Esophageal Cancer: Iran Story

Reza Malekzadeh, MD
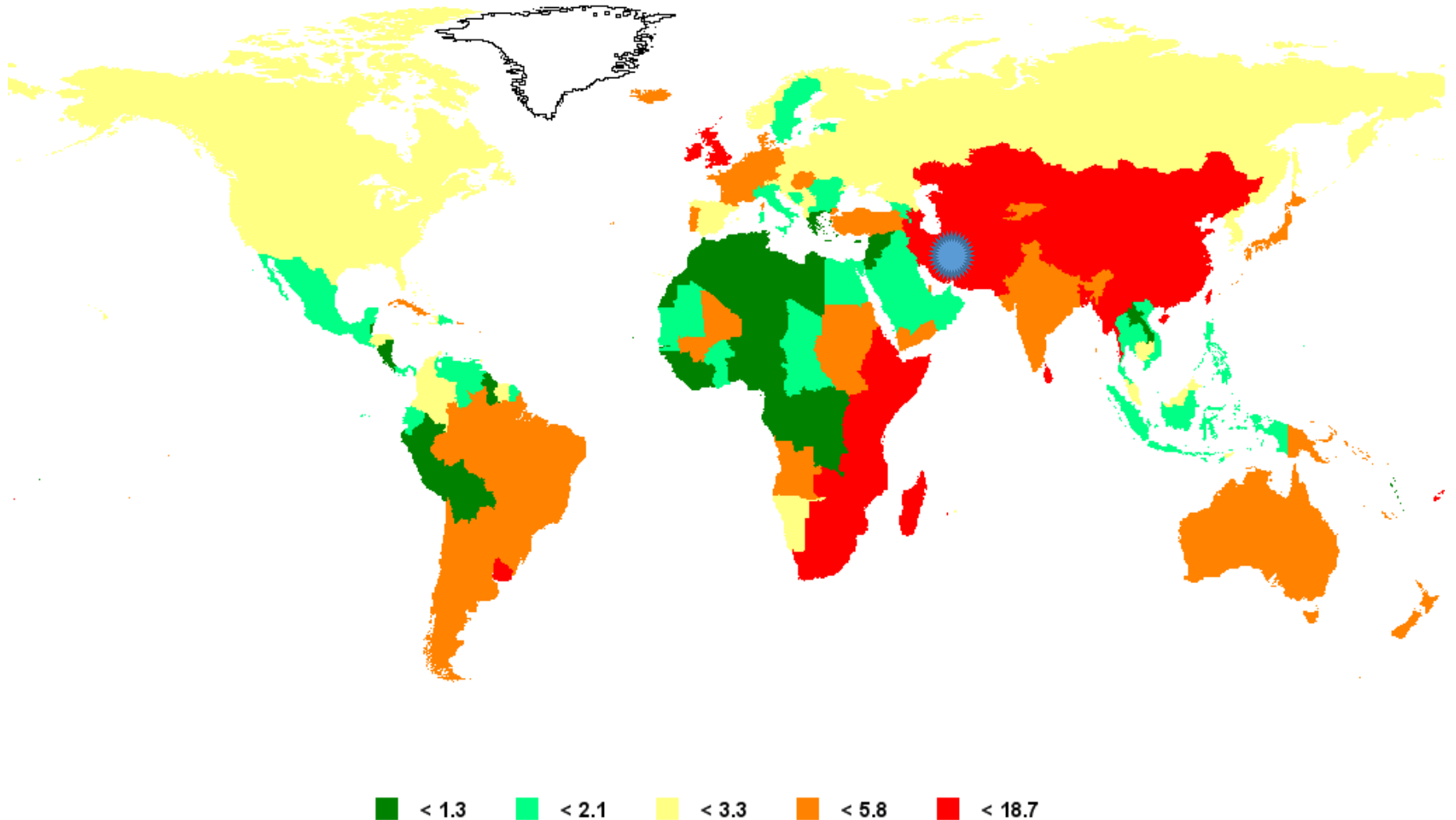
Digestive Disease Research Institute, Tehran University of Medical Sciences

