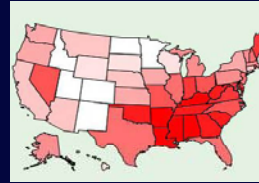
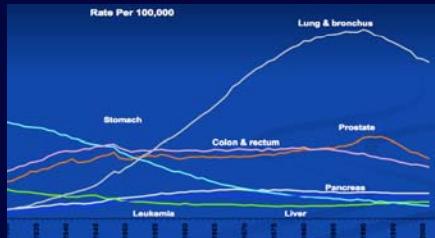
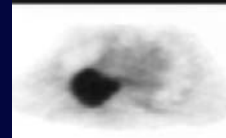


Lung Cancer Screening



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The Lung Cancer Epidemic

CA, Jemal (58)2, 71, 2008

	2002	2008
■ US		
Incidence	169,000	215,020
Mortality	154,900	161,840

■ Estimated Incidence Rate		
2008	Male	Female
US	89/100k	55/100k
KY	138/100k	75/100k

Distribution of Non-Small Cell Lung Cancer NSCLC by Stage and Prognosis

N = 3823

Clinical Stage	Proportion
I	13%
II	10%
IIIA	22%
IIIB	22%
IV	32%

Bulzebruck H, et al. *Cancer*. 1992;70:1102-1110.

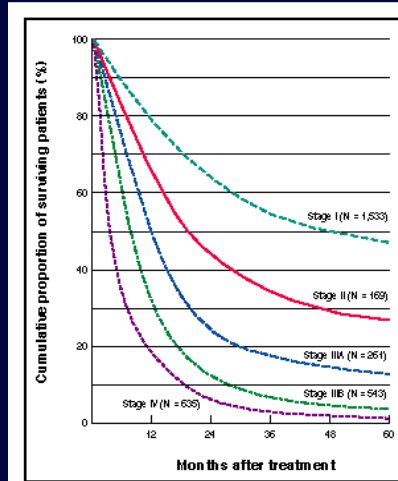
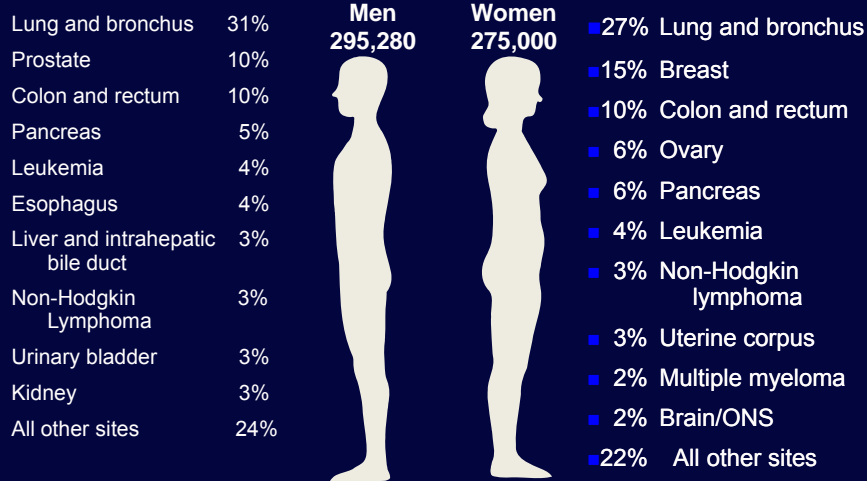


Figure 3. Survival rates after surgical resection by stage of disease (P < .001).

Adapted from Mountain (10).

2005 Estimated US Cancer Deaths*



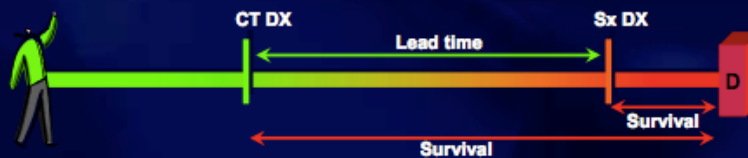
ONS=Other nervous system.
Source: American Cancer Society, 2005.

