

Review Article

Diabetes mellitus and cancer risk: Review of the epidemiological evidence

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(Received July 12, 2012/Revised October 9, 2012/Accepted October 10, 2012/Accepted manuscript online October 15, 2012/Article first published online December 6, 2012)

Diabetes mellitus and cancer are diseases of epidemic proportions across the globe. These diseases are influenced by many factors, both genetic and environmental. A possible association between diabetes and cancer risk has long been speculated. Increased incidence of several cancers has been observed in diabetes patients, notably pancreatic, hepatic, colorectal, breast, urinary tract, and endometrial cancers. In contrast, a decreased incidence of prostate cancer is observed in diabetes patients, implying a protective effect. Precise knowledge of the complex associations and interactions between these two conditions is of great importance for their prevention and treatment. Multiple potential mechanisms have been proposed, but they have tended to be site-specific. Possible common mechanisms for a biological link between diabetes and cancer include hyperinsulinemia, hyperglycemia, and inflammation. Today, 366 million people live with diabetes globally, and this figure is expected to increase. Thus, if diabetes is associated with even a small increase in cancer risk, this may have important consequences at the population level. The aim of this review is to summarize recent epidemiological evidence of an association between diabetes and total cancer and specific sites of cancer, and to consider causal associations between these diseases. (*Cancer Sci* 2013; 104: 9–14)

Diabetes mellitus is now a common and serious global health problem. It has grown in conjunction with rapid social and cultural changes, such as the aging of populations, urbanization, dietary changes, reduced physical activity, and other unhealthy behaviors, and is associated with various complications that decrease the quality of life and the survival of affected individuals.⁽¹⁾ Today, 366 million people have diabetes worldwide, and the number is predicted to reach 552 million by 2030.⁽²⁾ Japan reflects this situation. The National Diabetes Survey in Japan showed that the prevalence of diabetes increased from 8.2% in 1997 to 10.5% in 2007.⁽³⁾ In our Japanese community-based survey, the prevalence of glucose intolerance increased from 33.9% in 1988 to 43.5% in 2004.⁽⁴⁾ This trend is presumably attributable to the rapid Westernization of lifestyles in Japan, and is likely shared by the majority of East Asian populations.⁽⁵⁾

Growing evidence suggests that glucose metabolism abnormalities can represent an independent risk factor for the development of specific cancers and can affect their prognosis.^(6,7) Several epidemiological studies have found that diabetes patients have an increased incidence of several types of cancers, such as liver,⁽⁸⁾ biliary tract,⁽⁹⁾ pancreas,⁽¹⁰⁾ stomach,⁽¹¹⁾ colorectum,⁽¹²⁾ kidney,⁽¹³⁾ bladder,⁽¹⁴⁾ breast,⁽¹⁵⁾ and endometrium.⁽¹⁶⁾ In contrast, a reduced incidence of prostate cancer⁽¹⁷⁾ has been reported in individuals with diabetes (Table 1). However, the causal mechanisms involved in the association

between diabetes and cancer are not clear. It has been reported that some metabolic alterations, such as hyperinsulinemia, insulin resistance, and aberrant production of growth hormone can induce carcinogenesis. Additionally, several potential confounders (e.g. obesity, medications, and diet) may contribute to this association. In the present review, we discuss the epidemiological evidence of an association between diabetes and cancer as well as the mechanisms underlying the association.

