The Role of Obesity and Diabetes in Cancer

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Objectives

- Differentiate between modifiable cancer risk factors and non-modifiable cancer risk factors
- Identify which cancers have a strong link to diabetes
- Discuss the role of elevated insulin levels in cancer development
- Differentiate between the roles that genetics play in cancer development to the proposed role of nutrigenomics/Nutrigenetics has on cancer susceptibility
Leading Causes of Death

Worldwide
- 2nd leading cause of death – cancer (13% of all deaths)
- 12th leading cause of death – diabetes (8% of all deaths)

United States
- 2nd leading cause of death – cancer
- 7th leading cause of death – diabetes
Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2014

Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.
Overweight and Obesity Increase Risk for:

1. Esophageal Cancer
2. Liver Cancer
3. Kidney Cancer
4. Stomach Cancer
5. Colorectal Cancer
6. Advanced Prostate Cancer
7. Post-Menopausal Breast Cancer
8. Gallbladder Cancer
9. Pancreatic Cancer
10. Ovarian Cancer
11. Endometrial Cancer
American Institute of Cancer Research (AICR) estimates that 130,300 U.S. Cancer Cases Every Year Are Related to Excess Body Fat
AICR 2007 Nutrition Guidelines

1. Be as lean as possible without becoming underweight.
2. Be physically active for at least 30 minutes every day.
3. Avoid sugary drinks, and limit consumption of energy-dense foods (particularly processed foods high in added sugar, low in fiber or high in fat).
4. Eat more of a variety of vegetables, fruits, whole grains and legumes such as beans.
5. Limit consumption of red meats (such as beef, pork, and lamb) and avoid processed meats.
6. If consumed at all, limit alcoholic drinks to two for men and one for women a day.

7. Limit consumption of salty foods and foods processed with salt (sodium).

8. Do not rely on supplements to protect against cancer.

And always remember – do not smoke or chew tobacco.
AICR Dietary/Lifestyle Goals

- **Plant Based Diet**
  - 2/3 Plant Foods
    - Choose colorful produce
  - 1/3 Animal Protein
    - Incorporate meatless meals several times a week
    - Avoid eating processed meats such as cold cuts, bacon, sausage, and ham
    - WHO statement on processed meats

- **Physical Activity/Exercise** – work to have 30 minutes of moderate activity daily

- **Alcohol** – despite evidence of a heart protective effect with moderate alcohol consumption, there is not a similar effect with cancer. AICR recommends avoiding even small amounts of alcohol
AICR – 2007 Expert Report Updates
AICR CUP Updates – Release Dates

- Stomach Cancer – April 2016
- Bladder Cancer – December 2015
- Kidney Cancer – September 2015
- Gallbladder Cancer – June 2015
- Liver Cancer – March 2015
- Prostate Cancer – November 2014
- Breast Cancer Survivor – October 2014
- Ovarian Cancer – March 2014
- Endometrial Cancer – 2013
- Pancreatic Cancer – 2012
- Colorectal (bowel) Cancer – 2011
- Breast Cancer - 2010
To promote and support healthful eating patterns, emphasizing a variety of nutrient dense foods in appropriate portion sizes, in order to improve overall health and specifically to:

- Attain individualized glycemic, blood pressure, and lipid goals. General recommended goals from the ADA for these markers are as follows:*
  - A1C < 7%
  - Blood pressure < 140/80 mm Hg
  - LDL cholesterol < 100 mg/dL; triglycerides < 150 mg/dL; HDL cholesterol > 40 mg/dL for men; HDL cholesterol > 50 mg/dL for women
- Achieve and maintain body weight goals
- Delay or prevent complications of diabetes
To address individual nutrition needs based on personal and cultural preferences, health literacy and numeracy, access to healthful food choices, willingness and ability to make behavioral changes, as well as barriers to change.

To maintain the pleasure of eating by providing positive messages about food choices only when indicated by scientific evidence.

