Latest insights into the risk of cancer in diabetes

Hiroshi Noto[1,2]*, Atsushi Goto[2], Tetsuro Tsujimoto[1], Keiichiro Osame[3], Mitsuhiko Noda[1,2]

ABSTRACT

A growing body of evidence from observational studies and meta-analyses of the data suggest that diabetes mellitus is associated with an increased risk of cancer. Meta-analyses have shown that diabetes increases the risks of total cancer, and of site-specific cancers of the breast, endometrium, bladder, liver, colorectum and pancreas, and that it decreases the risk of prostate cancer. Insulin resistance and secondary hyperinsulinemia is the most frequently proposed hypothesis, and hyperglycemia itself might promote carcinogenesis. In addition to several facets of lifestyle including obesity, smoking and lack of exercise, treatment for diabetes might affect the risk of cancer. For instance, metformin, an insulin sensitizer, reportedly has a potential anticancer effect. In light of the exploding global epidemic of diabetes, even a modest increase in the cancer risk will translate into a substantial socioeconomic burden. The current insights underscore the need for clinical attention and better-designed studies of the complex interactions between diabetes and cancer. (J Diabetes Invest, doi: 10.1111/jdi.12068, 2013)

KEY WORDS: Cancer, Diabetes, Risk factors

INTRODUCTION

Emerging evidence from observational studies and meta-analyses of the data suggest that diabetes mellitus is associated with an increased risk of cancer. The mechanisms are yet to be investigated, but insulin resistance with secondary hyperinsulinemia is the most frequently proposed hypothesis, as insulin might have a possible mitogenic effect through binding the insulin-like growth factor-1 receptor[1]. In addition, hyperglycemia itself might promote carcinogenesis by increasing oxidative stress[2–5].

In light of the fact that cancer is the second leading cause of death worldwide, diabetes is the 12th[6], the current worldwide diabetes epidemic and the higher mortality in cancer patients with diabetes[7,8], elucidating the association between these diseases in general populations is crucial for making timely, rational, and informed decisions, not only in the areas of public health and socioeconomy, but also for the prevention and targeted management of diabetes in daily clinical practice. The American Diabetes Association and the American Cancer Society recently published a consensus statement that reviewed evidence regarding the association between diabetes and cancer incidence or prognosis, risk factors common to both diabetes and cancer, possible biological links between diabetes and cancer risk, and whether diabetes treatments influence risk of cancer or cancer prognosis[9].

[1]Departments of Diabetes and Metabolic Medicine, Center Hospital, [2]Department of Diabetes Research, Diabetes Research Center, Research Institute, National Center for Global Health and Medicine, and [3]Department of General Medicine, National Cancer Center Hospital, Tokyo, Japan
*Corresponding author. Hiroshi Noto Tel.: +81-3-3202-7181 Fax: +81-3-3207-1038
E-mail address: noto-tky@umin.net
Received 1 November 2012; revised 10 December 2012; accepted 10 December 2012

EPIDEMIOLOGY

Several meta-analyses have shown that diabetes is associated with increased risks of site-specific cancers of the liver, endometrium, pancreas, colorectum, bladder, breast and total cancer (Table 1). The evidence for non-Hodgkin's lymphoma remains inconclusive[18]. Exceptionally, the risk of prostate cancer in diabetes is significantly decreased[17].

Evidence has been accumulating to suggest that diabetic patients have a higher risk of cancer death than non-diabetic peo-

Table 1 | Cancer risk in diabetes: meta-analysis

Site	Risk ratio (95% CI)
Cancer incidence	
Overall[10]	
Men	1.14 (1.06–1.23)
Women	1.18 (1.08–1.28)
Combined	1.10 (1.04–1.17)
Liver[11]	2.50 (1.93–3.24)
Endometrium[12]	2.10 (1.75–2.53)
Pancreas[13]	1.82 (1.66–1.89)
Colorectum[14]	1.30 (1.20–1.40)
Bladder[15]	1.24 (1.08–1.42)
Breast[16]	1.20 (1.12–1.28)
Prostate[17]	0.84 (0.76–0.93)
Cancer mortality	
Overall[10]	
Men	1.10 (0.98–1.23)
Women	1.24 (1.11–1.40)
Combined	1.16 (1.03–1.30)

CI, confidence interval.

ple (Table 1)[10,19]. Furthermore, cancer patients with pre-existing diabetes have higher short-term[8] and long-term[7] mortalities.

The same as in Western countries, the prevalence of diabetes is markedly increasing in Asia. This trend is presumably attributable to the rapid Westernization of lifestyle, a trend that is likely shared by the majority of Asian populations[20]. Although cardiovascular disease is the main cause of mortality in Western countries, and patients with diabetes have a high risk of such disease, cancer is emerging as a major cause of death in Asian countries[21–23]. Our meta-analysis[24] showed that the pooled adjusted risk ratio (RR) of all-cancer mortality in diabetics was significantly higher than in non-diabetic people (RR 1.32, 95% confidence interval [CI] 1.20–1.45 for Asians; RR 1.16, 95% CI 1.01–1.34 for non-Asians). Diabetes was also associated with an increased RR of incidence across all cancer types (RR 1.23, 95% CI 1.09–1.39 for Asians; RR 1.15, 95% CI 0.94–1.43 for non-Asians). The RR of incident cancer for Asian men was significantly higher than for non-Asian men ($P = 0.021$).

