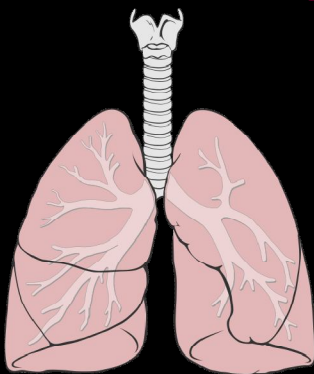


Women and Lung Cancer



(c) Farnik J. Lynch, 2006

Mary Pinder-Schenck, M.D.
Assistant Professor, Thoracic Program
Moffitt Cancer Center and Research Institute

INTRODUCTION



OUTLINE

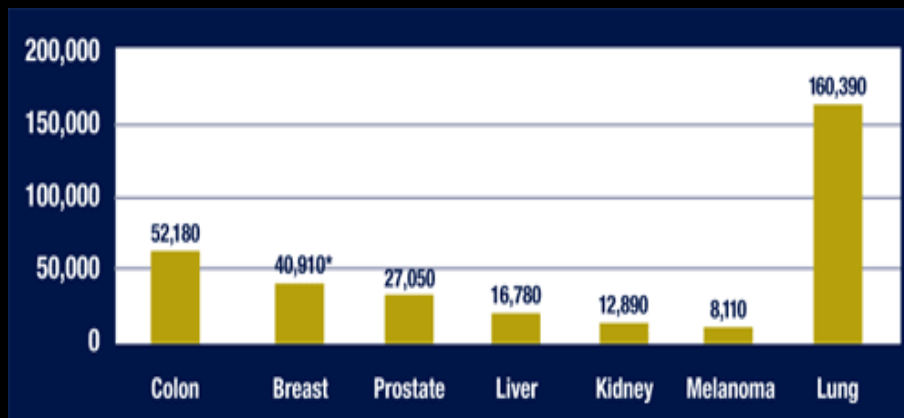
- Lung Cancer Facts and Figures
- How is lung cancer different in women?
 - Differences in susceptibility
 - Hormonal influences
 - Differences in prognosis
- Future of lung cancer treatment
- Questions

FACTS

- Lung cancer is second only to heart disease as a cause of death in the United States
- Lung cancer is the **LEADING** cause of cancer death for both men and women
- Worldwide, lung cancer kills over 1.3 million people annually
- In the U.S. over 150,000 people will die of lung cancer in 2009

Lung Cancer Alliance
<http://seer.cancer.gov>

Cancer Deaths 2007

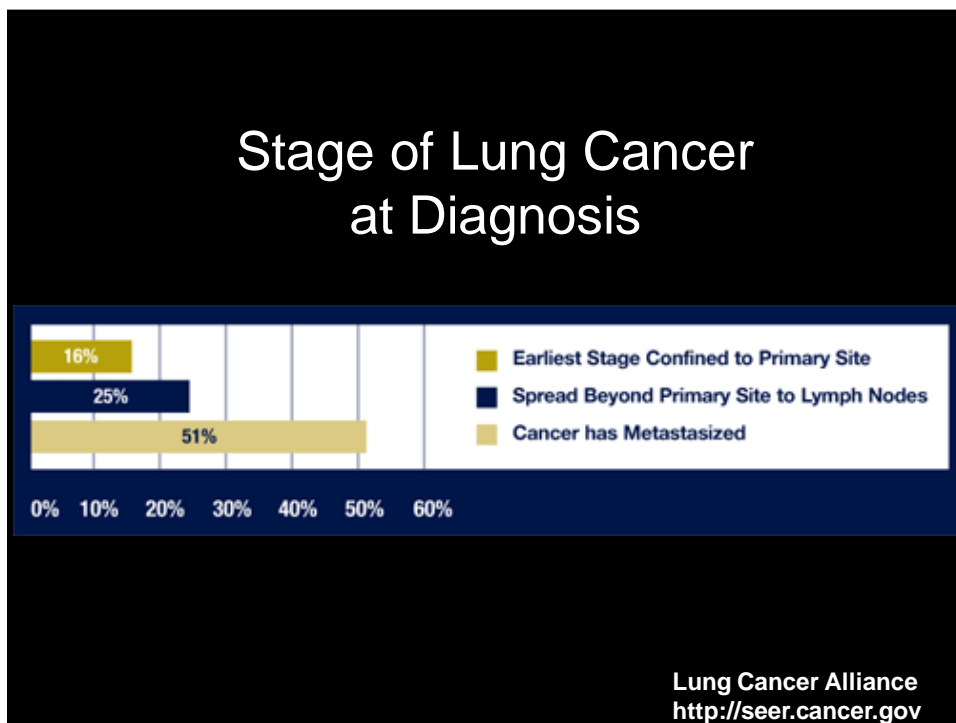
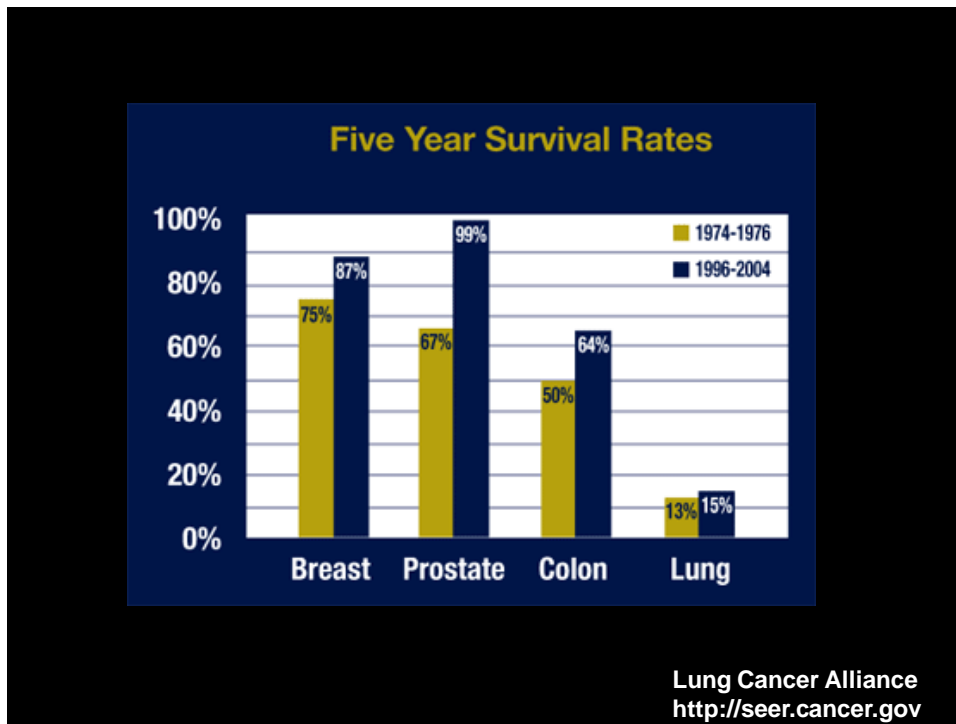


