Epidemiology of Lung Cancer
What Can We Do?

Wyatt E. Rousseau, MD

September 5, 2013

STOP SMOKING!

Only 2% of Lung Cancer patients are lifelong nonsmokers

Lung Cancer

- Most common cause of cancer death
- 159,500 deaths in 2013 projected*
- 118,000 combined colorectal, breast and prostate deaths*
- Smoking/Lung Cancer first linked in 1950- Doll and Hill (BMJ 1950; 2:739.)
- Surgeon General's 1964 statement - "cigarette smoking is the major cause of lung cancer…"

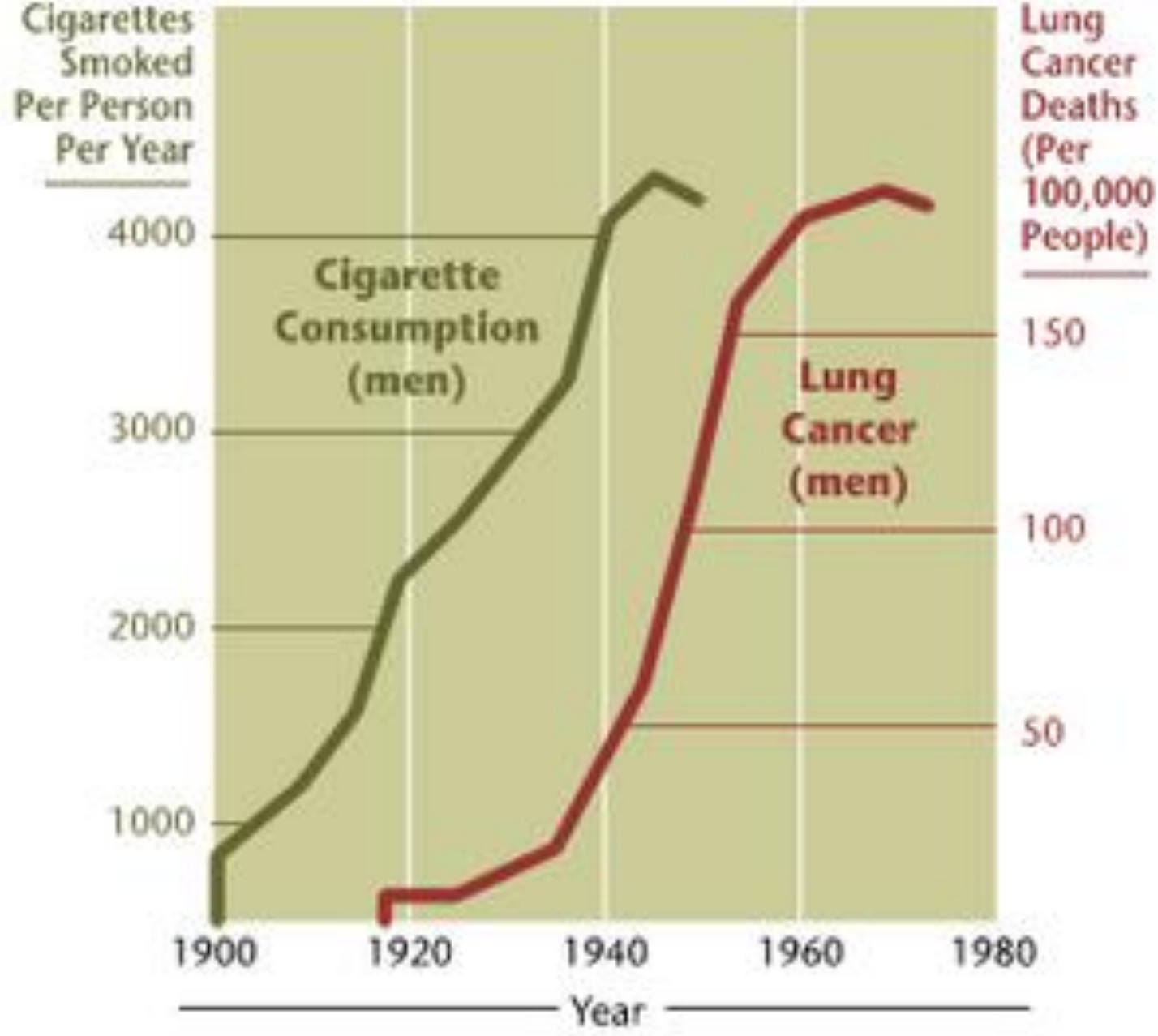
*Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63:11.

Tobacco – Cancer Linked Directly

A specific metabolite of benzo(a)pyrene, a constituent of tobacco smoke, damages three specific loci on the p53 tumor-suppressor gene that are known to be abnormal in 60% of primary lung cancer.

Denissenko et. al. Science 1996; 274:430.

20-Year Lag Time Between Smoking and Lung Cancer



Magnitude of Risk

- Total lifetime consumption
- Number of cigarettes
- Duration of smoking
- Age at onset
- Degree of inhalation
- Tar and Nicotine content
- Use of unfiltered cig.

Approximate 10-Year Risk of Developing Lung Cancer*†

	Duration of smoking					
	25 years		40 years		50 years	
Age	Quit	Smoking	Quit	Smoking	Quit	Smoking
1 pack per day smokers						
55	<1	1	3	5	NA	NA
65	<1	2	4	7	7	10
75	1	2	5	8	8	11
2 packs per day smokers						
55	<1	2	4	7	NA	NA
65	1	3	6	9	10	14
75	2	3	7	10	11	15

* Estimated risk of developing lung cancer is expressed as a percentage value. These tables assume that people who have quit smoking will continue to abstain for the next 10 years and those who are still smoking will keep smoking the same amount for the next 10 years. For individuals with occupational asbestos exposure, the risks should be multiplied by 1.24. There was a relative paucity of events observed among individuals in this study outside the given age ranges (ie, younger than age 55, older than age 85), making prediction outside the given age range potentially unreliable. NA: data not available.

† Reproduced with permission from: Bach, PB, Kattan, MW, Thornquist, MD, et al. Variations in lung cancer risk among smokers. J Natl Cancer Inst 2003; 95:470. Copyright © 2003 Oxford University Press.

Number of Cigarettes Smoked and Relative Risks of Death from Lung Cancer among Males

No. per Day	US Veterans	British Doctors
None	1.0	1.0
Current smokers	12.1	14.0
1-9	5.5	7.8
10-19	9.9	17.4
20-39	17.4	25.1
>40	23.9	--

Years after Quitting Smoking and Relative Risks of Lung Cancer - Males

Years after Cessation	US Veterans	British Doctors
0	11.3	15.8
1-4	18.8	16.0
5-9	7.5	5.9
10-14	5.0	5.3
15-19	5.0	
>20	2.1	2.0

Risk Reduction

- Abstinence > 15 years has an 80-90% reduction in risk compared with current smokers
- Lung CA risk **always** higher in former smokers than never smokers. Former smokers have 10-80% greater risk than nonsmokers

Newcombe and Carbone. Med Clin North Am 1992;76:305-31.

Lung Cancer Risk Reduction after Smoking Cessation. Ebbert et. al. J Clin Oncol 21:921-926, 2003

- 37,078 females
- Elevated risk even thirty years later
- Persisting risk of adenocarcinoma among former smokers
- Former light smokers still had a greater than 2-fold increased risk up to 30 years after smoking abstinence
- Although risk of cancer does not return to baseline for decades, significant decrease in first 10 years of abstinence

Other Risks – Smoking

- Cigar and Pipe Smoking –They DO inhale
- Marijuana and Cocaine Smoking – probably, but magnitude of risk not quantitated.
- Environmental Smoke – Passive or Second-hand – Yes, weaker links, but dose-response shown
- Hookah Smoking – not safer than cigarettes; may inhale more smoke due to duration of the session. ?Infection risk

Environmental Tobacco Smoke

- Duration longer. Dose-response
- Household exposure>25 smoker years doubled risk*
- Spousal tobacco use associated with 30% increase in risk (80 pk. yr. associated with 80% increase)#
- Risk increased 24% if lived with smoker@

*Janerich DT, et. al. N Engl J Med 1990;323:632.

#Fontham ET, et. al. JAMA 1994; 271:1752.

@Hackshaw AK, et. al. Br Med J 1997; 315:980.