Evidence on Cancer Screening

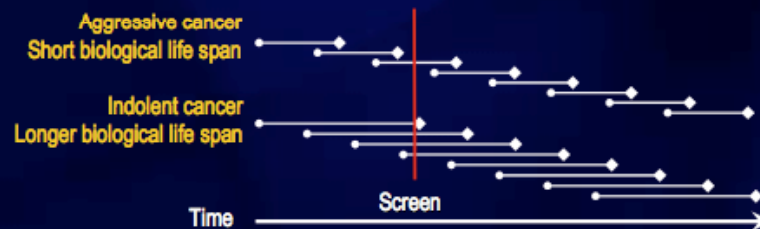
- Breast Cancer
 - Colon Cancer
 - Cervical Cancer
 - Skin Cancer ?
 - Bladder Cancer ?
 - Oral Cancer ?
 - Esophageal Cancer ?
 - Testicular Cancer ?
 - Prostate Cancer ?
 - Neuroblastoma ?
 - Gastric Cancer ?
- Basic Requirement
 - Ability to detect early, asymptomatic disease
 - Detection leads to decreased mortality
 - Definition
 - Survival: number alive at a certain time after diagnosis
 - Mortality: number of deaths within population

Biases entrained by screening

- Lead time: Earlier detection increases survival, even if death is not delayed

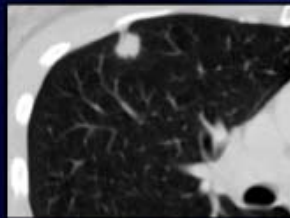
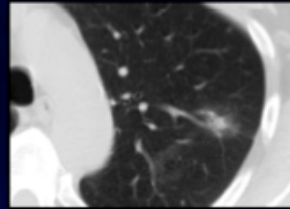
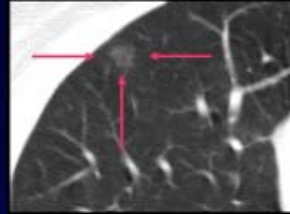


- Length bias: Screening detects more slowly growing cancers



What do we see on CT?

- **GG (non-solid):** Nodule with hazy increased lung attenuation which does not obscure underlying bronchovascular markings.
- **Mixed (part-solid):** Nodules containing both ground glass and solid components
- **Solid:** Nodules with attenuation obscuring the bronchovascular structures



Relationships between Morphology and Volume Doubling Time (VDT) Hasegawa et al Br J Radiol, 73, 1252-1259

- Calculated VDT in 61 CT-detected cancers based on serial CT's
- VDT vary between lung cancers of different attenuation

Category	N	VDT +/- SD	Visible on CXR
Ground glass	19	VDT= 813 days+/- 375	1
Mixed attenuation	19	VDT= 457 days+/- 260	1
Solid	23	VDT= 149 days+/- 125	16

Types of CT-detected lung cancers

- SEER data: BAC represents < 4% of NSCLC over 2 decades
- Observations from US CT-screening studies
 - Mayo CT 15% GG/Mixed (Lindell, Radiology 2007)
 - ELCAP 12% BAC (Flieder AM J Pathol 2006)
 - NY ELCAP 13% GG (Henschke, Radiology 2007)
 - I-ELCAP 06% BAC (I-ELCAP, NEJM 2006)

GG = Ground Glass, BAC= Bronchoalveolar Cancer

Overdiagnosis bias (pseudodisease)

Screening detects cancer (pseudodisease) that would remain subclinical before death from other causes

