The Obesity-Cancer Connection

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Defining Obesity

• Body mass index (BMI)
  – Weight (kg) divided by height (meters)²

NIH National Heart, Lung and Blood Institute

Obesity: A Global Epidemic

Men

Women

R Ahima J Clin Invest 2011 121:2076-2079
Obesity Trends Among U.S. Adults

- 35.7% U.S. adults are obese
- $147 billion estimated medical cost in U.S. in 2008

Source: Behavioral Risk Factor Surveillance System, CDC
Obesity: A Growing Epidemic at Home

Overweight and Obesity (BMI) Wisconsin - 2012

Overweight or Obese = 66.5%

Source: Behavioral Risk Factor Surveillance System, CDC
Obesity is Linked to Many Diseases

- Migraines
- Pseudotumor cerebri
- Dyslipidemia, hypercholesterolemia
- Non-alcoholic fatty liver disease
- Metabolic syndrome
- Type II diabetes mellitus
- Polycystic ovarian syndrome
- Venous stasis disease
- Gout
- Depression
- Obstructive sleep apnea
- Asthma
- Cardiovascular disease
- Hypertension
- GERD
- Stress urinary incontinence
- Degenerative joint disease
Obesity: A Deadly Disorder

AB de Gonzalez et al. 2010 NEJM 363:2211-2219
## Obesity is Associated with Increased Cancer Risk

### Table 1 | Summary of increased relative risk* of different cancers in obesity

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Men (95% CI)</th>
<th>Women (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>ND</td>
<td>1.12 (1.08–1.16)</td>
</tr>
<tr>
<td>Colon</td>
<td>1.24 (1.20–1.28)</td>
<td>1.09 (1.05–1.13)</td>
</tr>
<tr>
<td>Endometrial</td>
<td>NA</td>
<td>1.59 (1.50–1.68)</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>1.52 (1.33–1.74)</td>
<td>1.51 (1.31–1.74)</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.24 (1.15–1.34)</td>
<td>1.34 (1.25–1.43)</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>1.08 (1.02–1.14)</td>
<td>1.17 (1.04–1.32)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1.17 (1.05–1.30)</td>
<td>0.96 (0.92–1.01)</td>
</tr>
<tr>
<td>Myeloma</td>
<td>1.11 (1.05–1.18)</td>
<td>1.11 (1.07–1.15)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>1.06 (1.03–1.09)</td>
<td>1.07 (1.00–1.14)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>1.07 (0.93–1.23)</td>
<td>1.12 (1.02–1.22)</td>
</tr>
<tr>
<td>Prostate</td>
<td>1.03 (1.00–1.07)</td>
<td>NA</td>
</tr>
<tr>
<td>Rectal</td>
<td>1.09 (1.06–1.12)</td>
<td>1.02 (1.00–1.05)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1.33 (1.04–1.70)</td>
<td>1.14 (1.06–1.23)</td>
</tr>
</tbody>
</table>

CI, confidence interval; NA, not applicable; ND, not determined. *Relative risks are taken from a meta-analysis of data as reported in Rennehan et al.\(^3\) and Roberts et al.\(^172\). The relative risk per 5 kg per m\(^2\) increase in body mass index is reported for each site and sex.
Obesity Is Associated with Increased Cancer Mortality

404,576 US men and 495,477 women free of cancer at enrollment

**Table 1. Mortality from Cancer According to Body-Mass Index among U.S. Men in the Cancer Prevention Study II, 1982 through 1998.**

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Body-Mass Index</th>
<th>P for Trend</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18.5–24.9</td>
<td>25.0–29.9</td>
<td>30.0–34.9</td>
</tr>
<tr>
<td>All cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths</td>
<td>13,855</td>
<td>15,372</td>
<td>2683</td>
</tr>
<tr>
<td>Death rate‡</td>
<td>578.30</td>
<td>546.21</td>
<td>636.30</td>
</tr>
<tr>
<td>RR (95% CI)§</td>
<td>1.00</td>
<td>0.97 (0.94–0.99)</td>
<td>1.09 (1.05–1.14)</td>
</tr>
</tbody>
</table>

14% of cancer deaths in men attributed to obesity and overweight

**Table 2. Mortality from Cancer According to Body-Mass Index among U.S. Women in the Cancer Prevention Study II, 1982 through 1998.**

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Body-Mass Index</th>
<th>P for Trend</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18.5–24.9</td>
<td>25.0–29.9</td>
<td>30.0–34.9</td>
</tr>
<tr>
<td>All cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths</td>
<td>14,779</td>
<td>7107</td>
<td>2254</td>
</tr>
<tr>
<td>Death rate‡</td>
<td>329.30</td>
<td>339.75</td>
<td>382.62</td>
</tr>
<tr>
<td>RR (95% CI)§</td>
<td>1.00</td>
<td>1.08 (1.05–1.11)</td>
<td>1.23 (1.18–1.29)</td>
</tr>
</tbody>
</table>

20% of cancer deaths in women attributed to obesity and overweight

Diabetics Have a Higher Prevalence of Certain Cancers

• Diabetic men have a higher prevalence of:
  – Prostate cancer
  – Colon cancer
  – Pancreatic cancer
  – Rectal cancer
  – Bladder cancer
  – Kidney cancer

• Diabetic women have a higher prevalence of:
  – Breast cancer
  – Endometrial cancer
  – Leukemia
Diabetes is Associated with Increased Cancer Mortality

