 3.43) in women who were on oral antidiabetic medication, but not among women on insulin [57].

Breast cancer

With more than 200,000 cases and 40,000 deaths annually, breast cancer is the most common malignant neoplasm in women, affecting one in eight females [1]. Similarly to Type 2 DM, the incidence of breast cancer rises with age. The cumulative incidence in Western Europe and the USA ranges from less than 3% by age 55 years, to nearly 8% by 75 years [17].

Although breast cancer and diabetes frequently occur together (up to 16% of older breast cancer patients may suffer from diabetes) [15], epidemiological studies of breast cancer and diabetes have yielded mixed results. A large meta-analysis that was published in 2007 has identified five eligible
Gestational DM & cancer risk
Gestational diabetes, carbohydrate intolerance that is first recognized during pregnancy, is a known risk factor for diabetes in women. Gestational DM (GDM) complicates 2–5% of pregnancies in the USA [59], and is associated with adverse pregnancy outcomes such as fetal macrosomia and an increased cesarean section rate [60].

Only few studies have investigated the relationship between GDM and cancer, and they have provided inconsistent results [61]. They were explained by methodological limitations such as the use of self-reported GDM status and insufficient statistical power due to the relatively rare occurrence of cancer among young women. Similarly to DM, GDM seems to be related to pancreatic cancer. A large cohort study of 37,926 women with 28–40 years of follow-up documented five incident cases of pancreatic cancer in women with GDM history [62]. The investigators calculated an adjusted RR of 7.1. Similar to DM, a possible biological explanation for the higher risk of pancreatic cancer in women with GDM history is increased levels of insulin and IGF, which may promote cell proliferation, inhibit apoptosis and enhance angiogenesis, leading to accelerated tumor development and progression [63]. A strong association between GDM and pancreatic cancer was observed in a recent cohort of 185,315 women who underwent glucose challenge testing and were followed for an average of 5 years [Sella T, Chodick G, Bar-Chana M, Porath A, Shalev V. Gestational diabetes and risk of incident primary cancer: a large population based cohort study in Israel. Manuscript Submitted (2011)]. In this study, gestational diabetes was also associated with hematologic malignancies, particularly NHL and acute myeloid leukemia.

Studies on GDM and breast cancer have produced mixed results: positive, negative and a general lack of association. No association between GDM and breast cancer was found in a US study of 1239 women diagnosed with breast cancer and 1166 controls [64]. However, a long-term cohort study of 753 women in New Zealand who underwent glucose testing at 13 weeks of pregnancy reported on a positive association between higher glucose levels and an increased risk of breast cancer [65]. With regard to menopause status, GDM was related with an elevated risk of postmenopausal breast cancer [61] and a reduced risk of premenopausal breast cancer [66].

In addition to GDM, hyperglycemia, as measured by fasting and postload glucose, has also been suggested to be associated with an overall statistically significant increase in risk of cancer in women but not in men. In three large cohorts, nondiabetic women at the highest category of fasting plasma glucose had between 15 and 28% higher cancer risk compared with women at the lowest category [67–69]. Results for men were less conclusive. Similar to studies in DM patients, non-DM women with high levels of fasting glucose were at a statistically significantly increased risk of pancreatic cancer, malignant melanoma and urinary tract cancers. These associations were independent of BMI, which showed only a very modest correlation with glucose levels.

Cancer survival among DM patients
Previously published investigations suggested that, unlike the general population, diabetic women do not have a better survival compared with diabetic men [70,71]. Few studies that have investigated the influence of diabetes on the survival of female cancer patients have also shown poorer survival. A SEER registry study on 1800 postmenopausal breast cancer patients demonstrated a 76% higher risk of death within 30 months among DM patients [72]. Possible explanations for the poorer survival among DM patients include higher prevalence of life-threatening comorbid conditions such as cardiovascular diseases and DM complications, particularly among DM women [73,74]. The presence of diabetes among cancer survivors may also increase cancer recurrence and subsequent death, as was noted in a cohort study within a large randomized clinical trial [75]. In addition, DM patients diagnosed with cancer were found to receive less aggressive treatment, which may also explain poorer cancer survival [76].
Conclusion & future perspective

Future studies should no longer merely search for an association between diabetes and cancer, but rather provide useful information regarding the potential underlying mechanism. The design of future studies should facilitate the examination of the independent contribution of the various cancer risk factors and metabolic alterations associated with DM. For example, this can be achieved by assessing the interaction between BMI and hyperinsulinemia. Attention should also be given to the level of glucose balance in isolating the effect of hyperglycemia from hyperinsulinemia.

With the current body of knowledge it is clear that cancer is a multifactorial and complex process that can evolve in various mechanisms. This heterogeneity in tumor initiation and progression can explain the relatively weak links found so far between diabetes and breast cancer, the most important cancer among women. Future studies should look for a link between DM and breast cancer according to specific risk factors such as differences in receptor status (estrogen[^77^], progesterone[^77^], HER2[^77^]). In addition, the risk associated with specific mutations such as BRCA in breast cancer and APC mutations in colon cancer should be studied. Revealing the molecular mechanisms linking DM to cancer would hopefully lead to the development of new therapeutic and preventive approaches. Better characterization of DM patients who are at an increased risk of developing specific tumors can lead to recommendations regarding targeted and effective screening.

