Genetics of Nicotine Dependence & Impact of Smoking on Bladder Cancer Risk and Prognosis

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Current smoking in the US

- 50th anniversary of Surgeon General’s report
- Adult smoking rates have dropped
  - 42% in 1964  18% in 2013
- 42.1 million Americans are current smokers
  - 78% smoke daily  22% smoke some days
- Prevalence of current smoking among bladder cancer patients is 30-45%

USDHHS. *Exec Summary* 2014
CDC. *MMWR* 2014; Ostroff et al. *J Cancer Edu* 2000
Most smokers want to quit
• 70% current smokers express desire to quit
• 44% make active attempt to quit
• Only 4-7% achieve long-term cessation after unaided quit attempt
• Quit rates improve with behavioral counseling and cessation therapies

Why is it so difficult to quit smoking?

Fiore et al. *Treating Tob Use* 2008
Physiologic Effects of Nicotine

- After inhalation, nicotine reaches brain 10 seconds
- Activates **nicotinic acetylcholine receptors** (nAChRs) (yellow); most predominant are $\alpha_4\beta_2$ subtype
Physiologic Effects of Nicotine

- Induces release of dopamine from vesicles into synapse

NIH Publication No. 00-4871
Physiologic Effects of Nicotine

- Dopamine binds to its receptors, activating the reward pathway
- Continued smoking increases the number of nAChR’s
- Need to keep smoking to sustain reward/avoid withdrawal

NIH Publication No. 00-4871
Is Nicotine Dependence Genetic?

- **Twin studies:**
  - Heritability 50-75%; highest for CPD

- **Candidate gene studies:**
  - Many genes in reward/metabolism pathway are *polymorphic*
  - 80% nicotine metabolized to cotinine by *CYP2A6*
    - People are fast, intermediate or slow metabolizers
    - Fast metabolizers smoke more CPD, have harder time quitting smoking

Loukala et al. *Curr Addict Rep* 2014;
Genetics of Nicotine Dependence

• **Genome-wide association studies (GWAS)**
  – Agnostic search, interrogate 2 million variants

• **2010: Tobacco & Genetics (TAG) Consortium**
  – Meta-analysis of 16 GWAS
    n=74,053 whites (European ancestry (EA))

• **2012: STOMP Consortium**
  – Meta-analyses of 12 GWAS
    n=32,389 African Americans (African ancestry)

David et al. *Trans Psych* 2012; Chen et al. *Genet Epidemi* 2012
Furberg et al. *Nat Genetics* 2010
Genetics of Nicotine Dependence (ND)

• Both studies found variants that influence CPD nAChR gene cluster *CHRNA5-A3-B4* on chr15
  – Replicated in multiple studies

• Statistically significant, but effect size small
  – Variant increases amount smoked by 1 CPD

• **Clinical utility:** Pharmacogenetics (pgx)
  – ND variants may impact how a smoker responds to different cessation medications

Chen et al. *Genet Epidem* 2012; Saccone et al. *PLoS Genet* 2010
Furberg et al. *Genome Med* 2010
Pharmacogenetics of Smoking Cessation

- 2 PgX RCT trials of cessation medications
  - King et al. (2012) n=1,175 EA smokers
    - Response to varenicline influenced by nAChR variants
    - Response to bupropion influenced by CYP2B6 variants
  - Chen et al. (2014) n=709 EA smokers
    - NRT is effective in smokers with fast, but not slow, CYP2A6 metabolism variants

Chen et al. *Addiction* 2014
King et al. *Neuropsychopharmacol* 2012
Smoking & Bladder Cancer Risk

• Accounts for ~50% cases in men & women
• Impact of smoking (ever/never) has gotten stronger over time

1994-1998: OR 2.9 (95% CI: 2.0-4.2)
1998-2001: OR 4.2 (95% CI: 2.8-6.3)
2002-2004: OR 5.5 (95% CI: 3.5-8.9)

– Same trend as seen for lung cancer
– May be due to changes in cigarette composition (e.g., higher levels of bladder carcinogen, BaP)

Freedman ND *JAMA* 2011; Baris et al. *JNCI* 2010
Smoking and Bladder Cancer Risk

• Dose-response smoking behaviors & risk
  – **CPD**: The *more* you smoke=higher risk
  – **Duration**: The *longer* you smoke=higher risk
  – **Pack-years**: The *greater #* pack-years=higher risk
    • Difficult to interpret since a 10 pack-year smoker is:
      2 packs a day for 5 years ½ pack a day for 20 years
  – **Cessation**: Quitting decreases risk
    • Risk reduction of 30% after 1-4 years of quitting
    • Risk reduction of 60-70% after 25 years of quitting
    • **Risk never returns to that of never smoker**

