ESOPHAGEAL CANCER PREVENTION AND CONTROL IN IRAN
IAGH MEETING ABAN 1403

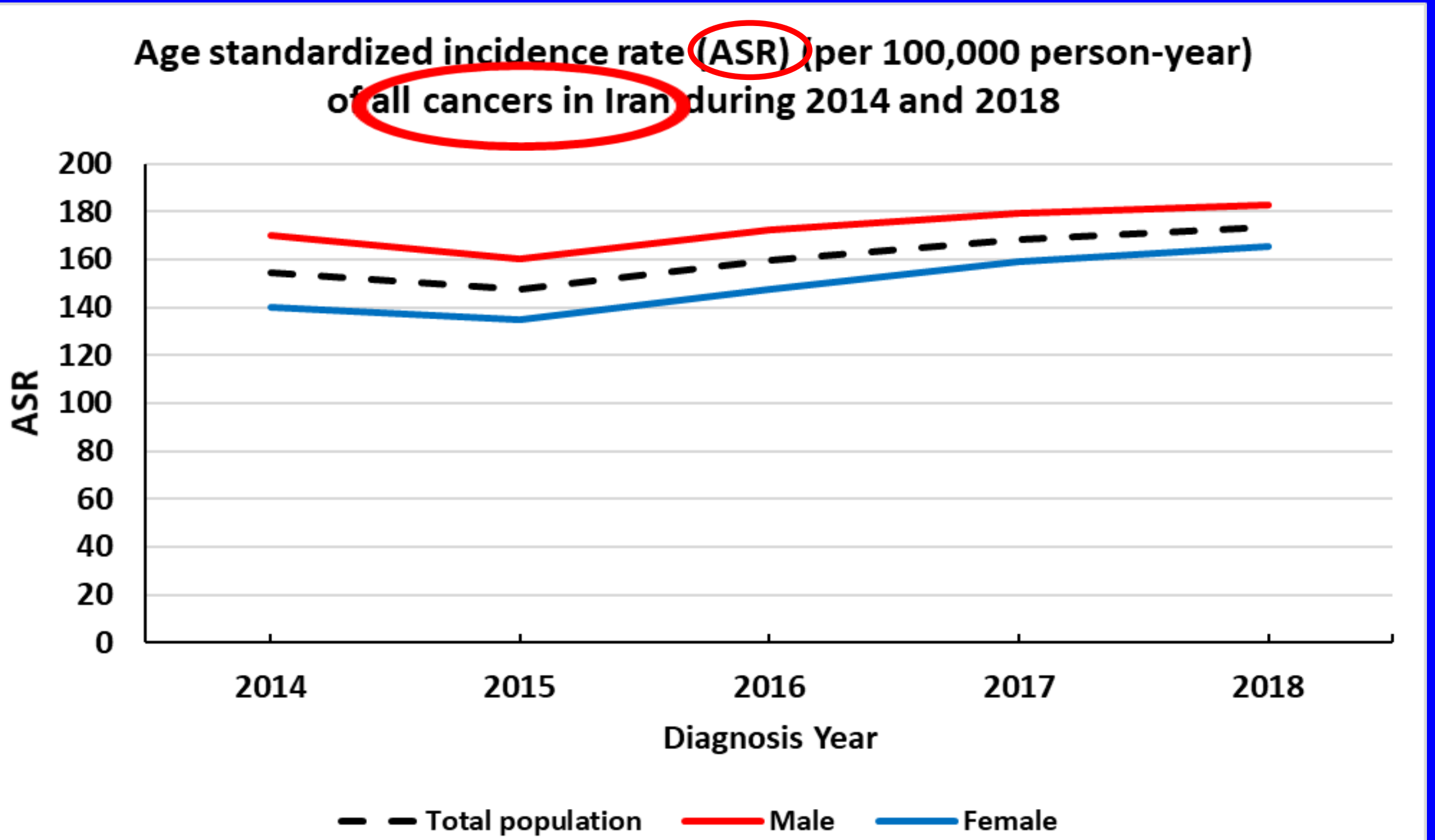
Reza Malekzadeh M.D
Professor of Medicine
Tehran University of Medical Sciences

Cancer in Iran INPCR

- Overall, **141,838 new cancer cases** were registered in Iran in 2018.
- 72,725 (51.3%) of these cases were male and 69,113 cases (48.7%) were female.
- The age standardized incidence rate (**ASR**) of all cancers (per 100,000) in total Iranian population was **173.77**
- The age standardized incidence rate (**ASR**) of all cancers (per 100,000) were **183.17** and **165.48** in **male** and **female**, respectively.

Number and ASR (per 100,000) of all cancers in Iran, 2014-2018

	2014		2015		2016		2017		2018	
	Number	ASR	Number	ASR	Number	ASR	Number	ASR	Number	ASR
Male	60,470	170.00	59,623	160.33	65,703	172.44	70,067	179.51	72,725	183.17
Female	51,662	139.98	52,133	135.03	58,460	147.33	64,910	159.15	69113	165.48
All	112,132	154.66	111,756	147.37	124,163	159.49	134,977	168.89	141838	173.77

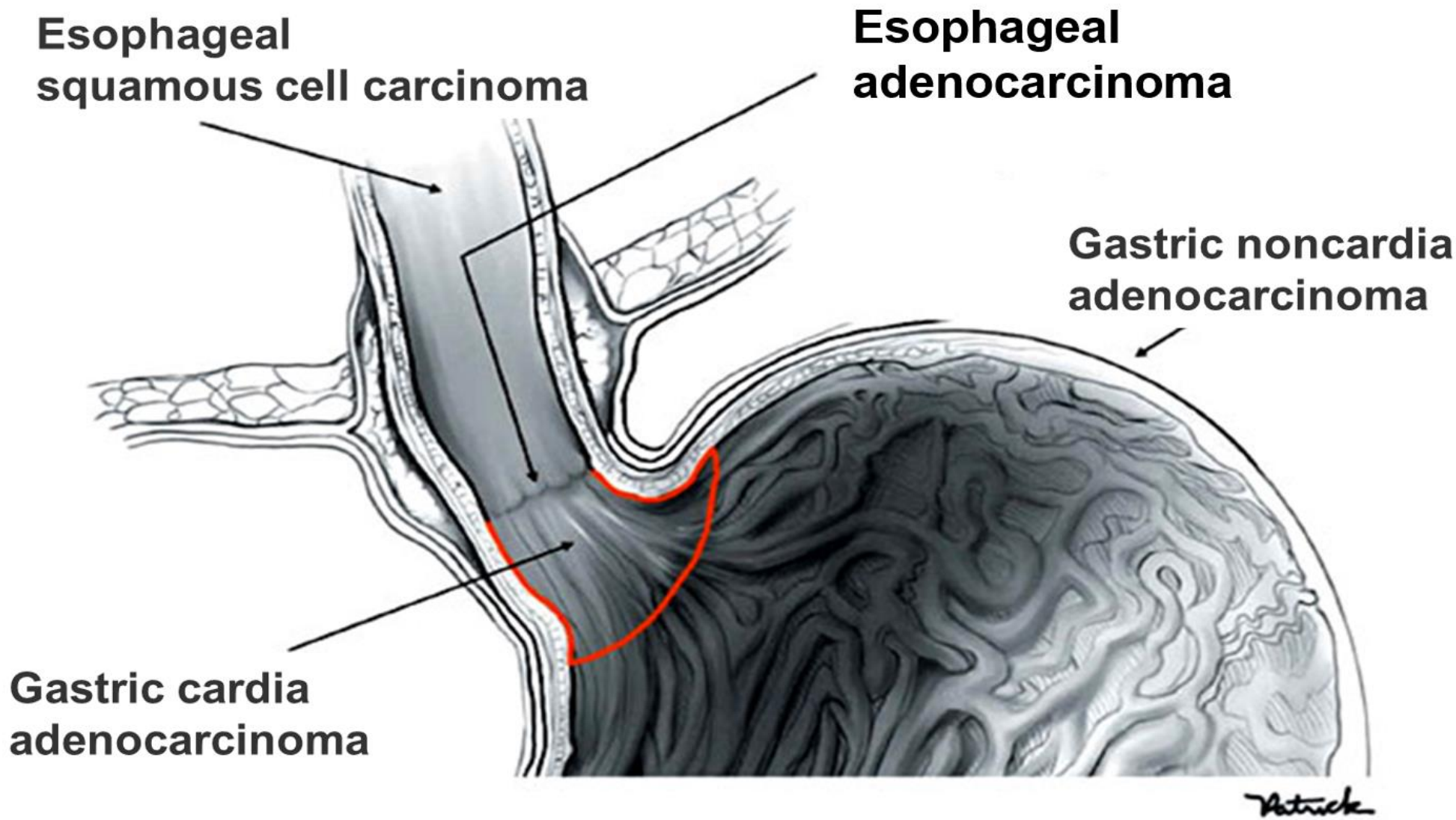

Age standardized incidence rate (ASR) (per 100,000 person-year)
of all cancers in Iran during 2014 and 2018
200
180
160
140
120
100
80
60
40
20
0
ASR
2014
2015
2016
2017
2018
Diagnosis Year
Total population
Male
Female

GI Cancers In Iran

EC,GC,CRC,PC

- Constitute 27% of Cancer death in Iran.
- Gastric cancer is the 3rd common cancer in Iran and constitute 16% of all cancer death in the country.
- **Oesophageal cancer is the 11th cancer and constitute 5% of all cancer death in the country**

Upper Gastrointestinal Cancers



Variation on the EC in different Provinces of Iran

- High incidence ASR>15

  Golestan, Zanjan, and North Khorasan

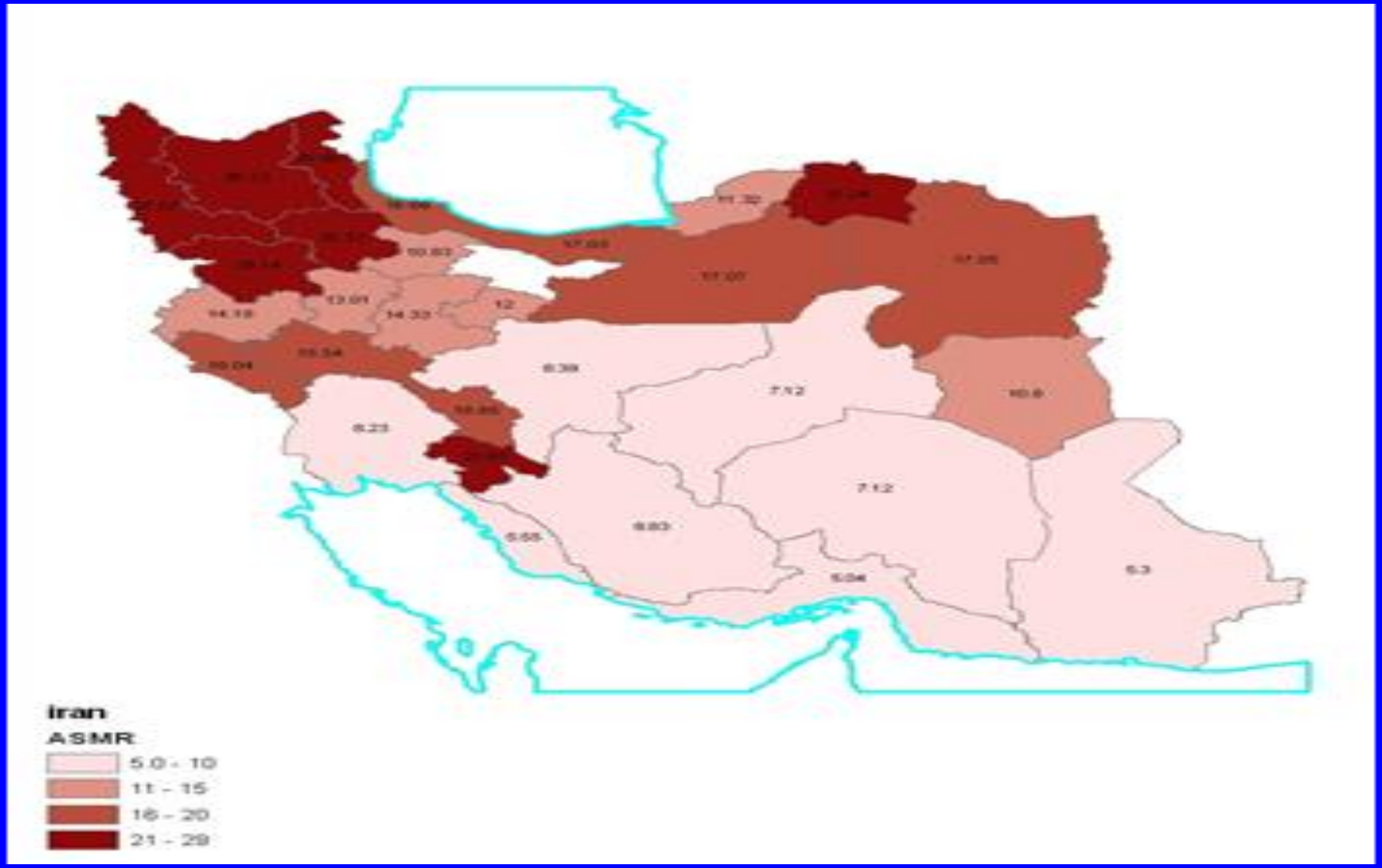
- Medium incidence ASR>10

  Ardabil, Azarbayjans, Khorasans ,Ilam,Kurdetan and Semnan.

