Summary:

The epidemics of obesity and diabetes mellitus type 2 (DM2) are ongoing. The incidence of many types of cancers rise in parallel to the rise in body mass index (BMI) of the population. Obesity is associated with significant increase in risk of many types of cancers in both males and females. Increase in BMI is associated with increase in cancer mortality. Obesity predisposes the patients to development of DM2. Mean fast glucose >6 mM (108 mg/dL) is associated with significant increase in cancer death, and the diagnosis of DM2 is associated with significant increase in relative risk of many types of cancer. There are multiple layers of reasons or mechanisms that can lead to the association of obesity and DM2 with increased cancer deaths. Deregulated energetics is a hallmark of cancer, and use of glycolysis to generate the cancer cell’s energy need from glucose is a major characteristic described by Warburg. Cancer cells often have coordinated upregulation of hypoxia induced factor-1 (HIF-1α) and Myc and downregulation of tumor suppressor p53 to result in an increase in flux through the glycolytic pathway. In the context of insulin resistance and obesity and DM2, elevated circulating insulin and insulin-like growth factors will stimulate the AKT signaling pathway which will lead to downstream upregulation of HIF-1α and Myc and downregulation of p53, and this coordinated downstream regulation will lead to increased glycolytic flux. This increased glycolytic flux confers the avidity of glucose uptake by cancer, and hyperglycemia in DM2 will translate into plenty of fuel for the cancer cells and their abilities to tolerate hypoxia, radiation and chemotherapy. Our experiment data show that insulin, glucose and adipokines promote cancer cell growth in vitro. Mouse model experiments show that obesity and diabetes promote cancer progression. In a case-matched study of pancreatic cancer patients, metformin usage is associated with decreased risk of pancreatic cancer. A clinically relevant question is whether different classes of anti-diabetic pharmacotherapy have different impacts on the clinical outcomes of cancer patients. Experimental data suggest that biguanides and thiazolidinediones may have direct inhibitory effect on cancer cells. Epidemiologic data also suggest that there is a difference in cancer risk and cancer mortality between patients with DM2 taking metformin and those taking insulin or secretagogues. Metformin and thiazolidinediones inhibit cancer cells in vitro, and they improve survival of mouse models of cancer and obesity or diabetes. Retrospective reviews of patients at our institution also show that metformin and thiazolidinediones usage are associated with improved overall survival of diabetic patients with prostate cancer or stage ≥2 HER2+ breast cancer. The American Diabetic Association and American Cancer Society issued a consensus statement that the possible mechanisms for a direct link between cancer and DM2 are hyperinsulinemia, hyperglycemia, and inflammation. The evidence for specific drugs affecting cancer risk is limited, and observed associations may have been confounded by indications for specific drugs, effects on other cancer risk factors such as body weight and hyperinsulinemia, and the complex progressive nature of hyperglycemia and pharmacotherapy in DM2. The consensus states that cancer risk should not be a major factor when choosing between available diabetes therapies for the average patient. Nevertheless, early evidence suggests that metformin may be associated with a lower risk of cancer and that exogenous insulin may be associated with an increased cancer risk. In this presentation, new evidence after the consensus conference has been presented. The future may see new recommendations for DM2 management in cancer patients to maximize patient survival.
Bibliography


The impact of obesity and diabetes on the outcome of malignancy

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Overview

• Background
• The Question:
  – Does obesity and diabetes worsen cancer outcome?
  – What medications can block the impact of obesity and diabetes on cancer?
• In vitro, In vivo and clinical evidence
• Recent and ongoing work
• Summary

“The world is getting too fat. Too bad!”
Increase in Obesity Paralleled Breast Cancer Incidence

Impact of Obesity on Cancer Risk

BMI & Cancer Mortality

Althuis et al., Int J Epidemiol. 2005;34:405-12.

