



EUROPEAN LUNG CANCER
CONFERENCE

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GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE



Chemoprevention of Lung cancer



Andrea De Censi, MD
Division of Medical Oncology
Ospedali Galliera, Genova;
Div. Prev, EIO, Milan



Barts and The London
Queen Mary's School of Medicine and Dentistry



Wolfson Institute of Preventive Medicine
Queen Mary University of London

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EIO; ICH, Milan



Eva Szabo, MD

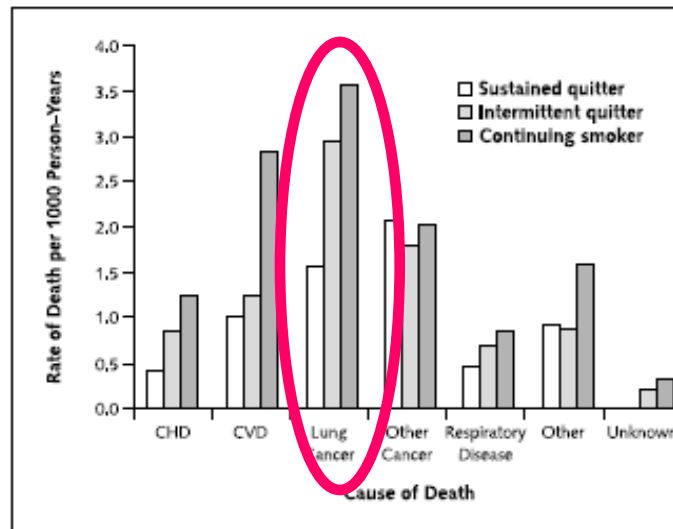
Division of Cancer Prevention

National Cancer Institute



Current Options for Risk Reduction in High Risk Smokers

- Smoking cessation



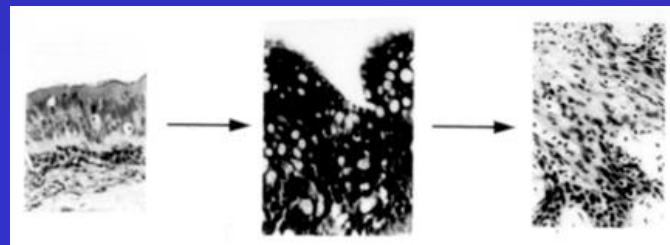
**Lung Health Study,
14.5 yr f/u
-Anthonisen et al.,
Ann Intern Med
2005;142:233**

- CT screening

- 20% decrease in lung cancer mortality- National Lung Screening Trial
 - NLST Research Team, NEJM 2011;365:395

Rationale for Lung Cancer Prevention

- **Metastatic cancer is rarely curable**
 - US lung cancer 5 yr survival is 16% (5% 1950's, 13% 1970's)
- **All big killers except for lung are drug-preventable**
 - Breast: SERMs, AIs
 - CRC: aspirin, anti COX2, HRT
 - Prostate: 5 alpha RI
- **Long preclinical phase with increasing histologic and molecular abnormalities, identifiable populations at risk, window of opportunity for intervention**

