Differential Effects of Cigarette Smoking on Cardiovascular Disease in Females

Diann Gaalema, PhD
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OUTLINE

• Cardiovascular disease (CVD) and smoking
• Sex differences in smoking and CVD
• Potential mechanism behind increased risk
• Rates of smoking in those with CVD by sex
• Challenges in smoking cessation in those with CVD
• Implications for secondary prevention
CARDIOVASCULAR DISEASE AND SMOKING
CARDIOVASCULAR DISEASE AND SMOKING

• Dangers of combusted tobacco use\(^1\)
  • Endothelial dysfunction
  • Blood vessel constriction
  • Platelet activation
  • Dyslipidemia
  • Chronic inflammatory state

• Outcomes
  • Accelerate atherosclerosis
  • Destabilize coronary artery plaques
  • Precipitate acute coronary events

• 50 years of smoking has led to 7,787,000 premature deaths due to cardiovascular and metabolic diseases\(^2\)

1. Barura et al., 2018. 2. USDHHS, 2014

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SEX DIFFERENCES IN CARDIOVASCULAR DISEASE AND SMOKING
SMOKING AND CVD – SEX DIFFERENCES

• Generally, an age gap in the development of CVD by sex
  • Age of first myocardial infarction\(^1\)
    • 72 for females
    • 65.6 for males
  
• Smoking appears to eliminate the age gap
  • Study of 11,762 men and 13,206 women
    • Looking at increased risk of MI in females smoking ≥20 cigarettes per day
      • Aged 25-54, HR = 3.8
      • Aged 55-69, HR = 2.2
      • Aged ≥70, HR = 1.6
    • Do not see this same pattern in males
  
• Similarly, we see males and females, who smoke, entering cardiac rehabilitation at a similar age\(^3\)
  • Elevated CO – 63, did not differ by sex
  • Low CO – 67, likely differed by sex

SMOKING AND CVD – MORE THAN JUST AGE AT FIRST EVENT

- Disparities in development of disease and outcomes
  - Within those who smoke, females have a 25% increased risk of developing CHD than males\(^1\)
  - Multivariate-adjusted RR for CHD mortality: males 2.50 (95% CI, 2.34–2.66), females, 2.86 (95% CI, 2.65–3.08)\(^2\)
- These discrepancies are even higher for certain types of CHD
- STEMI
  - Smoking is associated with a significantly greater increase in STEMI for females than males (IRR: 6.62 vs. 4.40)\(^3\)
  - Outcomes disparate here too, higher association between STEMI and 30-day mortality in females compared to males (OR 3.86 vs. 2.75)\(^4\)

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1. Huxley et al., 2011.
2. USDHHS 2014.
4. Vasiljevic et al., 2021
POTENTIAL MECHANISM OF INCREASED RISK
USE OF NICOTINE/COMBUSTION REDUCES ESTROGEN LEVELS

- The relationship between tobacco use, estrogen levels, and the risk of cardiovascular disease (CVD) in females is complex and multi-faceted

  + **Hypothalamic-pituitary-Ovarian Dysfunction**: Nicotine has been shown to adversely impact ovarian function by inhibiting the secretion of gonadotropin-releasing hormone (GnRH), essential for estrogen synthesis\(^1\)

  + **Hepatic Enzyme Induction**: Compounds in tobacco smoke induce the activity of cytochrome P450 liver enzymes, which accelerate the metabolism (e.g. 2'-hydroxylation) and clearance of estrogen from the body\(^2\)

  + **Inhibition of Aromatase Enzyme**: The aromatase enzyme (CYP19A1) converts androgens to estrogens. Nicotine and polycyclic aromatic hydrocarbons (PAH) appear to inhibit aromatase activity, reducing the endogenous production of estrogen\(^3,4\)

MECHANISMS OF INCREASED CVD RISK

- **Endothelial Dysfunction:** Estrogen plays a pivotal role in maintaining vascular health by enhancing nitric oxide (NO) production, an endothelial-derived vasodilator. Reduced estrogen levels diminish NO availability, promoting vasoconstriction and thereby increasing the risk of cardiovascular events.\(^1\)

- **Pro-inflammatory State:** Reduced estrogen levels tip the balance towards a pro-inflammatory state characterized by elevated levels of inflammatory markers such as C-reactive protein, interleukin-6, and tumor necrosis factor-α, further contributing to the pathogenesis of CVD.\(^2\)

- **Altered Lipid Metabolism:** Estrogen has a favorable effect on lipid profiles, increasing high-density lipoprotein (HDL) and reducing low-density lipoprotein (LDL) levels. Lowered estrogen due to tobacco use exacerbates dyslipidemia, a known risk factor for CVD.\(^3\)

- **Increased Platelet Aggregation:** Lower levels of estrogen have been linked to increased platelet aggregation and elevated plasma fibrinogen levels, enhancing the pro-thrombotic milieu conducive to MI and CVA.\(^4\)

- **Synergistic Negative Effects:** Combusted tobacco itself directly contributes to endothelial dysfunction, inflammation, and platelet aggregation. When combined with reduced estrogen levels, this results in a synergistic deleterious impact on cardiovascular health.\(^5\)

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Reduced estrogen levels

- Hypothalamic-Pituitary - Ovarian dysfunction
- Hepatic enzyme induction (P450 1A1 and 1A2)
- Inhibition of aromatase