- Dx of biologically nonlethal cancers



- Potentially lethal cancers are superseded by competing morbidities

Japanese Lung Screening Trial

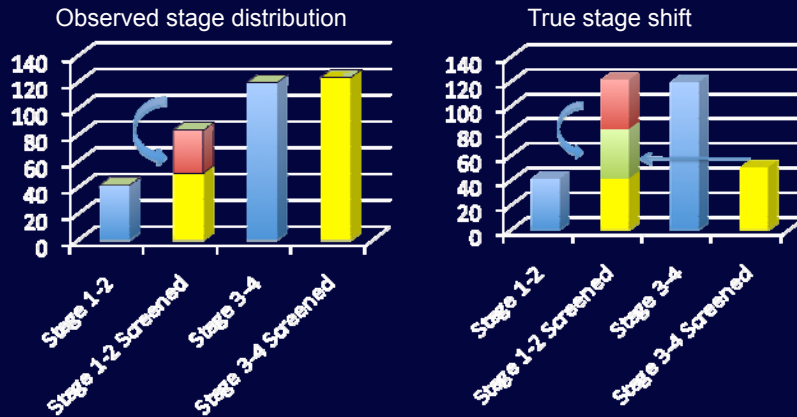
Sone S British J Cancer 2001, 84, 25-32

- Mobile CT screening in general population >40 yrs
 - Incidence 0.4% (13,700 scans over 3years, 60 LC's)
- Equal cancer rates in smokers and non-smokers
 - High proportion stage 1
 - 70% BAC or well differentiated adenoca
- Detection rate = 11 fold ↑↑ over annual incidence rates
 - Males **2-15 fold** over annual mortality rate
 - Females **10-25 fold** over annual mortality rate
 - Many CT-detected cancers will not become symptomatic

Will screening cause stage shift ?

Mayo Clinic CXR Screening Trial

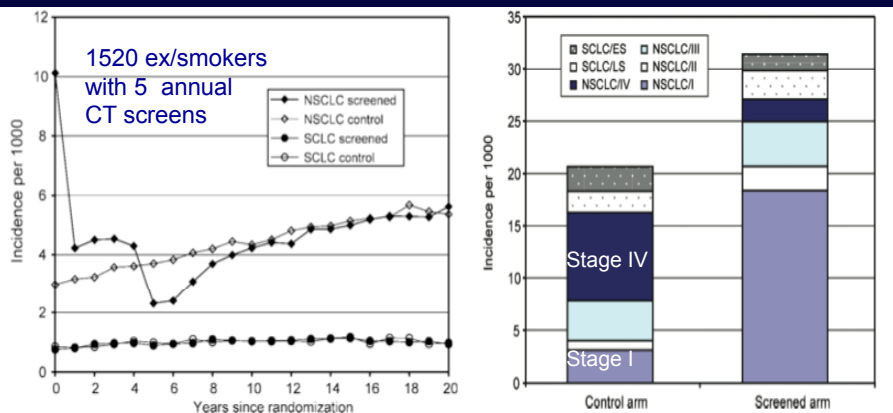
Marcus PM JNCI 2000, 92(16)1308, Fontana RS Cancer 1990, 67, 1155



CXR/Sputum q 4m vs yearly, >45 yrs smokers
Screening x 6 years, F/U for 11/24 yrs

