

The relationship between diabetes and cancer

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Introduction

The risk factors for type 2 diabetes and certain cancers, such as colorectal cancer – namely obesity, Western diet and a sedentary lifestyle – have long been recognised, if not exactly fully understood. More recent research has reported the link between hyperinsulinaemia, which is a characteristic of type 2 diabetes, and cancer (Calle and Kaaks, 2004; Khaw et al, 2004). This article describes screening, treatment, outcomes and the relationship between diabetes and cancer risk.

Diabetes and cancer are among the most important diseases of modern times. Both of these diseases have a significant impact upon the health and well-being of the individual as well as substantial costs to the community, the economy and the National Health Service.

Incidence

Diabetes and cancer are common diseases among adults in the UK. There are approximately 1.8 million people with diabetes in the UK, although it is estimated that there are a further 1 million people with undiagnosed type 2 diabetes (Diabetes UK, 2004). Cancer is one of the foremost causes of morbidity and mortality in the UK: more than 250 000 people are diagnosed each year (Office for National Statistics [ONS], 2004) and a quarter of all deaths in the UK are attributable to malignant disease (ONS, 2002). Both diseases are associated with an ageing population. Type 2 diabetes appears predominantly in people over the age of 40 (Williams and Pickup, 2004), while cancer occurs primarily in people aged 65 and over (Cancer Research UK, 2005).

The development of both diseases is also increasingly associated with the rising incidence of obesity (Packianathan and Finer, 2003). Type 2 diabetes in young adults, adolescents and children now accounts for up to one-third of new

cases of diabetes in Western nations, such as the US (Williams and Pickup, 2004), while there is now strong epidemiological evidence that excess body weight is associated with up to one-third of cancers of the colon, kidney, endometrium, oesophagus, gastric cardia and, in post-menopausal women, breast (Bianchini et al, 2002). As the UK population ages and the prevalence of obesity continues to rise, the co-existence or co-morbidities of these medical conditions – cancer and diabetes – will be progressively more common.

Aetiology

The relationship between adiposity and altered cancer risk has been variously described elsewhere (Bianchini et al, 2002; Farrant, 2003; Calle and Kaaks, 2004) and diverse mechanisms have been proposed. These include purely mechanical effects, such as the amplified incidence of gastro-oesophageal reflux associated with obesity, which increases the risk of adenocarcinoma of the oesophagus because of the continuous damage to the cells lining the gullet (Cassidy et al, 2002). Equally, excess body weight or adiposity is thought to increase the risk of cancers of the breast, endometrium and colon by alterations in the metabolism of endogenous steroids that have an effect on cell division, such as oestrogens and progesterone (Farrant, 2003). It is postulated that

ARTICLE POINTS

- 1 The development of both diabetes and cancer is increasingly associated with the rising incidence of obesity.
- 2 Recent reports have suggested that diabetes and high blood glucose levels appear to increase the risk of cancer independent of obesity.
- 3 Advertising local and national cancer screening programmes in diabetes clinics could increase awareness in vulnerable populations.
- 4 There are potential negative interactions between diabetes care and chemotherapeutic agents.
- 5 Thiazolidinediones could complement conventional cytotoxic chemotherapy, according to early studies.

KEY WORDS

- Diabetes
- Cancer risk
- Obesity
- Hyperinsulinaemia
- Insulin-like growth factor-1

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1 Insulin and insulin-like growth factor-1 have been shown to act as growth-promoting hormones that foster cell proliferation and inhibit apoptosis.

2 Adults with impaired glucose tolerance have a greater risk of cancer mortality.

3 Recent reports have suggested that diabetes and high blood glucose levels appear to increase the risk of cancer independent of obesity.

4 Men with type 2 diabetes have a reduced risk of prostate cancer.

these increased levels of steroids, which are sequestered and synthesised in fatty tissue, distort the normal balance between apoptosis and cell proliferation and differentiation (Bianchini et al, 2002). The advice about appropriate aerobic exercise and physical activity, avoidance of weight gain and adhering to weight control measures that the diabetes and dietetic services promote and provide will have corollary benefits of minimising the risks for the other chronic diseases too.

