

Diabetes mellitus, hyperglycaemia and cancer

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Summary

A moderate increase of cancer risk has been shown in diabetic patients and in subjects with abnormal glucose tolerance, mainly in digestive sites, independently of obesity, with on the contrary a protective effect for prostate cancer. Insulin-resistance with compensatory hyperinsulinemia, and elevated levels of circulating growth factors are usually considered as the link between cancer and hyperglycaemia, through activated cell proliferation. Antidiabetic treatments inducing elevated plasma insulin seem to increase cancer risk and, on the opposite, insulin-sensitizers antidiabetic drugs (metformine, thiazolidinediones) seem to reduce cancer risk. In 2009, a big fuss has been raised concerning a specific action of glargine insulin to increase cancer risk from an observational study in Germany accumulating methodological pitfalls, without any clear confirmation from other studies.

Unexplained poor glycaemic control in known diabetic patients should lead to screen for a cancer, and diagnosis of cancer should not distract from appropriate management of diabetes care.

Greater public awareness about healthy lifestyles (diet, physical activity) is needed to prevent these two major increasing Public Health issues, and in the meanwhile should reduce the frequency of obesity and cardiovascular diseases in the whole population.

Keywords : type 2 diabetes, cancer, hyperinsulinemia, growth factors, epidemiology

Résumé

Sauf pour la prostate, il existe un risque modérément accru de cancer, en particulier digestif, chez les diabétiques de type 2 et chez les sujets ayant des anomalies frustes de la glyco-régulation, indépendamment de l'obésité. Le mécanisme le plus plausible passe par l'insulino-résistance avec hyperinsulinémie, et par l'influence de l'insuline et des facteurs de croissance circulants sur la prolifération cellulaire. Les traitements antidiabétiques entraînant une élévation de l'insulinémie semblent augmenter le risque de cancer et à l'inverse, les traitements antidiabétiques augmentant la sensibilité à l'insuline (metformine, glitazones) paraissent le diminuer. En 2009, une étude observationnelle en Allemagne a alimenté des rumeurs sur un rôle spécifique de l'insuline glargine qui augmenterait particulièrement le risque de cancer mais cette étude accumulait les erreurs méthodologiques et ses résultats n'ont pas été confirmés dans d'autres pays.

Il faut rechercher un cancer devant un déséquilibre inexplicé d'un diabète connu et traiter le diabète sans relâchement en cas de cancer chez un diabétique.

Des mesures de prévention s'imposent devant l'expansion de ces deux grands fléaux pour la Santé Publique, en proposant à toute la population des modifications du mode de vie (alimentation, activité physique) qui réduiront dans le même temps l'obésité et les maladies cardiovasculaires.

Mots-clés : diabète, cancer, hyperinsulinémie, facteurs de croissance, épidémiologie

An association between diabetes and cancer has been debated for many years; some of the older studies were biased and had other methodological limitations.. Many were based on national vital statistics, but as diabetes is often not mentioned on death certificates, even as an associated cause of death, this approach is not reliable [1]. . This could explain why, nearly thirty years ago, a study in United Kingdom concluded that the risk of death by cancer death was reduced in diabetic patients [1]. Over the past 20 years, it became clear that only prospective studies of representative samples of the population, with a long follow-up, are able to provide some answers to the association between diabetes and cancer [2]. Because of the observational nature of most of the studies, the issue is still debated. This prevents conclusions on potential causal relations, and allocation bias may not be completely eliminated by adjustment for confounding factors such as obesity or physical activity [3,4,5]. In addition, while pancreatic cancer and diabetes are associated, it is difficult to assess the time sequence of diabetes and cancer [6].

In this review, data from recent, large, prospective studies and from meta-analyses are presented. The putative pathophysiological mechanisms which could explain the link between cancer occurrence and diabetes are then discussed as well as the potential role of diabetes treatment to trigger cancer, or conversely to prevent cancer. The section on treatment describes the glargine data recently published on-line, the 26th June 2009 on the Diabetologia website [7-10]. The issue of diabetes and cancer has thus been put under the spotlight.

This review is focused on type 2 diabetes or hyperglycaemia and cancer risk. There are few studies of type 1 diabetes and cancer. A small Danish study from 1985 showed in insulin-treated diabetic patients, an increased risk of pancreatic cancer [11], with the usual difficulty to determine the time sequence of these two diseases. A more recent article from Sweden showed a modest excess risk for stomach, cervix and endometrium cancers in tpe 1 diabetes, with conclusions limited from several limitations in the study design and statistical analysis [12].

Epidemiological data on the association between diabetes or hyperglycaemia and cancer

Although there are many publications on this topic, only the more recent and the most informative studies are discussed, all studies on large populations. They all adjust for age and most of them adjust also for body mass index (BMI), the main confounder in the association between type 2 diabetes and cancer; the impact of BMI on mortality from cancer was documented in a large prospective study on more than 900 000 adults in the US [5].

Japanese study by Inoue [13]

A population based cohort of 97 771 Japanese men and women, 40-69 years [47% men, mean age: 52±8 yrs (m±sd)], were included in 1990-1994, and followed for 10.7 years, on average. Participants completed a self-questionnaire at inclusion (80% responded) and they were considered to be a diabetic patient if they responded positively to either question: “Has a doctor ever told you that you have any of the following diseases? – diabetes mellitus (yes/no)...” or “Do you take any anti-diabetic drugs ? (yes/no)”: 6.7% of men and 3.1% of women were thus considered to be diabetic patients. During follow-up, 6 462 cancers were newly diagnosed (3 907 in men, 2 555 in women) using notifications from the major hospitals in the study area, population-based cancer registries and death certificates. After multiple adjustment for potential confounders (age, body mass index, smoking, alcohol, coffee and green vegetables consumption, physical activity as well as study area, histories of cerebrovascular or ischemic heart diseases), men and women with diabetes had a significantly higher risk of cancer (all sites) than those without diabetes, with hazards ratio of 1.27 (95% Confidence Interval (95%CI): 1.14-1.42) in men, and 1.21 (0.99-1.47) in women (Table 1) [13]. In men, the hazards ratio for liver cancer risk was 2.24, for pancreatic cancer 1.85, for kidney cancer by 1.9 and for colon cancer 1.36, all four significantly increased (Table 1). In women, only liver cancer and stomach cancer were significantly increased in diabetic patients, with hazards ratios of 1.94 and 1.61 respectively, while breast cancer risk was reduced, with a hazards ratio 0.83 (0.44-1.57), not statistically significant (Table 1) [13].

For breast cancer in diabetic women, data are contradictory. In a recent study in Taiwan, the mortality rate ratio, in comparison to the general population, was 1.37 (1.16-1.62) in women 55-64 years and 1.99 (1.56-2.53) in women 75 years and over [14]. A meta-analysis of five case-control and 15 cohort studies showed a relative risk (RR) of 1.20 (1.12-1.28), similar to the mortality risk 1.24 (0.95-1.62) [15].