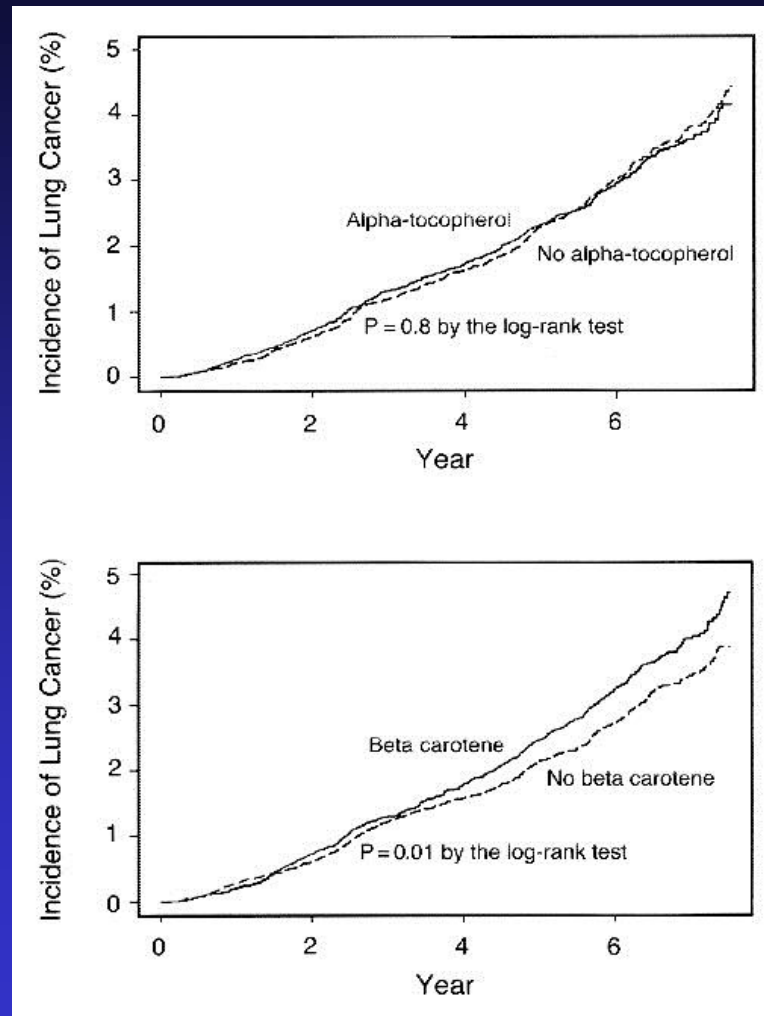


Efficacy: How Do We Identify Good Agents?

- **Knowledge of mechanism**
 - Example: HPV vaccine and cervical cancer
 - **Need:** understanding molecular pathogenesis
- **Preclinical (in vitro and animal models)**
 - Example: NSAID treated carcinogenesis and transgenic models
 - **Need:** models reflective of complexity of human disease
- **Observational epidemiology (cohort and case-control studies)**
 - Example: ASA and colon cancer incidence/mortality
- **Secondary endpoints from clinical trials (including other diseases)**
 - Example: Tamoxifen and contralateral breast cancer

Prevention may even be harmful!

The beta carotene disaster in smokers



The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. N Engl J Med 1994;330:1029-1035.



The NEW ENGLAND
JOURNAL of MEDICINE

Lung Cancer-Several Diseases Masquerading as One

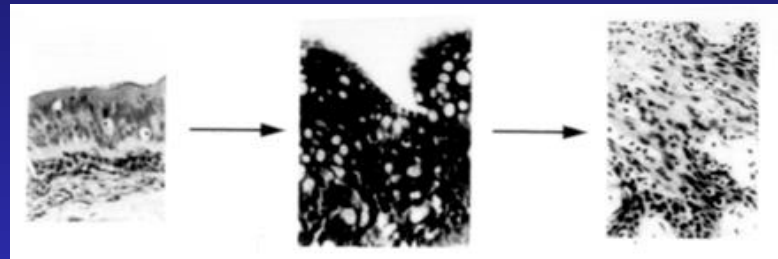
Implications for Trials Targeting Central vs. Peripheral Carcinogenesis