MECHANISMS

Hyperinsulinemia

Type 2 diabetes is characterized by insulin resistance and compensatory hyperinsulinemia, and people with type 2 diabetes are typically obese and lead sedentary lives, both of which also contribute to their hyperinsulinemia. Multiple and complex mechanisms are postulated. First, insulin might bind and activate its structurally related insulin-like growth factor-1 (IGF-1) receptor, which is the most frequently proposed mechanism to explain the clearly increased risk of cancer in diabetic patients (Figure 1)[1,25]. Second, hyperinsulinemia might increase cancer risk by unregulated insulin receptor signaling, leading to proliferative and anti-apoptotic effects[26]. Finally, the mitogenic activity of insulin might be enhanced at the cellular level by postreceptor molecular mechanisms including insulin residence time on the receptor and the intracellular upregulation of the insulin mitogenic pathway[27]. It has been reported that this mitogenic pathway, unlike the metabolic pathway, might not be blunted in the condition of insulin resistance[28].

Several findings were consistent with this insulin supply hypothesis. Pancreatic cancer has been reportedly induced more effectively with a carcinogen or by implantation of cancer cells when experimental insulin-deficient animals were given supplemental insulin[29]. In humans, patients with type 1 diabetes, who are insulin deficient, have a lower risk of cancer than patients with type 2 diabetes[30], although the evidence of the risk as compared with that in the general population remains inconclusive[31]. However, these speculations need to be interpreted with caution, as they are derived from retrospective observational studies and might not necessarily show causality because of possible biases and confounders, such as coexisting obesity

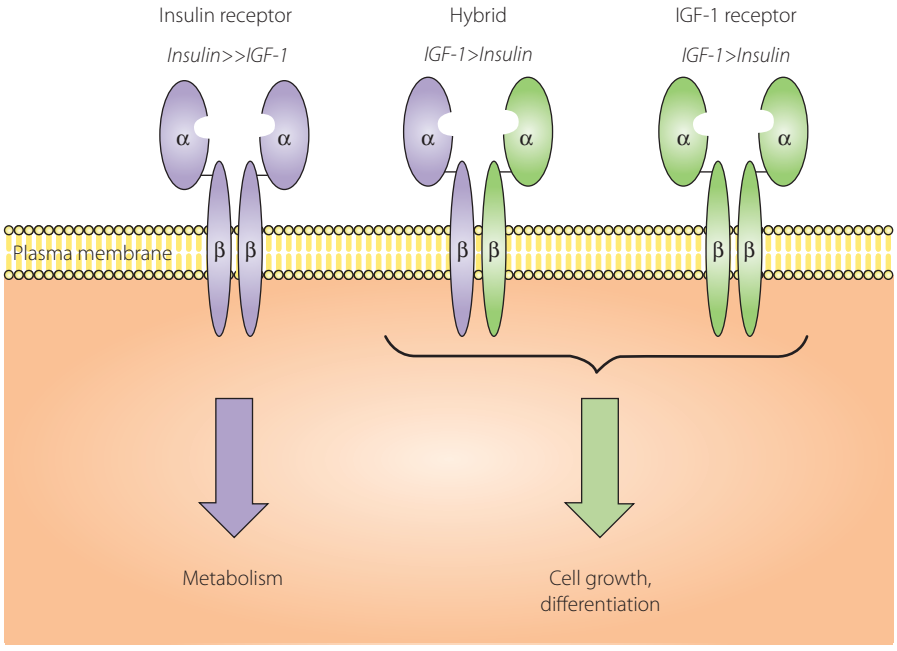

Figure 1 | The insulin/insulin-like growth factor-1 (IGF-1) receptor. Both the insulin receptor and the IGF receptor are encoded by single genes, which are processed into an α-chain and β-chain that remain linked by disulfide bonds. These α/β complexes can either homodimerize to form insulin receptors or IGF receptors, or heterodimerize to form hybrid receptors. Insulin binds preferentially to the insulin receptor, whereas IGF-1 binds preferentially to the IGF-1 and hybrid receptors. Although there is a great deal of overlap in their function, the insulin receptor is more closely linked with metabolic effects, whereas the hybrid receptor and IGF receptor are more closely linked with proliferation. Adapted from Biddinger *et al.*[25] with permission.

and age[32]. In fact, more recent studies have shown no or minimal increments in cancer risk[33], and the data from insulin-treated patients are controversial[34].