Arash Etemadi, MD PhD

National Cancer Institute, NIH, Bethesda, MD

NIH › **NATIONAL CANCER INSTITUTE**

DDRI

Esophageal cancer incidence

Legend: ■ < 1.3 ■ < 2.1 ■ < 3.3 ■ < 5.8 ■ < 18.7

IPHR-IARC Studies of ESCC in Iran in the 1970s
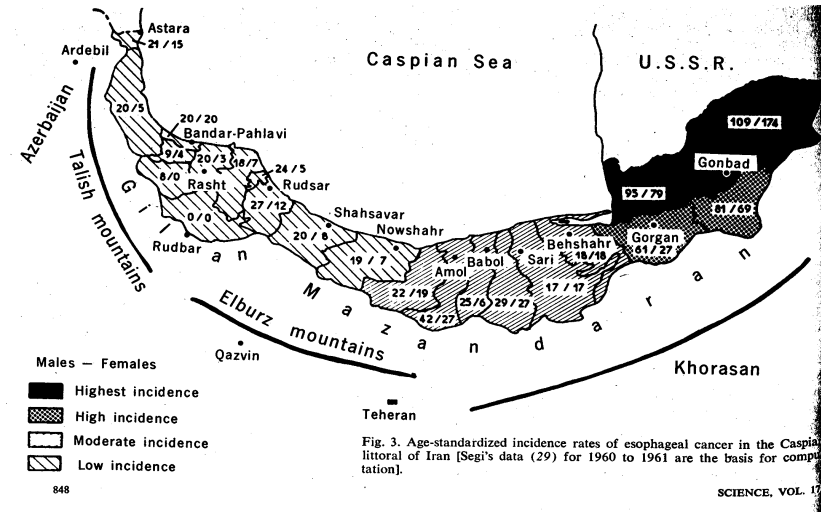
- Cancer Registry (1968-1971)
- Northeastern Iran is one of the highest-risk populations for ESCC in the world
- At least as common in women as in men

*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

Results from the Golestan Case-Control Study

| Exposure	Comparison	Adjusted OR (95% CI)	Reference
Family history	ESCC in first degree relatives vs. not	3.6 (2.3-5.7)	*Akbari et al, IJC 2006*
Cigarettes	Current vs. never	1.7 (1.1-2.7)	*Nasrollahzadeh et al, BJC 2008*
Opium	Ever vs. never	2.0 (1.4-2.9)	*Nasrollahzadeh et al, BJC 2008*
DMFT	32 vs. $\leq$ 15	2.1 (1.20-3.7)	*Abnet et al, CEBP 2008*
Formal Education	Middle school vs. none	0.2 (0.06-0.65)	*Islami et al, IJE 2009*
Tea temperature	Very hot vs. warm	8.2 (3.9-16.9)	*Islami et al, BMJ 2009*
Childhood obesity	Very obese at 15 vs. normal	3.2 (1.3-7.7) in women	*Etemadi et al, Ann Oncol 2012*
Reproductive history	$\geq$ 3 miscarriages vs. none	4.4 (2.1-9.3) in women	*Islami et al, EJCP 2013*
Ruminant contact	Ever vs. never	7.6 (3.9-14.9)	*Nasrollahzadeh et al, IJC 2015*
Drinking water	Unpiped vs. piped	4.3 (2.2-8.1)	*Golozar et al, EJCP 2016*