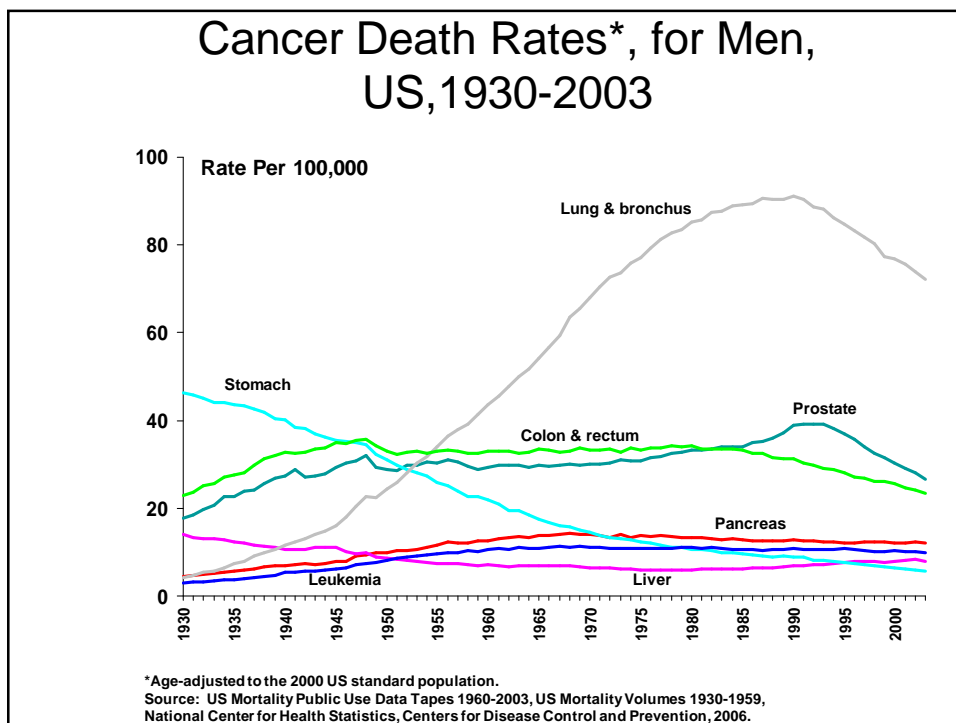
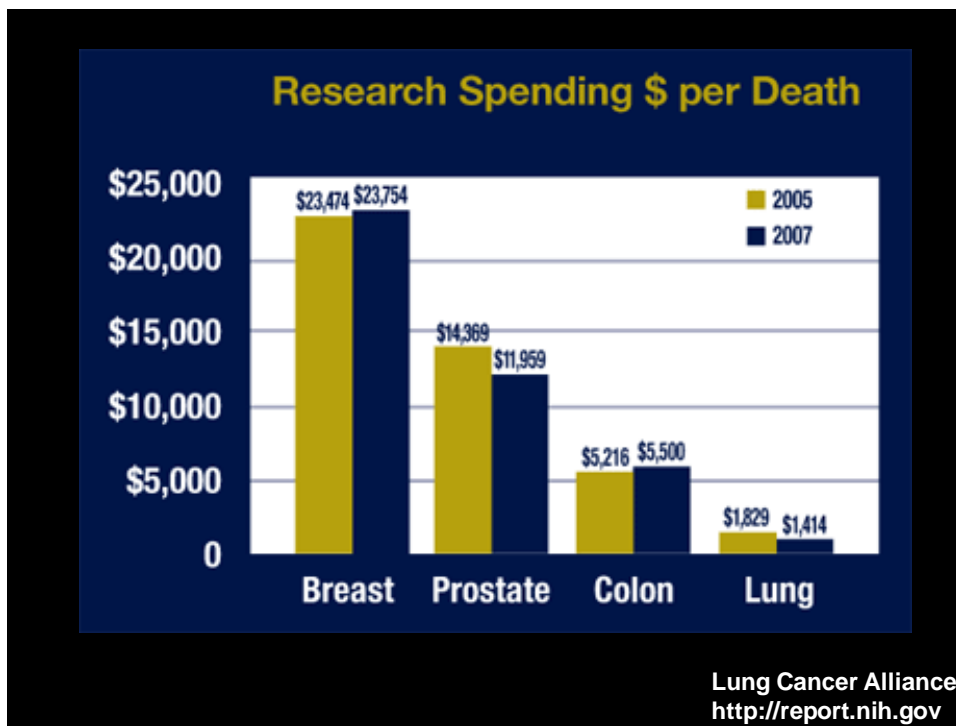
Lung Cancer Alliance
<http://seer.cancer.gov>

