New Risk Factors for ESCC?

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New hypotheses

- ?
- Microbiome
- Animal contact
- Other
New hypotheses

• **Tooth loss - Microbiome**
  • Multiple studies with tooth loss or similar variables
  • Modest odds ratios, but we are using weak variables
  • Direct assessment of microbiome may be better
    • Case-control studies probably not valuable
    • Cross-sectional studies across histologic spectrum
    • Methods need more development
Oral and Esophageal Microbiome

• Groups
  1. Endoscopically Normal
  2. Low Grade Dysplasia
  3. High Grade Dysplasia
  4. Early Stage/Asymptomatic cancers

• Recruit up to 200 subjects from each group
  • Selected from ongoing screening

• Also compare to cardia and noncardia gastric
New hypotheses

• **Animal Contact**

• **Two studies with intriguing results**

**Contact with ruminants is associated with esophageal squamous cell carcinoma risk**

Dariush Nasrollahzadeh\textsuperscript{1,2}, Weimin Ye\textsuperscript{1}, Ramin Shakeri\textsuperscript{2}, Masoud Sotoudeh\textsuperscript{2}, Shahin Merat\textsuperscript{2}, Farin Kamangar\textsuperscript{3}, Christian C. Abnet\textsuperscript{4}, Farhad Islami\textsuperscript{2,5}, Paolo Boffetta\textsuperscript{5}, Sanford M. Dawsey\textsuperscript{4}, Paul Brennan\textsuperscript{6} and Reza Malekzadeh\textsuperscript{2}

<table>
<thead>
<tr>
<th></th>
<th>Controls (%)</th>
<th>Cases (%)</th>
<th>Crude OR (95%CI)</th>
<th>Adjusted\textsuperscript{1} OR (95%CI)</th>
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<td>Equines</td>
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<tr>
<td>Never</td>
<td>234 (44.1)</td>
<td>121 (43.1)</td>
<td>Referent</td>
<td>Referent</td>
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<tr>
<td>Ever</td>
<td>297 (55.9)</td>
<td>160 (56.9)</td>
<td>1.04 (0.77–1.41)</td>
<td>0.96 (0.67–1.38)</td>
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<tr>
<td>Ruminants</td>
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<tr>
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<td>166 (31.3)</td>
<td>15 (5.3)</td>
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<tr>
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<td>365 (68.7)</td>
<td>266 (94.7)</td>
<td>9.06 (4.94–16.61)</td>
<td>7.63 (3.92–14.86)</td>
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New hypotheses

• **Animal Contact**
  • Two studies with intriguing results
  • We don’t really know how to interpret the results
    • Really an animal effect or something indirect?
  • How can this be explored?
    • Direct measurement of zoonotic disease serology
    • Genome sequences
    • Chips
New hypotheses

• ???
New New Ideas?

- Comparative studies with gastric cardia?
  - Relatively easy in China and Iran
- Clues from GWAS?
  - PLCE1
  - Geography specific hits
    - ADH2/ALDH2 example
    - HLA
- Mutation spectra-defined outcomes?
  - Tumors without P53 mutations
Summary

- Several understudied hypotheses
  - Replication
  - Explanation
- Search for new hypotheses
  - Informed by GWAS
  - Search for etiologic heterogeneity
Questions

• Why the co-occurrence with gastric cardia cancer?

• Can we develop new hypotheses by expanding GWAS?

• Should we start defining tumors by genomic changes for our risk factor analyses?