Prevention/Chemoprevention

Yuesheng Zhang

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Department of Cancer Prevention and Control

yuesheng.zhang@roswellpark.org

Topics to cover:

1. Why cancer prevention?
2. What is cancer prevention?
3. What is cancer chemoprevention?
4. The current status of cancer chemoprevention

Cancer Rates Are Increasing Globally

14.1 million new cases; 8.2 million cancer deaths; 32.6 million people living with cancer (within 5 years of diagnosis).

The most commonly diagnosed: lung (13.0%), breast (11.9%), colorectum (9.7%).
The most common cause to death: lung (19.4%), liver (9.1%) , stomach (8.8%).

About 30% of cancer deaths are due to five leading behavioral and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, and alcohol use.

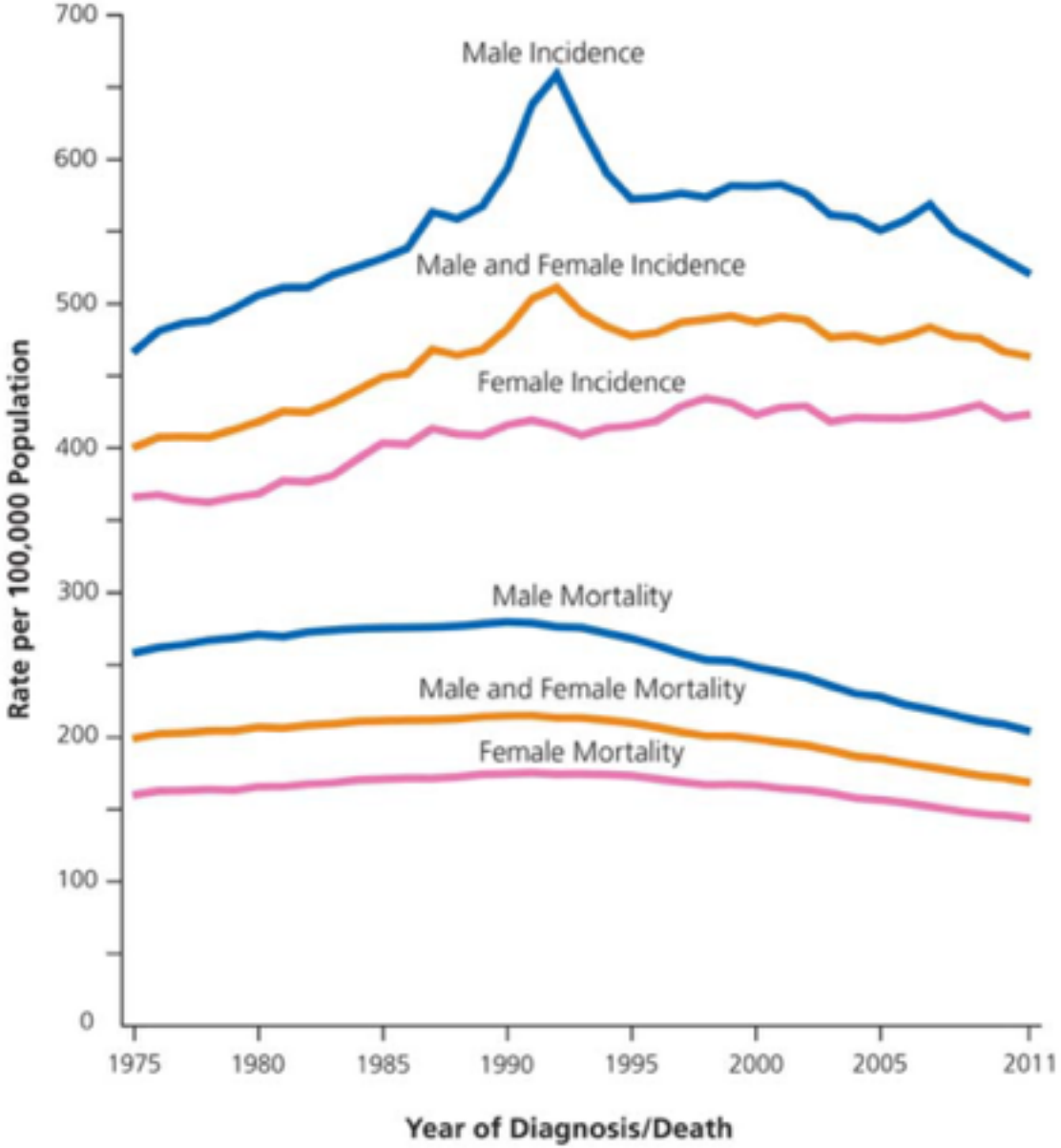
Tobacco use causes over 20% of global cancer deaths and about 70% of global lung cancer deaths