Of interest, diabetes has been reported to protect against the development of prostate cancer[17,35], which is testosterone-dependent. Testosterone deficiency is common in men with diabetes, because they have low levels of sex hormone-binding globulin, and testosterone levels have been shown to be partly influenced by insulin resistance[36]. The degree of the decrease in cancer risk as a result of testosterone deficiency is likely to be higher than the magnitude of the increase in cancer risk as a result of insulin resistance, and thus this effect of diabetes on prostate cancer might have contributed to the attenuation of the increase in cancer risk in men[19]. However, those meta-analyses[17,35] were mainly based on data for Caucasian men, and the reported risks for Asian men have been either significantly elevated in Taiwan[37,38] or non-significant in Japan[39] and Korea[3], which points to the possibility that the effect of diabetes on prostate cancer might not be universal, probably secondary to genetic/cultural/socioeconomic factors.

Hyperglycemia

Hyperglycemia has also been reported to promote carcinogenesis and cancer metastasis in type 2 diabetes[40]. Indeed, this forms the basis for 18F-fluorodeoxyglucose-positron emission tomography of cancers, which detects tissues with high rates of glucose uptake. In addition, hyperglycemia itself might promote carcinogenesis by generating oxidative stress[2,41], which is frequently observed to be increased in a variety of cells in diabetes. The increase in oxidative stress would damage DNA, the initial step in carcinogenesis[5]. Community-based prospective surveys have documented associations between plasma glucose levels and the risk of cancer[2,3,42]. The results of our study[24] support this hypothesis, because the results showed that the risk of both cancer incidence and mortality is also generally higher among Japanese[19] and Korean[3] patients with diabetes, who have been deemed to be insulinopenic[20,43]. However, a meta-analysis of large randomized-controlled trials (RCTs) of intensified glycemic control did not support the hypothesis that hyperglycemia is causally linked to increased cancer risk[44].

These observations point to the crucial need for understanding the role of glucose metabolism and insulin resistance in carcinogenesis[20,45].

Confounding Factors

Potential common risk factors of cancer and diabetes need to be addressed, because it remains to be clarified whether the association between diabetes and the risk of cancer is mainly a result of shared risk factors or whether diabetes itself causes some types of cancer.

First, several comorbidity confounders exist. Diabetes and cancer share multiple lifestyle-related risk factors (Table 2). For example, coexisting obesity and a sedentary lifestyle, which induce hyperinsulinemia, might be the true causes, and diabetes might merely be an innocent bystander. A meta-analysis showed that obesity is associated with increased risk for pancreas cancer, thyroid cancer, non-Hodgkin's lymphoma, leukemia and myeloma[46], whereas bariatric surgery resulted in 60% reduction in cancer mortality over the course of 7 years[47]. Exercise is suggestively associated with overall cancer, colon cancer, hepatocellular cancer, pancreas cancer and gastric cancer[48]. The other possible confounding factors include age, sex, diet, alcoholic intake, smoking, cirrhosis, hepatitis C viral infection[49] and the indication of insulin therapy. These factors are generally interrelated, and thus it is difficult to assess the contribution of each factor. Second, an alternative explanation is that diabetic patients might receive medical care more frequently and have more opportunities for cancer detection than non-diabetic subjects. Third, diabetes might develop as a consequence of cancer, as cancers generally cause insulin resistance and subsequent hyperglycemia by producing cytokines, such as tumor necrosis-α[50]. Fourth, the previous studies might have left room for confounding by treatment indication; differences between the treatment of cancer according to whether or not they had diabetes might have contributed to the increased mortality of the subjects. Diabetic patients often have other diabetes-related comorbidities that might influence the treatment decisions and prognosis. For example, diabetes might be accompanied by a higher risk of infection, and the diagnosis of cancer might result in inappropriate glucose management.

Table 2 | Shared risk factors of diabetes and cancer

Age
Sex
Genetic factors
Obesity
Diets
Lack of exercise
Smoking
Alcohol intake

MEDICAL TREATMENT OF DIABETES AND CANCER

Insulin, Sulfonylureas and Glinides

As discussed earlier, insulin injection might increase the risk of cancer because of its structural similarity to IGF-1. In fact, several reports based on observational studies suggested that insulin glargine usage might be associated with an elevated risk of cancer[51–54]. However, these observational studies were subject to considerable biases[34,55,56]: retrospective studies only show an association, and not necessarily causality; it is very difficult to adjust all possible confounders in observational studies; the effects of treatment by indication and informative censoring cannot be excluded. In contrast, the oncogenic effect of hyperinsulinemia might be offset by the cancer-protective effect through amelioration of hyperglycemia. RCTs and more recent cohort studies have not shown significant associations of insulin with cancer risk[57–62].

Table 3 | Metformin and cancer risk in diabetes: meta-analysis[69]

Site	Risk ratio (95% CI)
Cancer incidence*	
Overall	0.67 (0.53–0.85)
Liver	0.20 (0.07–0.88)
Lung	0.67 (0.45–0.99)
Colorectum	0.68 (0.53–0.88)
Cancer mortality	
Overall	0.66 (0.49–0.88)

*Risk ratios for the cancer of pancreas, breast, stomach and bladder were not statistically significant. CI, confidence interval.