To provide the individual with diabetes with practical tools for day-to-day meal planning rather than focusing on individual macronutrients, or single foods.
### ADA 2014 Nutrition Recommendations

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<tr>
<th>Task</th>
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<tbody>
<tr>
<td><strong>Effectiveness of nutrient therapy</strong></td>
<td>Nutrition therapy is necessary for people with type 1 and 2 diabetes as an effective component of the overall treatment plan.</td>
<td>A</td>
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<tr>
<td></td>
<td>People with diabetes should be referred to a registered dietitian who is a member of an interdisciplinary team for management of the complications of diabetes.</td>
<td>A</td>
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<td>For individuals with type 1 diabetes, and regardless of an intensive insulin therapy education program using the continuous subcutaneous insulin infusion, the amount of insulin administered should be controlled to achieve the HbA1c goal.</td>
<td>B</td>
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<tr>
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<td>Continuous subcutaneous insulin infusions are a useful strategy for people with the complications of diabetes.</td>
<td>A</td>
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<tr>
<td><strong>Therapeutic</strong></td>
<td>People with diabetes should reach an intensity of physical activity that is consistent with national standards and diabetes self-management should support their diabetes and is supported and monitored.</td>
<td>B</td>
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<td>Because diabetes self-management can lead to less energy and improved outcomes such as reductions in A1C, nutrition therapy should be included in diabetes self-management education.</td>
<td>B, C, D</td>
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#### Dietary recommendations

- **Energy balance**
  - For overweight or obese adults with type 2 diabetes, retarding any weight while maintaining a healthy eating pattern is recommended. | B, C, E |
  - Weight reduction is recommended in overweight adults. | B, C, E |

- **Micronutrients and fortificant supplements**
  - There is no clear evidence that infant formula or natural supplementation in people with diabetes who are able to tolerate supplements. | C |
  - Use of mineral supplements is recommended for people with diabetes. | C |

- **Biotics and/or probiotics**
  - A variety of dietary patterns (combination of different foods or food groups) are permissible to the management of diabetes. | E |
  - High-fiber carbohydrate-rich foods are recommended for people with diabetes. | E |

- **Dietary guidelines for carbohydrates**
  - A variety of dietary patterns (combination of different foods or food groups) are permissible to the management of diabetes. | E |
  - High-fiber carbohydrate-rich foods are recommended for people with diabetes. | E |

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### Additional Recommendations

- **Protein**
  - For people with diabetes and no evidence of diabetes-related disease, evidence is lacking for the use of specific amounts of protein in the diet for glycemic control or improving one or more CV risk factors; therefore, protein should be individualized. | C |

- **Sodium**
  - The recommendation for the general population to reduce sodium to less than 2,300 mg/day to help prevent hypertension. | R |

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<td><strong>Microalbuminuria and its progression</strong></td>
<td>Use of MiR in the management of diabetic kidney disease is shown to decrease albuminuria.</td>
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<td><strong>Prevention</strong></td>
<td>Ongoing monitoring of blood pressure is important.</td>
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<td>Weight reduction and weight management are important for reducing the risk of diabetes.</td>
<td>B, C</td>
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<td>Antioxidants and vitamin D supplementation is recommended for people with diabetes and chronic kidney disease.</td>
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Diabetes-Cancer Relationship

- Increased cancer risk and mortality
  - Epidemiological and cohort studies
  - Diabetes associated with 1.2-2 fold increase in incidence

- Factors in Diabetes-Cancer Relationship
  - Hyperinsulinemia
  - Hyperglycemia
  - Hyperlipidemia
  - Insulin-like Growth Factors (IGFs)
  - Adipokines
  - Inflammatory Cytokines
Diabetes – Cancer Relationships – Meta-analysis and Systematic Reviews

- Pancreatic cancer, thyroid cancer, non-Hodgkin’s lymphoma, leukemia, and myeloma
- Breast cancer and colorectal cancer
- Ovarian Cancer
High levels of fasting and post-prandial glucose are strongly correlated with increased cancer risk.

