

# **Chemoprevention of High-Risk Patient Populations**

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# Chemoprevention of High-Risk Populations:

- Significant variations in risk (of Lung Cancer)
- Factors associated with High Risk
- Markers of High Risk?

# Variations in Lung Cancer Risk Among Smokers

- 18172 subjects in the Carotene and Retinol Efficacy Trial (CARET)
- Age, Sex, Asbestos Exposure, Smoking History
- Estimate the absolute risk of Lung Cancer within 10 years
- Two models: 1. predicting probability of being diagnosed with lung cancer 2. predicting the probability that an individual will die without having been diagnosed with lung cancer = the competing risk
- Model applied to evaluate risk among smokers in a CT screening study (Mayo Clinic)

# Variations in Lung Cancer Risk Among Smokers

- **0.8%** chance to develop lung cancer within 10 years for 51 yr old women with 28 pack years before quitting 9 years earlier  
vs **15%** chance for 68 yr old smoker with 2 packs a day for 50 years
- **Risk prediction may be useful in screening and prevention studies**

# Cigarette Smoking and Histology of Lung Cancer: meta-analysis

No Studies*		Ever smoker		Current smoker		Ex-smoker	
		OR	95%CI	OR	95%CI	OR	95%CI
27	Squamous	11.3	9.39-13.5	25.4	18.4-35.1	13.9	8.28-15.5
22	SCLC	12.9	9.79-17.1	42.0	21.7-81.2	17.1	9.46-31.0
27	Adeno	3.22	2.62-3.98	6.18	4.59-8.32	4.59	2.54-8.30
8	Large Cell	5.64	4.15-7.67	9.94	4.25-23.3	6.42	3.94-10.5

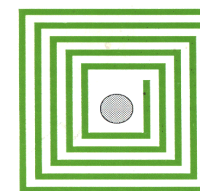
# Phase II and III Chemoprevention Studies

- **General' Population `**
- **(Ex-) Smokers**
- **Smokers with dysplasia (definition of dysplasia!)**
- **Asbestos-exposed workers**
- **NSCLC patients after surgery**
- **Head & Neck Cancer patients after surgery**

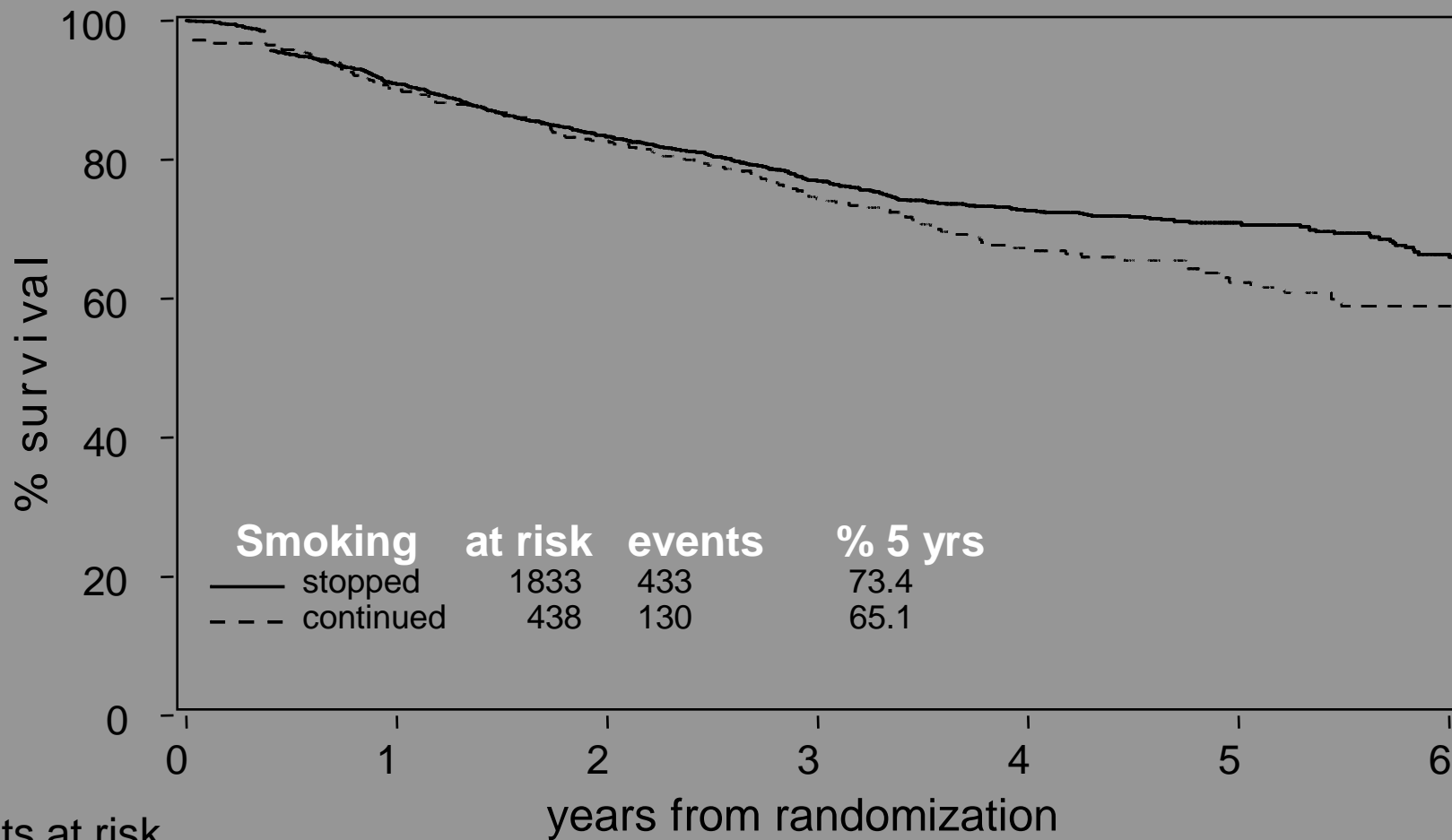
# Lung Cancer Incidence/Overall Mortality and Percentage Smokers in Primary Prevention Trials