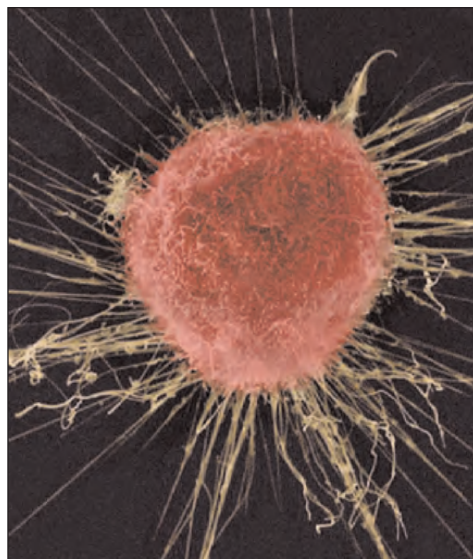
Obesity leads to the development of insulin resistance and is commonplace among people with type 2 diabetes (Krentz and Bailey, 2001). Insulin resistance in turn leads to, and is typified by, chronic hyperinsulinaemia.

Insulin and insulin-like growth factor-1 (IGF-1) have been shown to act as growth-promoting hormones that foster cell proliferation and inhibit apoptosis (Calle and Kaaks, 2004) and as such have been the subject of much recent research interest. Shi et al (2004) reported the results of a meta-analysis that confirmed that high circulating levels of IGF-1 increase the risk of breast cancer in premenopausal women, while high levels of IGF-1 are also associated with an increased risk of prostate cancer (Stattin et al, 2004). Richardson and Pollack (2005) reported that various studies have shown that adults with impaired glucose tolerance have a

greater risk of cancer mortality. It has been determined that type 2 diabetes is a risk factor for endometrial cancer (Anderson et al, 2001) and data from the long-running US Nurses Health Study suggest a slight but significant increased risk of breast cancer in post-menopausal women with type 2 diabetes (Michels et al, 2003).

Recent reports have suggested that diabetes and high blood glucose levels appear to increase the risk of cancer independent of obesity (Khaw et al, 2004; Jee et al, 2005). A prospective cohort study of almost 1.3 million Koreans, who are typically leaner than their Western counterparts, found that increased levels of fasting serum glucose were strongly linked with an increased risk of pancreatic cancer and significantly associated with an increased risk of cancers of the gullet, liver and colorectum in men and the cervix and liver in women (Jee et al, 2005). The Khaw et al (2004) study suggested that high blood glucose levels – even levels below those diagnostic of diabetes – could be linked to bowel cancer and people with diabetes could be up to 3 times more likely to get colorectal cancer.

The research thus far presented would seem to indicate a conclusive risk for certain cancers associated with diabetes; however, the complexity of relationships between cancer, type 2 diabetes and glucose metabolism means the converse is also true for risk of certain other cancers. This may also vary with time from diagnosis and treatment. Findings from various studies suggest, for example, that men with type 2 diabetes have a reduced risk of prostate cancer (Zhu et al, 2004; Rodriguez et al, 2005). Also, Hall et al (2005) reported that they found no additional increased risk of lung cancer in patients with diabetes, although they postulated that this may be accounted for by the shorter life expectancy of patients with diabetes, due to death from cardiovascular events for example, reducing the opportunity for lung cancer to develop or be made manifest.



An electron micrograph of a cancer cell.

Insulin use

The role of medication such as exogenous insulin (that is, the use of therapeutic insulin injections) in the development of cancer has been reported on. The US National Cancer Institute (NCI) highlighted research presented at the most recent *American Association for Cancer Research Annual Meeting* that men who had diabetes and took medication are at 4 times the risk of developing liver cancer and 2.5 times the risk of developing pancreatic cancer of men who did not have diabetes (NCI, 2004).

The journal *Gastroenterology* featured a study by Yang et al (2004), who found that continuous use of insulin for a period of more than 3 years was associated with a significant risk of developing colorectal cancer. Yang et al (2004) suggested that the increased risk of cancer may necessitate or legitimise more rigorous colorectal cancer screening measures for people with type 2 diabetes. However, Renehan and Shalet (2005) recognised that screening is itself not without adverse effects and further studies of the risks versus merits and actual benefits would need to be undertaken before any change of public health policy and procedure could be made.