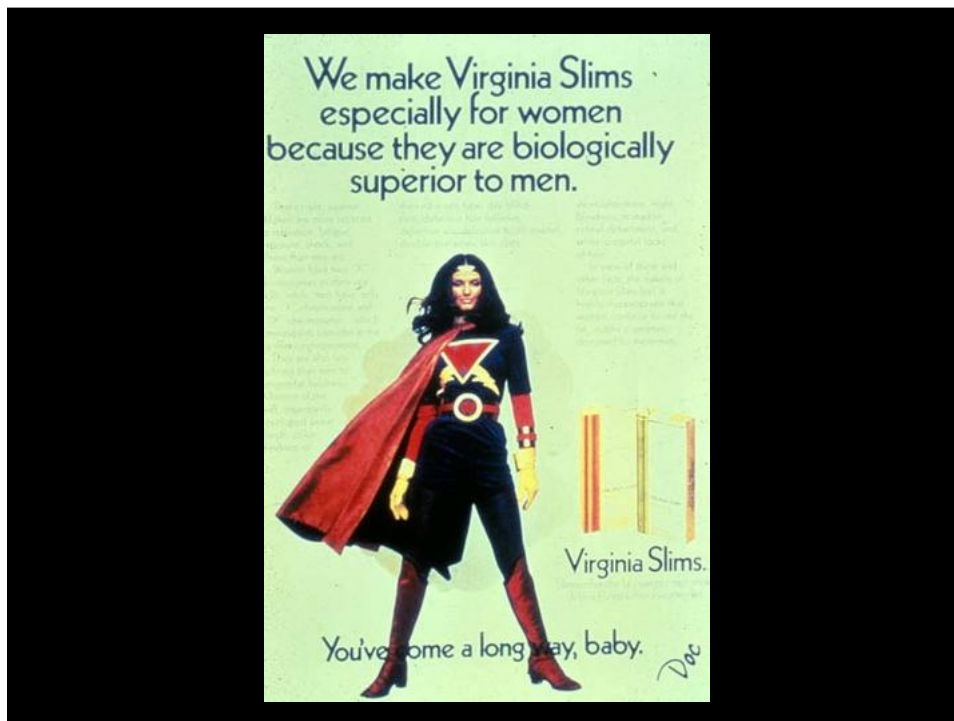
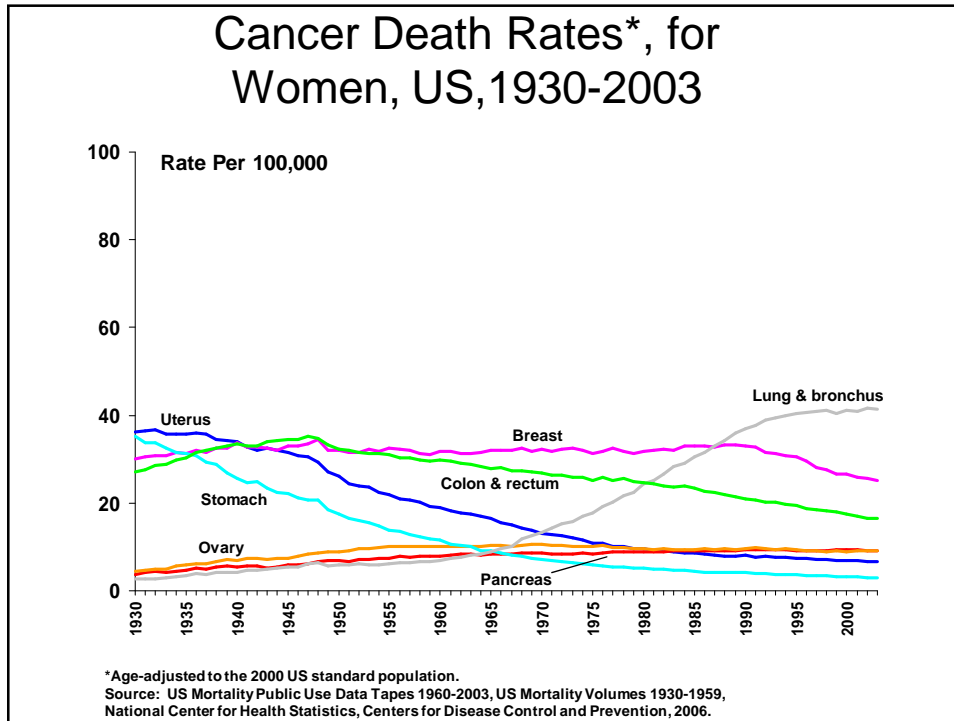
FACTS

- Lung cancer deaths in women surpassed breast cancer deaths in 1987
- More women die of lung cancer annually than of breast, ovarian and uterine cancer combined
- 65% of lung cancers occur in former or never smokers

Lung Cancer Alliance
<http://seer.cancer.gov>







**"Light a Lucky
and you'll never miss sweets
that make you fat"**

Constance Talmadge
Constance Talmadge
Charming Actress
Prize too

INSTEAD of eating between meals... instead of fattening sweets... beautiful women keep youthful slenderness these days by smoking Lucky. The smart and delicate women of the modern age take this means of keeping slender... when others nibble fattening sweets, they light a Lucky!

