Cancer, obesity, diabetes, and antidiabetic drugs: is the fog clearing?

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Abstract | The prevalence of obesity, of type 2 diabetes mellitus (T2DM), and of cancer are all increasing globally. The relationships between these diseases are complex, and thus difficult to elucidate; nevertheless, evidence supports the hypothesis that obesity increases the risks of both T2DM and certain cancers. Further complexity arises from controversial evidence that specific drugs used in the treatment of T2DM increase or decrease cancer risk or influence cancer prognosis. Herein, we review the current evidence from studies that have addressed these relationships, and summarize the methodological challenges that are frequently encountered in such research. We also outline the physiology that links obesity, T2DM, and neoplasia. Finally, we outline the practical principles relevant to the increasingly common challenge of managing patients who have been diagnosed with both diabetes and cancer.

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The concurrence of the obesity and type II diabetes mellitus (T2DM) pandemics with the growing burden of cancer globally has generated interest in defining the epidemiological and biological relationships between these medical conditions. In clinical practice, oncologists are increasingly required to plan cancer treatment for patients with pre-existing diabetes and/or obesity, and diabetologists often have to manage diabetes in patients who are being treated for cancer. T2DM and cancer are each associated with derangements in the PI3K signalling pathway, which is often excessive in neoplastic tissue, but subnormal in classic insulin target tissues (such as liver and muscle) of insulin-resistant diabetics. Many treatments for diabetes increase activation of the PI3K pathway, whereas certain cancer treatments inhibit this signalling cascade. Thus, unintended consequences of antidiabetic medications on neoplasia, or vice versa, are plausible.

The hypothesis that the antidiabetic medication metformin can improve cancer outcomes has generated so much interest that this approach is being studied in hundreds of oncology clinical trials. Meanwhile, controversy surrounds the possibility of increased cancer risks associated with other antidiabetic agents. Herein, we review the current epidemiological and biological evidence that diabetes or obesity and/or drugs used to treat diabetes can influence cancer risk and prognosis, as well as clinical situations in which cancer treatment is complicated by hyperglycaemia.

Historical and epidemiological links

The first presentation of possible associations between diabetes and cancer was probably made in 1888 by the French surgeon Theodore Tuffier[1]. Tuffier used his observations in diabetic and nondiabetic patients who had undergone cancer surgery to follow three lines of inquiry: whether diabetes affects cancer incidence; whether diabetes influences the course of cancer; and whether cancer affects the course of diabetes. These questions are more important now than they were historically because, in contrast to the situation in the past, cancer and diabetes are now dominant causes of morbidity and mortality worldwide. Obesity is now known to induce a state of chronic inflammation and insulin resistance, which culminates in T2DM[2]. Indeed, strong correlations between the incidence of T2DM and various measures of obesity have been reported[3]. As we discuss in this Review, the risk of certain cancers has also been associated with obesity, as well as with T2DM — although determining whether diabetes or antidiabetic treatments act independently of obesity to influence the risk or prognosis of specific cancer types, or of cancer in general, is challenging.

The number of overweight and obese individuals worldwide in 2013 was estimated at 2.1 billion, representing one-third of the world population[4]. Importantly, from 1980 to 2013, the prevalence of obesity increased among both adults and children, with a larger increase in the latter[4]. The impact of obesity early in life on subsequent cancer risk is not well characterized, although evidence indicates that obesity below the age of 44 years confers a higher risk of stroke and diabetes than obesity at ages greater than 65 years[5]. Thus, the rising obesity rates in children and adolescents is ominous. Of note, adults with a body-mass index (BMI) $\geq 25\,kg/m^2$ are at greater risk of dying from any cause than those with a BMI of 20.0–24.9 kg/m^2, and this risk

Key points

- The incidences of obesity, type 2 diabetes mellitus (T2DM), and many cancers are rapidly increasing worldwide; clinicians are increasingly required to treat patients with both T2DM and cancer, or both obesity and cancer
- Obesity is a risk factor for some cancers, and obesity at and weight gain after diagnosis are associated with adverse cancer outcomes; the interactions of diabetes and/or its treatments with cancer risk and outcomes are complex and controversial
- Laboratory findings provide a rationale for clinical trials of the antidiabetic drug metformin for cancer treatment; although the first two studies (in pancreatic cancer) revealed no survival benefit, many additional studies are ongoing
- Concerns about an increased cancer risk associated with other antidiabetic agents have been raised; in general, follow-up studies have failed to confirm such risks, but data on long-term exposure remain sparse and pharmacovigilance is necessary
- Certain drugs used in the treatment of cancer lead to metabolic toxicities, chiefly hyperglycaemia, which might be dose-limiting for some patients, especially those with pre-existing diabetes
- Clarification of the mechanisms underlying the relationships between obesity and neoplasia might provide clues relevant to novel cancer treatments and prevention strategies

has been shown to increase exponentially for individuals in higher BMI categories[6]; therefore, competing causes of death might attenuate the effect of obesity on cancer mortality.

In 2014, the global prevalence of T2DM in adults was estimated to be 9% of the population (~415 million individuals), with more than 80% of patients with diabetes residing in low-income and middle-income countries[7]. Data published in 2015 indicate that individuals with diabetes and no history of stroke or myocardial infarction are at almost twice the risk of dying from any cause than individuals without diabetes[8]. Moreover, a worldwide trend toward increased disability resulting from diabetes has been recognized[9]. Meanwhile, the number of deaths attributed to cancer globally was estimated to have exceeded 8 million in 2012, and is projected to rise over time, largely owing to the increasing cancer incidence in developing countries[10]; the incidence rates of certain cancers, such as breast cancer, lung cancer, prostate cancer, and non-Hodgkin lymphomas, has either stabilized or decreased in many developed countries since 2000, but this is not the case on a global basis[10].

In summary, the sharp rise in the global incidence of obesity and diabetes in the past 50 years is predicted to continue, owing to increasing incidence rates in developing countries[11], while the incidence of obesity in the US population might have plateaued at a high level[12]. These trends have revealed no evidence of a reduced association between obesity or diabetes and cancer incidence or mortality, at least in the case of breast cancer[13]. On the contrary, for most of the world population, cancer risk and mortality are rising in parallel with ongoing increases in the incidence rates of obesity and diabetes[14]. This pattern justifies research concerning not only the biology that links these three conditions, but also aspects of the clinical management of patients with both diabetes and cancer.

Cancer incidence

Obesity and the risk of cancer. Obesity is usually quantified on the basis of BMI, although this metric is not a perfect measure of adiposity[15]. In observational studies in adults, those with a BMI in the top quartile or with a gain in bodyweight have increases in the risks of kidney, gallbladder, liver, endometrial, ovarian, and pancreatic cancer[16–19]. Gallbladder cancer is an example of a malignancy for which tumorigenesis is strongly influenced by obesity, with a ~1.5-fold increased risk per 5 kg/m^2 above the BMI of 25 kg/m^2. Subcategories of other cancer types also associated with higher BMI include oesophageal adenocarcinoma and postmenopausal breast cancer[16,20,21]. Conversely, the available evidence indicates that obesity is not a key factor in the development of certain neoplasms, such as testicular cancer[22]. Moreover, some cancers, including squamous carcinomas of the lung and the head and neck, have been found in many studies to be less common in obese individuals; this pattern is probably driven by exposure to tobacco smoke, which is associated with a substantially increased risk of these neoplasms, and also with decreases in appetite and weight[23]. Thus, weight gain differentially affects carcinogenesis of different organs[17]. Possibly, different trajectories of weight gain or stability throughout life confer different risks of various obesity-associated cancers[24]. For example, a gain in bodyweight of more than 5% in women who had a BMI <25 kg/m^2 at the age 50 years was associated with increased risk of breast cancer over the subsequent decade[25]. Moreover, menopausal status has been shown to modify the association of BMI with incident breast cancer, indicating complex interactions between obesity and hormonal factors[26].

The effect of weight loss on cancer risk is not clear. Evidence indicates that among the very obese individuals considered to be candidates for bariatric surgery (who usually have a BMI >40 kg/m^2), this intervention might reduce subsequent cancer risk[27,28], although contrasting reports have been published[29]. Many obesity-associated endocrine abnormalities and possibly some obesity-associated characteristics of the microbiome are altered by bariatric surgery, but identifying specific mediators that link bariatric surgery to cancer risk remains an important research challenge. Large-scale trials comparing long-term cancer risk among obese individuals who do or do not reduce weight by lifestyle modifications are difficult to perform, owing to the need for compliance with a weight-loss regime over many years of observation. Would weight loss in the sixth decade of life 'undo' the effect of 20–30 years of obesity on cancer risk? The scant literature in support of this possibility comes from secondary analyses of prospective observational studies that were not originally designed to answer this question[30,31]. Even in the absence of conclusive data, advising obese individuals that achieving an ideal bodyweight might extend their life expectancy is sensible, considering the relationship between obesity and all-cause mortality[6]. This guidance applies to people with cancer or diabetes, as well as to those with both diseases, or neither.

Box 1 | **Biases in cohort studies of antidiabetic drugs and cancer outcomes**

Prevalent-user bias[196]
In the context of type II diabetes mellitus (T2DM), if many patients remain on treatment with a certain drug for a long time, this might suggest good glycaemic control, and failing to account for the exact time of use will introduce a bias, because these patients might be at a lower risk of certain outcomes. Including all users of antidiabetic medications from a given calendar date, regardless of how long they had used the drug for, results in the accrual of many prevalent users. A possible solution is the new-user design, which requires that follow-up begins before or at the time of initiation of the drug under study.

Detection bias and reverse causality[33,34,197]
Higher rates of new cancer diagnoses have been recorded in the first few months following the diagnosis of T2DM and after the initiation of a new class of antidiabetic medications. Thus, the cancer risk is overestimated if early events are ascribed to the exposure in question.

Immortal time bias[46]
In its most common form, this bias occurs when the entire follow-up period for a patient in the study is ascribed to a medication, whereas the treatment was actually started after the beginning of the follow-up period. This bias results in risk underestimation owing to extension of the observation time with periods during which the event could not have occurred (otherwise follow-up assessments would have been stopped). Thus, the timing of exposure should be properly determined.

Time-lag bias/confounding by indication[61]
When a first-line antidiabetic treatment is compared with 'add-on' therapy, an implicit confounding by indication occurs, such that the severity and progression of diabetes (which necessitated the addition of other antidiabetic agents to treatment) are difficult to account for. Accounting for the duration of 'treated diabetes' partly solves the problem for estimations of associations with cancer incidence, but considerable confounding remains for associations with cancer prognosis.

Residual confounding[46,61]
The management of diabetes is complex, and disease progression has a bearing on many biological processes, including cancer — the latency of which requires studies with long follow-up periods. During a long observation period, the care of a patient with diabetes changes from baseline, as do their comorbidities. At a minimum, this variation requires adjustments for multiple time-fixed proxy measurements for diabetes severity and the explicit inclusion of diabetes duration. In addition, an analysis with a time-varying update for study covariates can be performed, but requires a large dataset with multiple updates of parameters including glycated haemoglobin levels and usage of other antidiabetic medications. These challenges are intensified for studies of associations with cancer prognosis, because of the long follow-up periods and the complexity of cancer treatment.

Diabetes and the risk of cancer. Similarly to obesity-associated cancer, a diagnosis of diabetes is associated with an increased risk of only a subset of cancer types. In fact, when the heterogeneity between the observational studies is accounted for, high-quality evidence is available only for associations between prediagnostic T2DM and incident breast or colorectal cancer (20–30% increased risk), as well as both intrahepatic cholangiocarcinoma and endometrial cancer (for which the cancer risk was doubled)[32]. Notably, T2DM has also been linked to a doubling of liver and pancreas cancer incidence rates, but methodological considerations preclude these associations from being definitive[32]. As these cancers are all obesity-related neoplasms, common factors could plausibly drive the relationships of both obesity and diabetes with cancer. Most patients with T2DM are obese and are receiving pharmacotherapy; therefore, evaluating the independent effects of the obesity, the antidiabetic medications, and the underlying diabetes on cancer risk or outcomes is difficult. Bias is an additional important issue that must be taken into account (BOX 1). For example, a diagnosis of diabetes often increases the level of medical surveillance over that experienced by individuals without this disease, which can result in an apparent increase in cancer risk among the diabetic population, representing a form of detection bias[33]. Reverse causality is another bias that is exemplified by pancreatic cancer, in which diabetes can be one of the presenting symptoms of the neoplasm[34]. Finally, the varying effects of diabetes on the risks of different neoplasms render analyses of diabetes and overall cancer risk hard to interpret. In fact, a weighted average risk of cancer reflects mostly common cancers, and might mask important associations with less-common cancers, such as cholangiocarcinoma.