- Low Incidense ASR<10

  Hormozgan,Fars,Bushehr,Khuzestan,Tehran,Yazd Isfahan…

Six-fold north-south difference in the GS incidence rate in Iran.



IPHR-IARC Studies of ESCC in Iran in the 1970s



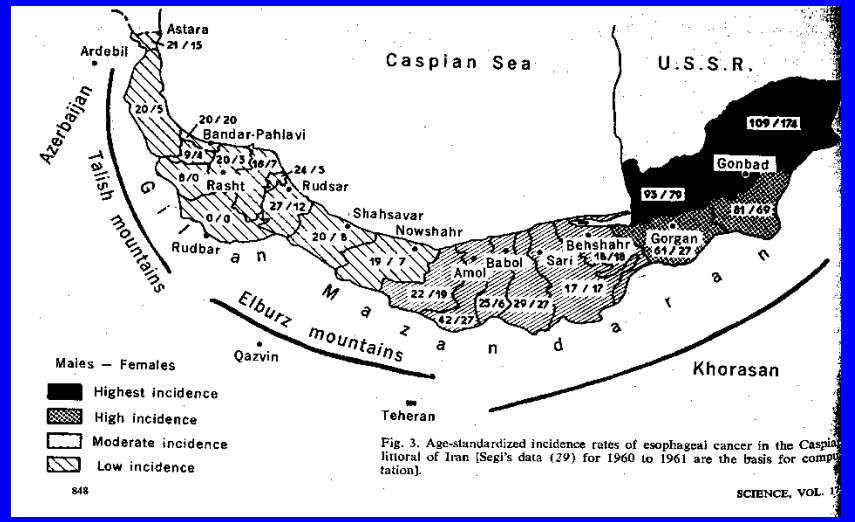
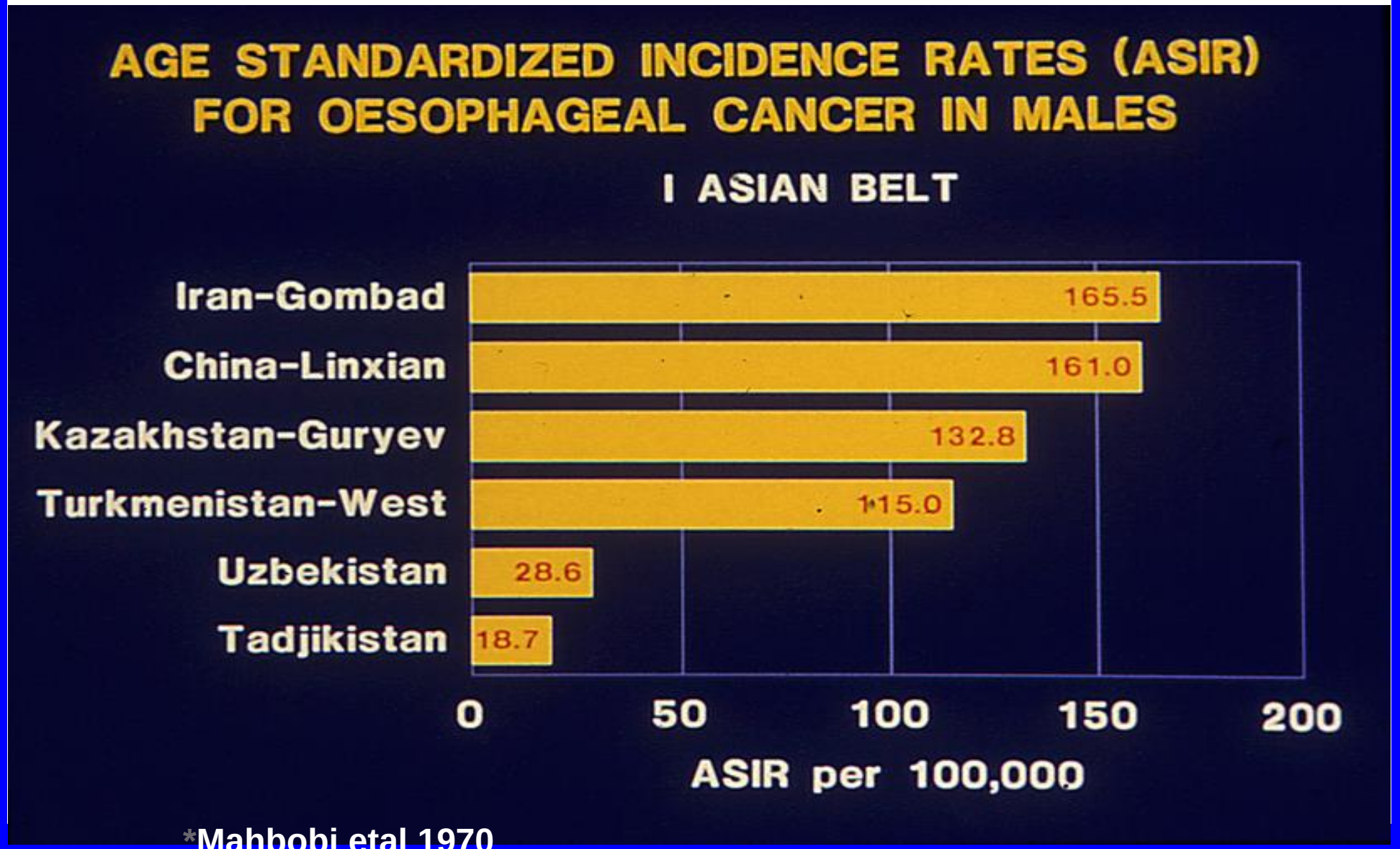


Fig. 3. Age-standardized incidence rates of esophageal cancer in the Caspian littoral of Iran [Segi's data (29) for 1960 to 1961 are the basis for computation].

- 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
- Possible causes: Bread, Tea, Opium, Low FAV, Low SES

*Incidence Rate in 1970's



*Mahbobi etal 1970



Gastro esophageal Malignancies in Northern Iran(GEMINI) Study 2000



GEMINI Meeting (Gastro-Esophageal Malignancies in Northern Ira
5-6 May 2009, IARC, Lyon



Gastric and Esophageal Malignancies In North of Iran Research Project Collaboration

DDRI

GEMINI

NATIONAL CANCER INSTITUTE

International Agency for Research on Cancer

World Health Organization



Golestan Cohort Study was an example of a successful Team Work with strong National and International Collaboration





GEMINI*

2000-2023

NATIONAL CANCER INSTITUTE

International Agency for Research on Cancer

World Health Organization

* Gastric and Esophageal Malignancies In Northern Iran

GEMINI Study : Timetable



Cancer Registry

Case-Control, Ecologic

Molecular Pathology/Genetics

Cohort

Early Detection/Screening

Prevention

Collaborators in the GEMINI project

International Agency for Research on Cancer
World Health Organization
Paolo Boffetta, Pierre Hainaut, Paul Brennan

Karolinska Institutet
Olaf Nyren, Weimin Ye

Mount Sinai School of Medicine
Paolo Boffetta

Maastricht University
Frederik-Jan van Schooten

The University of North Carolina at Chapel Hill
Susan J. Sumner

rijksuniversiteit groningen
Geertuida de Bock

dkfz. Deutsches Krebsforschungszentrum in der Helmholtz-Gemeinschaft
Michael Pawlita

University of Cambridge
Cancer Research UK
Nick Day, Bruce Ponder, Paul Pharoah, Rebecca Fitzgerald

University of Glasgow
Kenneth McColl

King's College London
David Phillips

University of Birmingham
Tom Marshall, K.K. Cheng

University of Toronto
Steven Narod

Johns Hopkins University
Paul Strickland

Morgan State University
Farin Kamangar

ESCC Rate in 2000 in Golestan Iran

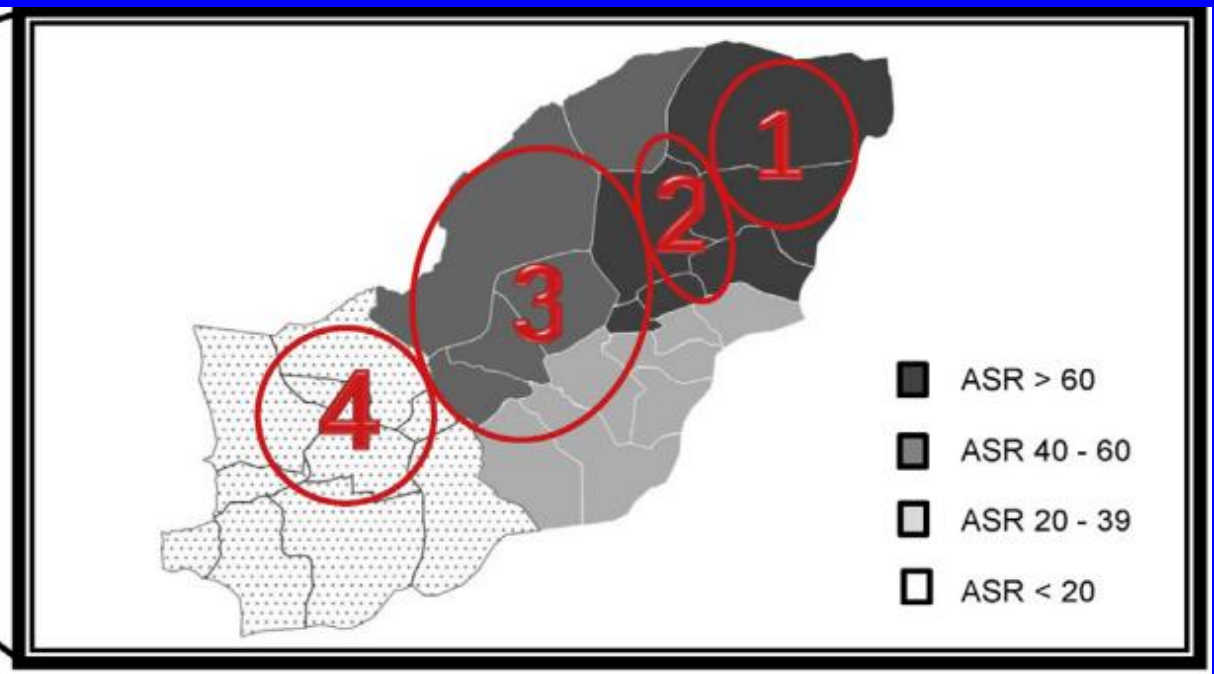
- The ASR for ESCC in NE of Iran has decreased from 60-150 in 1970;s to 40-60 in present time

ESCC within Golestan 2000

- Western Golestan (Gorgan,Kordko)
  ASR =20
- Eastern Golestan (Gonbad Kalaleh)
  ASR = 45
- Eastern Golestan (Rural Turkmen)
  ASR=75