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
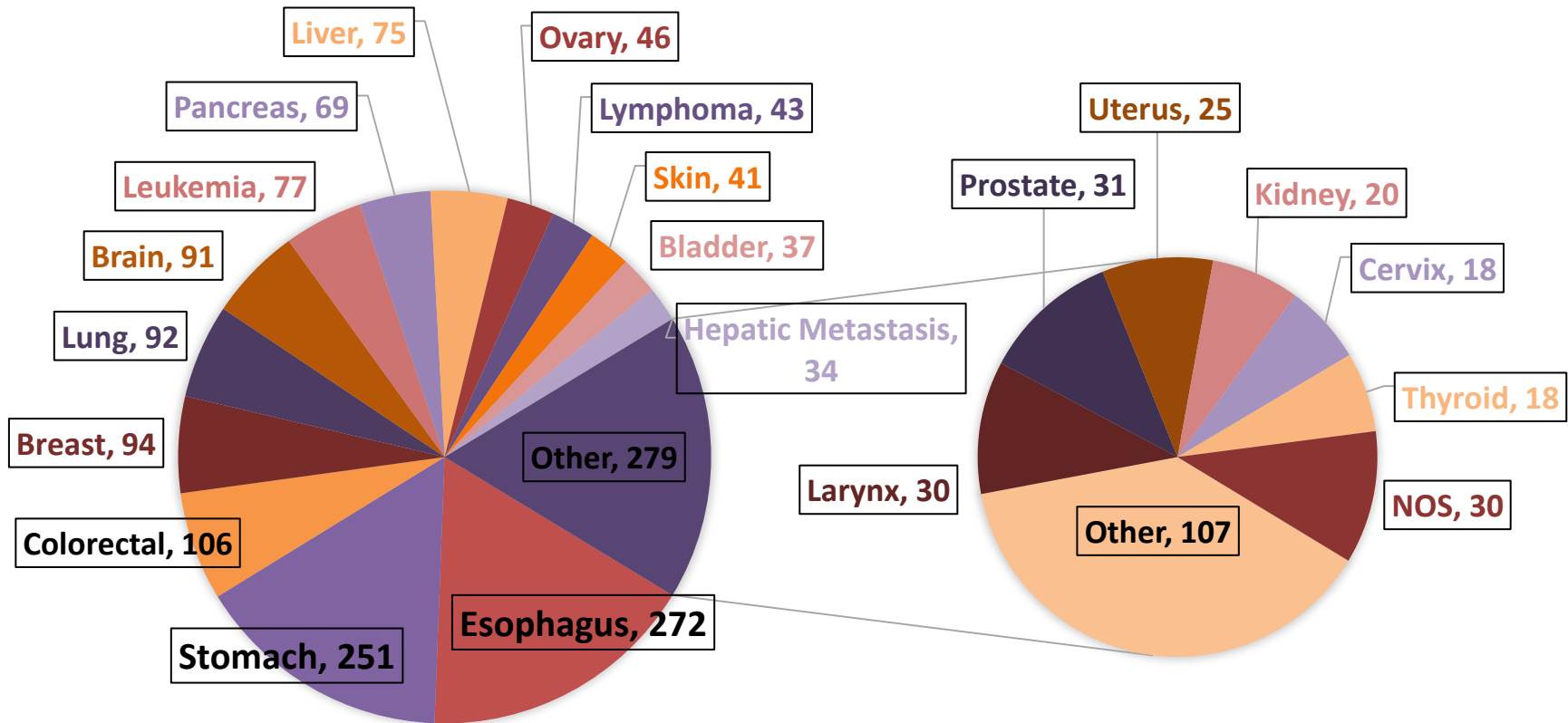
First cohort paper (201 cases): ESCC risk inversely associated with calcium (HR per 100-mg/d increase: 0.88; 95% CI: 0.81-0.96), and zinc intake (HR per 1-mg/d increase: 0.87; 95% CI: 0.77-0.98)
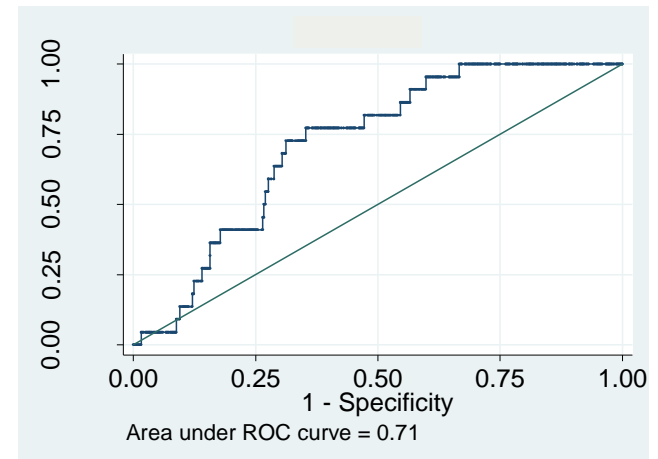
Hashemian et al, AJCN. 2015