	$\beta$ -carotene	Control	Smokers at entry %	
			Current	Former
<b>ATBC trial</b>				
Lung Cancer Incidence	56	47	100	0
Total Mortality	218	201		
<b>CARET trial</b>				
Lung Cancer Incidence	59	46	60	39
Total Mortality	144	119		
<b>PHS trial</b>				
Lung Cancer Incidence	6	6	11	99
Total Mortality	74	75		

Pastorino, JNCI 1998



# Overall Survival



Patients at risk

	0	1	2	3	4	5	6
continued	438	397	348	252	168	93	39
stopped	1833	1680	1455	1073	724	418	177

# CARET: 6-Year Follow-up after stopping $\beta$ -Carotene and Retinol Supplements

- Telephone and Mail f-up 6 years after premature 'termination' of trial
- RR of death from any cause for active intervention group in post-intervention phase 1.08 (95% CI=0.99-1.17) vs 1.17 (95% CI=1.03-1.57) in intervention phase
- Lung Cancer Incidence: RR 1.12 (0.97-1.31) in post-intervention vs 1.28 (1.04-1.57) in intervention phase
- Excess risk primarily restricted to females

# Predictors of Lung Cancer among Asbestos-exposed Men in CARET

- Subgroup Analyses of  $\beta$ -Carotene and Retinol Efficacy Trial
- Excessive rates of Lung Cancer among men with pleural plaques and radiographic asbestosis
- Lung Cancer risk related to duration of exposure to Asbestos (up to five fold higher risk)
- Strong synergy between 'fibrotic' radiographic lesions and active intervention (RR 12.45 vs 1.92): stronger negative effect of beta-carotene

# Physical Activity & Lung Cancer in volunteers included in CARET

- Sample of current and former smokers from CARET study
- Lower cancer incidence associated with more physical activity in men (not in women)
- Total physical activity associated with modestly lower risk of lung cancer in younger patients
- Control for confounding factors : smoking, gender, age and BMI

# Genetic Susceptibility for Lung Cancer: Interactions with Gender and Smoking History and Impact on Early Detection Policies

- Case Control Study: 764 cases and 677 controls (newly diagnosed cases from MD Anderson, controls from private hospital chain) matched for age, gender, smoking status
- DNA damage and repair (Bleomycin sensitivity test)

# Impact of Genetic Susceptibility on Probability of developing Lung Cancer by Smoking Status: lifetime probabilities of developing lung cancer

Smoking category	Male		Female	
	susceptible* (SE)	not susceptible	susceptible	not susceptible
Never	5.4 (0.4%)	0.8 (0.01%)	1.5 (0.03%)	0.7 (0.01%)
Former	21.4 (0.24%)	8.5 (0.1%)	7.9 (0.1%)	4.8 (0.03%)
Current	38.2 (0.3%)	18 (0.06%)	15.1 (0.2%)	9.6 (0.02%)

\* Susceptible = above the control 75<sup>th</sup> percentile for bleomycin sensitivity