Genetic Influences

- Glutathione S-transferase M1 is thought to detoxify carcinogens in tobacco smoke
- More polymorphisms in this gene, which decrease its activity, noted among women with lung cancer exposed to ETS compared with those not exposed, suggesting these mutations promote tumorigenesis
- Clearly established familial risk, but genetic basis still being elucidated

Occupational and Environmental Carcinogens

- **Asbestos** : Amphibole(Crocidolite)>Serpentine (Chrysotile) fibers

  Risk is multiplied by smoking: Risk of dying of lung cancer in asbestos workers increased 16-fold if they smoked >20 cigarettes per day and 9-fold if fewer than 20 cigarettes per day*
- **Radon** – gaseous decay of U-238, Ra-226 - can damage respiratory epithelium via emission of alpha particles. (summary risk 1.14)
- **Radiation therapy** can increase risk of second primary in patients treated for other malignancy

*Hammond EC et. al. Ann N Y Acad Sci 1979; 330:473.

Occupational and Environmental Carcinogens - 2

- Arsenic, bis-chloromethyl ether, chromium, formaldehyde, ionizing radiation, nickel, polycyclic aromatic hydrocarbons, hard metal dust, vinyl chloride
- Air pollution, wood smoke

Other Risk Factors

- Genetics -1st degree relatives have 1.5-3 fold risk
- Chronic inflammation including HIV infection
- Dietary Factors- low antioxidants, esp. Vitamins A and E. Beta-carotene conflicting data
- Preexisting Benign Lung Disease – IPF, Asbestosis, COPD
- Oncogenic Viruses not proven – Bronchioloalveolar Carcinoma in sheep, and Squamous cell CA assoc. with Human Papilloma Virus(HPV) DNA

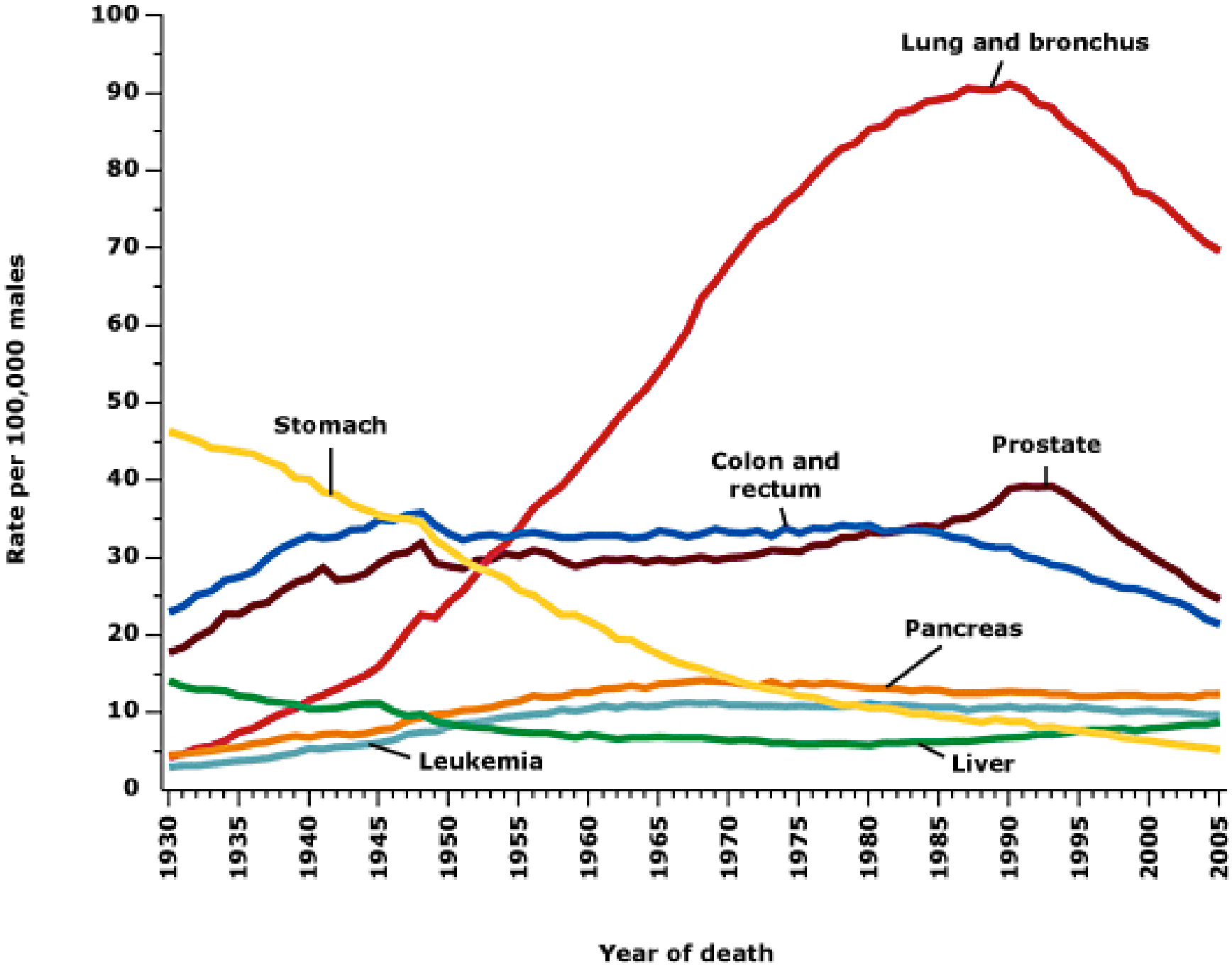
Dietary Factors

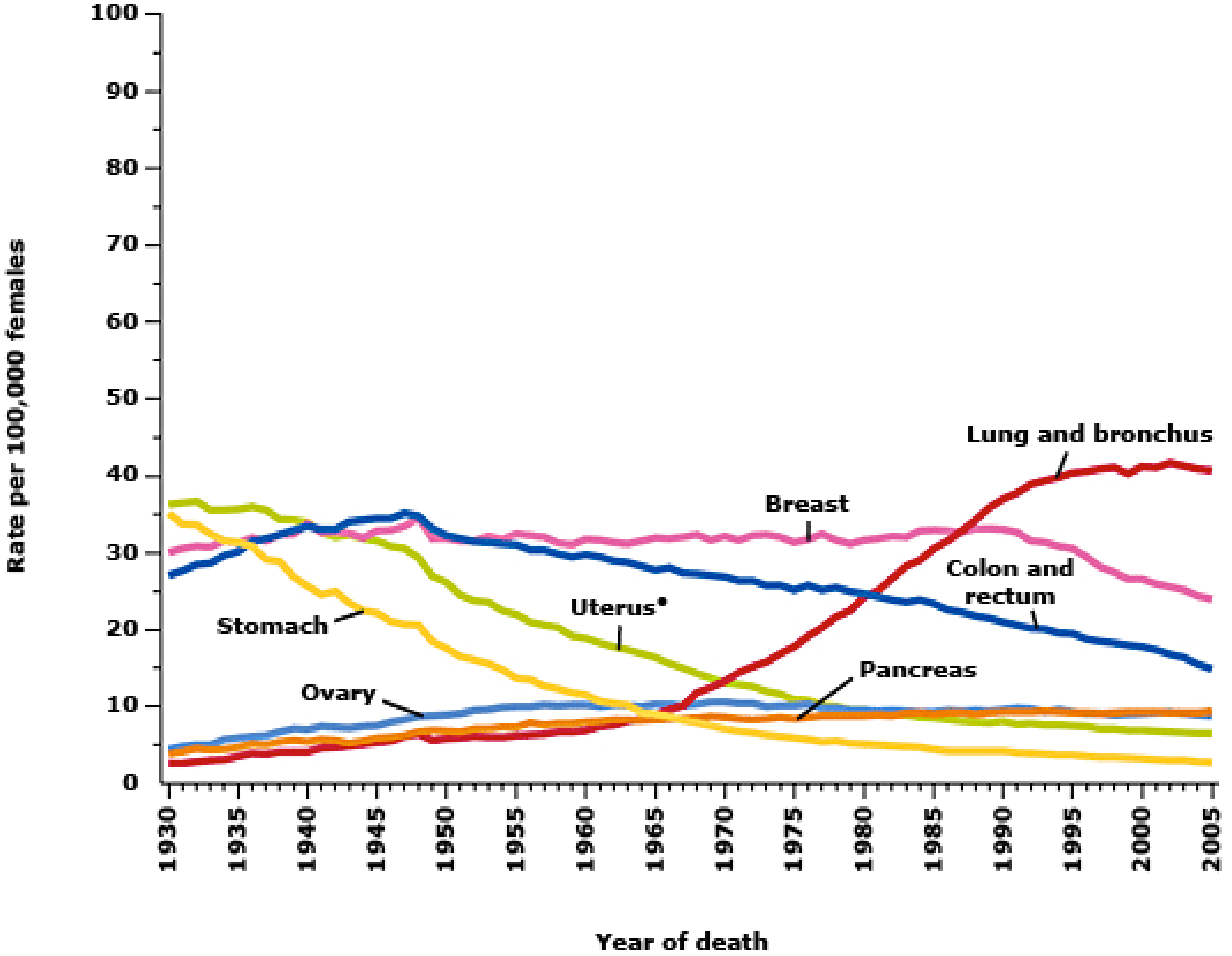
- CARET Trial-Heavy smokers who consumed more fruit and vegetables reduced their risk of cancer, but supplementation with Beta-carotene negated the effects of increased plant foods