Mayo Clinic CT Screening Study

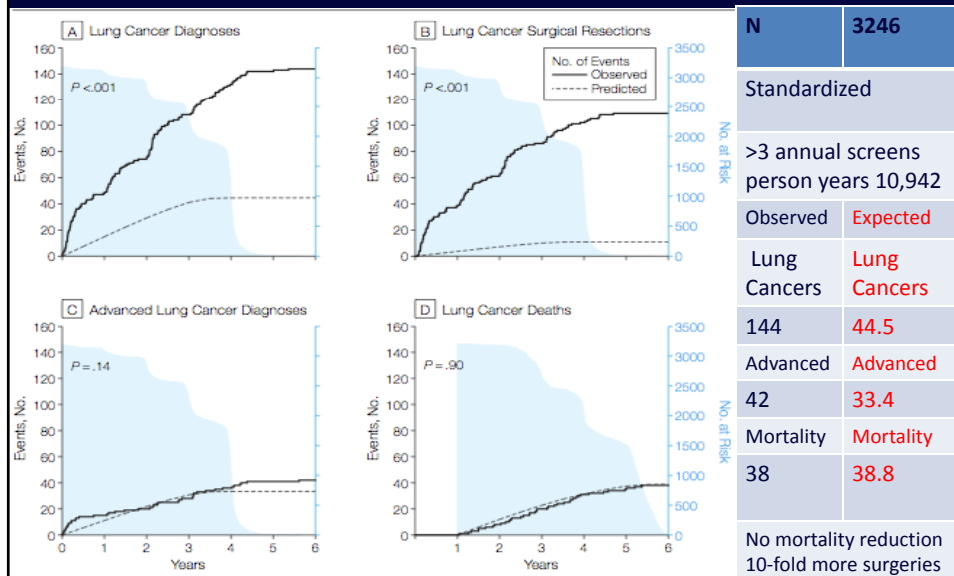
McMahon P, Radiology, 2008, 248(1), 279



4% mortality reduction at 6 years, 2% at 15 years based on simulation model
lung cancer specific mortality decreased by 28% at 6 years