Renehan et al. Lancet 2008; 371: 569–78
Obesity & Diabetes – the Continuing Epidemic

Association of Mean Fasting Glucose with Cancer Death

Impact of Diabetes Mellitus on Cancer Death

DM2 Prevalence

Mean Body Weight

Body Mass Index (BMI)

Year

Year

Association of Mean Fasting Glucose with Cancer Death

Replotted based on data from Seshasai et al. NEJM 2011, 364:829-41


144 mg/dL; HgbA1c=6.6%

Log (Hazard Ratio with diabetes)

Types of Cancer

Replotted based on data from Seshasai et al. NEJM 2011, 364:829-41
**Reasons why DM2 and obesity increase cancer deaths**

- Genetic
- Epigenetic
- Psychosocial
- Dietary

**Inflammation**

**Adipokines**

**Insulin/IGF1**

**Sex hormones**

**DM2**

**Cancer**

**Treatment**

R.I.P.

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**Hallmarks of Cancer**

**Enabling Characteristics**

- Genomic Instability/Mutations
- Inflammation

**Evade Apoptosis**

**Insensitive to Growth Arrest**

**Persistent Growth**

**Limitless Replication**

**Deregulated Energetics**

**Escape from Immune Surveillance**

**Angiogenesis**

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**Review**

**Roles of p53, Myc and HIF-1 in Regulating Glycolysis – the Seventh Hallmark of Cancer**

H.D. Nguyen, C. Liu, J. Han, F.L. Szall, C. De Menezes, S.J. Robertson, M. Grunberger, R. L. N. Pietras, and M. R. P. Hall

Department of Internal Medicine, McGovern Medical School, Houston, Texas, USA

Cell Mol Life Sci. 2011 Apr;68(7):1151-65

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Insulin & IGFs Stimulate Cell Proliferation

- Breast cancer cells MCF-7, ZR-75-1, and T-47D have functional insulin receptors. An agonist monoclonal antibody to the insulin receptor (MA-5), stimulated cell proliferation. Immunostaining of breast cancer specimens showed the insulin receptors in malignant epithelial cells.
- Epithelial ovarian carcinoma cells OV17, OV167, OV177, OV207, and OV266 have functional insulin receptors. Insulin (0.1–10 nM) stimulated cell proliferation.
- Pancreatic cancer cells MiaPaCa-2 have insulin receptors, and insulin and IGF1 stimulated cell proliferation. Insulin, IGF1, and IGF2 enhanced the growth of ASPC-1 and COLD-357 cells. Insulin promoted the growth of BxPC-3 cells.

Hyperglycemia

- Plenty of glucose to feed the “sugar suckers”
  - Tolerate hypoxia
  - Radioreistance
  - Chemoresistance

Diabetes Promotes Carcinogenesis in Animal Models

- Development of azoxymethane-induced colonic lesions is enhanced in db/db mice compared with db/+ or wild-type mice.
- In the classic two-stage skin carcinogenesis model and the C3(1)/T-Ag transgenic mouse mammary tumor model, A-ZIP/F-1 mice showed higher tumor incidence & number, and shorter latency than wild-type mice.
- A-ZIP/F-1 mice enhanced carcinogenesis due to TP53 deletion (p53 -/-).
- Hamster pancreatic carcinoma cell line H2T grows more rapidly when implanted in cheek pouches of streptozotocin (STZ)-diabetic hamsters.

Insulin promotes proliferation of cancer cells. Glucose also promotes proliferation of cancer cells but dependent on high insulin concentrations.

Adipocyte-conditioned Media Stimulate Breast Cancer Cell Growth

T47D proliferation after 48 hours treatment with 3T3-L1 pre-adipocyte or adipocyte media
Changes in Adipokine Profile Associated with Adipocyte Differentiation

Orthotopic Pancreatic Cancer Mouse Model with Insulin Resistance
- 2.5 x 10^5 Pano2/FG312 in matrigel (1:1)
- 50µL injected in the pancreas tail
Mouse model of ER+ breast cancer & obesity

MMTV-TGFα X A/a
FVB C57BL6

MMTV-TGFα; A/a MMTV-TGFα; a/a A/a a/a

Fat

Normal fasting glucose

Glucose intolerant

Insulin resistant

A

B

C

D

E
Obesity accelerates breast tumor formation in mice

Mouse model of HER2+ breast cancer & diabetes & obesity

MMTV-neu × Lepr<sup>db</sup>  
FVB C57BL6

MMTV-neu; Lepr<sup>db</sup>

MMTV-neu; Lepr<sup>+/−</sup>  MMTV-neu; Lepr<sup>−/−</sup>  MMTV-neu; Lepr<sup>db/db</sup>

HER2+ breast tumors in fat diabetic mice
Impaired glucose tolerance of MMTV-neu; Lepr\textsuperscript{db/db} mice

How can we modify these risk factors or reduce the risk?