Diabetes and cancer screening

One of the key challenges identified in *The NHS Cancer Plan* (Department of Health [DoH], 2000) was the need to ensure fair and equitable access to all aspects of cancer services and support across the UK. Areas of social and economic deprivation are unequivocally associated with inequalities of access, as well as people suffering from significantly lower survival rates than those from affluent areas (DoH, 2000). Although the national cancer screening programme has achieved good coverage it is recognised that certain populations, such as minority ethnic groups, people living in deprived areas and those with learning difficulties have unequal access (Chiu, 2003).

Giroux et al (2000) studied the cancer screening rates for Native American

and Alaskan women with diabetes, hypothesising that this group of patients would be more likely to receive screening because of established national standards and the frequency of medical care and contact that this group of patients experienced. Their findings suggested that women with diabetes did have more clinic visits (for their diabetes) but similar screening rates to women without diabetes, suggesting that this group subsequently missed opportunities for health promotion and cancer prevention strategies.

Similarly, Rosen and Schneider (2004) found that morbidly obese women – who were at an increased risk of developing and dying from colorectal cancer and were eligible for cancer screening by faecal occult blood testing and endoscopy – were less likely to be screened than those patients within a normal weight or body mass index range.

The findings of these studies may not be representative of the UK situation but they do serve to illustrate the erroneous assumptions that may be made about care needs and the reality of practice, as well as exemplifying the potential role that diabetes nurses and other practitioners in diabetes care may have in ensuring that their clients' health could be considered in its totality. Advertising local and national cancer screening programmes in diabetes clinics and assessing health needs holistically are examples of simple but effective strategies that could increase awareness in vulnerable populations.

Diabetes and chemotherapy

Chemotherapy, in the context of cancer care, is the use of cytotoxic drugs – cell-poisoning systemic medication – to control or eradicate cancerous growth, preventing malignant cells from dividing, proliferating, invading, metastasising and eventually killing the individual. Despite significant advances in the development of anti-cancer treatments with fewer adverse effects, the toxicity and tolerance of cytotoxic chemotherapy limit its effective use (Allwood et al, 2002).

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1 Although modern anti-emetics may successfully manage the nausea and vomiting associated with chemotherapy, the symptoms may persist and make alterations in diabetes medication necessary.

2 Several chemotherapeutic agents have neurotoxic side effects that may be permanent.

3 Reductions in dose, omissions of doses and delays in treatment because of toxicity may compromise the success of potentially curative treatment.

4 A number of chemotherapeutic agents may be cardiotoxic and the effect is cumulative.

5 Diabetic renal disease presents the same problems with the use of chemotherapy as reduced renal function would with any drug.

Most cytotoxic drug activity is not highly selective and does not discriminate between neoplastic cells and normal cells undergoing division; as a result, the patient experiences distressing and disabling immediate and acute effects, such as nausea and vomiting (Morgan, 2003). In the authors' experience, although modern anti-emetics may successfully manage these symptoms before there is too much effect or consequence to blood glucose control, nausea and vomiting may persist and make alterations in diabetes medication necessary. Oral hypoglycaemic agents may be omitted or insulin reduced on days that the individual receives chemotherapy. Sugary or high-calorie drinks may be encouraged if the individual does not feel able to eat; however, if symptoms are severe, people with insulin-treated diabetes may require an intravenous infusion of insulin and glucose to maintain glycaemic control.

People with diabetes may suffer from several concurrent disorders as a consequence of the condition, such as peripheral neuropathy, cardiovascular disease and chronic renal insufficiency, each of which will potentially have a profound impact upon the drug choice, dose and delivery, as well as being associated with longer-term difficulties.

Neuropathy is the most common chronic complication of diabetes (Krentz and Bailey, 2001), with distal symmetrical neuropathy – the classic 'glove and stocking' presentation – the most common neuropathy (Williams and Pickup, 2004). Krentz and Bailey (2001) suggest that management should include 'discontinuation or avoidance of drugs with neurotoxic potential' since these may exacerbate the symptom experience. However, several chemotherapeutic agents, such as vincristine (used in the treatment of lymphoma) and paclitaxel (used in ovarian and breast cancers), are important agents in chemotherapy regimens and have neurotoxic side effects, which may be permanent (e.g. RxMed, 2005).