Sulfonylureas and glinides induce hyperinsulinemia, and thus there is a concern of increased cancer risks[54,63–66]. However, the estimates in other reports are inconsistent[67]. Further investigations are required to verify its oncogenic safety.

Metformin

Metformin is an insulin sensitizer that is the drug of first choice in the management of type 2 diabetes[68], given its safety profile and lower cost. Our recent meta-analysis including observational studies and RCTs showed that metformin usage is associated with a lower risk of cancer incidence and mortality in diabetes[69] (Table 3), and similar effects have been seen across different regions in the world[38,65,67,70–73].

As shown in Figure 2, metformin activates activating adenosine 5′-mono-phosphate-activated protein kinase (AMPK) through LKB-1, a tumor suppressor protein kinase. AMPK, the mammalian target of rapamycin (mTOR) and the insulin-signaling pathway represent three interrelated components of a complex mechanism controlling cell responses to nutrient availability. AMPK inhibits protein synthesis and gluconeogenesis during cellular stress and inhibits mTOR, a downstream effector of growth factor signaling, which is frequently activated in malignant cells. In human breast cancer cells, it reduces HER-2 protein expression by inhibiting mTOR. Metformin also induces cell cycle arrest and apoptosis, and reduces growth factor signaling. To support the hypothesis of these direct effects, metformin reportedly potentiated the effect of neoadjuvant chemotherapy in early-stage breast cancer[74], decreased the risk of colorectal cancer in a small RCT involving non-diabetic subjects[75], and was associated with a decreased cancer risk while another insulin-sensitizer, thiazolidinedione, was not[76–79].

Our research[69] showed that metformin use is associated with reduced mortality and incidence of cancer at any site, supporting the generalizability of the proposed anticancer mechanisms. In contrast, the magnitude of the risk reduction

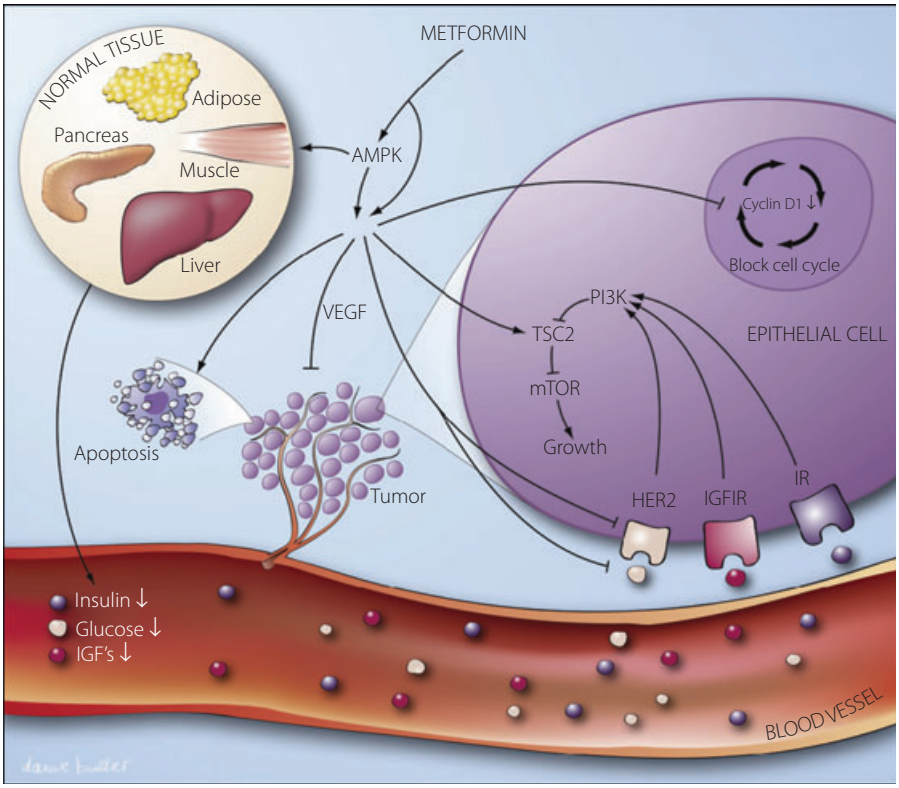

Figure 2 | Mechanisms of anti-oncogenic effect of metformin. AMPK, adenosine 5′-mono-phosphate-activated protein kinase; HER2, epithelial growth factor receptor 2; IGF, insulin-like growth factor; IGF-1R, insulin-like growth factor 1; IR, insulin receptor; mTOR, mammalian target of rapamycin; PI3K, phosphinositide 3-kinase; TSC2, tuberous sclerosis complex 2; VEGF, vascular endothelial growth factor. Adapted from Jalving *et al.*[87] with permission.