Neuhouser et al Cancer Epidemiol Biomarkers Prev 12:350-358, 2003

Men cf. Women

- Lung cancer mortality has been greater in men; magnitude is declining due to increasing lung cancer mortality in women, and decreasing mortality in men


Rate per 100,000 males
100
90
80
70
60
50
40
30
20
10
0
1930
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
Year of death
Lung and bronchus
Stomach
Colon and rectum
Prostate
Pancreas
Leukemia
Liver


Rate per 100,000 females
100
90
80
70
60
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40
30
20
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1930
1935
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1945
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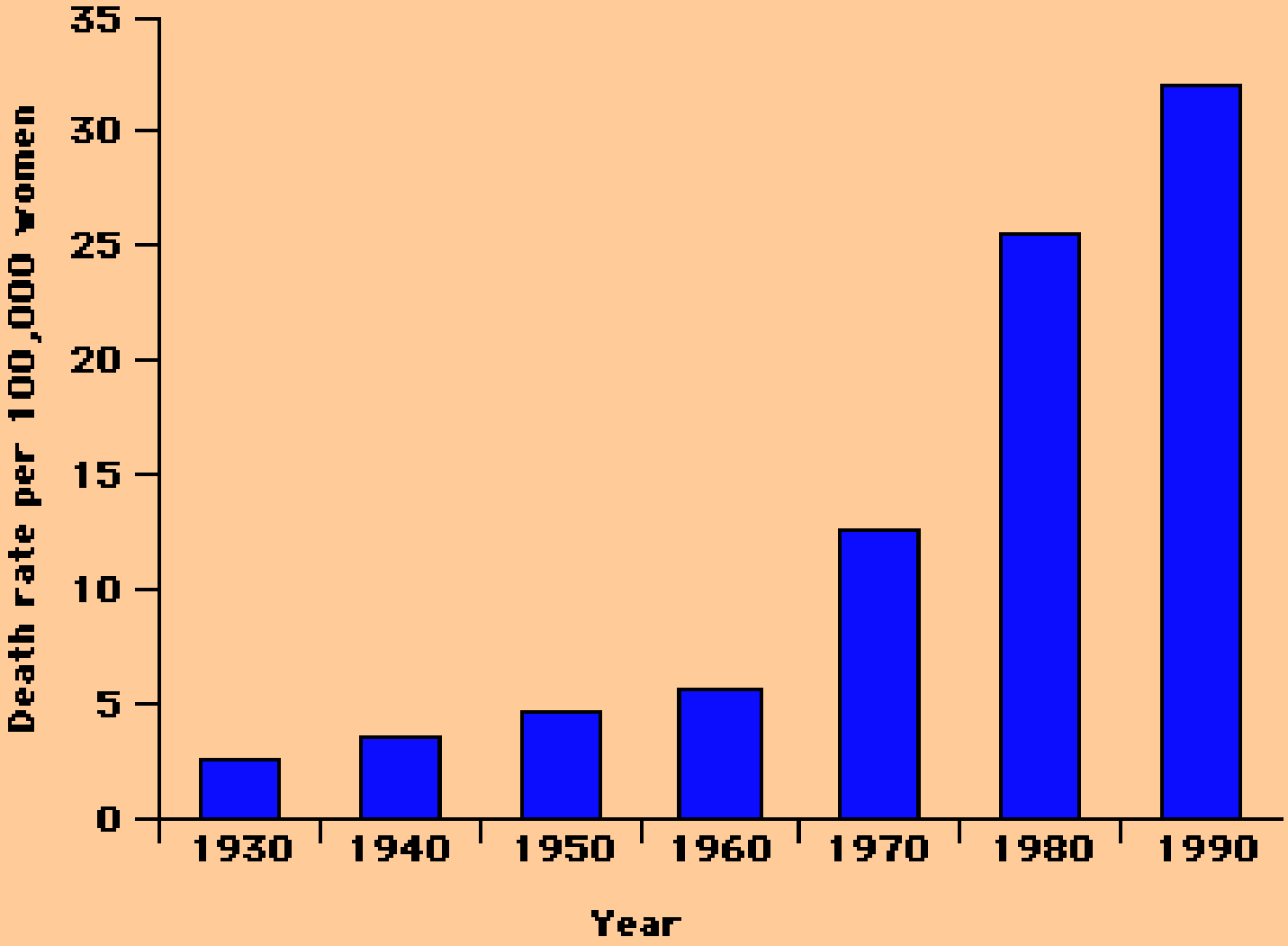
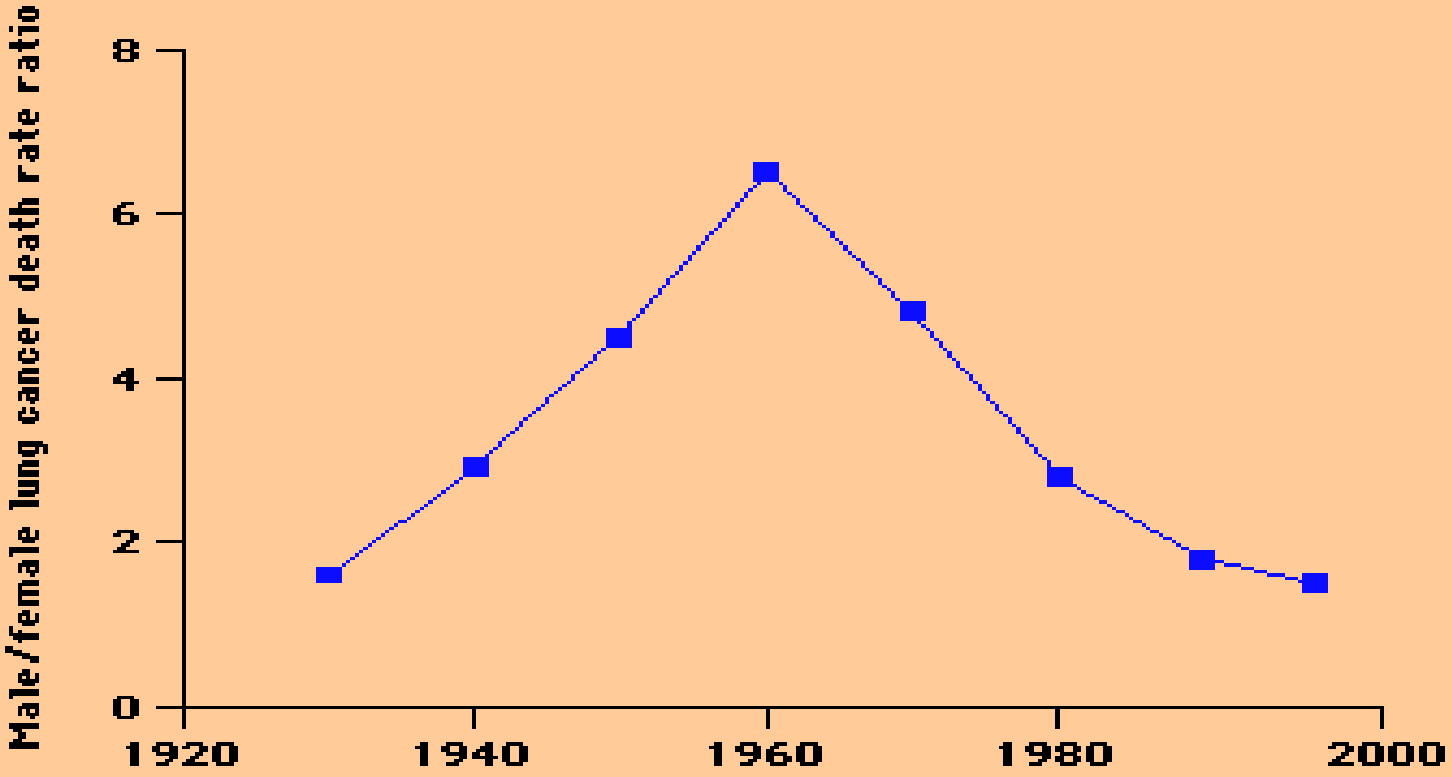
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
Year of death
Lung and bronchus
Breast
Colon and rectum
Uterus*
Stomach
Pancreas
Ovary



Increasing lung cancer death rates in women Lung cancer death rates per 100,000 women from 1930 to 1990 showing a dramatic and continuing increase since 1960. (Data from Parker, SL, Tong, T, Bolden, S, et al, CA - A Cancer Journal for Clinicians 1996; 46:5.)