Swedish study by Stattin [16]

Incident cancer was studied in 64 597 Swedish men and women (48% men) without previously known diabetes, aged 40 to 60 yrs (46 ± 10 years at baseline), over 8.3 ± 3.6 yrs. At baseline, fasting plasma glucose (FPG) and 2-hr capillary plasma glucose (2-hr PG) after a 75-g glucose load were measured, with values of 5.4 ± 1.0 mmol/l and 6.6 ± 1.7 mmol/l respectively. Repeat measurements of fasting and post-load glucose 10 years later were available for nearly 10 000 subjects. During follow-up, 2 478 cancer cases were diagnosed (46% in men) Comparing the relative risk for the top vs bottom quartile group, glucose was not associated with all-site cancer in men, but there was a strong association in the women, and using the second measurements; this relative risk increased to 1.75% for FPG and 1.63 for 2-hr PG [16]. In contrast, in men, even after excluding prostate cancer, which was negatively associated with plasma glucose, there was no significant relationship between glucose and cancer incidence; further, there was no cancer risk in those with impaired fasting glucose, impaired glucose tolerance or diabetes compared with men with glucose in the normal range. For individual cancer sites, high FPG was significantly associated with pancreatic cancer, malignant melanoma and endometrial cancer, while for 2-hr PG only endometrial cancer was significantly more frequent in the women of the top quartile group (Table 2) [16].

Korean study by Jee [17]

In 1992 Korean government employees, teachers, and their dependents were required by the National Health Insurance Corp to participate in a biennial medical examination which included FPG measurement; with 95% participation: 1 298 385 men and women (64% men) aged 30 to 95 yrs (47 ± 12 years at baseline) were followed for 9.4 yrs on average, with 53 833 incident cancers diagnosed (70% in men) [17]. There was a significantly higher risk in those with $FPG \geq 7.8$ mmol/l in comparison to those with $FPG < 5.0$ mmol/l, for both men and women, for all incident cancers and for cancer mortality (Table 3), with, in both sexes, a significantly increased risk of death from pancreatic and liver cancers. In men only, there was increased risk of fatal colorectal cancer associated with FPG (Table 3). Adjustment for BMI did not change these findings and linear trends in cancer mortality with increasing FPG were observed in all BMI strata [17]. Comparison between diabetic patients (defined by antidiabetic treatment or $FPG \geq 7.0$ mmol/l) and subjects with $FPG < 5.0$ mmol/l showed similar data [17].

Austrian study by Rapp [18]

Between 1988 and 2001, 140 813 inhabitants (45% men) of Voralberg province in Austria, 35 to 54 years (43 ± 15 years at baseline), without known cancer, were included in an epidemiological survey, with FPG measurement at baseline (65% participation). During the 8.4 ± 3.8 yrs follow-up, 5 212 cancers were diagnosed. Taking as a reference the subjects in the 2nd and 3rd quartiles of FPG (4.2 and 5.2 mmol/l), in both sexes subjects having diabetes at inclusion (FPG ≥ 7.0 mmol/l) had a significantly increased risk for incident cancer and, combining men and women, a significantly increased risk for liver cancer and gall bladder and bile duct cancer (Table 4) [18].

Meta-analyses on the association between diabetes and prostate cancer [19, 20]

A first, well conducted meta-analysis which included 14 studies (9 cohort studies and 5 case-control studies) published between 1971 and 2002, showed a slight but significant reduction of risk to develop prostate cancer in diabetic patients, with a relative risk of 0.91 (0.85-0.98) for the five cohort studies and 0.92 (0.70-1.22) for the nine case-control studies [19]. This result was confirmed by a second meta-analysis [20] which included 19 studies, 12 of which were included in the first meta-analysis: the relative risk was 0.84 (0.76-0.93). Including only those studies after the introduction of screening by prostate-specific antigen, the relative risk was reduced to 0.73 (0.64-0.83) [20].

Synthesis of the epidemiological data on the diabetes/hyperglycaemia-cancer association

From the epidemiological studies, there seems to be a slight increase in cancer incidence and cancer mortality in diabetic patients compared to people without diabetes, subjects and among non-diabetic individuals with higher compared to lower plasma glucose levels. Prostate cancer is an exception as it appears to be less frequent.

The digestive tract is the main cancer location in diabetic patients and hyperglycaemic non-diabetic subjects, particularly cancers of the liver, colon and rectum, but also pancreatic cancer. For colorectal cancer, the English “EPIC-Norfolk Study”, general population cohort, confirmed an increased risk for cancer incidence at 6 years in diabetic patients, with an age, sex, BMI, smoking adjusted relative risk: 2.78 (1.10-7.00). There was also a continuous association between HbA1c and colorectal cancer risk, with the lowest rates in those with HbA1c $< 5\%$ [21], and per 1% absolute increase in HbA1c the relative risk was 1.34 (1.12-1.59), after adjustment for age, sex, BMI and tobacco consumption [21]. This “dose-response” relationship, also observed in the Korean study [17], provides a strong argument that there

may be a causal link between high glycaemic level or diabetes and cancer and that the association probably is not just due to confounding factors, despite the fact that these studies are observational.

In any chronic disease, a diabetic patient has closer medical care than a healthy individual, with more frequent medical consultations, thus there is a higher probability of systematic cancer screening tests. However, a screening bias is unlikely to explain the diabetes-cancer association because of the increasing risk seen in general populations, between glycaemic level and cancer.

Speculative mechanisms for the link between glycaemic level and cancer

Several hypotheses have been proposed to explain the link between glycaemic level and cancer (Figure 1).

A common mechanism could induce both type 2 diabetes and cancer: type 2 diabetes and cancer are just associated, without any direct link, and no causal relationship. For example, environmental or lifestyle factors could contribute at the same time to type 2 diabetes and to cancer. It could be diet - around 35% of cancers in the US are attributable to dietary habits [22] and populations eating a lot of vegetables and fruit, with a low intake of animal fat and total calories, develop cancers less frequently [23]; these dietary habits have been shown to prevent or delay type 2 diabetes incidence [24-26]. Alternatively, physical activity could be the environmental factor, which is well known to be beneficial for cancer prevention [27], probably through hormonal modifications, and it has also been shown as an efficient “treatment” in type 2 diabetes prevention in various populations [24-26]. Diet and physical activity could be confounding factors in the link between diabetes and hyperglycaemia and cancer, but adjustment for BMI in the studies reported above make it difficult to believe diet and physical activity could completely explain the association between diabetes and hyperglycaemia and cancer.