Lucky Strike is a delightful blend of the world's finest tobaccos. These tobaccos are toasted—a subtle extra process which develops and improves the flavor. That's why Lucky is a delightful alternative for fattening sweets. That's why there's real health in Lucky Strike. That's why folks say: "It's good to smoke Lucky."

For years this has been no secret to those men who keep fit and trim. They know that Lucky makes their nerves and do not harm their physical condition. They know that Lucky Strike is the favorite cigarette of many prominent athletes, who must keep in good shape. They respect the opinion of 25,000 athletes who maintain that Lucky is less irritating to the throat than other cigarettes.

A reasonable proportion of sugar in the diet is recommended, but the authorities are over-estimating that too many fattening sweets are harmful and that too many such are eaten by the American people. So, for moderation's sake we say—

**"REACH FOR A LUCKY
INSTEAD OF A SWEET."**

"It's toasted"
No Throat Irritation—No Cough.

Reach for a Lucky instead of a sweet.



© 1941 The American Tobacco Co., Manufacturers

**"I'm going to grow
a hundred
years old!"**

...and possibly she may—for the amazing strides of medical science have added years to life expectancy

It's a fact—a warm, wonderful fact—that this five-year-old child, or your own child, has a life expectancy almost a whole decade longer than was her mother's, and a good 18 to 20 years longer than that of her grandmother. Not only the expectation of a longer life, but of a life by far healthier. Thank medical science for that. Thank your doctor and thousands like him... smiling cheerfully... that you and yours may enjoy a longer, better life.



According to a recent Nationwide survey:

**More Doctors smoke Camels
than any other cigarette!**

NOT ONE but three outstanding independent research organizations conducted this survey. And they asked not just a few thousand, but 113,597, doctors from coast to coast to name the cigarette they themselves preferred to smoke.

Answers came in by the thousands... from general physicians, diagnosticians, surgeons, nose and throat specialists too. The most-named brand was Camel.

If you are not now smoking Camels, try them. Let your "T-Zone" tell you (see right).

H. A. Bennett, Executive Director, Winston-Salem, N. C.

CAMELS *Castles of Tobacco*

THE "T-ZONE" TEST WILL TELL YOU

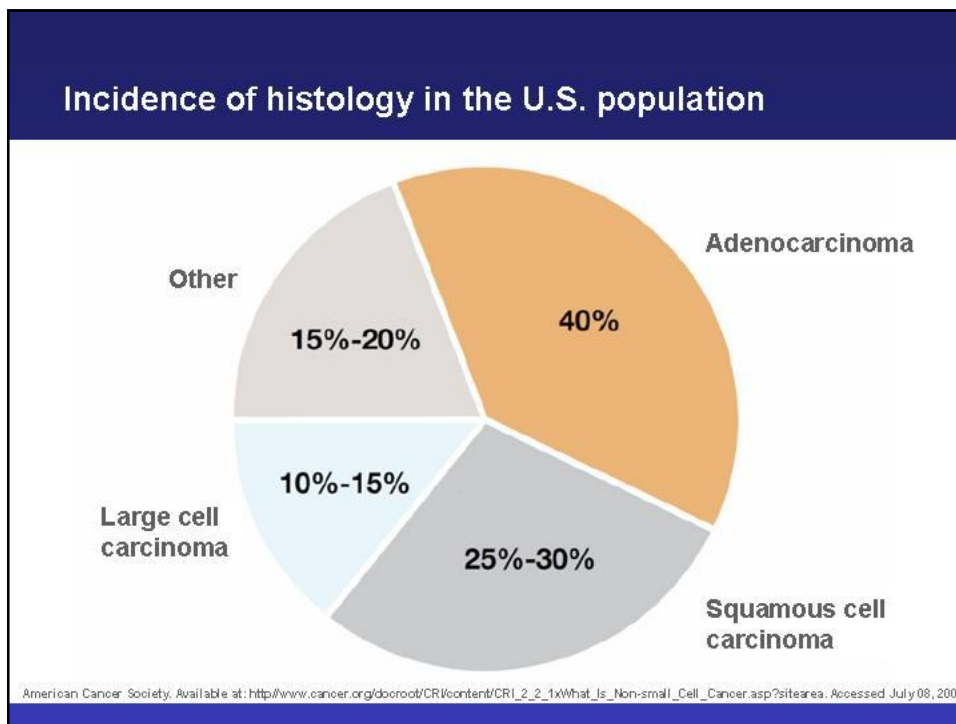
The "T-Zone"—T for taste and T for throat—is your own proving ground for any cigarette. Only your taste and throat can decide which cigarette turns out to be best to *smoke*—how it affects your throat.