Early detection

- In a pilot study, prevalence of dysplasia in endoscopy was ~6.0%.
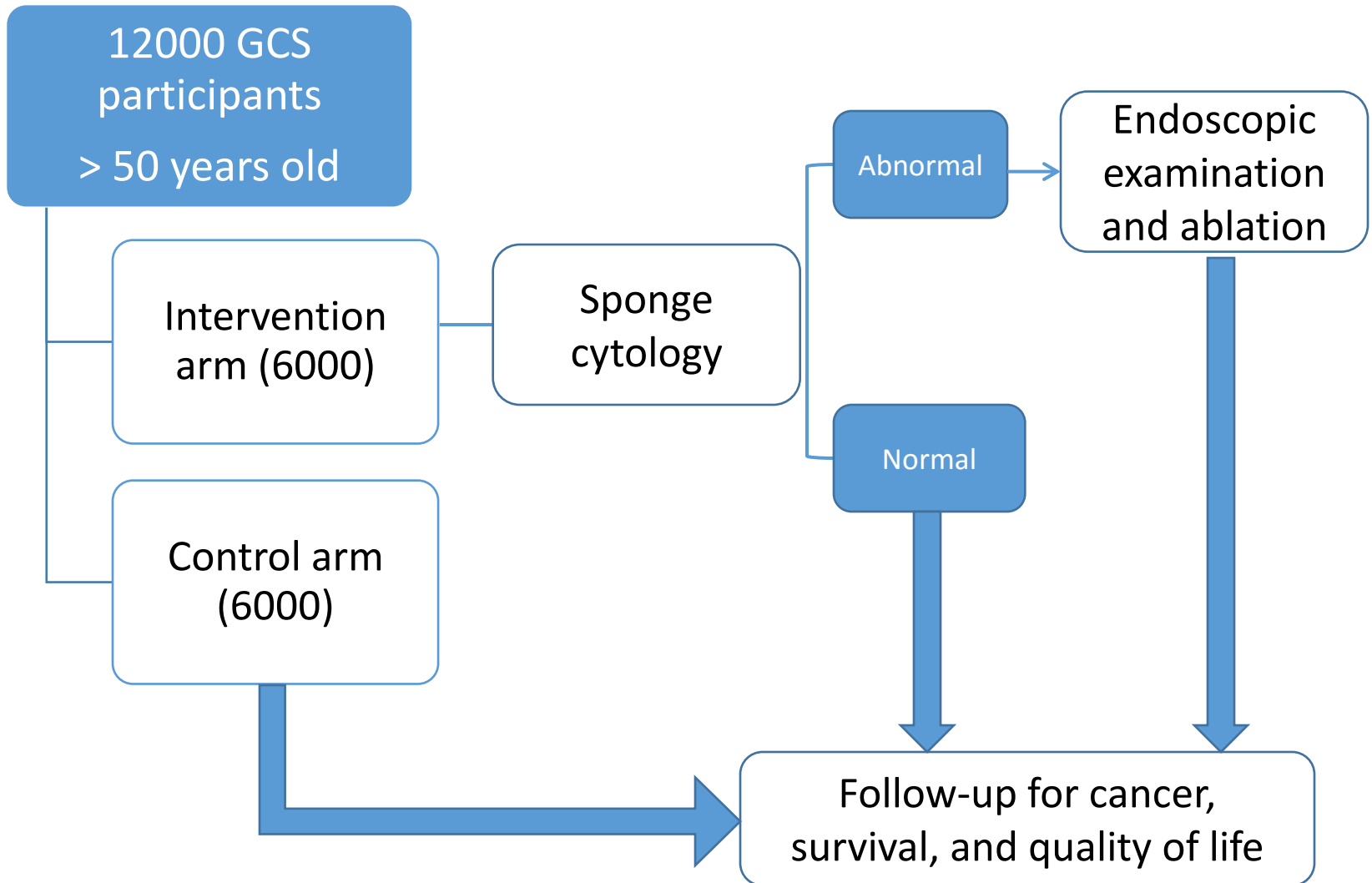
  Roshandel G et al, BJC 2014

- 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

Area under ROC curve = 0.71

Etemadi et al, Arch Irn Med. 2012

Non-endoscopic Esophageal cancer Screening Program (NESP)