ESCC still common in Rural Golestan 2010





Bruce Ponder :Cambridge /CRUK

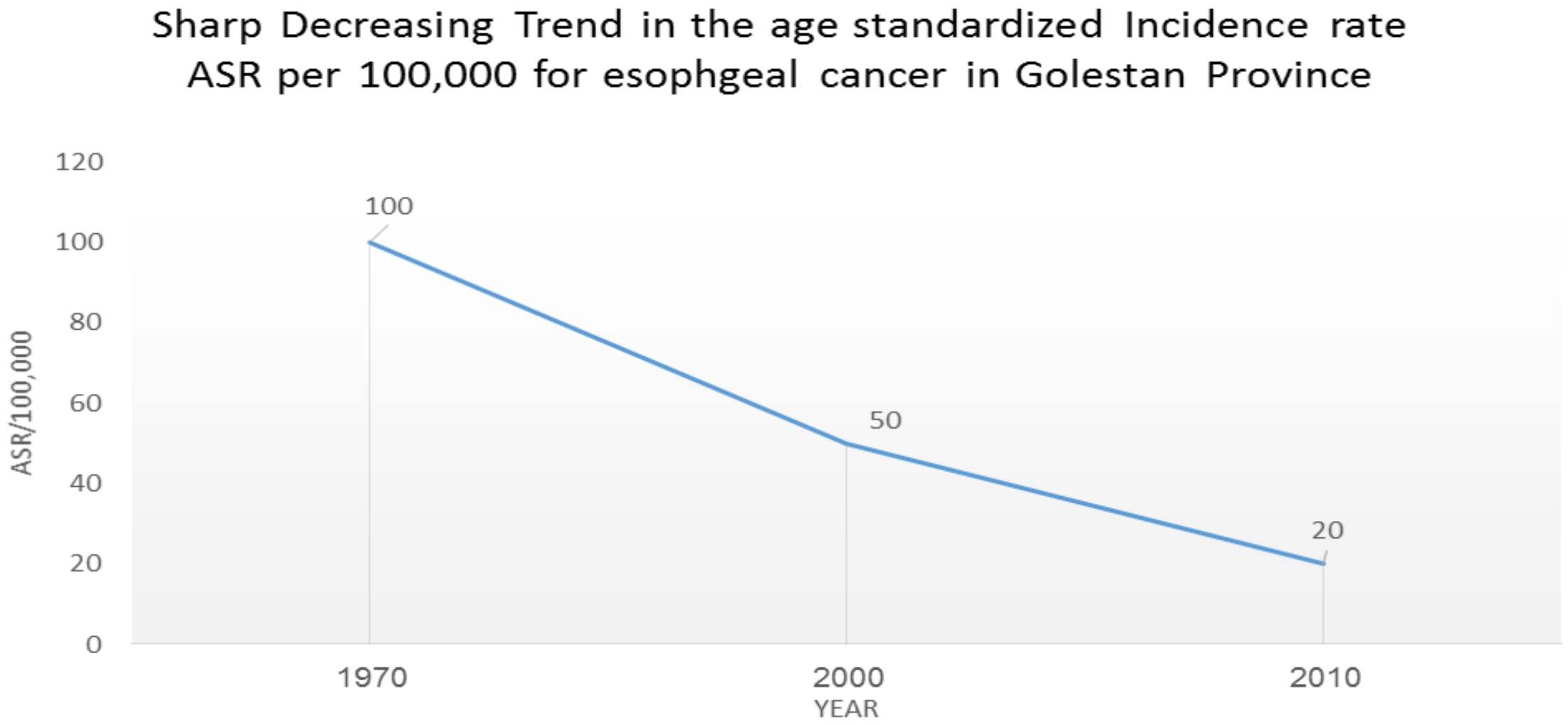


Comparing EC and GC Rate in Different Studies*

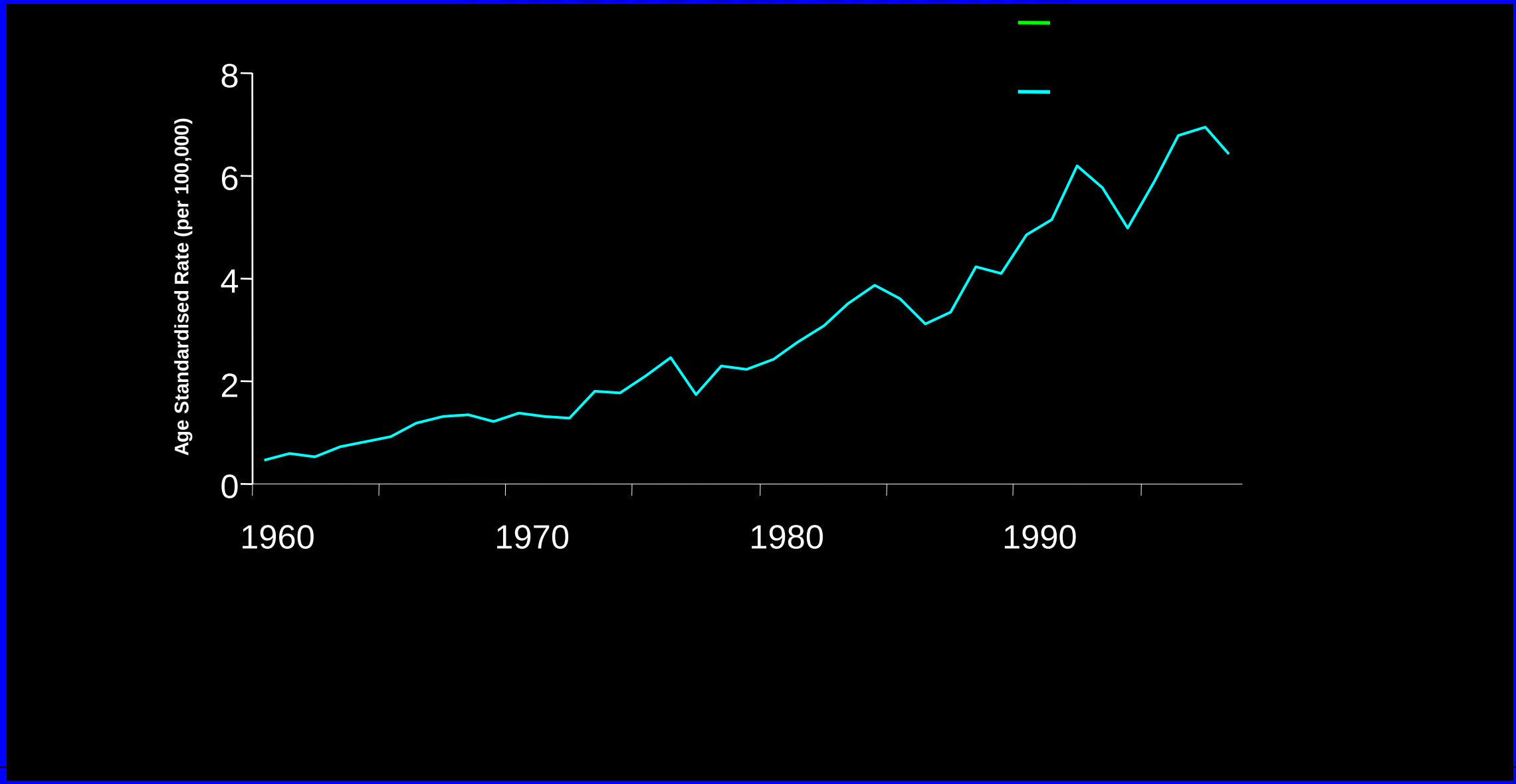
site	Gorgan Mahbobi 1970		GAS 1996-2000		EGCR 2003	
	male	female	male	female	male	female
Oesophagus	93.1	110	43.44	36.27	35.58	29.21
stomach	-	-	27.8	8.3	27.81	15.7

*Semnani &Malekzadeh 2006

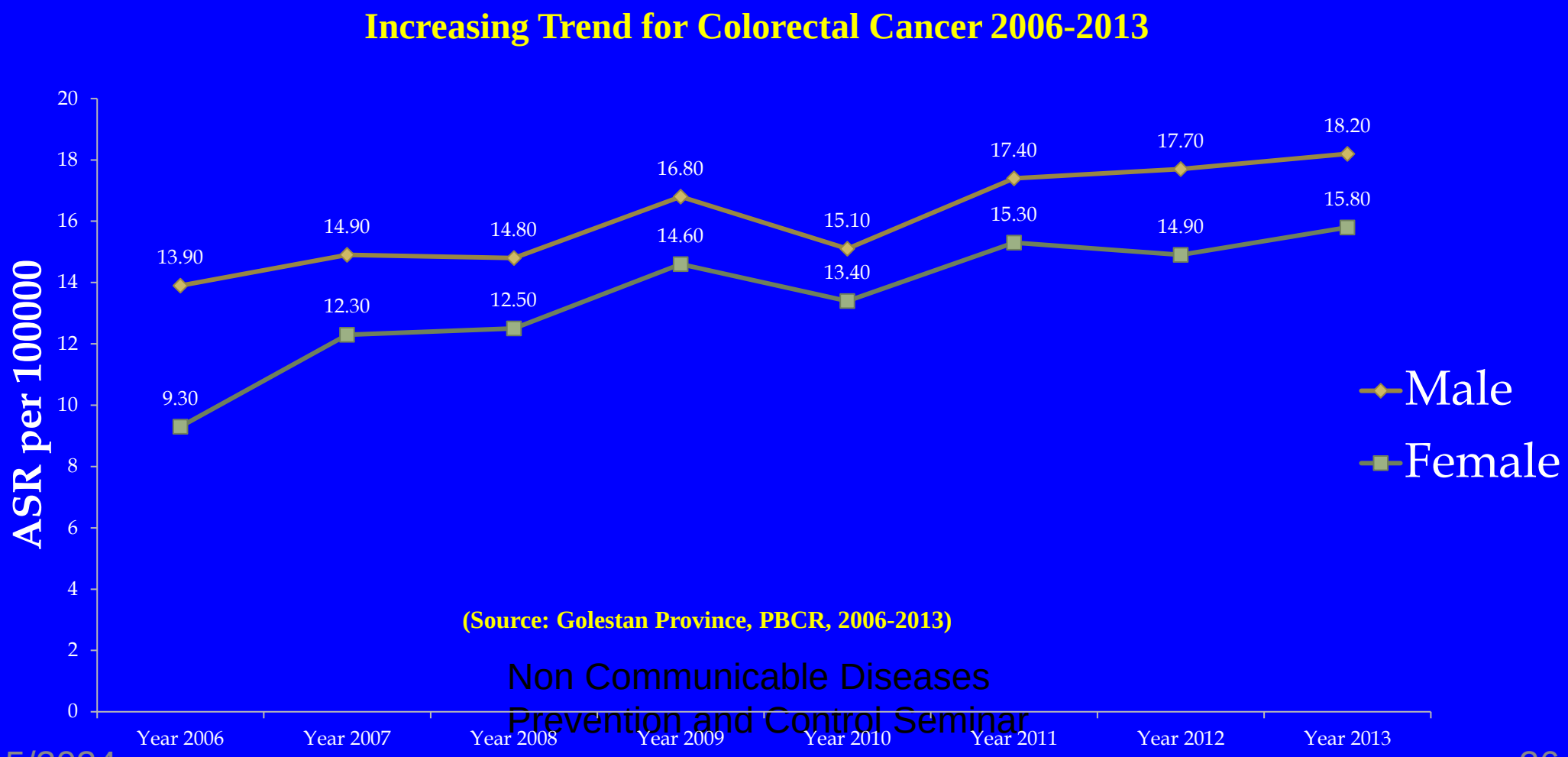
Transition of Cancer Pattern



Increasing Incidence of Esophageal Adenocarcinoma



Transition of Cancer Pattern



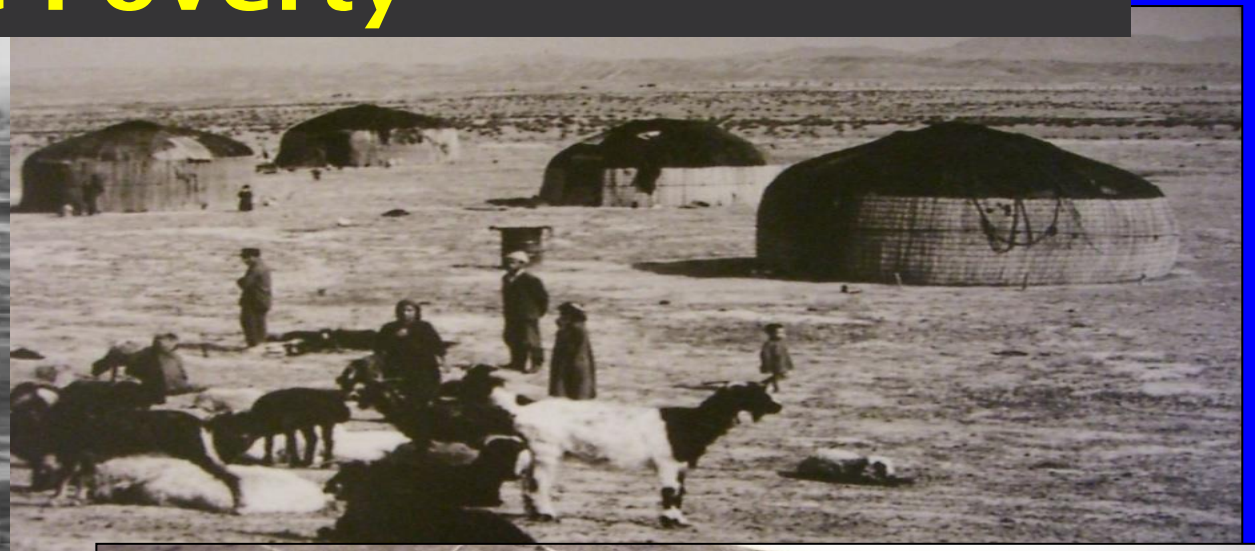
(Source: Golestan Province, PBCR, 2006-2013)

Reasons for Declining ESCC

- Misclassification of Cardia Caner as ESCC.
- Overestimating in the past CR : diagnosis was based only on clinical sign with 5% pathological confirmation.
- Underestimating in present CR.
  - ✓ Changes in Exposure to Carcinogens.