The pathophysiological hypotheses to explain the link between diabetes or hyperglycaemia and cancer rely on biological, particularly hormonal, mechanisms involving insulin-resistance. Indeed, in the genesis of type 2 diabetes, reduced insulin sensitivity plays a key role, inducing compensatory hyperinsulinism with an increased level of circulating Insulin-like Growth Factors (IGF), well known to stimulate cell proliferation in many organs, including the liver, pancreas, colon, ovary, breast [28,29], the sites with an increased risk of cancer in type 2 diabetic patients. This effect is enhanced by the action of insulin in excess, to bind and to activate the IGF-1 receptor and to reduce the level of the binding protein IGF-

BP1, leading to increased levels of circulating free IGF-1 [30]. Prospective studies have shown cancer mortality to be predicted by high levels of insulin [31] and growth hormone (GH) [32], (both from the Paris Prospective Study) and of IGF1 in the Rancho Bernardo Study [33]. In the Paris Prospective Study, 6 237 policemen with a mean age of 47 years at baseline (range: 44-55 years), with a mean follow-up of 23.8 years, 1 739 died with 778 deaths by cancer, including 25 by liver cancer. Both fasting insulin and insulin measured 2-h after an OGTT were significantly associated with fatal liver cancer, with hazards ratios adjusted for age and BMI 2.45 (1.63-3.70) and 3.05 (1.95-4.77) respectively, with an insulin dose-response relationship [31]. In this study, insulin was negatively associated with fatal lip, oral cavity, and pharynx cancer, stomach cancer, and larynx cancer, probably due to a confounding effect of alcohol consumption which was not accurately assessed [31]. In a subgroup of 864 policemen of the Paris Prospective Study, serum GH was measured at baseline on fasting (median value = 0.5 µg/l) and at 2-hours after an OGTT (95^{ème} percentile: 1.1 µg/l) and 171 died (64 by cancer) after a mean follow-up of 18 years. After having excluded three men with a high GH level, probably due to acromegaly, all-cause mortality was associated with fasting GH > 0.5 µg/l ($P = 0.02$) and with 2-hr GH > 1.1 ng/ml ($P = 0.004$) and age and BMI-adjusted hazards ratio of cancer death for 2-hr GH > 1.1 ng/ml was significantly increased: 2.59 (1.17-5.73; $P = 0.04$) [32]. In the Rancho Bernardo Study, 633 men aged 73.4±7.5 years had serum IGF-1 measured at baseline, and 368 died with 74 deaths by cancer during the 18-year follow-up. A positive association was found between IGF-1 levels (median value 96 ng/ml) and all-cancer mortality ($P = 0.039$). For the 46% of men with IGF-1 above 100 ng/ml, the adjusted hazards ratios of fatal cancer was 1.82 (1.11-2.96) compared with to men with lower levels; the risk of cancer mortality gradually increased with higher IGF-1 levels, with an adjusted hazards ratio of 1.61 (1.28-2.02) for IGF-1 120-159 ng/ml, 2.05 (1.41-2.98) for 160-199 ng/ml and 2.61 (1.46-4.64) for IGF-1 ≥ 200 ng/ml [33]. Overall, there are convergent arguments to consider that hyperinsulinemia plays a pivotal role in the association between diabetes or hyperglycaemia and cancer. This hypothesis is also supported by the association between the different types of diabetes treatments and cancer risk as shown below.

The reduced risk for prostate cancer in diabetic men, could be due to the lower level of plasma androgens in type 2 diabetic men [34], as higher androgens levels are known to be associated with an increased risk of prostate cancer [35]. Furthermore, a genetic mechanism could be involved, as there are genes associated with the risk for both diseases; in particular

an HNF-1B allele carries a risk for type 2 diabetes but is protective against prostate cancer [36].

Treatment of type 2 diabetes and cancer

Before the “glargine controversy”, a potential role for pharmacological treatments of type 2 diabetes in cancer had been suggested from pharmaco-epidemiological studies. The largest, population-based and prospective study is from the Saskatchewan province in Canada [37]. The database covers 90% of the residents of the province, with 900 000 individuals; it includes information on drug prescriptions. In this region, a cancer registry, hospital charts and vital statistics are well validated. Between 1991 and 1996, 10 309 new sulfonylurea (SU) or metformin users, aged 30 years or over, who received treatment for diabetes for at least one year, were identified and then followed over 5.4 ± 1.9 years: 55% were men, and the mean age was 63 ± 13 years. The two treatment cohorts were generally comparable, although the SU cohort was significantly older (66.9 ± 13.1 vs 61.8 ± 13.1 years, $P < 0.0001$) and included more men (59% vs 54%, $p < 0.0001$), but the metformin cohort was more likely to also be treated by insulin (16.3% vs 9.2%, $p < 0.0001$). Within the metformin cohort, 82% of the patients eventually used a combination of SU and metformin therapy. Overall, the mean number person-years of follow-up was 39 026 for metformin and 16 700 for SU. Crude cancer mortality rates were 4.85% (162 out of 3 340) for SU users and 3.52% (245 out of 6 969) for those initially treated by metformin ($P = 0.001$), corresponding to cancer mortality rates of 6.3 and 9.7 per 1 000 patient-years for metformin and SU cohorts respectively and a crude HR for cancer mortality of 1.6 (1.3-1.9; $P < 0.0001$) for the SU vs the metformin cohort. In multivariate Cox regression analyses, adjusted for age, sex, insulin use and co-morbidity, the SU cohort had a significantly higher cancer-related mortality compared with the metformin cohort with an adjusted hazards ratio of 1.3 (1.1-1.6; $P = 0.012$). In addition, patients treated by insulin as add-on to SU or to metformin ($n = 1443$) had a cancer death rate of 9.9 per 1 000 patient-years vs 6.8 per 1 000 patient-years for those without insulin use, with a multiple adjusted hazards ratio of 1.9 (1.5-2.4; $P < 0.0001$) for insulin use, and a gradual increased risk for cancer death with higher insulin exposure [37]. This study has some limitations: it examined only cancer mortality and not cancer incidence; differences in patient characteristics could intervene as confounding factors in the cancer/diabetes treatment relation, such as glycaemic control, BMI, tobacco consumption, which were not recorded. In addition, as

acknowledged by the authors, their data do not indicate whether the results come from a protective effect of metformin or deleterious effects of SU and insulin [37].

Indeed, the hypothesis of a protective effect of metformin on cancer through activation of AMPK, itself activated by the LKB1 protéine kinase, known to have an anti-tumor action [38, 39] had led Scottish authors to conduct a pilot case-control study which was published one year before the Saskatchewan study [40]. They used record linkage of databases, developed in Tayside, covering 314 127 residents of this area in 1993-2001, with 11 876 newly diagnosed type 2 diabetic patients during this period. Among them, 923 patients were hospitalized during the study period for a newly diagnosed cancer, at least one year after diabetes diagnosis. Each individual with cancer and with type 2 diabetes, a case, was compared with two randomly selected controls with diabetes but without cancer, matched on age, year of diabetes diagnosis and sex. Previous use of metformin was compared between the two groups: 36.4% in cases and 39.7% controls in the preceding year, with a crude odds ratio of 0.86 (0.73-1.02), while the crude odds ratio for any exposure to metformin from 1993 was 0.79 (0.67-0.93). Adjustment for confounding factors such as tobacco consumption (data available for 73% patients), BMI (available for 62%), blood pressure (available for 67%) and socio-economic status (available for 99%) did not greatly affect the risk estimates, with odds ratios 0.85 (0.71-1.01) for metformin use in the preceding year and 0.77 (0.64-0.92) for its use from 1993. In addition, a clear dose-response effect was seen between metformin use and cancer risk [40]. This pilot study has been followed by an observational cohort study in the same Tayside region in Scotland [41]. Using record-linkage, after excluding diabetic patients with known cancer, 4085 type 2 diabetic patients aged ≥ 35 years newly treated by metformin in 1994-2003 were identified and compared with 4085 type 2 diabetic patients aged ≥ 35 years who had never used metformin, matched for the year of diabetes diagnosis. Cancer was diagnosed in 7.3% of the metformin users and 11.6% in the non-metformin users, with a median time to cancer of 3.5 and 2.6 years respectively ($P < 0.001$). The unadjusted hazards ratio (HR) for cancer was 0.46 (0.40-0.53). After adjusting for age, sex, BMI, HbA1c, smoking, deprivation, SU and insulin use, using a Cox model, there was still a significant reduction of cancer risk associated with metformin, with an adjusted hazards ratio: 0.63 (0.53-0.75) [41]. A decreased risk was found for specific cancer sites: lung, breast and bowel cancer, but only the latter reached statistical significance with an adjusted hazards ratio: 0.60 (0.38-0.94). Overall mortality was also significantly reduced under metformin with an adjusted hazards ratio: 0.42 (0.38-0.47). In addition, after 2 years of metformin treatment, a dose-response effect appeared in metformin users [41]. Similar results were observed for the