- No specific recommendations regarding glucose control for cancer patients in the literature.
- Should we just follow the sick day guidelines?
- Does treatment of DM2 improve cancer specific survival of diabetic cancer patients?
- Are some medications for DM2 better than others with respect to cancer survival?

- No specific recommendations regarding weight control for cancer patients in the literature.
- Are there medications that can counter-balance the risk with respect to cancer survival in obesity?
Relationship among DM2, obesity & cancer

**Background Factors**
- Genes
- Environment/Diet
- Age

**Endogenous Factors**
- DM2
- Obesity
- Glucose
- Insulin
- IGF1
- Adipokines

**Exogenous Factors**
- Radiation
- Anti-obesity drugs
- Diet & exercise
- Anti-diabetic drugs
- Chemotherapy

**Background Factors**
- Genes
- Environment/Diet
- Age

**Treatments of Obesity**
- Diet & Lifestyle management
- Pharmacotherapy
- Surgery

**Anti-Obesity Pharmacotherapy**
- Appetite Suppressants
  - Epi, NE, dopamine reuptake inhibitors
    - Mazindol
  - Sympathomimetics
    - Phentermine
    - Diethylpropion
    - Benzphetamine
    - Phendimetrazine
- Lipase inhibitor
  - Orlistat
- Beta3-adrenergic receptor agonists
- Thiazolidinediones
  - Rosiglitazone
  - Pioglitazone
- Biguanides
  - Metformin
- Incretin Mimetics
  - Exenatide
  - Liraglutide
- Amylin Analogs
  - Pramlintide
**Anti-Diabetic Pharmacotherapy**

- **Insulin & Insulin Analogs**
  - Recombinant human insulin or insulin analogs (regular, isophane, zinc suspension, protamine suspension, etc.)
  - Aspart
  - Lispro
  - Glargine
  - Detemir
  - Glulisine

- **Sulfonylureas**
  - Tolazamide
  - Tolbutamide
  - Chlorpropamide
  - Glyburide (glibenclamide)
  - Glipizide
  - Glimepiride

- **Meglinides**
  - Repaglinide
  - Nateglinide

- **Alpha-glucosidase Inhibitors**
  - Acarbose
  - Miglitol

- **Thiazolidinediones**
  - Rosiglitazone (restricted use)
  - Pioglitazone

- **Biguanides**
  - Metformin

- **Incretin Mimetics**
  - Exenatide
  - Liraglutide

- **DPP-4 Inhibitors**
  - Velagliflozin
  - Sitagliptin

- **Amylin Analogs**
  - Pramlintide

- **Subtype 2 of the sodium-glucose transport proteins (SGLT2)**
  - Dapagliflozin

**Anti-Insulin Resistance Drugs and Cancer**

- **Thiazolidinediones**
  - Agonist of Peroxisome proliferator-activated receptor-gamma (PPARγ)
  - Decrease cellular proliferation and induce apoptosis of various tumor cell lines
  - May involve upregulation of PTEN

- **Biguanides**
  - Reversible inhibition of Complex 1 of oxidative phosphorylation
  - Activation of AMPK via LKB1
  - Inhibit cell growth through decreasing mTOR and S6 kinase activation

**RESEARCH POINTERS**

*Metformin and reduced risk of cancer in diabetic patients*

*BMJ 2005;330:1304–5*

**What the paper suggests**

*Metformin may reduce risk of cancer in patients with type 2 diabetes.*

**What readers should know**

*Reduced information about risk of cancer likely due to lack of real-time data and interpretation in that specific context.*
Patients with DM2 exposed to sulfonylureas and exogenous insulin had a significantly increased risk of cancer-related mortality compared with patients exposed to metformin. It is uncertain whether this increased risk is related to a deleterious effect of sulfonylurea and insulin or a protective effect of metformin or due to some unmeasured effect.