Normal → Hyperplasia/Metaplasia → Dysplasia → Cancer

Mild/Moderate/Severe/CIS

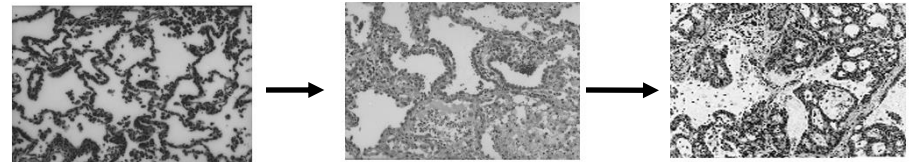
Squamous

Bronchial dysplasia model



Adenomatous

Helical CT detected nodules



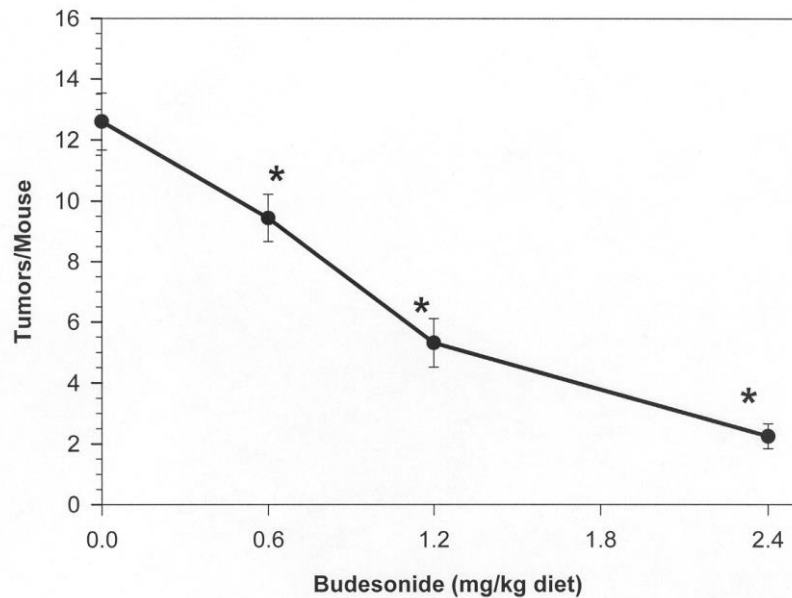
- **Molecular pathogenesis different**
 - several histologies; molecular differences within histologies (e.g., EGFR vs K-ras)
- **Animal models – different responses to same interventions**

Targeting Inflammation for Lung Cancer Prevention: Rationale for Corticosteroids

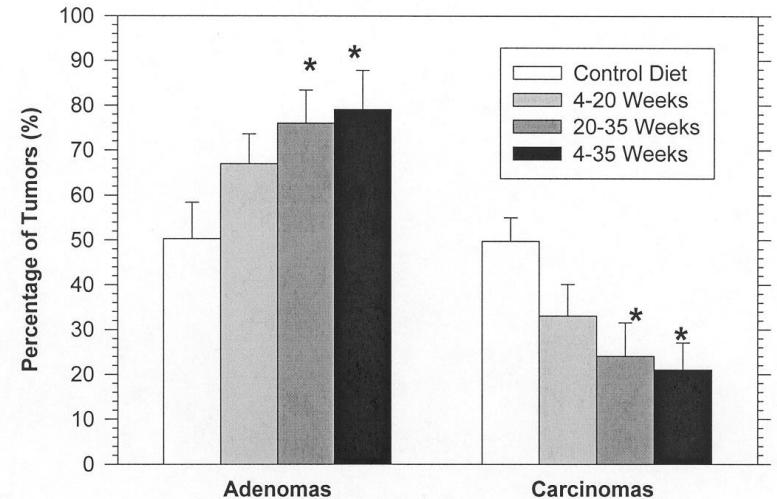
- **Animal data showing role for steroids in cancer prevention**
 - 1970's – skin
 - Early 1990's – lung (oral steroids)
 - Late 1990's – lung (inhaled steroids)
- **Epidemiology/Human data –**
 - Mainly negative (but studies of short exposure duration)
 - VA cohort with COPD (n=10,474, 423 lung cancers, 3.4 y followup) – HR 0.39 (95% CI, 0.16-0.96)
 - Parimon T et al., AJRCCM 175:712, 2007