About 65% of all cancer deaths occurred in low- and middle-income countries.

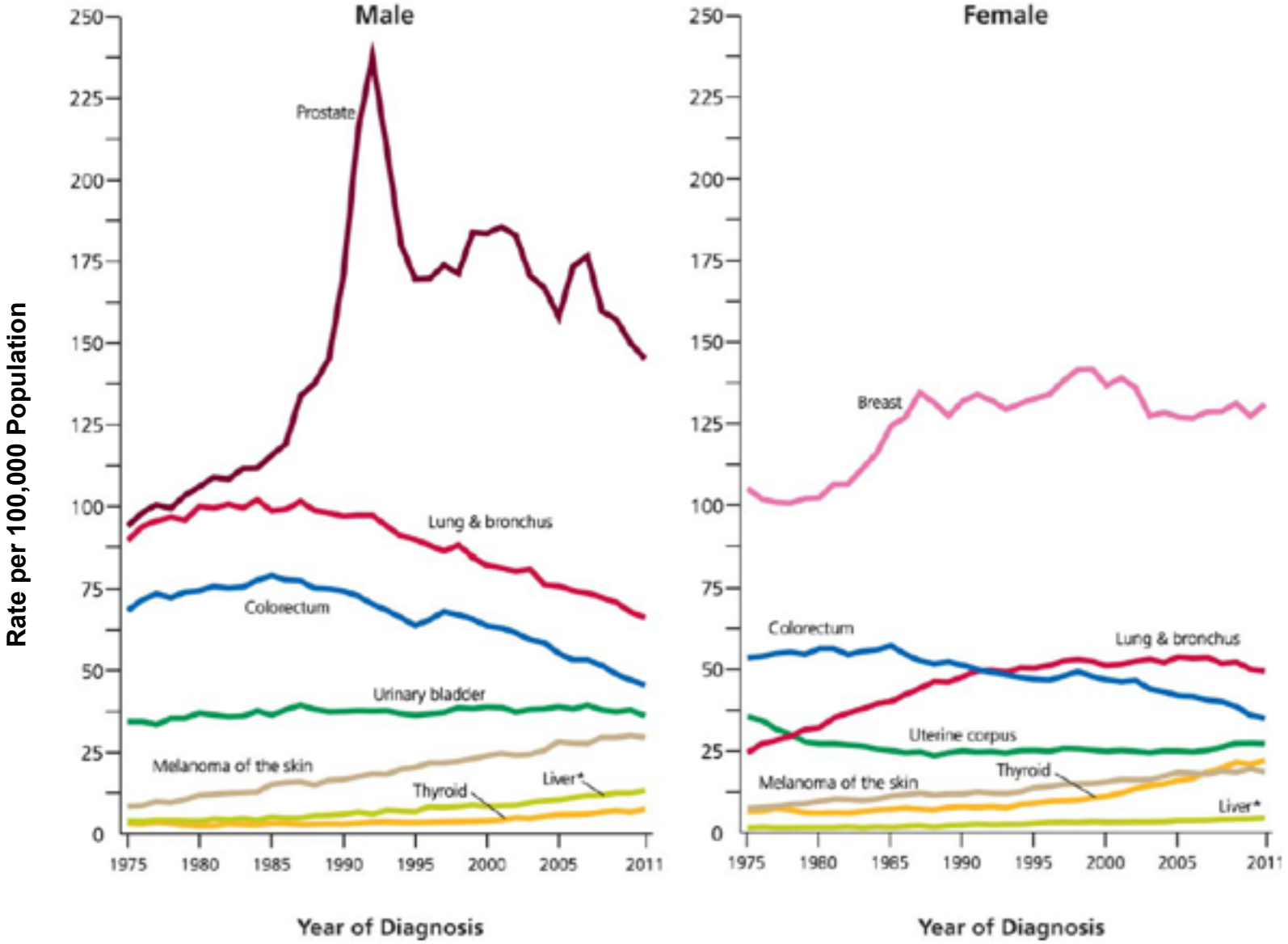
Projections for 2030: 21.7 million new cases, 13.1 million deaths.