Given the association between DM and cancer, study efforts focus on molecules and genes involved in insulin signal transduction and insulin resistance pathways, which can mediate this association. One group of such molecules is the adipocytokines. These molecules are secreted by adipocytes and are involved in pathological processes such as obesity, insulin resistance and atherosclerosis. Emerging evidence points to their possible involvement in tumor development. Leptin, which is involved in regulation of insulin activity, also promotes angiogenesis and may have a direct effect on proliferation of breast cell lines[^77]. Furthermore, it has been shown *in vitro* that leptin can activate estrogen receptor (ER) without its ligand[^78]. This may explain why in some studies DM was mainly associated with ER-positive tumors[^77]. Another adipocytokine, adiponectin, which increases insulin sensitivity, was found to be negatively correlated with breast and endometrial cancer[^79,80]. Genome-wide association studies found relationships between adipokine gene variants and risk for CRC, which was affected by interaction with diabetes-related genes[^81]. Further studies are required to establish these relationships and identify target molecules for potential treatments.

This article also highlights some previously neglected areas of research. Although over 200,000 pregnant American women are diagnosed with gestational diabetes every year, relatively little is known about the relationship between history of GDM and subsequent risk of cancer. This is probably due to their relatively young age and low absolute cancer risk, and requires large study populations and a long follow-up. Future studies need to overcome these significant challenges to strive to conduct high-quality investigations of this potentially important area.

Another important field for investigation that was only partially addressed in this article is the association between treatments for diabetes and cancer risk. Available evidence points to a potentially reduced cancer risk with metformin, and increased risk with the use of exogenous insulin, especially long-acting insulin analogue (glargine), as was indicated in four recent studies published in *Diabetologia*[^82]. In one UK study[^83], diabetics receiving insulin or sulfonylureas had a higher risk of cancer compared with patients treated with metformin. In a study from Germany, the risk of cancer was positively associated with insulin dose, particularly among users of glargine[^84]. A higher risk of breast cancer was calculated among users of insulin glargine in two other studies from Scotland[^85] and Sweden[^86]. The results of these studies could be confounded by the indication for the use of these drugs, diabetes duration, degree of glucose control and drug effects on other cancer risk factors such as body weight and hyperinsulinemia. Metformin, which improves insulin resistance and lowers insulin serum level, has already been studied as a treatment for PCOS and liver steatosis in the absence of diabetes with some promising results. In *vitro*, metformin inhibited proliferation of endometrial cell lines. It was suggested that AMPK activation, which mediates the metabolic effect of metformin, inhibits cell proliferation through inhibition of the mTOR pathway[^87]. The role of metformin in cancer prevention, especially in women, warrants further investigation.

Until specific recommendations regarding primary and secondary prevention of cancer can be developed for diabetic patients, women
with diabetes or gestational diabetes should be strongly encouraged by their healthcare professionals to undergo appropriate cancer screenings as recommended for all people of their age. Also, the importance of adhering to a healthy lifestyle including weight management, smoking cessation, physical activity and healthy diet cannot be overstressed. Healthcare professionals should be alert to the possibility of the occurrence of cancer in these patients.

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Executive summary
- Cancer and type 2 diabetes mellitus (T2DM) are major public health problems in the western world.
- In both sexes, T2DM patients are at an increased risk of digestive organ malignancies (liver, pancreas and colon), as well as bladder cancer. Compared with non-diabetic women, females with T2DM have a 20% higher risk of developing breast cancer (mostly postmenopausal), and a twofold risk of developing endometrial cancer.
- The biological mechanisms that may explain the increased cancer risk among DM women include higher circulating levels of insulin (which has a known mitogenic activity in cells), hyperglycemia and increased oxidative stress. The pro-oncogenic effects of hyperinsulinemia can occur directly through the insulin/IGF-1 axis by several possible pathways, or indirectly by reducing liver synthesis of sex hormone-binding globulin, as well as by increasing the production of estradiol and androgens independently of obesity.
- A few studies have suggested that women with T2DM have poorer cancer survival compared with non-diabetic female cancer patients. This could be explained by a higher prevalence of life-threatening comorbid conditions, higher cancer recurrence or less aggressive treatment.
- Future studies should look for a link between T2DM and breast cancer according to specific tumor features such as differences in receptor status (estrogen+, progesterone-/- and HER2+/-). In addition, the risk associated with specific mutations such as BRCA in breast cancer and APC mutations in colon cancer should be studied.
- The available evidence points to a potentially reduced cancer risk with metformin, while recent studies indicate an increased risk with the use of exogenous insulin, especially long-acting insulin analogue. Both associations require further investigation.

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