association between metformin use and cancer death in a recent Dutch prospective, observational, study which enrolled in 1998-9, 289 type 2 diabetic patients treated by metformin (age: 67±11 yrs, diabetes duration: 4.9 yrs) and 1064 type 2 diabetic patients without metformin use (age: 68±12 yrs, diabetes duration: 7.1 yrs) [42]. After a median follow-up of 9.6 years, 570 patients had died (122 by cancer). Compared to the general population, the standardized mortality rate by cancer was 1.47 (1.22-1.76) for diabetic patients, but was non-significantly decreased to 0.88 (0.51-1.44) in patients using metformin, and 1.62 (1.32-1.96) in diabetic patients not using metformin. Multivariate analysis using the Cox model with adjustment for age, sex, BMI, diabetes duration, HbA1c, smoking, use of SU and insulin showed an adjusted hazards ratio for cancer death of 0.43 (0.23-0.80) for metformin users vs non users, and a dose-response effect was found with, for every increase of 1g of metformin, a hazards ratio: 0.58 (0.36-0.93) [42].

The influence of insulin therapy on colorectal cancer incidence in type 2 diabetic patients has been studied in the United Kingdom between 1987 and 2002, using the General Practice Research Database [43]. They studied patients with more than three years of follow-up after diabetes diagnosis and excluded patients diagnosed with colorectal cancer in the first three years after diabetes diagnosis, patients who had less than one year of insulin therapy, and patients who developed colorectal cancer after less than one year of insulin therapy; the incidence of colorectal cancer in insulin users was 197 per 100 000 patient-years vs 124 per 100 000 patient-years without insulin treatment. The age- and sex-adjusted hazards ratio associated with ≥ 1 year of insulin use was 2.1 (1.2-3.4; $P = 0.005$). A nested case-control study showed that for each incremental year of insulin therapy, an odds ratio of 1.21 (1.03-1.42; $P = 0.02$) [43].

For thiazolidinediones (TZD), few studies are available due to their recent arrival on the market. In the randomized PROActive study, over a 3-year follow-up, a significant protective effect was found for breast cancer in the pioglitazone group compared to the control group receiving placebo (0.12% vs 0.42%; $P = 0.034$), but an increased, marginally significant, risk for bladder cancer was observed under pioglitazone ($P = 0.069$) [44]. A retrospective analysis of a database from ten Veteran Affairs medical centres in the US showed a significant reduction in lung cancer (adjusted for age, ethnicity, BMI, use of insulin and other diabetic treatments) with a relative risk of 0.67 (0.51-0.87), while colorectal and prostate cancers were also reduced without reaching statistical significance [45]. A meta-analysis of 80 randomized clinical trials of rosiglitazone with duration > 24 weeks, with only five studies of more than 52 weeks duration, showed that rosiglitazone was not associated

with a significant reduction in the risk of all-cancer incidence, as the odds ratio was 0.91 (0.71-1.16; $P = 0.44$), with the greatest reduction, still non-significant, for lung cancer incidence with an odds ratio of 0.67 (0.30-1.51) [46]. However, as the largest trial in the analysis (the ADOPT trial) had a longer follow-up in the rosiglitazone arm than in the comparators [47], the authors also calculated the actual incidence density of cancer in different treatment groups and found a significant lower incidence of malignancies in the rosiglitazone-treated patients than in the comparators: 0.23 (0.19-0.26) vs 0.44 (0.34-0.58) cases per 100 patient-years ($P < 0.05$) [46].

Most of the studies reported are observational, making it difficult to conclude in terms of causality. Indeed, allocation bias is frequent and may be the rule in such studies, as diabetes treatments are not chosen at random by the physician, who takes into account patient characteristics before deciding on the drug(s) to prescribe. Thus, in observational studies, treatment groups may differ at baseline and adjustments (or matching in case-control studies) for known confounders can only reduce, not eliminate, biases, and unknown confounders cannot be adjusted for. Nevertheless, it seems that a protective effect of insulin-sensitizers (metformin, and to a lesser extent TZDs) for cancer and, in contrast, a negative impact of insulin itself or insulin-secretagogues such as the SU on cancer risk, are highly consistent with the pathophysiological mechanisms suggested previously to explain the increased risk of cancer in type 2 diabetic patients and hyperglycaemic subjects. Indeed, for diabetes treatment as for diabetes per se., hyperglycaemia and hyperinsulinemia appear to play pivotal roles in cancer risk.

Concerning diabetes treatments and prostate cancer, a Finnish case-control study showed an identical decreased risk with the various diabetic oral agents and insulin, and the odds ratio for prostate cancer decreased in a dose-dependent fashion for all diabetes drugs [48]. The duration of the diabetes treatment was inversely associated with overall prostate cancer and the risk of advanced cancer. They concluded that diabetes, instead of the medication itself, is the reason for the diabetes-cancer association. The finding of a negative association between prostate cancer and diabetes duration supports the hypothesis of a hormonal mechanism in the protection for prostate cancer in diabetic patients [34, 49].

The “insulin glargine controversy”

This controversy started with the paper published by Hemkens et al. [7] who aim investigated the risk of malignant neoplasms and mortality in diabetic patients treated either with human insulin or with one of the three insulin analogues. The hypothesis was that the increased