Increased CVD risk

- Endothelial dysfunction
- Pro-inflammatory state
- Altered lipid metabolism
- Increased platelet aggregation

Exposure to combusted byproducts and nicotine
RATES OF SMOKING IN THOSE WITH CARDIOVASCULAR DISEASE BY SEX
SMOKING RATES BY SEX IN THOSE WITH CVD

- Historically, males have been more likely to smoke which may have led to less focus on the issue of smoking in females
- Over the last several decades, the prevalence of smoking in the United States has dramatically decreased
  - Decreasing faster in certain populations
- Looking at the NHANES, risk factors by sex over time in those 20-79 years of age
  - Current smoking decreasing faster in males
- A pattern replicated in other vulnerable populations
  - Female smoking rates may actually overtake that of males

1. Peters et al., 2019. 2. Cepeda-Benito et al., 2018
SMOKING RATES BY SEX IN CARDIAC REHABILITATION

- AACVPR Registry Database
  - Data from certified programs nation-wide
  - Over 400,000 patients from 2012-2021
    - ~30% female

- Current smoking rates at entry are equal
  - Females: 7.6%
  - Males: 7.8%

Unpublished data
CHALLENGES OF SMOKING CESSATION IN THOSE WITH CARDIOVASCULAR DISEASE
SMOKING CESSATION IS CHALLENGING

- Efficacious medications available
  - NRT
  - Bupropion
  - Varenicline
  - Combination therapies likely best

- Efficacy and safety demonstrated, including in those with CVD$^{1-5}$
  - Still strong hesitancy for use in populations with CVD

- In a study of 282 hospitals and over 30,000 patients hospitalized with CHD who were currently smoking$^6$
  - Only 22.7% of patients received any sort of medication for smoking cessation
  - 90% of those were for nicotine patch alone

RELYING ON NRT MAY BE PROBLEMATIC FOR FEMALES

- NRT may not be as effective for females as males\(^1,2\)
  - Females may be less sensitive to the pharmacological effects of nicotine\(^3\)
  - Females metabolize nicotine faster than males
  - Under dosed on nicotine replacement therapy?

1. Smith et al., 2017. 2. Piper et al., 2010. 3. Perkins et al.

### Treatment comparison

<table>
<thead>
<tr>
<th>Head-to-head comparisons</th>
<th>Risk ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
</tr>
<tr>
<td>Varenicline vs. TN</td>
<td>1.41 [1.12, 1.76]</td>
</tr>
<tr>
<td>Bupropion SR vs. TN</td>
<td>1.02 [0.83, 1.25]</td>
</tr>
<tr>
<td>Varenicline vs. Bupropion SR</td>
<td>1.38 [1.08, 1.77]</td>
</tr>
</tbody>
</table>

| **Men**                  |                     |
| Varenicline vs. TN       | 1.16 [0.91, 1.47]   |
| Bupropion SR vs. TN      | 1.04 [0.82, 1.33]   |
| Varenicline vs. Bupropion SR | 1.11 [0.85, 1.45] |

| **Combined**             |                     |
| Varenicline vs. TN       | 1.25 [1.02, 1.53]   |
| Bupropion SR vs. TN      | 1.01 [0.82, 1.23]   |
| Varenicline vs. Bupropion SR | 1.24 [0.99, 1.55] |

| Versus placebo           |                     |
| **Women**                |                     |
| TN vs. Placebo           | 1.45 [1.24, 1.70]   |
| Varenicline vs. Placebo  | 2.04 [1.71, 2.44]   |
| Bupropion SR vs. Placebo | 1.48 [1.23, 1.77]   |

| **Men**                  |                     |
| TN vs. Placebo           | 1.69 [1.41, 2.03]   |
| Varenicline vs. Placebo  | 1.96 [1.65, 2.34]   |
| Bupropion SR vs. Placebo | 1.76 [1.43, 2.19]   |

| **Combined**             |                     |
| TN vs. Placebo           | 1.59 [1.38, 1.84]   |
| Varenicline vs. Placebo  | 1.99 [1.71, 2.33]   |
| Bupropion SR vs. Placebo | 1.61 [1.35, 1.91]   |
RELYING ON NRT MAY BE PROBLEMATIC FOR FEMALES

• Other medications may work better for females\(^1\)

• Relying on NRT for treating smoking in those with CVD may continue to widen sex disparities

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1. McKee et al., 2016
IMPLICATIONS FOR SECONDARY PREVENTION/CARDIAC REHABILITATION
IMPLICATIONS FOR CARDIAC REHABILITATION/SECONDARY PREVENTION

- Smoking can interfere with gains during CR
- UVMMC Clinical CR database
  - 2208 patients who completed CR
    - 553 female
- Improvement in fitness (Peak VO2)
  - Effect of current smoking (self-report)
  - No sex effect

Unpublished data
IMPLICATIONS FOR CARDIAC REHABILITATION/SECONDARY PREVENTION

• Do those who smoke differ by sex?
• Carbon monoxide measured on 1122 patients entering CR
  • 322 females
• Focused on those with CO ≥ 4
  • Examined differences by sex

Females with elevated CO had CO levels double that of males
EFFECT OF SMOKING ON OUTCOMES IN CR/PR

Check out the poster session

More in-depth on how smoking affects outcomes
THANK YOU

Diann Gaalema, PhD
digaalem@utmb.edu
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