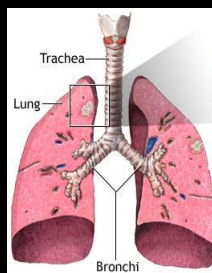


Lung Cancer Basics

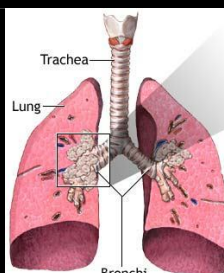
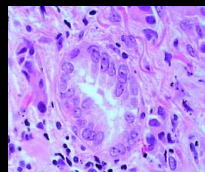
- Non-small cell (85%)
 - Adenocarcinoma
 - Bronchioloalveolar carcinoma
 - Squamous cell carcinoma
 - Large cell carcinoma
 - Other
- Small cell (15%)



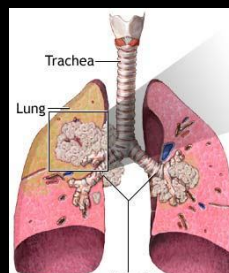
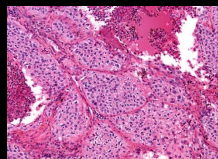
Lung Cancer Basics



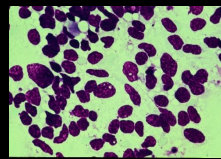
Adenocarcinoma

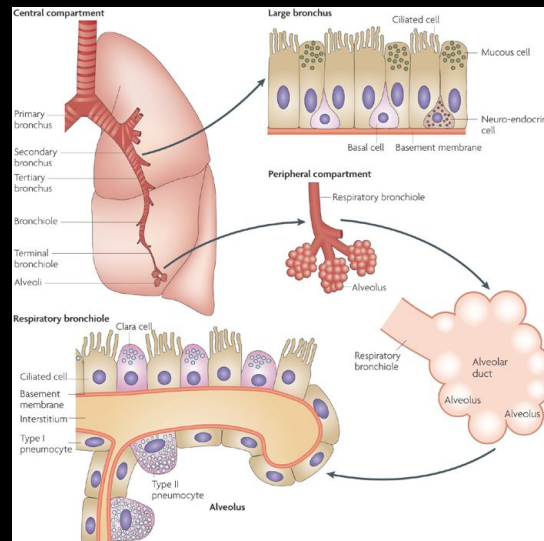


Squamous Cell



Small Cell





Sun, Nature 2007

Risk Factors

- All types of lung cancer are associated with tobacco (including second-hand smoke!)
 - Association strongest for SCLC and squamous cell
 - Most cancers in never-smokers are adenocarcinomas

Risk Factors

- Radon gas
- Asbestos
- Radioactive ores, such as uranium
- Inhaled chemicals or minerals, such as arsenic, beryllium, cadmium, vinyl chloride, nickel compounds, chromium compounds, coal products, mustard gas, and chloromethyl ethers
- Diesel exhaust
- Air pollution
- Cooking oils??
- Viral??

Case #1

- Mrs. H is a 70 year old woman who had a cough that did not go away. A CT scan showed a lung mass and swollen lymph nodes in the chest.



Case #1

- Mrs. H smoked 1ppd for 30 years but quit 25 years ago. Her husband, who accompanies her, smoked 2 ppd and didn't quit until 15 years ago.
- She asks why she got lung cancer and her husband did not.

Women and Tobacco

- Are women more susceptible to the effects of tobacco?
 - Women are more likely to have abnormal lung function than men in response to smoking
 - Decline in lung function in women greater than for men with same amount of tobacco smoking
 - Risk of hospitalization for COPD higher for women than men

Women's susceptibility to lung cancer

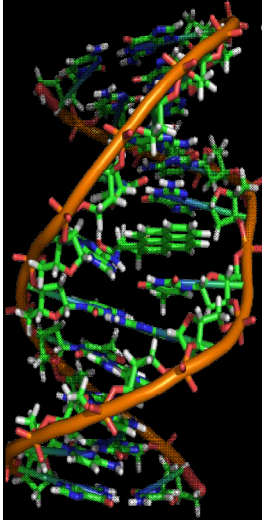
Reference	Study Type	Increase in Lung Cancer compared to non-smoker		
		M	F	
Risch, Am J Epi 1993	Case control	9.6	27.9	40 ppy
Harris, Int J Epi 1993	Case control	24.5	42	White men vs. white women: 40 ppy
Zhang, JNCI 1996	Case control	11.6	21.4	White men vs. white women: 40 - 49 ppy
Osann, Int J CA 1993	Case Control	37.5	86	
Henschke, Lung CA 2006	Analysis of smokers on screening study		1.9 compared to men	

Women's susceptibility to lung cancer

- ELCAP is a screening study for people considered high-risk for lung cancer
- ~17,000 patients were included in analysis
- Women had nearly double the risk of being diagnosed with lung cancer during the study
- Women diagnosed with lung cancer similar in age (67 vs. 68) but smoked less (47 vs. 64 pack years)
- 73% of the cancers in women were adenocarcinomas compared to 59% in men
- Women were 50% less likely to die of their lung cancer

Henschke, JAMA 2006

Women's susceptibility to lung cancer



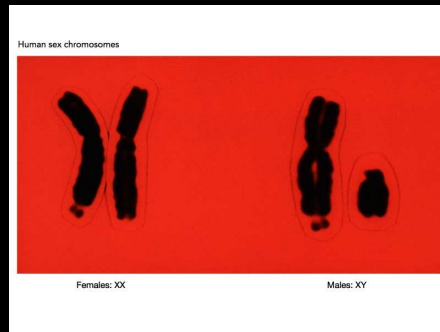
- Why would women be more susceptible to tobacco carcinogens?
 - Lung cancers in women smokers show more mutations than in male smokers or female never-smokers
 - Higher smoking-related DNA adducts are seen in women with lung cancer, including never-smokers

*Kure, Carcinogenesis 1996
Toyooka, Hum Mutat 2003
Ryberg, Cancer Res 1994*

Women's susceptibility to lung cancer

- CYP1A1 is an enzyme involved in metabolism of carcinogens
- Yields highly reactive substances that bind to DNA
- Increased levels CYP1A1 in lung of women smokers
- Estrogen may contribute