WHO GLOBOCAN2012

Trends in Cancer Incidence and Mortality Rates in US, 1975 - 2011

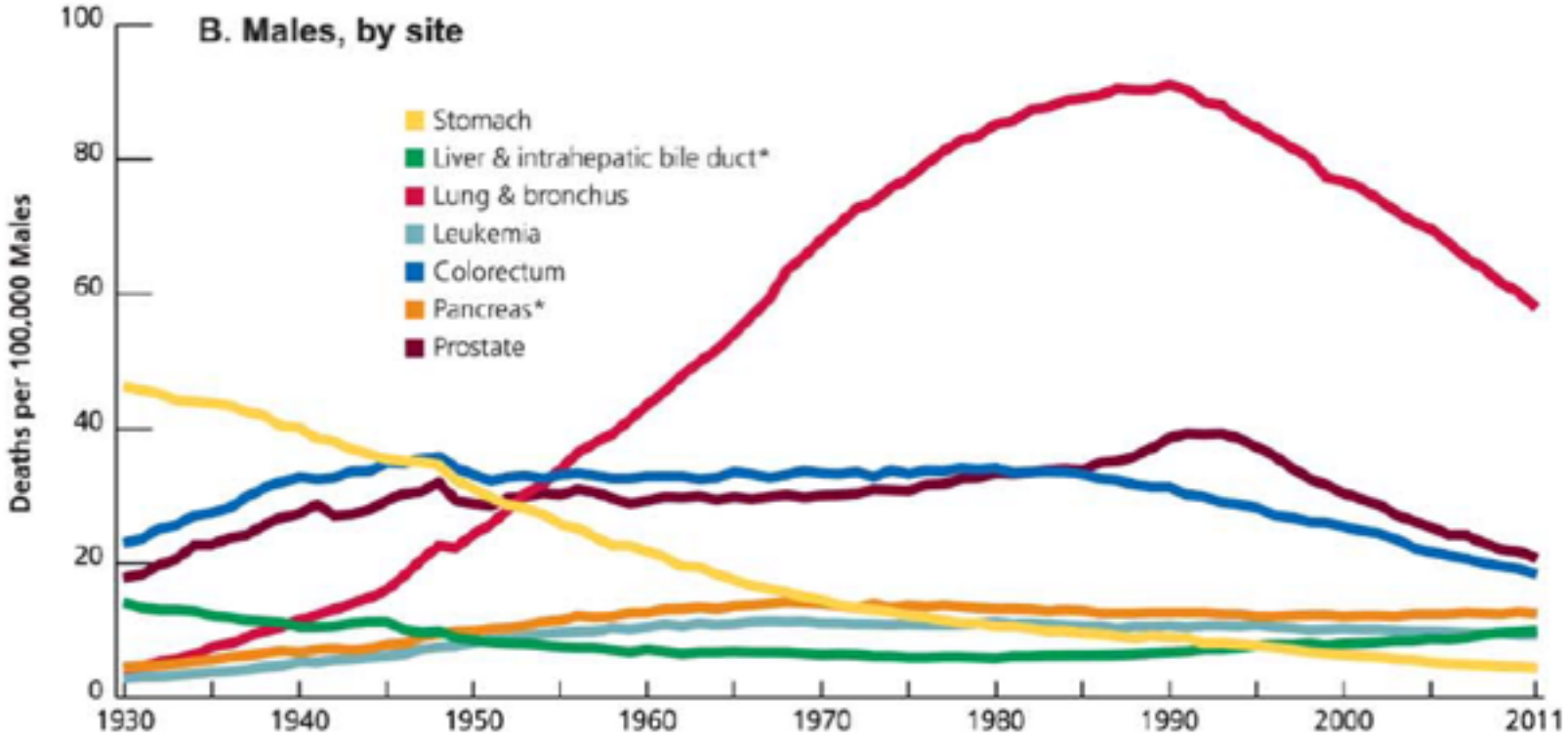


CA Cancer J Clin 2015;65:5-29.