mitogenic potency of insulin analogues, mainly glargine insulin, compared to human insulins, as seen in cell experiments [50], could also induce an increased risk for cancer in diabetic patients treated by these insulin analogues. The study used the database from the largest health insurance fund in Germany, the Allgemeine Ortskrankenkasse (AOK). The study included patients without known cancer, for whom insulin treatment was started during between January 1998 and June 2005: treated only by human insulin (NPH*) (n = 95 804) or aspart (NovoRapid*) (n = 4 103) or lispro (Humalog*) (n = 3 269) or glargine (Lantus*) (n = 23 855). These 127 031 diabetic patients were followed for a mean 1.63 years (median: 1.41 years; maximum follow-up: 4.41 years) with overall 5 009 incident cases of cancer and 18 253 deaths. A positive association was found between cancer incidence and insulin dose, whatever the insulin type. The annual cancer incidence and death rate were higher with human insulin (2.50 and 9.24 per 100 patient-years respectively) and lower but similar for those treated with the three insulin analogues: 2.16 for aspart, 2.13 for lispro and 2.14 for glargine, with death rates of 5.75, 6.91 and 6.30 respectively; the daily insulin doses used were lower with glargine (25.9±22.5 U/d), in particular compared with human insulin (43.8±37.4 U/d). The authors compared the cancer and mortality risk at different levels of insulin doses, using numerous statistical models to take into account differences in the baseline characteristics of the four insulin treated groups. With human insulin treatment as a reference, no statistical difference was shown for aspart and lispro for cancer and mortality risk, whatever the dose used. In contrast, for insulin glargine, compared with human insulin, at each dose reported (10, 20 and 50 U/d), there was a significant increase in cancer risk, with adjusted (for all covariates and interactions) hazards ratios of 1.09 (1.00-1.19) at 10 U/d, 1.19 (1.10-1.30) at 30 U/d and 1.31 (1.20-1.42) at 50 U/d while mortality risk was significantly decreased with insulin glargine at 10 U/d with adjusted hazards ratio 0.76 (0.70-0.83), not significantly decreased at 30 U/d with adjusted hazards ratio 0.96 (0.90-1.01) but significantly increased at 50 U/d with hazards ratio 1.20 (1.11-1.30), always in comparison with human insulin [7]. No information was available about cancer sites nor about the type of diabetes, BMI nor glycaemic control. The authors conclude that their 'results based on observational data, support safety concerns surrounding the mitogenic properties of glargine in diabetic patients', because given 'the overall relationship between insulin dose and cancer, and the lower dose with glargine, the cancer incidence with glargine was higher than expected compared with human insulin' [7]. Indeed, as soon as the paper was online on June 26th 2009, there have been many comments [51-54] but the replies from the authors have not been convincing [55]. A major concern was the contrast between the crude cancer incidence and

death rates, favourable to insulin glargine compared to human insulin, and the data reported comparing the insulin types at different levels of insulin doses. Over adjustment for insulin dose should be considered. Unfortunately, Hemkens et al did not report data concerning weight (to adjust insulin dose between the four insulin treatment groups), nor glycaemic control. If identical glycaemic control had been obtained in the treatment groups, with a lower dose in insulin glargine users, adjustment for insulin dose would not have been appropriate. However, three randomized clinical trials in which insulin glargine and NPH insulin were up-titrated to reach identical glycaemic targets have shown that similar doses of insulin glargine were needed as for human insulin [56-58]. Therefore, the hypothesis of over-adjustment can be ruled out, and it can be deduced that poorer glycaemic control was achieved in the insulin glargine-treated group in the study by Hemkens et al. [7]. It is thus important to understand the reason why a higher glycaemic target was set for the patients treated with insulin glargine. As a positive association between the length of exposure to high levels of plasma glucose and the risk of developing diabetes-related microvascular complications has been demonstrated [59] and is well known by physicians, the most probable explanation for the less ambitious glycaemic control aimed for in the insulin glargine-treated group may be that these patients were considered by their practitioners to have a shorter life expectancy than those treated by other insulin regimens. This suggests an allocation bias may be present in the Hemkens et al. study [7]. As the insulin glargine users were not older than the human insulin users (69.5 ± 11.6 vs 69.6 ± 13.1 years, respectively), it probably means that they were in worse health. This is not obvious from the few baseline characteristics shown in the paper by Hemkens et al., which were used for multiple adjustments. Therefore, one can only speculate on the reasons why physicians considered the insulin glargine-treated patients had a shorter life-expectancy, and we can suppose that characteristics differed between the two groups at baseline that could not, unfortunately, be adjusted for. As the authors conclude that there is a higher cancer incidence during the very short follow-up period (mean 1.63 years, median 1.41 years), a possible explanation, the simplest, is that, at least for some of the diabetic patients treated with insulin glargine, the practitioner knew they had a cancer, that was not yet registered in the health insurance fund. Indeed, this provocative suggestion becomes plausible when one examines the procedures used to select 'adult patients without known malignant disease', as the authors state that they 'considered participants to be without known malignant disease if they had not received a corresponding diagnosis within 3 years prior to inclusion in the study', and that they 'excluded participants with the slightest suspicion of a malignant disease (e.g. patients with the ICD-10 [International Classification of Diseases, 10th revision,

German Modification] diagnosis Z03.1—observation for suspected malignant neoplasm)’ [7]. This information implies that the coding forms in the hospital records were the only source for diagnosing a previous cancer and to exclude an insulin-treated diabetic patient. Table 1 of the German paper [7] shows that the insulin glargine-treated patients had been hospitalised less often than the human insulin users in the three preceding years (35.5% had one or two hospital stays, and 16.2% had more than two hospital stays vs 41.3% and 23.4%, respectively, $p < 0.0001$). Thus, the explanation for the results reported could be that some diabetic patients having a recent cancer were included by error. Their practitioner knew they had cancer, treated them with insulin glargine and set the glycaemic target at a higher level, using lower insulin doses. As they had not yet been hospitalised, cancer had not been notified to the health insurance fund. An important point is the very short treatment duration to induce tumor development. Another major criticism comes from the methods and this has ethical consequences. In spite of multiple comparisons and multiple models, we are told that because the study was intended to generate hypotheses, no adjustments were made for multiple testing’ [7], and a paper whose author list includes Bender, a co-author of the Hemkens et al. study, is cited to justify that decision [60]. In the paper by Bender and Lange it is written that ‘ “Significant” results based upon exploratory analyses should clearly be labelled as exploratory results. To confirm these results the corresponding hypotheses have to be tested in further confirmatory studies.’ [60]. Indeed, even if we can accept this opinion, which could be challenged, it is unacceptable in the situation of diabetes treatment and cancer risk, as no confirmatory study using a randomised design can be performed now or in the future to validate, or, more probably, to refute the hypothesis of a causal association between insulin glargine and cancer risk, for obvious ethical and practical reasons. This opinion is not shared by the authors who replied “We think that a randomised controlled trial has been, and still is, theoretically possible, if patients at risk of cancer would give their informed consent to be randomly allocated to insulin glargine or human insulin” [55]. Indeed, while ethics policy differ widely from one country to another country, it is unlikely that diabetic patients, anywhere in the world, would accept to give informed consent to participate in a study aiming to assess if a treatment can induce cancer or not [54]. To have raised a scientific issue that can never be resolved, by using a flawed methodology, is unethical. In conclusion, probably the right and safe decision would have been to adopt the opinion of the three of the six referees who initially recommended rejection [61], and not publish the study by Hemkens et al., especially given that the Editorial accompanying the publication states: ‘There is no evidence of an overall increase in the rate of cancer development in patients on insulin glargine, and

some suggestion that the risk may actually be reduced.’ [61]. Unfortunately, the news of these results spread quickly, and troubled for a long time, probably forever, many diabetic patients who were using glargine insulin, often with great satisfaction, as well as their care providers.

The German paper had been received by Edwin Gale, the Chief-Editor of *Diabetologia* in August 2008 and a special advisory group, convened by the EASD, agreed that it would be premature to publish the German findings in isolation, and that replication was needed [61]. Therefore, three other observational analyses were commissioned to examine the safety of insulin glargine. These studies were published on-line at the same time, on June 26th 2009, and in the September 2009 issue of *Diabetologia* [8-10].