Gonbad 1972
Absolute Poverty









Gonbad 2002

Improvement in Social Determinant of Health









The Golestan Case-Control Study



- Recruitment in 2003-2007
- 300 ESCC cases, recruited from referrals to Atrak Clinic
- 571 neighborhood controls (primary control group), matched for residence, gender & age
- 300 Atrak Clinic controls (secondary control group), matched for gender & 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

Golestan GC and ESCC CCS's Atrak Clinic





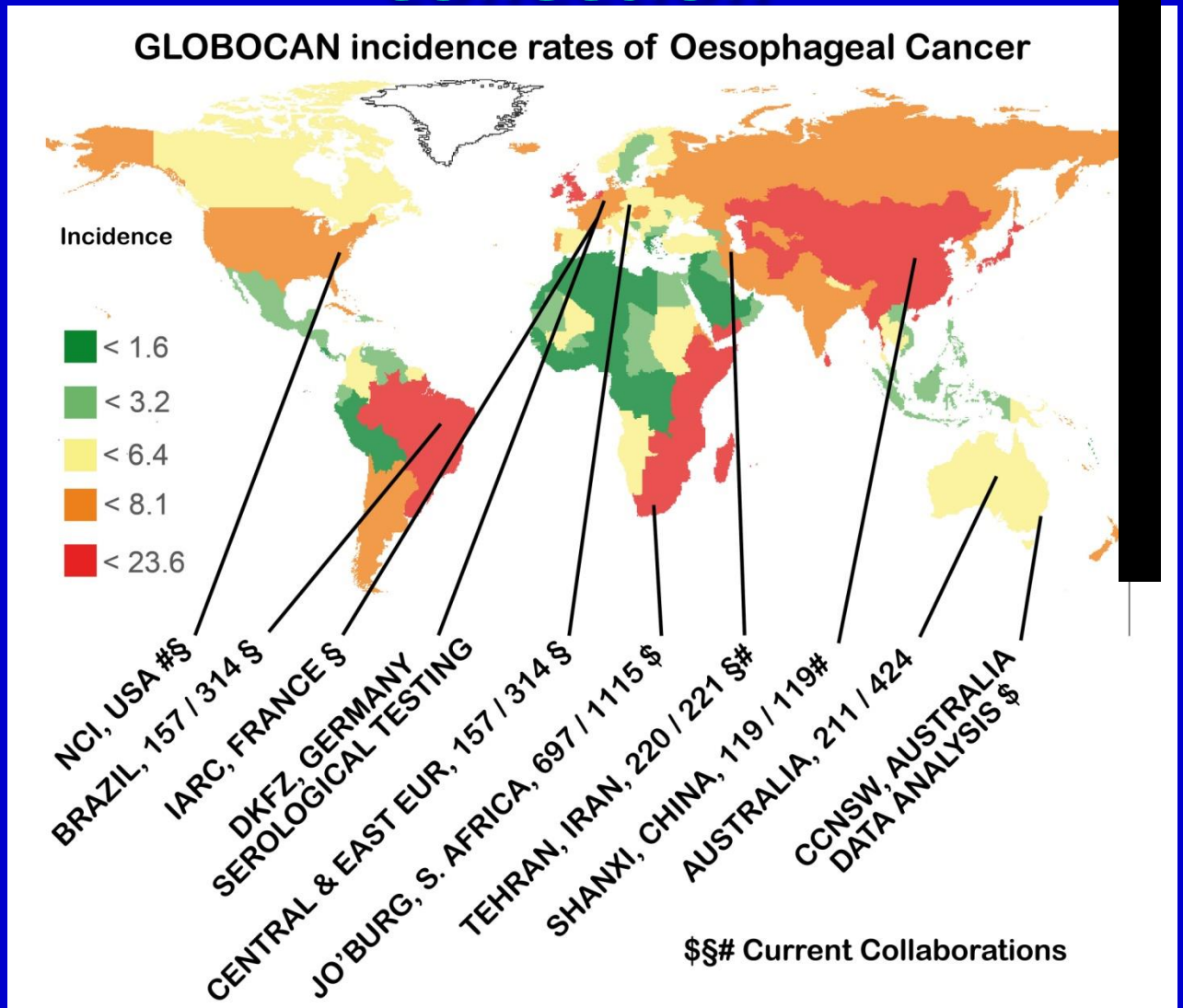
InterSCOPE

International Collaboration on HPV and squamous cell cancer of the Oesophagus



Interscpoe

N=4068, 44 years of cumulative data collection

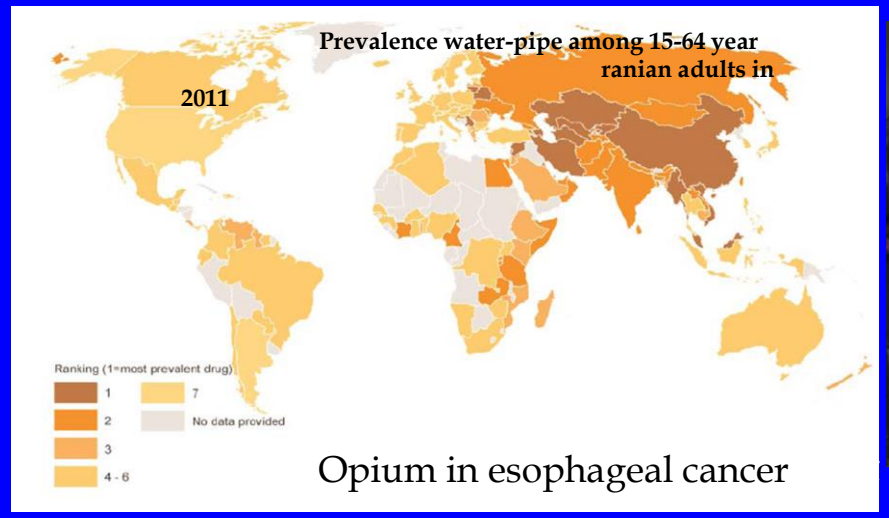


Results from the ESCC Golestan Case-Control Study

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. ≤ 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	≥ 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*

Country specific Risk factors Example ESCC in IR Iran

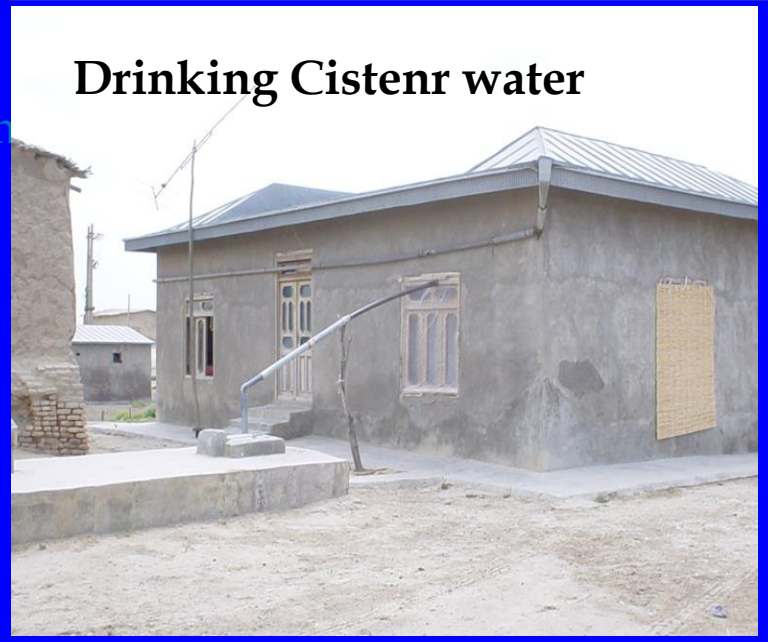
- Opium
- Waterpipe
- Oral Health
- Hot tea
- Drinking water source



Opium in esophageal cancer







Evidence for the role of polycyclic aromatic hydrocarbons (PAHs)

- **Median urine 1-OHPG = 4.2 pmol/ml (compared with ~ 0.35 in the US)**

Kamangar et al, Anticanc Res 2005

- **Mean DNA adducts in female non-smokers: 5.8 per 10^8 nucleotides (compared with 1.4 in Dutch smokers, and 1.7 in Czech coke oven workers)**

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 (5.31 – 135)

Abedi-Ardekani et al, Gut 2010

Large prospective cohort platforms are the ideal context to study Cancer prevention

- Excitingly, large prospective cohort platforms with well-characterized bio specimens provide the ideal context to study the long Prediagnostic period, and recent investments in these now enable studies relevant to etiology and prevention .
- Establishment of prospective cohort studies, in EMRO countries : Golestan and Persian Cohort Studies and biobank in Iran

Golestan Cohort Study

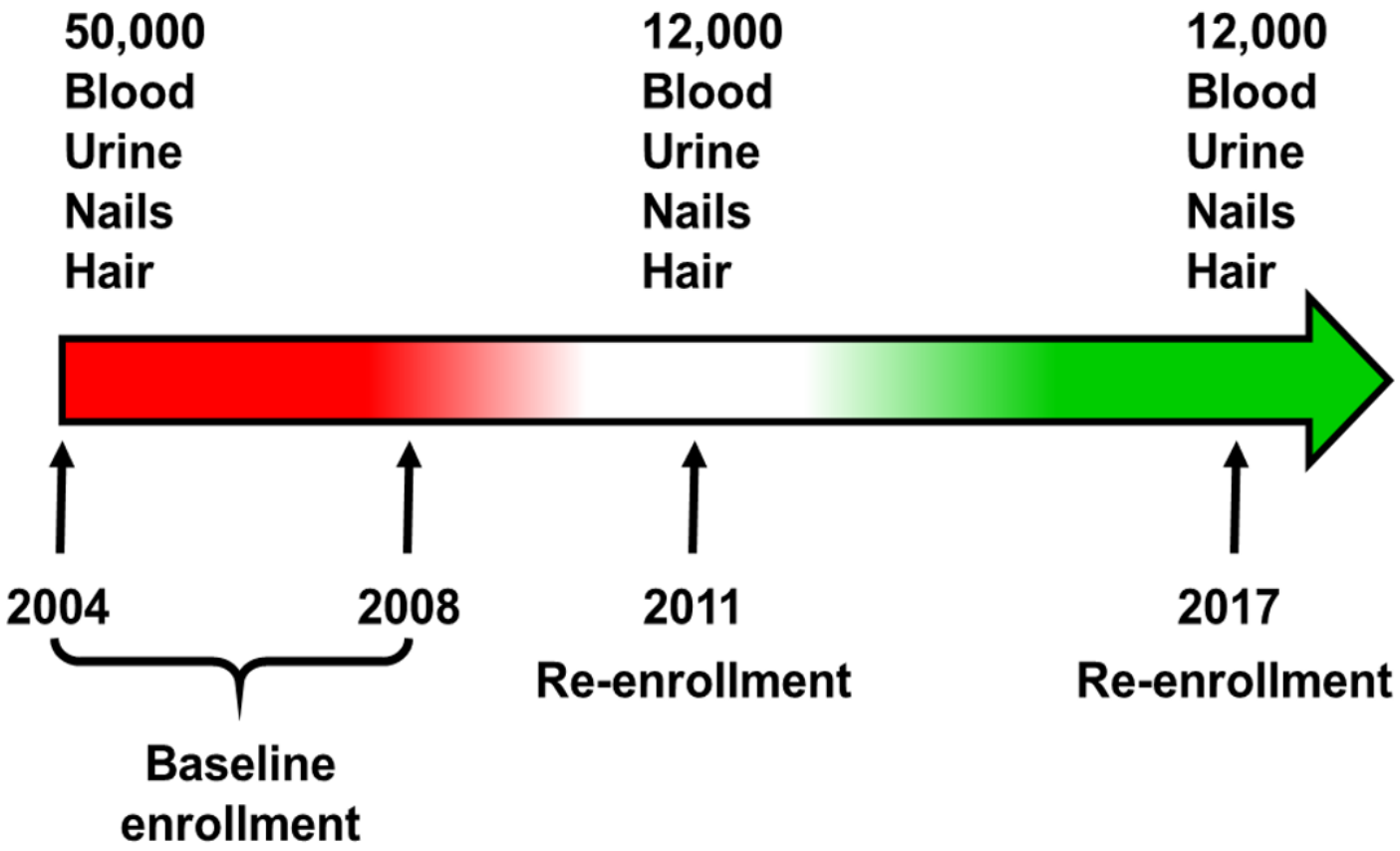




- Recruited in 2004-2008 in Gonbad and 326 rural villages
- 50,045 adults, 40-75 yrs, 58% F, 80% rural, 74% Turkmen
- Participation rates: women 80%, men 65%