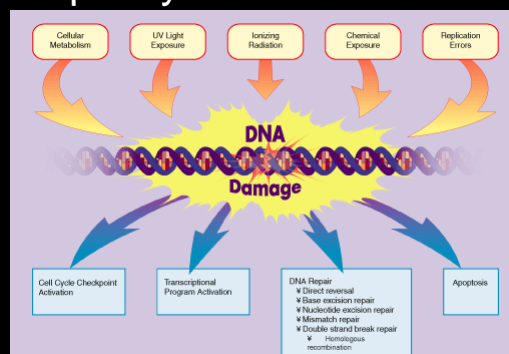
Women's susceptibility to lung cancer



- GRP is a substance that stimulates cells to grow in the lung
- The gene for GRP's receptor is on X chromosome so women have 2 copies
- GRPR is increased with exposure to nicotine or estrogen

Women's susceptibility to lung cancer

- Ability to repair DNA damage implicated in lung cancer
- Women, on the whole, have lower DNA repair capacity



Women's susceptibility to lung cancer

- What about never-smokers?
- Among Asian women, >50% of lung cancers occur in never-smokers
- In U.S., rates of lung cancer in never-smokers are higher in women than men
- Incidence of lung cancer in never-smokers appears to be increasing

Wakelee, J Clin Oncol 2007.

Case #2

- JT is a 49 year old woman, never-smoker. She was in an automobile accident and taken to ER. CT scan of abdomen caught a nodule in the lower lung. Biopsy revealed adenocarcinoma. At the time of surgery, lymph nodes were involved. She is undergoing chemotherapy. She was on HRT after hysterectomy at age 40. She wants to know if this contributed to her lung cancer.

Hormonal Influences

- Both normal lung and lung tumors express estrogen receptors
- Estrogen can be synthesized in the lung
- Higher blood estrogen levels associated with worse outcome in women AND men
- SCLC cells used to be grown in HITES medium (hydrocortisone, insulin, transferrin, estrogen, selenium)
- Anti-estrogens reduce lung tumor growth in mice

Hormonal Influences

Menopausal hormone therapy associated with:		
Increased Risk	Null	Reduced Risk
Taioli J Natl Cancer Inst 1994;86:867	Kreuzer Int J Epidemiol 2003;32(2):263-71	Olsson Obstet Gynecol 1996;87:6
Liu Int J Cancer 2005;117:662	Elliott Contraception 2006;73:331	Schabath Clin Cancer Res 2004;10:113
	Baik Proc ASCO 2009;1501	Schwartz J Clin Oncol 2007;25:5785
		Ramnath Oncology 2007;73:305
		Rodriquez Cancer Epidemiol Biomarkers Prev 2008;17:655

Eligible postmenopausal
Age 50-79
No prior breast cancer
No prior hysterectomy

N= 16,608 ——— Placebo

Conjugated equine estrogen (CEE) 0.625 mg/d + medroxyprogesterone acetate (MPA) 2.5 mg/d

Intervention 5.6 yrs

Chlebowski RT, Schwartz A, Wakelee H et al. Proc ASCO;27:CRA 1500
WHI Writing JAMA 2002; 288: 321
Chlebowski JAMA 2003; 289: 3253
Shumaker et al JAMA 2003;289:2651-62

	HR 95% CI
CHD	1.29 (1.02-1.63)
Breast Ca	1.26 (1.00-1.59)
Stroke	1.41 (1.07-1.85)
PE	2.13 (1.39-3.25)
Endometrial Ca	0.83 (0.47-1.47)
Colorectal Ca	0.63 (0.43-0.92)
Hip Fracture	0.66 (0.45-0.98)
Global Index	1.15 (1.03-1.28)
Dementia	2.05 (1.21-3.48)

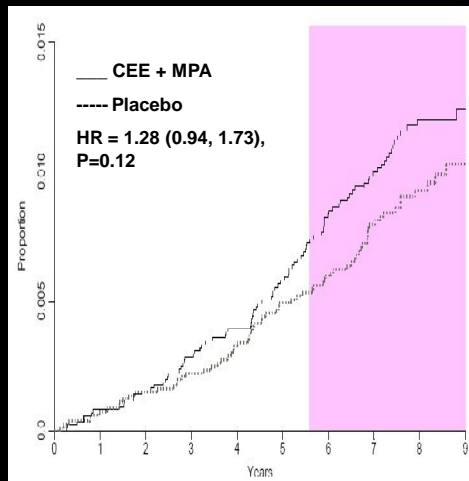
WHI: Tobacco Exposure

	CEE+MPA (n,%)	Placebo (n,%)
Smoking status		
Never	4178 (49.6 %)	3999 (50.0 %)
Past	3362 (39.9 %)	3157 (39.5 %)
Current	800 (10.5 %)	838 (10.5 %)
Yrs of smoking		
< 5	1119 (13.6 %)	1004 (12.8 %)
5-<20	1168 (14.2 %)	1140 (14.6 %)
≥ 20	1763 (21.4 %)	1679 (21.5 %)

Also balanced were “cigarettes/d” (< 25, 25+) and “years smoked” (< 30, 30+)

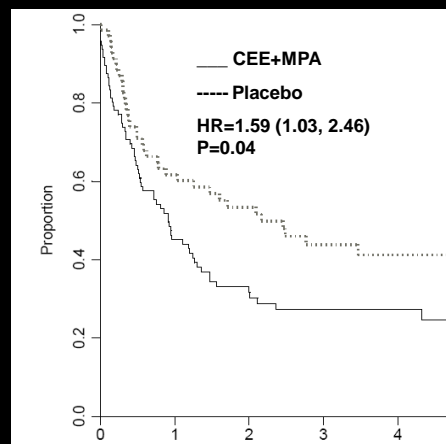
Chlebowski, Schwartz, Wakelee, et al. Proc ASCO 2009;27:CRA1500.