Gender Differences – Death Rate



Lung cancer deaths in men and women Ratio of lung cancer deaths in men and women between 1930 and 1996. The ratio was greater than 6:1 in 1960 but has fallen below 2:1. (Data from Parker, SL, Tong, T, Bolden, S, et al, CA – A Cancer Journal for Clinicians 1996; 46:5.)

Men cf. Women among Never Smokers

- Age-adjusted incidence of lung CA among never smokers is higher in women than men
- In US, 19% of lung CA in women arose in never smokers, cf. only 9% for men

Endocrine Factors & Lung CA

- Early age at menopause (<40) associated with reduced risk of AdenoCA lung
- Hormone replacement therapy associated with higher risk AdenoCA lung

In a 2004 article, the above were suggested, but subsequently 3 case control studies failed to confirm.

However survival longer and age at Dx older among women who had not received HRT.

Consider stopping Hormone Replacement Therapy in lung CA pts.*

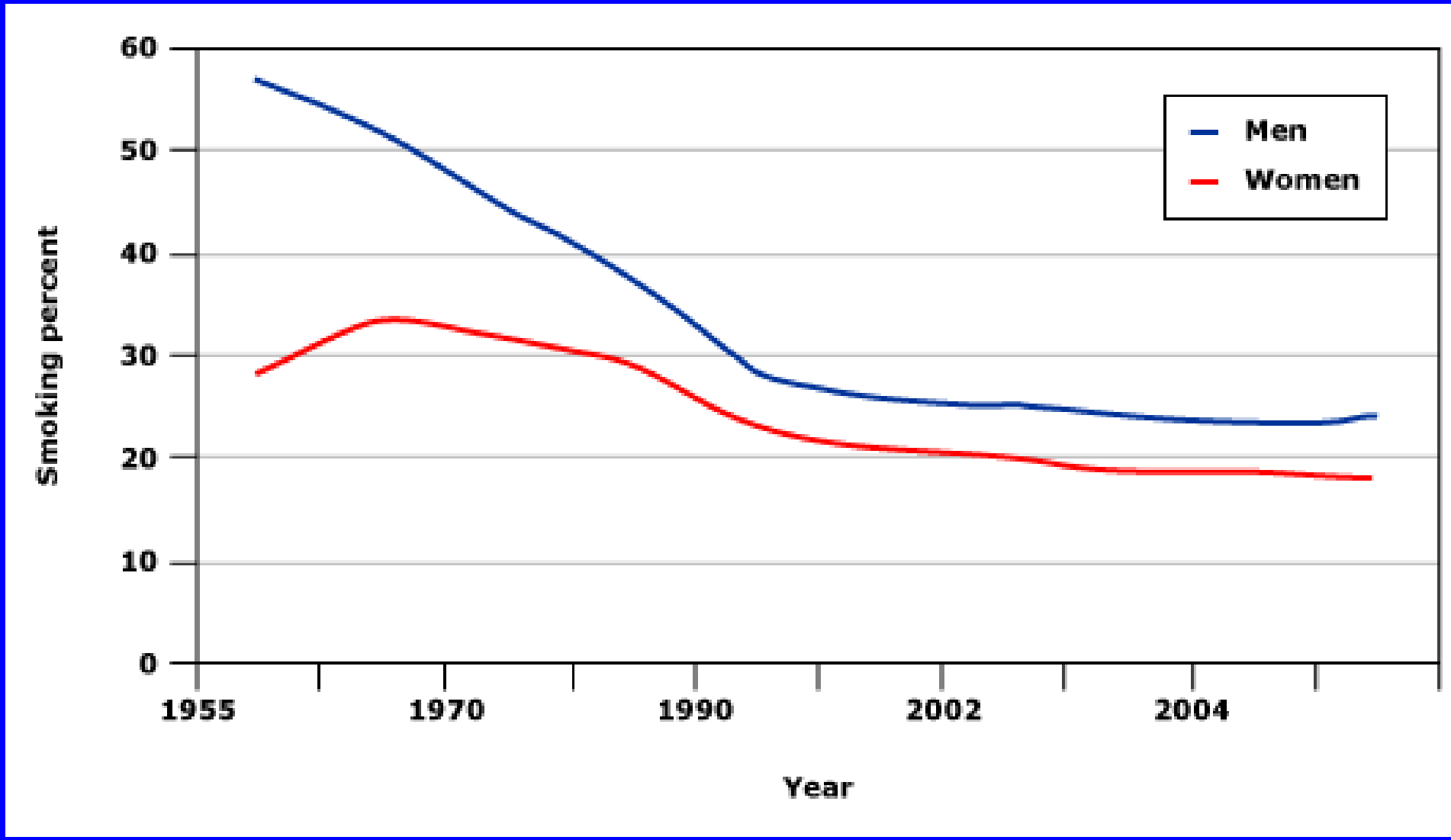
*Siegfried, JM. J Clin Oncol 2006; 24:9.

Gender Histology Differences

Distribution of Lung Cancer by Histology

Lung cancer histology	Men (n=1153)	Women (n=833)
Adenocarcinoma	28.9 percent	34.8 percent
Squamous cell carcinoma	31.2 percent	20.5 percent
Small cell carcinoma	16.9 percent	20.3 percent
Large cell carcinoma	9.2 percent	8.8 percent
Other/unspecified	13.8 percent	15.6 percent

(Data from Osann, KE, Anton-Culver, H, Kuosaki, T, et al, Int J Cancer 1993;54:44.)


60
50
40
30
20
10
0
Smoking percent
1955
1970
1990
2002
2004
Year
Men
Women

Smoking Prevalence per CDC 2011

- 19% of Adults, down from 21% in 2005
- Men 21.6%, Women 16.5%
- American Indian/Alaskan 31.5%; Asians 9.9%; Blacks 19.4%; Hispanics 12.9%; Whites 20.6%
- Lower prevalence among more affluent
- Lower prevalence as education level rises

Good News

- From Federal Interagency Forum on Child and Family Statistics: In 2012, the percentages of 8th-,10th-, and 12th-grade students who reported smoking cigarettes daily in the past 30 days were the lowest in the history of the survey.
- In 2012, some 2 percent of 8th-grade students, 5 percent of 10th-grade students, and 9 percent of 12th-grade students reported smoking cigarettes daily in the past 30 days, compared with their respective peaks in the mid-1990s of 10, 18, and 25 percent.

