Obesity, Type 2 Diabetes and Cancer: Where we are now?

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Abstract

The typical adult diagnosed with type 2 diabetes at age 60 loses approximately 5 years of their life. This excess mortality was previously considered to be primarily due to cardiovascular disease. Aggressive strategies targeting cardiovascular risk factors have been successful in reducing mortality. A recent study demonstrated that cancer is now the commonest cause of death in patients with type 2 diabetes. Multiple studies have shown a link between obesity, malignancy and cancer mortality. Diabetes has been associated with the incidence of breast, endometrial, pancreatic and colorectal cancer plus increased cancer-related mortality independent of obesity. Hyperinsulinemia leads to the production of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha which increases the dysregulation of many metabolic pathways, further increasing the inflammatory response, drives tumor growth and inhibits apoptosis. There is considerable evidence that cancer patients with diabetes are treated less aggressively or receive modified anti-cancer treatment compared with cancer patients without diabetes. Studies also report that people with diabetes have a more advanced stage of cancer at diagnosis, poorer response to treatment and increased risk of treatment-related adverse effects and increased short-term mortality. It has been suggested that oral glucose-lowering medications and insulin treatment may have an impact on cancer risk. Further studies need to be undertaken to investigate the mechanism of obesity compared with type 2 diabetes in the development of specific malignancies. In addition, should screening for cancer be part of the management of type 2 diabetes?

Keywords: Obesity; Type 2 diabetes; Cancer; Hyperinsulinemia

Introduction

The association between obesity, type 2 diabetes and cancer has recently received increased attention. This is in part due to the significant increases in the prevalence of obesity and type 2 diabetes. Obesity is a huge and increasing problem with over 25% of adults in the UK now being classified as obese (BMI>30 kg/m^2). In parallel to the rise in obesity the incidence of diabetes has increased sharply [1,2] and there is a litany of evidence demonstrating that a diagnosis of diabetes is associated with an increase in all-cause mortality risk [3,4]. The typical adult diagnosed with type 2 diabetes at age 60 loses approximately 5 years of their life to the disease [5]. The excess in mortality was previously considered to be primarily due to cardiovascular disease.

Numerous studies have, however, shown that aggressive strategies targeting cardiovascular risk factors have been successful in significantly reducing cardiovascular mortality [6,7]. The rates of vascular disease mortality in both diabetes and non-diabetes individuals have declined more than other types of morbidities leading to a change in proportional mortality [8,9]. In the USA it has been shown that, while the proportion of deaths as a result of vascular diseases in adults with diabetes declined significantly over time (from 47.8% to 34.1%), the proportion of deaths from cancer remained relatively stable, ranging from 15.9% to 19.9% [8]. In contrast, an Australian national diabetes registry reported an increase in the proportion of cancer deaths between 1997 and 2010, from 19% to 25% in women and from 25% to 34% in men with type 2 diabetes [9,10].

It has also been reported that the rates of cancer have fallen in the USA. When stratified by age group, declines in cancer mortality rates were also noted in older age groups with type 2 diabetes. This overall reduction in cancer may reflect the impact of national screening programs and therapeutic advances plus reductions in exposure to risk factors such as smoking and ultraviolet light [10]. For pancreas and breast cancers, relative declines were greater for adults with diabetes than without diabetes. It is probable that for both of these cancers, adults with diabetes had a higher mortality rate and population-wide uptake of screening programs may have caused greater absolute and relative reductions among adults with diabetes [10]. In contrast, the relative reductions for lung cancer were considerably less for adults with than without diabetes. In the USA it has previously been reported

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that tobacco use between 1999 and 2010 declined faster in people without diabetes than in people with diabetes. It therefore seems likely that the smaller reduction in rates of lung cancer mortality may be due to the slower decline in smoking rates in the diabetes population [11]. There has been, however, a significant increase in cancer rates observed among those aged <40 years. In the USA, the risk of developing several obesity-related cancers has increased in younger adults with steeper increases observed in successively younger generations since the 1950s [12].

We recently published a population-based study demonstrating that cancer, not cardiovascular disease, is now the commonest cause of death in patients with type 2 diabetes in the west of Scotland [13]. There remains, however, many unanswered questions. A literature search was performed to ascertain further clarity on the relationship between obesity, type 2 diabetes and cancer.