Table 4 | Risk of bladder cancer in pioglitazone users

	Hazard ratio (95% CI)
Exposure to pioglitazone	1.2 (0.9–1.5)
Cumulative treatment periods (months)	
<12	0.8 (0.6–1.3)
12–24	1.4 (0.9–2.1)
≥24	1.4 (1.03–2.0)
P_{trend}	0.03
Cumulative dosage (mg)	
1–10,500	1.0 (0.7–1.5)
10,500–28,000	1.2 (0.8–1.8)
>28,000	1.4 (0.96–2.1)
P_{trend}	0.08

Adapted from Lewis *et al.*[79] with permission. CI, confidence interval.

varies among site-specific cancers. This variance might result from differences in carcinogenesis at certain sites. For instance, elevated levels of insulin and glucose might exert an important influence in the development or growth of epithelial malignant tumors of the colon[80–82], pancreas[83,84] and breast[85], and metformin reportedly prevents incident colon cancer in non-diabetic subjects[75]. An animal study suggested that metformin prevented smoking-related lung cancer in mice, probably by inducing some hormone from the liver[86]. The fact that one preliminary study suggested a promising effect of metformin on pathological complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer[74] might point to the possibility that metformin simply augmented the efficacy of chemotherapy for breast cancer[77,87]. Several prospective clinical trials to evaluate its safety and efficacy are currently ongoing[34,87].

Pioglitazone

Pioglitazone is another insulin sensitizer that activates peroxisome proliferator-activated receptor-γ. Recent reports including meta-analyses have suggested that it might significantly increase the risk of bladder cancer in a exposure/dose-response pattern[73,78,79,88–94] (Table 4), whereas its effect on total cancer or cancers at other sites might be neutral[95]. The carcinogenic effect was also seen in an animal study[96], although the mechanism is not clarified yet. The risk is not conclusive at present[65,73,97,98], and several surveys are in progress. It is currently not on the market in France and Germany because of this potential harm.

α-Glucosidase Inhibitors

Data on the cancer risk associated with α-glucosidase inhibitors are sparse. An increased risk of bladder cancer was reported in one study[78], whereas it was not confirmed in another[65].

Glucagon-Like Peptide-1 Analogs and Dipeptidyl Peptidase-4 Inhibitors

The risk of pancreas cancer and thyroid cancer was reportedly elevated among exenatide, a glucagon-like peptide-1 analog, users[99]. An increased risk of thyroid C-cell cancer was seen in rodent studies. The risk of pancreas cancer might be increased with sitagliptin, a DPP-4 inhibitor[99]. Although a meta-analysis suggested oncogenic safety of dipeptidyl peptidase-4 (DPP-4) inhibitors[100], the included studies were of short follow-up periods and the long-term effect remains elusive.

FUTURE DIRECTIONS

In light of the exploding global epidemic of diabetes, a modest increase in the risk of cancer will translate into a substantial socioeconomic burden. The present review underscores the need for diabetes prevention, particularly by weight management, and for investigation of effective cancer prevention, screening policies and implementation of diabetes treatment with potentially protective effects against cancer. Attention should be directed to elucidating the association between these diseases in populations with increased risks to make timely, rational and informed decisions, not only in the public health area and socioeconomic area, but also for the prevention and targeted management of diabetes in routine clinical practice. For the time being, healthful diets, physical activity and weight management should be promoted for all. Patients with diabetes should be strongly encouraged by their healthcare professionals to undergo appropriate cancer screenings as recommended for all people of their age and sex, and cancer risk should not be a major factor in choosing between available diabetes therapies for the average patient[9].

ACKNOWLEDGEMENTS

The present study was supported by a Health Sciences Research Grant (Comprehensive Research on Diabetes/Cardiovascular and Life-Style Related Diseases H22-019) from the Ministry of Health, Labour and Welfare of Japan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The authors have declared that no competing interests exist.

REFERENCES

1. White MF. The insulin signalling system and the IRS proteins. *Diabetologia* 1997; 40(Suppl 2): S2–S17.
2. Barclay AW, Petocz P, McMillan-Price J, *et al.* Glycemic index, glycemic load, and chronic disease risk – a meta-analysis of observational studies. *Am J Clin Nutr* 2008; 87: 627–637.
3. Jee SH, Ohrr H, Sull JW, *et al.* Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* 2005; 293: 194–202.
4. Stocks T, Rapp K, Bjorge T, *et al.* Blood glucose and risk of incident and fatal cancer in the metabolic syndrome and cancer project (me-can): analysis of six prospective cohorts. *PLoS Med* 2009; 6: e1000201.
5. Abe R, Yamagishi S. AGE-RAGE system and carcinogenesis. *Curr Pharm Des* 2008; 14: 940–945.
6. Lopez AD, Mathers CD, Ezzati M, *et al.* Global and regional burden of disease and risk factors, 2001: systematic

