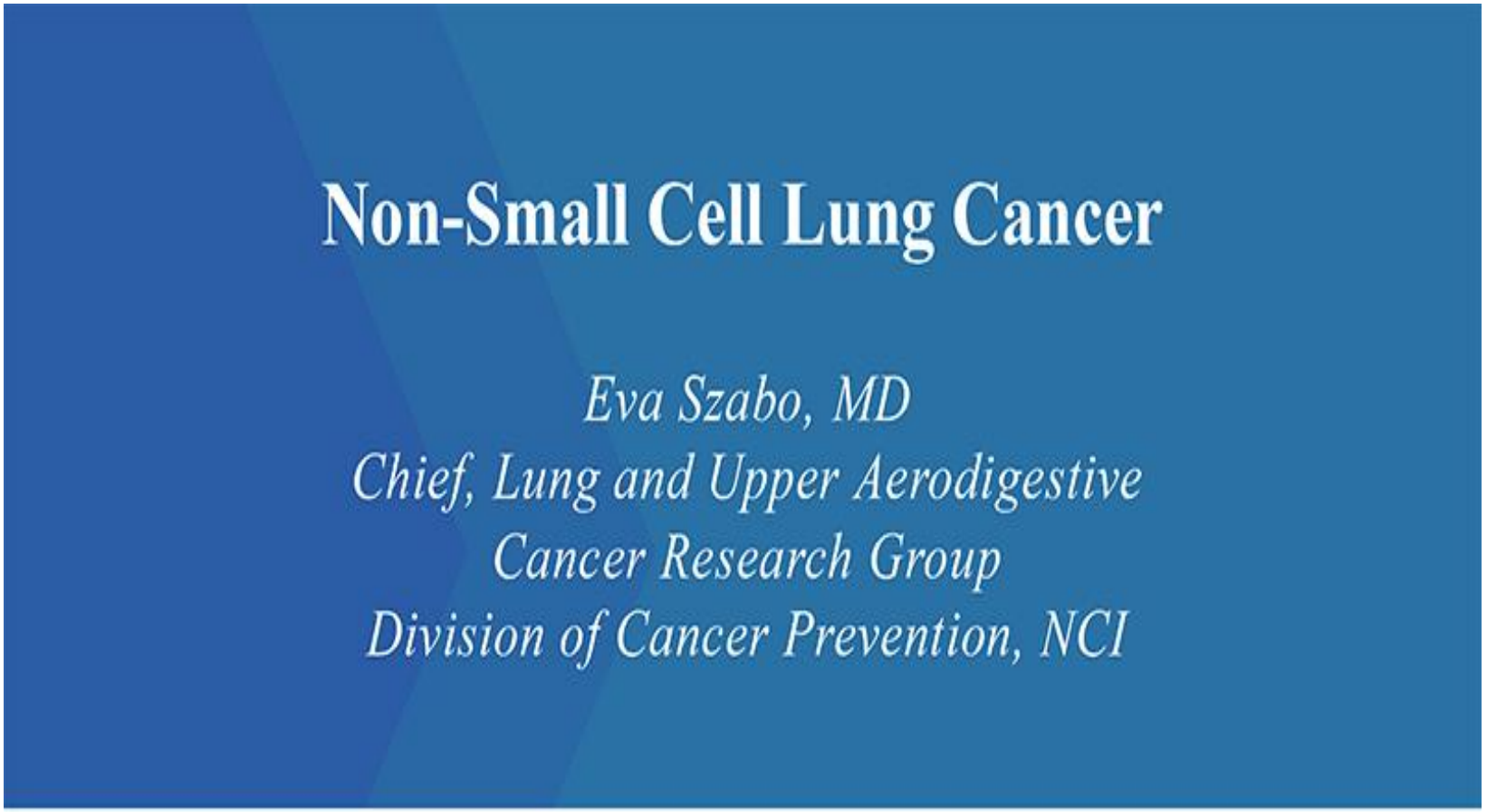
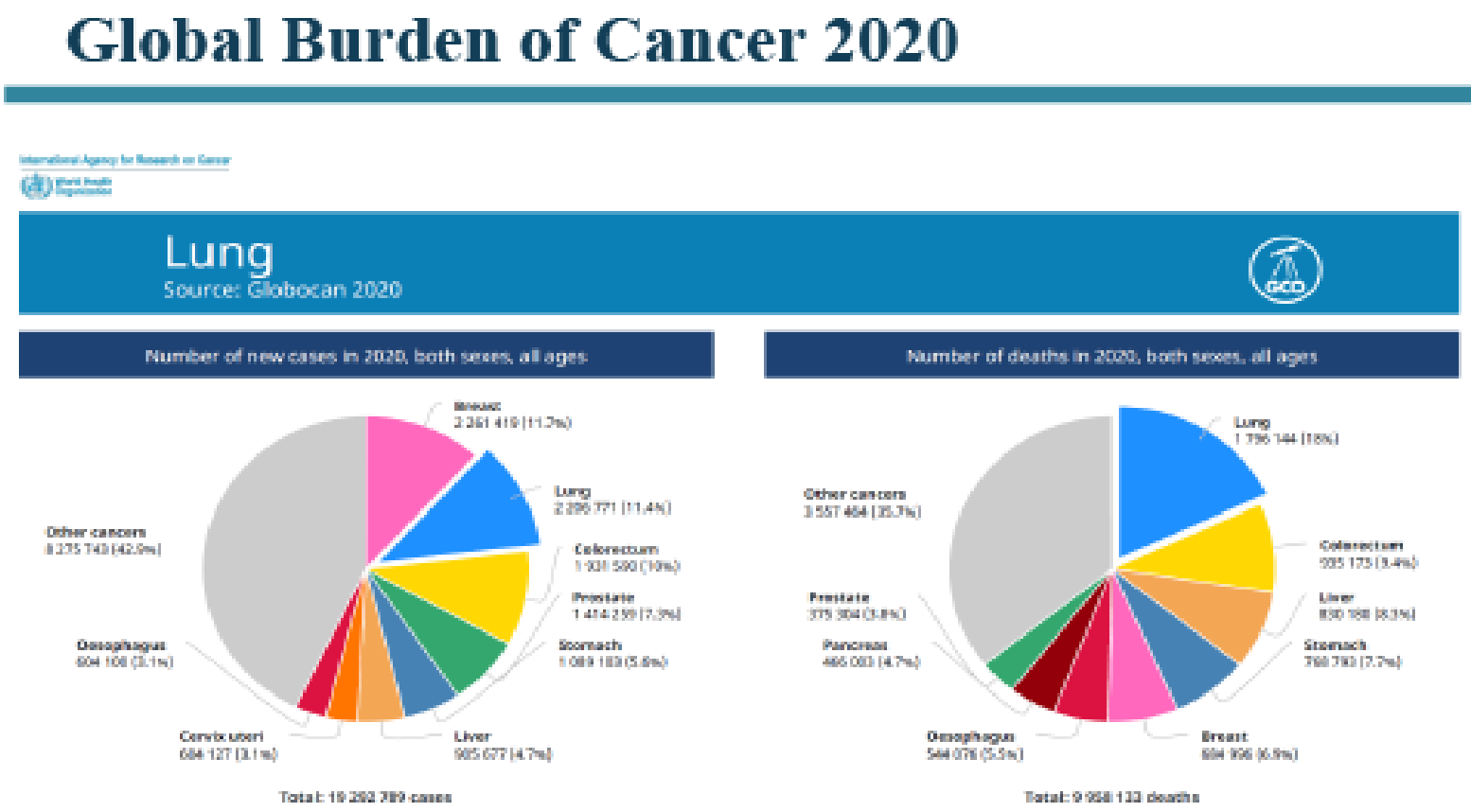
Non-small cell lung cancer



Global cancer burden

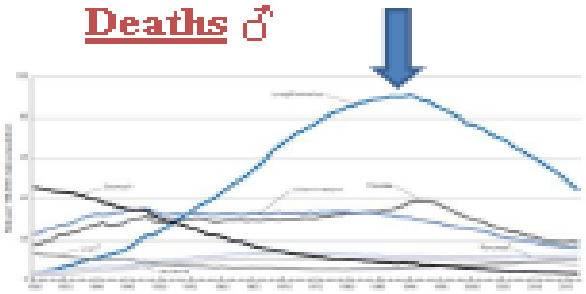


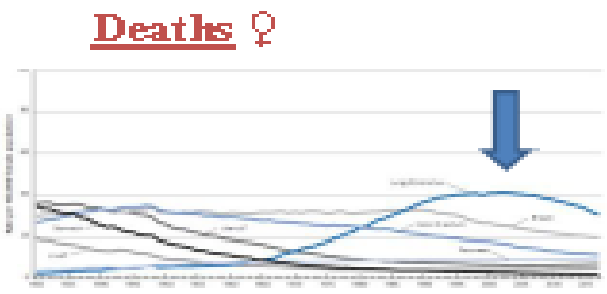
https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf

US lung cancer statistics, 2021

US Lung Cancer Statistics, 2021

- 235,760 estimated new cases (lung and bronchus)
- 131,880 estimated deaths
- leading cause of cancer deaths
  - greater than breast+prostate+colon
  - death rate per 100,000 decreasing (90.56 in 1990; 67.45 in 2006)
    - Incidence declining in men since mid-1980's, women since mid-2000's
- 21% five-year survival
  - 5% in 1950's, 12% in 1970's
- 22% of all male and female cancer deaths