- Lifestyle questionnaire
- Food frequency questionnaire
- Blood, urine, hair and nails

Golestan Cohort Study



As of 1/1/2018

6629 Deaths

332 Esophageal cancers

319 Gastric cancers



The follow up success rate

- First year: 99.7%
- Second year: 99.8%,
- Third year: 99.8%
- Fourth year: 99.8%
- Fifth year : 99.8%
- Sixth year: 99.7%

Type of Cancers in GCS

لیست آمار مرگ در کوهورت گلستان		
ردیف	علت	۱۴۰۲/۱۰/۰۹
۱	قلبی	۳۴۰۲
۲	کانسر	۲۴۳۰
۳	مغزی	۱۶۳۴
۴	covid ۱۹	۶۹۶
۵	سپتی سمی	۴۶۳
۶	حوادث	۴۱۹
۷	کهولت سن	۳۵۳
۸	پنومونی آسپیراسیون	۳۲۸
۹	COPD	۲۹۰
۱۰	ایست قلبی	۲۶۱
جمع کل		۱۲۹۱۲

لیست آمار سرطان در کوهورت گلستان		
ردیف	علت	۱۴۰۲/۱۰/۰۹
۱	مری	۵۰۰
۲	معده	۴۹۴
۳	کلورکتال	۲۴۳
۴	ریه	۲۱۸
۵	تومور مغزی	۱۷۶
۶	سینه	۱۷۴
۷	خون	۱۶۱
۸	کبدnos	۱۴۹
۹	پانکراس	۱۴۲
۱۰	رحم ، سرویکس	۱۰۶
جمع کل		۳۲۲۱

Answer to Question

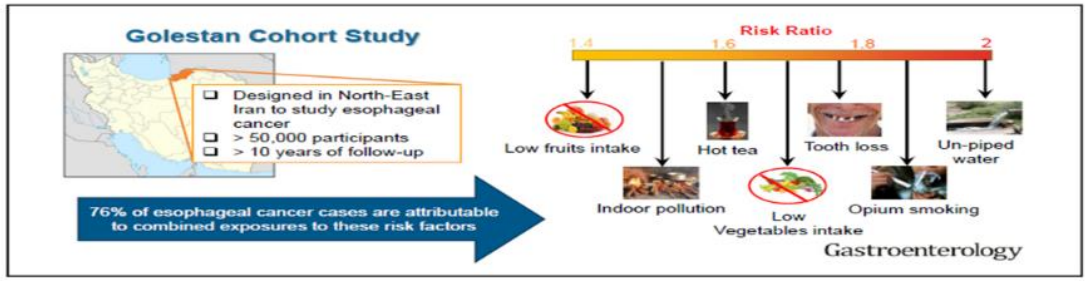
What is the etiology of ESCC in NE Golestan?

Gastroenterology 2019;156:1416–1427

Individual and Combined Effects of Environmental Risk Factors for Esophageal Cancer Based on Results From the Golestan Cohort Study

Mahdi Sheikh,[1,2] Hossein Poustchi,[3,4] Akram Pourshams,[1,4] Arash Etemadi,[1,5] Farhad Islami,[1,6] Masoud Khoshnia,[1,7] Abdolsamad Gharavi,[1,7] Maryam Hashemian,[1,5] Gholamreza Roshandel,[1,7] Hooman Khademi,[1] Mahdi Zahedi,[8] Behnoush Abedi-Ardekani,[2] Paolo Boffetta,[9] Farin Kamangar,[10] Sanford M. Dawsey,[5] Paul D. Pharaoh,[11] Christian C. Abnet,[5] Nicholas E. Day,[11] Paul Brennan,[2] and Reza Malekzadeh[1,3,4]

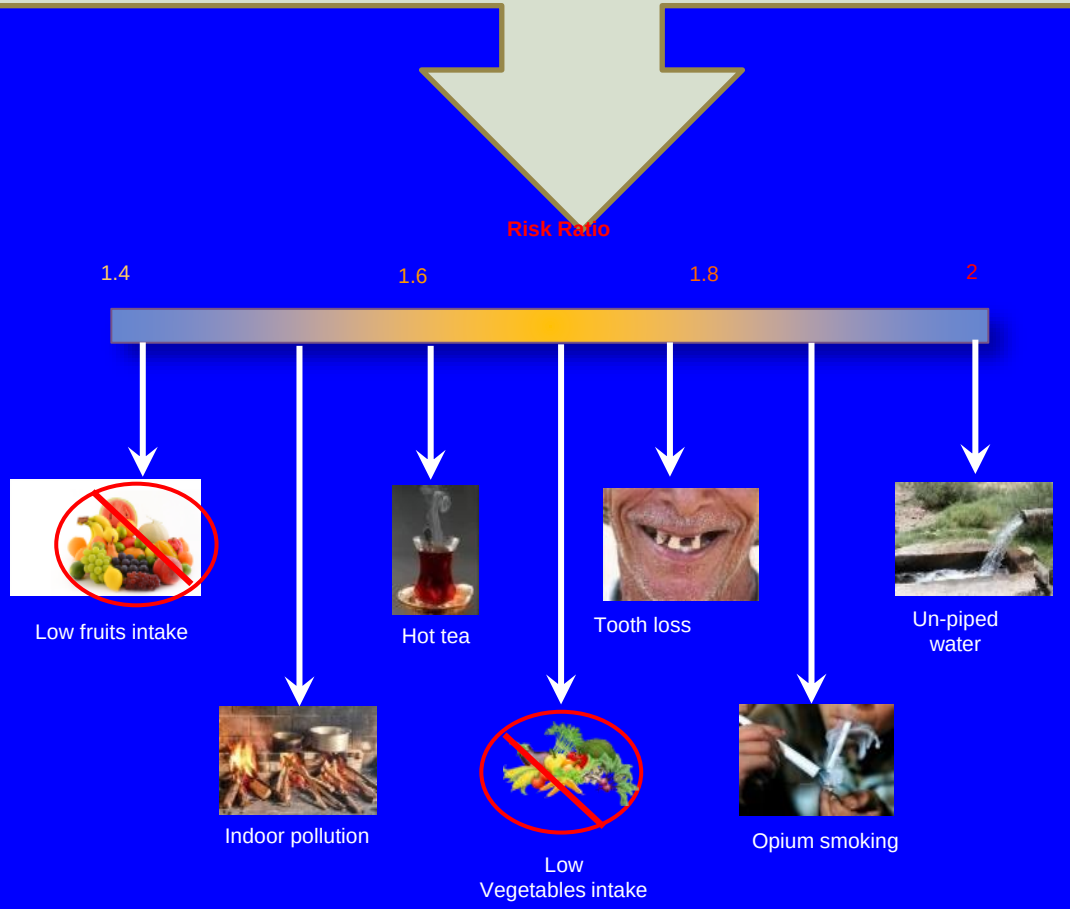
[1]Digestive Oncology Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran; [2]Section of Genetics, International Agency for Research on Cancer, World Health Organization, Lyon, France; [3]Liver and Pancreatobiliary Diseases Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran; [4]Digestive Disease Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran; [5]Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland; [6]Surveillance and Health Services Research, American Cancer Society, Atlanta, Georgia; [7]Golestan Research Center of Gastroenterology and Hepatology, Golestan University of Medical Sciences, Gorgan, Iran; [8]Ischemic Disorders Research Center, Golestan University of Medical Sciences, Gorgan, Iran; [9]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, New York; [10]Department of Biology, School of Computer, Mathematical, and Natural Sciences, Morgan State University, Baltimore, Maryland; and [11]Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom



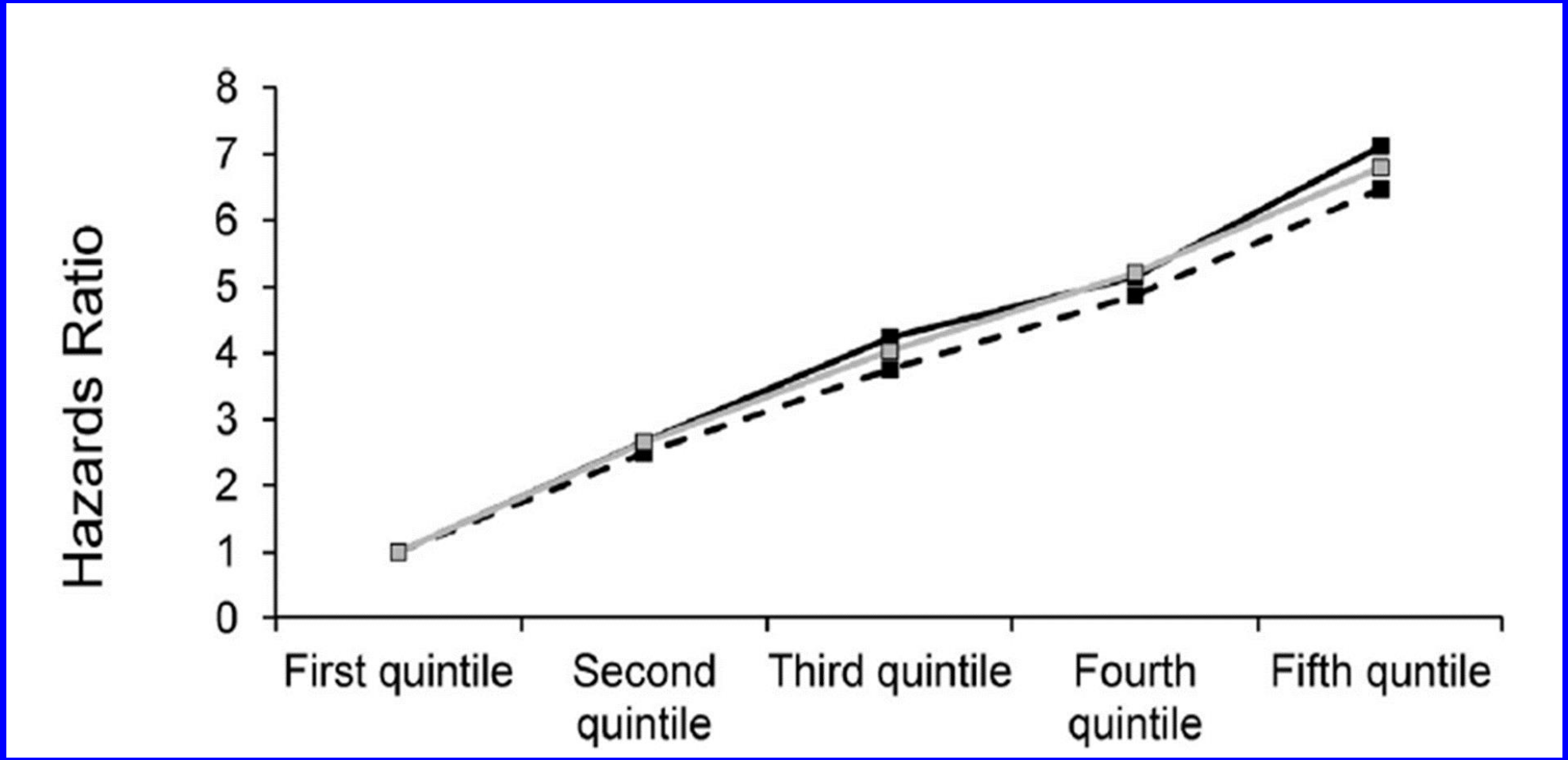
76% of esophageal cancer cases are attributable to combined exposures to these risk factors



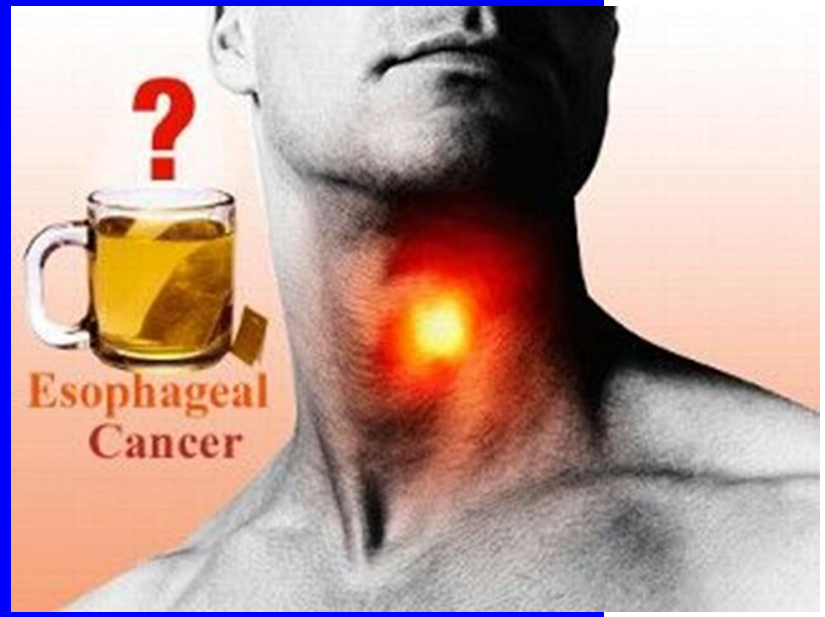
- North-East Iran, known for having unusual rates of esophageal cancer
- The study was initiated in 2004 through collaboration between scientists in Iran, IARC and the NCI to study esophageal cancer
- > 50,000 participants
- > 10 years of follow-up with <1% loss