analysis of population health data. *Lancet* 2006; 367: 1747–1757.
7. Barone BB, Yeh HC, Snyder CF, *et al.* Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA* 2008; 300: 2754–2764.
8. Barone BB, Yeh HC, Snyder CF, *et al.* Postoperative mortality in cancer patients with preexisting diabetes: systematic review and meta-analysis. *Diabetes Care* 2010; 33: 931–939.
9. Giovannucci E, Harlan DM, Archer MC, *et al.* Diabetes and cancer: a consensus report. *Diabetes Care* 2010; 33: 1674–1685.
10. Noto H, Tsujimoto T, Sasazuki T, *et al.* Significantly increased risk of cancer in patients with diabetes mellitus. *Endocr Pract* 2011; 17: 616–628.
11. El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clin Gastroenterol Hepatol* 2006; 4: 369–380.
12. Friberg E, Orsini N, Mantzoros CS, *et al.* Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia* 2007; 50: 1365–1374.
13. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, *et al.* Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer* 2005; 92: 2076–2083.
14. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst* 2005; 97: 1679–1687.
15. Larsson SC, Andersson SO, Johansson JE, *et al.* Diabetes mellitus, body size and bladder cancer risk in a prospective study of Swedish men. *Eur J Cancer* 2008; 44: 2655–2660.
16. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. *Int J Cancer* 2007; 121: 856–862.
17. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 2056–2062.
18. Chao C, Page JH. Type 2 diabetes mellitus and risk of non-Hodgkin lymphoma: a systematic review and meta-analysis. *Am J Epidemiol* 2008; 168: 471–480.
19. Noto H, Osame K, Sasazuki T, *et al.* Substantially increased risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis of epidemiologic evidence in Japan. *J Diabetes Complications* 2010; 24: 345–353.
20. Chan JC, Malik V, Jia W, *et al.* Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009; 301: 2129–2140.
21. Hotta N, Nakamura J, Iwamoto Y, *et al.* Causes of death in Japanese diabetics: a questionnaire survey of 18,385 diabetics over a 10-year period. *J Diabetes Invest* 2010; 1: 66–76.
22. Tseng CH. Mortality and causes of death in a national sample of diabetic patients in Taiwan. *Diabetes Care* 2004; 27: 1605–1609.
23. Yang X, So WY, Kong AP, *et al.* Development and validation of a total coronary heart disease risk score in type 2 diabetes mellitus. *Am J Cardiol* 2008; 101: 596–601.
24. Noto H, Tsujimoto T, Noda M. Significantly increased risk of cancer in diabetes mellitus patients: a meta-analysis of epidemiologic evidence in Asians and non-Asians. *J Diabetes Invest* 2012; 3: 24–33.
25. Biddinger S, Emanuelli B. Insulin Resistance in the Metabolic Syndrome. In: Ahima A (ed). *Metabolic Basis of Obesity*, 1st edn. Springer, New York, 2011; 175–198.
26. Gallagher EJ, Leroith D. Minireview: IGF, Insulin, and Cancer. *Endocrinology* 2011; 152: 2546–2551.
27. Vigneri P, Frasca F, Sciacca L, *et al.* Diabetes and cancer. *Endocr Relat Cancer* 2009; 16: 1103–1123.
28. Corbould A, Zhao H, Mirzoeva S, *et al.* Enhanced mitogenic signaling in skeletal muscle of women with polycystic ovary syndrome. *Diabetes* 2006; 55: 751–759.
29. Fisher WE, Boros LG, O'Dorisio TM, *et al.* GI hormonal changes in diabetes influence pancreatic cancer growth. *J Surg Res* 1995; 58: 754–758.
30. Lindblad P, Chow WH, Chan J, *et al.* The role of diabetes mellitus in the aetiology of renal cell cancer. *Diabetologia* 1999; 42: 107–112.
31. Zendehdel K, Nyren O, Ostenson CG, *et al.* Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. *J Natl Cancer Inst* 2003; 95: 1797–1800.
32. Johnson JA, Gale EA. Diabetes, insulin use, and cancer risk: are observational studies part of the solution-or part of the problem? *Diabetes* 2010; 59: 1129–1131.
33. van Staa TP, Patel D, Gallagher AM, *et al.* Glucose-lowering agents and the patterns of risk for cancer: a study with the General Practice Research Database and secondary care data. *Diabetologia* 2012; 55: 654–665.
34. McFarland MS, Cripps R. Diabetes mellitus and increased risk of cancer: focus on metformin and the insulin analogs. *Pharmacotherapy* 2010; 30: 1159–1178.
35. Bonovas S, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: a meta-analysis. *Diabetologia* 2004; 47: 1071–1078.
36. Grossmann M, Thomas MC, Panagiotopoulos S, *et al.* Low testosterone levels are common and associated with insulin resistance in men with diabetes. *J Clin Endocrinol Metab* 2008; 93: 1834–1840.
37. Tseng CH. Prostate cancer mortality in Taiwanese men: increasing age-standardized trend in general population and increased risk in diabetic men. *Ann Med* 2011; 43: 142–150.
38. Tseng CH. Diabetes and risk of prostate cancer: a study using the National Health Insurance. *Diabetes Care* 2011; 34: 616–621.
39. Inoue M, Iwasaki M, Otani T, *et al.* Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. *Arch Intern Med* 2006; 166: 1871–1877.