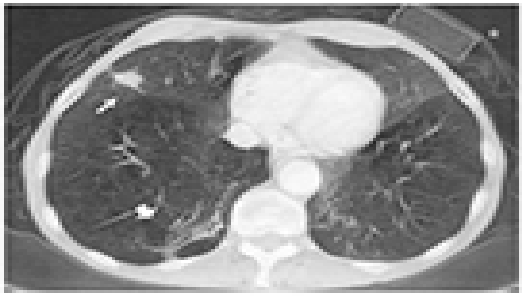




https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf

Risk factors

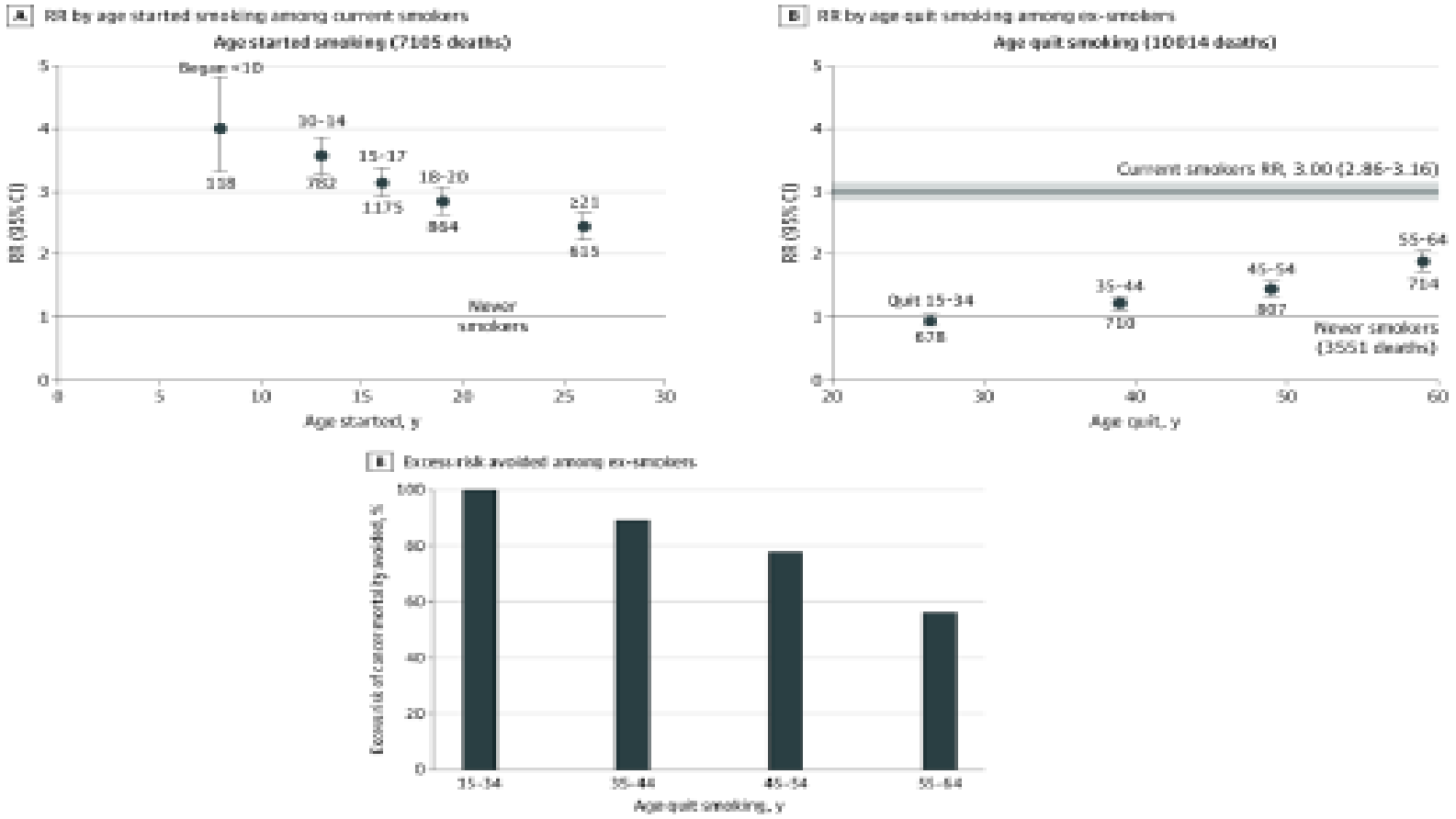
Risk Factors



- Tobacco, tobacco, tobacco (85% lung ca.)
  - Including passive smoking
  - Prior aerodigestive malignancy
  - COPD
- Other exposures
  - Asbestos, radon, polycyclic aromatic hydrocarbons, chromium, nickel, inorganic arsenic – mining, ship building, oil refining
- Genetic predisposition
  - Familial lung cancer – Germline mutations - EGFR T790M
    - Bell et al., Nat Gen 2005;37:1315
  - 15q24-25.1 – nicotinic acetylcholine receptor subunits CHRNA3 and CHRNA5, OR=1.3, attributable risk ~14%
    - Amos et al., Nat Gen 2008;40:616, Hung et al. Nature 2008;452;633, Thorgeirsson et al. Nature 2008;452:638
  - CH3NA3/5 is also susceptibility locus for COPD
    - Pillai et al. PLoS Genet 2009;5:1

Tobacco and cancer

Association Between Tobacco and All Cancer Death

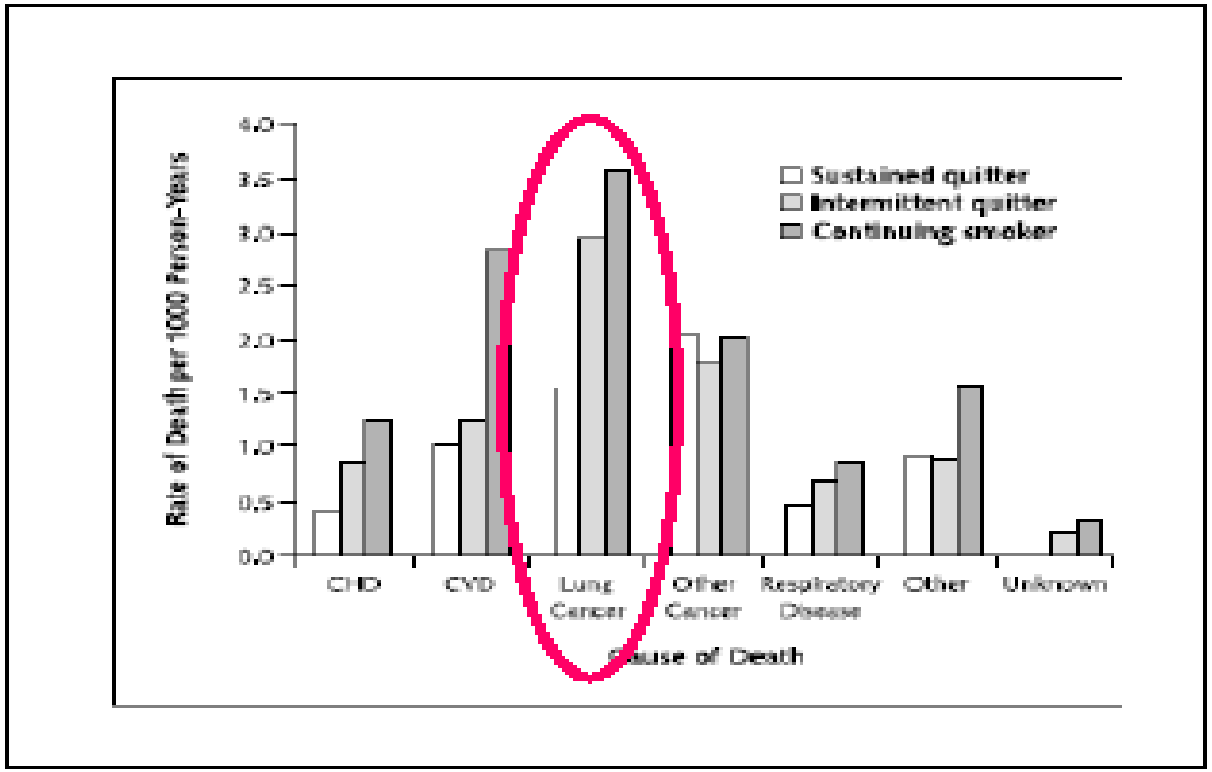


Thompson B et al., Addict Chron. Published online October 21, 2021. doi 10.1001/jamaoncol.2021.4994

Smoking cessation

Effect of Smoking Cessation on Lung Cancer Deaths

Lung Health Study, 14.5 yr F/U



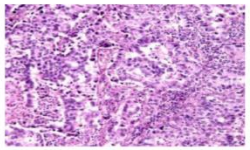
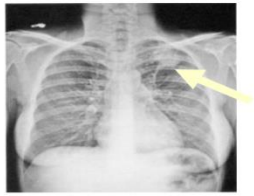
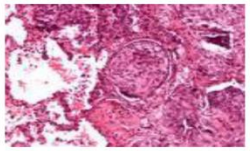
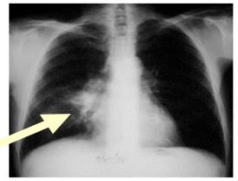
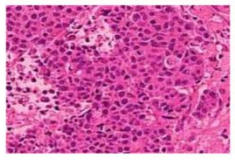
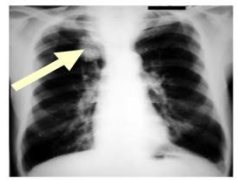
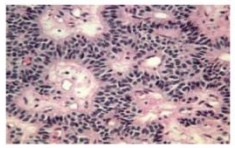
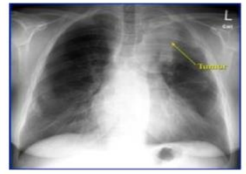
Lung Health Study, 14.5 yr f/u

-Anthonisen et al., Ann Intern Med 2005;142:233

Pathology: NSCLC

Pathology: Non-small Cell Lung Cancer

- **Adenocarcinoma, inc bronchoalveolar**
  - **40%**
- **Squamous cell carcinoma**
  - **20%**
- **Large cell carcinoma**
  - **15%**
- **Others (carcinoid, etc.)**

Lung carcinogenesis

The Continuum of Lung Carcinogenesis

Opportunities for Intervention

Normal → Hyper/Metaplasia → Dysplasia → Early-Late Cancer

Prevention

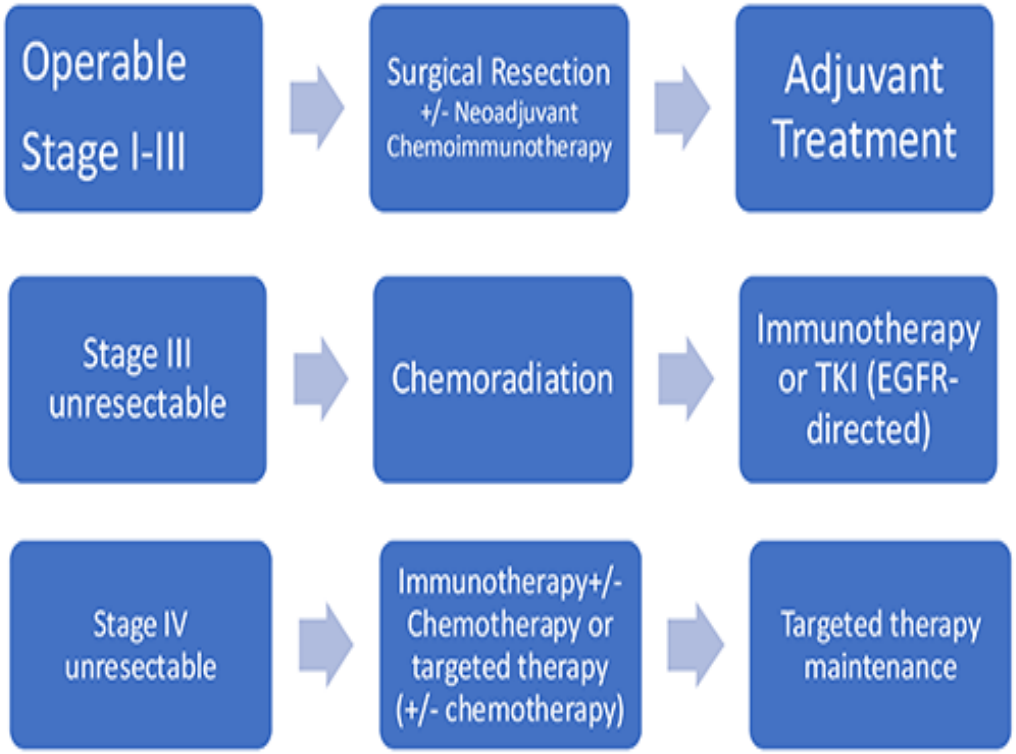
Early Detection

Treatment

Treatment strategies

Treatment Strategies for Lung Cancer

- **NSCLC: treatment based on stage, resectability, and presence of targetable mutations**



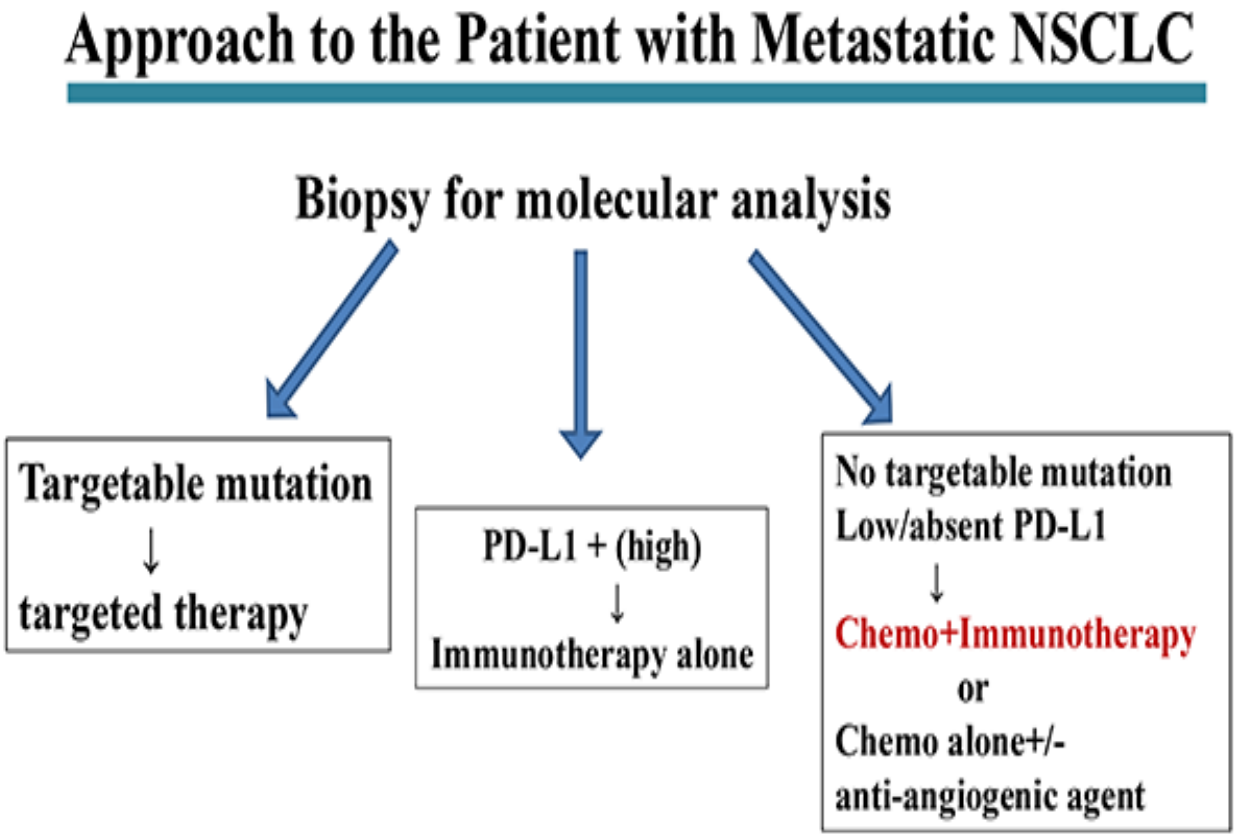
- **Small cell lung cancer: chemotherapy + immunotherapy**
  - **+thoracic radiation for limited stage; prophylactic cranial radiation to prevent brain metastases**