Effect of Budesonide on Mouse Lung Tumorigenesis

Pereira et al., Carcinogenesis 2002



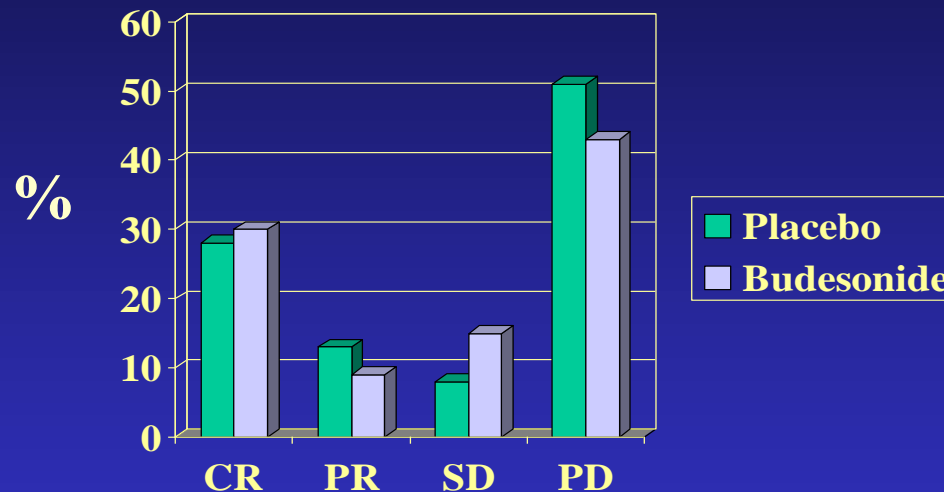
-82% decrease in tumors



-Shift from adenoma to carcinoma

Phase IIb Trial of Inhaled Budesonide in Bronchial Dysplasia

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



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

Peripheral Lung Carcinogenesis Trial Design

Veronesi G et al. Cancer Prev Res 2011;4:34

202 participants with persistent spiral CT-detected peripheral nodules



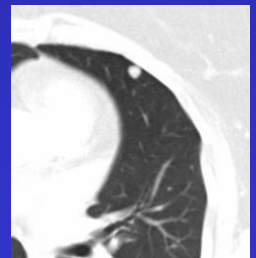
Randomize

inhaled budesonide vs. placebo x 1 year



repeat spiral CT

Primary endpoint: shrinkage of lung nodules

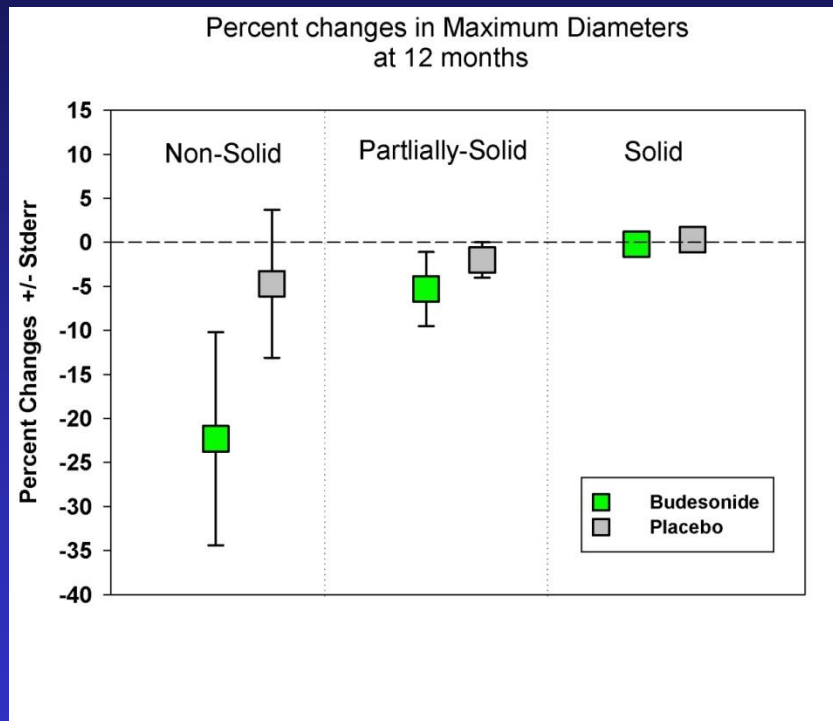


Phase IIb Budesonide Chemoprevention Trial

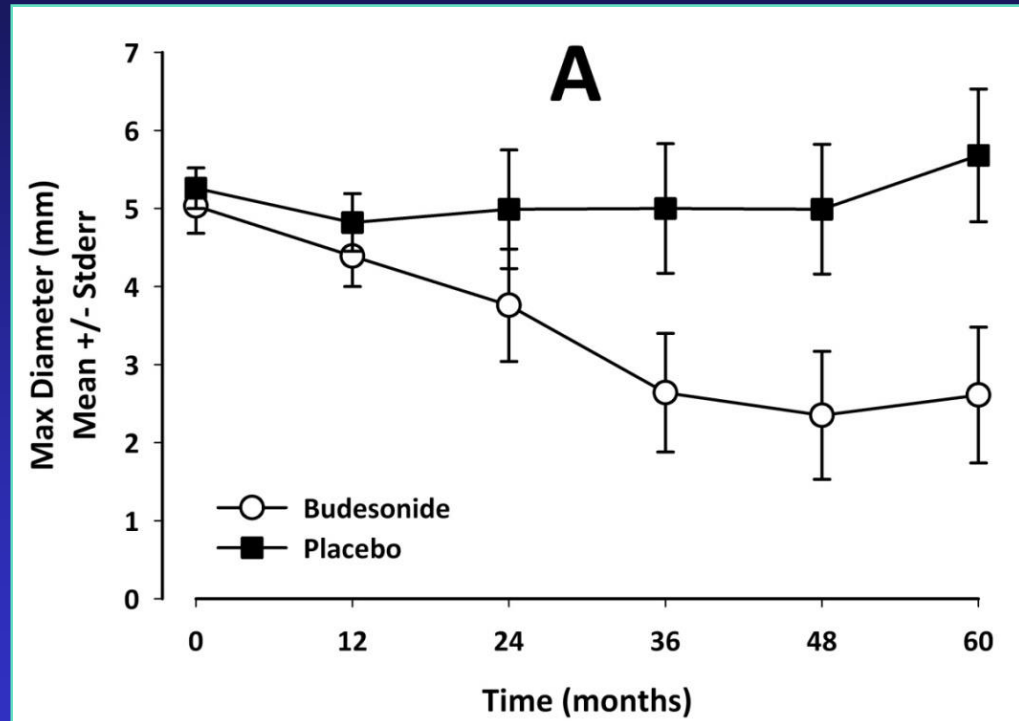
Lesion Specific Analysis

Veronesi G et al. CaPR 2011; Ann Oncol 2015

12 months

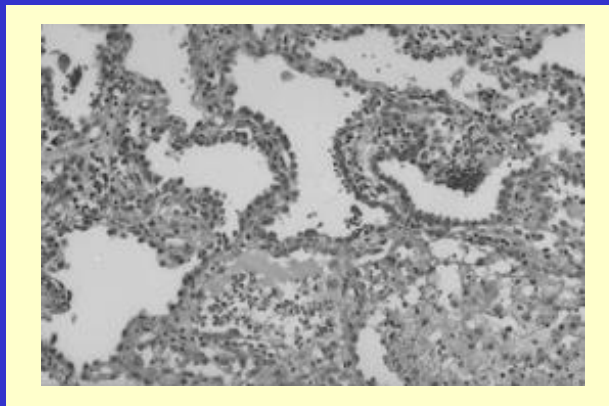