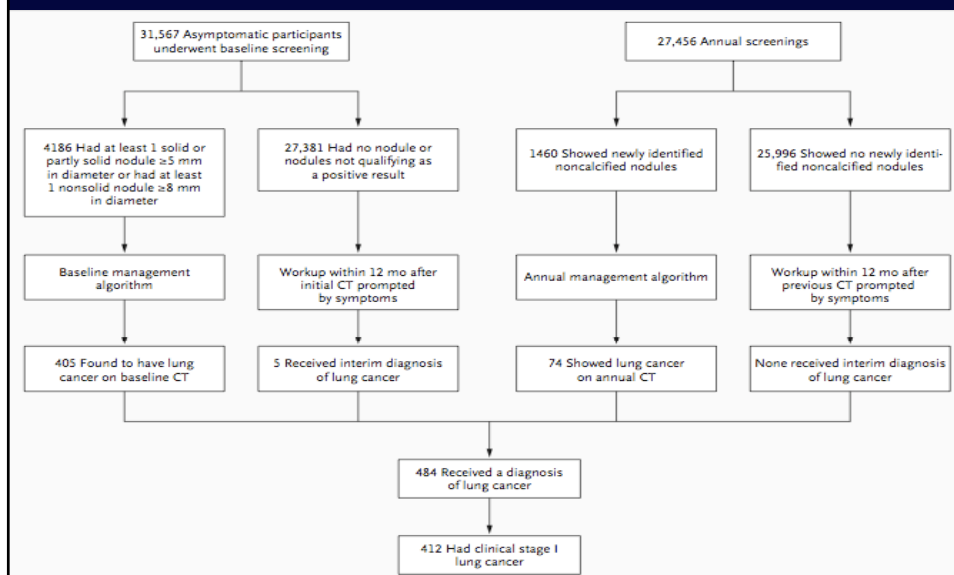
CT Screening and Lung Cancer Outcomes

Bach P, JAMA, 2007, 297, 953

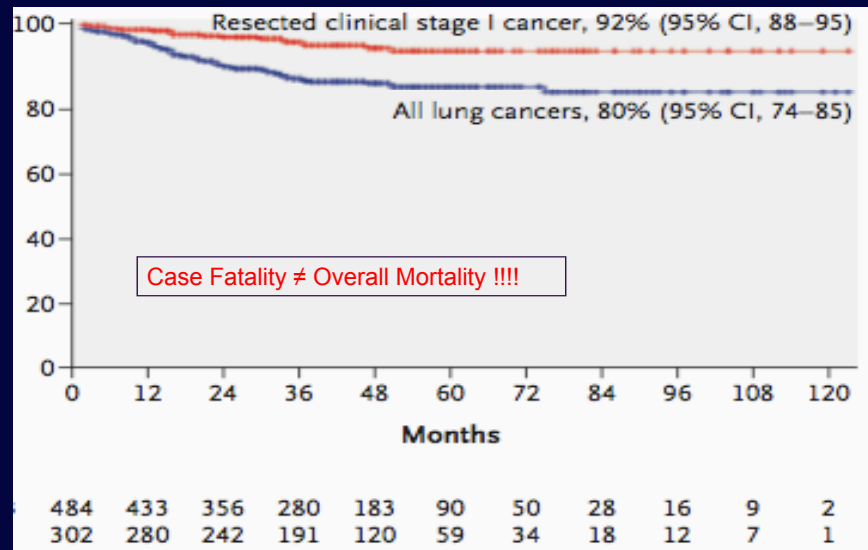


International Early Lung Cancer Action Program (I-ELCAP)

NEJM, 2006, 355 (17), 1763



International Early Lung Cancer Action Program (I-ELCAP)
NEJM, 2006,355 (17), 1763



Lessons from CT Observational Trials

- CT more sensitive for **nodule detection** than CXR
- CT picks up more **cancers** than CXR: **4:1**
 - Increase in early stage lung cancers
 - Oversampling of BAC/well differentiated adenocarcinoma
- Uncertain Stage Shift

Lessons Learned

- Measure the right endpoint

Lung cancer deaths/total lung cancers (Case Fatality Rate) is not avoiding the screening biases of lead time, length, overdiagnosis

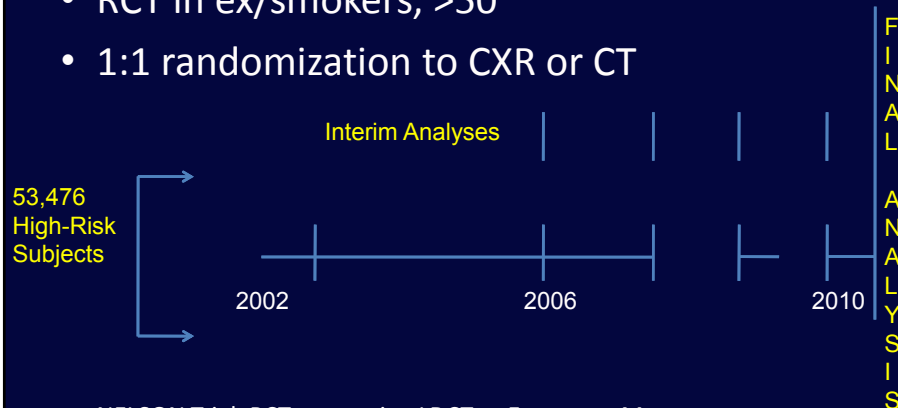
A much better endpoint is:

total (lung cancer) deaths = best measure of screening effect
total population screened

- Comparison Trial needed to follow outcome in all screened and unscreened participants
- Verify cause of deaths by review of medical records