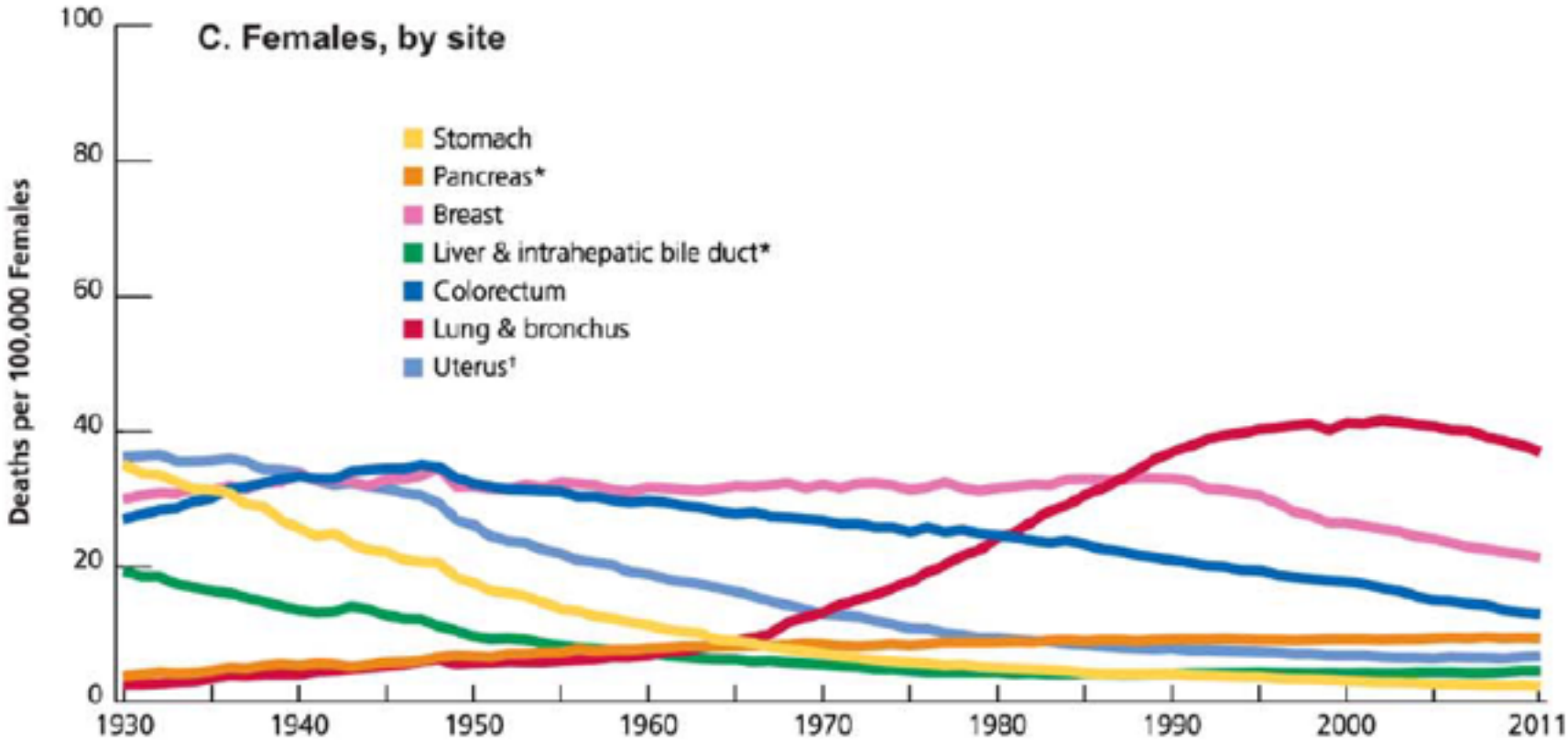
Annul Age-Adjusted Cancer Incidence Rates in the United States

