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

Table 2. Animal contact among esophageal squamous cell carcinoma cases and matched controls

	Controls (%)	Cases (%)	Crude OR (95%CI)	Adjusted[1] OR (95%CI)
Equines				
Never	234 (44.1)	121 (43.1)	Referent	Referent
Ever	297 (55.9)	160 (56.9)	1.04 (0.77–1.41)	0.96 (0.67–1.38)
Ruminants				
Never	166 (31.3)	15 (5.3)	Referent	Referent
Ever	365 (68.7)	266 (94.7)	9.06 (4.94–16.61)	7.63 (3.92–14.86)

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?**

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