Treatment options

Treatment Options for Metastatic NSCLC

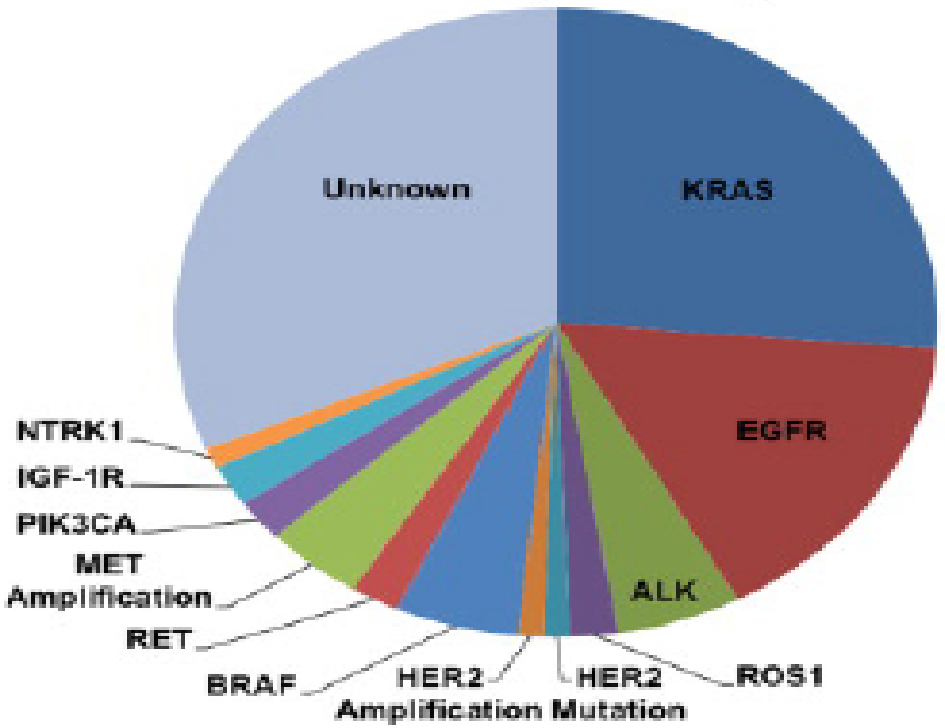
- **Chemotherapy**
  - Platinum doublets, iv
  - Adjuvant, metastatic disease
  - Still a mainstay of treatment
- **Targeted therapy**
  - For minority of patients with targetable mutations
  - Oral therapies, better tolerance
  - Extended survival
- **Immunotherapy**
  - Now a definitive role, frontline and second line

Metastatic NSCLC



Personalizing Therapy for NSCLC

Personalizing Therapy for NSCLC
Genetic Abnormalities in Lung Adenocarcinoma



Targetable mutations/gene fusions

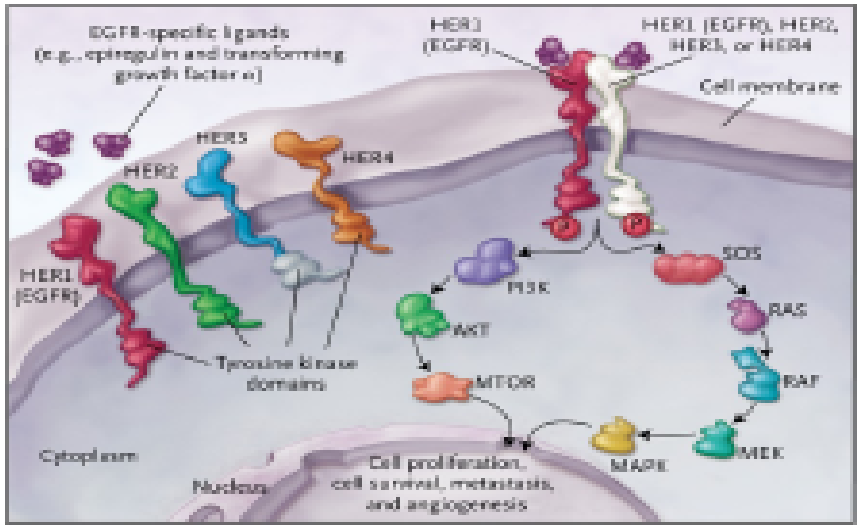
- EGFR
  - multiple drugs
- ALK
  - multiple drugs
- ROS1
  - crizotinib
- BRAF-V600E only
  - dabrafenib/trametinib
- RET
  - Experimental drugs (BLU-667)
- NTRK
  - larotrectinib
- MET ex 14 skipping
  - crizotinib
- HER2/Neu – exon 20 mutations
  - HER2 antibodies + chemo

Response rates 50-80%

Berge and Doebele Sem Oncol 2014; Hunter et al. Nature 2004; Heinmoller P et al. Clin Cancer Res 2003; Drilon A et al. JCO 2016 suppl; Drilon A NEJM 2018

EGFR and NSCLC

EGFR as a Target for NSCLC

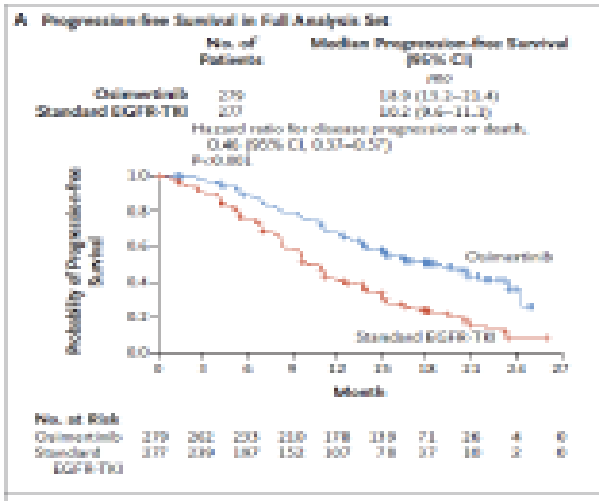


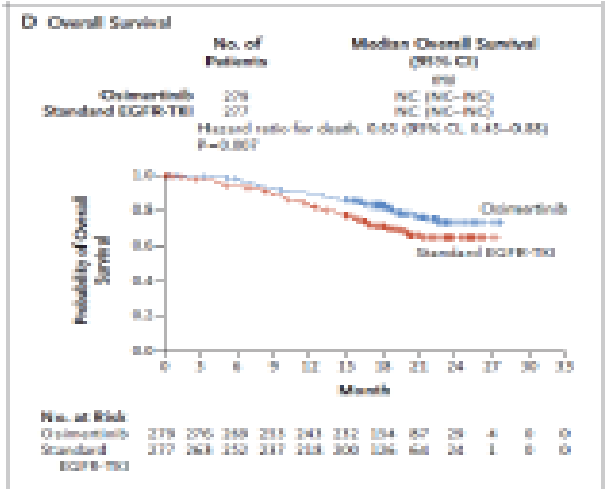
- Epidermal growth factor receptor (EGFR) mutated in ~15% NSCLC
- Oncogenic driver; primarily in non-smokers
- Targeted therapies tyrosine kinase inhibitors (TKIs) highly active
  - 60-80% response rates EGFR-MT disease
  - Progression-free survival 10-14 months (c/w chemo 4-6 months)
  - Median survival 30 vs. 24 months with chemo
    - Maemondo et al N Engl J Med 2010;362:2380
- Multiple TKIs approved for frontline use; 3rd generation TKI (osimertinib) superior
- Mechanisms of resistance well understood (T790M; osimertinib)

Osimertinib

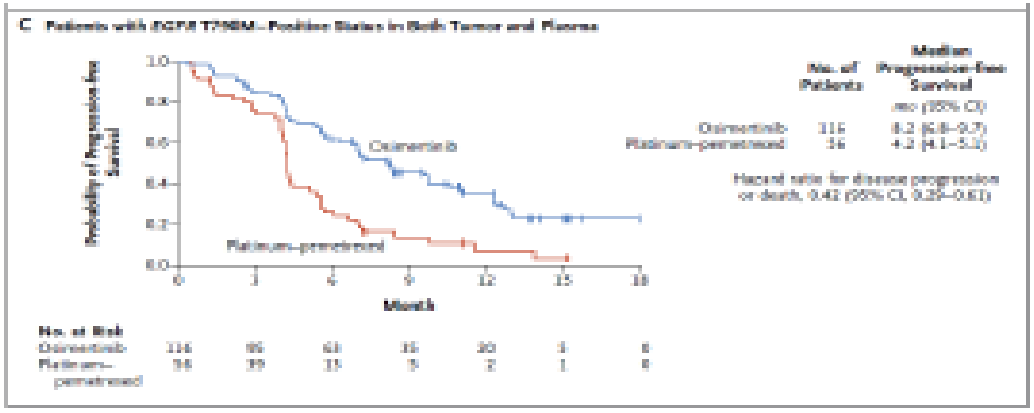
Osimertinib in Chemotherapy-naïve Patients

No prior Rx





Prior frontline TKI but no prior chemo

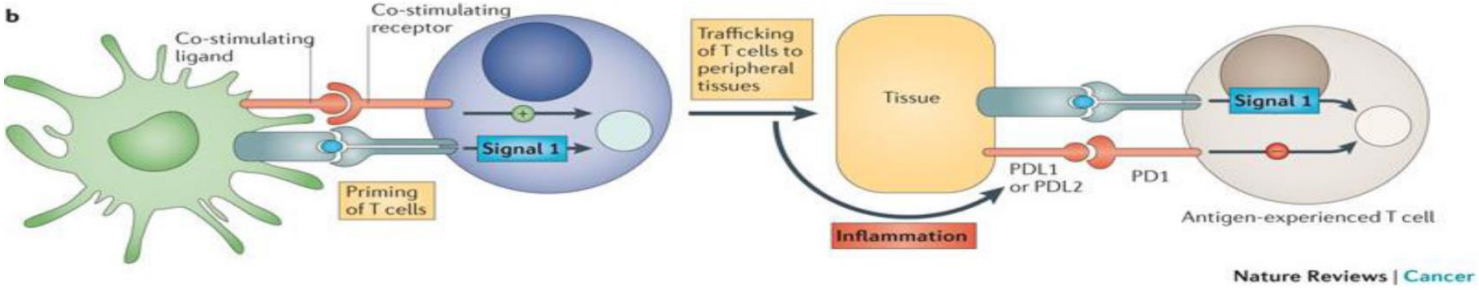


Mok TS et al. NEJM 2016
Soria J-C et al. NEJM 2017

New Approaches-Immunotherapy

New Approaches - Immunotherapy

- PD-1
  - T-cell co-inhibitory receptor, regulates T-cell activation
  - Main role: to limit activity of T cells in peripheral tissues during inflammatory response to infection and to limit autoimmunity
  - ligands PD-L1 (frequently expressed on tumors) and PD-L2
  - Blockade of PD-L1/PD-1 interaction potentiates immune response (to tumor)



Pardoll D Nat Rev Cancer 2012;12:252

Cancer prevention

Cancer Prevention

The use of natural or synthetic agents to suppress or reverse carcinogenesis

- Regress existing neoplastic lesions (treat intraepithelial neoplasia)
- Prevent development of new neoplastic lesions (preneoplastic and cancer)
- Suppress recurrence of neoplastic lesions