5-yr f/u



-Overall response negative, but trend toward regression in non-solid lesions (putative precursors of adenocarcinoma)

Adenocarcinoma Precursor: Atypical Adenomatous Hyperplasia



- Natural history unknown
- 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 – Risk of Lung Cancer

Pinsky et al. Cancer Prev Res 2014

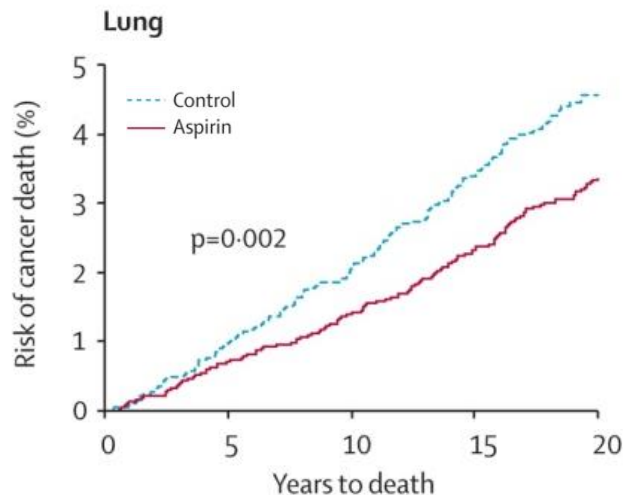
	0-23 Months	24-59 Months	60-84 Months
	HR (95% CI)	HR (95% CI)	HR (95% CI)
≥1 10+ mm NCN (vs. only 4-9 mm NCNs)	12.8 (9.5-17.2)	4.7 (2.9-7.5)	N.S.
≥1 NCN w/ Spiculated or Poorly Defined Margins (vs. only NCNs with smooth margins)	4.1 (3.0-5.5)	2.3 (1.5-3.5)	N.S.
≥1 Persistent NCN (vs. non-persistent NCNs)	N/A	4.8 (2.8-8.3)	N.S.
≥1 NCN w/ Ground Glass Attenuation (vs. soft tissue attenuation)	0.3 (0.2-0.4)	N.S.	3.1 (1.4-6.6)

Interpretation:

Increased long-term risk of ground glass nodules suggests *some* are lung cancer precursors