Of note, evidence indicates that diabetes is associated with a reduced risk of prostate cancer (RR 0.86, 95% confidence interval (CI) 0.80–0.92)[35]; however, in Asian populations, current findings range from no association to an increased risk[35,36]. The basis for the inverse association reported in non-Asian populations is unknown, but several explanations are possible. One potential explanation is that diabetes is associated with reduced circulating androgen levels[37]: although circulating androgen levels have not been convincingly linked to prostate-cancer risk, prostate tissue androgen levels might influence this risk, and might also be lower among patients with diabetes. Another possibility is that the inverse association between diabetes and prostate cancer is driven by long-term exposure to metformin among patients with T2DM (see following section). By contrast with the modest reduction in prostate-cancer risk associated with diabetes, limited evidence suggests that prostate-cancer risk is increased among obese men[38]. Moreover, obesity clearly worsens the prognosis of patients with prostate cancer[39].

Antidiabetic medications and the risk of cancer. Remarkably, many drugs used in the treatment of diabetes have been reported to be associated with cancer risk. Use of metformin has been associated with a reduced cancer risk (as reviewed elsewhere[40]), whereas other agents, including insulin glargine, pioglitazone, incretin-based therapies (glucagon-like peptide 1 receptor (GLP-1R) agonists and dipeptidyl peptidase 4 (DPP4) inhibitors), and sulfonylureas, have been associated with an increased risk of cancer[41] (BOX 2). One might assume that studies of such associations would be simple to execute, but they are in fact subject to many pitfalls. In particular, the choice of an appropriate control group is challenging because the severity of diabetes might be associated with both cancer risk and with the choice of antidiabetic treatment. Unsurprisingly, therefore, many contradictory reports and controversies exist in the literature. The dramatic findings of some early studies — such as a halving of cancer risk with long-term metformin exposure[42], and a greatly increased breast-cancer risk resulting from insulin glargine exposure[43] — have not been confirmed by subsequent research[44,45]. These controversies remain active, but the earlier reports are now regarded with scepticism by many investigators[46,47].

Box 2 | **Summary of the potential associations between antidiabetic medications and cancer**

Metformin
The results of many observational studies suggest a protective effect of metformin on cancer development and progression[41]; however, substantial concerns have been raised regarding the methods used to capture exposure to metformin, the appropriate comparator, and the allocation of observation time to exposure groups[46]. The complexity of the interplay between diabetes mellitus and cancer makes analyses of an altered cancer prognosis associated with metformin use challenging. Ongoing clinical trials are addressing the hypothesis that metformin has antineoplastic activity, but results published to date relate only to surrogate markers, or are negative[124,126].

Sulfonylureas
Limited evidence suggests that the use of sulfonylureas is associated with an increased cancer risk[65], but this evidence is not definitive. Differences in cancer risk between sulfonylureas have been suggested and warrant further research[66].

Thiazolidinediones
Rosiglitazone has not been associated with substantial differences in cancer risk[198]; however, whether pioglitazone use increases the risk of bladder cancer is the subject of ongoing debate[70,73].

Dipeptidyl peptidase-4 inhibitors (DPP4i)
Early concerns about an increased risk of acute pancreatitis and pancreatic cancer associated with DPP4i use have, for the most part, been refuted in more-recent studies; nevertheless, controversies over this relationship persist[82]. Furthermore, laboratory findings have raised the possibility that DPP4i can accelerate tumour metastasis[199].

Glucagon-like peptide-1 receptor (GLP-1R) agonists
Use of GLP-1R agonists is probably not associated with an elevated risk of pancreatic cancer[200]. Laboratory studies suggest GLP-1R signalling promotes intestinal growth, and GLP-1R agonists may promote colonic tumorigenesis[86]. To date, no observational studies have been performed to address this potential relationship.

Human insulin
Observational studies have shown no increased risk of breast cancer in patients treated for diabetes with human insulin[44].

Insulin analogues
Glargine use has been associated with an increased breast-cancer risk in some studies that were later criticized for methodological flaws[47]. No increased risk of breast cancer has been detected in trials of insulin analogues[201], but the follow-up durations are limited.

Other antidiabetic agents
Insufficient data are available on the risk of cancer associated with the use of α-glucosidase inhibitors, meglitinide, colesevelam, and sodium glucose transporter 2 inhibitors for the treatment of diabetes. Gaps in our knowledge exist because not all agents have been rigorously studied in relation to cancer risk or prognosis.

Pharmacotherapy for T2DM is sequential in nature: medications are added successively to (for the most part) a metformin backbone in order to maintain glycaemic control[48]. Considering this sequencing, each 'add-on' therapy denotes diabetes progression, usually defined by hyperglycaemia. Diabetes progression is associated with increased risk of well-known microvascular and macrovascular complications, and might also be related to increased cancer risk. Thus, associations between specific antidiabetic agents and an altered cancer risk or prognosis do not necessarily imply a causal relationship. Simplistically, the associations reported to date seem to correlate progression of diabetes with incident cancer, and metformin — the drug generally used early in diabetes management — seems to be protective against cancer in many studies, relative to other drugs that are used at more-advanced stages of T2DM (such as insulin). Regardless of whether these associations are causal or noncausal in nature, statistical heterogeneity between the results of the pooled studies exceeded 90%, both for those on metformin and those on insulin[41]. Essentially, this heterogeneity might signify inherent differences in the methods used to capture the use of the drugs or to record the diagnoses of cancer, and exceeds the cutoff value proposed to denote 'strong evidence' (REF. 32). Furthermore, interpreting reports on associations of antidiabetic medications with the risk for all cancers combined is difficult, in light of the site-specific nature of the obesity and diabetes associations.

Since 2005, when the first observational study on the association between metformin use and cancer risk was published[42], interest in the potential use of metformin to influence cancer biology, and thereby alter clinical cancer risk and outcomes, has been growing[49]. The best possible scenario is tantalizing: 'repurposing' of a safe, inexpensive drug for new indications in cancer treatment or prevention. As reviewed elsewhere[50], it is biologically plausible that metformin could reduce cancer risk by acting directly on cells at risk of transformation, and/or by altering their hormonal environment. Some retrospective studies of cancer incidence among patients with diabetes treated with metformin reported large protective effects of this agent, as compared with other antidiabetic drugs[51–53]. In other studies, however, metformin use was not associated with statistically significant reductions in cancer risk[40,45,51,53]. Moreover, many of the observational studies that examined the association between metformin use and incident cancer have been criticized for various sources of bias[46]. These biases primarily revolve around two axes, the first being the classification of observation time to different exposure categories, and the second being the implicit effect of the natural history

of T2DM, both of which can be described as time-related biases (BOX 1). Plainly put, by incorrectly classifying various observational periods as periods of metformin use, one can easily change the likelihood of a cancer event, and thus create a spurious protective association (immortal time bias). Furthermore, when metformin use is compared with the use of antidiabetic drugs that are typically introduced at a later stage of T2DM (without accounting for the duration of disease), the progression of diabetes can confound any association between drug use and cancer (time-lag bias or confounding by indication). Of note, observational studies in which these biases were accounted for revealed no associations between metformin use and specific cancer types[45,54,55].

Clinical trials of true 'prevention' indications in disease-free individuals require a large number of participants and long observation times. At present, such research on cancer prevention with metformin is limited (in contrast to the abundance of trials examining the possible benefits of metformin in patients with a cancer diagnosis), despite the considerable interest in determining if the cancer-risk reduction observed in some of the retrospective studies in diabetic populations could be extended prospectively to nondiabetic individuals. One notable example is a placebo-controlled phase III trial of metformin for the secondary prevention of colorectal polyps and adenomas in individuals who had undergone polypectomy[56]. The trial had some imbalances between treatment arms; however, the data revealed a significant decrease in the incidence of recurrent polyps (RR 0.67, $P=0.034$) and adenomas (RR 0.60, $P=0.016$) at 1 year in the nondiabetic patients who were treated with low-dose oral metformin (250 mg daily)[56]. We speculate that these results, if confirmed, relate to the high concentration of metformin in the colonic lumen (relative to the blood) following oral ingestion: colon epithelial cells are probably exposed to higher drug levels than most other organs.

Another ongoing debate relates to the use of insulin analogues. This debate was sparked by four clinical studies published in 2009, which raised concern that the use of insulin glargine heightens cancer risk (particularly breast-cancer risk) relative to other types of insulin[43,57–59]. A plausible biological mechanism for this association was provided by laboratory evidence of enhanced insulin-like growth factor I receptor (IGF-1R) activation and mitogenic activities of glargine relative to other insulins[60]. The clinical studies have, however, been criticized for methodological flaws, and their findings have not been replicated in subsequent studies[44,47,61].

Theoretically, sulfonylureas could influence cancer risk because this class of antidiabetic agent increase insulin secretion[62], and some cancers express insulin receptors[63]. Indeed, results have suggested an increased cancer risk is associated with the use of sulfonylureas, compared with non-use of such agents[64]; however, these data are mostly from case–control studies, whereas cohort studies and clinical trials have revealed no such association[65]. Nevertheless, investigators have reported an increased risk of any cancer with long-term use of the commonly used sulfonylurea glyburide, as compared with the use of other sulfonylurea medications (which are indicated for the same stage of T2DM)[66]. Confirmation and a delineation of the mechanistic basis for this finding are active research topics.

Controversy also surrounds the use of the antidiabetic agent pioglitazone, a thiazolidinedione, and the risk of bladder cancer[67]. Following an early signal from a clinical trial[68], an increased risk of bladder cancer was reported to be associated with use of pioglitazone for >2 years[69]. These findings, alongside those detailed in other reports[70], led the FDA to issue a 'boxed warning' on the possible association to the labelling information for pioglitazone[71], whereas the drug has been removed from the market in France. The results of subsequent studies of this agent[72,73] have been reassuring, although this debate is far from over[74,75]. From a methodological standpoint, the conflicting results of the aforementioned studies might reflect the inclusion of prevalent users of pioglitazone in the analyses (prevalent-user bias)[46] (BOX 1).

Incretin mimetics (GLP-1R agonists) and incretin enhancers (DPP4 inhibitors) are other classes of antidiabetic medications associated with concerns regarding an increased cancer risk. The initial concern related to a possible association of incretin-based therapy with acute pancreatitis, which is a known risk factor for pancreatic cancer[76]. Indeed, an increased risk of pancreatitis resulting from use of incretin-based therapies was reported in adverse-event databases[76,77]; however, subsequent population-based studies have produced conflicting results[78–80]. Furthermore, additional data from regulatory authorities and clinical trials have not demonstrated a relationship between the use of incretin-based therapy and pancreatic cancer[81,82]. In addition, some laboratory studies indicate specific effects of GLP-1R agonists on thyroid c-cells[83,84], although the clinical evidence is insufficient to support the conclusion that these drugs are associated with an increased risk of thyroid cancer[85]. Similarly, data from a murine model raise a theoretical concern of an increased risk of colon cancer with the use of incretin-based therapy[86], but whether this association is clinically relevant remains to be determined.

Cancer prognosis

Relationships with obesity. Among patients with cancer, cachexia and weight loss are well known negative prognostic factors[87]; however, data from the Cancer Prevention Study II (REF. 88) demonstrate that a high BMI at the time of diagnosis of many cancer types is associated with increased all-cause mortality. In this important prospective cohort study involving more than one million men and women in the USA[89], no information was obtained or reported on the cause of death, raising the possibility of residual confounding by cardiovascular mortality. Prediagnostic BMI has been associated in a dose-dependent manner with both cancer-specific mortality and the time to distant metastasis in patients with breast cancer[90,91]. In addition, postdiagnostic weight gain has been linked with increased all-cause mortality in patients with breast cancer[92]. Moreover, endometrial cancer death rates are strongly associated with obesity, with around a sixfold increase in mortality among very obese women (BMI ≥40 kg/m^2),

compared with those with a BMI in the ideal range (18.5–24.9 kg/m^2)[88]. In addition, strong evidence indicates that patients with prostate cancer who are in the top quartile of bodyweight have a markedly increased risk of prostate-cancer-specific death[39].

