Diabetes, chronic kidney disease and cancer risk

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Diabetes and cancer

The possible association between diabetes and cancer was first launched in 1932, when cancers in the intestine, uterus and pancreas were reported to occur more frequently among patients with diabetes [1]. However, it took some 70 years before the scientific community once more focused on this association. Several observational studies published over the last 10–15 years show unequivocally that there is an association between certain forms of cancer and type 2 diabetes. Figure 1 shows the relative risk for patients with type 2 diabetes to develop cancers by organ of origin. The relative risk appears to be highest for liver, pancreas and endometrial cancers [2–4]. There is also a 20–50% increase in incidence of breast, colon, kidney and bladder cancers [5–8], whereas cancer of the prostate actually appears to occur at a lower rate in these patients, although the outcomes of prostate cancer may be worse once established [9]. Indeed, it is a general finding that once the cancer has been diagnosed, the chance of dying from the cancer is higher in patients with diabetes than in patients without diabetes [10].

A difficulty in inferring a cause and effect relationship between type 2 diabetes and cancer is that both conditions are more prevalent with age and also with obesity. Obesity itself increases the risk of certain cancer forms, e.g. endometrial cancer, breast cancer, kidney cancer, colorectal cancer and pancreas cancer [11], and obesity itself also increases the risk of dying from the cancer disease [12]. It has therefore been postulated that the mechanism for cancer related to type 2 diabetes at least in part is a consequence of metabolic dysfunctional changes associated with obesity, insulin resistance, hyperinsulinaemia and also hyperglycaemia. The cancer rate is increased also in type 1 diabetes, but the cancer forms differ from type 2 diabetes in that the stomach, the cervix and the endometrium are the predominant sites in this condition [13].

Risk factors for cancer in diabetes

Several mechanisms have been suggested for the increased cancer risk in type 2 diabetes [14–16]. First, it has been postulated that hyperinsulinaemia may be an operative mechanism for transformation to malignancy. Insulin serves as a growth factor for epithelial tumours in vitro, and also increases the bioavailability of insulin-like growth factor-1 (IGF-1) which is another tumour growth factor. Second, the metabolism of tumour cells rely heavily on insulin-independent constitutive glucose consumption, where glycolysis leading to pyruvate is metabolized to lactate rather than entering the Krebs cycle despite sufficient oxygen availability, thereby leading to synthesis of tumour DNA and proteins. In addition, lactate formation induces lowered pH in neighbouring tissue, which might destruct normal cells. The concept of this effect was first described by Warburg in 1927 [17], and was later referred to as the Warburg effect. Third, fat cells in obesity release a number of cytokines (e.g. IL-6, leptin, TNF-α, monocyte chemoattractant protein, plasminogen activator inhibitor-1) that might promote tumour growth. Fourth, persons with diabetes have increased susceptibility to immune system disorders that might cause infections and malignant disease.

It is also of substantial interest that hypoglycaemic therapy itself may have effects on tumour growth. Actually two recent population studies have indicated that the risk of incident cancers were lower with metformin use compared with use of insulin or sulfonylurea medication.
A shortcoming of these studies is that the metformin groups tended to be younger than the comparator groups, and statistical correction reduces, but never eliminates the effect of such discrepancies. Residual effects of earlier treatment cannot be ruled out. Furthermore, since sulfonylurea and insulin treatment induce hyperinsulinaemia, it is hard to dissect whether the difference is caused by metformin being protective or the comparator being harmful. On the other hand, in vitro studies on the effects of metformin in breast and ovarian cancer cells have shown that metformin has an inhibitory effect on cell division by halting the transition of cells from G1 phase to S phase and thus also proliferation. Similar effects were found on prostate cancer cells but via different pathways [20]. It is also noteworthy that metformin acts by increasing the AMP-activated protein kinase signalling pathway, at least in breast cancer cells [21]. This also leads to an inhibition of the mammalian target of rapamycin complex, an effect which may prevent tumour growth.