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:

PAH antibody Staining	Cases	Controls	Adjusted OR (95% CI)
First quintile	2	20	Reference
Second quintile	6	21	2.42 (0.39 – 14.8)
Third Quintile	14	21	5.77 (1.06 – 31.4)
Fourth Quintile	20	21	11.3 (2.16 – 59.6)
Fifth Quintile	49	20	26.6 (5.21 – 135)

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

	Measured Tea Temperature		
	< 65°C	65-69°C	$\geq$ 70°C
Tea temperature (questionnaire)			
Warm or lukewarm	32,414	3749	467
Hot	5,385	4246	1757
Very hot	37	48	421

Weighted kappa = 0.49

Islami et al, BMJ 2009

Mortality by September 30th, 2015
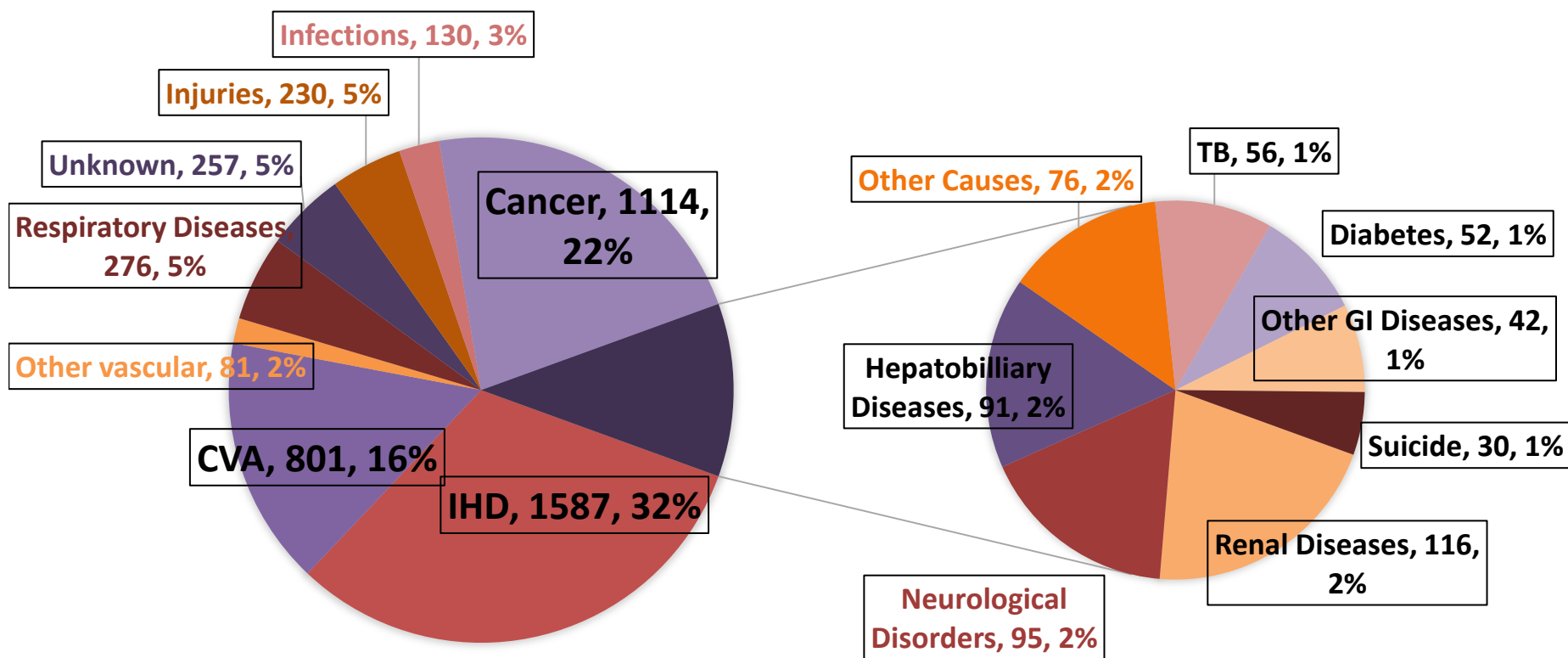
Cancer Events by September 30th , 2015