Lung Cancer Incidence



Chlebowski, Schwartz, Wakelee, et al. Proc ASCO 2009;27:CRA1500.

Lung Cancer Survival



70 % vs 54 % mortality, 4 yr

Chlebowski, Schwartz, Wakelee, et al. Proc ASCO 2009;27:CRA1500.

Lung Cancer Deaths by Tobacco Use

	CEE+MPA deaths/ppts (% cumulative)	Placebo deaths/ppts (% cumulative)	HR (95% CI)
All *	67/8052 (0.8%)	39/7678 (0.5%)	1.61 (1.09, 2.39)
Never Smoker**	9 / 4178 (0.2%)	5 / 3999 (0.1%)	1.67 (0.56, 5.00)
Past	29 / 3362 (0.9%)	15 / 3157 (0.5%)	1.83 (0.98, 3.42)
Current Smoker	27 / 800 (3.14%)	19 / 838 (2.3%)	1.39 (0.77, 2.51)

* P-value = 0.02;

**Interaction P-value = 0.79, smoking status and randomization arm (% cumulative) = % risk over entire 7.9 years (median) study period

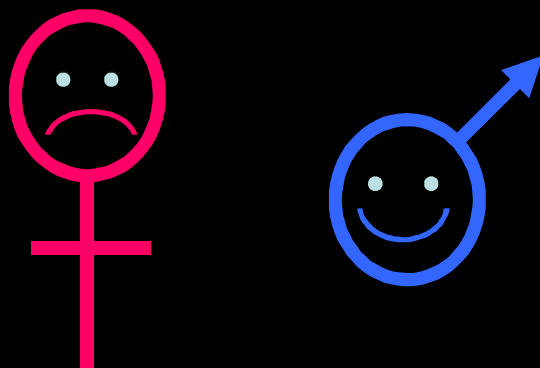
Chlebowski, Schwartz, Wakelee, et al. Proc ASCO 2009;27:CRA1500.

WHI Conclusions

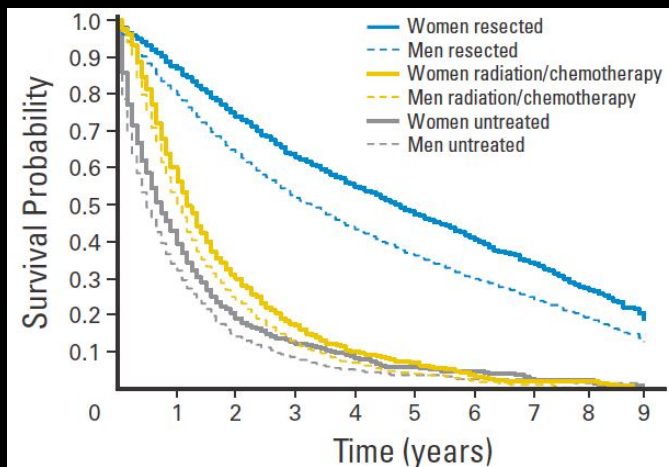
- CEE + MPA for somewhat over 5 years significantly increases death from NSCLC, the leading cause of cancer death in women
- In current smokers about 1 in 100 experienced an avoidable NSCLC death with CEE+MPA over the 8 year study period
- Current smokers using combined hormone therapy should discontinue tobacco use
- Current smokers should carefully consider this mortality risk before beginning, or continuing combined hormone therapy
- Future therapies for NSCLC should explore the use of estrogen blockade in a subset of selected patients

Chlebowski, Schwartz, Wakelee, et al. Proc ASCO 2009;27:CRA1500.

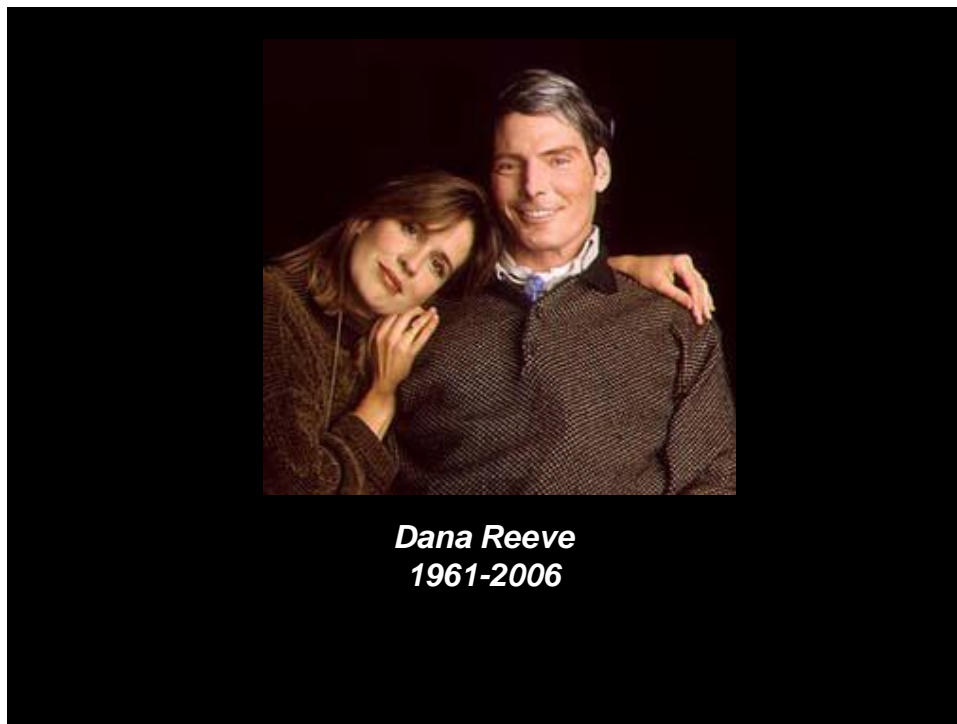
- Now that was depressing...



