Esophageal Cancer: Iran Story

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Esophageal cancer incidence
IPHR-IARC Studies of ESCC in Iran in the 1970s

- Cancer Registry (1968-1971)
- Northeastern Iran is one of the highest-risk populations for ESCC in the world
- At least as common in women as in men
*Gastric and Esophageal Malignancies In North of Iran*
The Golestan Case-Control Study

- Recruitment in 2003-2007
- 300 ESCC cases, recruited from referrals to Atrak Clinic
- Primary controls: 571 neighborhood controls, matched for residence, sex & age
- Secondary controls: 300 Clinic controls, matched for sex & age, same endoscopy as cases

- Lifestyle questionnaire
- Food frequency questionnaire
- Blood, hair and nails
- Cases and clinic controls: fixed & frozen biopsies from tumors + normal esophagus and stomach
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<th>Exposure</th>
<th>Comparison</th>
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<td>Ruminant contact</td>
<td>Ever vs. never</td>
<td>7.6 (3.9-14.9)</td>
<td>Nasrollahzadeh et al, IJC 2015</td>
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<td>Drinking water</td>
<td>Unpiped vs. piped</td>
<td>4.3 (2.2-8.1)</td>
<td>Golozar et al, EJCP 2016</td>
</tr>
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Golestan Cohort Study

- Recruited in 2004-2008
- 50,045 adults, 40-75 yrs, 80% rural
- Participation rates: women 80%, men 65%
- Lifestyle questionnaire
- Food frequency questionnaire
- Blood, urine, hair and nails
Follow-up

- Annual follow-up (cancer, mortality and other events) ongoing
  - >99% success rate over a median of 8 years (Lost-to-follow-up = 407)
- 4,524 deaths till March 2015, most common causes:
  - Cardiovascular 51%
  - Cancer 24%
  - External causes 6%
  - Respiratory disease 5%
- A random subgroup of the original cohort (n=11,418): repeated risk factor assessment, sample collection and blood biochemistry tests every 5 years.
Cancer Events until September 2015

Total number of incident (primary) cancers: 1607

First cohort paper (201 cases): ESCC risk inversely associated with calcium (HR per 100-mg/d increase: 0.88; 95% CI: 0.81-0.96), and zinc intake (HR per 1-mg/d increase: 0.87; 95% CI: 0.77-0.98)  

Hashemian et al, AJCN. 2015
Early detection

• In a pilot study, prevalence of dysplasia in endoscopy was ~6.0%.

\[ \text{Area under ROC curve} = 0.71 \]

Roshandel G et al, BJC 2014

• The low prevalence means:
  • Limited rationale for routine endoscopic screening
  • Limited usefulness for a risk-factor based model
  • Need for a less invasive screening method (e.g. capsule sponge)
  • Need for biomarkers

Etemadi et al, Arch Irn Med. 2012
Non-endoscopic Esophageal cancer Screening Program (NESP)

12000 GCS participants
> 50 years old

Intervention arm (6000)

Control arm (6000)

Sponge cytology

Abnormal
Endoscopic examination and ablation

Normal

Follow-up for cancer, survival, and quality of life
Biomarkers of polycyclic aromatic hydrocarbons (PAHs) exposure

• Median urine 1-OHPG metabolite much higher than US
  *Kamangar et al, Anticanc Res 2005*

• Mean PAH-DNA adducts in female non-smokers higher than smokers in other populations
  *Etemadi et al, IJC 2013*

• Higher PAH intake from staple food in Golestan compared with low-risk areas.
  *Hakami R et al, Nutr Canc 2008*

• Monoclonal antibody in the normal tissue biopsies of cases and controls:

<table>
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<th>PAH antibody Staining</th>
<th>Cases</th>
<th>Controls</th>
<th>Adjusted OR (95% CI)</th>
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<td>49</td>
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<td>26.6 (5.21 – 135)</td>
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*Abedi-Ardekani et al, Gut 2010*
More collaborations

• Urinary biomarkers of PAH in collaboration with FDA and CDC
• Opium GWAS and metabolomic studies in collaboration with National Institute on Drug Abuse (NIDA)
Summary

1. GEMINI provides a good example of an expanding multi-institutional international collaboration
2. The case-control study has identified a number of plausible risk factors
3. The cohort infrastructure, samples availability (including in NCI and IARC) provides a great opportunity to replicate CCS findings and test new hypotheses
4. Interventional studies on early detection are being planned
5. PAH as an important hypothesis, and possible role in risk stratification
Difficult questions

• How can we replicate these findings (except in the Golestan Cohort Study)?
• Is it important to determine the reasons for a declining incidence of ESCC? How?
• What is the possible reason for the low rate of dysplasia in this population? How can this be studied further?
• What is the best strategy for early detection?
Thank You!
Tea Drinking Habits and ESCC Risk
Agreement Between Questionnaire Responses and Measured Tea Temperatures in the Golestan Cohort Study