Effect of Aspirin on Lung Cancer Mortality

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



Number at risk

Aspirin	6258	5816	5243	4485	2634
Control	4244	3948	3545	3006	1493

-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

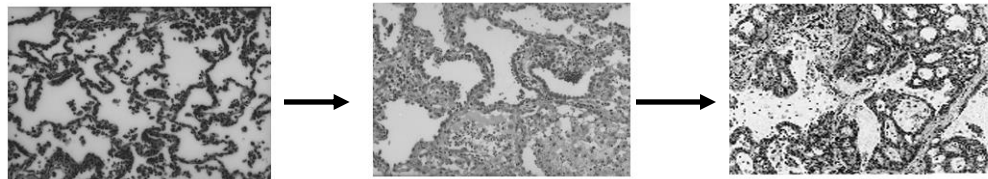
-benefit only after 5 yrs

Evolution of Intraepithelial Neoplasia

Normal → Hyperplasia/Metaplasia → Dysplasia → Cancer

Mild/Moderate/Severe/CIS

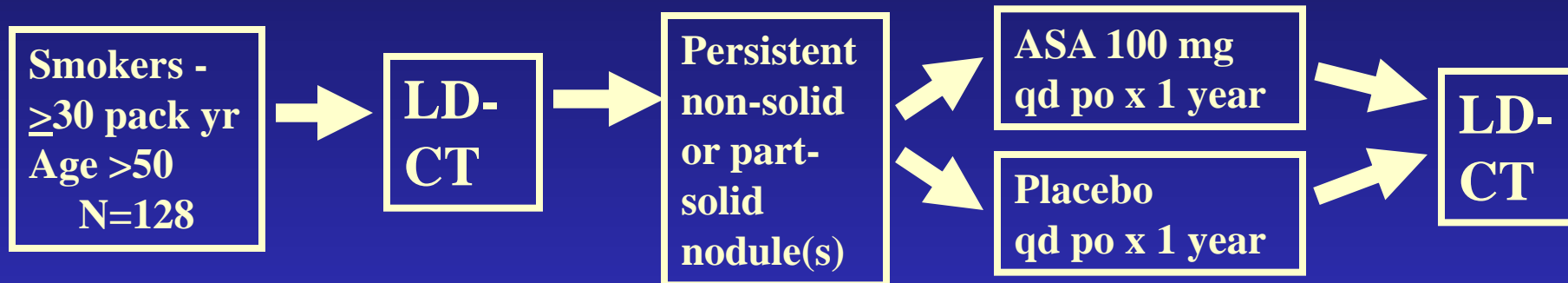
Adenomatous



*If lung cancer death 5+ yrs post ASA use, then stage IV dx at 4+ yrs,
Early stage and precursors present at 0-4 yrs post onset ASA use
Therefore, ASA effect on precursors should be measurable with
one year of use*

Phase IIb Aspirin Chemoprevention Trial

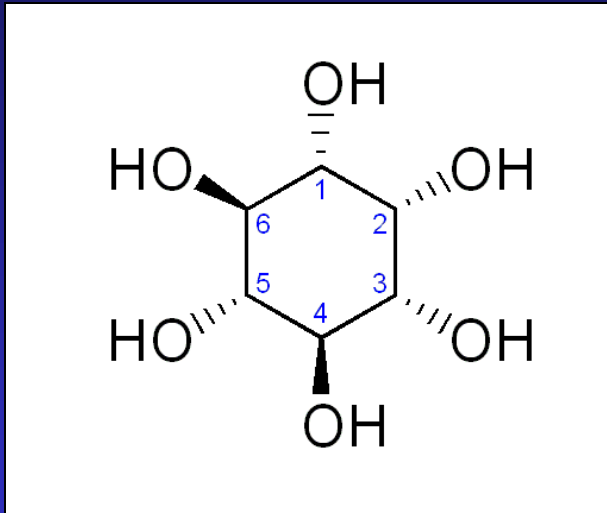
Giulia Veronesi, EIO/ICH, Milan



1° Endpoint: #/Size non-solid lung nodules

**2° Endpoint: COX/LOX urinary metabolites (PGEM, LTE4),
miRNA signature , nodule-based endpoints**

myo-Inositol



- Glucose isomer
- Source of several second messengers & signaling molecules
- Dietary sources (grains, beans, fruits, rice)
- Studied in psychiatric conditions (+/-), diabetic neuropathy(+/-), polycystic ovary syndrome (+)