Epidemiological Evidence of Increased Risk of Cancer in Patients with Diabetes

Total cancer. Recently, numerous epidemiological studies have shown an association between diabetes and the risk of developing cancer.^(18–23) During a 10-year follow-up of a cohort of 7148 patients with type 2 diabetes in Italy, a 16% (95% confidence interval [CI], 2–30%) increase in mortality from total cancer was observed in women, but no significant increase was observed in men.⁽¹⁸⁾ A cohort study of 64 597 Swedish participants without diabetes showed that women with fasting plasma glucose levels of 6.1–6.9 mmol/L and >6.9 mmol/L had a 1.31-fold (95%CI, 1.11–1.54) and 1.51-fold (95%CI, 1.13–1.97) greater incidence of cancer, respectively.⁽¹⁹⁾ Obesity has been considered a possible confounding factor for the association between diabetes and cancer risk. However, adjustment for body mass index had no material effect on risk estimates. The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) Study, which examined data on 44 655 individual participants from 17 European population-based or occupational cohorts, revealed that the multivariate-adjusted hazard ratios (RRs) of cancer mortality were 1.12 (95%CI, 1.02–1.23) in subjects with prediabetes, 1.28 (95%CI, 1.08–1.51) in those with newly diagnosed diabetes, and 1.57 (95%CI, 1.29–1.91) in those with known diabetes (Fig. 1).⁽²⁰⁾ There were no substantial differences in the associations between the sexes. The risk of total cancer deaths was higher in individuals with prediabetes or diabetes, irrespective of body mass index. Similar results were found in Asian populations. A 10-year follow-up study of 1 298 385 Koreans indicated linear trends of increases in cancer mortality and incidence with higher fasting plasma glucose levels, even in the prediabetes range of 6.1–6.9 mmol/L.⁽²¹⁾ In our Japanese community-based cohort study of 2476 individuals with a 14-year follow-up, the risk of cancer mortality doubled in individuals with diabetes as compared to those with normal glucose tolerance levels (RR 2.10; 95%CI, 1.41–3.12). Additionally, impaired fasting glucose and impaired glucose tolerance were significantly associated with 1.49-fold (95%CI,

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Table 1. Recent meta-analyses of diabetes mellitus and risk of specific site of cancer

Cancer site	Author (year)	Studies	No. of cases/subjects,†	Summary RR (95% CI)
Liver	Wang <i>et al.</i> (2012) ⁽⁸⁾	18 cohort studies	18 258/3 626 369	2.01 (1.61–2.51)
Biliary tract	Ren <i>et al.</i> (2011) ⁽⁹⁾	8 case-control studies and 13 cohort studies	1836/165 861† 2595/5 494 975	1.43 (1.18–1.72), all studies 1.63 (1.07–2.47), case-control studies 1.49 (1.19–1.86), cohort studies
Pancreas	Ben <i>et al.</i> (2011) ⁽¹⁰⁾	35 cohort studies	20 410/21 616 592	1.94 (1.66–2.27)
Stomach	Ge <i>et al.</i> (2011) ⁽¹¹⁾	4 case-control studies and 17 cohort studies	3211/60 731† 12 759/8 036 686	Women: 1.18 (1.01–1.39), all studies 0.97 (0.64–1.46), case-control studies 1.12 (0.99–1.22), cohort studies Men: not significant
Colorectum	Jiang <i>et al.</i> (2011) ⁽¹²⁾	30 cohort studies	61 690/8 201 654	1.27 (1.21–1.34)
Kidney	Larsson <i>et al.</i> (2011) ⁽¹³⁾	9 cohort studies	9520/5 769 987	1.42 (1.06–1.91)
Bladder	Larsson <i>et al.</i> (2006) ⁽¹⁴⁾	7 case-control studies, 3 cohort studies, and 6 cohort of diabetic patients	4427/12 189† 1619/1 923 472 2965/196 637	1.24 (1.08–1.42), all studies 1.37 (1.04–1.80), case-control studies 1.43 (1.18–1.74), cohort studies 1.01 (0.91–1.12), cohort studies with diabetic patients
Breast	Larsson SC <i>et al.</i> 2007 ⁽¹⁵⁾	5 case-control studies and 15 cohort studies	14 374/14 762† 16 483/1 400 822	1.20 (1.12–1.28), all studies 1.18 (1.05–1.32), case-control studies 1.20 (1.11–1.30), cohort studies
Endometrium	Friberg <i>et al.</i> (2007) ⁽¹⁶⁾	13 case-control studies and 3 cohort studies	6912/17 689† 684/71 402	2.10 (1.75–2.53), all studies 2.22 (1.80–2.74), case-control studies 1.62 (1.21–2.16), cohort studies
Prostate	Kasper <i>et al.</i> (2006) ⁽¹⁷⁾	7 case-control studies and 12 cohort studies	2481/4726† 16 610/1 054 354	0.84 (0.76–0.93), all studies 0.89 (0.72–1.11), case-control studies 0.81 (0.71–0.92), cohort studies

†Number of cases/controls in case-control studies. CI, confidential interval, RR, relative risk.