The Swedish study included 114 841 patients (type 1 diabetic patients: 15.3%), who were prescribed insulin during the second trimester 2005 (5 970 glargine only, 20 316 glargine associated with other insulins and 88 555 insulins other than glargine), then recorded cancer occurrence in 2006-2007, using high-quality national cancer and causes of death registers [8]. Compared to other insulins, no significant increase of cancer risk was observed with glargine alone nor with glargine associated with other insulins, with relative risks of 1.06 (0.90-1.25) and 1.02 (0.91-1.15) respectively. However, in women a significantly increased risk of breast cancer was observed with glargine alone, with an adjusted relative risk of 1.97 (1.30-3.00), without a dose-response relationship, while a non-significant increase was seen with glargine associated with other insulins, relative risk 1.17 (0.81-1.68) [8]. In contrast, for women, all-cause death was significantly reduced with glargine alone [relative risk 0.83 (0.71-0.96)] and when associated with other insulins [0.87 (0.77-0.97)], with reference to insulins other than glargine. Furthermore, for women the relative risk of myocardial infarction was also significantly reduced with glargine alone [0.77 (0.59-1.00)] and glargine associated with other insulins [0.88 (0.74-1.05)] [8]. In their conclusion, the Swedish authors consider the results on breast cancer to be inconsistent and probably due to random fluctuations, explained by the multiple comparisons and statistical tests they performed [8].

The Scottish study used a nationwide diabetes clinical database that covers the majority of the Scottish population with diagnosed diabetes, and examined patients with diabetes who were exposed to any insulin therapy between January 1st January 2002 and December 31st 2005, thus including 49 197 insulin-treated patients (type 2 diabetic patients: 73.7%) [9]. As in the Swedish study, comparisons were between 3 groups of insulin-treated patients: those using glargine alone, those using glargine associated with other insulins and those treated by other insulins than glargine. Two sub-studies were conducted, one on a fixed cohort based on exposure during a four month period in 2003 (n = 36 254 in whom 715 cases

of cancer occurred) and the other on a cohort of new insulin users across the period (n = 12 852 in whom 381 cancers occurred). In the fixed cohort, no increase of cancer incidence was found in those receiving any insulin glargine compared with those not receiving insulin glargine, with hazards ratio 1.02 (0.77-1.36), but the data were contradictory between the two glargine subgroups, those with glargine alone having an adjusted hazards ratio of 1.55 (1.01-2.37), while those with glargine associated with other insulins had an adjusted hazards ratio 0.81 (0.55-1.18). A similar difference was observed for breast cancer (n = 81 for insulins other than glargine, n = 6 for glargine alone, n = 5 for glargine associated with other insulins) with hazards ratios: 1.49 (0.79-2.83) for combined glargine treatment, 3.39 (1.46-7.85) with glargine alone and 0.87 (0.34-2.17) with glargine associated with other insulins, compared with insulins other than glargine. In addition, in the second cohort of new insulin users, there was no significant difference between the three treatment groups, with respect to all cancer or to breast cancer [9]. The Scottish authors conclude that “overall, insulin glargine use was not associated with an increased risk of all cancers or site-specific cancers in Scotland over a 4 year time frame. Given the overall data, we consider the excess of cases of all cancers and breast cancer in the subgroup of insulin glargine only users to more likely reflect allocation bias rather than an effect of insulin glargine itself” [9].

The third study was a retrospective cohort study in UK was conducted through the Health Information Network (THIN), of patients treated by general practitioners [10]. They included 62 809 diabetic patients diagnosed after age 40, who started a treatment by oral diabetic drugs or insulin from year 2000, among whom 2 106 developed a cancer (annual incidence: 1.1%). Data were analyzed according to four treatment groups: metformin only, SU only, association of metformin and SU, and changing from oral drugs to insulin, this last group being split further, to assess glargine alone. Diabetic patients without pharmacological treatment were also included, and they had a similar hazards ratio to patients treated by metformin monotherapy, who had the lowest risk of cancer. In comparison to patients treated with metformin, the adjusted hazards ratios were 1.36 (1.19-1.54) with SU only, 1.08 (0.96-1.21) with metformin and SU associated and 1.42 (1.27-1.60) with insulin treatment in patients previous treated with oral drugs. Adding metformin to insulin was associated with a significant reduction of cancer risk with a hazards ratio of 0.54 (0.43-0.66). Concerning the type of insulin, no difference was seen for cancer risk: taking glargine only as a reference, the adjusted hazards ratios were 1.24 (0.90-1.70) for human basal insulin (NPH), 0.88 (0.66-1.19) with human biphasic and 1.02 (0.76-1.37) with analogue biphasic. As to the different sites of cancer, compared with metformin, insulin significantly increased the risk for colorectal cancer

with adjusted hazards ratio 1.69 (1.23-2.33) and for pancreatic cancer: 4.63 (2.64-8.10), but not the risk of breast cancer 1.07 (0.79-1.44) nor of prostate cancer 1.10 (0.79-1.52); SU were associated with similar risks to insulin. As to breast cancer, its risk was slightly decreased, not significantly, with glargine alone compared to overall non-glargine insulins, with a hazards ratio of 0.86 (0.42-1.75) [10].

Conclusion

An association between type 2 diabetes or hyperglycaemia and the risk of cancer appears to exist, with a gradually increased risk of cancer, in particular for cancers of the digestive tract, with increasing glycaemic levels. In contrast, for prostate cancer, hyperglycaemia appears to carry a lower risk. A causal relationship is probable, with a key role played by hyperinsulinemia and growth factors, independently of (and in addition to) the risk of cancer linked with obesity. In addition to the few studies directly demonstrated the association between cancer and insulin, GH and IGF-1, this hypothesis is supported by many studies showing a deleterious influence on the risk cancer of diabetic treatments inducing hyperinsulinemia and, in contrast, the protective effect of insulin-sensitizing drugs such as metformin and perhaps the thiazolidinediones. Indeed, these data need to be confirmed by other large prospective pharmaco-epidemiological studies. Probably they will also confirm that the “glargine controversy” raised by a flawed German study can be forgotten, but this could be difficult for diabetic patients who have heard and read about the study.

Although this review on the risk of cancer in diabetic patients, is exciting in its epidemiological aspects as in its speculative pathophysiological mechanisms, it must be remembered that the priority in the care of type 2 diabetic patients is to avoid micro- and macro-vascular complications, particularly cardiovascular morbidity and mortality; death from cardiovascular disease is two fold higher than death by cancer in diabetic populations [62].

In addition, as obesity, metabolic disorders including diabetes, cardiovascular diseases and cancers are increasing all over the world, it is urgent to implement, prevention programmes aiming at improving lifestyle in the whole population, in both developed and developing countries, to reduce the impacts on individuals and on society of these major increasing public health issues [63,64].

CONFLICTS OF INTEREST

Dominique Simon has served as a speaker for Glaxo-Smith Kline, sanofi-aventis, Servier; and on advisory panels for Astra-Zeneca, Bristol Myers Squibb, Glaxo-Smith Kline and Novartis.