40. Richardson LC, Pollack LA. Therapy insight: influence of type 2 diabetes on the development, treatment and outcomes of cancer. *Nat Clin Pract Oncol* 2005; 2: 48–53.
41. Gapstur SM, Gann PH, Lowe W, *et al.* Abnormal glucose metabolism and pancreatic cancer mortality. *JAMA* 2000; 283: 2552–2558.
42. Seshasai SR, Kaptoge S, Thompson A, *et al.* Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011; 364: 829–841.
43. Kadowaki T, Miyake Y, Hagura R, *et al.* Risk factors for worsening to diabetes in subjects with impaired glucose tolerance. *Diabetologia* 1984; 26: 44–49.
44. Stefansdottir G, Zoungas S, Chalmers J, *et al.* Intensive glucose control and risk of cancer in patients with type 2 diabetes. *Diabetologia* 2011; 54: 1608–1614.
45. Karin M, Lawrence T, Nizet V. Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. *Cell* 2006; 124: 823–835.
46. Renehan AG, Tyson M, Egger M, *et al.* Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008; 371: 569–578.
47. Adams TD, Gress RE, Smith SC, *et al.* Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007; 357: 753–761.
48. Inoue M, Yamamoto S, Kurahashi N, *et al.* Daily total physical activity level and total cancer risk in men and women: results from a large-scale population-based cohort study in Japan. *Am J Epidemiol* 2008; 168: 391–403.
49. Noto H, Raskin P. Hepatitis C infection and diabetes. *J Diabetes Complications* 2006; 20: 113–120.
50. McCall JL, Tuckey JA, Parry BR. Serum tumour necrosis factor alpha and insulin resistance in gastrointestinal cancer. *Br J Surg* 1992; 79: 1361–1363.
51. Hemkens LG, Grouven U, Bender R, *et al.* Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. *Diabetologia* 2009; 52: 1732–1744.
52. Jonasson JM, Ljung R, Talback M, *et al.* Insulin glargine use and short-term incidence of malignancies – a population-based follow-up study in Sweden. *Diabetologia* 2009; 52: 1745–1754.
53. Colhoun HM. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. *Diabetologia* 2009; 52: 1755–1765.
54. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia* 2009; 52: 1766–1777.
55. Smith U, Gale EA. Does diabetes therapy influence the risk of cancer? *Diabetologia* 2009; 52: 1699–1708.
56. Hernandez-Diaz S, Adami HO. Diabetes therapy and cancer risk: causal effects and other plausible explanations. *Diabetologia* 2010; 53: 802–808.
57. Rosenstock J, Fonseca V, McGill JB, *et al.* Similar risk of malignancy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: findings from a 5 year randomised, open-label study. *Diabetologia* 2009; 52: 1971–1973.
58. Home PD, Lagarenne P. Combined randomised controlled trial experience of malignancies in studies using insulin glargine. *Diabetologia* 2009; 52: 2499–2506.
59. The ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in Dysglycemia. *N Engl J Med* 2012; 367: 319–328.
60. Fagot JP, Blotiere PO, Ricordeau P, *et al.* Does insulin glargine increase the Risk of cancer compared with other basal insulins?: a French nationwide cohort study based on national administrative databases. *Diabetes Care* 2013; 36: 294–301.
61. Morden NE, Liu SK, Smith J, *et al.* Further exploration of the relationship between insulin glargine and incident cancer: a retrospective cohort study of older Medicare patients. *Diabetes Care* 2011; 34: 1965–1971.
62. Yang X, Ko GT, So WY, *et al.* Associations of hyperglycemia and insulin usage with the risk of cancer in type 2 diabetes: the Hong Kong diabetes registry. *Diabetes* 2010; 59: 1254–1260.
63. Monami M, Lamanna C, Balzi D, *et al.* Sulphonylureas and cancer: a case-control study. *Acta Diabetol* 2009; 46: 279–284.
64. Hsieh MC, Lee TC, Cheng SM, *et al.* The influence of type 2 diabetes and glucose-lowering therapies on cancer risk in the Taiwanese. *Exp Diabetes Res* 2012; 2012: 413782.
65. Tseng CH. Diabetes and risk of bladder cancer: a study using the National Health Insurance database in Taiwan. *Diabetologia* 2011; 54: 2009–2015.
66. Chang CH, Lin JW, Wu LC, *et al.* Oral insulin secretagogues, insulin, and cancer risk in type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2012; 97: E1170–E1175.
67. Yang X, So WY, Ma RC, *et al.* Use of sulphonylurea and cancer in type 2 diabetes – The Hong Kong Diabetes Registry. *Diabetes Res Clin Pract* 2010; 90: 343–351.
68. Nathan DM, Buse JB, Davidson MB, *et al.* Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; 32: 193–203.
69. Noto H, Goto A, Tsujimoto T, *et al.* Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. *PLoS ONE* 2012; 7: e33411. doi:33410.31371/journal.pone.0033411.
70. Lee MS, Hsu CC, Wahlqvist ML, *et al.* Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals. *BMC Cancer* 2011; 11: 20.