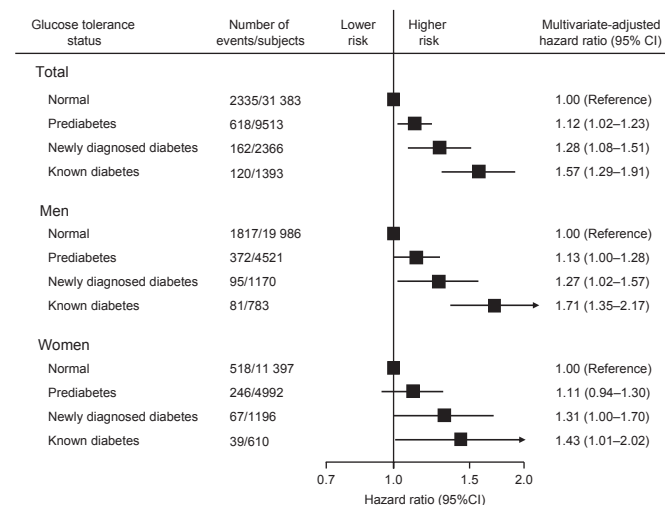


Fig. 1. Relationship between glucose tolerance status and the risk of cancer mortality: results of the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) Study. The risk estimates were adjusted for age, sex, study cohort, systolic blood pressure, cholesterol, body mass index, and smoking status. The results have been adapted from Zhou *et al.*⁽²⁰⁾ CI, confidence interval.

1.05–2.11) and 1.52-fold (95%CI, 1.05–2.22) higher mortality, respectively, from any cancer.⁽²²⁾ A recent meta-analysis from individual participant data on 123 205 deaths among 820 900 people in 97 prospective studies, in which our study was also involved, clearly showed that diabetes was associated with a 1.27-fold (95% CI, 1.20–1.34) higher risk of death from any cancer after adjusting for confounding factors, including body mass index, and cancer mortality increased significantly among individuals whose fasting glucose levels exceeded 5.6 mmol/L.⁽²³⁾ Thus, epidemiological studies provide

evidence that diabetes and prediabetes are associated with an increased risk of total cancer.

Liver cancer. Some epidemiological evidence has suggested a significant association between diabetes and liver cancer, after taking important confounding factors into account, specifically alcohol consumption and hepatitis B or C virus infection.^(8,24,25) In a population-based case-control study carried out in the USA consisting of 2061 cases of hepatocellular carcinoma and 6183 controls, diabetes was associated with a 2.87-fold (95%CI, 2.49–3.30) increase in the risk of liver cancer, even after excluding from the study population individuals with hepatitis B or C virus infections, alcoholic liver diseases, or hemochromatosis.⁽²⁴⁾ Similar results were obtained in a case-control study carried out in Greece on 333 cases of hepatocellular carcinoma and 363 controls. Diabetes patients were at a 1.86-fold (95%CI, 0.99–3.51) increase in the risk of liver cancer after adjusting for aforementioned risk factors.⁽²⁵⁾ A recent systematic review of 18 cohort studies also indicated a significant association between diabetes and an increased risk of hepatocellular carcinoma; the incidence of hepatocellular carcinoma increased by 101% (95%CI, 61–151%) and that of mortality by 56% (95%CI, 30–87%) in individuals with diabetes compared to those without.⁽⁸⁾ Subgroup analyses revealed that the increased risk of hepatocellular carcinoma in individuals with diabetes was independent of alcohol consumption, a history of cirrhosis, and hepatitis B or C virus infection. These findings strongly support a positive association between diabetes and the risk of hepatocellular carcinoma.

Diabetes patients may have a greater risk of biliary tract cancer. A meta-analysis investigated the possible association between diabetes and biliary tract cancers, such as gallbladder cancer and extrahepatic cholangiocarcinoma.⁽⁹⁾ This meta-analysis included 8 case-control and 13 cohort studies, and found that diabetes was associated with an increased risk of biliary tract cancer, as compared to no diabetes (RR 1.43; 95%CI, 1.18–1.72). In some studies, although not in all, diabetes was independently associated with an increased risk of biliary

stones,^(26,27) which are considered major risk factors for biliary tract cancer. Biliary stones may act as an intermediate factor between diabetes and biliary tract cancer.