The paradox that a high baseline bodyweight, at least for some cancers, adversely affects disease outcomes, whereas weight loss in patients with advanced-stage cancer is associated with poor outcomes might be interpreted as implying that bodyweight itself is neither a positive nor a negative prognostic factor. Rather, bodyweight might function as a surrogate for risk factors that vary with the hormonal, metabolic, or immune–inflammatory processes influencing outcome at different time points during the natural history of neoplastic disease. For example, one could infer that in patients with a high baseline bodyweight, carcinogenesis occurred in an environment with high insulin levels, which might influence the molecular pathology of the disease and, therefore, patient prognosis[93]. By contrast, development of cachexia after cancer is established might signify disruption of the inflammatory response by an aggressive cancer[87]. Despite research on the feasibility of weight loss in obese patients with early stage cancer[94], one cannot assume *a priori* that achieving weight loss would improve prognosis: long-term follow-up studies with stratification according to the degree of weight loss among patients with cancer who are obese at the time of diagnosis would be needed to address this question. Furthermore, laboratory evidence suggests that certain physiological derangements related to obesity that are associated with cancer risk persist after weight loss[95].

Another challenge in studying associations between obesity and cancer outcomes is that adiposity might be associated with the way in which individuals present with cancer. For instance, the finding that patients with renal-cell carcinoma and a high BMI (>25 kg/m^2) had improved cancer-specific survival than those with an ideal BMI (in direct contrast to studies in patients with breast[96], ovarian[97], or prostate[39] cancer), became statistically insignificant after adjusting for tumour grade and stage[98]. From a confounding standpoint, this phenomenon might be explained by earlier disease detection in obese individuals (lead-time bias) (BOX 1). This resonates with the 'obesity paradox' paradigm that has been proposed in cardiovascular medicine, whereby patients who are overweight or mildly obese seem to have improved survival following a diagnosis of cardiovascular disease[99]. In Asian patients with T2DM, obesity has also been reported to be inversely associated with cancer mortality[100]. Thus, properly accounting for complexities not only in the relevant cancer biology, but also in the analytical challenges in studying relationships between cancer and obesity is important. Despite the evidence discussed that obesity at time of diagnosis is associated with a poor prognosis, among patients with cancer-related cachexia, a low BMI is clearly associated with poor survival.

The influence of diabetes. On the basis of a pooled analysis of 97 prospective-study cohorts, comprising 820,900 people, the Emerging Risk Factors Collaboration reported a 25% increased risk of death from cancer in patients with diabetes, compared with nondiabetic patients[101]. For site-specific cancer deaths, the statistically significant associations were highest in magnitude for liver and pancreatic cancer (hazard ratios (HRs) of 2.16 and 1.51, respectively), moderate for ovarian and colorectal cancer (HR 1.45 and 1.40, respectively), and lower for lung and breast cancer (HR 1.27 and 1.25, respectively)[101]. This analysis has, however, attracted criticism relating to missing data on cause of death or cancer site in many of the pooled studies[32].

Pooled analyses on cancer-specific mortality associated with prediagnostic diabetes are scant. Nevertheless, a meta-analysis revealed a 32% increase in all-cause mortality in diabetic patients with colorectal cancer, compared with those without diabetes, whereas cancer-specific mortality was not associated with diabetes[102]. In patients with prostate cancer, all-cause mortality and prostate-cancer-specific mortality have been demonstrated to be increased in those with versus those without diabetes[103,104]. Of note, a more-recent publication from the Metabolic Syndrome and Cancer Project investigators[105] reported comparable prostate-cancer-specific mortality in diabetic and nondiabetic patients on the basis of a competing-risks analysis. In a meta-analysis, pre-existing diabetes was also found to be associated with a 49% increase in all-cause mortality in patients with breast cancer[106]. Breast-cancer-specific mortality in relation to diabetes status at diagnosis has been examined in several studies, with mixed results[107–110].

Of course, any evidence of increased cancer mortality among diabetic populations is highly influenced by the cancer incidence and by BMI (which is typically higher in patients with diabetes), and might also be influenced by medications used to treat diabetes. Thus, although the broad association of diabetes with cancer prognosis is important from a public health perspective, the simple question 'does diabetes influence cancer prognosis?' underestimates the complex interplay of factors that can affect cancer outcomes.

Effects of antidiabetic medications. Interest in metformin is not confined to the hypothesis that use of this agent will reduce cancer risk when taken by individuals without cancer; a separate hypothesis is that metformin will improve cancer outcomes when given to patients with cancer, in either the adjuvant or the advanced-stage disease settings. This hypothesis is mechanistically plausible and supported by laboratory models that demonstrate antineoplastic activity of metformin[50]. Findings of some population studies support the view that metformin favourably influences the outcomes of diabetic patients with cancer, but we must emphasize that whether these data are relevant to nondiabetic patients is unknown. For example, in a population of patients with T2DM and prostate cancer in Ontario, Canada, cumulative metformin use was associated with a 24% reduction in prostate-cancer-specific mortality for every 6 months of added use, compared with non-use[111]. Although other studies have produced conflicting results[112], the summary prostate-cancer-specific mortality data from a meta-analysis revealed a trend in the same direction as

the Ontario study, but were not statistically significant (HR 0.76, $P = 0.33$)[113]. In the same meta-analysis, metformin use was associated with significantly reduced all-cause mortality (HR 0.88, $P < 0.001$), and reduced biochemical recurrence of prostate cancer (HR 0.79, $P = 0.047$)[113]. Metformin use has also been examined in studies that investigated outcomes of other cancer types, some of which have been pooled in meta-analyses with summary results interpreted as encouraging[114]. For example, reduced HER2+-breast-cancer-specific mortality has been reported for metformin users versus non-users[115]. In this study, exposure to metformin was defined dichotomously over the entire observation time, such that the comparator group might have had more-advanced T2DM, requiring additional treatments when metformin is inadequate; therefore, a longer duration of diabetes in the comparator group might confound the association — referred to as time-lag bias[46] (BOX 1). Another example is a study of cancer outcomes in diabetic patients with ovarian cancer: using never-users as the comparator, disease recurrence in metformin users was reported to be reduced by 62% in these individuals[116]. This conclusion implies that metformin is among the most-active drugs available for the treatment of ovarian cancer, but must be interpreted with great caution given the possibility of bias.

Evidence from murine models indicates that metformin is active against bladder cancer, when administered either by direct intravesical administration or orally[117,118]. The effectiveness of oral metformin in a model of bladder cancer is of particular interest — the bladder mucosa is exposed to high concentrations of the drug, which is concentrated and excreted via the kidneys in the urine. If this model is found to be clinically relevant, these findings would represent a step forward in the pharmacological treatment of superficial bladder cancer, which is currently based on inconvenient and uncomfortable bladder installations. Metformin use has been reported to be associated with improved recurrence-free survival after radical cystectomy in diabetic patients with bladder cancer[119], but this result requires confirmation.

In view of the tantalizing, but inconclusive, evidence from observational studies, interventional clinical trials of metformin in the treatment of many cancer types have been initiated[49]. Indeed, >100 such trials are in progress[120] — no doubt owing, in part, to the fact that the drug is inexpensive, safe, and widely available. Results reported to date are limited to those from studies with surrogate study end points, some of which revealed reductions in tumour proliferation rates on sequential biopsies in subsets of patients[121–123], and two randomized trials in patients with pancreatic cancer with survival end points, in which no advantage of adding metformin to chemotherapy was found[124,125]. In an interim analysis of an ongoing placebo-controlled trial of metformin in the adjuvant treatment of early stage breast cancer, a modest reduction of fasting insulin levels in the metformin arm was reported[126]. This finding is noteworthy because prior work showed that high insulin levels are an adverse prognostic factor in this disease[127]; however, the magnitude of the decline in insulin levels associated with metformin treatment was small relative to the magnitude of the between-individual variation in insulin levels that has been linked to cancer prognosis. The final results of this trial and other ongoing randomized clinical trials are, therefore, eagerly awaited.

Studies reporting on the effect of antidiabetic medications other than metformin on cancer prognosis are both scant and hard to interpret, owing to the complexity of pharmacotherapy for T2DM, and the many sources of bias this complexity introduces. For example, the investigators of a population-based study reported that short-term sulfonylurea use was associated with increased breast-cancer-specific mortality, but concluded that this finding might have been confounded by selective prescribing of these medications to patients with cancer that had progressed[128].

Biological mechanisms

A number of review articles have detailed current hypotheses concerning the mechanisms linking obesity and diabetes to neoplasia[129–133], which are summarized in FIG. 1. Laboratory studies, including early work undertaken more than 65 years ago[134], have shown that cancer burden is decreased by caloric restriction in rodent models, whereas cancer burden increases when energy intake is in excess of expenditure[135]. Attributing these observations to the notion that excess caloric intake provides more energy to feed the cancer would be simplistic. One general alternative concept is that the altered endocrine milieu of obesity and T2DM facilitates carcinogenesis and/or aggressive neoplastic behaviour[130]. Insulin, insulin-like growth factors (IGFs), adipokines (such as leptin and adiponectin), and inflammatory cytokines are example candidate mediators of these pro-tumorigenic effects. In keeping with this hypothesis, findings from a nested case–control of the European Prospective Investigation into Cancer and Nutrition (EPIC) study[136], published in April 2016, provide evidence that hormonal correlates of obesity are more closely linked to cancer risk than obesity itself.

In addition to the well-recognized effects of insulin on carbohydrate metabolism in classic target tissues, such as liver, muscle, and fat, considerable laboratory evidence indicates that this peptide hormone can act as a mitogen for epithelial cells that express the insulin receptor[63]. Insulin levels are elevated in patients with T2DM and obesity, as a consequence of insulin resistance in classic insulin target tissues, and exposure of transformed cells to elevated insulin levels is commonly postulated to increase cancer burden[39,127,137]. Separate evidence demonstrates that patients with *PTEN* haploinsufficiency (which is associated with increased PI3K/AKT/mTOR signalling downstream of the insulin receptor) not only have an increased cancer risk compared to those without this genetic aberration, but also tend to be hypersensitive to insulin and obese[138]. These findings independently suggest that signalling downstream of the insulin receptor, whether as the result of PTEN deficiency or excess insulin expression, is related to cancer risk. Results also suggest that, notwithstanding the fact that established obesity leads to insulin resistance, inhibition of PI3K can prevent obesity[139]. Thus, the PI3K signalling is important in both neoplasia and obesity.