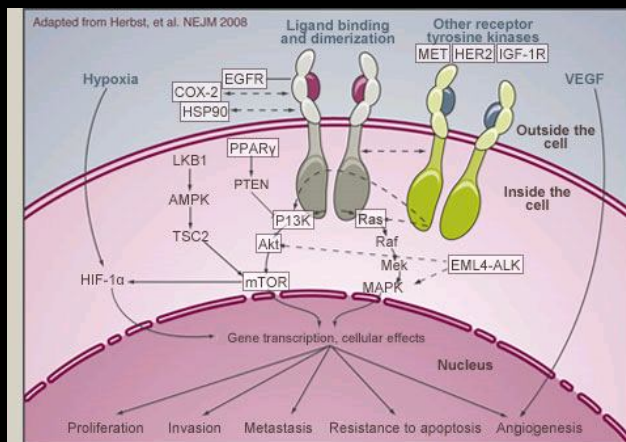
Lung Cancer Prognosis



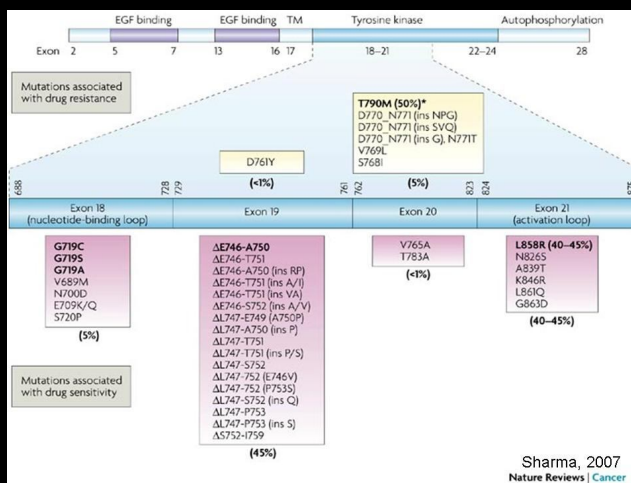
Wisnivesky and Halm JCO 2007; 25:1705



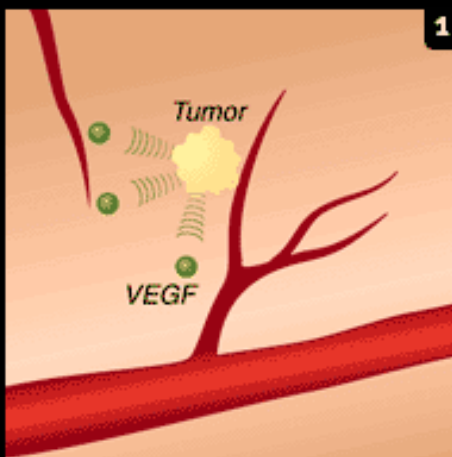
Response to Therapy: Tarceva



Response to Therapy: Tarceva

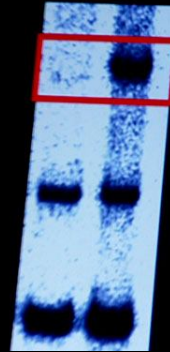
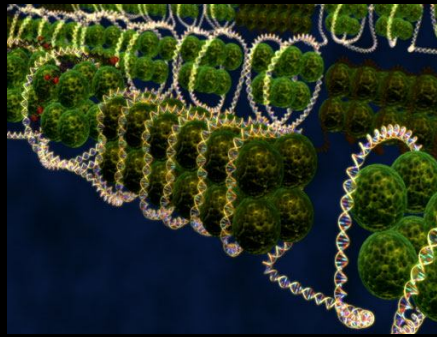


Response to Therapy: Avastin

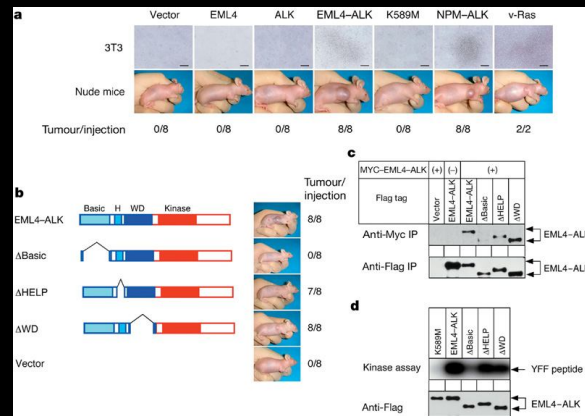


Future Directions: Epigenetics

- <http://www.pbs.org/wgbh/nova/genes/>



Future Directions: Personalized Medicine



Soda, Nature 2007

Conclusions

- Lung cancer is an epidemic in women
- There are important differences between men and women in risk of lung cancer, prognosis and response to different therapies
- Estrogen appears important but is only one part of the story
- Lung cancer in never-smokers is a growing and poorly understood problem
- Lung cancer research is desperately underfunded

WEBSITES

- <http://www.joanslegacy.org>
- <http://www.lungcanceralliance.org/>
- <http://www.nationallungcancerpartnership.org/>
- <http://www.lcfamerica.org/welcome.html>
- <http://www.cancergrace.org>