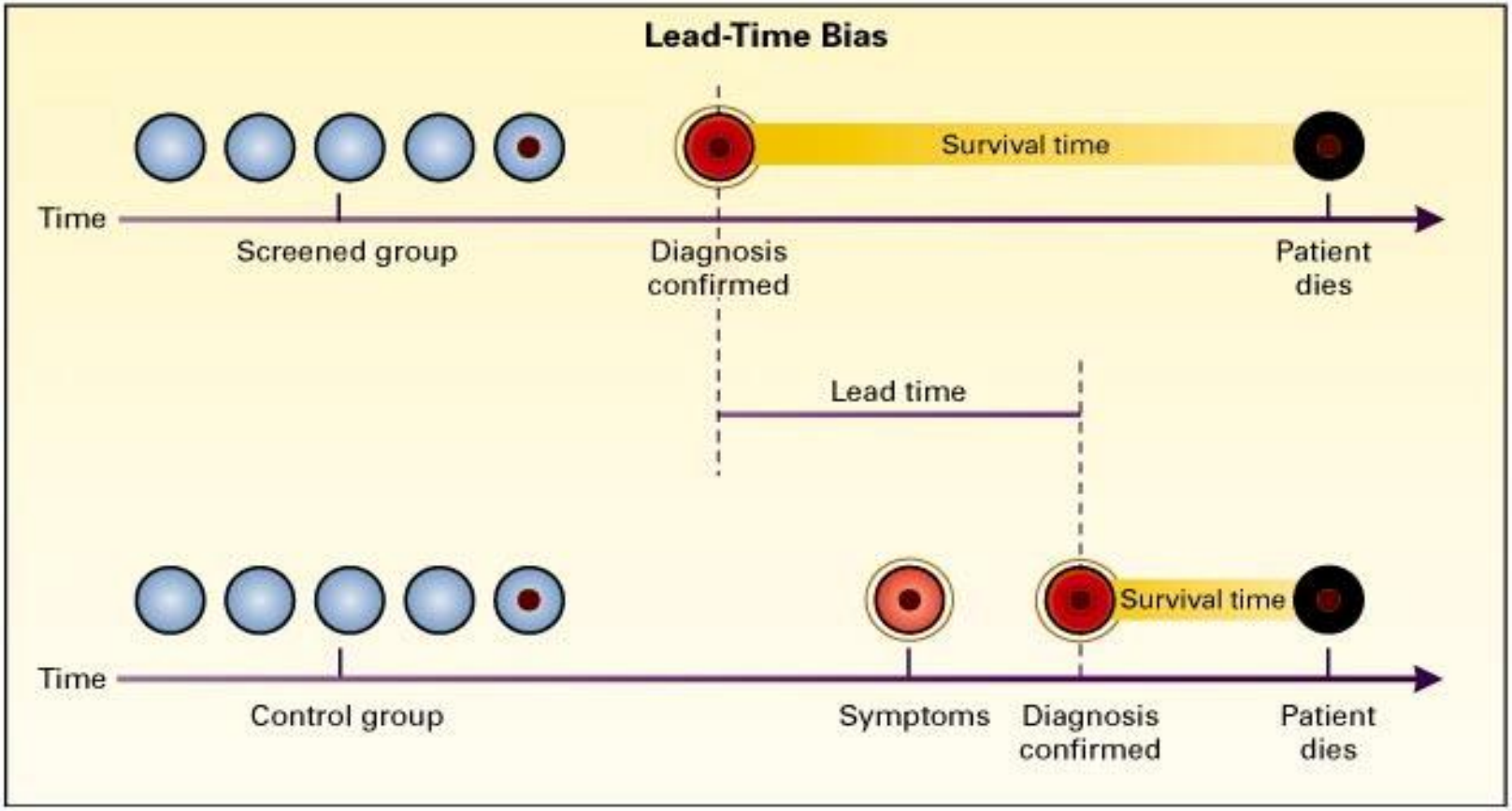
Lung Cancer Screening

- Seventy-five percent present with symptoms not amenable to cure. Five year survival overall 16%
- Prevention more effective than treatment
- Outcome related to stage at diagnosis: 60% five year survival Stage I NSCC; 5% stage IV

Screening Biases

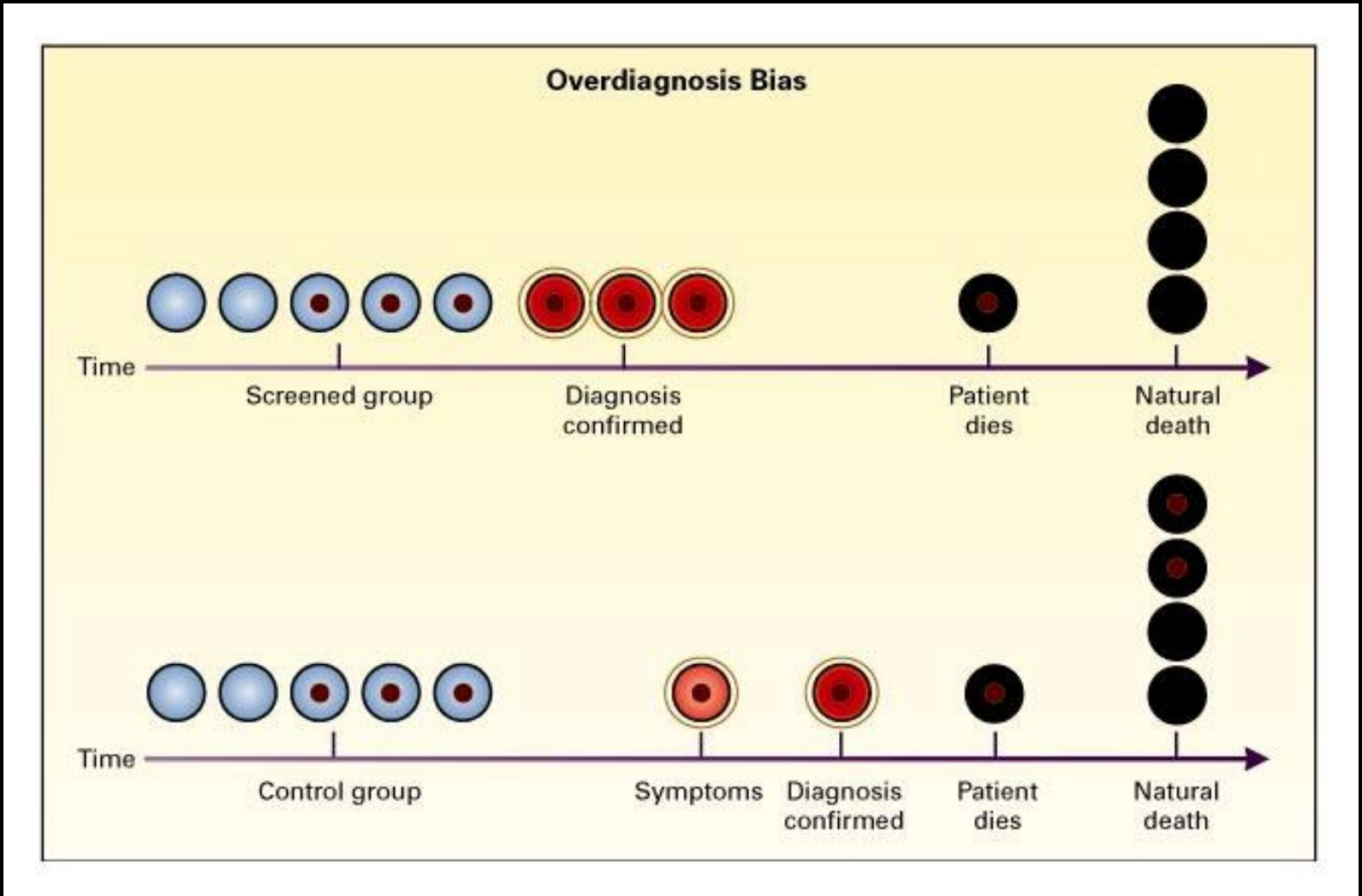
- Lead time
- Overdiagnosis
- Length time
- Volunteer

Lead-Time Bias.



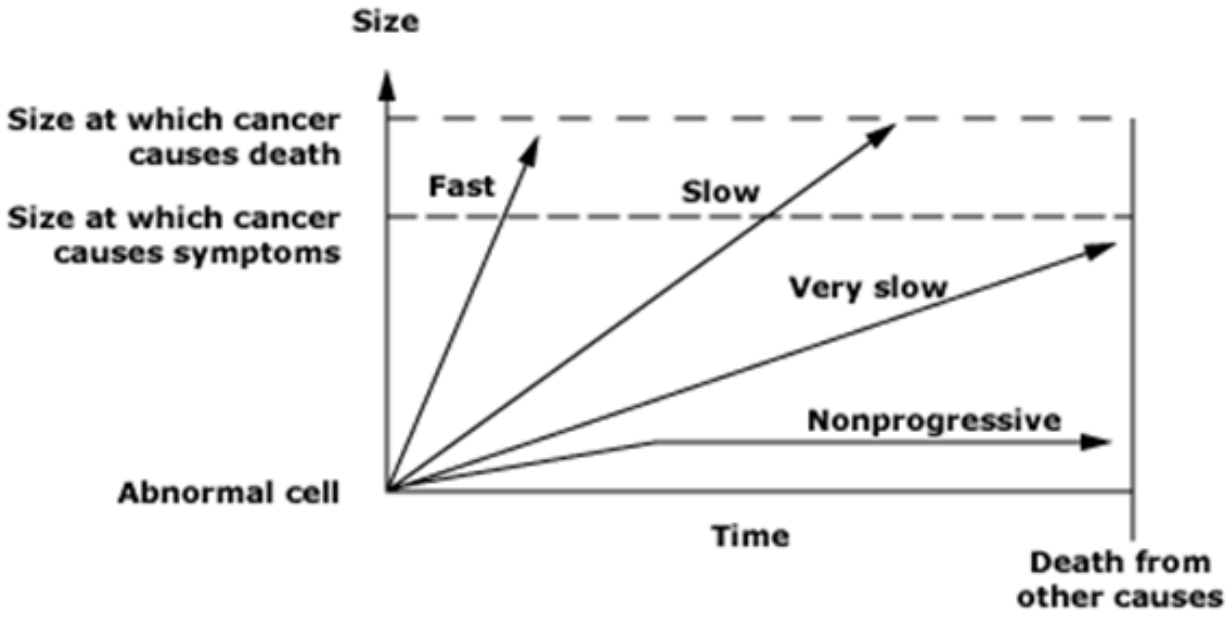
Patz EF Jr et al. N Engl J Med 2000;343:1627-1633.

Overdiagnosis Bias.