# Lung Cancer Risk Modeling

- Relatively few modeling exercises in Lung Cancer

**Building on:**

- **Epidemiological/Clinical**
  - **Biological**
  - **Genetic**
- Data**
- 
- ```
graph LR; A[Epidemiological/Clinical] --> D[Data]; B[Biological] --> D; C[Genetic] --> D;
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# Risk Model for Prediction of Lung Cancer

- Variables with significant association with lung cancer:
  - environmental tobacco smoke
  - family history of cancer
  - dust exposure
  - prior respiratory disease
  - smoking history variables
- Tested in a case-control study

# Risk Model for Prediction of Lung Cancer

## Conclusions:

- Easily obtained clinical information can be used to identify individual who may benefit from increased screening surveillance
- Validation in independent cohorts

# LLP risk model: an individual risk prediction model for lung cancer

Multivariate conditional logistic regression models

- 579 case and 1157 matched (age/sex) controls
- Gender
- Age years; mean  $\pm$  SD
- Smoking duration periods of 20 years
- Pneumonia (yes/no)
- Asbestos exposure (yes/no)
- Prior malignancy (yes/no)
- Family history (no vs early vs late onset)

# Sputum Atypia as a Predictor of Incident Lung Cancer:

## Cohort of Heavy smokers with COPD

- > 30 pack-years + COPD
- 2006 individuals, 79% > 60 yrs, 70% males (median number of pack years 57)
- 17.7 % moderate atypia or more (no association with pack-years, NSAID's or COPD)
- Fruit &Vegetables inversely correlated with atypia (p=0.04)
- 1.86 Lung Cancer Incidence rate per 100 person-years
- Severe Atypia and CIS represent high risk for Lung Cancer: Hazard ratio up to 34.3 (15.7-74.9)

# Promotor Methylation in Sputum

- Methylation of specific genes detected in sputum samples could predict Lung Cancer up to 18 months prior to clinical diagnosis ([Belinsky et al, Cancer Res 2006](#))
- Concomitant promoter methylation of multiple genes (26) in lung adenocarcinomas, differences between smokers and never smokers. Some genes similarly (methylated) silenced in breast and colon cancers ([Tessema et al, Carcinogenesis 2009](#))
- Evaluation of methylation status in ECOG selenium prevention study

# Clara Cell Proteins

- CC10, a 10-kDa anti-inflammatory protein secreted by Clara cells
- High BAL CC10 levels are associated with regression of bronchial dysplasia and smoking cessation

Chen et al, Cancer Epidemiol & Biomarkers 2007,  
Clin Cancer Res 2008

# Baseline C-Reactive Protein associated with Incident Cancer and Survival in pts with Cancer

- 10,408 individuals (Danish General Population) with CRP measurement, follow-up 16 years (excl. individuals with cancer at baseline)
- CRP levels more than 3 vs 1 mg/L associated with increased risk  
HR 1.3 Any type cancer  
HR 2.2 Lung Cancer  
HR 1.9 Colorectal Cancer
- Risk of early death with CRP more than 3 vs 1mg/L  
HR 1.8 Any type cancer (localized disease)

# Progression of Airway Dysplasia and C-Reactive Protein in Smokers at high risk of Lung Cancer

- 105 subjects who completed intervention in Budesonide Trial
- CRP, interleukins 6 and 8, and monocyte chemo-attractant protein 1 in plasma
- Baseline CRP levels of participants developing dysplastic lesions were 64% higher than those without progressive lesions (p=0.027)
- 13% of participants with CRP  $\leq$  0.5 mg/L developed progressive disease vs 54% of participants with CRP  $>$  0.5 mg/L developed progressive disease (p=0.011).

# Connective Tissue-Activating Peptide III Biomarker for Early Lung Cancer Detection?

- Connective Tissue-activating peptide III (CTAPIII)/neutrophil activating protein-2 (NAP-2) and Haptoglobin higher in venous than arterial blood of Lung Cancer pts.
- CTAPIII/NAP-2 levels decreased after tumor resection
- In two independent cohorts CTAPIII/NAP-2 was significantly associated with lung cancer
- Accuracy of Lung Cancer Prediction Model including Age, Smoking, FEV1 was improved

Yee et al, J Clin Oncol, 2009

# Volatile biomarkers in Breath

- Volatile organic compounds (VOC's) excreted in breath
- 193 subjects with lung cancer and 211 controls
- 2:1 split in training and prediction set
- Employing a 16 VOC model (mean typicality) scores were significantly higher in lung cancer patients
- 84.6% sensitivity, 80.0 specificity
- Accuracy comparable with CT?

# Screening with LDCT

- LDCT screening may decrease lung cancer mortality
- Three yrs results of Dante trial (2,472 males from 60-75 yrs randomized to yearly LDCT or medical examination only:

60 (4.7%) lung cancers in screening arm

34 (2.8%) in control arms

same amount of advanced cancers in both arms

# MicroRNAs and Lung Cancer

- Potential prognostic value
- Potential diagnostic value
- Screening with MicroRNA's?

# Conclusions

- Significant variations in Lung Cancer Risk among smokers
- Several New Markers associated with increased Risk : None of them validated
- Integration of risk models in (phase IIB) Chemoprevention Trials seems attractive