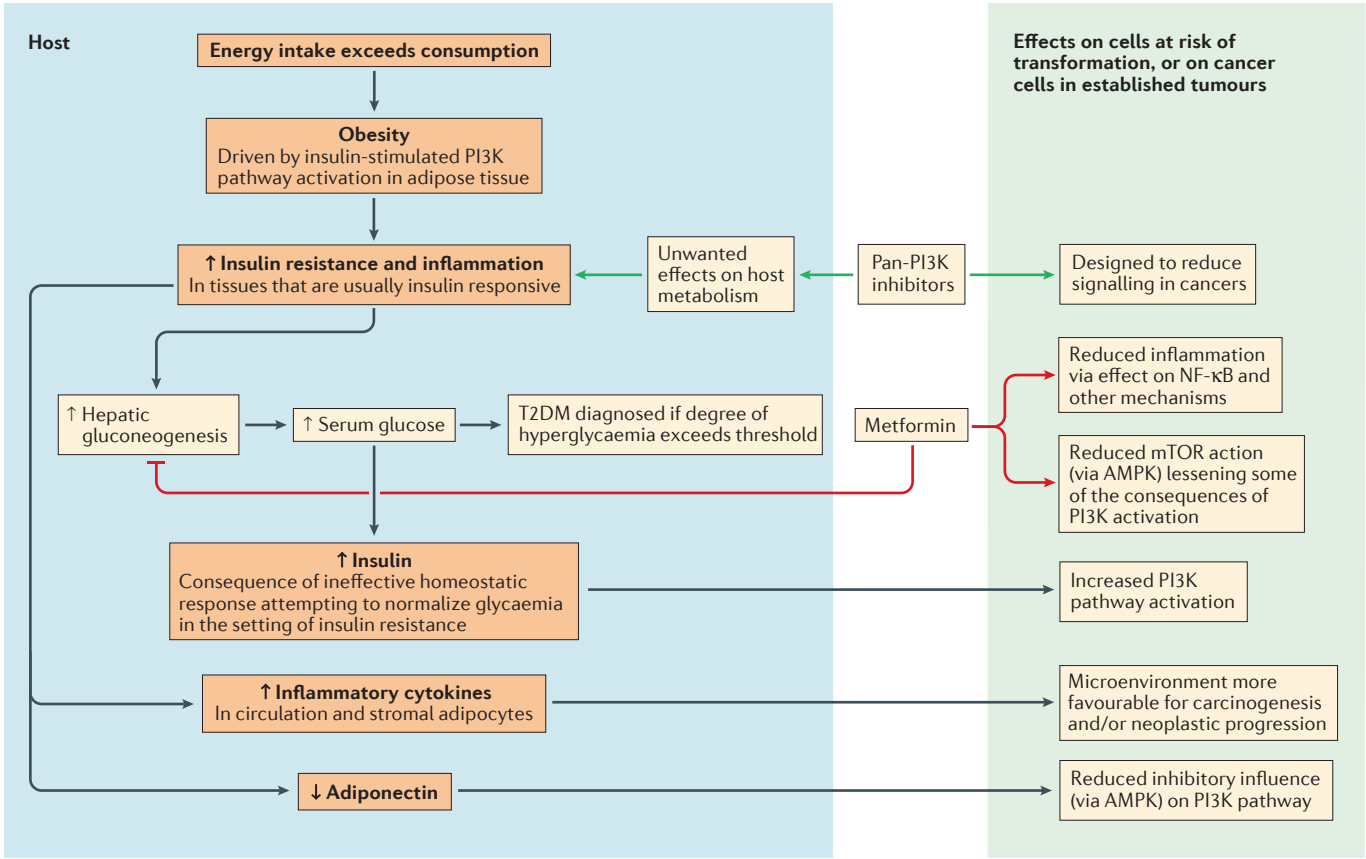

Figure 1 | **Simplified representation of the physiological processes that might link obesity, diabetes, and neoplasia.** When caloric intake exceeds energy expenditure insulin levels rise and excess energy is stored in adipose tissue. Insulin signals adipocytes to take up glucose and convert it to lipids as a way of storing energy to be used at times of inadequate caloric intake. Chronic excess of caloric intake over energy consumption, however, can lead to insulin resistance in insulin-target tissues, one of the consequences of which is increased hepatic gluconeogenesis — an important cause of hyperglycaemia. If the degree of hyperglycaemia surpasses a defined threshold, type 2 diabetes mellitus (T2DM) will be diagnosed. Importantly, as glucose levels rise, insulin secretion increases, which can reduce glucose levels in some patients, leading to a normoglycaemic, but hyperinsulinaemic, state; however, T2DM characterized by both hyperglycaemia and hyperinsulinaemia develops eventually. Hyperinsulinaemia is hypothesized to stimulate the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathway in at least a subset of cancers or cells at risk of malignant transformation, promoting tumour growth or resulting in increased rates of carcinogenesis, respectively. This hypothesis is supported by data from animal models, but remains to be investigated rigorously in the clinic. Other metabolic features of obesity that might influence neoplasia include increased levels of inflammatory cytokines, which stimulate various processes involved in cancer development, and reduced levels of adiponectin, an adipokine that normally inhibits cell proliferation via activation of AMP-activated protein kinase (AMPK). Metformin decreases hyperglycaemia, hyperinsulinaemia, and the consequences of these conditions predominantly by decreasing hepatic gluconeogenesis. This drug might also act directly on cancers or cells at risk of transformation by inducing energy stress, which slows cell proliferation via activation of AMPK and/or other mechanisms. On the other hand, the use of inhibitors of the PI3K pathway to target this signalling cascade in cancer cells could potentially have unintended metabolic consequences, such as hyperglycaemia, owing to off-tumour effects on tissues involved in the regulation of blood glucose, such as adipocytes. mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB.

Historically, researchers postulated that insulin has only 'metabolic effects', mediated by the insulin receptor, and only IGFs acting on the IGF-1R could mediate 'mitogenic effects'. We now recognize that such a strict dichotomy might not reflect the more complex biological reality, as many normal and transformed cell types simultaneously express insulin receptors, IGF-IR, and hybrid insulin/IGF-I receptors[140]. The signalling pathways activated downstream of these different receptors are similar, and the consequences of activation of the insulin receptor, the IGF-1R, or hybrid receptors depend on cell type. For example, an insulin concentration that inhibits gluconeogenesis in a normal hepatocyte might lead to increased proliferation of insulin-responsive prostate cancer cells.

One issue that warrants more attention is the lack of evidence for a major effect of exogenous insulin therapy on cancer risk or prognosis. Circulating insulin levels are generally higher among insulin-treated patients with T2DM than in obese diabetics not receiving

insulin; therefore, if a simple dose–response relationship exists between cancer burden and insulin level, one would expect clear evidence of adverse events related to cancer among long-term insulin users — to date, no such evidence has been presented. One possibility is that a plateau effect occurs, whereby pharmacological doses of insulin do not result in more insulin-receptor activation in nonclassic insulin target tissues than that associated with obesity, but this hypothesis has not been investigated in detail.

IGF-I is often mentioned as a candidate mediator of the obesity–cancer relationship, as a relationship between IGF-I levels and the risk of certain cancers has been reported[63,141] and, more recently, has been confirmed in a meta-analysis[142]; however, evidence that IGF-I levels are increased substantially with obesity is sparse, although starvation does lower circulating IGF-I concentrations[143]. Levels of IGF-binding protein 1 (which reduces IGF bioactivity), however, are suppressed by insulin, and this effect might, in certain tissues, lead to increased IGF signalling in obese individuals[144] — thus potentially increasing their cancer risk.

Oestrogens have been implicated in the increased risk of postmenopausal breast cancer that is associated with obesity[145]. Specifically, higher levels of circulating oestradiol are detected in obese versus non-obese postmenopausal women, and local oestrogen production (as a result of increased aromatase activity within the breast) might also be associated with obesity and, therefore, obesity-related cancer risk[145].

Evidence implicating adiponectin as a candidate pro-tumorigenic mediator is somewhat more recent than the findings relating to insulin, IGF-I, and oestrogens[146–149]. Adiponectin is an adipokine (a cell-signalling peptide released by adipocytes), but paradoxically is detected at lower circulating levels in obese compared with lean individuals[150]. Evidence indicates that, in at least a subset of cancers, adiponectin-receptor signalling leads to activation of AMP-activated protein kinase, which has multiple effects on cellular metabolism, including inhibition of mTOR signalling and of mRNA translation, that suppress cell proliferation[151]. Hence, low adiponectin levels in the context of obesity might promote the growth of neoplastic cells. By contrast, leptin levels increase with increasing weight, and leptin has pro-inflammatory, pro-proliferative, and antiapoptotic actions[152].

Chronic inflammation is clearly associated with obesity[132], and might cause changes in the tissue microenvironment that facilitate carcinogenesis. For example, in obesity, macrophages resident in adipose tissue produce pro-inflammatory cytokines, including TNFα, IL-6, and IL-1β, which can promote neoplastic transformation via activation of NF-κB and JNK signalling[153,154]. Emerging frontiers of research include studies of the relationships between obesity and the gut microbiota, between tissue and circulatory markers of obesity-related inflammation[154], and between the gut microbiota and inflammation[155–157].

The mechanisms proposed to explain the associations of obesity with cancer risk and outcome might also be relevant to any influences antidiabetic medications have on neoplasia. Metformin reduces blood glucose levels, as well as circulating levels of insulin. These effects are largely attributable to decreased hepatic gluconeogenesis, and distinguishes metformin from other treatments for diabetes (which have been suggested to increase cancer risk) that either raise or have limited effects on insulin concentrations[50]. These patterns suggest that changes in insulin levels mediate the effects of antidiabetic drugs on cancer risk and/or biology, although caution is required to avoid oversimplification. One must consider that insulin therapy, as noted, does not have clear oncological adverse effects, despite obviously raising circulating insulin levels; that the decline in insulin achieved by metformin might or might not be sufficient in magnitude to influence tumour biology; and that not all cancers are insulin responsive. Furthermore, some antidiabetic drugs, including metformin, have effects on inflammation[158,159], on the microbiome[160], or on tumour cells directly[50] that are potentially relevant to neoplastic disease.

Cancer treatments and diabetes outcomes

While the possibility that drugs used to treat diabetes can influence cancer risk and/or outcome should be regarded as an important research topic, clear evidence exists that certain cancer treatments can lead to clinically important abnormalities in glucose homeostasis.

Glucocorticoids. Among oncologists, glucocorticoids are perhaps the most widely used class of drug that perturb glycaemia. These agents are used as antineoplastic drugs for certain malignancies, and also for other purposes in oncological practice, such as reduction of intracranial pressure in patients with gliomas or brain metastases, or to alleviate cancer-related pain[161]. Glucocorticoids can cause insulin resistance by attenuating transcription and phosphorylation of the IRS proteins, which are immediately downstream of the insulin receptor and are necessary for signal transduction by this receptor, as well as by downregulating the phosphorylation of MAPK[162]. Steroid-related hyperglycaemia might also be related to increased hepatic gluconeogenesis[163]. In a study of patients who were treated with high-dose steroids[164], hyperglycaemia >10 mmol/l (180 mg/dl) was detected in 70% of the patients within 48 h of treatment. The prognostic relevance of this biological effect is unclear, but hyperglycaemia has been reported to be a poor prognostic factor in paediatric patients with acute lymphoblastic leukaemia[165,166]. Hyperglycaemia in the context of high-dose steroid therapy is also associated with hyperinsulinaemia[167]. Indeed, despite the benefits of steroid therapy, the hyperinsulinaemia induced by such treatment might, in certain contexts, contribute mechanistically to adverse cancer outcomes, as supported by the laboratory finding that experimental type I diabetes mellitus (characterized by hypoinsulinaemia and hyperglycaemia) slows, rather than accelerates, the growth of tumours in preclinical models[168]. This finding also implies that cancers are able to satisfy their glucose requirements under normoglycaemic conditions and that hyperglycaemia *per se* does not confer a major growth advantage.

The management of steroid-induced hyperglycaemia is, for the most part, empirical. One retrospective study demonstrated control of hyperglycaemia using insulin in patients with haematological malignancies who were receiving high-dose dexamethasone; both basal bolus insulin and sliding-scale insulin were used[169]. A clear biological rationale exists, however, for attempting to control hyperglycaemia with metformin as a first-choice therapy, as this agent tends to lower both insulin and glucose levels[50].

Androgen-deprivation therapy. Androgen-deprivation therapy (ADT) is commonly used in the treatment of prostate cancer. ADT was originally achieved by bilateral orchiectomy or high-dose oestrogen therapy, but now typically involves the use of gonadotropin-releasing hormone (GnRH) agonists. Testosterone levels are linked to muscle mass and body composition, and low levels of testosterone are associated with increased risk of insulin resistance, hyperinsulinaemia and the metabolic syndrome (high blood pressure, obesity, and diabetes) in men[170,171]. Indeed, the use of ADT has been repeatedly associated with incident diabetes, with a 36% increased risk demonstrated in a pooled analysis of data from observational studies[172]. Moreover, diabetic patients with prostate cancer have been shown to have worsened diabetes control after 1 year and 2 years of ADT[173]. Importantly, the association of ADT use with incident diabetes persisted after adjustment for baseline comorbidities[174]. The prognostic importance of this association remains unclear; however, the weight gain and hyperinsulinaemia that are consequences of ADT could plausibly contribute to not only overall and prostate-cancer-specific morbidity and mortality, but also the evolution of castration-resistant prostate cancer[39,175,176]. Thus, attention should be given to interventions, such as exercise, diet, and possibly metformin, as strategies to minimize the adverse metabolic effects of ADT.

Inhibitors of the insulin-signalling pathway. As discussed previously, intracellular signalling networks downstream of the insulin receptor are intrinsic to most cells. An elementary principle of diabetology is that insulin reduces blood glucose by activating the insulin receptor and downstream signalling pathways (particularly the PI3K pathway) in classic insulin target tissues, including liver, muscle, and fat. This leads to increased glucose uptake and decreased gluconeogenesis, and thus to the lowering of blood glucose levels. In cancer cells, however, the PI3K pathway drives neoplastic behaviour[177]. In some cancers, receptors of the insulin and/or IGF family are key activators of the PI3K pathway, but this cascade is more commonly activated by oncogenic events, such as loss of PTEN function, overexpression of HER2, or activating mutations in PI3K itself. Several inhibitors of this pathway have been developed as cancer treatments, including small molecules that inhibit AKT or PI3K[178,179], and rapalogs that inhibit mTOR (see next section). As most of these inhibitors are not tissue-specific in their actions, it is not surprising that undesired inhibition of insulin action in the liver, muscle, and fat has been documented among patients with cancer treated with these agents, resulting in metabolic toxicity characterized by hyperglycaemia[180]. A study of pooled phase I clinical trials of inhibitors of PI3K, AKT, or mTOR in patients with advanced-stage solid tumours has revealed a 6.7% incidence of severe hyperglycaemia, compared with 0% in the control groups[181]; it is perhaps surprising that metabolic toxicity is not more common given that pan-PI3K inhibitors would be expected to antagonize insulin action in all tissues. A plausible explanation for this finding is simply that the conventional dosing of these agents does not achieve full inhibition of the PI3K pathway. The preferred treatment for the metabolic toxicity of PI3K-pathway inhibitors is metformin, as insulin therapy carries at least a theoretical risk of activating this signalling cascade not only in the classic insulin-sensitive tissues, but also in the subset of cancers that express insulin receptors. Specific inhibitors of PI3Kδ, expression of which is confined to haematopoetic cell lineages, represent an interesting exception. Idelalisib is one such inhibitor and is approved for the treatment of B-cell lymphomas[182]. This agent does not perturb glucose regulation, and is clinically useful in patients with B-cell malignancies to a greater extent than that of pan-PI3K inhibitors in the treatment of various solid tumours. The efficacy of idelalisib might be at least partially attributable to the absence of metabolic toxicity that enables more-aggressive dosing to achieve complete blockade of PI3Kδ in the target tissues.