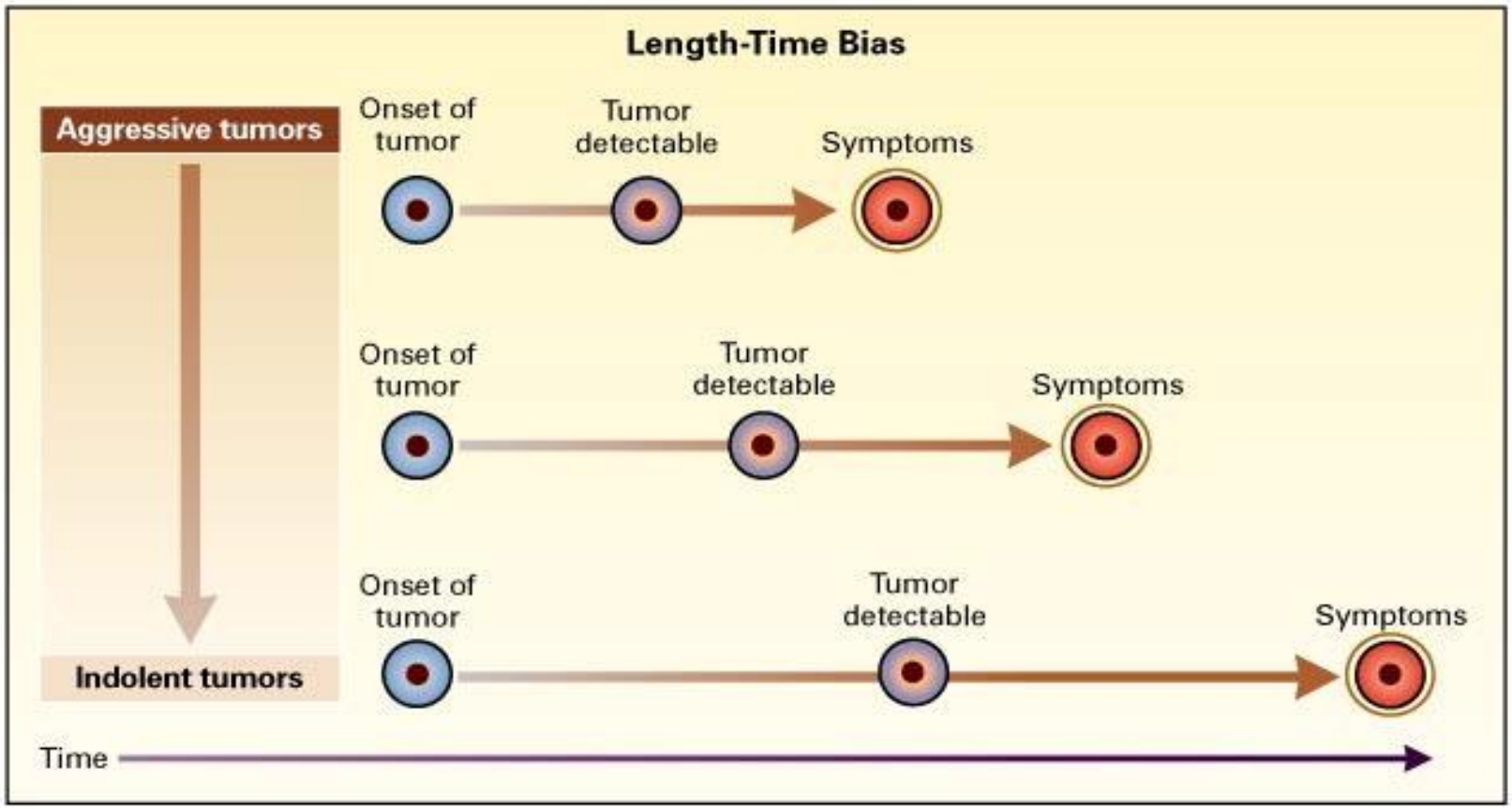
Patz EF Jr et al. N Engl J Med 2000;343:1627-1633.

Mechanism of overdiagnosis in cancer screening



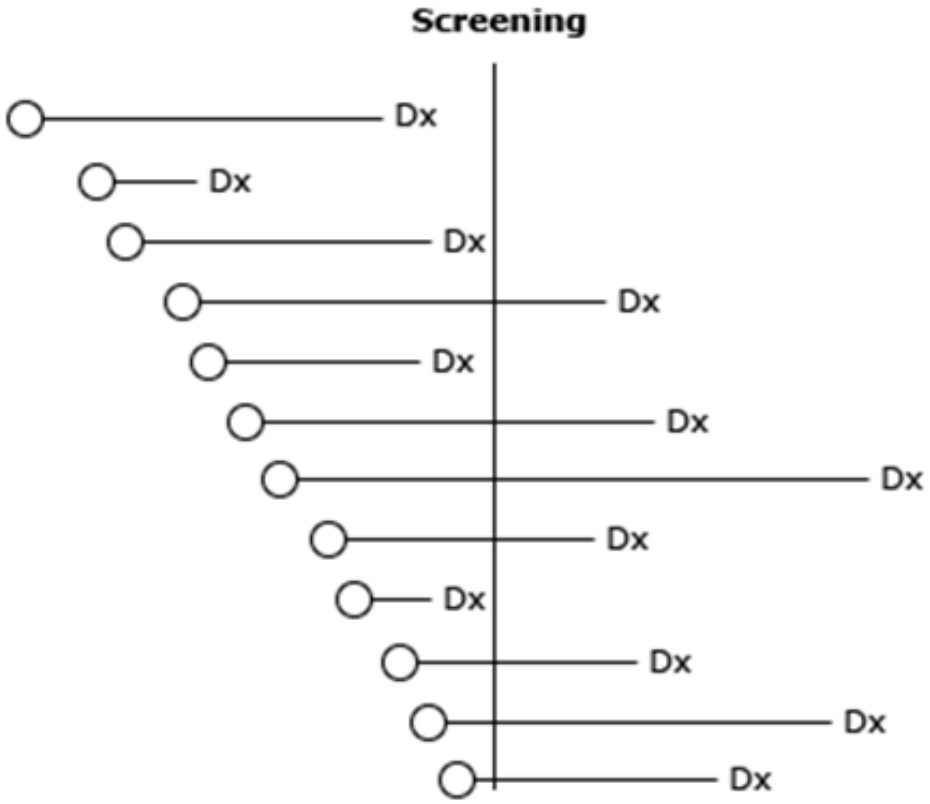
Note that nonprogressive, as well as some very slow growing, cancers will never cause clinical harm. When these cancers are found on screening, overdiagnosis has occurred. Overdiagnosis is an extreme form of length-time bias.

Length-Time Bias.



Patz EF Jr et al. N Engl J Med 2000;343:1627-1633.

Length-time bias



Cases that progress rapidly from onset (O) to symptoms and diagnosis (Dx) are less likely to be detected during a screening examination.

Volunteer Bias

- Volunteers may not represent general population
- May volunteer because they have the condition
- May volunteer because health conscious and therefore at lower risk

Lung Cancer Screening – CT- previous paradigm

- Nodules found, but with op. mort. 3.8% for pulmonary wedge resection in community hosp., the mortality benefit of CT screening for unselected patients not yet clear. Eight/39 were surgeries for benign disease

Swensen et al Radiology 226:756-761, 2003

Harms of Screening

- Abnormalities that require further evaluation, mostly benign nodules (96% false +, i.e. no cancer and 11% led to invasive study
- Radiation may independently lead to risk of cancer
- Prolonged f/u leads to anxiety
- Some indolent cancers may fall into overdiagnosis catagory

Lung Cancer Screening- CT

- National Lung Screening Trial (NLST) reported 20% fewer lung cancer deaths among trial participants screened with low-dose helical CT compared with those screened with CXR*. All cause mortality 7% lower in screened group.

*National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011; 365: 395.

Definitions/clarification

- Spiral = Helical = Multidetector – all synonyms
- Faster, lower radiation dose
- 2.5 mm slices routinely
- Less volume averaging
- Less mis-registration due to fast speed

NLST

- 53,454 high risk persons: 55-74y.o., 30 pk yr smokers; smoking or quit <15 yrs.
- Nodules > or = 4mm.
- False + 96.4 and 94.5 for CT and CXR respectively.
- Surgery in 297 of CT and 121 of CXR; complication rate low, 1.4 % and 1.6 % respectively.

What to Do?

- Radiation effects of multiple scans; surgical complications among patients who do not have cancer; risks from other evaluations such as liver or kidney lesions.
- Screening CT not currently covered by all insurances; Medicare reimburses $300 for non-contrast helical CT.
- But now the US Preventative Services Task Force as well as ASCO and ATS are recommending CT screening for the group described in the NLST

What to Do?