The adjusted HRs of developing ESCC among the quintiles of the combined exposures score



Hot drink



BMJ

RESEARCH

Tea drinking habits and oesophageal cancer in a high risk area in northern Iran: population based case-control study

Farhad Islami, research fellow,[1,2,3] Akram Pourshams, associate professor,[1] Dariush Nasrollahzadeh, PhD student,[1,4] Farin Kamangar, research fellow,[5] Saman Fahimi, PhD student,[1,6] Ramin Shakeri, research fellow,[1] Behnoush Abedi-Ardekani, pathologist,[1] Shahin Merat, associate professor,[1] Homayoon Vahedi, associate professor,[1] Shahryar Semnani, associate professor and director,[7] Christian C Abnet, investigator,[5] Paul Brennan, group head,[2] Henrik Møller, professor and director,[3] Farrokh Saidi, professor,[1] Sanford M Dawsey, senior investigator,[5] Reza Malekzadeh, professor and director,[1] Paolo Boffetta, group head and cluster coordinator[2]

[1]Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences, 14117 Tehran, Iran
[2]International Agency for Research on Cancer, Lyon, France
[3]King's College London, Thames Cancer Registry, London
[4]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden
[5]Division of Cancer Epidemiology

ABSTRACT

Objective To investigate the association between tea drinking habits in Golestan province, northern Iran, and risk of oesophageal squamous cell carcinoma.

Design Population based case-control study. In addition, patterns of tea drinking and temperature at which tea was drunk were measured among healthy participants in a cohort study.

Setting Golestan province, northern Iran, an area with a high incidence of oesophageal squamous cell carcinoma.

INTRODUCTION

Oesophageal squamous cell carcinoma constitutes most of the oesophageal cancers worldwide.[1,2] In Europe and America it is mainly caused by tobacco and alcohol use and is more common in men than in women.[3] However, in Golestan province of Iran, which has one of the highest incidence rates for oesophageal squamous cell carcinoma in the world,[4] this cancer has relatively unique epidemiological features: smoking and alcohol consumption are not major risk

WHO/IARC Monograph

- 2016 IARC monograph on Hot drink as a carcinogen for Esophagus cancer was released

Adequate Evidence

BMJ

BMJ 2012;344:e2502 doi: 10.1136/bmj.e2502 (Published 17 April 2012) Page 1 of 12

RESEARCH

Opium use and mortality in Golestan Cohort Study: prospective cohort study of 50 000 adults in Iran

OPEN ACCESS

Cancer Epidemiology, Biomarkers & Prevention

Reliability and Validity of Opiate Use Self-Report in a Population at High Risk for Esophageal Cancer in Golestan, Iran

ORIGINAL ARTICLE

Smoking water-pipe, chewing nass and prevalence of heart disease: a cross-sectional analysis of baseline data from the Golestan Cohort Study, Iran

BJC

British Journal of Cancer (2

Keywords: oesophageal squamous cell carcinoma; screening; cytological exa

Pilot study of cytological tes oesophageal squamous cell in a high-risk area in Northe

UICC global cancer control

IJC

International Journal of Cancer

Opium: An emerging risk factor for gastric adenocarcinoma

Opium use: an emerging risk factor for cancer?

CrossMark

British Journal of Cancer (2008) 98, 1857 – 1863
© 2008 Cancer Research UK All rights reserved 0007 – 0920/08 $30.00
www.bjcancer.com

ORIGINAL CONTRIBUTIONS

Opium, tobacco, and alcohol use in relation to oesophageal squamous cell carcinoma in a high-risk area of Iran

Lancet Oncol 2014; 15: e69–77

Department of Public Health Analysis, School of Community Health and Policy, Morgan State University, Baltimore, MD, USA (Prof F Kamangar MD); Digestive Oncology Research Center, Digestive Disease

Opium Use and Risk of Mortality from Digestive Diseases: A Prospective Cohort Study

Eur J Epidemiol (2014) 29:95–1
DOI 10.1007/s10654-014-9883-6

MORTALITY

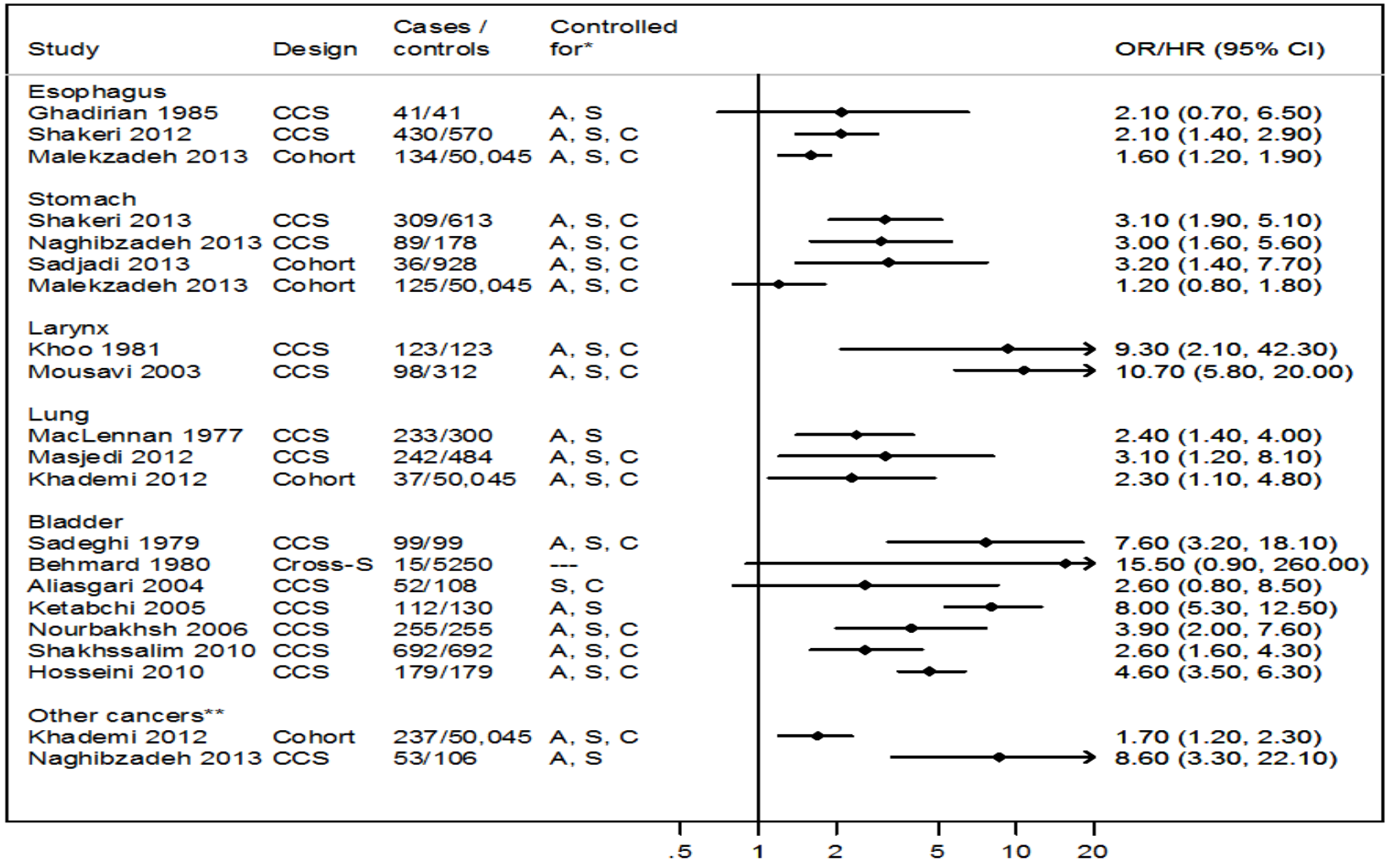
Impact of body size and physical activity and adult life on overall and cause-specif cohort study from Iran

OPEN ACCESS Freely available online

PLoS one

Is Opium a Real Risk Factor for Esophageal Cancer or Just a Methodological Artifact? Hospital and Neighborhood Controls in Case-Control Studies

Opium as an important etiology of cancer in Iran



Kamangar Islami Malekzadeh :Opium use: an emerging risk factor for cancer. Lancet Oncology 2014

IARC/WHO Future Monograph

- 2018 Expecting a new monograph recognizing Opium will as carcinogen similar to Tobacco

Gastric Microbiota in ESCC

Bacterial overgrowth in high PH stomach harboring bacteria with high production of nitrosamine

- Multiplexing was optimized for 95 samples.

Cases	Controls
18 dysplasia	39 normal esophagus
19 ESCC	19 esophagitis

- DNA was extracted from a snap frozen gastric biopsy.
- Primer for region V3-V4 was applied to amplify 16S rRNA with 400-500 bp amplicons.
- Amplicons were purified and pooled.
- Pooled library was sequenced on GS-FLX Titanium.

Order	ESCC + dysplasia (%)	Controls (%)	FDR
Clostridiales	27.8	14.8	**0.01***
Erysipelotrichales	1.5	0.5	**0.01***

New Hypotheses

- **Tooth Loss-Microbioma**
  - Multiple CCS with tooth loss or similar variable
  - Modest odd ratios but we using weak variables
- Direct assessment of microbiome may be better.
- CCS probably not valuable
- Cross sectional studies across the histologic spectrum.
- Methods need more development

ESCC prevention.

- Primary prevention



- Secondary prevention



10 Modifiable Risk factors: For primary prevention

- A number of risk factors were identified to play a role in pathogenesis of ESCC.

- Decrease exposure to PAH
- Become Educated .
- High-temperature beverages
- Quitting cigarette and opium
- Poor oral health
- Prevent Obesity
- Eat more fruit and vegetables
- Drink pipe water
- Eat more Fish and less red meat and Salt
- Screening if First degree relative with UGI cancer



Poster designed for Community Health centers and schools IN NE Iran

سرطان مری و معده
شایعترین نوع سرطان در گلستان

آیا می دانید سرطان مری و معده حدود نیمی از مرگ و میر ناشی از سرطان را در استان گلستان تشکیل می دهد؟



مصرف چای و مایعات داغ،خطر ابتلا به سرطان مری را تا ۸ برابر افزایش می دهد

پس از ریختن چای،کمی صبر کنید تا خنک تر شود.مطمئن باشید از لذت آن نمی کاهد



مصرف تریاک احتمال سرطان مری و معده را تا ۳.۷ برابر افزایش می دهد

با راهنمایی پزشک، از امروز برای رهایی از تریاک اقدام کنید



بهداشت نامناسب دهان و دندان خطر ابتلا به سرطان مری و معده را تا ۲ برابر افزایش می دهد

مسواک زدن مرتب و رعایت بهداشت دهان ودندان را فراموش نکنید



مصرف سیگار و دیگر مواد مخدر احتمال سرطان مری و معده را ۳ برابر بیشتر می کند

برای سلامتی خود و فرزند دلبندتان، همین حالا سیگار و مواد مخدر را ترک کنید



مصرف آب آلوده خطر ابتلا به سرطان مری و معده را تا ۷ برابر افزایش می دهد

از آب لوله کشی و تصفیه شده برای آشامیدن استفاده کنید



عدم مصرف سبزیجات و میوه جات تازه احتمال ابتلا به سرطان مری و معده را تا ۲ برابر افزایش می دهد

حداقل ۵ بار در روز از انواع میوه و سبزیجات تازه میل کنید.



مصرف غذاهای برشته و سوخته احتمال ابتلا به سرطان مری و معده را تا ۱/۵ برابر افزایش می دهد

غذاها را آب پز و بخارپز کنید و نمک آن را به حداقل برسانید. مصرف زیاد غذاهای سرخ کردنی و شور مضر است



چاقی خطر ابتلا به سرطان مری و معده را افزایش می دهد

با روزی ۳۰ دقیقه پیاده روی هم تناسب اندام وهم سلامتی خود را به دست می آورید

Pamphlet for the public and teachers in NE Iran

برنامه ها و اهداف آینده کهورت گلستان چیست؟

اولین و مهمترین هدف کهورت گلستان شناخت عوامل خطر و سپس پیشگیری از بیماری ها در ساکنین این استان بوده است. این پیشگیری در دو سطح اولیه و ثانویه طی برنامه های مختلف اجرا خواهد شد:

- **پیشگیری اولیه:** گروه هدف در این پیشگیری کودکان و نوجوانان استان گلستان هستند. در راستای این هدف، در مدارس به کودکان آموزش داده خواهد شد تا بوسیله راه کارهای مشخصی، خود را در مقابل عوامل خطر بیماری های مزمن حفظ کنند تا از بروز بیماری پیشگیری شود. این آموزش ها در غالب آموزش معلمین بهداشت مدارس و نیز توضیع کتابچه های آموزشی شامل توصیه های مختلفی درباره بهداشت دهان و دندان، مصرف روزانه میوه و سبزیجات تازه، کاهش مصرف غذاهای چرب و پرهیز از غذاهای سوخته و همچنین سیگار، ناس، تریاک و الکل میباشد.