Drugs designed to specifically attenuate signalling by the IGF-1R, or more broadly the insulin–IGF-I receptor family, have been demonstrated to be active in preclinical models, leading to clinical trials of these agents, many of which had disappointing results[63,183]. Anti-IGF-1R agents increased the risk of hyperglycaemia in some patients[63,183]. With such agents, mechanisms of hyperglycaemia other than inhibition of the PI3K pathway in liver, muscle, and adipose tissue might operate: blocking the IGF-1R increases growth-hormone levels[63,184], which can lead to insulin resistance[185,186]. This insulin resistance can lead to not only to the observed hyperglycaemia, but also to hyperinsulinaemia. Cancer cells with insulin receptors would therefore be predicted to be resistant to IGF-1R-targeting therapies. Insulin-receptor family tyrosine-kinase inhibitors would be expected to be more effective than agents that only target the IGF-1R, but also to cause serious metabolic toxicity, as they are not specifically targeted to neoplastic tissue and block both IGF-1R and the insulin receptor. In reports of early trials, however, tolerability of these agents was good[187], although efficacy was not sufficient to justify further clinical research. These findings are compatible with the possibility that the dosing used was suboptimum: full inhibition of the insulin receptor might have been efficacious for patients with cancers that depend on insulin or IGFs, but would also have been expected to lead to serious hyperglycaemia.

Rapamycin and rapalogs. Temsirolimus and everolimus are mTOR inhibitors approved for the treatment of certain advanced-stage solid tumours, including renal-cell carcinoma, pancreatic neuroendocrine tumours,

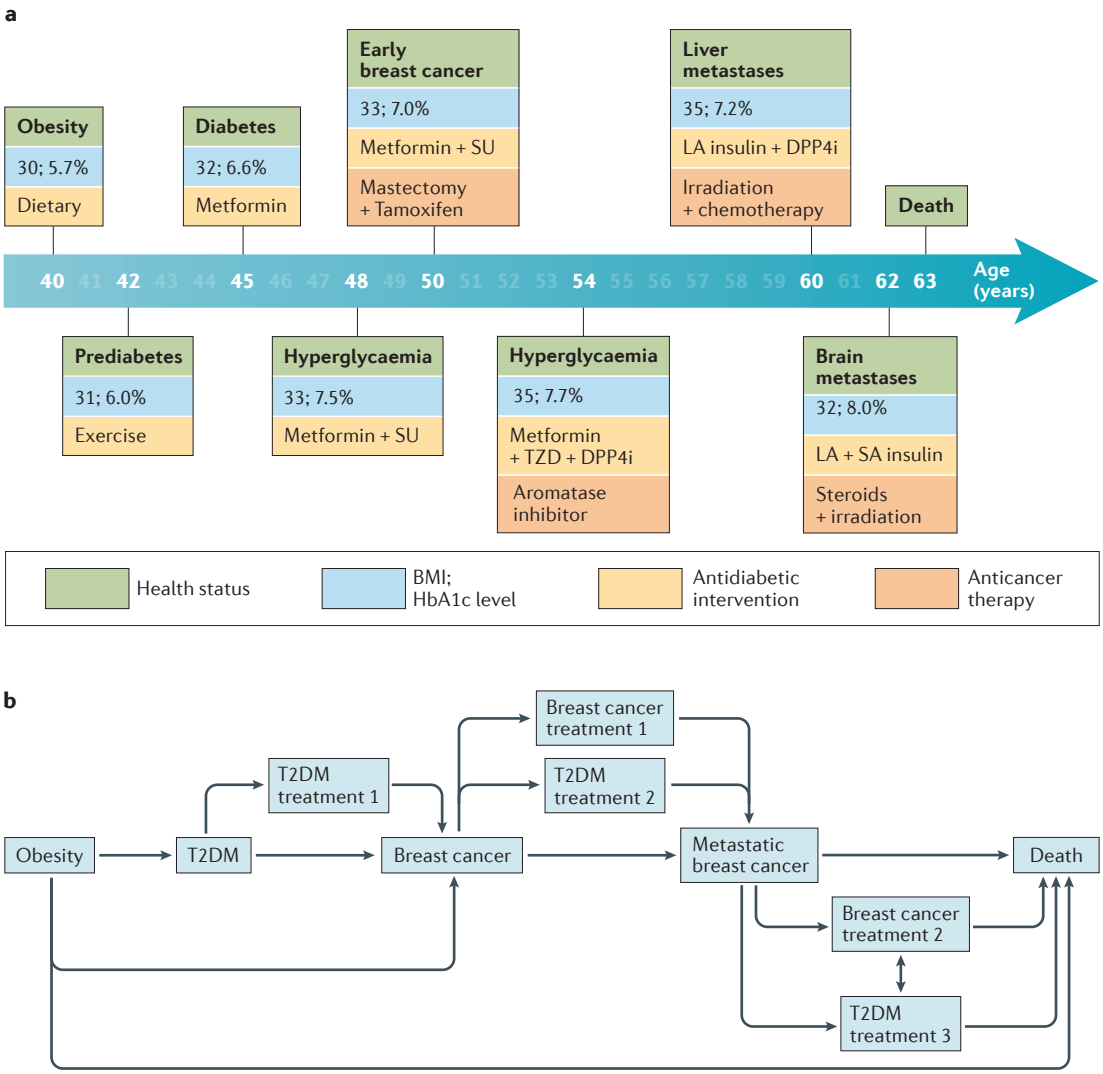

Figure 2 | **Clinical vignette and putative causal relationships between obesity, diabetes, antidiabetic medications, cancer, and cancer treatments. a** | A hypothetical patient with obesity, type 2 diabetes mellitus (T2DM), and breast cancer is depicted. Treatment for early stage breast cancer is commenced on the background of dual antidiabetic therapy with metformin and a sulfonylurea (SU). Further dysglycaemia leads to metformin, thiazolidinedione (TZD), and a dipeptidyl peptidase-4 inhibitor (DPP4i) triple therapy for T2DM, with continuation of adjuvant hormonal therapy for breast cancer. When liver metastases are diagnosed and hyperglycaemia worsens, metformin and TZD are withdrawn; chemotherapy and irradiation are then administered as anticancer therapy, and long-acting (LA) insulin is prescribed to achieve better glycaemic control. Following the diagnosis of brain metastases, the patient is given steroids, necessitating the addition of short-acting (SA) insulin to antidiabetic therapy (with DPPi withdrawal). **b** | The directed acyclic schematic depicts the possible causal relationships between obesity, T2DM, antidiabetic medications, cancer, and cancer treatments. Obesity is associated with increased mortality in general, but can also lead to T2DM and, possibly, cancer, which further increase morbidity and mortality. Cancer and cancer treatment influence the progression and treatment of T2DM, and possibly vice versa. An example of a hypothesized interaction is the reduction of breast-cancer risk associated with metformin treatment of T2DM. An example of a known clinical interaction is that steroid treatments for brain metastases or chemotherapy-induced vomiting can lead to increased insulin requirements in patients with insulin-dependent diabetes and cancer. BMI, body mass index; HbA1c, haemoglobin A1c (glycated haemoglobin).

and oestrogen-receptor-positive, HER2-negative breast cancer. Diabetic patients were ineligible to enrol on many of the clinical trials that led to the approval of these drugs, limiting current data on hyperglycaemia associated with their use. Nevertheless, in a phase III trial involving patients with renal-cell carcinoma[188], combination therapy with temsirolimus and bevacizumab was associated with 22% and 6% all-grade and severe hyperglycaemia, respectively, and everolimus has been reported to be associated with comparable rates of hyperglycaemia in clinical trial populations[189]. Mechanisms of metabolic toxicity of rapalogs are complex, and include reduced insulin secretion from pancreatic beta cells, as well as insulin resistance[190,191]. With expanding

indications for rapalogs[192], oncologists must be mindful of the risks of metabolic toxicity. Metformin represents the preferred option for the management of rapalog-induced hyperglycaemia, particularly in patients who also have hyperinsulinaemia.

Diabetes in cancer survivors. Intensive treatment of various childhood cancers can be curative, but evidence of a substantially increased risk of diabetes among long-term survivors has been reported[193,194], although the underlying mechanism has not been established — and might be multifactorial. In survivors of Hodgkin lymphoma, abdominal irradiation (and specifically irradiation of the para-aortic lymph nodes) has been identified as a risk factor for subsequent diabetes[195]. Conceivably, radiation exposure can damage pancreatic beta cells, leading to reduced insulin secretion. Thus, survivors of childhood cancer and Hodgkin lymphoma should be screened to monitor glycaemic control.

Conclusions

The relationship between obesity and T2DM is clear, and maintaining a BMI <25 kg/m^2 is important for diabetes prevention and management. Strong evidence from population studies indicates that obesity also increases the risk of certain cancers, and this association is of relevance to global public health, given the rapid increase in obesity rates worldwide. Furthermore, both historical and contemporary laboratory studies provide strong evidence that caloric restriction inhibits carcinogenesis, whereas obesity promotes this process. On the other hand, associations of diabetes and its treatments with neoplastic disease are more complex and challenging to unravel. Studies of relationships between specific pairs of variables (such as BMI at the time of diagnosis and survival among patients with breast cancer, or metformin use and prostate-cancer risk) are informative and useful starting points for research in this area, but remain subject to methodological challenges and typically do not account for the complexity relating to the simultaneous effects of many interacting variables. The vignette provided in FIG. 2 illustrates the typical interactions between obesity, diabetes, and cancer that are frequently seen in the clinic.

Increasingly, clinicians face the challenge of managing patients with both diabetes and cancer. Despite important gaps in our knowledge, metformin is a rational choice of first-line treatment for diabetes in patients with cancer, whether the hyperglycaemia is a result of cancer treatment or related to a prior diabetes diagnosis.

Adding cancer-risk reduction to the other well-recognized reasons for the general population to avoid obesity is also reasonable. Obese patients with newly diagnosed cancer might benefit from bodyweight reduction, but this hypothesis is challenging to investigate and has not been rigorously validated. By contrast, weight loss is clearly associated with an adverse prognosis among patients with advanced-stage cancer.

As clinicians increasingly encounter obese and/or diabetic patients with cancer, clinical trials of new drug candidates in oncology should not exclude obese or diabetic patients, unless a clear reason exists to do so, in order that the research will not provide data restricted to the nondiabetic and normal weight subset of patients with cancer.

Early reports of major favourable or unfavourable effects of various drugs used to treat diabetes on cancer risk or prognosis have frequently not been confirmed by subsequent studies. This disparity does not prove the absence of associations, but rather implies that, if they exist, they are modest in magnitude, and are possibly confined to patient subsets defined by variables related to patient energy balance and/or specific tumour characteristics. For example, metformin could plausibly reduce the proliferation rate of a subset of cancers, but only if cancers have particular molecular characteristics, and only if patient-specific pharmacokinetic variables lead to a sufficiently high level of drug exposure. Thus, research in this area remains active, and investigation of the relationships between diabetes, obesity, and cancer is relevant to efforts to discover novel metabolic approaches to cancer prevention and treatment.