Reductions in dose, omissions of doses and delays in treatment because of

toxicity may compromise the success of potentially curative treatment, whatever the reason or need (Bonadonna and Valagussa, 1981; Allwood et al, 2002). It is therefore evident that clearer communication and closer co-operation between cancer clinicians and diabetes teams regarding the monitoring of this aspect of care would be beneficial to either prevent or minimise the complication and the resultant impact upon the individual's quality of life.

Cardiovascular risk

It is well established that type 2 diabetes is associated with accelerated atherosclerosis and heart disease, with approximately 70% of people with type 2 diabetes dying prematurely from cardiovascular disease (Campbell, 2001). Diabetes has been said to be as great a cardiovascular risk factor as a combination of hypertension and smoking (Press, 2004). A number of chemotherapeutic agents, such as doxorubicin (used in the treatment of lymphoma, myeloma, lung cancer and breast cancer), may be cardiotoxic and the effect is cumulative (Mallinson, 2003). It is recommended that all patients over the age of 60 or with a history of heart disease should have an echocardiogram or multiple-gated acquisition (MUGA) scan prior to treatment to ensure that there is satisfactory left-ventricular function (Summerhayes and Daniels, 2003).

The macrovascular and microvascular disease associated with diabetes and the potential for direct damage to the myocardium, even given the lack of any evidence of coronary heart disease (Williams and Pickup, 2004), might suggest that people with diabetes must have their cardiac competence assessed and be monitored closely during and after treatment with clear documentation of the potential long-term side effects of their chemotherapy in the diabetes case records.

Diabetic renal disease presents the same problems with the use of chemotherapy as reduced renal function would with any drug: side effects may be exacerbated, sensitivity to the

medication may be increased, efficacy and response may be reduced and the failure to adequately excrete the drug or its metabolites may lead to greater toxicity (British Medical Association/Royal Pharmaceutical Society of Great Britain, 2004).

To illustrate the difficulties regarding decisions determining treatment regimen, cisplatin (used in the treatment of many cancers) is contraindicated if the glomerular filtration rate is <40 ml/min, while people with abnormal kidney function tend to develop lung dysfunction when bleomycin (a drug used in the treatment of cervical cancer, lymphoma and germ cell tumours) is administered (Summerhayes and Daniels, 2003).

Diabetes and future cancer treatments

Several recent studies have described an exciting novel potential use of some of the existing drugs commonly used to treat type 2 diabetes. Ray et al (2004) and Galli et al (2004) have reported early *in vitro* studies which showed that thiazolidinediones (TZDs), which are used as oral antidiabetic agents, could offer a complementary approach to the conventional cytotoxic chemotherapeutic management of conditions such as multiple myeloma (ciglitazone [available in the US]) and pancreatic cancers (rosiglitazone and pioglitazone).

TZDs are peroxisome proliferator-activated receptor gamma (PPAR γ) ligands – chemical-signalling molecules that bind to a cell membrane, subsequently changing the receptor protein structure, which leads to activation and alteration in cell function and activity. Cancer cells such as myeloma cells, which express the PPAR γ receptor, were found to die (Ray et al, 2004) by apoptosis (or ‘programmed cell death’) in response to treatment with TZDs, which inhibited cancer cell growth and division by blocking the intracellular signals that promote division, proliferation and development. Further laboratory investigation will be needed before any clinical studies and bedside application can take place, but the

pharmacological effect and potential of these drugs does possibly herald a future cancer treatment modality.

Conclusion

Diabetes and cancer are significant diseases in their own right but it is increasingly evident that the nature and complexity of these conditions is, in many cases, interlinked. The compromises and complications necessitated by the severe co-morbidities associated with diabetes obviously have a significant bearing on the actual treatment of cancer and its aftercare, especially where the person with diabetes survives his or her cancer but suffers from long-term sequelae, which affect the quality of life. Nurses working in diabetes or cancer and palliative care will need to develop more effective relationships and ways of working together, as well as a better understanding of the associated conditions and treatments, in order to organise and deliver care based on and responding to the individual’s needs and not solely their own specialist sphere of influence. ■

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