Rationale for *myo*-Inositol in Lung Cancer Prevention

- **Efficacy**

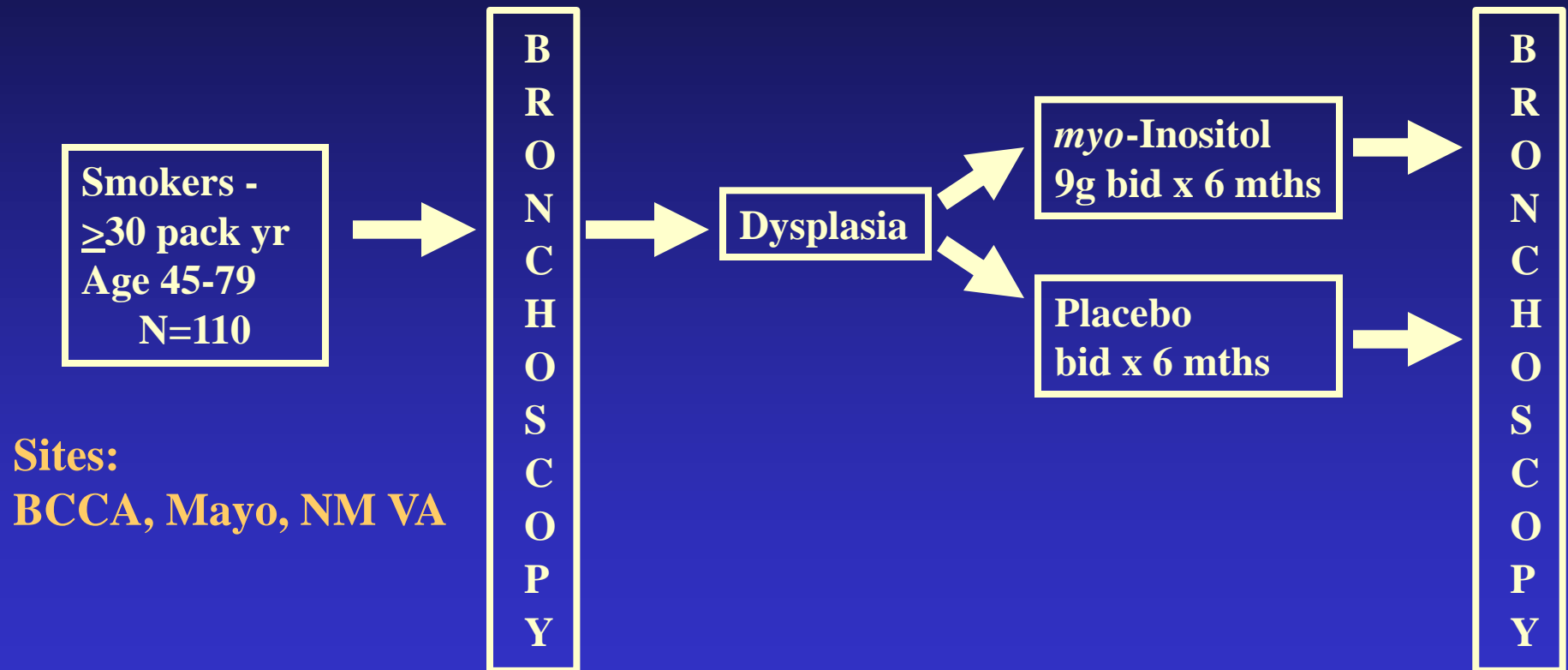
- Multiple animal studies show inhibition of carcinogen induced tumors in mice (40-50%)
 - Estensen and Wattenberg, Carcinogenesis 1993;14:1975
 - Hecht et al., Carcinogenesis 2002;23:1455
- Inhibits carcinogenesis in mainstream/sidestream smoke-exposed A/J mice by 53%
 - Witschi H et al., Carcinogenesis 1999;20:1375
- Combination with budesonide ↑↑ efficacy up to 80%
 - Estensen and Wattenberg, Carcinogenesis 1993;14:1975
 - Witschi et al. Carcinogenesis 1999;20:1375
 - Wattenberg et al. Carcinogenesis 2000;21:179

- **Safety**

- Used in multiple short term trials for psychiatric and diabetic neuropathy indications – no toxicity reported
- Generally Regarded as Safe (GRAS) by US FDA terminology