Classically applied to agents (chemoprevention), but also includes vaccines and immune approaches (immunoprevention)

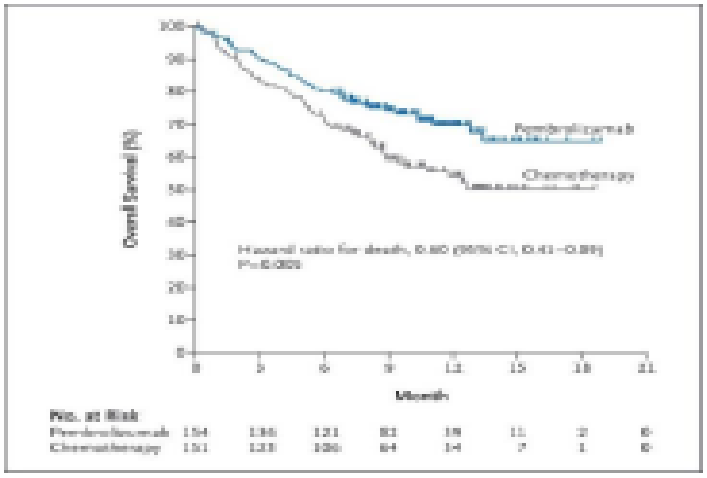
Sporn MB Cancer Res 1976;36:26990

Immunotherapy

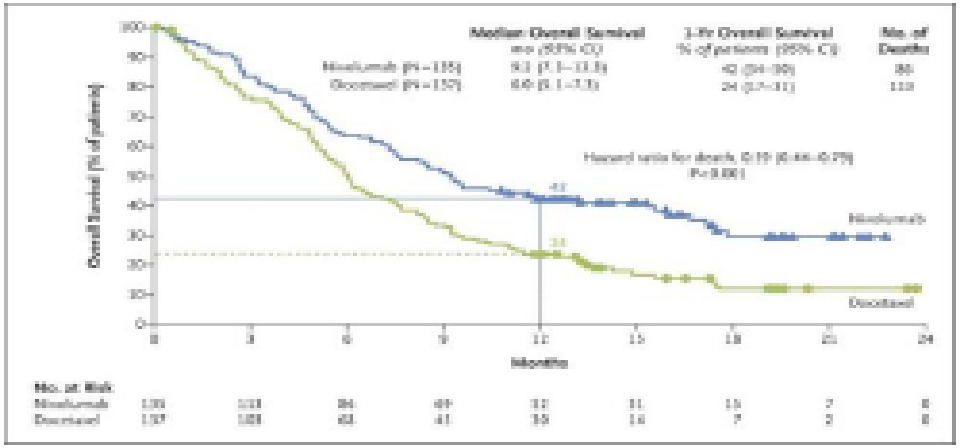
Immunotherapy

- **Anti-PD-1 or PD-L1 antibodies approved for frontline NSCLC, second line Rx, in combination with chemo (frontline), and maintenance post-chemoradiation**
  - **Tail of the survival curves suggests long term benefit for minority of patients**

Frontline treatment



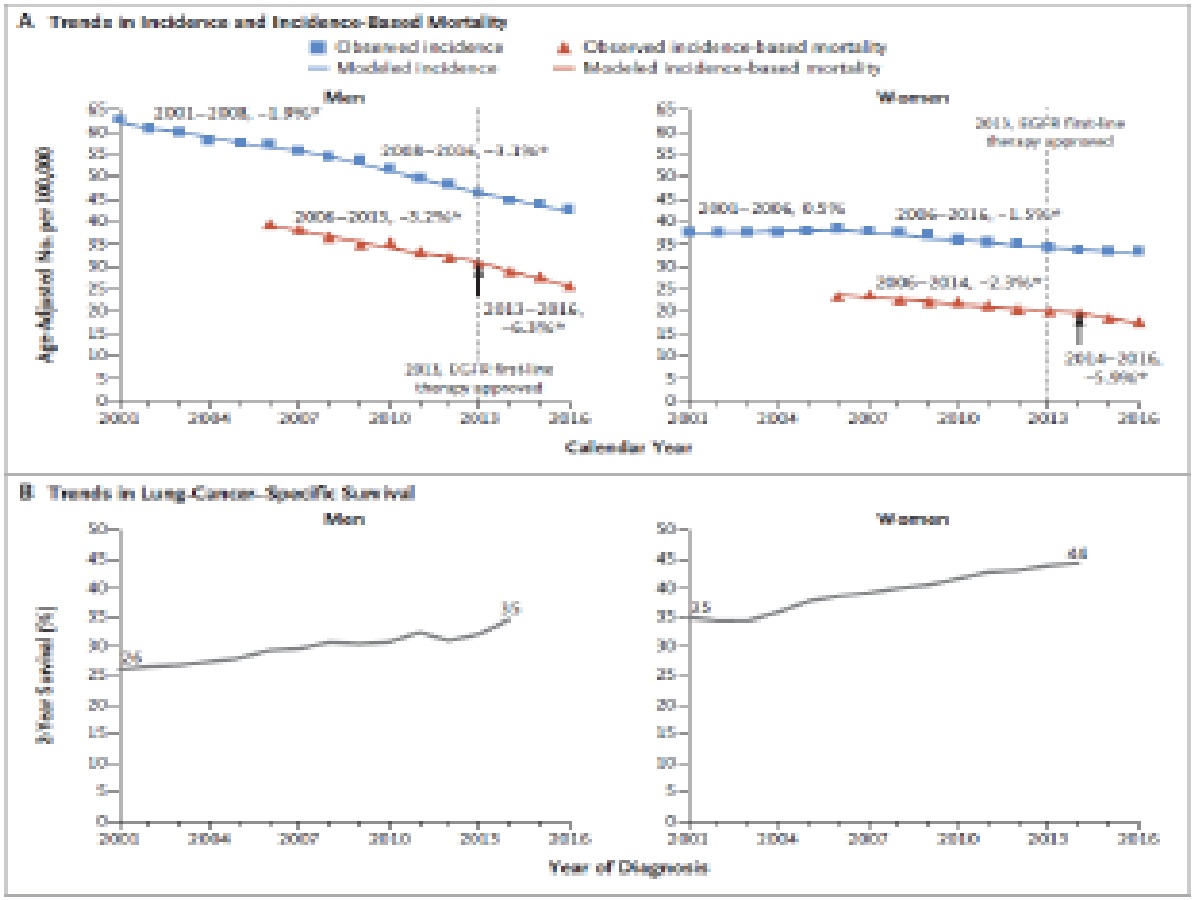
Second line treatment



Reck M et al. NEJM 2016;375:1823-1833
Brahmer J et al. NEJM 2015;373:123-135

NSCLC mortality

↓ Mortality from NSCLC with Improved Therapy



Mortality decreased faster than incidence

- 2013-2016 -Mortality ↓6.3% annually (men)
- 2008-2016 - Incidence ↓3.1% annually (men)
- Lung cancer specific survival improved from 26% to 35% from 2001 to 2016
- Similar in women, across all races/ethnic groups
- For SCLC, decreased mortality was same as decreased incidence
- **Conclusion: treatment advances (esp. targeted therapies) responsible**

Howlader N et al., NEJM 2020 383:640

Approaches to reducing cancer morbidity and mortality

- **Prevention (primary, secondary, tertiary)**
- **Early detection**

- **Better therapeutics**

Lung carcinogenesis

The Continuum of Lung Carcinogenesis

Opportunities for Intervention

Normal → Hyper/Metaplasia → **Dysplasia** → Early-Late Cancer

Prevention

Early Detection

Treatment

Cancer Chemoprevention

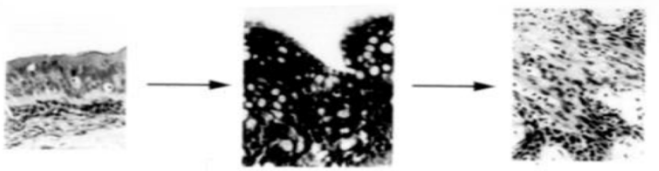
The use of natural or synthetic agents to suppress or reverse carcinogenesis

- **Regress existing neoplastic lesions (treat intraepithelial neoplasia)**
- **Prevent development of new neoplastic lesions (preneoplastic and cancer)**
- **Suppress recurrence of neoplastic lesions**

Lung Cancer Prevention

Rationale for Lung Cancer Prevention

- **Metastatic cancer is rarely curable**
  - **US lung cancer 5 yr survival is ~15% (5% 1950's, 13% 1970's)**
- **Cancer is preventable**
  - **P1, STAR breast cancer prevention trials with tamoxifen and raloxifene**
    - *Fisher B et al., JNCI 1998;190:1371; Vogel, VG et al., JAMA 2006;295:2727*
  - **Multiple animal studies with multiple agents**
- **Long preclinical phase with increasing histologic and molecular abnormalities, identifiable populations at risk**



Lung premalignancy

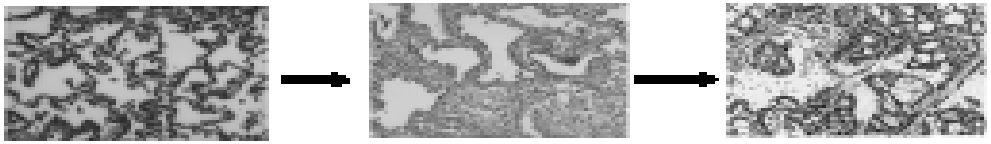
Evolution of Lung Premalignancy

Normal → Hyperplasia/Metaplasia → Dysplasia → Cancer

Mild/Moderate/Severe/CIS

Squamous (central)

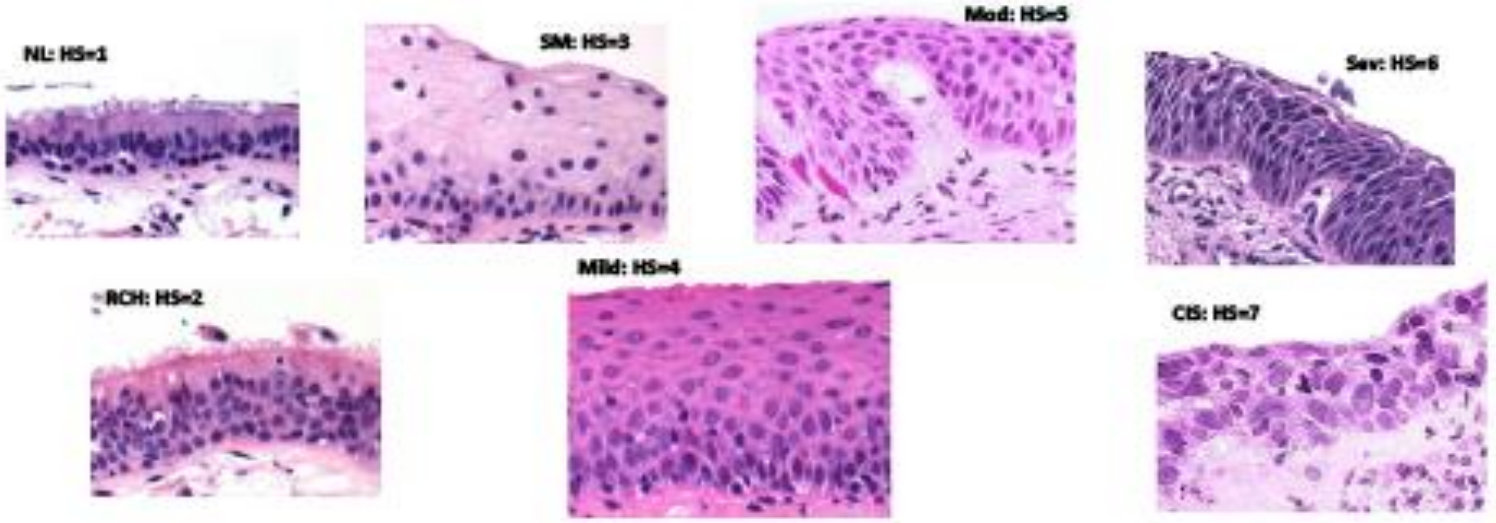
Adenomatous (peripheral)