CA Cancer J Clin 2015; 65: 5-29



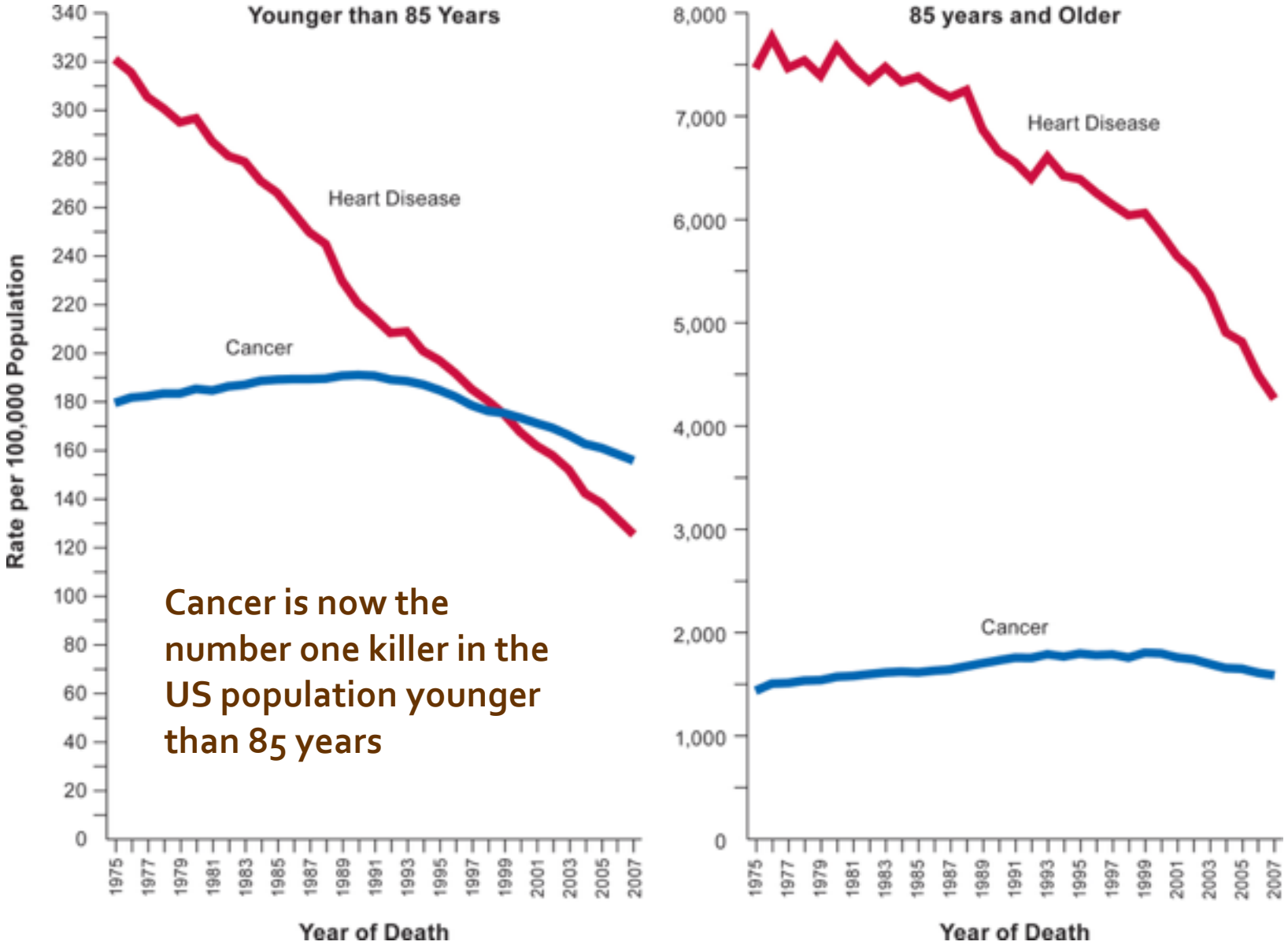
Annual Age-Adjusted Cancer Death Rates Among Males in the United States