Liver, 75, 5%
Ovary, 46, 3%
Pancreas, 69, 4%
Lymphoma, 43, 3%
Uterus, 25, 2%
Leukemia, 77, 5%
Skin, 41, 3%
Prostate, 31, 2%
Kidney, 20, 1%
Brain, 91, 6%
Bladder, 37, 2%
Cervix, 18, 1%
Lung, 92, 6%
Hepatic Metastasis, 34, 2%
Breast, 94, 6%
Thyroid, 18, 1%
Other, 279, 17%
Larynx, 30, 2%
Colorectal, 106, 7%
NOS, 30, 2%
Other, 107, 7%
Stomach, 251, 16%
Esophagus, 272, 17%
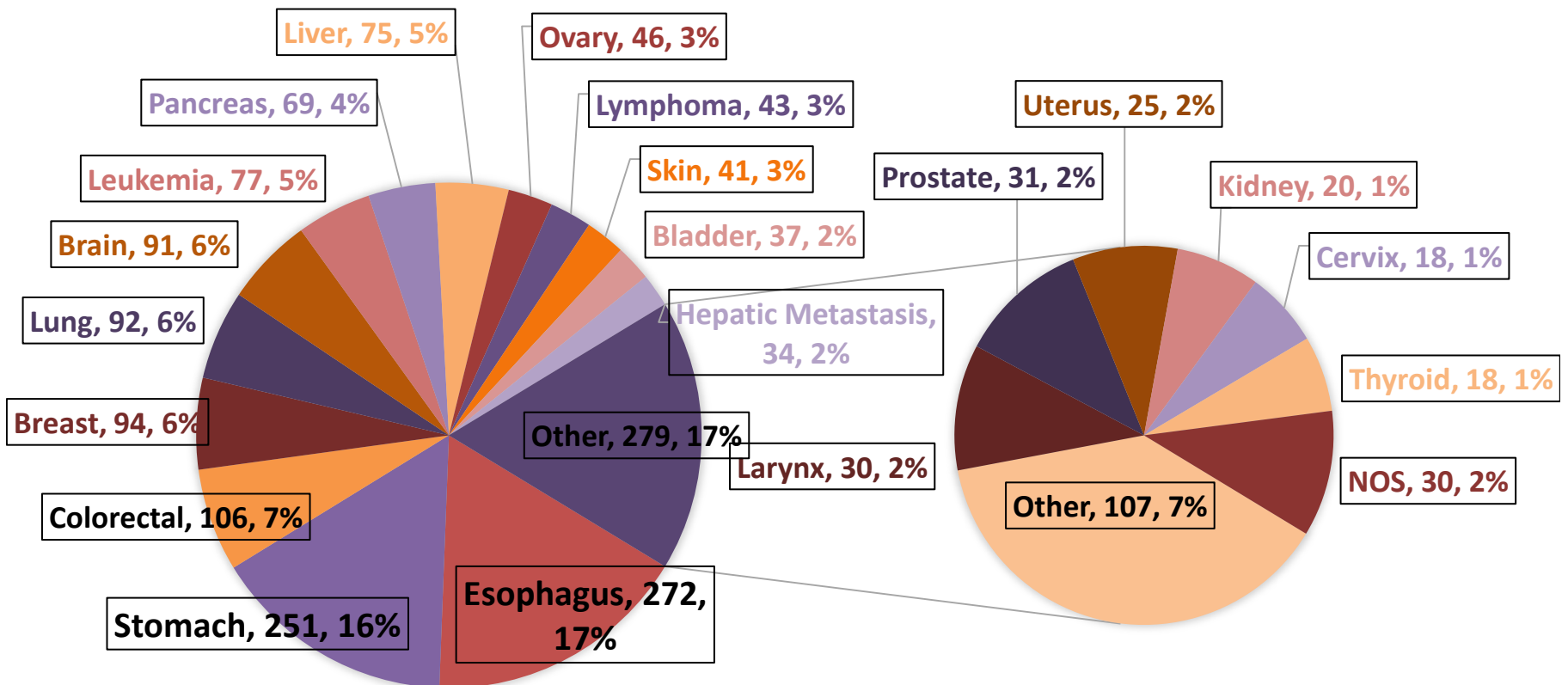
Results from the Golestan Case-Control Study