Diabetes, kidney failure and cancer risk

In a study presented in the present issue of this journal [22], the association of kidney failure to cancer incidence was investigated in diabetes patients. The study is a post hoc analysis of a randomized intervention trial in type 2 diabetes patients, the ADVANCE study [23]. In short, the patients were randomized in a two-by-two factorial design to receive a thiazide diuretic (indapamide) or placebo on top of an ACE-inhibitor (perindopril) and also to a normal or intensified (HbA1C <6.5%) hypoglycaemic regimen based on a sulphonylsulphonylurea urea preparation (gliclazide). Among the 11 140 patients included in this study, 700 incidents of new malignancies (6.4%) occurred after 5 years of follow-up of >99% of the patients. The study was not designed to address cancer rates in the diabetic population compared with non-diabetic subjects, since a non-diabetic control group was not enrolled. However, the somewhat surprising finding was a lack of association of kidney failure and overall and case-specific cancer risk in the type 2 diabetes patients. A weakness in their study, as also acknowledged by the authors, was that there were very few patients with advanced kidney failure. Actually <20% of the patients had CKD stage IIIb or more. Obviously, any association with CKD IIIb, IV or V to cancer in diabetes patients could not be revealed by the present study due to limited statistical power. Another weakness is a relatively short follow-up time concerning new malignancies.

The risk of cancer associated with renal failure has previously been addressed in a large study from Australia and New Zealand comparing the incidence rates in CKD patients to those in the background population [24]. They found in pre-dialysis patients (probably stage IV or V) only some 16% increase in cancers versus an increase of 35% in dialysis patients. The risk of renal cancer was found to be 5–10 times higher in the same patients. It is of interest that also in the ADVANCE cohort renal cancers were marginally increased in those with eGFR <60mL/min/1.73 m2 (P = 0.07).

In a Californian cohort study of outcomes related to stages of CKD by Go et al. [25], the relative risk of overall mortality was clearly exponential with higher degrees of CKD although they did not address malignancies specifically. It is noteworthy, however, that previous cancers were twice as prevalent in patients with CKD stage IIIb or more. The hazard rates of overall death rates (including malignancies) increased exponentially, the increase in risk for patients with CKD stage IIIa was 17% and reached 600% with CKD stage V. It therefore appears likely that the risk of cancer associated with renal failure first reaches clinical importance in late stage III kidney failure. Therefore, the association between CKD and cancer type 2 diabetes patients in the ADVANCE study is not necessarily in conflict with previous findings. Actually the authors of the

Fig. 2. Hazard ratio for cancer related to GFR. With permission from Wong et al. [26].
present report themselves have provided solid data in a previous study of association of CKD and cancer risk in older people [26]. This was a cohort study of 3654 people aged 49–97 years with 10 years of follow-up. Data from this publication are presented in Figure 2. Obviously the hazard ratios for cancer start peaking at ~45 mL/min/1.73 m² (CKD stage IIIb). The risk for men seems to be somewhat more pronounced.

Another feature of CKD is albuminuria that is a well-known risk factor for end-stage renal disease and also an important risk marker of premature cardiovascular events and death [27]. In a Norwegian cohort study of >5000 health survey participants without diabetes, the risk of cancer related to albuminuria was addressed during 10 years of follow-up [28]. Those with the highest quintiles of albuminuria had a higher risk of cancer. The risk was highest for bladder cancer (8-fold risk) and lung cancers (2.4-fold risk). These associations were independent of renal function and thus deal with another important association of kidney disease and cancer risk.

Conclusions

There is an increased risk of cancer with chronic kidney failure stage IIIb or more. There is also an increased risk of cancer incidents both with type 1 and type 2 diabetes, but the organ specificity of the cancer risk is different between the two types of diabetes. The risk of cancer in combined kidney failure and diabetes remains to be explored in more advanced stages of kidney failure.

Conflict of interest statement. The manuscript or any part of its content has not previously been presented in any form. There is no conflict of interest to declare from either of the authors.

(See related article by Wong et al. The risk of cancer in people with diabetes and chronic kidney disease. Nephrol Dial Transplant 2012; 27: 3337–3344.)

References


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