Pancreatic cancer. Diabetes has been thought to increase the risk of pancreatic cancer. A recent meta-analysis of 35 cohort studies documented a 94% (95%CI, 66–127%) increase in the risk of pancreatic cancer in individuals with diabetes relative to those without diabetes.⁽¹⁰⁾ Although there was significant evidence of heterogeneity in the association across the studies included, subgroup analyses revealed that the increased risk of pancreatic cancer was independent of geographic location, sex, study design, alcohol consumption, body mass index, and smoking status. Interpretation of the causal nature of the association between diabetes and pancreatic cancer is complicated by the fact that abnormal glucose metabolism may be a consequence of pancreatic cancer. However, this meta-analysis also found that diabetes was associated with a 1.83-fold (95%CI, 1.38–2.43) increased risk of pancreatic cancer among individuals who have had diabetes for at least 5 years, implying that reverse causality has little influence on the association.

Gastric cancer. Evidence linking diabetes to gastric cancer was reported in a meta-analysis of 4 case-control and 17 cohort studies, in which diabetes was significantly associated with a 1.18-fold (95%CI, 1.01–1.39) increased risk of gastric cancer in women, whereas no such association was found in men with diabetes. There was strong evidence of heterogeneity among the studies in this meta-analysis.⁽¹¹⁾ Similarly, a prospective study of 97 771 Japanese with a follow-up of 11 years showed that diabetes was significantly associated with an increased incidence (61%) of gastric cancer (95%CI, 2–154%) in women, whereas the association was not significant in men (RR 1.23; 95%CI, 0.98–1.54), after adjusting for potential confounding factors, such as smoking status, body mass index, physical activity, and dietary factors.⁽²⁸⁾ However, the risk estimates used in this prospective study were not adjusted for the status of *Helicobacter pylori* infection. We also investigated the association between fasting glucose levels and the incidence of gastric cancer in a 9-year cohort study of 2466 Japanese. As a consequence, the multivariate-adjusted RR of developing gastric cancer was 2.3 (95%CI, 1.1–5.0) in individuals with modestly elevated fasting plasma glucose levels (5.3–5.8 mmol/L) and 3.1 (95%CI, 1.5–6.4) in individuals with more elevated levels (>5.8 mmol/L), compared to those with values below 5.3 mmol/L.⁽²⁹⁾ This excess risk was documented only in individuals with *H. pylori* infection, suggesting that hyperglycemia is a possible cofactor increasing the risk posed by *H. pylori* (Fig. 2). The same was true in an investigation of association between hemoglobin A1c levels and the incidence of gastric cancer.⁽³⁰⁾

Colorectal cancer. Lifestyle factors, such as a lack of exercise and obesity, are thought to be convincing risk factors for colorectal cancer.⁽³¹⁾ The association between diabetes and colorectal cancer has been elucidated in numerous epidemiological studies, and meta-analyses have been published.⁽¹²⁾ A recent meta-analysis of 30 cohort studies documented that diabetes was associated with an increased incidence of colorectal cancer (RR 1.27; 95%CI, 1.21–1.34) and with mortality from colorectal cancer (RR 1.20; 95%CI, 1.03–1.40) (Fig. 3). Although there was strong evidence of heterogeneity among the studies in that meta-analysis, subgroup analysis and meta-regression analysis by controlling for confounders showed that the increased risk of colorectal cancer in individuals with diabetes was independent of geographic location (Europe versus Asia), sex, family history of colorectal cancer, smoking, physical activity, and body mass index. This association may be attributable to slower bowel transit times in individuals with diabetes, which could contribute to the increased exposure of colonic mucosa to potential carcinogens (e.g. bile acid).^(32,33)

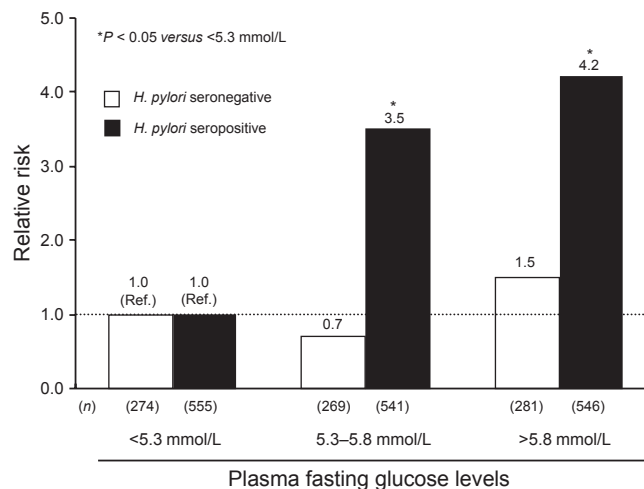


Fig. 2. Age- and sex-adjusted relative risks of gastric cancer according to fasting glucose levels under stratification by *Helicobacter pylori* (*H. pylori*) status. The results have been adapted from Yamagata *et al.*⁽²⁹⁾ Ref., Reference.