Premalignant squamous lesions

Premalignant Squamous Lesions

Bronchial Dysplasia – precursor and risk marker



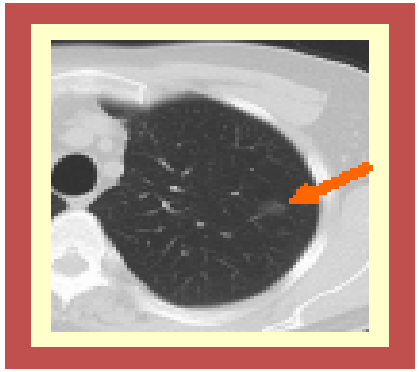
- 164 pts. with low or high-grade lesions
  - 33.5% developed invasive cancer, median 16.5 mths
  - 41% cancers developed from abnormal site, 59% from other sites (central or peripheral)
  - High grade lesions assoc with cancer; COPD and prior hx lung ca assoc with OS

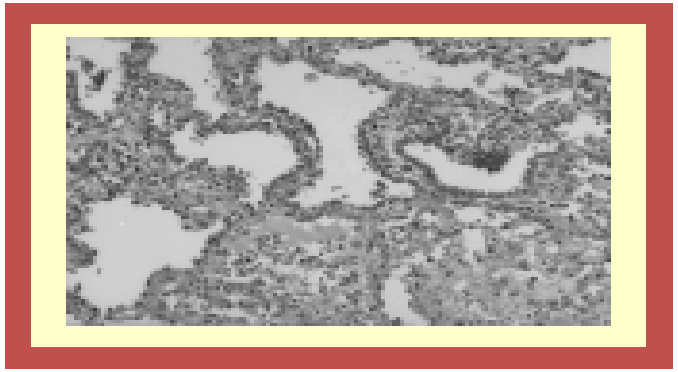
- *Bronchial dysplasia both precursor and risk marker for abnormal field*

Van Boerdonk et al., Am J Respir Crit Care Med 2015;192:1483

Atypical adenomatous hyperplasia

Adenocarcinoma Precursor: Atypical Adenomatous Hyperplasia (AAH)





- **Natural history not well understood**
- **Localized ground glass opacities on CT:**
  - AAH 25%; bronchoalveolar ca 50%; invasive adenoca 10%; fibrosis 15%
    - *Nakajima et al., J Comput Assist Tomogr 2002;26:323*
  - AAH 63%; bronchoalveolar ca 34%; scar 3%
    - *Ohtsuka et al., Eur J Cardio-Thor Surg 2006;30:160*

Non-solid nodules

Non-Solid Nodules – Natural History

- Prospective trial, 795 patients with 1229 subsolid nodules (GGNs, ≤3 cm, solid component ≤5 mm)
  - f/u 4.3±2.5 years
  - 1046 pure GGN ⟶ 5.4% became part solid
  - 81 heterogeneous GGN ⟶ 19.8% became part solid
  - Resected nodules (in 80 patients)
    - 35/997 pure GGNs (9 MIA, 21 AIS, 5 AAH)
    - 7/78 heterogeneous GGNs (5 MIA, 2 AIS)
    - 49/174 part solid GGNs (12 invasive, 26 MIA, 10 AIS, 1 AAH)

  - *1% of all nodules became invasive cancer (all were part solid)*
  - *3.3% became MIA, 2.7% AIS, 0.5% AAH*

Kakinuma et al., J Thor Oncol 2016;11:1012

Targeting inflammation

Targeting Inflammation for Lung Cancer Prevention: Rationale

- **Animal data showing role for steroids in cancer prevention**
  - **1970's – skin**
  - **Early 1990's – lung (oral steroids)**
  - **Late 1990's – lung (inhaled steroids)**
- **Epidemiology/Human data –**
  - **Mainly negative (but studies of short exposure duration)**
  - **VA cohort with COPD (n=10,474) – HR 0.39 (95% CI, 0.16-0.96)**
    - **Parimon T et al., AJRCCM 175:712, 2007**

Phase IIb budesonide trial

DCP Phase IIb Trial of Inhaled Budesonide in Bronchial Dysplasia

112 smokers with dysplasia by bronchoscopy

↓ Helical CT

Screened (sputum): 1040
Cancers detected: 13

Budesonide vs. Placebo x 6mths

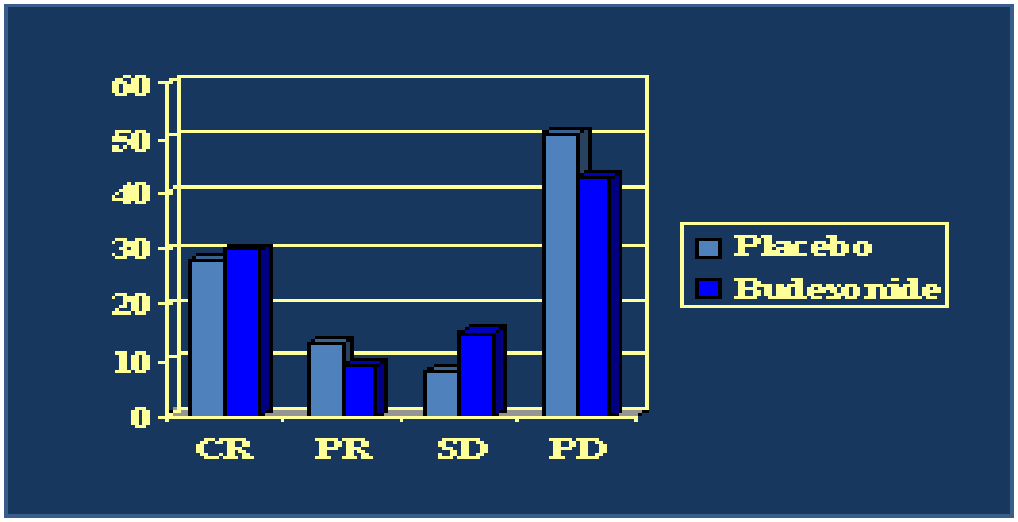
↓ Bronch, Spiral CT)

1° Endpoint: bronchial dysplasia (#sites/grade)
2° Endpoints: multiple biomarkers

Lam et al., Clin Cancer Res 2004;10:6502

Bronchial dysplasia

Phase IIb Trial of Inhaled Budesonide in Bronchial Dysplasia



- **Bronchial dysplasia – no effect of 6 mth Rx**
- **CT-detected lung nodules - 27% vs. 12% resolved (p=0.024)**

Lam et al., Clin Cancer Res 2004;10:6502

Chemoprevention trial. Phase IIb Trial

Peripheral Lung Carcinogenesis Trial Design
Phase IIb Budesonide Chemoprevention Trial

202 participants with persistent LD-CT-detected peripheral nodules

↓ Randomize

inhaled budesonide vs. placebo x 1 year

↓

repeat LD-CT

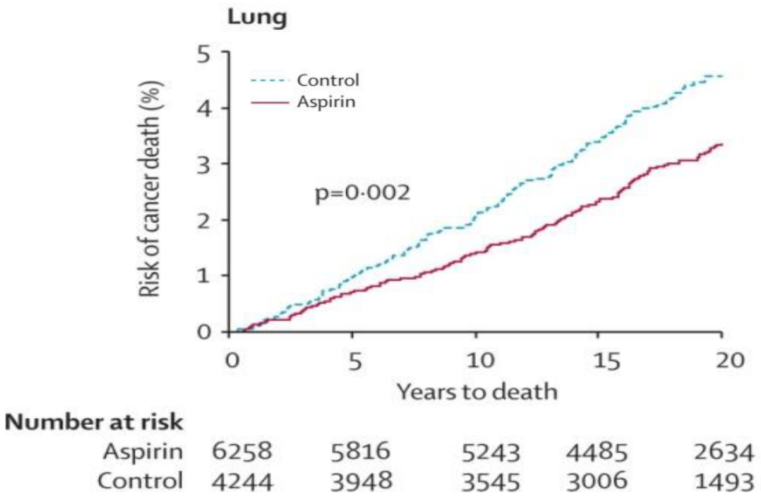
Primary endpoint: shrinkage of lung nodules

-*Veronesi et al., Cancer Prev Res 2011;4:34-42*

Aspirin and Mortality

Effect of Aspirin on Lung Cancer Mortality

-Rothwell et al., Lancet 2011;377:31



-individual patient data from trials of ASA vs. none

-lung:

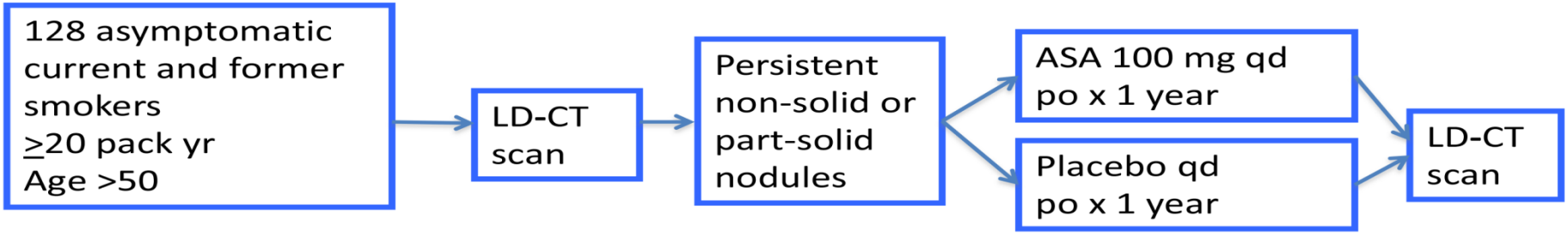
f/u	0-10 yrs	0-20 yrs
HR	0.68	0.71
	(0.50-0.92, p=0.01)	(0.58-0.89, p=0.002)

-adenocarcinoma only

-benefit only after 5 yrs

Phase II Trial

A Randomized Phase II Trial of Low Dose Aspirin versus Placebo in High-Risk Individuals with CT Screen Detected Subsolid Lung Nodules
PIs: Giulia Veronesi, MD and Bernardo Bonanni, MD; IEO

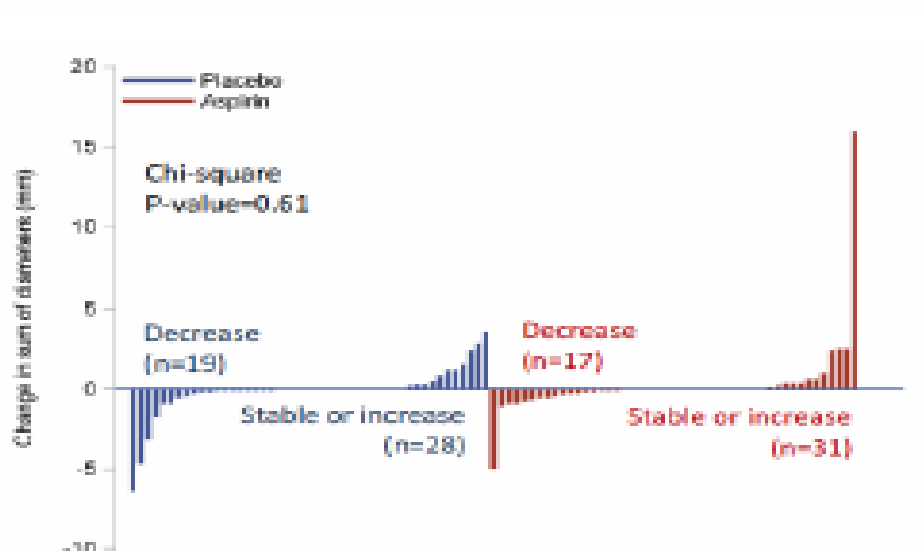


1° Endpoint: #/Size semisolid lung nodules
2° Endpoints: COX/LOX urinary metabolites (hs-CRP, PGEM, LTE4), miRNA signature, nodule-based endpoints