Obesity

It is estimated that about one third of all cancer cases are caused by dietary factors and Cancer Research UK states that obesity is the second most common cause of cancer after smoking [14]. Multiple studies have shown a link between obesity and malignancy with a number demonstrating a linear relationship between Body Mass Index (BMI) and cancer mortality [15,16]. The World Cancer Research Fund has estimated that in the United States, excess adiposity accounts for about 17% of the risk for postmenopausal breast cancer, 15% to 17% for colorectal cancer, 20% to 28% for kidney cancer, plus 17% to 20% for pancreatic cancer [17]. Based on meta-analyses or pooled analyses, relative risks range from 1.2 to 1.5 for overweight (BMI>25 kg/m^2) and 1.5 to 1.8 for obesity (BMI>30 kg/m^2) with respect to cancers of the colon, gastric cardia, liver, gallbladder, pancreas, and kidney. The relative risks for esophageal adenocarcinoma and endometrial cancer are even higher with up to more than fourfold risk in those with BMI>40 kg/m^2 [18].

Obesity is associated with metabolic and endocrine disruptions, which include alterations in sex hormone metabolism, insulin, insulin-like growth factor signaling and inflammatory pathways [19,20]. Weight loss decreases intra-abdominal fat and the levels of the endogenous insulin's sensitizer adiponectin, which, in turn, improves insulin resistance, reduced inflammatory biomarkers, oxidative stress, angiogenesis pro-inflammatory cytokines (21-23), and may lead to lower cell proliferation and a lower likelihood of developing cancers [24]. In the Nurses' Health Study cohort, substantial and sustained weight loss over several years was associated with lower postmenopausal breast cancer incidence [25]. The Women's Health Initiative observational cohort found that intentional weight loss in postmenopausal women with obesity was associated with a lower risk of obesity-related cancer and most strongly with a lower endometrial cancer risk [26]. Data from bariatric surgery generally showed reduced cancer risks in women but not in men [27]. In the nonrandomized Swedish Obese Subjects study, women who underwent bariatric surgery experienced reduced cancer incidence [28]. Reduced cancer risks were also observed among female bariatric surgery patients in Utah [29] and in the Kaiser Permanente cohort [30]. These interventions appear to provide insight into the possible molecular and endocrine roles in obesity-related cancer and evidence supporting the hypothesis that weight loss reduces the risk of obesity-related cancers.BMI is generally used as a measure of obesity. It is, however, well recognized that waist circumference is a better measure of obesity. Waist circumference correlates better with visceral adiposity and insulin resistance, as well as other markers of metabolic risk including dyslipidemia, glucose intolerance, and hypertension [31]. Compared with BMI, few studies have specifically examined the contribution of waist circumference to cancer risk and mortality. In the Nurses' Health Study population, it was found that waist circumference was associated with postmenopausal breast cancer risk, specifically in women who had not received postmenopausal hormone replacement therapy [32]. A meta-analysis reported that adjusting for BMI revealed that waist circumference may be specifically associated with breast cancer risk in premenopausal women while BMI was not [33]. In a further meta-analysis, a 4% increased risk of colon cancer was found to be associated with every 2 cm increase in waist circumference [34]. Interestingly, although multiple studies report that BMI is inversely associated with lung cancer risk, the Women's Health Initiative revealed that waist circumference was positively associated with lung cancer risk in current and former smokers [35].

Type 2 Diabetes and Cancer

The recognition of the association of diabetes and cancer is not new. The first reported case of diabetes associated with cancer was reported by the English physician Bright in 1832. He reported a patient with polyuria, polydipsia, sweet urine, and carcinoma of the pancreas. Maynard in 1910 reported that diabetes was associated with an increased risk of numerous cancers [36]. At the time this was considered controversial and disputed by many diabetes experts and epidemiologists. Bell in 1957 stated that it was "well known" that carcinoma of the pancreas was frequently associated with glycosuria and hyperglycaemia; however, it was not known whether there was an increased incidence of "true" diabetes in subjects with pancreatic carcinoma, or if subjects with "true" diabetes demonstrated an increased incidence of carcinoma of the pancreas [37].

More recently diabetes has been independently associated with the incidence of several types of cancer plus increased cancer-related mortality [38]. Positive associations have been shown between type 2 diabetes and the risk of mortality from cancers of the colon, liver, pancreas, breast, endometrial and bladder [39]. While associations for prostate and lung cancers are inconsistent [40]. Some evidence also supports an association between diabetes and risk of all-cause mortality in individuals with cancer [41], but the evidence for cancer-specific mortality remains inconsistent [42]. The evidence also suggests that there is a direct association between type 2 diabetes and a higher risk of cancer mortality, independent of the effects of obesity. This has been demonstrated for breast, endometrial, pancreatic and colorectal cancer [43,44].