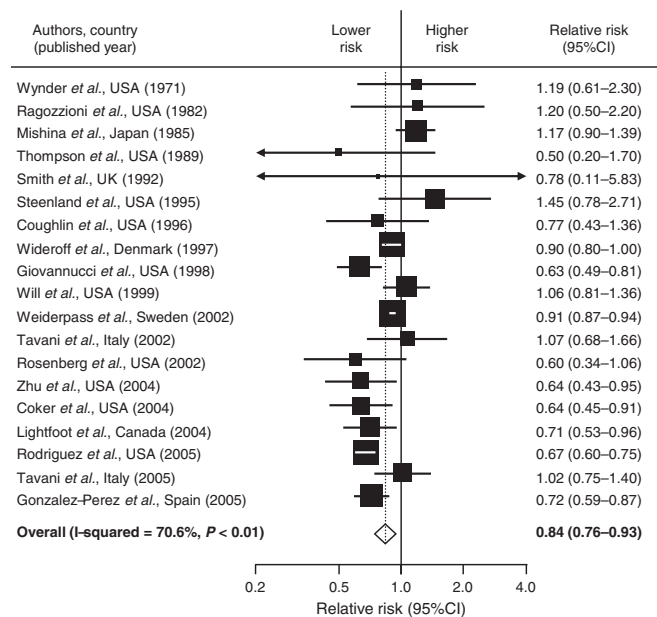


Fig. 3. Meta-analysis of 19 studies that examined the association between diabetes mellitus and prostate cancer. The pooled risk estimate was computed using a random-effects model because there was significant heterogeneity in the association among studies included. The results are adapted from Kasper & Giovannucci⁽¹⁷⁾. CI, confidence interval.

Urinary organ cancer. A meta-analysis of nine cohort studies reported a significant association between diabetes and kidney cancer (RR 1.42; 95%CI, 1.06–1.91).⁽¹³⁾ However, this association was weaker and not statistically significant when the studies were restricted to those that were controlled for body mass index or obesity. This finding suggests that the observed association is attributable in part to obesity as a confounding factor.

The results of epidemiological studies that investigated the association between diabetes and bladder cancer were inconsistent. In a meta-analysis of 16 studies (7 case-control studies, 3

cohort studies, and 6 cohort studies of diabetes patients), individuals with diabetes had a modest (24%) increase in the risk of bladder cancer (95%CI, 8–42%).⁽¹⁴⁾ However, there was strong evidence of between-study heterogeneity, and a funnel plot showed some asymmetry. Thus, the possibility that the association is due to confounding or bias cannot be ruled out.

Sex-specific cancers. Breast cancer is the most common malignancy affecting women worldwide. Its incidence rises with age and is associated with hormonal factors, benign breast disease, family history of breast cancer, and genetic factors.⁽³⁴⁾ A meta-analysis of 20 studies (5 case-control and 15 cohort studies) showed a 20% (95%CI, 12–28%) increased risk of breast cancer in women with diabetes, with the vast majority of the cases being type 2 diabetes.⁽¹⁵⁾ The same was true among studies that were controlled for body mass index. Increased exposure to estrogen in diabetes is thought to be one of the biological mechanisms between diabetes and breast cancer.⁽³⁵⁾ However, the data on the influence of menopausal status on the association between diabetes and breast cancer are inconclusive.

