Pathophysiology of Tobacco Induced Cancers

Roy S. Herbst, MD, PhD
Ensign Professor of Medicine
Professor of Pharmacology
Chief of Medical Oncology
Director, Thoracic Oncology Research Program
Associate Cancer Center Director for Translational Research

February 27, 2014
Goals of this presentation

• Pathogenesis of tobacco induced cancer
  – Epidemiology and mechanism
  – Focus on lung and head and neck cancer

• Joint AACR/NCI efforts related to tobacco control
  – Tobacco use in patient’s receiving treatment for cancer
  – Clinical trials

• New Approaches to treatment of tobacco induced disease- the lung cancer master protocol
Goals of this presentation

• Pathogenesis of tobacco induced cancer
  – Epidemiology and mechanism
  – Focus on lung and head and neck cancer
The Health consequences causally linked to smoking

Figure 1.1A  The health consequences causally linked to smoking

Cancers
- Oropharynx
- Larynx
- Esophagus
- Trachea, bronchus, and lung
- Acute myeloid leukemia
- Stomach
- Liver
- Pancreas
- Kidney and ureter
- Cervix
- Bladder
- Colorectal

Chronic Diseases
- Stroke
- Blindness, cataracts, age-related macular degeneration
- Congenital defects—maternal smoking: orofacial clefts
- Periodontitis
- Aortic aneurysm, early abdominal aortic atherosclerosis in young adults
- Coronary heart disease
- Pneumonia
- Atherosclerotic peripheral vascular disease
- Chronic obstructive pulmonary disease, tuberculosis, asthma, and other respiratory effects
- Diabetes
- Reproductive effects in women (including reduced fertility)
- Hip fractures
- Ectopic pregnancy
- Male sexual function—erectile dysfunction
- Rheumatoid arthritis
- Immune function
- Overall diminished health

Note: The condition in red is a new disease that has been causally linked to smoking in this report.
Tobacco is the Single Largest Cause of Cancer in the World

- Tobacco use causes cancer in no less than 18 organ sites.
- Smoking causes more than 85% of lung cancers.
- One in three cancer deaths in the U.S. is directly linked to tobacco.
- The 2014 Surgeon Generals Report added the association of tobacco with hepatocellular and colorectal cancer.
# Epidemiology of Tobacco-Related Cancers in the US, Estimated in 2012

<table>
<thead>
<tr>
<th>Cancer type</th>
<th># cases</th>
<th># deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>226,160</td>
<td>160,340</td>
</tr>
<tr>
<td>Head and neck*</td>
<td>52,610</td>
<td>11,500</td>
</tr>
<tr>
<td>Esophageal</td>
<td>17,460</td>
<td>15,070</td>
</tr>
<tr>
<td>Stomach</td>
<td>21,320</td>
<td>10,540</td>
</tr>
<tr>
<td>Pancreas</td>
<td>43,920</td>
<td>37,390</td>
</tr>
<tr>
<td>Kidney</td>
<td>64,770</td>
<td>13,570</td>
</tr>
<tr>
<td>Bladder</td>
<td>73,510</td>
<td>14,880</td>
</tr>
<tr>
<td>Uterus</td>
<td>47,130</td>
<td>8,010</td>
</tr>
<tr>
<td>Cervix</td>
<td>12,170</td>
<td>4,220</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>143,460</td>
<td>51,690</td>
</tr>
<tr>
<td>Ovary</td>
<td>22,280</td>
<td>15,500</td>
</tr>
<tr>
<td>AML</td>
<td>13,780</td>
<td>10,200</td>
</tr>
</tbody>
</table>

* larynx, oral cavity, nasopharynx, pharynx
Epidemiology of Tobacco-Related Cancers Worldwide in 2008