CA Cancer J Clin 2015; 65: 5-29



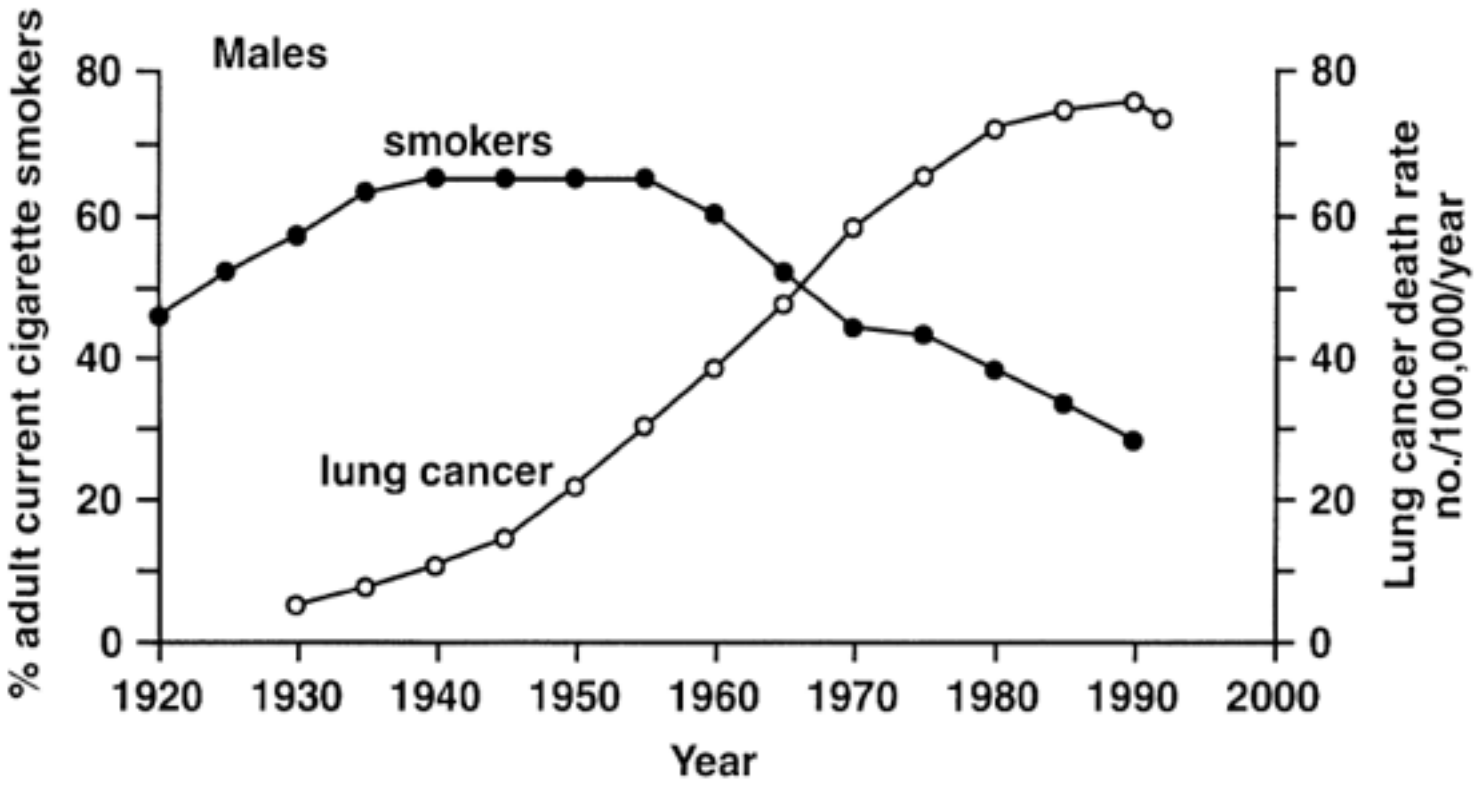
Annul Age-Adjusted Cancer Death Rates Among Females in the United States