Exposure	Cases (%)	Control (%)	Adjusted OR (95% CI)
Cigarettes			
Never	232 (78)	471 (83)	Reference
Ever	67 (22)	99 (17)	1.47 (0.98-2.21)
Opium			
Never	210 (70)	465 (81)	Reference
Ever	90 (30)	106 (18)	2.00 (1.39-2.88)
DMFT			
< 15	33 (12)	102 (18)	Reference
23-26	31 (11)	69 (12)	1.62 (0.85-3.09)
32	129 (46)	222(40)	2.10 (1.19-3.70)
Formal Education			
None	267 (89)	474 (83)	Reference
Primary school	25 (8)	64 (11)	0.52 (0.27-0.98)
> Middle school	8 (3)	33 (6)	0.20 (0.06-0.65)

Nasrollahzadeh et al, BJC 2008; Abnet et al, CEBP 2008; Islami et al, IJE 2009

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Tea temperature	Very hot vs. warm	8.16 (3.9-16.9)	Islami et al, BMJ 2009
Candidate genes	ADH1B His/His vs. Arg/Arg	0.63 (?)	Akbari et al, Canc Res 2009
Childhood obesity	Very obese at 15 vs. not	3.2 (1.3-7.7) in women	Etemadi et al, Ann Oncol 2012
Reproductive history	$\geq$ 3 miscarriages vs. none	4.43 (2.11-9.33) in women	Islami et al, EJCP 2013

# Tea Drinking Habits and ESCC Risk in the Golestan Case-Control Study
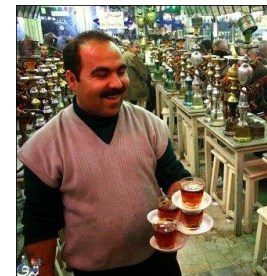
Exposure	Cases (%)	Control (%)	Adjusted OR (95% CI)
Tea temperature			
Warm or lukewarm	127 (43)	394 (69)	Reference
Hot	108 (36)	155 (27)	2.07 (1.28-3.35)
Very hot	63 (21)	19 (3)	8.16 (3.93-16.9)
Interval between pouring and drinking tea (min)			
≥ 4	132 (44)	394 (69)	Reference
2-3	112 (38)	138 (24)	2.49 (1.62-3.83)
< 2	54 (18)	35 (6)	5.41 (2.63-11.1)

Islami et al, BMJ 2009

Caspian Littoral Study1970

Mahboubi E, et al. Br. J. Cancer, 28: 197-214, 1973

PAH Antibody Staining of Normal Esophageal Mucosa and ESCC Case Status in the Golestan Case-Control Study
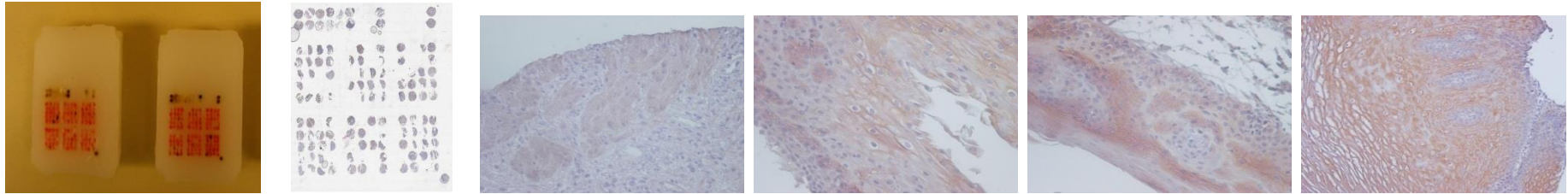
- TMAs made from normal biopsies from 120 cases and 120 clinic controls

- 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

8E11 Mab Staining	Cases	Controls	Adjusted OR (95% CI)
First quintile	2	20	Reference
Second quintile	6	21	2.42 (0.39 – 14.8)
Third Quintile	14	21	5.77 (1.06 – 31.4)
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Abedi-Ardekani et al, Gut 2010