<table>
<thead>
<tr>
<th>Cancer type</th>
<th># cases</th>
<th># deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>1,606,911</td>
<td>1,375,919</td>
</tr>
<tr>
<td>Head and neck*</td>
<td>631,786</td>
<td>355,217</td>
</tr>
<tr>
<td>Esophageal</td>
<td>481,645</td>
<td>406,198</td>
</tr>
<tr>
<td>Stomach</td>
<td>987,904</td>
<td>736,976</td>
</tr>
<tr>
<td>Pancreas</td>
<td>278,470</td>
<td>266,543</td>
</tr>
<tr>
<td>Kidney</td>
<td>264,146</td>
<td>110,824</td>
</tr>
<tr>
<td>Bladder</td>
<td>382,130</td>
<td>150,143</td>
</tr>
<tr>
<td>Uterus</td>
<td>288,265</td>
<td>73,818</td>
</tr>
<tr>
<td>Cervix</td>
<td>529,601</td>
<td>274,668</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>570,795</td>
<td>288,323</td>
</tr>
<tr>
<td>Ovary</td>
<td>222,613</td>
<td>139,472</td>
</tr>
</tbody>
</table>

* larynx, oral cavity, nasopharynx, pharynx

WHO GLOBOCAN 2008
How Smoking Causes Cancer

• Cigarette smoke contains more than 7,000 compounds of which >60 are known carcinogens (600 added to enhance flavor/nicotine absorption)

• Inhaling this mix of chemicals induces tissue injury and changes in the cellular environment fostering the proliferation and transformation into cancer

• Mutations result in loss of normal growth control, silencing of tumor progression genes, and promotion of cancer

• Field effects, second (or more) primary cancers are common
Effects of stopping smoking at various ages on the cumulative risk (%) of death from lung cancer by age 75 for men

Molecular Carcinogenesis of Lung Cancer

Molecular Carcinogenesis of Head and Neck Cancer

- Normal
- Hyperplasia
- Mild Dysplasia
- Moderate Dysplasia
- Severe Dysplasia
- Carcinoma in situ
- Invasive Carcinoma
- Metastasis

E-cadherin
CXCR4/SDF-1
VEGF(R)s, PDGF(R)
FGF(R), TGFα/β(R)
ILK-8(R)

LOH: 3p14, 9p21, 17p13
LOH: 8p, 11q, 13q, 14q
LOH: 6p, 4q27, 10q23

EGFR, Rb, p53, p65, Cox-2, p16, Cyclin D1, PTEN

Genomic instability/aneuploidy

MMPs

Chemoprevention

Therapy

Complexity of Tobacco-Related Carcinogenesis

Early
- Normal Epithelium
- 3p LOH/Small Telomeric Deletions
- Microsatellite Alterations
- 9p21 LOH
- Telomerase Dysregulation
- MYC Overexpression
- 8p21-23 LOH
- Loss of Fhit immunostaining
- p53 LOH
- Aneuploidy
- Methylation

Intermediate
- Hyperplasia
- Dysplasia
- Telomerase Upregulation
- MYC Overexpression

Late
- CIS
- Invasive Carcinoma
- 3p LOH/Contiguous Deletions
- 5q21 APC-MCC LOH
- Methylation
- TP53 Mutations

Cigarette Smoke Carcinogen Adducts at Lung Cancer Mutational Hotspots in P53

- Identification of p53 G:C to T:A mutations in lung cancer smokers
- Cigarette smoke carcinogen BPDE adducts in p53 mapped to guanines in codons 157, 248, and 273 - major mutational hotspots in human lung cancer

Takeshima et al. Lancet 1993; 342:1520-21
Widespread Dispersed p53 Mutation in Respiratory Epithelium of a Smoker

66-yr-old Smoker – Male
TP53 Mutation
Codon 245 (G:C to T:A)

Link between Cigarette Smoking and Cancer through Carcinogens in Tobacco Smoke

Initiation of cigarette smoking/nicotine addiction → Regular cigarette smoking → Uptake of carcinogens → Metabolic activation → DNA adducts → Persistence miscoding → Mutations in oncogenes and tumor-suppressor genes → Loss of normal growth control mechanisms → Cancer

Receptor binding → Protein kinase A and B activation and other changes

Excretion → Metabolic detoxification → Normal DNA → Repair → Apoptosis

Uptake of cocarcinogens and tumor promoters Gene promoter hypermethylation → Tumor-suppressor gene inactivation and other changes
Lung Cancer Mutation Consortium: Squamous Cell Cancers also have driver mutations

Genetic Profiles by Histologic Subtype

Oncogenic drivers differ between adenocarcinomas and squamous cell carcinomas

Goals of this presentation

• Pathogenesis of tobacco induced cancer
  – Epidemiology and mechanism
  – Focus on lung and head and neck cancer

• Joint AACR/NCI efforts related to tobacco control
  – Tobacco use in patient’s receiving treatment for cancer
  – Clinical trials

• New Approaches to treatment of tobacco induced disease- the lung cancer master protocol
Tobacco and Cancer: An AACR Policy Statement

- Includes research and policy recommendations for:
  - Preventing tobacco use
  - Treating tobacco addiction and fostering cessation
  - Reducing exposure to second hand smoke
  - Addressing tobacco-related cancer
Primary recommendations:

- Provide patients in all clinical cancer settings, including clinical trials, with evidence-based tobacco cessation assistance.