One meta-analysis based on 16 studies (13 case-control and 3 cohort studies) has shown an increased risk of endometrial cancer in women with diabetes.⁽¹⁶⁾ The site-specific biological mechanism underlying the development of endometrial cancer in women with diabetes is hyperinsulinemia, which may increase levels of bioactive estrogen by decreasing concentrations of circulating sex hormone-binding globulin.⁽³⁶⁾ Estrogen has been shown to increase cancer risk by stimulating the proliferation of endometrial cells⁽³⁷⁾ when unopposed by progesterone.⁽³⁸⁾

The prostate differs from other sites of cancer in its association with diabetes. A meta-analysis of 19 studies (9 case-control and 10 cohort studies) has shown that men with diabetes were at a significantly decreased risk of developing prostate cancer (Fig. 3).⁽¹⁷⁾ The suggested mechanism underlying this inverse association is thought to be reduced testosterone level, which is commonly observed in men with diabetes or with obesity secondary to low levels of sex hormone-binding globulin.⁽³⁹⁾ Furthermore, several studies have determined that variants of the *HNF1B* gene at 17q12, which predispose haplotype-carrying subjects to diabetes, were associated with a decreased risk of prostate cancer.⁽⁴⁰⁾ However, it is unknown whether or not *HNF1B* alters levels of various metabolic and hormonal factors that may influence prostate cancer risk in men with diabetes.

Type 1 and Type 2 Diabetes and Cancer Risk

Diabetes is divided into two subtypes, type 1 and type 2, which differ in metabolic and hormonal characteristics. In type 1 diabetes patients (5–10% of all diabetics), hyperglycemia is associated with an absolute deficiency of endogenous insulin secretion, whereas hyperglycemia and hyperinsulinemia coexist for a long time in type 2 diabetes, because of insulin resistance in peripheral tissues. Despite these considerable pathogenetic and clinical differences, most studies on the association between diabetes and cancer have been carried out without distinction between the two subtypes of diabetes. Because type 1 diabetes is less frequent than type 2 diabetes, especially in adult populations, it is reasonable to suppose that the large majority of the epidemiological data on cancer incidence and mortality has been obtained in type 2 diabetes patients. Therefore, it is questionable whether these data can be automatically extended to type 1 diabetes patients.

A few studies have elucidated the association between type 1 diabetes and the risk of cancer. A cohort of 29 187 Swedish patients who were hospitalized for type 1 diabetes showed a 20% increase in overall cancer incidence (standardized inci-

dence ratio [SIR] 1.2; 95% CI, 1.0–1.3), when data for the entire Swedish population were used as a reference.⁽⁴¹⁾ In this study, patients with type 1 diabetes had excess risks of cancers of the stomach (SIR 2.3; 95% CI, 1.1–4.1), cervix (SIR 1.6; 95%CI, 1.1–2.2), and endometrium (SIR 2.7; 95%CI, 1.4–4.7). In addition, a meta-analysis including three cohort studies and six case-control studies found that the overall RR for pancreatic cancer in young-onset or type 1 diabetes was 2.00 (95%CI, 1.37–3.01) as compared with no diabetes, without significant heterogeneity between cohort studies and case-control studies.⁽⁴²⁾ However, the relationship between type 1 diabetes and excess cancer risk remains inconclusive because the method of diagnosing diabetes subtypes in these studies is not reliable.

Interpretation of Epidemiological Evidence between Diabetes and Cancer Risk

An accumulation of epidemiological evidence based on observational studies has indicated a statistically significant association between diabetes and cancer risk. However, the evidence does not directly prove biological causality, and we cannot fully exclude the possibility of bias or a confounding of the association.

A case-control study is generally dependent on the collection of retrospective data and thus is inherently more sensitive to recall and selection bias than a prospective study design. Additionally, there is a consensus that a systematic review can provide a more reliable estimation of published research than can traditional narrative reviews. However, in a systematic literature review, publication bias is an inevitable problem, because negative or inconclusive results tend to be unpublished and to be unavailable for analysis. Thus, the risk estimates from a systematic review of published studies may be overestimated. Surveillance bias may also occur in the association between diabetes and cancer risk: diabetes patients visit physicians more frequently than do non-diabetes patients, and consequently, cancer may be detected more in diabetes patients than in those without diabetes.

