Evidence for the role of obesity in prostate cancer progression

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Quick update on body fatness and prostate cancer incidence and mortality
Death from prostate cancer by BMI, Cancer Prevention Study II, 1982-1998

Calle E et al. 2003; NEJM 348:1625-1638

P-trend < 0.001
Obesity and prostate cancer, Health Professionals Follow-up Study

Obesity and prostate cancer risk in the NIH-AARP Diet and Health Study

Wright ME et al. Cancer. 2007;109:675-84

P-trend = 0.0006

RR

2.12
1.08-4.15

P-trend = 0.02

0.67
0.50-0.89

P-trend = 0.0006
Cause versus bias?

• **Obesity →**
  - Risk (causation)
    • ↑ Risk of death from prostate cancer
    • ↓ Risk of nonaggressive prostate cancer
  - Detection bias
    • ↓ PSA (lower production, hemodilution)
    • ↑ Prostate volume

Freedland SJ et al. Cancer Causes Control 2006;17:5-9;
Freedland SJ et al. J Urol 2006;175:500-504;
Bañez LL et al. JAMA 2007;298:2275-2280
What about obesity / weight gain and poor outcome after prostate cancer diagnosis?

• Emerging support that the extent of body fatness and weight gain
  – Before diagnosis
  – Circa diagnosis

• are risk factors for recurrence and prostate cancer death in men with prostate cancer.

Considerations (fully or partially) specific to prostate cancer outcomes

• To confirm or refute associations observed thus far

• For studies going forward
Consideration 1

• What is the optimal prostate cancer outcome to capture biology and import?
  – Biology and import: Progression to metastasis or death from prostate cancer.

  – Nature of outcome that can be studied may depend on the type of treatment, though.
    • Especially when studying men with clinically localized prostate cancer (patients selected for curability → few deaths)
      – Surgery - biochemical recurrence
      – Radiation therapy or active surveillance - rising PSA
Consideration 2

- Confounding - Body fatness appears to be a risk factor for advanced stage and high-grade prostate cancer AND stage/grade are prognostic factors
  - Must take into account stage and grade in the analysis to determine whether body fatness/weight gain are associated with poor outcome in men with prostate cancer.

![Diagram showing the relationship between body fatness/weight gain, advanced stage/high-grade prostate cancer, and recurrence/death from prostate cancer.]
Consideration 3

- Etiologically relevant measurement - Timing of body fatness / weight gain relative to the diagnosis / treatment of prostate cancer
  - Pre-diagnostic
  - At diagnosis / treatment
  - Post diagnosis / treatment

Normal → Precursors → Prostate cancer
How can body fatness influence outcomes after treatment, especially after prostatectomy?

Body fatness

Escaped prostate cancer cells

Nascent bony mets

Prostate cancer focus

Prostatectomy

No prostate, no prostate cancer focus

Recurrence / death from prostate cancer

Body fatness
Consideration 4

• Does the influence of weight gain on outcome differ by starting body fatness?
  – Lean, gain weight
  – Obese, gain weight
  – Lean, no weight gain
  – Obese, no weight gain

• Considerations 3 and 4 coupled: Full evaluation of body fatness and weight gain over the life course.
  – Requires prospective study of men without the diagnosis, followed to diagnosis (and treatment), and then followed to death
  – Requires repeated measures of body fatness, including circa the diagnosis /treatment
Consideration 5

• Confounding and modifying effects by factors that are highly correlated with body fatness
  – Physical inactivity
  – Diabetes
  – Energy intake
  – Smoking

• Statistical analyses

\[
\text{Obesity} \rightarrow \text{Poor outcome} \\
\text{Physical inactivity} \rightarrow \text{Physical inactivity} \rightarrow \text{Obesity} \rightarrow \text{Poor outcome} \\
\text{Smoking} \rightarrow \text{Smoking} \rightarrow \text{Obesity} \rightarrow \text{Poor outcome}
\]
Consideration 6

- Alternative explanations
- Greater technical difficulty when treating obese men relative to lean men (e.g., positive surgical margins)
  - Lower likelihood of cure unrelated to prostate cancer biology
- Different choice of treatment by obese and non-obese men
  - Where the treatment may have a different likelihood of cure irrespective of extent of body fatness
- Won’t discuss further today, but needs to be evaluated.
Consideration 7

- Hormonal therapy for men with metastatic prostate cancer causes central adiposity and metabolic perturbations.
  - What is the influence of this milieu on prostate cancer death (beyond obvious increase in risk of death from other causes)?

- Won’t discuss further today, but needs to be evaluated.
Consideration 8

- Surveillance for the early recurrence (e.g., post-prostatectomy)
  - What is the influence of body fat on PSA produced by cells that have escaped from the prostate?
    - ↓ PSA (lower production, hemodilution) in men who are obese compared with lean
  - Detection bias - time to recurrences would be falsely LONGER in obese compared with lean men

- Won’t discuss further today, but needs to be evaluated.
BMI and risk of biochemical recurrence after prostatectomy, JHH

| Table 3. RR of time to biochemical progression after RP by BMI relative to normal weight |
|-----------------------------------------------|---|----------------|
| Adjusting for preop clinical characteristics:* | RR | 95% CI         | p Value |
| Overwt                                        | 1.50 | 1.14–1.97     | <0.001  |
| Mild obesity                                  | 1.97 | 1.42–2.72     |
| Moderate + severe obesity                     | 1.52 | 0.77–3.00     |
| Adjusting for clinical + pathological characterics: † |     |                | 0.03     |
| Overwt                                        | 1.23 | 0.93–1.62     |
| Mild obesity                                  | 1.51 | 1.09–2.10     |
| Moderate + severe obesity                     | 1.29 | 0.65–2.54     |

* Age, race, biopsy Gleason sum, clinical stage, preoperative PSA and year of surgery.
† Age, race, clinical stage, preoperative PSA, year of surgery, pathological Gleason sum, margin status, extraprostatic extension, seminal vesicle invasion and lymph node metastasis.

Pre-diagnostic obesity and prostate cancer death in men with prostate cancer, Physicians’ Health Study

A. Baseline BMI: Overall study period 1982-2007

Unadjusted

Pre-diagnostic body mass index and prostate cancer death in men with prostate cancer, PHS

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>RR*</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>25.0-29.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30.0+</td>
<td></td>
<td>0.0042</td>
</tr>
</tbody>
</table>

*Adjusted for age at diagnosis, baseline smoking status, time interval from BMI measurement to prostate-cancer diagnosis, clinical stage, and Gleason grade.

BMI 30+ vs < 25 kg/m²:
- Adj excluding for stage/grade – RR=2.66
- Adj including for stage/grade – RR=1.95

Men who gain weight have a higher risk of prostate cancer recurrence after prostatectomy, JHH

Adjusted for weight 5 years before surgery, height, physical activity 1 year after surgery, age, race/ethnicity, family history, year of surgery, stage, grade, and smoking status.

Men who gain weight have a higher risk of recurrence after prostatectomy, JHH

Summary

• Evidence building that obesity/weight gain is a risk factor for poor outcome in men diagnosed with prostate cancer
  – Opposite may be true (weight loss), but much more work is needed
• Many knowledge gaps
• Many methodologic issues that need to be addressed

• Bottom line: May be an important modifiable risk factor for poor outcome in men with prostate cancer.