1. Tuffier, T. Diabete et neoplasmes. *Archives generales de medecine* **7**, 129–140 (1888).
2. Bapat, S. P. *et al.* Depletion of fat-resident T_{reg} cells prevents age-associated insulin resistance. *Nature* **528**, 137–141 (2015).
3. Langenberg, C. *et al.* Long-term risk of incident type 2 diabetes and measures of overall and regional obesity: the EPIC-InterAct case-cohort study. *PLoS Med.* **9**, e1001230 (2012).
4. Ng, M. *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* **384**, 766–781 (2014).
5. Singh, G. M. *et al.* The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. *PLoS ONE* **8**, e65174 (2013).
6. Berrington de Gonzalez, A. *et al.* Body-mass index and mortality among 1.46 million white adults. *N. Engl. J. Med.* **363**, 2211–2219 (2010).
7. [no authors listed]. Diabetes Fact Sheet. *WHO* http://www.who.int/mediacentre/factsheets/fs312/en/ (2015).
8. Di Angelantonio, E. *et al.* Association of cardiometabolic multimorbidity with mortality. *JAMA* **314**, 52–60 (2015).
9. Murray, C. J. *et al.* Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. *Lancet* http://dx.doi.org/10.1016/s0140-6736(15)61340-x (2015).
10. Torre, L. A. *et al.* Global cancer statistics, 2012. *CA Cancer J. Clin.* **65**, 87–108 (2015).
11. Guariguata, L. *et al.* Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res. Clin. Pract.* **103**, 137–149 (2014).
12. Ogden, C. L., Carroll, M. D., Fryar, C. D. & Flegal, K. M. Prevalence of obesity among adults and youth: United States, 2011–2014. *NCHS Data Brief* 1–8 (2015).
13. Youlden, D. R. *et al.* The descriptive epidemiology of female breast cancer: an international comparison of screening, incidence, survival and mortality. *Cancer Epidemiol.* **36**, 237–248 (2012).
14. Arnold, M. *et al.* Global burden of cancer attributable to high body-mass index in 2012: a population-based study. *Lancet Oncol.* **16**, 36–46 (2015).
15. Wells, J. C., Coward, W. A., Cole, T. J. & Davies, P. S. The contribution of fat and fat-free tissue to body mass index in contemporary children and the reference child. *Int. J. Obes Relat. Metab. Disord.* **26**, 1323–1328 (2002).
16. Kaaks, R. & Kühn, T. Epidemiology: obesity and cancer — the evidence is fattening up. *Nat. Rev. Endocrinol.* **10**, 644–645 (2014).
17. Keum, N. *et al.* Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies. *J. Natl Cancer Inst.* **107**, http://dx.doi.org/10.1093/jnci/djv088 (2015).
18. Renehan, A. G., Tyson, M., Egger, M., Heller, R. F. & Zwahlen, M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* **371**, 569–578 (2008).
19. World Cancer Research Fund and the American Institute for Cancer Research. Continuous update project report: diet, nutrition, physical activity and liver cancer. http://wcrf.org/sites/default/files/Liver-Cancer-2015-Report.pdf (2015).
20. World Cancer Research Fund and the American Institute for Cancer Research. Continuous update project report. Food, nutrition, physical activity, and the prevention of breast cancer. http://wcrf.org/sites/default/files/Breast-Cancer-2010-Report.pdf (2015).
21. World Cancer Research Fund and the American Institute for Cancer Research. Continuous update project report: diet, nutrition, physical activity, and prostate cancer. http://wcrf.org/sites/default/files/Prostate-Cancer-2014-Report.pdf (2015).

22. Lerro, C. C., McGlynn, K. A. & Cook, M. B. A systematic review and meta-analysis of the relationship between body size and testicular cancer. *Br. J. Cancer* **103**, 1467–1474 (2010).
23. Yang, Y. *et al.* Obesity and incidence of lung cancer: a meta-analysis. *Int. J. Cancer* **132**, 1162–1169 (2013).
24. Song, M. *et al.* Trajectory of body shape across the lifespan and cancer risk. *Int. J. Cancer* http://dx.doi.org/10.1002/ijc.29981 (2015).
25. Neuhouser, M. L. *et al.* Overweight, obesity, and postmenopausal invasive breast cancer risk: a secondary analysis of the women's health initiative randomized clinical trials. *JAMA Oncol.* **1**, 611–621 (2015).
26. Reeves, G. K. *et al.* Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ* **335**, 1134 (2007).
27. Adams, T. D. *et al.* Long-term mortality after gastric bypass surgery. *N. Engl. J. Med.* **357**, 753–761 (2007).
28. Sjostrom, L. *et al.* Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. *Lancet Oncol.* **10**, 653–662 (2009).
29. Douglas, I. J., Bhaskaran, K., Batterham, R. L. & Smeeth, L. Bariatric surgery in the United Kingdom: a cohort study of weight loss and clinical outcomes in routine clinical care. *PLoS Med.* **12**, e1001925 (2015).
30. Eliassen, A. H., Colditz, G. A., Rosner, B., Willett, W. C. & Hankinson, S. E. Adult weight change and risk of postmenopausal breast cancer. *JAMA* **296**, 193–201 (2006).
31. Parker, E. D. & Folsom, A. R. Intentional weight loss and incidence of obesity-related cancers: the Iowa Women's Health Study. *Int. J. Obes Relat. Metab. Disord.* **27**, 1447–1452 (2003).
32. Tsilidis, K. K., Kasimis, J. C., Lopez, D. S., Ntzani, E. E. & Ioannidis, J. P. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. *BMJ* **350**, g7607 (2015).
33. Carstensen, B., Witte, D. R. & Friis, S. Cancer occurrence in Danish diabetic patients: duration and insulin effects. *Diabetologia* **55**, 948–958 (2012).
34. Geier, A. S. *et al.* Cancer detection rates following enrolment in a disease management programme for type 2 diabetes. *Diabetologia* **56**, 1944–1948 (2013).
35. Bansal, D., Bhansali, A., Kapil, G., Undela, K. & Tiwari, P. Type 2 diabetes and risk of prostate cancer: a meta-analysis of observational studies. *Prostate Cancer Prostat. Dis.* **16**, 151–158 (2013).
36. Tseng, C. H. Diabetes and risk of prostate cancer: a study using the National Health Insurance. *Diabetes Care* **34**, 616–621 (2011).
37. Dhindsa, S. *et al.* Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J. Clin. Endocrinol. Metab.* **89**, 5462–5468 (2004).
38. Freedland, S. J. & Aronson, W. J. Obesity and prostate cancer. *Urology* **65**, 433–439 (2005).
39. Ma, J. *et al.* Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. *Lancet Oncol.* **9**, 1039–1047 (2008).
40. Gandini, S. *et al.* Metformin and cancer risk and mortality: a systematic review and meta-analysis taking into account biases and confounders. *Cancer Prev. Res. (Phila.)* **7**, 867–885 (2014).
41. Wu, L., Zhu, J., Prokop, L. J. & Murad, M. H. Pharmacologic therapy of diabetes and overall cancer risk and mortality: a meta-analysis of 265 studies. *Sci. Rep.* **5**, 10147 (2015).
42. Evans, J. M., Donnelly, L. A., Emslie-Smith, A. M., Alessi, D. R. & Morris, A. D. Metformin and reduced risk of cancer in diabetic patients. *BMJ* **330**, 1304–1305 (2005).
43. Colhoun, H. M. & Group, S. E. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. *Diabetologia* **52**, 1755–1765 (2009).
44. Bronsveld, H. K. *et al.* Treatment with insulin (analogues) and breast cancer risk in diabetics; a systematic review and meta-analysis of *in vitro*, animal and human evidence. *Breast Cancer Res.* **17**, 100 (2015).
45. Kowall, B., Stang, A., Rathmann, W. & Kostev, K. No reduced risk of overall, colorectal, lung, breast, and prostate cancer with metformin therapy in diabetic patients: database analyses from Germany and the UK. *Pharmacoepidemiol. Drug Saf.* **24**, 865–874 (2015).
46. Suissa, S. & Azoulay, L. Metformin and the risk of cancer: time-related biases in observational studies. *Diabetes Care* **35**, 2665–2673 (2012).
47. Pocock, S. J. & Smeeth, L. Insulin glargine and malignancy: an unwarranted alarm. *Lancet* **374**, 511–513 (2009).
48. Garber, A. J. *et al.* AACE/ACE comprehensive diabetes management algorithm 2015. *Endocr. Pract.* **21**, 438–447 (2015).
49. Pollak, M. Overcoming drug development bottlenecks with repurposing: repurposing biguanides to target energy metabolism for cancer treatment. *Nat. Med.* **20**, 591–593 (2014).
50. Pollak, M. N. Investigating metformin for cancer prevention and treatment: the end of the beginning. *Cancer Discov.* **2**, 778–790 (2012).
51. Decensi, A. *et al.* Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. *Cancer Prev. Res. (Phila.)* **3**, 1451–1461 (2010).
52. Libby, G. *et al.* New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes Care* **32**, 1620–1625 (2009).
53. Noto, H., Goto, A., Tsujimoto, T. & Noda, M. Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. *PLoS ONE* **7**, e33411 (2012).
54. Mamtani, R. *et al.* Incidence of bladder cancer in patients with type 2 diabetes treated with metformin or sulfonylureas. *Diabetes Care* **37**, 1910–1917 (2014).
55. Tsilidis, K. K. *et al.* Metformin does not affect cancer risk: a cohort study in the UK Clinical Practice Research Datalink analyzed like an intention-to-treat trial. *Diabetes Care* **37**, 2522–2532 (2014).
56. Higurashi, T. *et al.* Metformin for chemoprevention of metachronous colorectal adenoma or polyps in post-polypectomy patients without diabetes: a multicentre double-blind, placebo-controlled, randomised phase 3 trial. *Lancet Oncol.* http://dx.doi.org/10.1016/s1470-2045(15)00565-3 (2016).
57. Currie, C. J., Poole, C. D. & Gale, E. A. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia* **52**, 1766–1777 (2009).
58. Hemkens, L. G. *et al.* Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. *Diabetologia* **52**, 1732–1744 (2009).
59. Jonasson, J. M. *et al.* Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden. *Diabetologia* **52**, 1745–1754 (2009).
60. Mayer, D., Shukla, A. & Enzmann, H. Proliferative effects of insulin analogues on mammary epithelial cells. *Arch. Physiol. Biochem.* **114**, 38–44 (2008).
61. Wu, J. W., Filion, K. B., Azoulay, L., Doll, M. K. & Suissa, S. The effect of long-acting insulin analogs on the risk of cancer: a systematic review of observational studies. *Diabetes Care* http://dx.doi.org/10.2337/dc15-1816 (2016).
62. Proks, P., Reimann, F., Green, N., Gribble, F. & Ashcroft, F. Sulfonylurea stimulation of insulin secretion. *Diabetes* **51** (Suppl. 3), S368–S376 (2002).
63. Pollak, M. The insulin and insulin-like growth factor receptor family in neoplasia: an update. *Nat. Rev. Cancer* **12**, 159–169 (2012).
64. Chang, C. H., Lin, J. W., Wu, L. C., Lai, M. S. & Chuang, L. M. Oral insulin secretagogues, insulin, and cancer risk in type 2 diabetes mellitus. *J. Clin. Endocrinol. Metab.* **97**, E1170–1175 (2012).
65. Kowall, B., Rathmann, W. & Kostev, K. Are sulfonylurea and insulin therapies associated with a larger risk of cancer than metformin therapy? A retrospective database analysis. *Diabetes Care* **38**, 59–65 (2015).
66. Tuccori, M., Wu, J. W., Yin, H., Majdan, A. & Azoulay, L. The use of glyburide compared with other sulfonylureas and the risk of cancer in patients with type 2 diabetes. *Diabetes Care* **38**, 2083–2089 (2015).
67. Loke, Y. K. & Mattishent, K. Bladder cancer: pioglitazone—when is a prescription drug safe? *Nat. Rev. Urol.* **12**, 655–656 (2015).
68. Dormandy, J. A. *et al.* Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* **366**, 1279–1289 (2005).
69. Lewis, J. D. *et al.* Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care* **34**, 916–922 (2011).
70. Azoulay, L. *et al.* The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. *BMJ* **344**, e3645 (2012).
71. U.S. Food and Drug Administration. FDA Drug Safety Communication: update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer. http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm (2012).
72. Levin, D. *et al.* Pioglitazone and bladder cancer risk: a multipopulation pooled, cumulative exposure analysis. *Diabetologia* **58**, 493–504 (2015).
73. Lewis, J. D. *et al.* Pioglitazone use and risk of bladder cancer and other common cancers in persons with diabetes. *JAMA* **314**, 265–277 (2015).
74. Faillie, J. L. & Hillaire-Buys, D. Examples of how the pharmaceutical industries distort the evidence of drug safety: the case of pioglitazone and the bladder cancer issue. *Pharmacoepidemiol. Drug Saf.* http://dx.doi.org/10.1002/pds.3925 (2015).
75. Tuccori, M. *et al.* Pioglitazone use and risk of bladder cancer: population based cohort study. *BMJ* **352**, i1541 (2016).
76. Elashoff, M., Matveyenko, A. V., Gier, B., Elashoff, R. & Butler, P. C. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* **141**, 150–156 (2011).
77. Raschi, E., Piccinni, C., Poluzzi, E., Marchesini, G. & De Ponti, F. The association of pancreatitis with antidiabetic drug use: gaining insight through the FDA pharmacovigilance database. *Acta Diabetol.* **50**, 569–577 (2013).
78. Azoulay, L. Incretin-based drugs and adverse pancreatic events: almost a decade later and uncertainty remains. *Diabetes Care* **38**, 951–953 (2015).
79. Gokhale, M. *et al.* Dipeptidyl-peptidase-4 inhibitors and pancreatic cancer: a cohort study. *Diabetes, Obes. Metabolism* **16**, 1247–1256 (2014).
80. Tseng, C. H. Sitagliptin and pancreatic cancer risk in patients with type 2 diabetes. *Eur. J. Clin. Invest.* **46**, 70–79 (2016).
81. Green, J. B. *et al.* Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* **373**, 232–242 (2015).
82. Egan, A. G. *et al.* Pancreatic safety of incretin-based drugs—FDA and EMA assessment. *N. Engl. J. Med.* **370**, 794–797 (2014).
83. Waser, B., Beetschen, K., Pellegata, N. S. & Reubi, J. C. Incretin receptors in non-neoplastic and neoplastic thyroid C cells in rodents and humans: relevance for incretin-based diabetes therapy. *Neuroendocrinology* **94**, 291–301 (2011).
84. Rosol, T. J. On-target effects of GLP-1 receptor agonists on thyroid C-cells in rats and mice. *Toxicol. Pathol.* **41**, 303–309 (2013).
85. Drab, S. R. Glucagon-like peptide-1 receptor agonists for type 2 diabetes: a clinical update of safety and efficacy. *Curr. Diabetes Rev.* http://dx.doi.org/10.2174/1573399812666151223093841 (2015).
86. Koehler, J. A. *et al.* GLP-1R agonists promote normal and neoplastic intestinal growth through mechanisms requiring Fgf7. *Cell. Metab.* **21**, 379–391 (2015).
87. Argiles, J. M., Busquets, S., Stemmler, B. & Lopez-Soriano, F. J. Cancer cachexia: understanding the molecular basis. *Nat. Rev. Cancer* **14**, 754–762 (2014).
88. Calle, E. E., Rodriguez, C., Walker-Thurmond, K. & Thun, M. J. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *N. Engl. J. Med.* **348**, 1625–1638 (2003).
89. Calle, E. E. & Terrell, D. D. Utility of the National Death Index for ascertainment of mortality among cancer prevention study II participants. *Am. J. Epidemiol.* **137**, 235–241 (1993).
90. Chan, D. S. *et al.* Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. *Ann. Oncol.* **25**, 1901–1914 (2014).
91. Copson, E. R. *et al.* Obesity and the outcome of young breast cancer patients in the UK: the POSH study. *Ann. Oncol.* **26**, 101–112 (2015).
92. Playdon, M. C. *et al.* weight gain after breast cancer diagnosis and all-cause mortality: systematic review and meta-analysis. *J. Natl Cancer Inst.* **107**, djv275 (2015).
93. Pettersson, A. *et al.* Modification of the association between obesity and lethal prostate cancer by TMPRSS2:ERG. *J. Natl Cancer Inst.* **105**, 1881–1890 (2013).
94. Goodwin, P. J. *et al.* Randomized trial of a telephone-based weight loss intervention in postmenopausal women with breast cancer receiving letrozole: the LISA trial. *J. Clin. Oncol.* **32**, 2231–2239 (2014).