Beverley Balkau has served as a speaker for sanofi-aventis and on advisory panels for Astra Zeneca, Bristol Myers Squibb and sanofi-aventis, and has research funding from Abbott.

FIGURE LEGEND

Pathways for the association between diabetes and cancer

References

- [1] Fuller JH, Elford J, Goldblatt P, Adelstein AM. Diabetes mortality: new light on an underestimated public health problem. *Diabetologia* 1983;24:336-41
- [2] Green A, Hougaard P. Epidemiological studies of diabetes mellitus in Denmark. 5. Mortality and causes of death among insulin-treated diabetic patients. *Diabetologia* 1984;20:468-70
- [3] Steenland K, Nowlin S, Palu S. Cancer incidence in the National Health and Nutrition Survey I. Follow-up data: diabetes, cholesterol, pulse, and physical activity. *Cancer Epidemiol Biomarkers Prevention* 1995;4:807-11
- [4] Shoff SM, Newcomb PA. Diabetes, body size, and risk of endometrial cancer. *Am J Epidemiol* 1998;148: 234-40
- [5] Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *N Engl J Med* 2003;348:1625-38
- [6] Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer* 2005;92:2076-83
- [7] Hemkens LG, Grouven U, Bender R, Günster C, Gutschmidt S, Selke GW, et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. *Diabetologia* 2009;52:1732-44
- [8] Jonasson JM, Ljung R, Talbäck M, Haglund B, Gudbjörnsdóttir S, Steineck G. Insulin glargine use and short-term incidence of malignancies – a population-based follow-up study in Sweden. *Diabetologia* 2009;52:1745-54
- [9] Colhoun HM, SDRN Epidemiology Group. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. *Diabetologia* 2009;52:1755-65
- [10] Currie CJ, Poole CD, Gale EAM. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia* 2009;52:1766-77
- [11] Green A, Jensen OM. Frequency of cancer among insulin-treated diabetic patients in Denmark. *Diabetologia* 1985;28:128-30
- [12] Zendejdel K, Nyrén O, Östenson CG, Adami HO, Ekblom A, Ye W. Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. *J Nat Cancer Inst* 2003;23:1797-1800

- [13] Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S, for the Japan Public Health Center-based Prospective Study Group. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. *Arch Int Med* 2006;166:1871-7
- [14] Tseng CH, Chong CK, Tai TY. Secular trend for mortality from breast cancer and the association between diabetes and breast cancer in Taiwan between 1995 and 2006. *Diabetologia* 2009;52:240-6
- [15] Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. *Int J Cancer* 2007;121:856-62
- [16] Stattin P, Björ O, Ferrari P, Lukanova A, Lenner P, Lindahl B G, et al. Prospective study of hyperglycemia and cancer risk. *Diabetes Care* 2007;30:561-7
- [17] Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* 2005;293:194-2002
- [18] Rapp K, Schroeder J, Klenk J, Ulmer H, Concin H, Diem G, et al. Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. *Diabetologia* 2006;49:945-52
- [19] Bonovas S, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: a meta-analysis. *Diabetologia* 2004;47:1071-8
- [20] Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2006;15:2056-62
- [21] Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Preliminary communication: glycated haemoglobin, diabetes, and incident colorectal cancer in men and women: a prospective analysis from the European Prospective Investigation into Cancer-Norfolk Study. *Cancer Epidemiol Biomarkers Prev* 2004;13:915-9
- [22] Doll R. The lessons of life: keynote address to the nutrition and cancer conference. *Cancer Res* 1992;52 (7 Suppl.):2024S-9S
- [23] International Agency for Research on Cancer: IARC handbooks of cancer prevention. Vol.8: Fruit and vegetables. Lyon, France 2003
- [24] Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and diabetes study. *Diabetes Care* 1997;20:537-44
- [25] Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al., for the Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl*

J Med 2001;344:1343-50

- [26] Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393-403
- [27] Friedenreich CM. Physical activity and cancer prevention: from observational to intervention research. *Cancer Epidemiol Biomarkers Prev* 2001;10:287-301
- [28] Khandwala HM, McCutcheon IE, Flyvberg A, Friend KE. The effects of insulin-like growth factors on tumorigenesis and neoplastic growth. *Endocr Rev* 2000;21:215-44
- [29] Wolf I, Sadetzki S, Catane R, Karasik A, Kaufman B. Diabetes mellitus and breast cancer. *Lancet Oncol* 2005;6:103-11
- [30] Le Roith D. Seminars in medicine on the Beth Israel Deaconess Medical Center: insulin-like growth factors. *N Engl J Med* 1997;336:633-40
- [31] Balkau B, Kahn HS, Courbon D, Eschwège E, Ducimetière P. Hyperinsulinemia predicts fatal liver cancer but is inversely associated with fatal cancer at some other sites. The Paris Prospective Study. *Diabetes Care* 2001;24:843-9
- [32] Maison P, Balkau B, Simon D, Chanson P, Rosselin G, Eschwège E. Growth hormone, a risk factor for premature mortality in healthy subjects. Data from the Paris Prospective Study. *BMJ* 1998;316:1132-3
- [33] Major JM, Laughlin GA, Kritz-Silverstein D, Wingard DL, Barrett-Connor E. Insulin-like growth factor-1 and cancer mortality in older men. *J Clin Endocrinol Metab* 2010;95:1054-9
- [34] Goodman-Gruen D, Barrett-Connor E. Sex differences in the association of endogenous sex hormone levels and glucose tolerance status in older men and women. *Diabetes Care* 2000;23:912-8
- [35] Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst* 1996;88:1118-26
- [36] Frayling TM, Colhoun H, Florez JC. A genetic link between type 2 diabetes and prostate cancer. *Diabetologia* 2008;51:1757-60
- [37] Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. *Diabetes Care* 2006;29:254-8
- [38] Hawley SA, Boudeau J, Reid JL, Mustard KJ, Udd L, Makela TP, Alessi DR, Hardie DG. Complexes between the LKB1 tumor suppressor, STRAD alpha/beta and MO25 alpha/beta are upstream kinases in the AMP-activated protein kinase cascade. *J Biol* 2003;2:28