Accrual as of October 15, 2015: 47 participants

Aspirin trial

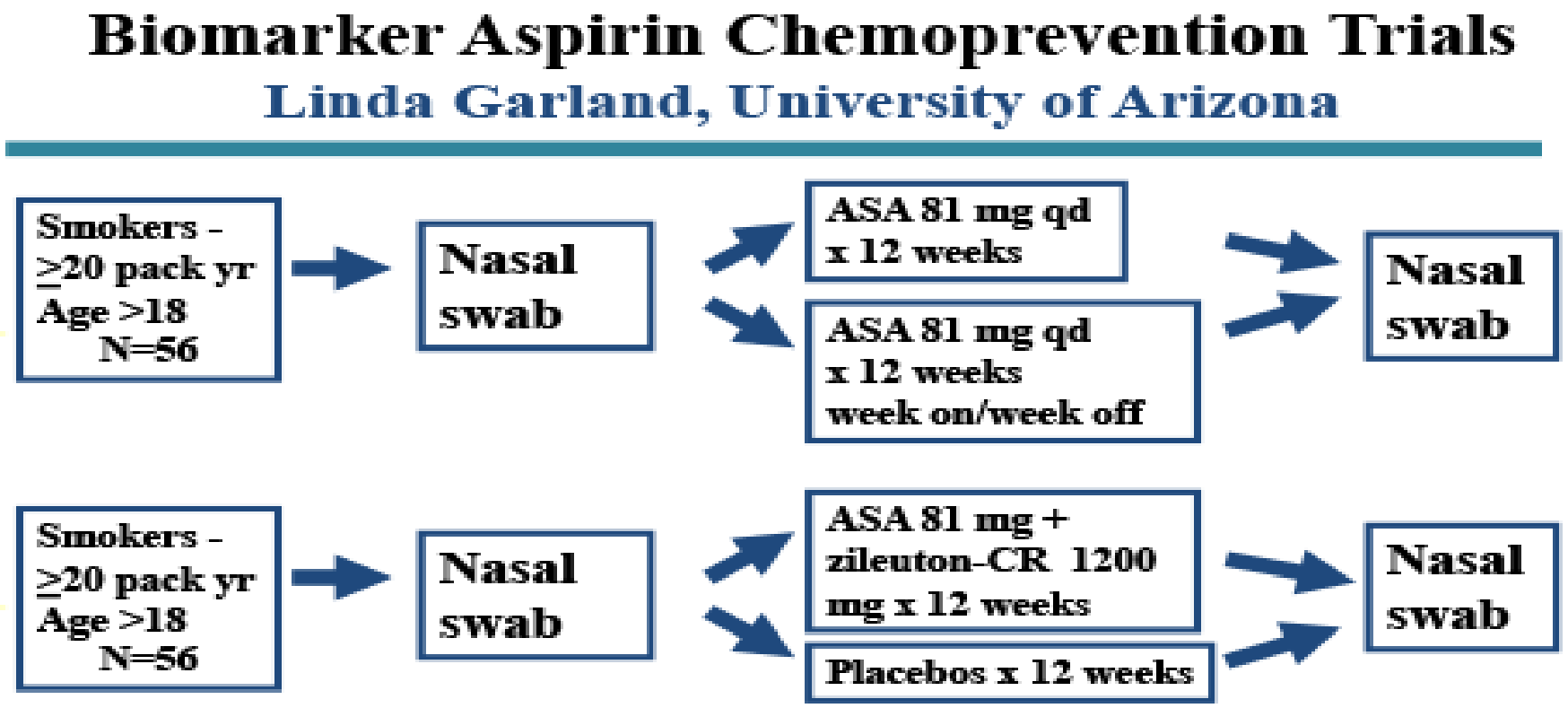
Phase II Trial of Low Dose Aspirin Trial



-98 participants randomized
-no difference in nodule size, new nodules
-no differences by sex, smoking status
-underpowered to detect differences in new cancers

Serrano D et al., JNCI Cancer Spectrum 2020 epub

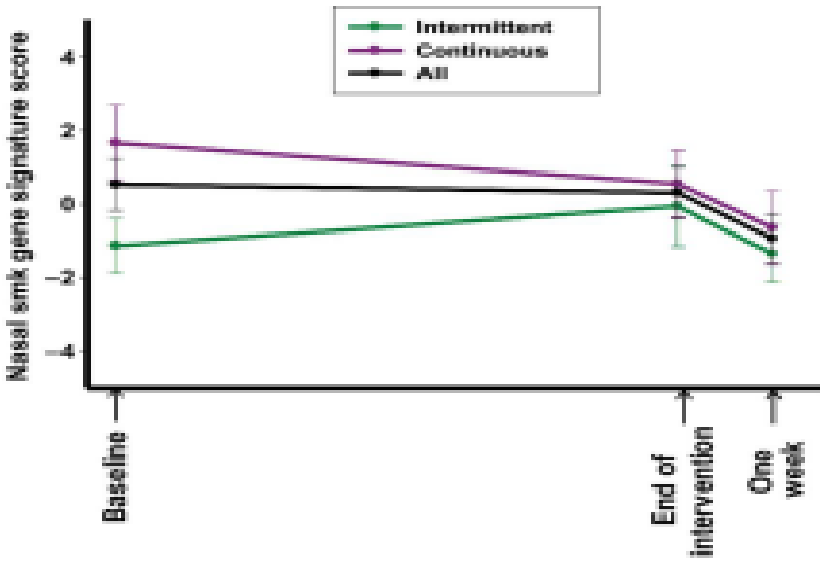
Biomarkers

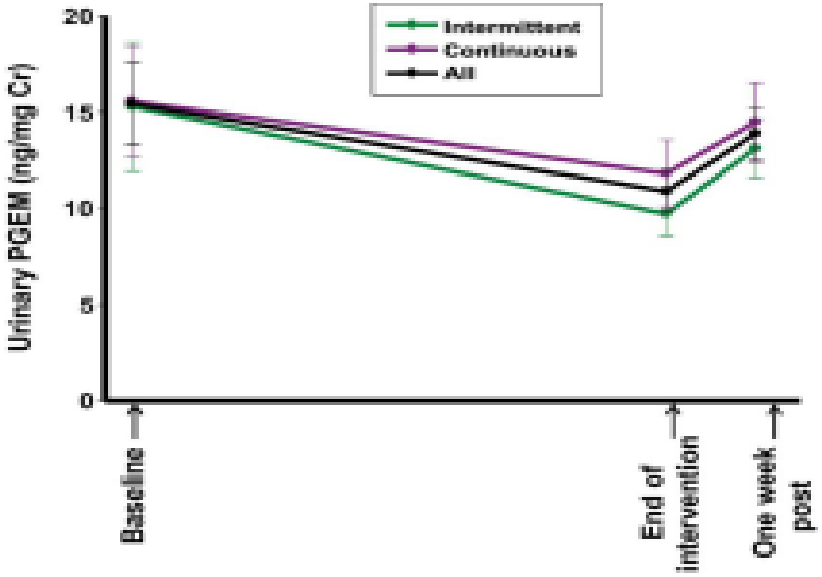


1° Endpoint: smoking gene expression signature (nasal epithelium)
2° Endpoint: PI3K gene expression signature, lung cancer gene expression Signature, COX/LOX urinary metabolites (PGEM, LTE4)

Aspirin

Minimal Effects of Continuous vs. Intermittent Aspirin on Nasal Smoking Gene Signature Score

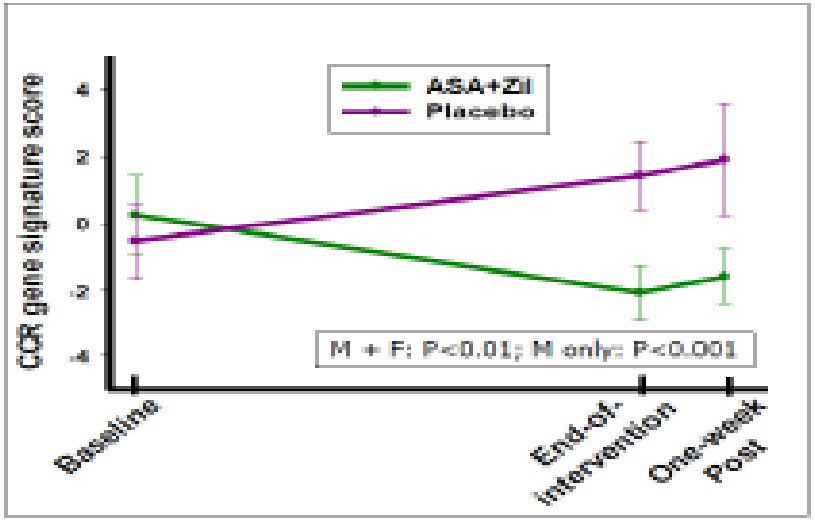


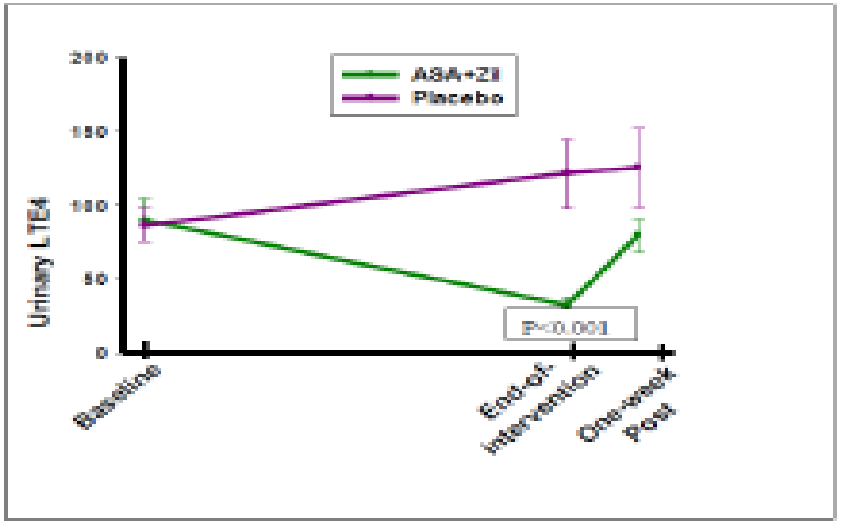


Garland LL et al. Cancer Prev Res 2019;12:809-820

Aspirin and zileuton

Effect of Aspirin and Zileuton on Nasal Dysplasia Gene Signature Score



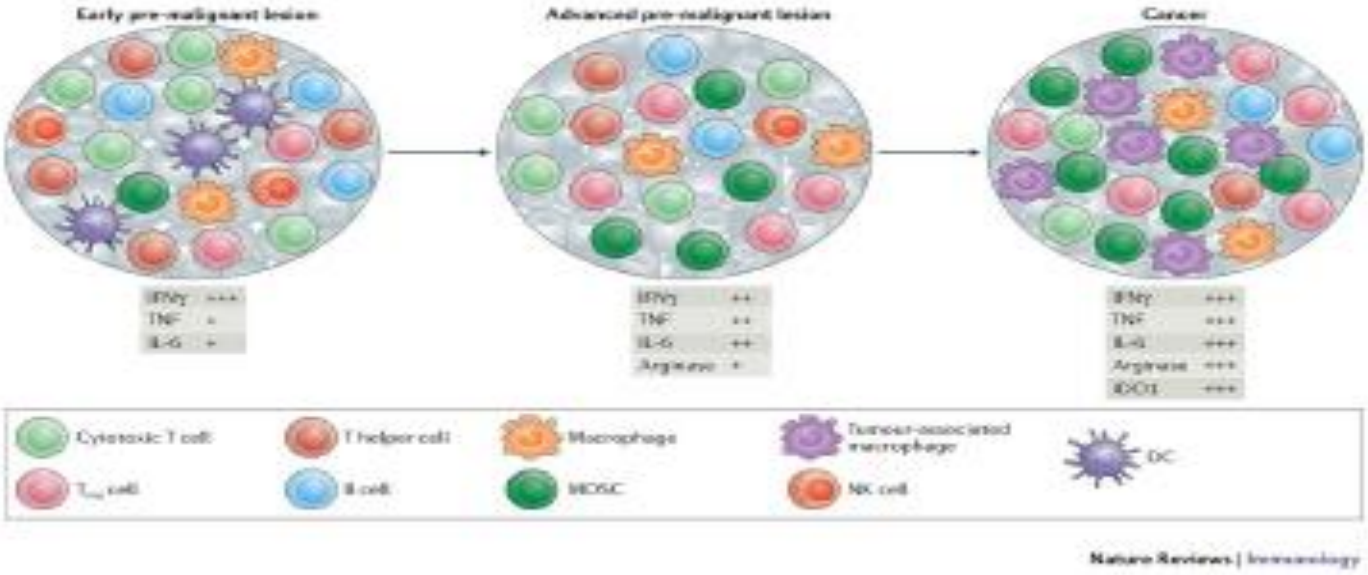


- Significant decrease in dysplasia gene score
- No effect on nasal smoking gene signature score
- Significant effect on lipoxygenase metabolism (LTE4)
- Minimal effect on cyclooxygenase metabolism
  - PGEM borderline suppressed (p=0.07