95. Rossi, E. L. *et al.* Obesity-associated alterations in inflammation, epigenetics, and mammary tumor growth persist in formerly obese mice. *Cancer Prev. Res. (Phila.)* **9**, 339–348 (2016).
96. Widschwendter, P. *et al.* The influence of obesity on survival in early, high-risk breast cancer: results from the randomized SUCCESS A trial. *Breast Cancer Res.* **17**, 129 (2015).
97. Nagle, C. M. *et al.* Obesity and survival among women with ovarian cancer: results from the Ovarian Cancer Association Consortium. *Br. J. Cancer* **113**, 817–826 (2015).
98. Hakimi, A. A. *et al.* An epidemiologic and genomic investigation into the obesity paradox in renal cell carcinoma. *J. Natl Cancer Inst.* **105**, 1862–1870 (2013).
99. Lavie, C. J., McAuley, P. A., Church, T. S., Milani, R. V. & Blair, S. N. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. *J. Am. College Cardiol.* **63**, 1345–1354 (2014).
100. Tseng, C. H. Obesity paradox: differential effects on cancer and noncancer mortality in patients with type 2 diabetes mellitus. *Atherosclerosis* **226**, 186–192 (2013).
101. Seshasai, S. R. *et al.* Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N. Engl. J. Med.* **364**, 829–841 (2011).
102. Stein, K. B. *et al.* Colorectal cancer outcomes, recurrence, and complications in persons with and without diabetes mellitus: a systematic review and meta-analysis. *Dig. Dis. Sci.* **55**, 1839–1851 (2010).
103. Snyder, C. F. *et al.* Does pre-existing diabetes affect prostate cancer prognosis? A systematic review. *Prostate Cancer Prostat. Dis.* **13**, 58–64 (2010).
104. Bensimon, L., Yin, H., Suissa, S., Pollak, M. N. & Azoulay, L. Type 2 diabetes and the risk of mortality among patients with prostate cancer. *Cancer Causes Control* **25**, 329–338 (2014).
105. Haggstrom, C. *et al.* Prostate cancer, prostate cancer death, and death from other causes, among men with metabolic aberrations. *Epidemiology* **25**, 823–828 (2014).
106. Peairs, K. S. *et al.* Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. *J. Clin. Oncol.* **29**, 40–46 (2011).
107. Luo, J. *et al.* Pre-existing diabetes and breast cancer prognosis among elderly women. *Br. J. Cancer* **113**, 827–832 (2015).
108. Wu, A. H. *et al.* Diabetes and other comorbidities in breast cancer survival by race/ethnicity: the California Breast Cancer Survivorship Consortium (CBCSC). *Cancer Epidemiol. Biomarkers Prev.* **24**, 361–368 (2015).
109. Fleming, S. T., Rastogi, A., Dmitrienko, A. & Johnson, K. D. A comprehensive prognostic index to predict survival based on multiple comorbidities: a focus on breast cancer. *Med. Care* **37**, 601–614 (1999).
110. Srokowski, T. P., Fang, S., Hortobagyi, G. N. & Giordano, S. H. Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. *J. Clin. Oncol.* **27**, 2170–2176 (2009).
111. Margel, D. *et al.* Metformin use and all-cause and prostate cancer-specific mortality among men with diabetes. *J. Clin. Oncol.* **31**, 3069–3075 (2013).
112. Bensimon, L., Yin, H., Suissa, S., Pollak, M. N. & Azoulay, L. The use of metformin in patients with prostate cancer and the risk of death. *Cancer Epidemiol. Biomarkers Prev.* **23**, 2111–2118 (2014).
113. Stopsack, K. H., Ziehr, D. R., Rider, J. R. & Giovannucci, E. L. Metformin and prostate cancer mortality: a meta-analysis. *Cancer Causes Control* http://dx.doi.org/10.1007/s10552-015-0687-0 (2015).
114. Zhang, Z. J. & Li, S. The prognostic value of metformin for cancer patients with concurrent diabetes: a systematic review and meta-analysis. *Diabetes Obes. Metab.* **16**, 707–710 (2014).
115. He, X. *et al.* Metformin and thiazolidinediones are associated with improved breast cancer-specific survival of diabetic women with HER2$^+$ breast cancer. *Ann. Oncol.* **23**, 1771–1780 (2012).
116. Romero, I. L. *et al.* Relationship of type II diabetes and metformin use to ovarian cancer progression, survival, and chemosensitivity. *Obstetr. Gynecol.* **119**, 61–67 (2012).
117. Liu, Z. *et al.* High sensitivity of an Ha-RAS transgenic model of superficial bladder cancer to metformin is associated with approximately 240-fold higher drug concentration in urine than serum. *Mol. Cancer Ther.* **15**, 430–438 (2016).
118. Peng, M. *et al.* High efficacy of intravesical treatment of metformin on bladder cancer in preclinical model. *Oncotarget* http://dx.doi.org/10.18632/oncotarget.6933 (2016).
119. Nayan, M. *et al.* The effect of metformin on cancer-specific survival outcomes in diabetic patients undergoing radical cystectomy for urothelial carcinoma of the bladder. *Urol. Oncol.* **33**, 386. e387–e313 (2015).
120. US National Library of Medicine. *ClinicalTrials.gov*, https://clinicaltrials.gov/ct2/results?term=%22cancer%22+AND+%22metformin%22+AND+%22treating%22&Search=Search (2015).
121. DeCensi, A. *et al.* Differential effects of metformin on breast cancer proliferation according to markers of insulin resistance and tumor subtype in a randomized presurgical trial. *Breast Cancer Res. Treat.* **148**, 81–90 (2014).
122. Lord, S. R. *et al.* Neoadjuvant window studies of metformin and biomarker development for drugs targeting cancer metabolism. *J. Natl Cancer Inst. Monogr.* **2015**, 81–86 (2015).
123. Hadad, S. M. *et al.* Evidence for biological effects of metformin in operable breast cancer: biomarker analysis in a pre-operative window of opportunity randomized trial. *Breast Cancer Res. Treat.* **150**, 149–155 (2015).
124. Kordes, S. *et al.* Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol.* **16**, 839–847 (2015).
125. Reni, M. *et al.* (Ir)relevance of metformin treatment in patients with metastatic pancreatic cancer: an open-label, randomized phase 2 trial. *Clin. Cancer Res.* http://dx.doi.org/10.1158/1078-0432.ccr-15-1722 (2015).
126. Goodwin, P. J. *et al.* Effect of metformin versus placebo on and metabolic factors in NCIC CTG MA.32. *J. Natl Cancer Inst.* **107,** http://dx.doi.org/10.1093/jnci/djv006 (2015).
127. Goodwin, P. J. *et al.* Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *J. Clin. Oncol.* **20**, 42–51 (2002).
128. Vissers, P. A. *et al.* The association between glucose-lowering drug use and mortality among breast cancer patients with type 2 diabetes. *Breast Cancer Res. Treatment* **150**, 427–437 (2015).
129. Gallagher, E. J. & LeRoith, D. Obesity and diabetes: the increased risk of cancer and cancer-related mortality. *Physiol. Rev.* **95**, 727–748 (2015).
130. Pollak, M. Do cancer cells care if their host is hungry? *Cell. Metabolism* **9**, 401–403 (2009).
131. Allott, E. H. & Hursting, S. D. Obesity and cancer: mechanistic insights from transdisciplinary studies. *Endocr. Relat. Cancer* **22**, R365–R386 (2015).
132. Iyengar, N. M., Hudis, C. A. & Dannenberg, A. J. Obesity and cancer: local and systemic mechanisms. *Annu. Rev. Med.* **66**, 297–309 (2015).
133. Renehan, A. G., Zwahlen, M. & Egger, M. Adiposity and cancer risk: new mechanistic insights from epidemiology. *Nat. Rev. Cancer* **15**, 484–498 (2015).
134. Tannenbaum, A. & Silverstone, H. The influence of the degree of caloric restriction on the formation of skin tumors and hepatomas in mice. *Cancer Res.* **9**, 724–727 (1949).
135. Algire, C., Amrein, L., Zakikhani, M., Panasci, L. & Pollak, M. 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* **17**, 351–360 (2010).
136. Murphy, N. *et al.* A nested case–control study of metabolically defined body size phenotypes and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). *PLoS. Med.* **13**, e1001988 (2016).
137. Wolpin, B. M. *et al.* Hyperglycaemia, insulin resistance, impaired pancreatic beta-cell function, and risk of pancreatic cancer. *J. Natl Cancer Inst.* **105**, 1027–1035 (2013).
138. Pal, A. *et al.* PTEN mutations as a cause of constitutive insulin sensitivity and obesity. *N. Engl. J. Med.* **367**, 1002–1011 (2012).
139. Ortega-Molina, A. *et al.* Pharmacological inhibition of PI3K reduces adiposity and metabolic syndrome in obese mice and rhesus monkeys. *Cell. Metabolism* **21**, 558–570 (2015).
140. Belfiore, A., Frasca, F., Pandini, G., Sciacca, L. & Vigneri, R. Insulin receptor isoforms and insulin receptor/insulin-like growth factor receptor hybrids in physiology and disease. *Endocr. Rev.* **30**, 586–623 (2009).
141. Chan, J. M. *et al.* Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science* **279**, 563–566 (1998).
142. Travis, R. C. *et al.* A meta-analysis of individual participant data reveals an association between circulating levels of IGF-I and prostate cancer risk. *Cancer Res.* **76**, 2288–2300 (2016).
143. Thissen, J. P., Underwood, L. E. & Ketelslegers, J. M. Regulation of insulin-like growth factor-I in starvation and injury. *Nutr. Rev.* **57**, 167–176 (1999).
144. Baxter, R. C. IGF binding proteins in cancer: mechanistic and clinical insights. *Nat. Rev. Cancer* **14**, 329–341 (2014).
145. Key, T. J. *et al.* Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J. Natl Cancer Inst.* **95**, 1218–1226 (2003).
146. Hofmann, J. N. *et al.* A prospective study of circulating adipokine levels and risk of multiple myeloma. *Blood* **120**, 4418–4420 (2012).
147. Inamura, K. *et al.* Prediagnosis plasma adiponectin in relation to colorectal cancer risk according to KRAS mutation status. *J. Natl Cancer Inst.* **108,** http://dx.doi.org/10.1093/jnci/djv363 (2016).
148. Bao, Y. *et al.* A prospective study of plasma adiponectin and pancreatic cancer risk in five US cohorts. *J. Natl Cancer Inst.* **105**, 95–103 (2013).
149. Hofmann, J. N. *et al.* Low levels of circulating adiponectin are associated with multiple myeloma risk in overweight and obese individuals. *Cancer Res.* **76**, 1935–1941 (2016).
150. Arita, Y. *et al.* Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem. Biophys. Res. Commun.* **257**, 79–83 (1999).
151. Zakikhani, M., Dowling, R. J., Sonenberg, N. & Pollak, M. N. The effects of adiponectin and metformin on prostate and colon neoplasia involve activation of AMP-activated protein kinase. *Cancer Prev. Res. (Phila.)* **1**, 369–375 (2008).
152. Vansaun, M. N. Molecular pathways: adiponectin and leptin signaling in cancer. *Clin. Cancer Res.* **19**, 1926–1932 (2013).
153. Font-Burgada, J., Sun, B. & Karin, M. Obesity and cancer: the oil that feeds the flame. *Cell. Metabolism* **23**, 48–62 (2016).
154. Iyengar, N. M. *et al.* Systemic correlates of white adipose tissue inflammation in early-stage breast cancer. *Clin. Cancer Res.* http://dx.doi.org/10.1158/1078-0432.ccr-15-2239 (2015).
155. Zhang, D. *et al.* Neutrophil ageing is regulated by the microbiome. *Nature* **525**, 528–532 (2015).
156. Ridaura, V. K. *et al.* Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* **341**, 1241214 (2013).
157. Ussar, S. *et al.* Interactions between gut microbiota, host genetics and diet modulate the predisposition to obesity and metabolic syndrome. *Cell. Metabolism* **22**, 516–530 (2015).
158. Moiseeva, O. *et al.* Metformin inhibits the senescence-associated secretory phenotype by interfering with IKK/NF-κB activation. *Aging Cell* **12**, 489–498 (2013).
159. Lee, S. Y. *et al.* Metformin ameliorates inflammatory bowel disease by suppression of the STAT3 signaling pathway and regulation of the between Th17/Treg balance. *PLoS ONE* **10**, e0135858 (2015).
160. Forslund, K. *et al.* Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. *Nature* **528**, 262–266 (2015).
161. Haywood, A. *et al.* Corticosteroids for the management of cancer-related pain in adults. *Cochrane Database Syst. Rev.* **4**, CD010756 (2015).
162. Ferris, H. A. & Kahn, C. R. New mechanisms of glucocorticoid-induced insulin resistance: make no bones about it. *J. Clin. Invest.* **122**, 3854–3857 (2012).
163. Mazziotti, G., Gazzaruso, C. & Giustina, A. Diabetes in Cushing syndrome: basic and clinical aspects. *Trends Endocrinol. Metabolism* **22**, 499–506 (2011).
164. Fong, A. C. & Cheung, N. W. The high incidence of steroid-induced hyperglycaemia in hospital. *Diabetes Res. Clin. Pract.* **99**, 277–280 (2013).
165. Ariaans, G. *et al.* Cancer-drug induced insulin resistance: innocent bystander or unusual suspect. *Cancer Treat. Rev.* **41**, 376–384 (2015).