Diabetes mellitus classed as independent risk factor for numerous malignancies, 24 types to date.
- Varying levels of Correlations –
  - Highest Frequency: endometrial, cervical, ovarian, stomach, lung, and kidney cancers
  - Moderate Frequency: pancreas and hepatocellular cancers
  - Other group reported - increased occurrence in persons with diabetes: leukemia, melanoma, liver, pancreas, bile ducts, rectum, and kidney cancers

Cancer screening is required for patients with pre-existing Diabetes Mellitus.
Diabetes-Cancer Relationship

Cancers with well-studied links Diabetes Links

- Breast Cancer
  - 23% increase in incidence
  - 38% cancer specific mortality

- Colorectal Cancer
  - 25% increase in incidence
  - 30% cancer specific mortality
Diabetes – Cancer Relationship

- Diabetes and Colorectal Cancer (CRC)
  - Colorectal Cancer – third leading cause of cancer related death
  - 650,000 deaths/year
  - Elevated A1C – independent predictor of aggressive clinical behaviors
  - Positive association remains consistent for men and women
  - Studies primarily completed in North America, Europe, and Asia
  - Uncontrolled Type 2 Diabetes Mellitus – associated more with right-sided and advanced CRC
  - Chronic insulin therapy associated with increased CRC risk
  - Possible role of prolonged GI transit time may be related to diabetic neuropathy
Diabetes – Cancer Relationship - CRC

- Risk Factors
  - Sedentary Lifestyle
  - Obesity
  - Western Diet
  - Metabolic Syndrome
  - Genetic factors
  - Lack of Exercise
  - Smoking
  - Alcohol
  - Age
Obesity has a role in increased CRC risk of the diabetes population:

- Insulin resistance
- Increased inflammatory makers - Interleukin (IL) – 1, IL-6, tumor necrosis factor – alpha
- High levels of androgens and estrogens
Prophylaxis for Colorectal Cancer

- Aspirin, NSAIDS, Cyclooxygenase 2 (COX-2) inhibitors
- Statins
  - Small reduction in risk to diabetic patients
  - Preclinical results: simvastatin results in the inhibition of IL-8 & IL-6 for CRC cell lines, decreased synthesis and release of pro-inflammatory cytokines by the tumor cells

Metformin – 173 clinical trials exploring use in cancer

- Associated with reduced mortality and incidence of cancer at any site (J Diab Invest 2013)
- Improves cancer response to XRT, enhanced apoptosis
Diabetes – Cancer Relationship – CRC specific

- Role of Homocysteine
  - Increased homocysteine shown to be risk factor for DM type 2
  - Associated with aberrant methylation of DNA
  - May lead to inactivation of tumor suppressor genes and CRC growth
Management Issues for Diabetic Patients with Cancer

- Corticosteroids – glucocorticoids induced hyperglycemia
  - Used as anti-emetic, to reduce edema, and improve intake, or assist with pain management
- Androgen deprivation therapy (ADT)
  - Done with leutenizing hormone releasing hormone
  - Linked to increased risk of type 2 diabetes mellitus
  - Leads to worsening glycemic control in patients with pre-existing DM
- Chemotherapy - may induce hyperglycemia
  - Platinum based (e.g. Cisplatin)
  - 5 Fluorouracil based chemo
  - mTOR inhibitors (everolimus)
  - ABL kinase inhibitor (nilotinib)
Nutritional Genomics in Action

**NUTRIGENETICS** (polymorphisms)

**NUTRIGENOMICS** (gene expression)

Adapted from Dr. Peter Gillies. JADA 2003;103:S50-5.
A

DNA molecule

Gene (coding region)

Common genotype

AACT

TTCA

Protein

Chromosome

B

Variant genotype

AACT

TTCA

SNP Site

Protein altered
Is there a single SNP that links diabetes and cancer?


A polymorphism in the fibroblast growth factor receptor 4 gene has been associated with cancer progression and treatment resistance and is now reported to increase insulin secretion, providing a possible genetic link between hyperinsulinemia and cancer.