National Lung Screening Trial (NLST) Design and Time Posts

- RCT in ex/smokers, >50
- 1:1 randomization to CXR or CT

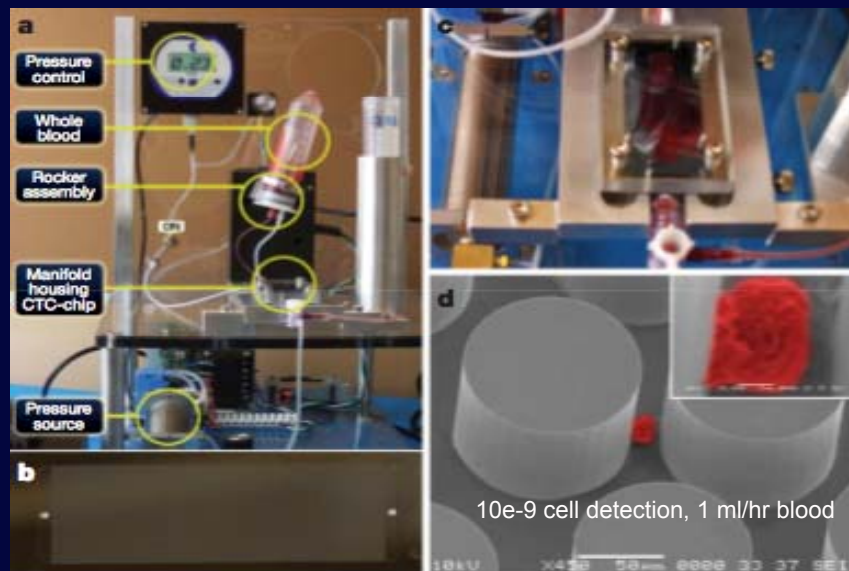


- NELSON Trial, RCT comparing LDCT vs Expectant Management
- 20,000 current and former smokers
- 25% reduction in mortality as endpoint