166. Sonabend, R. Y. *et al.* Hyperglycaemia during induction therapy is associated with poorer survival in children with acute lymphocytic leukemia. *J. Pediatr.* **155**, 73–78 (2009).
167. Chow, E. J. *et al.* Glucocorticoids and insulin resistance in children with acute lymphoblastic leukemia. *Pediatr. Blood Cancer* **60**, 621–626 (2013).
168. Dool, C. J. *et al.* IGF1/insulin receptor kinase inhibition by BMS-536924 is better tolerated than alloxan-induced hypoinsulinemia and more effective than metformin in the treatment of experimental insulin-responsive breast cancer. *Endocr. Relat. Cancer* **18**, 699–709 (2011).
169. Gosmanov, A. R., Goorha, S., Stelts, S., Peng, L. & Umpierrez, G. E. Management of hyperglycaemia in diabetic patients with hematologic malignancies during dexamethasone therapy. *Endocr. Pract.* **19**, 231–235 (2013).
170. Yu, I. C., Lin, H. Y., Sparks, J. D., Yeh, S. & Chang, C. Androgen receptor roles in insulin resistance and obesity in males: the linkage of androgen-deprivation therapy to metabolic syndrome. *Diabetes* **63**, 3180–3188 (2014).
171. Laaksonen, D. E. *et al.* Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care* **27**, 1036–1041 (2004).
172. Bosco, C., Crawley, D., Adolfsson, J., Rudman, S. & Van Hemelrijck, M. Quantifying the evidence for the risk of metabolic syndrome and its components following androgen deprivation therapy for prostate cancer: a meta-analysis. *PLoS ONE* **10**, e0117344 (2015).
173. Keating, N. L., Liu, P. H., O'Malley, A. J., Freedland, S. J. & Smith, M. R. Androgen-deprivation therapy and diabetes control among diabetic men with prostate cancer. *Eur. Urol.* **65**, 816–824 (2014).
174. Keating, N. L., O'Malley, A. J., Freedland, S. J. & Smith, M. R. Does comorbidity influence the risk of myocardial infarction or diabetes during androgen-deprivation therapy for prostate cancer? *Eur. Urol.* **64**, 159–166 (2013).
175. Lubik, A. A. *et al.* Insulin increases *de novo* steroidogenesis in prostate cancer cells. *Cancer Res.* **71**, 5754–5764 (2011).
176. Gunter, J. H., Lubik, A. A., McKenzie, I., Pollak, M. & Nelson, C. C. The interactions between insulin and androgens in progression to castrate-resistant prostate cancer. *Adv. Urol.* **2012**, 248607 (2012).
177. Cully, M., You, H., Levine, A. J. & Mak, T. W. Beyond PTEN mutations: the PI3K pathway as an integrator of multiple inputs during tumorigenesis. *Nat. Rev. Cancer* **6**, 184–192 (2006).
178. Yap, T. A., Bjerke, L., Clarke, P. A. & Workman, P. Drugging PI3K in cancer: refining targets and therapeutic strategies. *Curr. Opin. Pharmacol.* **23**, 98–107 (2015).
179. Ma, C. X. *et al.* A phase I study of the AKT inhibitor MK-2206 in combination with hormonal therapy in postmenopausal women with estrogen receptor positive metastatic breast cancer. *Clin. Cancer Res.* http://dx.doi.org/10.1158/1078-0432.ccr-15-2160 (2016).
180. Busaidy, N. L. *et al.* Management of metabolic effects associated with anticancer agents targeting the PI3K-Akt-mTOR pathway. *J. Clin. Oncol.* **30**, 2919–2928 (2012).
181. Geuna, E. *et al.* Complications of hyperglycaemia with PI3K-AKT-mTOR inhibitors in patients with advanced solid tumours on phase I clinical trials. *Br. J. Cancer* **113**, 1541–1547 (2015).
182. Gopal, A. K. *et al.* PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N. Engl. J. Med.* **370**, 1008–1018 (2014).
183. Iams, W. T. & Lovly, C. M. Molecular pathways: clinical applications and future direction of insulin-like growth factor-1 receptor pathway blockade. *Clin. Cancer Res.* **21**, 4270–4277 (2015).
184. Haluska, P. *et al.* Safety, tolerability, and pharmacokinetics of the anti-IGF-1R monoclonal antibody figitumumab in patients with refractory adrenocortical carcinoma. *Cancer Chemother. Pharmacol.* **65**, 765–773 (2010).
185. Nellemann, B. *et al.* Growth hormone-induced insulin resistance in human subjects involves reduced pyruvate dehydrogenase activity. *Acta Physiol. (Oxford)* **210**, 392–402 (2014).
186. Yuen, K. C., Chong, L. E. & Riddle, M. C. Influence of glucocorticoids and growth hormone on insulin sensitivity in humans. *Diabet. Med.* **30**, 651–663 (2013).
187. Puzanov, I. *et al.* A phase I study of continuous oral dosing of OSI-906, a dual inhibitor of insulin-like growth factor-1 and insulin receptors, in patients with advanced solid tumors. *Clin. Cancer Res.* **21**, 701–711 (2015).
188. Rini, B. I. *et al.* Randomized phase III trial of temsirolimus and bevacizumab versus interferon alfa and bevacizumab in metastatic renal cell carcinoma: INTORACT trial. *J. Clin. Oncol.* **32**, 752–759 (2014).
189. Motzer, R. J. *et al.* Nivolumab versus everolimus in advanced renal-cell carcinoma. *N. Engl. J. Med.* **373**, 1803–1813 (2015).
190. Yang, P. *et al.* Paradoxical effect of rapamycin on inflammatory stress-induced insulin resistance *in vitro* and *in vivo*. *Sci. Rep.* **5**, 14959 (2015).
191. Verges, B. & Cariou, B. mTOR inhibitors and diabetes. *Diabetes Res. Clin. Pract.* **110**, 101–108 (2015).
192. Baselga, J. *et al.* Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N. Engl. J. Med.* **366**, 520–529 (2012).
193. Meacham, L. R. *et al.* Diabetes mellitus in long-term survivors of childhood cancer. Increased risk associated with radiation therapy: a report for the childhood cancer survivor study. *Arch. Intern. Med.* **169**, 1381–1388 (2009).
194. Holmqvist, A. S. *et al.* Adult life after childhood cancer in Scandinavia: diabetes mellitus following treatment for cancer in childhood. *Eur. J. Cancer* **50**, 1169–1175 (2014).
195. van Nimwegen, F. A. *et al.* Risk of diabetes mellitus in long-term survivors of Hodgkin lymphoma. *J. Clin. Oncol.* **32**, 3257–3263 (2014).
196. Ray, W. A. Evaluating medication effects outside of clinical trials: new-user designs. *Am. J. Epidemiol.* **158**, 915–920 (2003).
197. van Staa, T. P., Patel, D., Gallagher, A. M. & de Bruin, M. L. Glucose-lowering agents and the patterns of risk for cancer: a study with the General Practice Research Database and secondary care data. *Diabetologia* **55**, 654–665 (2012).
198. Jones, N. P., Curtis, P. S. & Home, P. D. Cancer and bone fractures in observational follow-up of the RECORD study. *Acta Diabetol* **52**, 539–546 (2015).
199. Wang, H. *et al.* NRF2 activation by antioxidant antidiabetic agents accelerates tumor metastasis.. *Sci. Transl. Med.* **8**, 334ra351 (2016).
200. Devaraj, S. & Maitra, A. Pancreatic safety of newer incretin-based therapies: are the "-tides" finally turning? *Diabetes* **63**, 2219–2221 (2014).
201. Bordeleau, L. *et al.* The association of basal insulin glargine and/or n-3 fatty acids with incident cancers in patients with dysglycemia. *Diabetes Care* **37**, 1360–1366 (2014).

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Competing interests statement
The authors declare no competing interest.