Confounding is likely to happen in the association between diabetes and cancer risk, because diabetes and cancer share several risk factors, including obesity and low physical activity. Thus, the increased risk of cancer in diabetes patients may in part reflect confounding by these risk factors. Even though the risk estimates were adjusted for these possible confounding factors in most epidemiological studies, residual confounding cannot be excluded completely. Furthermore, reverse causality may also exist. Cancer causes insulin resistance through the production of inflammatory cytokine (e.g. tumor necrosis factor- α) and subsequent hyperglycemia and diabetes.^(43,44)

Accordingly, several possible biases or confounding factors might exist in the relationship between diabetes and cancer risk. Nevertheless, it is evident that diabetes increases the risk of cancer from an epidemiological viewpoint. To confirm a causal association, it would be necessary to identify the biological mechanisms involved through experimental studies, and to ascertain whether or not intervention against key factors of this mechanism reduces cancer risk in humans.

Possible Biological Mechanisms Underlying the Association between Diabetes and Cancer

Although biological mechanisms underlying the association between diabetes and cancer have been inconclusive, several possible mechanisms have been proposed, such as hyperinsulinemia, hyperglycemia, and inflammation.

Type 2 diabetes is characterized by insulin resistance and secondary hyperinsulinemia. The role of insulin in promoting cancer growth was first recognized in studies with experimen-

tal animals. When insulin deficiency was induced by alloxan in rats, insulin given to these animals appeared to display intrinsic growth-stimulating effects on the mammary tumor tissue induced by 7,12-dimethylbenz(a)anthracene dissolved in sesame oil.⁽⁴⁵⁾ Most cancer cells express insulin receptors, thus hyperinsulinemia has been thought to promote carcinogenesis by directly stimulating the proliferating pathway after insulin receptors.⁽⁴⁶⁾ Elevated insulin levels may occur early in the natural history of diabetes and decline as diabetes advances. If hyperinsulinemia has a role in promoting cancer initiation and/or progression, these aspects should be considered when estimating the risk of an individual diabetes patient developing cancer. Intriguingly, this hypothesis may be supported by evidence that treatment with metformin, which increases insulin sensitivity and decreases hyperinsulinemia, is associated with a lower incidence of cancer in diabetes patients than in those being treated with insulin or sulfonylurea.^(47,48)

Apart from the direct effects of insulin on cancer cells, it is possible that hyperinsulinemia promotes carcinogenesis indirectly through the effect of insulin-like growth factor (IGF)-1. Insulin reduces the production of IGF binding protein-1 and consequently increases the bioactive IGF-1. Insulin-like growth factor-1 has more potent mitogenic and anti-apoptotic activities than insulin and could act as a stimulus for growing preneoplastic and neoplastic cells.⁽⁴⁹⁻⁵¹⁾

Hyperglycemia itself has also been reported to promote tumor cell proliferation and metastasis in type 2 diabetes.⁽⁵²⁾ A clinical study of diabetes patients and healthy volunteers demonstrated that diabetes is associated with increased production of reactive oxygen species and greater oxidative damage to DNA, which may lead to mutational changes in oncogenes and tumor suppressor genes, and thereby to the development of cancer.⁽⁵³⁾ However, the aforementioned study using a rat model with alloxan showed reduced tumor growth, possibly

implying that hyperglycemia itself does not lead to induce neoplastic growth.⁽⁴⁵⁾ Thus, the effect of hyperglycemia itself on carcinogenesis should be further elucidated.

The metabolic abnormalities that characterize diabetes, especially under conditions of poor metabolic control, cause a permanent pro-inflammatory condition. Inflammatory cytokines produced by adipose tissues, such as interleukin-6, monocyte chemoattractant protein, and plasminogen activator inhibitor-1, may play important roles in the carcinogenic process, cancer progression, or poor prognosis. Additionally, increased leptin and decreased adiponectin levels may also contribute to the increased risk of cancer among individuals with obesity and type 2 diabetes.⁽⁵⁴⁾ This chronic pro-inflammatory state reduces intracellular antioxidant capacity, predisposing susceptible cells to malignant transformation. In fact, high concentrations of diverse free radicals and oxidants generate potent reactive oxygen species that can damage cell DNA by direct oxidation or by interfering with the mechanisms of DNA repair.

Conclusions

Epidemiologic evidence suggests that individuals with diabetes are at significantly higher risk for many forms of cancer except prostate cancer. The excess risk of cancer conferred by diabetes is moderate. Nevertheless, the cancer risk among diabetes patients may become a clinical, social, and economic burden in the future because of the growing worldwide frequency of diabetes. Further investigation is needed to develop a more rational approach to cancer prevention and treatment among individuals with diabetes.

Disclosure Statement

The authors have no conflict of interest.

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