- Ninety-four million current and former smokers in US at risk for lung cancer.
- But what to do about non-smokers?
- Risk stratification and targeting populations is on-going*

*International Early Cancer Action Program Investigators. Survival of patients with Stage I Lung Cancer detected on CT Screening. NEnglJMed 2006; 355:1763

Prevalence of Cigarette Smoking

- There are 1.3 billion tobacco smokers globally per WHO estimates
  - 47% of men and 12% of women are smokers worldwide
- 45 million adults (20.9% of adults) in the United States are current cigarette smokers
  - 23.4% of all males, 18.5% of all females
  - Cigarette smoking has declined by almost 50% since 1965 – reflecting the efforts of the Surgeon General and other public health programs

1. WHO Tobacco Free Initiative. *Tobacco and Poverty, A Vicious Circle*. 2004. 2. Talwar A et al. *Med Clin N Am*. 2004;88:1517-1534. 3. CDC. *MMWR*. 2005;54:1121-1124. 4. CDC *Sustained State Programs for Tobacco Control*. 2004. 5. CDC. The 2004 Surgeon General's Report. *The Health Consequences of Smoking*. 2004.

Effective Treatment Components

- **Counseling**
- **Pharmacotherapy**
- **Systems interventions**

Fiore et al. *Treating Tobacco Use and Dependence. Clinical Practice Guideline.* Rockville, MD: US Department of Health and Human Services, Public Health Service. June 2000.

Key Counseling Messages

- Quit date
- Past quit experience
- Anticipate challenges
- Other smokers in household
- Alcohol

Fiore et al. *Treating Tobacco Use and Dependence. Clinical Practice Guideline.* Rockville, MD: US Department of Health and Human Services, Public Health Service. June 2000.

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Who Should Receive Pharmacotherapy?

- **All smokers trying to quit except**
  - When contraindicated
  - Patients smoking <10 cigarettes/day
  - Pregnant or breastfeeding women
  - Adolescent smokers

Fiore et al. *Treating Tobacco Use and Dependence. Clinical Practice Guideline.* Rockville, MD: US Department of Health and Human Services, Public Health Service. June 2000.

Introduction

- Nicotine replacement therapies (NRT) were the first medications approved by the FDA for smoking cessation followed by bupropion SR
- There are currently 5 forms of NRT available in the U.S.:
  - Nicotine gum – OTC (2 mg approved as Rx 1984; 4 mg Rx 1992; OTC 1996)
  - Nicotine patch – Rx and OTC (approved as Rx 1991; OTC 1996)
  - Nicotine nasal spray – Rx (1996)
  - Nicotine inhaler – Rx (1997)
  - Nicotine lozenge – OTC (2002)
- Bupropion SR received an indication as an aid to smoking cessation (1997)
- It has been nearly a decade since approval of a new prescription pharmacotherapy as an aid for smoking cessation

1. Cummings KM et al. *Annu Rev Public Health.* 2005;26:583–99.
2. FDA Center for Drug Evaluation and Research. Available at: http://www.fda.gov/cder. Accessed 6/9/2006.

A Meta-Analysis of Smoking Cessation Pharmacotherapies:
Majority Used 7-Day Point-Prevalence Abstinence Rates* (at ~6 Months)

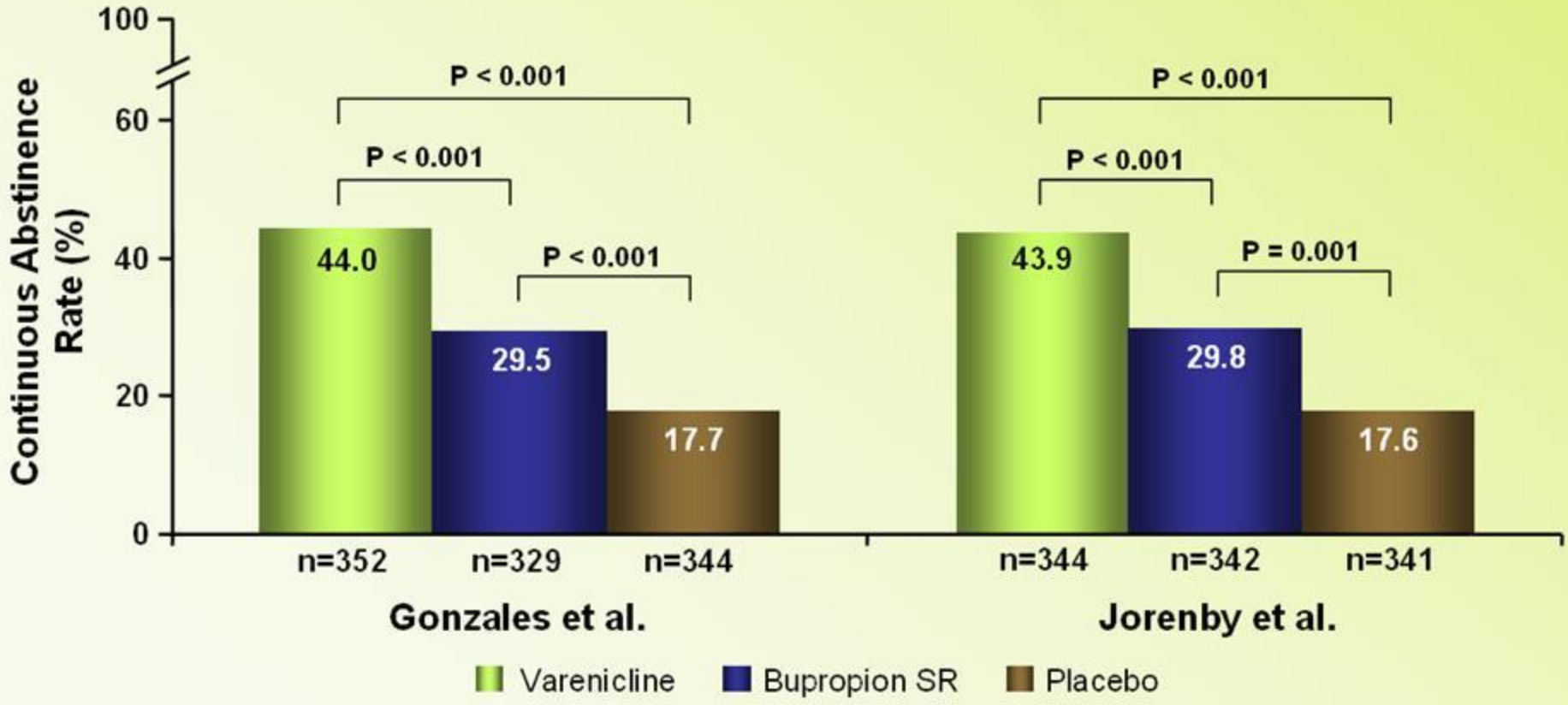
Cessation Pharmacotherapy	Number of Studies Included	Estimated Abstinence Rate (95%CI)	Estimated Odds Ratio (95%CI)
Nicotine gum	13	23.7 (20.6, 26.7)	1.5 (1.3,1.8)
vs Placebo		17.1	--
Nicotine patch	27	17.7 (16.0, 19.5)	1.9 (1.7, 2.2)
vs Placebo		10.0	--
Nicotine inhaler	4	22.8 (16.4, 29.2)	2.5 (1.7, 3.6)
vs Placebo		10.5	--
Nicotine nasal spray	3	30.5 (21.8, 39.2)	2.7 (1.8, 4.1)
vs Placebo		13.9	--
Bupropion SR	2	30.5 (23.2, 37.8)	2.1 (1.5, 3.0)
vs Placebo		17.3	--

- Based on odds ratios, NRT and bupropion SR are twice as effective as placebo
- Estimated abstinence rates were predominantly based on 7-day point-prevalence data at 6 months

*A commonly used primary efficacy measure in past clinical trials

Adapted from Fiore MC et al. *U.S. DHHS, U.S. Public Health Service*, 2000.