Hyperglycaemia is the hallmark of both type 1 and type 2 diabetes. Type 1 diabetes, a condition of insulin deficiency due to autoimmune destruction of the pancreas is not classically associated with obesity or the metabolic syndrome. Interestingly, type 1 diabetes has not been linked with the same increased risk of cancer [45]. This suggests that hyperglycemia is not the primary mechanism that leads to increased cancer incidence. Cancer cells have altered metabolism and use more glucose than non-tumor cells to support energy generation by aerobic glycolysis. Studies, however, have shown that hyperglycemia, in the absence of hyperinsulinemia, and does not increase cancer cell growth or replication [46].

There are several further mechanisms by which diabetes may increase the risk for cancer and increased cancer-specific mortality among people with cancer. Obesity and type 2 diabetes are both associated with adipose tissue inflammation [47]. This leads to

hyperinsulinemia and increased level of Insulin-like Growth Factor-1 (IGF-1). The resultant hyperinsulinemia leads to the production of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha which increases the dysregulation of many metabolic pathways, further increasing the inflammatory response, drives tumor growth and inhibits apoptosis [48,49]. IGF-1 has been found to be over-expressed in a number of cancers including breast, colorectal, liver and prostate [49]. In addition, metformin (biguanide), which inhibits gluconeogenesis, lowers blood glucose levels and reduces secondary circulating insulin concentrations, has the potential to inhibit cell proliferation and cause partial arrest in cancer cell lines [50]. Many studies have demonstrated that patients taking metformin, had a lower cancer incidence and mortality than diabetes patients on no therapy or insulin therapy [50,51]. Other studies have not shown statistically significant reductions in cancer risk [52].

Hyperinsulinemia, which is a key part of insulin resistance, is associated with dyslipidemia, which in type 2 diabetes, often takes the form of elevated circulating triglycerides and decreased high-density lipoprotein [53]. Most patients with type 2 diabetes over the age of 40 years are started on a 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statin) for cardiovascular risk protection (ref A). Statin therapy reduces LDL- and total-cholesterol levels and has been shown to reduce cancer mortality. Cholesterol has many roles particularly forming a major component of the cell membrane and it is suggested that increased cholesterol availability may allow for rapid cell turnover [16]. Studies into the use of statins in breast cancer showed hydrophilic statins (e.g. pravastatin, rosuvastatin) only had a survival benefit when started after diagnosis compared to lipophilic statins (e.g. atorvastatin, simvastatin) which showed benefit when taken before or after diagnosis. It seems likely that cholesterol is not oncogenic, but that cholesterol may promote tumor progression [54].

There is considerable evidence that cancer patients with diabetes are treated less aggressively or receive modified anti-cancer treatment as compared with cancer patients without diabetes [10]. Studies also report that people with diabetes have a more advanced stage of cancer at diagnosis, poorer response to treatment and increased risk of treatment-related adverse effects and increased short-term mortality compared with cancer patients without diabetes [10,55-58].

Furthermore, hyperglycaemia may have an impact on the chemotherapy outcomes and several studies have shown that hyperglycaemia increases the toxicity of agents such as 5-fluorouracil and carboplatin by up to 30% [44]. In addition, insulin treatment and oral glucose-lowering medications have been associated with increased cancer risk, although the causal association of this connection remains unclear [59,60].

Conclusion

Most studies related to obesity, type 2 diabetes and cancer are observational. There will always be concerns about observational studies and registered causes of death. Cause-of-death reporting is affected by medical opinion and subjective judgment may shift over time. In most observational studies, diabetes is self-reported and changes in diabetes definitions will impact on the affected population with diagnosed diabetes. This will miss undiagnosed diabetes or incident cases of diabetes post baseline and lead to misclassification for a small number of participants. In addition, the types of diabetes are not included in the most analysis making the assumption that the vast majority (~90% to 95%) have type 2 diabetes. Furthermore, small case numbers may lead to an increased risk of a type 1 statistical error.

Further studies need to be undertaken to determine the importance of and investigate the mechanism of obesity-related cancer compared with type 2 diabetes in the development of specific malignancies. Further investigation is also needed to be undertaken on the impact of age, sex, race/ethnicity, duration of diabetes, glycemic control, diabetes-related medication and socio-economic status on the development of diabetes-related cancers. In addition, should screening for cancer be part of the management of type 2 diabetes?

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