- **پیشگیری ثانویه:** گروه هدف در این مورد افراد بزرگسال و مسنی هستند که سال ها در معرض عوامل خطر قرار گرفته اند. برای این گروه آموزش های لازم جهت تغییر عادات نادرست مانند ننوشیدن چای داغ، مصرف بیشتر میوه جات و سبزیجات، در معرض دود آتش و ذغال قرار نگرفتن، و ترک تریاک و ناس داده خواهد شد. طرح پیشگیری از سرطان مری و معده با استفاده از روش کپسول هم اکنون در سطح استان گلستان در دست اجرا است.



آیا میدانستید...

- تحقیقات کهورت گلستان سبب شد تا ۷۵ نفر از جوانان ایران در سطوح مختلفی همچون کارشناسی ارشد، دکترا و پسا دکترا ادامه تحصیل داده و مدرک خود را دریافت کنند.
- ۲۰٪ از این افراد را جوانان خود استان گلستان تشکیل دادند.
- کهورت گلستان برای ۷۰ نفر از اهالی مناطق مختلف استان گلستان کارآفرینی کرد.

هیچ کدام از این موفقیت ها بدون همکاری شما امکان پذیر نبود!



تعدادی از همکاران کهورت گلستان

کلینیک فوق تخصصی اترک طی سالهای گذشته خدماتی بسیاری را به افراد شرکت کننده در کوهورت عرضه کرده است.



این خدمات شامل:

- ویزیت پزشک فوق تخصص گوارش
- آندوسکپی
- کولونوسکپی
- فیبرواسکن
- آزمایشات تخصصی

بوده و برای همه شرکت کنندگان کوهورت بصورت رایگان انجام پذیرفته است.

کهورت گلستان:

حاصل ۱۰ سال همکاری شما با دانشمندان ایرانی







Secondary prevention of ESCC

- To identify high risk individuals and detection of ESD lesions

(Screening programs)

- Removal of the dysplastic lesion (e.g. EMR)



GEMINI ENDOSCOPIC SCREENING PILOT STUDY (GESP)

DDRC/TUMS

Cambridge/EC research group

NCI/NIH

Alternative approach



Cytosponge + Biomarker

Sensitivity and Specificity for the Cytosponge compared with endoscopy based on the outcome of interest

Outcome of interest		p53+	Atypia+	P53+ or Atypia+	P53+ and Atypia+
Dysplasia (all types)	Sensitivity	26.3%	43.8%	47.1%	22.2%
	Specificity	89.4%	99.5%	84.3%	100%
Dysplasia (High-grade)	Sensitivity	100%	100%	100%	100%
	Specificity	89.9%	98.0%	83.8%	100%

Pilot study results are promizing

FULL PAPER

BJC

British Journal of Cancer (2014), 1–7 | doi: 10.1038/bjc.2014.506

Keywords: oesophageal squamous cell carcinoma; screening; cytological examination; p53; Northern Iran

Pilot study of cytological testing for oesophageal squamous cell dysplasia in a high-risk area in Northern Iran

G Roshandel[1,2], S Merat[1], M Sotoudeh[1], M Khoshnia[2], H Poustchi[1], P Lao-Sirieix[3], S Malhotra[3], M O'Donovan[3], A Etemadi[1,4], A Nickmanesh[1], A Pourshams[1], A Norouzi[2], I Debiram[3], S Semnani[2], C C Abnet[4], S M Dawsey[4], R C Fitzgerald[3] and R Malekzadeh[*,1]

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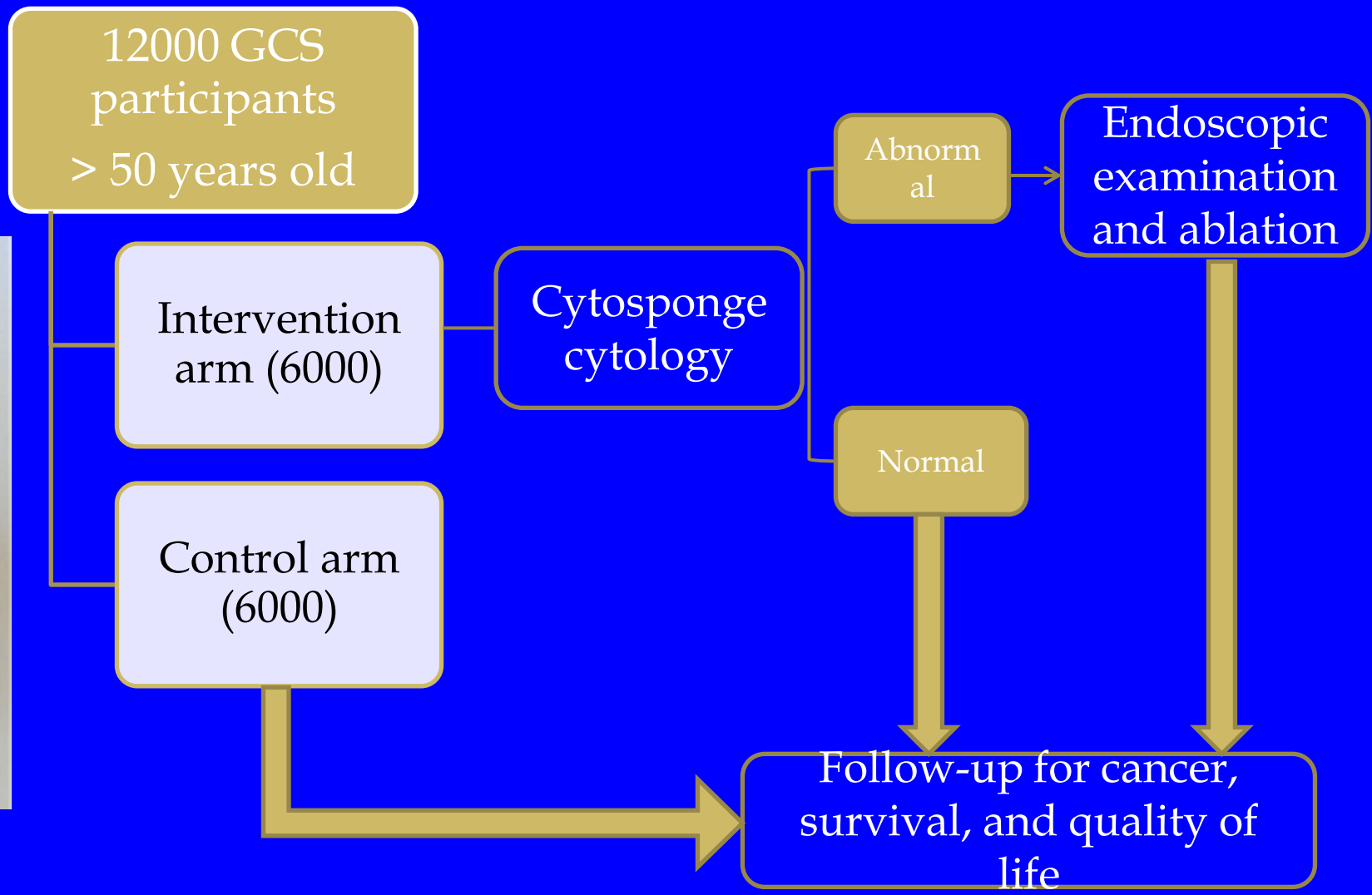
Background: Oesophageal squamous cell carcinoma (ESCC) is a fatal disease with 5-year survival rates of <5% in Northern Iran. Oesophageal squamous dysplasia (ESD) is the precursor histologic lesion of ESCC. This pilot study was conducted to assess the feasibility, safety, and acceptability of non-endoscopic cytological examination of the oesophagus and to provide initial data on the accuracy of cytological atypia for identifying patients with ESD in this very-high-risk area.

Methods: Randomly selected asymptomatic participants of the Golestan Cohort Study were recruited. A cytological specimen was taken using a capsule sponge device and evaluated for atypical cells. Sections of the cytological specimen were also stained for p53 protein. Patient acceptability was assessed using a visual analogue scale. The cytological diagnosis was compared with a chromoendoscopic examination using Lugol's solution.

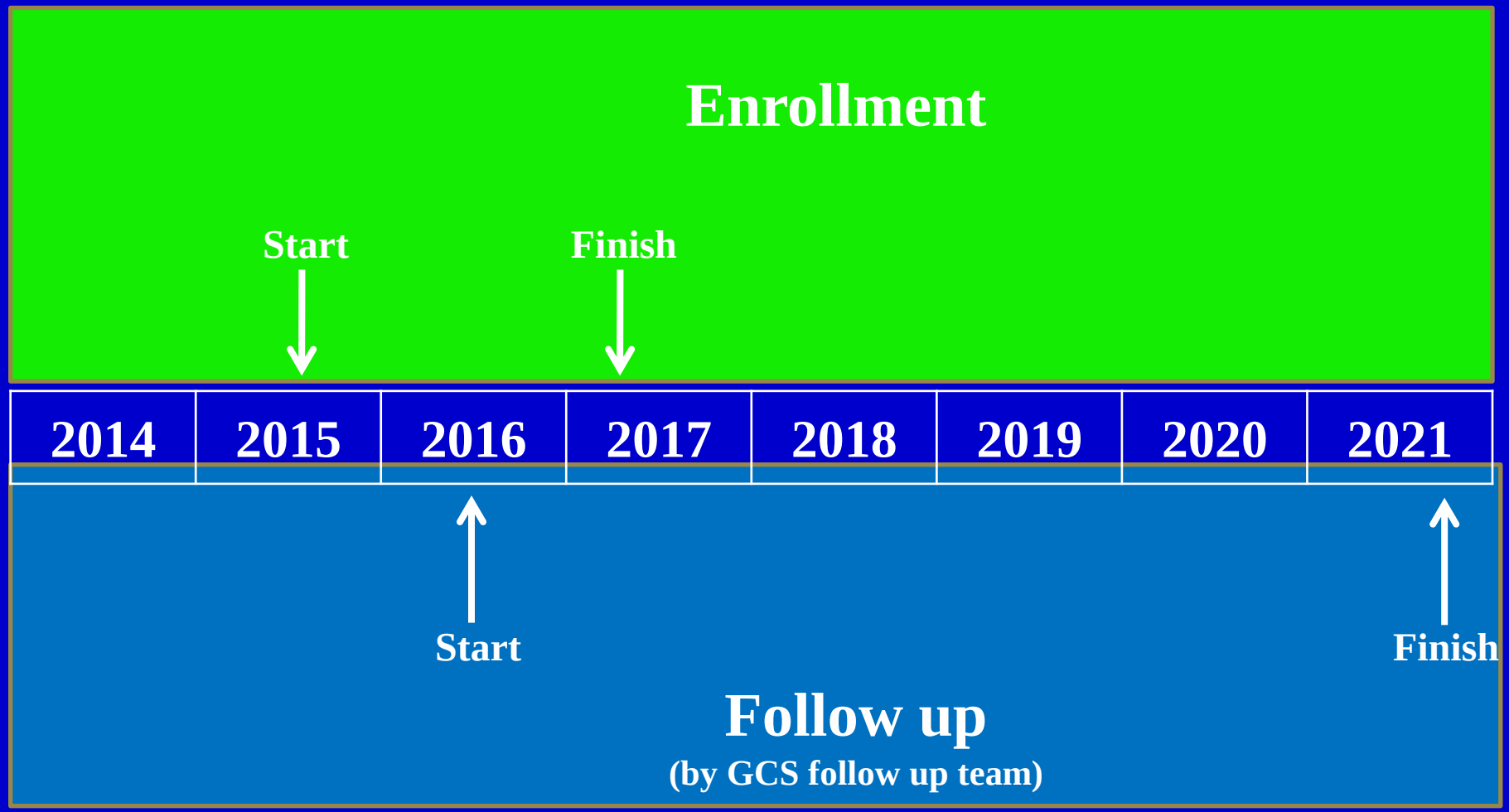
Results: Three hundred and forty-four subjects (43% male, mean (s.d.) age 55.6 (7.9) years) were referred to the study clinic. Three hundred and twelve met eligibility criteria and consented, of which 301 subjects (96.5%) completed both cytological and endoscopic examinations. There were no complications. Most of the participants (279; 92.7%) were satisfied with the examination.