-unpublished

Cancer Immunoprevention

Cancer Immunoprevention:
Potential for prevention of multiple cancers

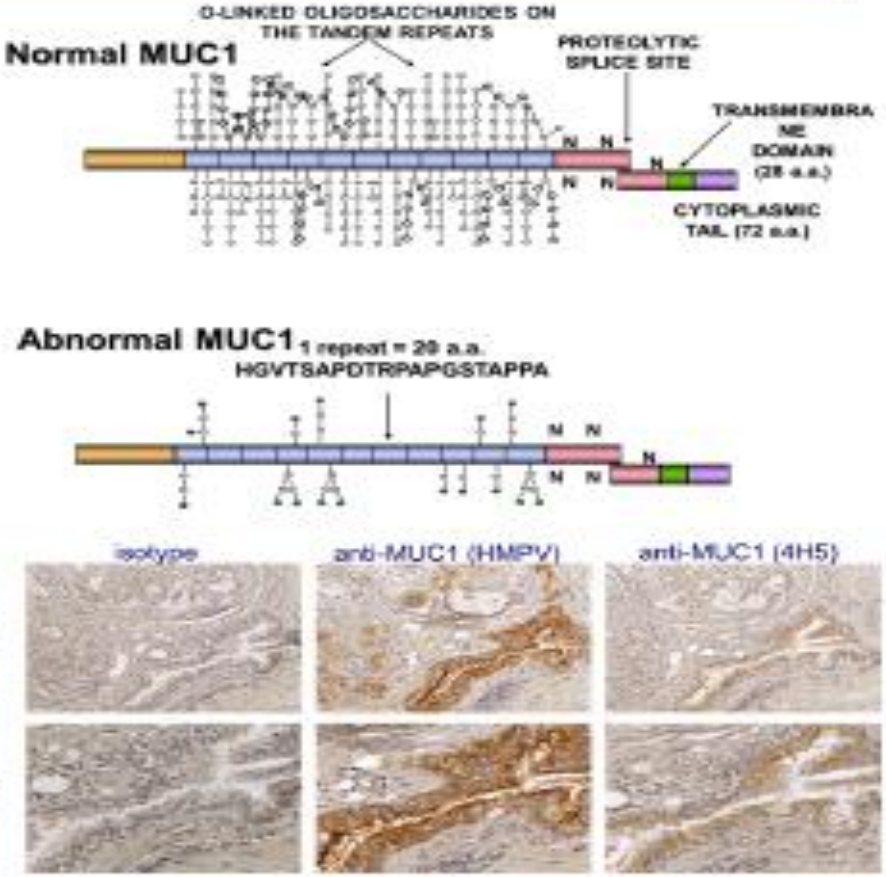


Finn OJ Nature Rev Immunol 2018

MUC1

MUC1

- Human tumor-associated antigen discovered in 1989
- Expressed on all human adenocarcinomas
- Differentially glycosylated compared to normal cells
  - –particularly VNTR region
- Cancer therapy target; may be more immunogenic at preinvasive stage
  - –Highly expressed in many premalignancies

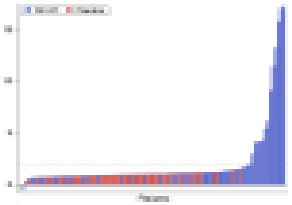


Courtesy of Olja Finn and Paul Limburg

MUC1 vaccine

MUC1 Vaccine in Patients with Newly Diagnosed Advanced Colorectal Adenomas (O. Finn Vaccine)

- **Trial overview**
  - Age 40-70 years; recent advanced colorectal adenoma
  - MUC1 vaccine vs. placebo at weeks 0, 2, 10 (Part I) and 53 (Part II)
  - Primary endpoint: ΔMUC1 IgG level at week 12 vs. week 0
  - Secondary endpoints: ΔMUC1 IgG level at week 55 vs. week 53; adenoma recurrence at up to week 156
- **Results**
  - 102 participants evaluable (MUC1 n=52; placebo n=50)
  - 2-fold IgG↑ (=response) in 25% MUC1
  - Response correlated with low baseline PMN-MDSC levels (p=.000
  - Adenoma recurrence ↓38% in responders (<u>not</u> intent-to-treat)



- **Ongoing immunogenicity study in heavy smokers undergoing CT screening**

Schoen RE, P Limburg & O Finn, personal communications

Metformin

Metformin

- Cancer incidence literature mixed and affected by multiple confounders and time-related biases
- DCP meta-analysis, RR=0.69, 95%CI, 0.52-0.90
  - Correction for BMI or time-related biases reduced RR to 0.82 and 0.90, respectively

Endpoints	Groups	SRR (95%CI)	I^2	n studies*
Cancer incidence	All studies	0.69 (0.52, 0.90)	88	19
	Adjusted for BMI	0.82 (0.70, 0.96)	76	11
	Adjusted for time related bias	0.90 (0.89, 0.91)	56	8
	Prospective studies	0.71 (0.47, 1.07)	89	12
	Randomized Clinical Trials	0.95 (0.69, 1.30)	5	5
Cancer mortality	All studies	0.66 (0.54, 0.81)	21	7
	Adjusted for BMI	0.60 (0.45, 0.80)	0	5
	Adjusted for time related bias	0.45 (0.16, 1.26)	0	3
	Prospective studies	0.48 (0.23, 0.97)	0	4

Gandini S et al. Cancer Prev Res 2014;7:867

Metformin Trial

Phase IIa Metformin Trial in Oral Leukoplakia

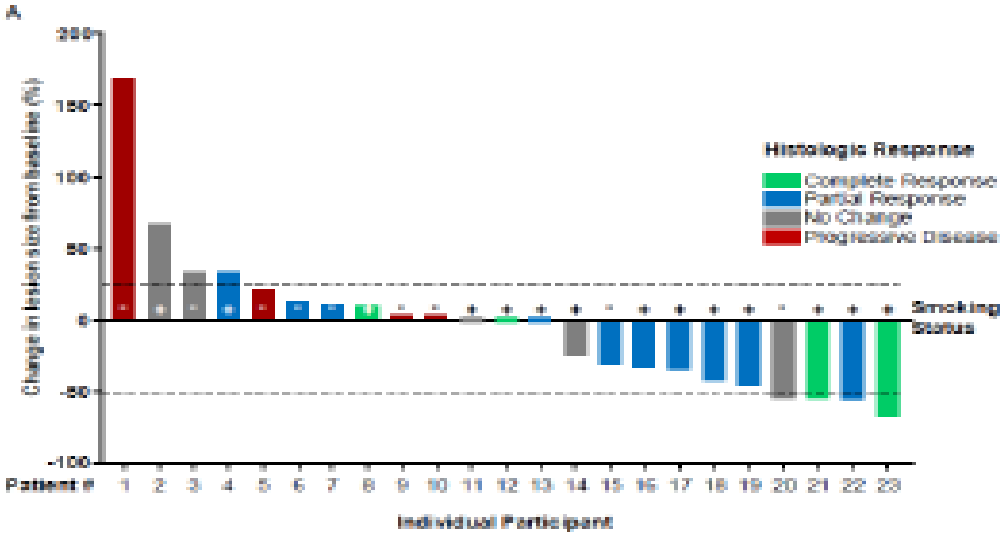
Clinical and Lesion Histologic Responses (n=23)

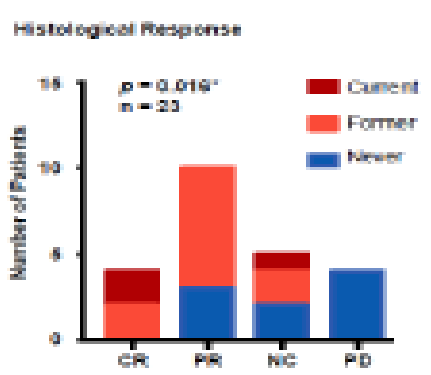
Post Intervention Clinical Response, n (%)

CR - Complete Response	0 (0.0)
PR - Partial Response	4 (17.4)
NC - No Change	15 (65.2)
PD - Progressive Disease	4 (17.4)

Post Intervention Lesion Histological Response, n (%)

CR - Complete Response	4 (17.4)
PR - Partial Response	10 (43.5)
NC - No Change	5 (21.7)
PD - Progressive Disease	4 (17.4)

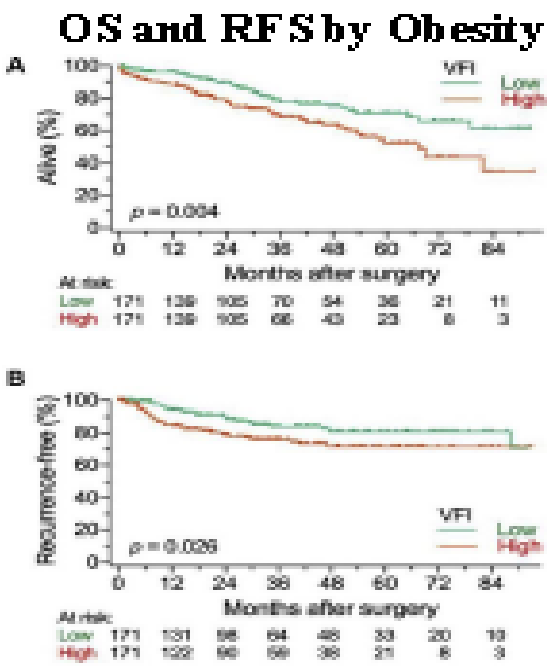


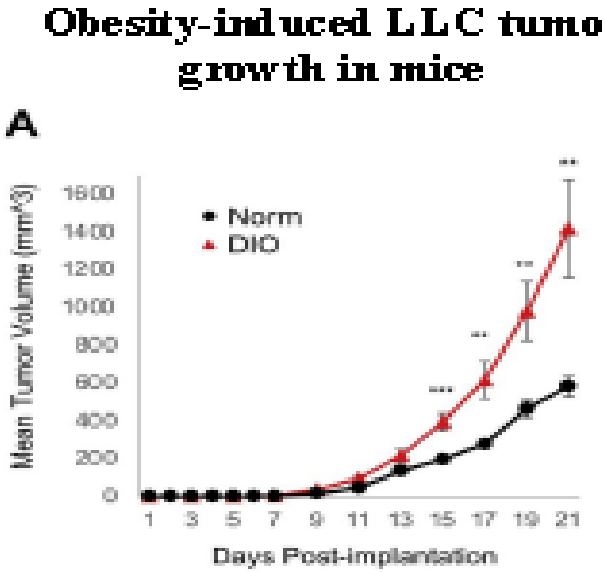


Gutkind JS et al. JCI Insight 2021

Obesity

Visceral Obesity Promotes Lung Cancer Progression and an Immune Suppressive Tumor Microenvironment





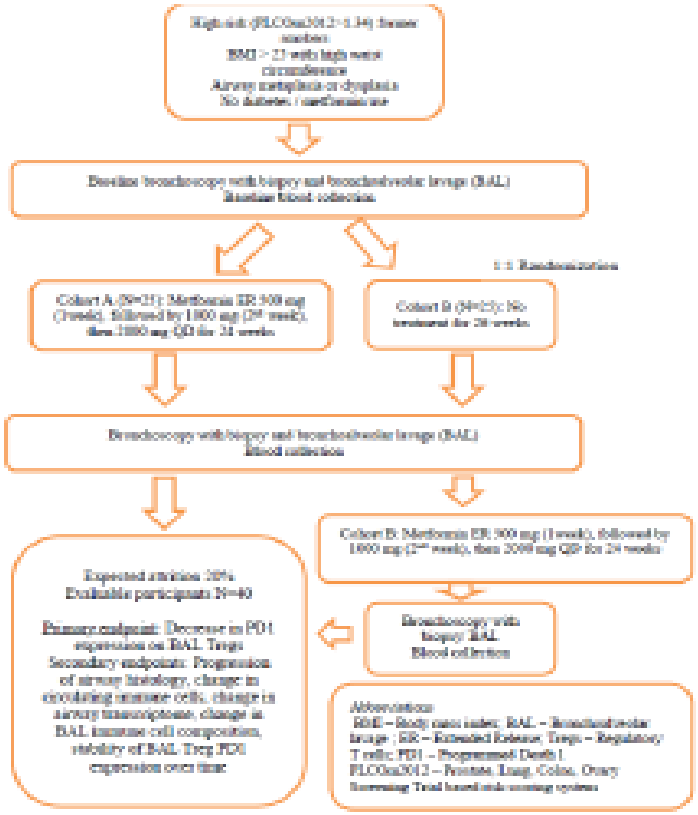
- Obesity affects TME
  - Effector cell deficits, exhausted phenotypes
  - ↑ Tregs, MDSCs, activated phenotypes
- Metformin assoc with OS in stage I pts. with high BMI
- Metformin reverses obesity effects in mice