Chantix™ (varenicline) Phase 3 Studies: Efficacy Measurements: CO-Confirmed 4-Wk Continuous Abstinence Rates Wks 9–12

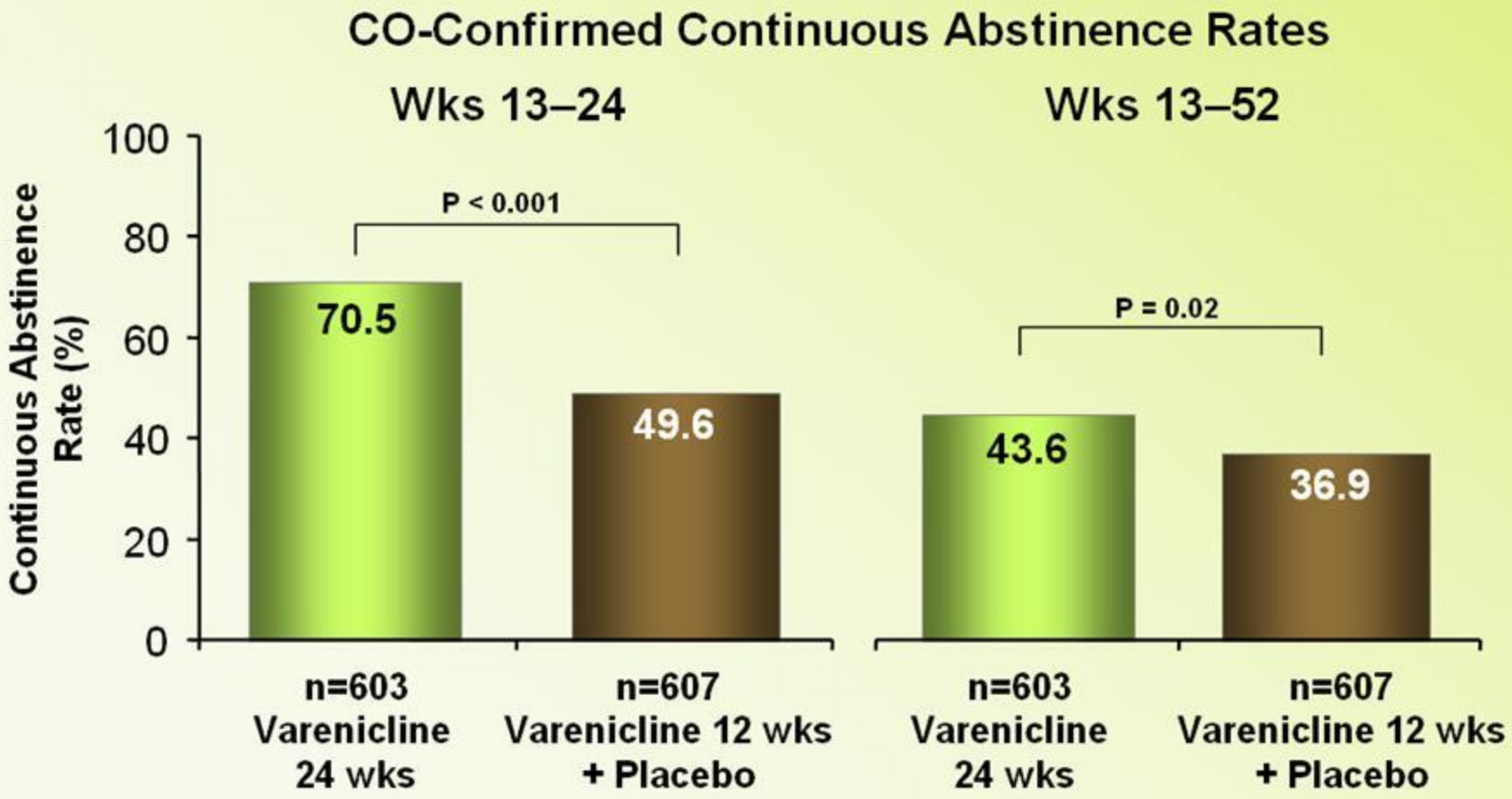


The 9-12 week Continuous Abstinence Rate is defined as the percentage of subjects who abstained from smoking (not even a puff) from Week 9 through 12 of the study as confirmed by both subject self-report and by end-expiratory carbon monoxide (CO) measurement

The most frequently reported adverse events (>10%) with Chantix were nausea, headache, insomnia, and abnormal dreams

1. Gonzalez D et al. *JAMA*. 2006;296:47-55. 2. Jorenby DE et al. *JAMA*. 2006;296:56-63.

Tonstad Maintenance of Abstinence in Quitters Who had Previously Received 12 Weeks of Chantix™ (varenicline) Therapy



The most frequently reported adverse events (>10%) with Chantix were nausea, headache, insomnia, and abnormal dreams

1. Tonstad S et al. *JAMA*. 2006;296:64-71.

Pharmacotherapy Not Recommended in USPHS Guideline

- **SSRIs and tricyclic antidepressants (other than nortriptyline)**
- **Anxiolytics, benzodiazepines, beta blockers**
- **Silver acetate**
- **Mecamylamine**

Fiore et al. *Treating Tobacco Use and Dependence. Clinical Practice Guideline.* Rockville, MD: US Department of Health and Human Services, Public Health Service. June 2000.

Pharmacotherapy

Factors to Consider

- Contraindications
- Patient preference
- Previous patient experience
- Clinician familiarity with medication

Fiore et al. *Treating Tobacco Use and Dependence. Clinical Practice Guideline.* Rockville, MD: US Department of Health and Human Services, Public Health Service. June 2000.

Effective Treatment Components

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The 5 As

For Patients Willing to Quit

- **ASK** about tobacco use
- **ADVISE** to quit
- **ASSESS** willingness to make a quit attempt
- **ASSIST** in quit attempt
- **ARRANGE** for follow-up

Fiore et al. *Treating Tobacco Use and Dependence. Clinical Practice Guideline.* Rockville, MD: US Department of Health and Human Services, Public Health Service. June 2000.

The 5 Rs

To Motivate Patients Unwilling to Quit at This Time

- **RELEVANCE:** tailor advice and discussion to each patient
- **RISKS:** outline risks of continued smoking
- **REWARDS:** outline the benefits of quitting
- **ROADBLOCKS:** identify barriers to quitting
- **REPETITION:** reinforce the motivational message at every visit

Fiore et al. *Treating Tobacco Use and Dependence. Clinical Practice Guideline.* Rockville, MD: US Department of Health and Human Services, Public Health Service. June 2000.

QUITTING TAKES HARD WORK AND A LOT OF EFFORT, BUT—

You Can Quit Smoking

SUPPORT AND ADVICE FROM YOUR CLINICIAN

A PERSONALIZED QUIT PLAN FOR: _____

WANT TO QUIT?

- Nicotine is a powerful addiction.
- Quitting is hard, but don't give up.
- Many people try 2 or 3 times before they quit for good.
- Each time you try to quit, the more likely you will be to succeed.

GOOD REASONS FOR QUITTING:

- You will live longer and live healthier.
- The people you live with, especially your children, will be healthier.
- You will have more energy and breathe easier.
- You will lower your risk of heart attack, stroke, or cancer.

TIPS TO HELP YOU QUIT:

- Get rid of ALL cigarettes and ashtrays in your home, car, or workplace.
- Ask your family, friends, and coworkers for support.
- Stay in nonsmoking areas.
- Breathe in deeply when you feel the urge to smoke.
- Keep yourself busy.
- Reward yourself often.

QUIT AND SAVE YOURSELF MONEY:

- At $3.00 per pack, if you smoke 1 pack per day, you will save $1,100 each year and $11,000 in 10 years.
- What else could you do with this money?

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Public Health Service
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(over)

Five Keys for Quitting

1. GET READY.

- Set a quit date and stick to it—not even a single puff!
- Think about past quit attempts. What worked and what did not?

2. GET SUPPORT AND ENCOURAGEMENT.

- Tell your family, friends, and coworkers you are quitting.
- Talk to your doctor or other health care provider.
- Get group, individual, or telephone counseling.

3. LEARN NEW SKILLS AND BEHAVIORS.

- When you first try to quit, change your routine.
- Reduce stress.
- Distract yourself from urges to smoke.
- Plan something enjoyable to do every day.
- Drink a lot of water and other fluids.

4. GET MEDICATION AND USE IT CORRECTLY.

- Talk with your health care provider about which medication will work best for you:
- Bupropion SR—available by prescription.
- Nicotine gum—available over-the-counter.
- Nicotine inhaler—available by prescription.
- Nicotine nasal spray—available by prescription.
- Nicotine patch—available over-the-counter.

5. BE PREPARED FOR RELAPSE OR DIFFICULT SITUATIONS.

- Avoid alcohol.
- Be careful around other smokers.
- Improve your mood in ways other than smoking.
- Eat a healthy diet and stay active.

Your Quit Plan

1. YOUR QUIT DATE:

_____

_____

2. WHO CAN HELP YOU:

_____

_____

3. SKILLS AND BEHAVIORS YOU CAN USE:

_____

_____

4. YOUR MEDICATION PLAN:

Medications: _____

Instructions: _____

_____

5. HOW WILL YOU PREPARE?

_____

_____

_____

Quitting smoking is hard. Be prepared for challenges, especially in the first few weeks.

Followup plan: _____

Other information: _____

Referral: _____

_____

Clinician Date

U.S. Government Printing Office: 2000 — 523-252

USPHS Guideline Web Site

www.surgeongeneral.gov/tobacco

Electronic Cigarettes

- Battery operated
- May contain nicotine and/or flavorings
- Atomizer creates a vapor cloud of whatever liquid contained in cartridge
- FDA has warned against due to lack of regulation of nicotine and possible carcinogens detected
- DMN 9/2/13 article noting e-cigarettes mimicking tobacco industry marketing