Non-endoscopic Esophageal cancer Screening Program (NESP) using Cytosponge + Biomarker





Timeline of the NESP



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)
- Case-control studies of waterpipe use in relation to lung and aerodigestive cacners in the south of Iran (in collaboration with Iran Cancer Institute)

Contribution To Motograph Genetic Study
International collaboration in genetic studies

Mutography for ESCC

CANCER RESEARCH UK

GRAND CHALLENGE AWARDS

CHALLENGE 3

Discover how unusual patterns of mutation are induced by different cancer-causing events

mutographs of cancer:

discovering the causes of cancer through mutational signatures

A large international collaboration

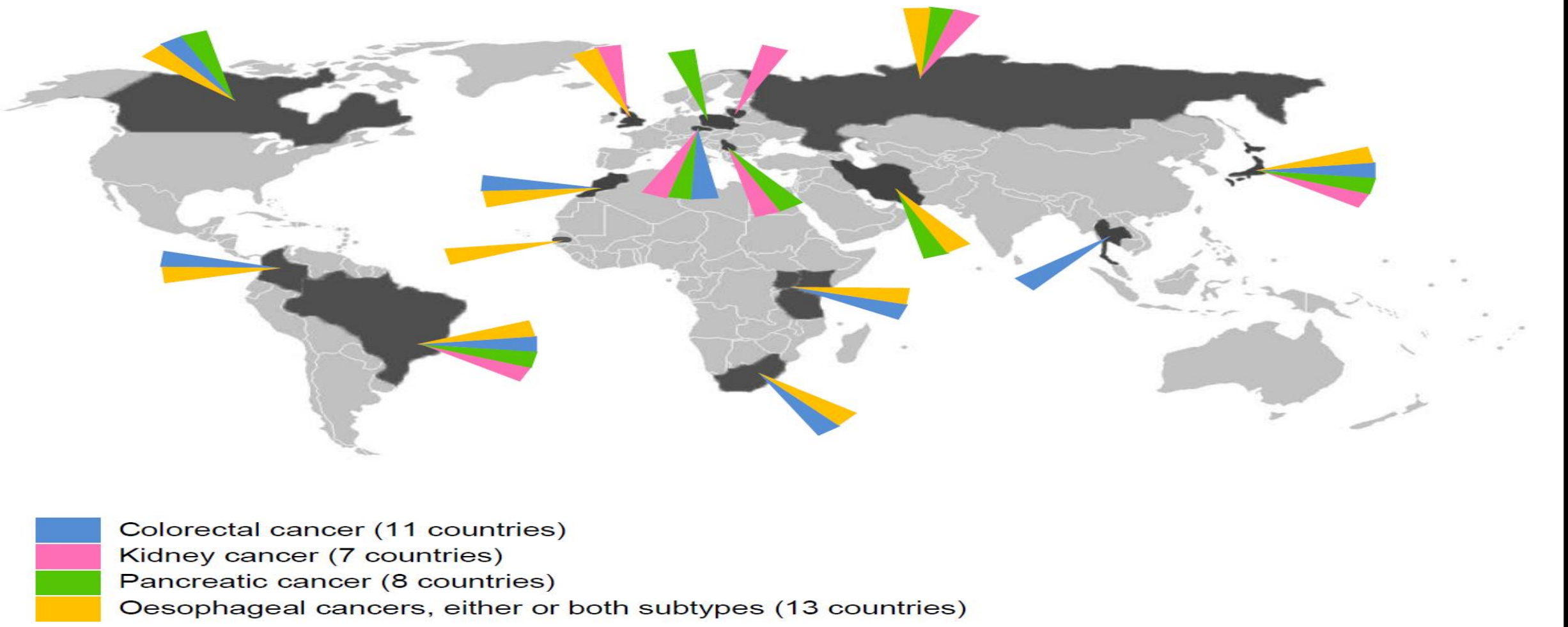


Figure 1: Countries contributing samples and information to *mutographs*WP1

Mutographs International Meeting
From mutational signatures to cancer prevention



Mutational Signature for ESCC 2021

nature genetics

ARTICLES

https://doi.org/10.1038/s41588-021-00928-6

Check for updates

Mutational signatures in esophageal squamous cell carcinoma from eight countries with varying incidence

Sarah Moody[1,25], Sergey Senkin[2,25], S. M. Ashiqul Islam[3,4,5], Jingwei Wang[1], Dariush Nasrollahzadeh[2,6], Ricardo Cortez Cardoso Penha[2], Stephen Fitzgerald[1], Erik N. Bergstrom[3,4,5], Joshua Atkins[2], Yudou He[3,4,5], Azhar Khandekar[3,4,5], Karl Smith-Byrne[2], Christine Carreira[7], Valerie Gaborieau[2], Calli Latimer[1], Emily Thomas[1], Irina Abnizova[1], Pauline E. Bucciarelli[1], David Jones[1], Jon W. Teague[1], Behnoush Abedi-Ardekani[2], Stefano Serra[8], Jean-Yves Scoazec[9], Hiva Saffar[10], Farid Azmoudeh-Ardalan[11], Masoud Sotoudeh[6], Arash Nikmanesh[6], Hossein Poustchi[6], Ahmadreza Niavarani[6], Samad Gharavi[6], Michael Eden[12], Paul Richman[13], Lia S. Campos[14], Rebecca C. Fitzgerald[15], Luis Felipe Ribeiro[16], Sheila Coelho Soares-Lima[16], Charles Dzamalala[17], Blandina Theophil Mmbaga[18], Tatsuhiro Shibata[19], Diana Menya[20], Alisa M. Goldstein[21], Nan Hu[21], Reza Malekzadeh[6], Abdolreza Fazel[22], Valerie McCormack[23], James McKay[2], Sandra Perdomo[2], Ghislaine Scelo[2,24], Estelle Chanudet[2], Laura Humphreys[1], Ludmil B. Alexandrov[3,4,5], Paul Brennan[2] and Michael R. Stratton[1]✉

Esophageal squamous cell carcinoma (ESCC) shows remarkable variation in incidence that is not fully explained by known lifestyle and environmental risk factors. It has been speculated that an unknown exogenous exposure(s) could be responsible. Here we combine the fields of mutational signature analysis with cancer epidemiology to study 552 ESCC genomes from eight countries with varying incidence rates. Mutational profiles were similar across all countries studied. Associations between specific mutational signatures and ESCC risk factors were identified for tobacco, alcohol, opium and germline variants, with modest impacts on mutation burden. We find no evidence of a mutational signature indicative of an exogenous exposure capable of explaining differences in ESCC incidence. Apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like (APOBEC)-associated mutational signatures single-base substitution (SBS)2 and SBS13 were present in 88% and 91% of cases, respectively, and accounted for 25% of the mutation burden on average, indicating that APOBEC activation is a crucial step in ESCC tumor development.

APOBEC – an avenue for further exploration?

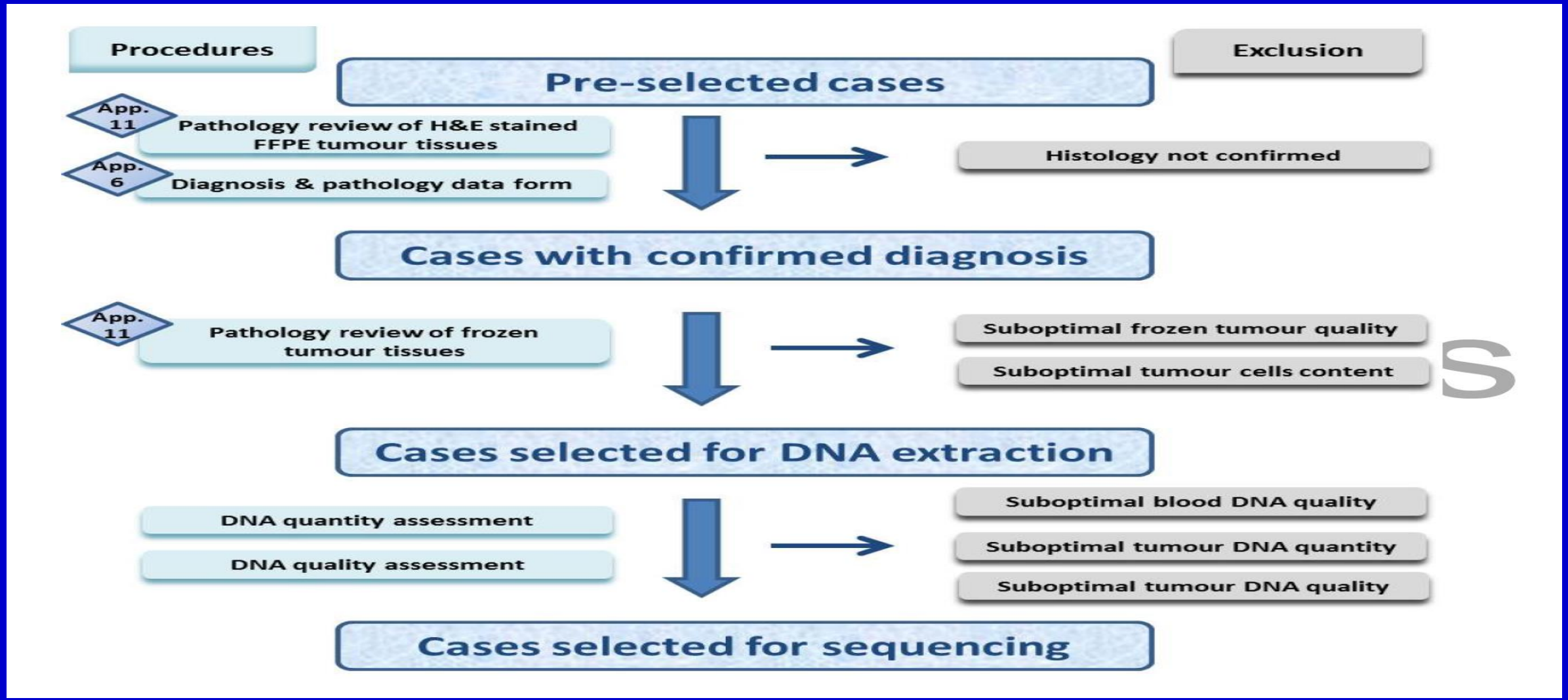
- Most importantly, we found evidence of two particular mutational signatures in around 90% of ESCC cases, which is a far higher number than most other cancer types.
- These two signatures are called SBS2 and SBS13 in the reference set of mutational signatures housed in COSMIC and are associated with the activity of the APOBEC family of proteins.

Summary of ESCC risk factors included in this study

		Brazil	China	Iran	Japan	Kenya	Malawi	Tanzania	UK
Total number of cases		30	138	178	37	68	59	35	7
Sex	Female	5	59	[illegible]	9	22	28	10	5
	Male	25	79	100	28	46	31	25	2
Age at diagnosis (years)	0–45	0	9	11	0	10	13	3	1
	45–55	5	50	35	6	13	12	5	0
	55–65	17	51	43	16	16	18	11	1
	65–75	5	27	52	12	20	12	13	2
	75+	3	1	37	3	9	4	3	3
Tobacco status	Current smoker	25	44	33	18	25	10	13	4
	Ex-smoker	4	26	14	11	12	11	10	1
	Never	1	68	131	8	31	38	12	2
Alcohol status	Current drinker	25	12	0	17	37	7	22	4
	Ex-drinker	4	7	4	15	15	17	4	1
	Never	1	119	174	5	16	35	9	1
	Missing								1
Fuel (indoor air poll.)	Biomass		101	84		67	59	32	
	Non-biomass		31	92		1		3	
	Missing	30	6	2	37				7
Family history of ESCC	No		129	137		58	53	23	
	Yes		9	39		3	4	6	
	Missing	30	0	2	37	7	2	6	7
Food and drink temp.	Lukewarm		74	82		11	7	0	
	Hot		14	74		37	10	20	
	Very hot		50	20		19	16	13	
	Missing	30	0	2	37	68	26	2	7
Opium status	Ever user			62					
	Never			110					
	Missing	30	138	6	37	68	59	35	7

Poll., pollution; temp., temperature.

Gemini contributed 300 ESCC samples for Pilot Phase



Conclusions

1. Golestan Cohort study provides a good example of multi-institutional international collaboration .
2. The case-control study has identified a number of plausible risk factors, which need confirmation in the cohort study
3. The cohort infrastructure, samples availability (including in NCI and IARC) provides a great opportunity to test new hypotheses
4. PAH exposure is a relevant and important hypothesis
5. Early detection is a significant challenge in this population

Thank you