**Metformin & Rosiglitazone Improves Survival of MMTV-neu: lepr db/db**

![Graph showing the survival of MMTV-neu: lepr db/db mice treated with control, metformin, rosiglitazone, metformin + rosiglitazone, and the log rank test results.](image)

**Graph showing the survival of MMTV-neu: lepr db/db mice treated with control, metformin, rosiglitazone, metformin + rosiglitazone, and the log rank test results.**
Antidiabetic Therapies Affect Risk of Pancreatic Cancer

BACKGROUND AIMS: Antidiabetic drugs have been found to have various effects on cancer in experimental systems and in epidemiologic studies, although the association between these outcomes and the risk of human pancreatic cancer has not been explored. We investigated the effects of antidiabetic therapies on the risk of pancreatic cancer. METHODS: A hospital-based case-control study was conducted at St. Luke’s Roosevelt Hospital Center. Diabetic patients and matched control subjects were recruited from the hospital’s diabetes clinic and the hospital’s general population. The outcomes of interest were the development of pancreatic cancer before and after the use of antidiabetic drugs. Results: The overall risk of pancreatic cancer was significantly reduced among diabetic patients who used antidiabetic drugs compared to matched control subjects. The risk was further reduced among diabetic patients who used metformin compared to those who used other antidiabetic drugs. The risk was also reduced among diabetic patients who used antidiabetic drugs before the diagnosis of pancreatic cancer compared to those who used antidiabetic drugs after the diagnosis of pancreatic cancer. In addition, smoker patients were more likely to use antidiabetic drugs than non-smoker patients. Conclusions: The use of antidiabetic drugs may reduce the risk of pancreatic cancer. Further studies are needed to confirm these findings and to elucidate the mechanisms by which antidiabetic drugs may reduce the risk of pancreatic cancer.
Cancer-Specific Mortality of Stage ≥2 HER2+ Breast Cancer

Summary

- Insulin, glucose and adipokines promote cancer cell growth in vitro.
- Obesity and diabetes promote cancer progression in 3 mouse models.
- Metformin & thiazolidinediones inhibit cancer cells in vitro.
- Metformin & thiazolidinediones improve survival of mouse models of cancer and obesity or diabetes.
- Metformin usage is associated with decreased risk of pancreatic cancer in retrospective review.
- Metformin & thiazolidinediones usage are associated with improved overall survival of diabetic patients with prostate cancer or stage ≥2 HER2+ breast cancer in retrospective reviews.
**Diabetes and Cancer: A Consensus Report**

- ADA and ACS - consensus conference in December 2009.
- CA Cancer J Clin 2010;60;207-221.
- Conclusions & Recommendations:
  - Possible mechanisms for a direct link: hyperinsulinemia, hyperglycemia, and inflammation.
  - The evidence for specific drugs affecting cancer risk is limited, and observed associations may have been confounded by indications for specific drugs, effects on other cancer risk factors such as body weight and hyperinsulinemia, and the complex progressive nature of hyperglycemia and pharmacotherapy in DM2. Nevertheless, early evidence suggests:
    - Metformin is associated with a lower risk of cancer
    - Exogenous insulin is associated with an increased cancer risk
  - Cancer risk should not be a major factor when choosing between available diabetes therapies for the average patient.

**Implications for Clinical Practice**

- DM2 and obesity are potentially modifiable factors that impact on cancer patient survival.
- No clear data to guide clinical management of DM2 in cancer patients.
- Diet and lifestyle changes are fundamental.
- A cancer patient is not “the average patient”. Some pharmacotherapies for diabetes may be more beneficial for cancer patients than other agents.
- More research is needed to change the standard of care to optimize cancer patient survival.