### Table: Cancer Death

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Deaths</th>
<th>Hazard Ratio with Diabetes (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>533</td>
<td>2.16 (1.62–2.88)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2189</td>
<td>1.51 (1.24–1.83)</td>
</tr>
<tr>
<td>Ovary</td>
<td>1149</td>
<td>1.45 (1.03–2.02)</td>
</tr>
<tr>
<td>Colorectum</td>
<td>3876</td>
<td>1.40 (1.20–1.63)</td>
</tr>
<tr>
<td>Bladder</td>
<td>834</td>
<td>1.40 (1.01–1.96)</td>
</tr>
<tr>
<td>Oral</td>
<td>475</td>
<td>1.38 (0.90–2.12)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>547</td>
<td>1.36 (0.83–2.23)</td>
</tr>
<tr>
<td>Kidney</td>
<td>815</td>
<td>1.28 (0.89–1.85)</td>
</tr>
<tr>
<td>Lung</td>
<td>7823</td>
<td>1.27 (1.13–1.43)</td>
</tr>
<tr>
<td>Breast</td>
<td>3338</td>
<td>1.25 (1.02–1.52)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>795</td>
<td>1.21 (0.86–1.69)</td>
</tr>
<tr>
<td>Stomach</td>
<td>1531</td>
<td>1.16 (0.92–1.46)</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>310</td>
<td>1.11 (0.58–2.11)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>3425</td>
<td>0.93 (0.77–1.13)</td>
</tr>
<tr>
<td>Prostate</td>
<td>2217</td>
<td>0.89 (0.71–1.10)</td>
</tr>
<tr>
<td>Endocrine and nervous</td>
<td>1209</td>
<td>0.88 (0.60–1.27)</td>
</tr>
<tr>
<td>Site unspecified or other</td>
<td>8680</td>
<td>1.17 (1.07–1.27)</td>
</tr>
</tbody>
</table>
Metformin Use in Diabetics is Associated with Reduced Cancer Mortality

- Cancer mortality
  - 4.9% for sulfonylurea
  - 3.5% for metformin users
  - 5.8% for insulin

Sl Bowker et al. 2006 Diabetes Care 29:254–258
Obesity: An Energy Imbalance

Energy Intake > Energy Burned
Visceral and Subcutaneous White Adipose Tissue
Fat is a Metabolically Active Organ

How Does Obesity Fuel Cancer?

- TNFα and IL-6
- Inflammation
- Insulin resistance
- Elevated insulin levels
- Estradiol
- Leptin
Inflamed Breast Tissue in Obese Women Increases Aromatase Levels

Aromatase: Increases Estradiol levels

Subbaramaiah K et al. 2012 Cancer Discovery 2:356-365
Targeting Obesity to Prevent and/or Treat Cancer

• Lifestyle interventions
  – Diet
  – Physical activity

• Metformin
  – Many clinical trials in diverse cancers

• Anti-inflammatory agents
  – NSAIDs, aspirin, omega-3 fatty acids and others
  – Many clinical trials in diverse cancers

• Bariatric Surgery
  – Morbidly obese patients: BMI > 40 or > 35 with risk factors
Diet and Breast Cancer Recurrence

• Women’s Interventional Nutrition Study (WINS)
  – Randomized control study of 2437 women with breast cancer
  – Reduced fat diet (20% of calories) versus control
  – 24% reduction in breast cancer recurrence in low fat diet group
  – 6 pound weight loss

  RT Chlebowski et al. 2006 J Natl Cancer Inst 98:1767-1776

• Women’s Healthy Eating and Living (WHEL) study
  – Randomized control study of 3088 women with breast cancer
  – Diet high in vegetables, fruit and fiber and low in fat versus control
  – No difference in breast cancer recurrence or mortality
  – No weight loss

  JP Pierce et al. 2007 JAMA 298:289-298
Physical Activity and Breast Cancer Recurrence

- Health, Eating, Activity and Lifestyle (HEAL) study
  - Prospective observational study of 933 women with breast cancer
  - Self-reported physical activity
  - Women reporting 2-3 hours of brisk walking per week 2 years after diagnosis had a 67% reduction in death compared to inactive women
  - Women who increased physical activity after diagnosis had a 45% reduction in death compared to women who remained inactive after diagnosis

M Irwin et al. 2008 J Clin Oncol 26:3958-3964
Metformin Study in Early Breast Cancer

- 39 newly diagnosed non-diabetic breast cancer patients were treated with metformin before surgery
- Modest reduction in weight & BMI, improved insulin sensitivity
- Decreased proliferation and increased cell killing in the breast tumors
- Promising pilot study that suggests that metformin treatment may improve clinical outcomes

Saroj Niraula et al. 2012 Br Ca Res Treat 69:7507-7511
Bariatric Surgery and Cancer Incidence

• Swedish Obese Subjects (SOS) Study
  – Prospective study of 4047 obese patients (men and woman) who underwent bariatric surgery or conventional treatment

  – Sustained 19.9 kg weight reduction in bariatric group at 10 years versus 1.3 kg weight gain in the control group

  – Women: 42% reduction in first-time cancers in the bariatric group

  – Men: no difference in first-time cancers between the groups

  – Reduction in cancer incidence in obese women but not obese men treated with bariatric surgery

Obesity and Cancer: Summary

• Obesity is associated with an increased risk of many types of cancer and increased cancer mortality

• Obesity results in metabolic changes that fuel cancer
  – Hormones: Estradiol and Leptin
  – Inflamed fat drives insulin resistance: increased insulin and insulin-like growth factors

• Obesity is a promising target for cancer prevention and therapy
  – Diet and physical activity
  – Metformin, anti-inflammatory agents
  – Bariatric Surgery