- Evaluate the confounding effects of tobacco on cancer treatment, disease progression, comorbid events, and survival in all oncology clinical trials from registration to survival endpoints.
Problem (Clinical)

Cancer patients and survivors who smoke cigarettes have worse health outcomes (including higher all-cause and cancer-specific mortality, and risk of tobacco-related second primary cancer).

Smokers may have higher risk of recurrence, poorer response to treatment, and increased toxicity.
Clinical significance of smoking by cancer patients

• Relative risk of all-cause mortality*
  – Current smokers 1.5 (relative to never smokers)
  – Former smokers 1.3

• Relative risk of cancer-specific mortality**
  – Current smokers 1.6 (relative to never smokers)
  – Former smokers 1.05

* Phipps, 2011 (colorectal cancer)
** Kenfield, 2011 (prostate cancer)
Problem

There are many scientific questions related to tobacco use in the cancer patient population.

Current approaches to data collection:
- Not widely assessed in trials or practice
- Inconsistent tobacco use assessment methods
- Little follow-up during/after treatment
Current practice

• NCI-Designated Cancer Centers
  – < 50% include tobacco use as a vital sign in the medical record

• NCI-funded phase III Cooperative Group trials
  – 22% record cigarette smoking status at enrollment, and
  – 4% during follow-up.

Goldstein, NTR, 2012; Warren, IJC, 2012
NCI-AACR Cancer Patient Tobacco Use Assessment Task Force

• History
  – Formed March, 2013
  – Conference calls, writing groups, and in-person meeting September 2013 (Bethesda)

• Goal
  – Develop recommendations for assessing and documenting tobacco use in clinical trials
  – Identify research priorities

• Progress
  – Drafted two tiers of measurement items and protocol for the timing and conduct of the assessment in cancer clinical trials.
    • Tier 1: minimum set of baseline and follow-up items recommended for clinical trials in any cancer patient or survivor study.
    • Tier 2: longer menu of curated items for use when more comprehensive assessment is feasible.
    • Items focus on tobacco use history, status, and intensity
  – Recommended assessment items for specific NCTN trials in development
Draft recommended measures
Tier 1 (minimal) paraphrased

Baseline:
• Ever smoked 100+ cigarettes in lifetime?
• How long since smoked?
• How many years smoked?
• Average number of cigarettes per day?

Follow-up:
• How long since smoked?
Task Force Roster

Jeffrey S. Abrams, MD
Thomas H. Brandon, PhD
Jan C. Buckner, MD
Paul M. Cinciripini, PhD
K. Michael Cummings, PhD, MPH
Carolyn Dresler, MD, MPA,
Sonia A. Duffy, PhD, RN, FAAN
Michael C. Fiore, MD, MPH, MBA
Ellen R. Gritz, PhD
Dorothy K. Hatsukami, PhD
Roy S. Herbst, MD, PhD
Jennifer A. Hobin, PhD
Fadlo R. Khuri, MD, FACP
Stephanie R. Land, PhD
Scott J. Leischow, PhD
Sandra Mitchell, CRNP, PhD, AOCN
Carol Moinpour, PhD

Jamie S. Ostroff, PhD
Sheila Prindiville, MD, MPH
Nancy Rigotti, MD
Linda Sarna, PhD, RN, FAAN, AOCN
Robert A. Schnoll, PhD
Peter Shields, MD
Benjamin Toll, PhD
K. (Vish) Viswanath, PhD
Graham Warren, MD, PhD
• Research and review articles published in AACR journals
• Editorial Overview: AACR Celebrates 50 Years of Tobacco Research and Policy
• Commentary from Howard Koh
• Q&As with Howard Koh and Mitchell Zeller
Tobacco Science and Policy at AACR Annual Meeting 2014