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<th>Tea temperature (questionnaire)</th>
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<tr>
<td></td>
<td>&lt; 65°C</td>
</tr>
<tr>
<td>Warm or lukewarm</td>
<td>32,414</td>
</tr>
<tr>
<td>Hot</td>
<td>5,385</td>
</tr>
<tr>
<td>Very hot</td>
<td>37</td>
</tr>
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Weighted kappa = 0.49

Islami et al, BMJ 2009
Mortality by September 30th, 2015

- **Cancer, 1114, 22%**
- **IHD, 1587, 32%**
- **CVA, 801, 16%**
- **Respiratory Diseases, 276, 5%**
- **Injuries, 230, 5%**
- **Unknown, 257, 5%**
- **Other vascular, 81, 2%**
- **Infections, 130, 3%**
- **Respiratory Diseases, 276, 5%**
- **Other causes, 76, 2%**
- **Hepatobiliary Diseases, 91, 2%**
- **Neurological Disorders, 95, 2%**
- **Other GI Diseases, 42, 1%**
- **TB, 56, 1%**
- **Diabetes, 52, 1%**
- **Suicide, 30, 1%**
- **Renal Diseases, 116, 2%**
- **Other Causes, 76, 2%**
Cancer Events by September 30th, 2015

- Esophagus, 272, 17%
- Stomach, 251, 16%
- Breast, 94, 6%
- Lung, 92, 6%
- Colorectal, 106, 7%
- Liver, 75, 5%
- Pancreas, 69, 4%
- Leukemia, 77, 5%
- Brain, 91, 6%
- Lung, 92, 6%
- Breast, 94, 6%
- Colorectal, 106, 7%
- Stomach, 251, 16%
- Ovary, 46, 3%
- Lymphoma, 43, 3%
- Skin, 41, 3%
- Prostate, 31, 2%
- Bladder, 37, 2%
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</tr>
<tr>
<td>Never</td>
<td>232 (78)</td>
<td>471 (83)</td>
<td>Reference</td>
</tr>
<tr>
<td>Ever</td>
<td>67 (22)</td>
<td>99 (17)</td>
<td>1.47 (0.98-2.21)</td>
</tr>
<tr>
<td><strong>Opium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>210 (70)</td>
<td>465 (81)</td>
<td>Reference</td>
</tr>
<tr>
<td>Ever</td>
<td>90 (30)</td>
<td>106 (18)</td>
<td>2.00 (1.39-2.88)</td>
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<td><strong>DMFT</strong></td>
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<td>\leq 15</td>
<td>33 (12)</td>
<td>102 (18)</td>
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<tr>
<td>23-26</td>
<td>31 (11)</td>
<td>69 (12)</td>
<td>1.62 (0.85-3.09)</td>
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<td>129 (46)</td>
<td>222 (40)</td>
<td>2.10 (1.19-3.70)</td>
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<td><strong>Formal Education</strong></td>
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<tr>
<td>None</td>
<td>267 (89)</td>
<td>474 (83)</td>
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</tr>
<tr>
<td>Primary school</td>
<td>25 (8)</td>
<td>64 (11)</td>
<td>0.52 (0.27-0.98)</td>
</tr>
<tr>
<td>\geq Middle school</td>
<td>8 (3)</td>
<td>33 (6)</td>
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<td>Candidate genes</td>
<td>ADH1B His/His vs. Arg/Arg</td>
<td>0.63 (?)</td>
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<tr>
<td>Warm or lukewarm</td>
<td>127 (43)</td>
<td>394 (69)</td>
<td>Reference</td>
</tr>
<tr>
<td>Hot</td>
<td>108 (36)</td>
<td>155 (27)</td>
<td>2.07 (1.28-3.35)</td>
</tr>
<tr>
<td>Very hot</td>
<td>63 (21)</td>
<td>19 ( 3)</td>
<td>8.16 (3.93-16.9)</td>
</tr>
<tr>
<td><strong>Interval between pouring and drinking tea (min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 4</td>
<td>132 (44)</td>
<td>394 (69)</td>
<td>Reference</td>
</tr>
<tr>
<td>2-3</td>
<td>112 (38)</td>
<td>138 (24)</td>
<td>2.49 (1.62-3.83)</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>54 (18)</td>
<td>35 ( 6)</td>
<td>5.41 (2.63-11.1)</td>
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Islami et al, BMJ 2009
Caspian Littoral Study 1970

PAH Antibody Staining of Normal Esophageal Mucosa and ESCC Case Status in the Golestan Case-Control Study

- TMAs made from normal biopsies from 120 cases and 120 clinic controls
- IHC performed with Mab 8E11, which recognizes BPDE-DNA/RNA/protein adducts, free BPDE, & other PAHs
- Staining intensity quantified x3 by image analysis and averaged

<table>
<thead>
<tr>
<th>8E11 Mab Staining</th>
<th>Cases</th>
<th>Controls</th>
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