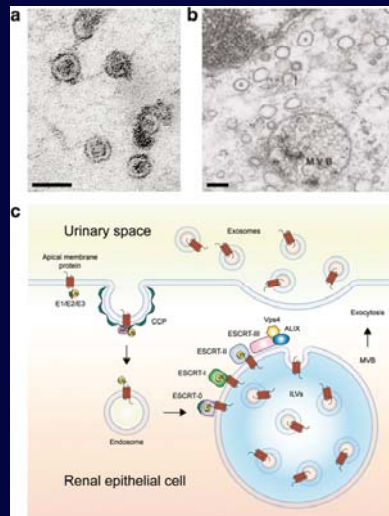
Biomarkers for Lung Cancer Screening

Rare Circulating Tumor Cells

Nagrath S et al, *Nature*, 450, 12/07, Maheswaran S et al, *NEJM*, 2008, 159,366



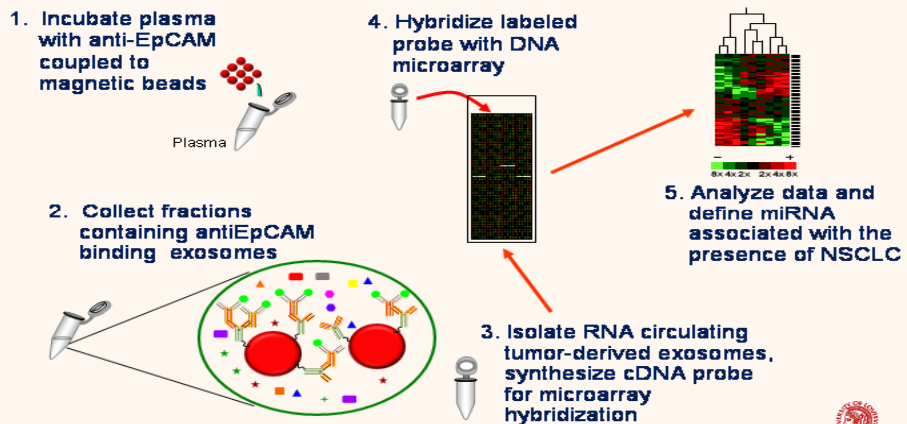
Exosomes and MiRNA



Exosomal microRNA: A Diagnostic Marker for Lung Cancer

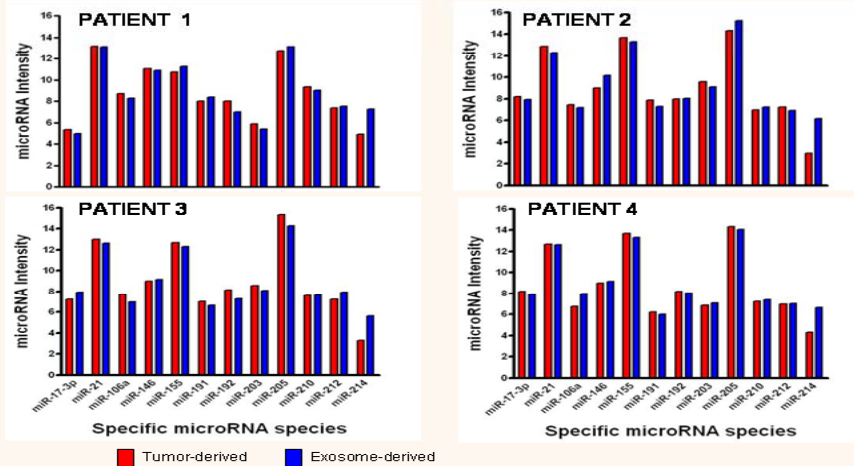
Goetz H. Kloecker, Guilherme Rabinowits, Cicek Gerçel-Taylor, Jamie M. Day, Douglas D. Taylor
 Clinical Lung Cancer, 2008, 9(5), #7, full article in press

ISOLATION OF CIRCULATING EXOSOMES



MiRNA from Tumor and Exosomes

Goetz H. Kloecker, Guilherme Rabinowits, Cicek Gercel-Taylor, Jamie M. Day, Douglas D. Taylor
 Clinical Lung Cancer, 2008, 9(5), #7, full article in press



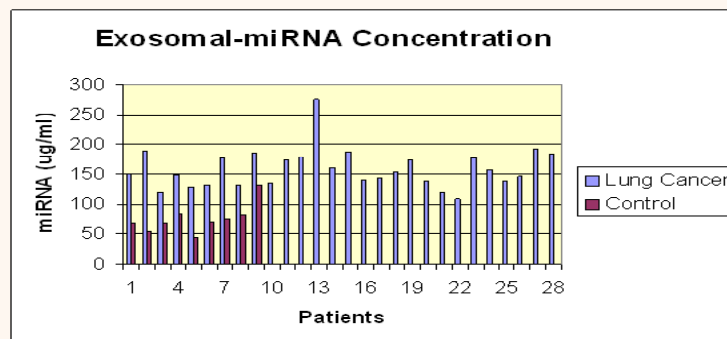
- Intensities for specific miRNAs derived from the tumors and from exosomes isolated from the sera of these patients.



MiRNA in Cancer Patients and Controls

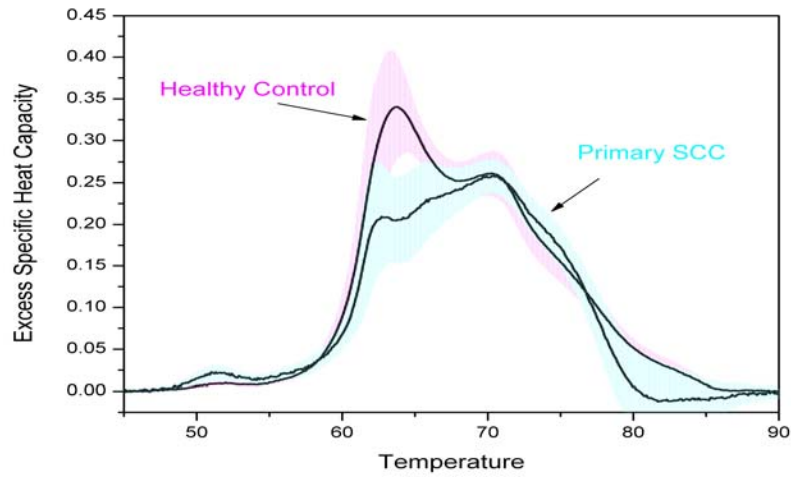
Goetz H. Kloecker, Guilherme Rabinowits, Cicek Gercel-Taylor, Jamie M. Day, Douglas D. Taylor
 Clinical Lung Cancer, 2008, 9(5), #7, full article in press

RESULTS



Plasma Thermogram and Lung Cancer

R Chaires, D Xiung, A Mitha, GH Kloecker, ASCO-NCI-EORTC Meeting 2008, #77



Any Questions ?