• Honoring the 50th Anniversary Surgeon General’s Report—*The Health Consequences of Smoking: 50 Years of Progress*
  
  *Speakers: Roy S. Herbst, Jonathan Samet, Graham Warren, Robert Croyle, Mitchell Zeller*

• Advancing Tobacco Regulatory Science: Meet Experts in FDA CTP
  
  *Speakers: Carolyn M. Dresler, Cathy L. Backinger, Dana M. van Bemmel, Nicolette Borek*
AACR-ASCO Policy Statement on Electronic Cigarettes

• Subcommittee of AACR and ASCO members

• Statement will include recommendations for
  – Research
  – Clinical practice
  – Regulation
Goals of this presentation

• Pathogenesis of tobacco induced cancer
  – Epidemiology and mechanism
  – Focus on lung and head and neck cancer

• Joint AACR/NCI efforts related to tobacco control
  – Tobacco use in patient’s receiving treatment for cancer
  – Clinical trials

• New Approaches to treatment of tobacco induced disease- the lung cancer master protocol
Targeting microRNA

Targeting EGFR Resistance

Targeting PD-1/B7-H1(PD-L1)

Targeting lung cancer risk characteristics for personalized prevention by smoking cessation
BATTLE-2 – Targeting Kras

**Protocol enrollment**  
Biopsy performed

**Stage 1:** (n=200)  
Adaptive Randomization 
by KRAS mut status

**Stage 2:** (n=200)  
Refined Adaptive Randomization 
“Best” discovery markers/signatures

**Primary endpoint:** 8-week disease control (N = 400)

**Discovery Markers:**

- **Protein expression (IHC):** p-AKT (Ser473), PTEN, HIF-1α, LKB1
- **Mutation analysis (Sequenom):** PI3KCA, BRAF, AKT1, HRAS, NRAS, MAP2K1 (MEK1), MET, CTNNB1, STK11 (LKB1)
- **mRNA pathways activation signatures:** Affymetrix®
  - BATTLE-1: WT-EGFR- Erlotinib, EMT, and Sorafenib
  - BATTLE-2: new “discovery” signatures
- **Protein profiling – RPPA** (n=174)
- **NGS-Foundation Medicine**
- **RNA sequencing**

NCI RO1 funded, Yale, MDACC
S1400 Master Protocol
Unique Private-Public Partnerships with the NCTN
Rationale for Master Protocol Design

- **Multi-arm Master Protocol**
  - Homogeneous patient populations & consistent eligibility from arm to arm
  - Each arm independent of the others
  - Infrastructure facilitates opening new arms faster
  - **Phase II-III design** allows rapid drug/biomarker testing for detection of “large effects”

- **Screening** large numbers of patients for multiple targets by a broad-based NGS platform reduces the screen failure rate
- Provides a **sufficient “hit rate”** to engage patients & physicians
- **Bring safe & effective drugs to patients faster**
- Designed to facilitate **FDA approval** of new drugs
Significantly mutated genes in lung SQCC.

Phase II/III Biomarker-Driven Master Protocol for Second Line Therapy of Squamous Cell Lung Cancer
TT=Targeted therapy, CT=chemotherapy (docetaxel), E=erlotinib

*Archival FFPE tumor, fresh CNB if needed

Target/M: Drug target and biomarker
The Lung Master Protocol trial will be managed with multiple partners.

Oversight Committee
NCI, ex-Industry, Advocates, PI’s (ex-officio), FNIH [supported by FNIH]

Executive Operations Group
Roy Herbst, Vali Papadimitrakopoulou, co-chairs

Project Management Office
FNIH, SWOG, FOCR

Partner Science Focus Group

Contract, Fundraising, Data Sharing, IP

Drug and Biomarker Selection Committee

Assay Company RFP, selection

Partner Science Focus Group

Clinical Project Management

Sites 1,2,3…n

DSMB

Working Groups

IND management

DSMB

Working Groups

IND management
Conclusions

• Association of tobacco with cancer is well documented

• Unique concerns in patient’s getting therapy for cancer- issues being addressed

• While primary and secondary prevention is of course critical- better therapeutic options/trial designs for smoking related cancers are underway
THANK YOU!