71. Yang YX, Hennessy S, Lewis JD. Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. *Gastroenterology* 2004; 127: 1044–1050.
72. Lai SW, Chen PC, Liao KF, *et al.* Risk of hepatocellular carcinoma in diabetic patients and risk reduction associated with anti-diabetic therapy: a population-based cohort study. *Am J Gastroenterol* 2012; 107: 46–52.
73. Chang CH, Lin JW, Wu LC, *et al.* Association of thiazolidinediones with liver cancer and colorectal cancer in type 2 diabetes mellitus. *Hepatology* 2012; 55: 1462–1472.
74. Jiralerspong S, Palla SL, Giordano SH, *et al.* Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. *J Clin Oncol* 2009; 27: 3297–3302.
75. Hosono K, Endo H, Takahashi H, *et al.* Metformin suppresses azoxymethane-induced colorectal aberrant crypt foci by activating AMP-activated protein kinase. *Mol Carcinog* 2010; 49: 662–671.
76. Li D, Yeung SC, Hassan MM, *et al.* Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology* 2009; 137: 482–488.
77. Decensi A, Puntoni M, Goodwin P, *et al.* Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. *Cancer Prev Res (Phila)* 2010; 3: 1451–1461.
78. Piccinni C, Motola D, Marchesini G, *et al.* Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. *Diabetes Care* 2011; 34: 1369–1371.
79. Lewis JD, Ferrara A, Peng T, *et al.* Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care* 2011; 34: 916–922.
80. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. *Am J Clin Nutr* 2007; 86: s836–s842.
81. Zakikhani M, Dowling RJ, Sonenberg N, *et al.* The effects of adiponectin and metformin on prostate and colon neoplasia involve activation of AMP-activated protein kinase. *Cancer Prev Res (Phila)* 2008; 1: 369–375.
82. Algire C, Amrein L, Zakikhani M, *et al.* Metformin blocks the stimulative effect of a high-energy diet on colon carcinoma growth *in vivo* and is associated with reduced expression of fatty acid synthase. *Endocr Relat Cancer* 2010; 17: 351–360.
83. Raimondi S, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an overview. *Nat Rev Gastroenterol Hepatol* 2009; 6: 699–708.
84. Schneider MB, Matsuzaki H, Haorah J, *et al.* Prevention of pancreatic cancer induction in hamsters by metformin. *Gastroenterology* 2001; 120: 1263–1270.
85. Xue F, Michels KB. Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. *Am J Clin Nutr* 2007; 86: s823–s835.
86. Memmott RM, Mercado JR, Maier CR, *et al.* Metformin prevents tobacco carcinogen–induced lung tumorigenesis. *Cancer Prev Res (Phila)* 2010; 3: 1066–1076.
87. Jalving M, Gietema JA, Lefrandt JD, *et al.* Metformin: taking away the candy for cancer? *Eur J Cancer* 2010; 46: 2369–2380.
88. Hillaire-Buys D, Faillie JL, Montastruc JL. Pioglitazone and bladder cancer. *Lancet* 2011; 378: 1543–1544; author reply 1544-1545.
89. Neumann A, Weill A, Ricordeau P, *et al.* Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. *Diabetologia* 2012; 55: 1953–1962.
90. Azoulay L, Yin H, Filion KB, *et al.* The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. *BMJ* 2012; 344: e3645.
91. Mamtani R, Haynes K, Bilker WB, *et al.* Association between longer therapy with thiazolidinediones and risk of bladder cancer: a cohort study. *J Natl Cancer Inst* 2012; 104: 1411–1421.
92. Actos. Product information as approved by the CHMP on 20 October 2011, pending endorsement by the European Commission. 2011. Available at: http://www.ema. europa.eu/docs/en_GB/document_library/Other/2011/07/WC500109185.pdf (accessed December 20 2011).
93. Zhu Z, Shen Z, Lu Y, *et al.* Increased risk of bladder cancer with pioglitazone therapy in patients with diabetes: a meta-analysis. *Diabetes Res Clin Pract* 2012; 98: 159–163.
94. Colmers IN, Bowker SL, Majumdar SR, *et al.* Use of thiazolidinediones and the risk of bladder cancer among people with type 2 diabetes: a meta-analysis. *CMAJ* 2012; 184: E675–E683.
95. Ramos-Nino ME, MacLean CD, Littenberg B. Association between cancer prevalence and use of thiazolidinediones: results from the Vermont Diabetes Information System. *BMC Med* 2007; 5: 17.
96. Suzuki S, Arnold LL, Pennington KL, *et al.* Effects of pioglitazone, a peroxisome proliferator-activated receptor gamma agonist, on the urine and urothelium of the rat. *Toxicol Sci* 2010; 113: 349–357.
97. Tseng CH. Pioglitazone and bladder cancer: a population-based study of Taiwanese. *Diabetes Care* 2012; 35: 278–280.
98. Li W, Macdonald TM, Mackenzie IS. Pioglitazone and bladder cancer: a propensity score matched cohort study. *Br J Clin Pharmacol* 2013; 75: 254–259.
99. Elashoff M, Matveyenko AV, Gier B, *et al.* Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 2011; 141: 150–156.
100. Monami M, Dicembrini I, Martelli D, *et al.* Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. *Curr Med Res Opin* 2011; 27 (Suppl 3): 57–64.