- [39] Lizcano JM, Göransson O, Toth R, Deak M, Morrice NA, Boudeau J, Hawley SA, Udd L, Mäkelä TP, Hardie DG, Alessi DR. LKB1 is a master kinase that activates 13 kinases of the AMPK subfamily, including MARK/PAR-1. *EMBO J* 2004;23:833-43
- [40] Evans JMM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. *Br Med J* 2005;330:1304-5
- [41] Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JMM. New users of metformin are at low risk of incident cancer. *Diabetes Care* 2009;32:1620-5
- [42] Landman GWD, Kleefstra N, Van Hateren KJJ, Groenier KH, Gans ROB, Bilo HJG. Metformin associated with lower cancer mortality in type 2 diabetes. *Diabetes Care* 2010;33:322-6
- [43] Yang YX, Hennesy S, Lewis JD. Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. *Gastroenterology* 2004;127:1044-50
- [44] Dormandy J, Charbonnel B, Eckland DJA, Erdmann E, Massi-Benedetti M, Skene AM, et al, on behalf of the PROactive Study Group. 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* 2005;366:1279-89
- [45] Govindarajan R, Ratnasinghe L, Simmons DL, Siegel ER, Midathada MV, Kim L et al. Thiazolidinediones and the risk of lung, prostate, and colon cancer in patients with diabetes. *J Clin Oncol* 2007;25:1476-81
- [46] Monami M, Lamanna C, Marchionni N, Mannucci E. Rosiglitazone and risk of cancer. A meta-analysis of randomized clinical trials. *Diabetes Care* 2008;31:1455-60
- [47] Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin or glyburide monotherapy. *N Engl J Med* 2006;355:2427-43
- [48] Murtola TJ, Tammela LJ, Lahtela J, Auvinen A. Antidiabetic medication and prostate cancer risk: a population-based case-control study. *Am J Epidemiol* 2008;168:925-31.
- [49] Simon D, Preziosi P, Barrett-Connor E, Roger M, Saint-Paul M, Nahoul K, et al. The influence of aging on plasma sex hormones in men: the Telecom Study. *Am J Epidemiol* 1992;135:783-91.
- [50] Kurtzhals P, Schäffer L, Sørensen A, Kristensen C, Jonassen I, Schmid C, Trüb T. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. *Diabetes* 2000;49:999-1005
- [51] Pocock SJ, Smeeth L. Insulin glargine and malignancy: an unwarranted alarm. *Lancet*

2009;374:511-3

- [52] Garg SK, Hirsch IB, Skyler JS. Insulin glargine and cancer – An unsubstantiated allegation. *Diabetes Techn Ther* 2009;11:473-6
- [53] Nagel JM, Mansmann U, Wegscheider K, Röhm J. Insulin resistance and increased risk for malignant neoplasms: confounding the data on insulin glargine. *Diabetologia* 2010;53:206-8
- [54] Simon D. Diabetes treatment with insulin glargine and risk of malignancy: methodological pitfalls and ethical issues. *Diabetologia* 2010;53:204-5
- [55] Grouven U, Hemkens LG, Bender R, Sawicki PT. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues. Reply to Nagel JM, Mansmann U, Wegscheider K et al. (letter) and Simon D (letter). *Diabetologia* 2010;53:209-11
- [56] Yki-Järvinen H, Kauppinen-Mäkelin R, Tikkanen M, Vähätalo M, Virtamo H, Nikkilä K, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia* 2006;49:442–51
- [57] Pan CY, Sinnassamy P, Chung KD, Kim KW, on behalf of the LEAD Study Investigators Group. Insulin glargine vs NPH insulin therapy in Asian type 2 diabetes patients. *Diabetes Res Clin Pract* 2007;76:111–8
- [58] Riddle MC, Rosenstock J, Gerich J, on behalf of the Insuline Glargine 4002 Study Investigators. The Treat-to-Target Trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003;26:3080–6
- [59] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352:837–53
- [60] Bender R, Lange S. Adjusting for multiple testing-when and how? *J Clin Epidemiol* 2001;54:343–9
- [61] Smith U, Gale EAM. Does diabetes therapy influence the risk of cancer? *Diabetologia* 2009;52:1699–708
- [62] Romon I, Jouglu E, Weill A, Eschwège E, Simon D, Fagot-Campagna A. Description de la mortalité et des causes de décès dans une cohorte d'adultes diabétiques, en France métropolitaine – ENTRED 2001. *Bull Epidémiol Hebd* 2009;42-43:469-72
- [63] Eyre H, Kahn R, Robertson RM, on behalf of the ACS/ADA/AHA Collaborative writing Committee. Preventing cancer, cardiovascular disease, and diabetes – A common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. *Diabetes Care* 2004;27:1812-24

[64] Hercberg S, Chat-Yung S, Chaulia M. The French National Nutrition and Health Program: 2001-2006-2010. *Int J Public Health* 2008;53:68-77

Table 1

Adjusted hazards ratios* (95% confidence intervals) for incident cancer in diabetic patients in comparison with non-diabetic patients in the Japan Public Health Center-Based Prospective Study [13].

Men		Women	
All sites	1.27 (1.14-1.42)	All sites	1.21 (0.99-1.47)
Liver	2.24 (1.64-3.04)	Stomach	1.61 (1.02-2.54)
Pancreas	1.85 (1.07-3.20)	Liver	1.94 (1.00-3.73)
Kidney	1.92 (1.06-3.46)	Ovary	2.42 (0.96-6.09)
Colon	1.36 (1.00-1.85)	Pancreas	1.33 (0.53-3.31)
Stomach	1.23 (0.98-1.54)	Breast	0.83 (0.44-1.57)
Prostate	0.82 (0.51-1.33)		

* adjusted for age, body mass index, smoking, alcohol, coffee and green vegetables consumption, physical activity, study area, histories of cerebrovascular or ischemic heart diseases

Table 2

Relative Risks* (95% confidence intervals) for incident cancer according to the fourth in comparison to the first quartile group of fasting and 2-hour post load glucose in the Västerbotten Intervention Project of northern Sweden [16]. These results changed little after adjustment for BMI.

	Fasting glucose	2hr glucose
All sites		
men	1.08 (0.92-1.27)	0.98 (0.84-1.16)
women	1.26 (1.09-1.47)	1.31 (1.12-1.52)
Pancreas	2.49 (1.23-5.45)	0.91 (0.47-1.78)
Melanoma	2.16 (1.14-4.35)	1.65 (0.89-3.17)
Urinary Tract	1.69 (0.95-3.16)	1.18 (0.65-2.17)
Prostate (men)	0.96 (0.74-1.26)	0.79 (0.61-1.02)
Endometrium (women)	1.86 (1.09-3.31)	1.82 (1.07-3.23)

*adjusted for age, calendar year and smoking

Table 3

Hazards ratios* (95% confidence intervals) for incident and fatal cancer according to fasting plasma glucose ≥ 7.8 mmol/l compared to < 5.0 mmol/l in Korean men and women [17].

	Men	Women
Incident cancer - all sites	1.22 (1.16-1.27)	1.15 (1.01-1.25)
Fatal cancer - all sites	1.29 (1.22-1.37)	1.23 (1.09-1.39)
Fatal pancreatic cancer§	1.91 (1.52-2.41)	2.05 (1.43-2.93)
Fatal liver cancer	1.57 (1.40-1.76)	1.33 (1.01-1.81)
Fatal colon/rectum cancer§	1.31 (1.03-1.67)	0.85 (0.58-1.24)

* adjusted for age, smoking, alcohol use

§ in women: glucose ≥ 7.0 mmol/l compared to < 5.0 mmol/l

Table 4

Hazards ratios* (95% confidence intervals) for incident cancer according to fasting plasma glucose \geq 7.0 mmol/l compared to fasting plasma glucose 4.2 to 5.2 mmol/l in Vorarlberg, Austria [18].

	Men	Women
All sites	1.20 (1.03-1.39)	1.28 (1.08-1.53)
Liver cancer	3.56 (1.58-8.02)	
Gallbladder and bile duct§	3.35 (1.16-9.70)	

* adjusted for age, BMI, smoking and occupational group