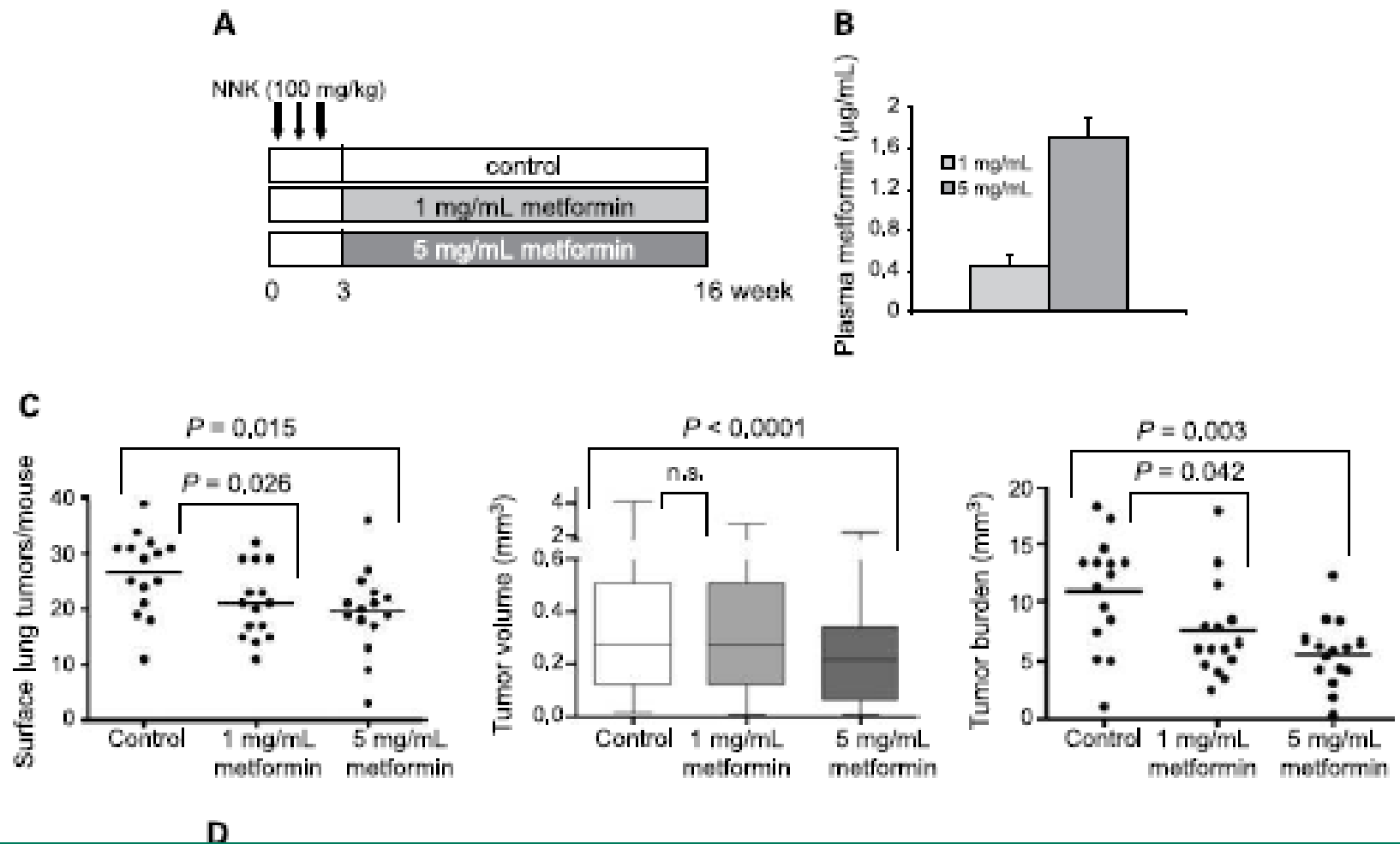
Phase IIb *myo*-Inositol Chemoprevention Trial

Stephen Lam, British Columbia Cancer Agency



1° Endpoint: Bronchial dysplasia

2° Endpoint: Multiple biomarkers (gene expression), CT-detected lung nodules



The Future

- **Innovative agents**
 - Understanding molecular mechanisms of lung carcinogenesis (sq and adeno), TCGA of premalignancy
 - Molecularly targeted agents
 - repurposing “old” drugs (eg, ASA, budesonide, metformin)
 - Emphasis on effects in multiple cancers and/or chronic disease states
- **Innovative early phase trial designs**
 - High throughput technologies (e.g., gene expression analysis) to detect drug effects on pathways in a short time frame

Thank you!