Yendamuri S et al. J Thor Oncol 2019;14:2181
Barbie J et al. J Thor Oncol 2021;16:1333

Metformin

Metformin in High Risk Overweight/Obese Former Smokers

- High risk former smokers, $PLCO_{m2012}$>1.34
- BMI>25 and high waist circumference
- 1° endpoint: PD1 in BAL Tregs
- 2°: airway histology

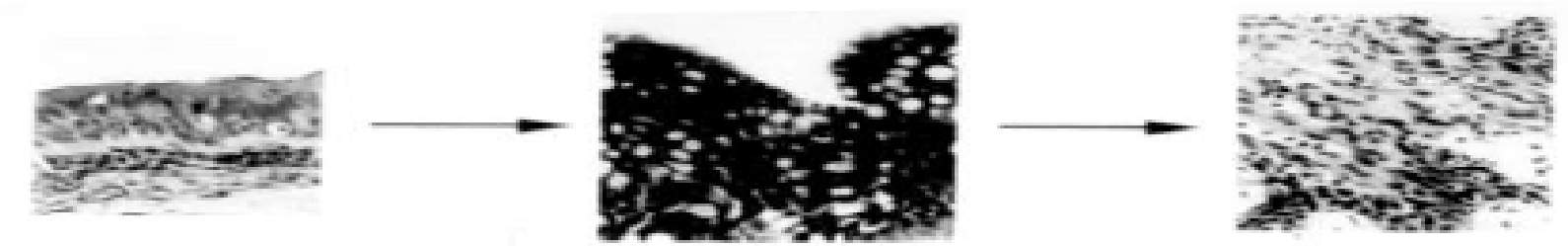


PI: Sai Yendamuri, MD
Roswell Park Cancer Center
CP-CTNet Site:
Northwestern University

Intervention

The Continuum of Lung Carcinogenesis

Opportunities for Intervention



Normal → Hyper/Metaplasia → Dysplasia → Early-Late Cancer

Prevention

Early Detection

Treatment

Lung Cancer Screening

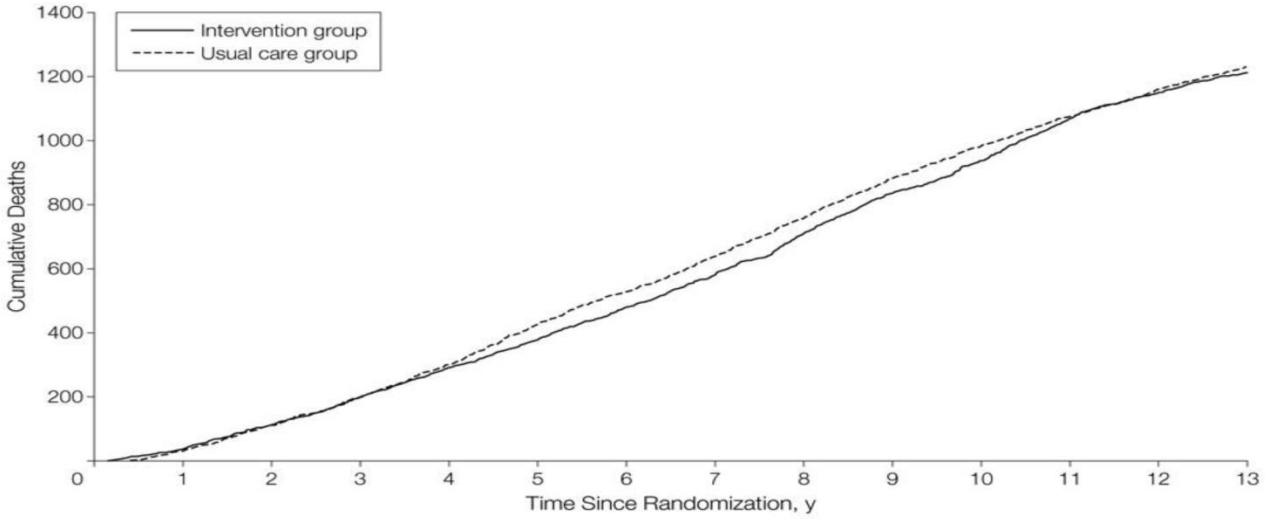
Issues in Lung Cancer Screening

- **Lead-time bias** = earlier diagnosis but no postponement of death (survival appears longer)
- **Length bias** = diagnosis of more indolent disease with longer preclinical phase (better prognosis, better outcome)
- **Overdiagnosis** = identification of clinically unimportant lesions that would not be diagnosed otherwise
- **Morbidity/mortality/cost of screening and subsequent work-up**

PLCO Trial

PLCO CXR Randomized Trial - Mortality

154,901 participants, PA CXR vs. usual care x 4 screens, 13 yr f/u



Intervention group													
Cumulative deaths	36	113	196	292	378	480	582	711	838	937	1070	1150	1213
Cumulative person-years	77 268	154 053	230 270	305 833	380 691	454 773	527 937	600 004	670 274	735 098	789 540	832 441	864 227
Usual care group													
Cumulative deaths	30	111	198	301	426	527	639	761	884	987	1076	1162	1230
Cumulative person-years	77 286	154 116	230 348	305 902	380 725	454 719	527 804	599 790	669 955	734 523	788 854	831 678	863 330

Oken, MM et al. JAMA 2011;306:1865-73

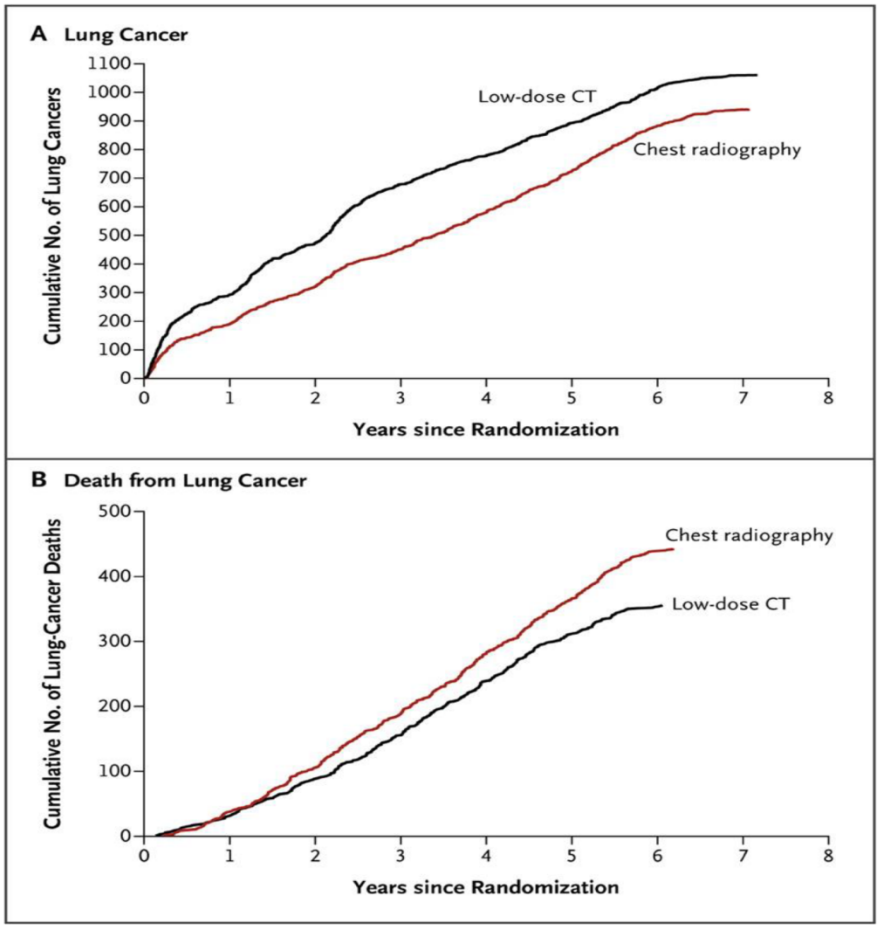
NLST (National Lung Screening Trial)

- **NLST design**
  - **53,454 smokers (current and former)**
  - **30 pack-yr smoking hx; quit ≤15 yrs ago**
  - **Age 55-74**
  - **Helical CT vs. chest X-ray (prevalence, then x2)**
- **NLST results**
  - **CT - 24.2% 'positive' tests, 354 lung cancer deaths**
  - **CXR – 6.9% 'positive' tests, 442 lung cancer deaths**
  - **20.0% reduction in lung cancer mortality**
  - **6.7% reduction in all cause mortality**

NLST Research Team. N Engl J Med 2011;365:395-409

Lung Cancer and Deaths

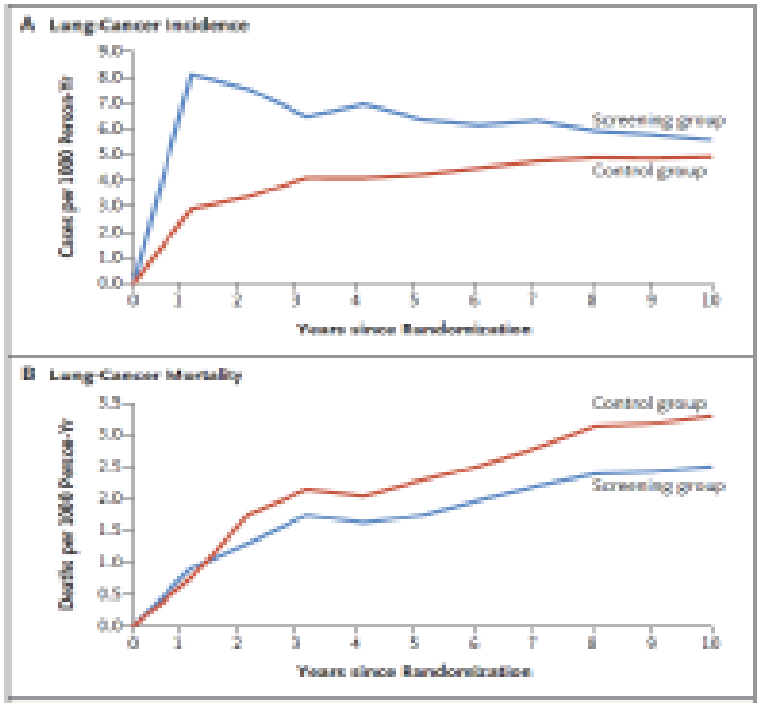
Cumulative Lung Cancers and Deaths from Lung Cancer



NLST Research Team N Engl J Med 2011;365:395-409

CT screening

NELSON CT Screening Trial



- 13,195 men and 2594 women
- age 50-74
- Screening baseline, yr 1, yr 3, yr 5.5
- Volumetric analysis
- 10 yr follow-up
- Men: RR=0.76
- Women: RR=0.67

Summary

Summary

- **Tremendous progress has been made in understanding lung carcinogenesis**
  - **Pathologic classification oversimplifies molecular complexity**
    - **Heterogeneity in tumors and premalignant lesions complicates efforts to intervene**
  - **Precision medicine applicable to significant (but small) subset of advanced stage patients, increased survival**
  - **Early days of immunotherapy – prolonged survival in small subset of patients**
    - **Applications to prevention not yet clear**
  - **Early detection with helical CT – decreased lung cancer mortality**
  - **New targets and tools available for chemoprevention research**

“An ounce of prevention is worth a pound of cure”

-Benjamin Franklin

Acknowledgments

Acknowledgments

- DCP Phase II Consortia Program
- Stephen Lam, British Columbia Cancer Agency
- Giulia Veronesi, Humanitas Cancer Institute
- European Institute of Oncology Chemoprevention Group
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