Freedman *JAMA* 2010; Brennan et al. *Ca Causes Control* 2001
Brennan et al. *Int J Ca* 2000
Smoking & Bladder Cancer Subtypes

• Highest risk for aggressive disease
  
  Low-grade superficial:  OR 2.2 (95% CI: 1.8-2.8)
  High-grade superficial: OR 2.7 (95% CI: 2.1-3.6)
  Muscle-invasive:        OR 3.7 (95% CI: 2.5-5.5)

• Tobacco-specific carcinogens (4-ABP, BaP)
  – Induce DNA adducts and signature mutations in $p53$ tumor suppressor gene

Jiang et al. *Int J Ca* 2012; Wallerand et al. *Carcinogenesis* 2005
Jebar et al. *Oncogene* 2005
Smoking, Genes & Bladder Cancer Risk

- Garcia-Closas et al. examined joint effect of smoking & genetic variants on risk
  Pooled data from 7 studies
  - n=3,942 EA bladder cancer cases
  - n=5,680 EA controls

Polygenic risk score (PRS)
- 12 candidate genetic variants
- Grouped into low to high genetic risk categories
- Calculated absolute risk: likelihood of getting bladder cancer in 30 years if you are a 50 year old white male

Garcia-Closas et al. Cancer 2013
Cumulative 30-year absolute risk in a 50-year old US male overall and by polygenic risk score (PRS)

Garcia-Closas et al. *Cancer* 2013
Smoking, Genes & Bladder Cancer Risk

• Clinical utility: Use PRS to...
  – Target *prevention of smoking* in never smokers
    • Requires genotyping all never smokers only to target highest PRS group: *should discourage all from starting*
  – Target *smoking cessation interventions*
    • May give false assurance to lowest PRS group: *should encourage all to quit*
  – Define study population for *screening*
    • Generalizability limited: *Studies needed among women, different ancestries*

Garcia-Closas et al. *Cancer Res* 2013
Furberg & Bochner. *Nat Urol Rev* 2014
Cessation & Bladder Cancer Prognosis

• 2 Systematic Reviews
  – Most studies cross-sectional, focus on smoking history at diagnosis
    • Suggest smoking adversely impacts outcomes

• Does quitting smoking after diagnosis improve prognosis?
  – Conduct prospective study among smokers, follow-up after diagnosis for change in status
  – Biochemically-verify smoking status
    • Misreporting among general population smokers 32%
    • Misreporting among cancer patients that smoke ~50%
## Cessation & Bladder Cancer Prognosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Continued Smokers</th>
<th>Quit Around Diagnosis</th>
<th>Former Smokers</th>
<th>Recurrence Risk Continued vs. Former Smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleshner et al. 1999</td>
<td>1999</td>
<td>N=286 NMIBC patients</td>
<td>108 (38%)</td>
<td>51 (18%)</td>
<td>127 (44%)</td>
<td>1.40 (95% CI: 1.03-1.91)</td>
</tr>
<tr>
<td>Chen et al. 2007</td>
<td>2007</td>
<td>N=201 NMIBC patients</td>
<td>78 (39%)</td>
<td>59 (29%)</td>
<td>64 (32%)</td>
<td>2.4 (95% CI: 1.2-4.0)</td>
</tr>
</tbody>
</table>

Cessation & Lung Cancer Prognosis

• Parsons et al. Systematic Review & M-A
  – 10 RCTs/observational prospective studies
  – Measured effect of *quitting smoking after diagnosis* on lung cancer outcomes

• Continued smoking increased risk of
  – All-cause mortality 2.94 (95% CI: 1.15-7.54)
  – Second primary tumor 4.31 (95% CI: 1.09-16.09)
  – Recurrence 1.26 (95% CI: 1.06-1.50)

“Smoking Cessation should be strongly promoted…”

Parsons et al. *BMJ* 2010; Kalemkerian et al. *JNCCN* 2011
Policy Statements

• Collectively this research prompted:
  2014 Surgeon General’s Executive Report
  White papers from: ASCO & AACR

• Call for tobacco use assessment &
treatment to be recognized as a standard
of quality cancer care

  “...improved provision of cessation assistance to all
  patients with cancer who use tobacco or have recently
  quit is needed...”

Toll et al. AACR policy statement. Clin Cancer Res 2013
Hanna et al. ASCO policy statement. JCO 2013
Thank you