CA Cancer J Clin 2015; 65: 5-29



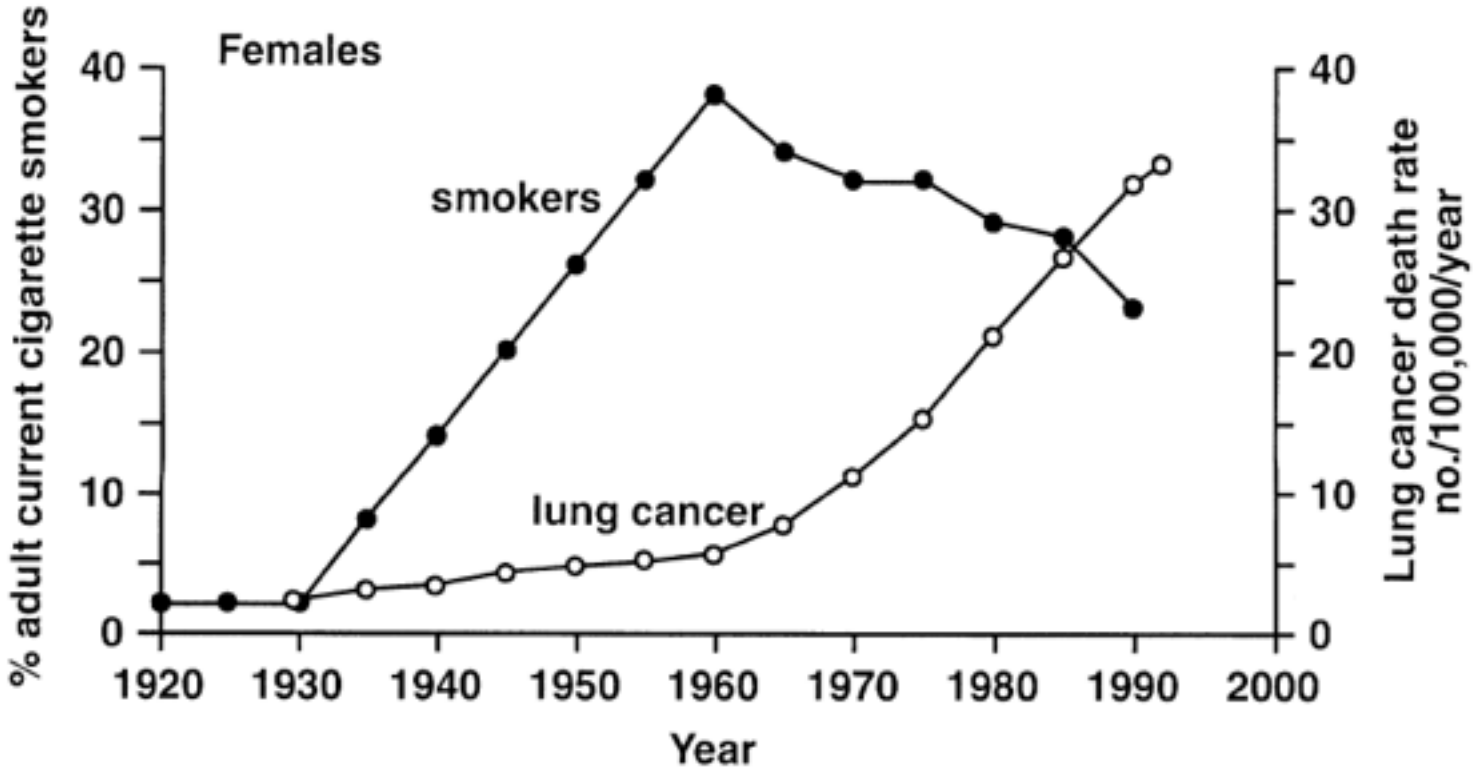
Cancer is now the number one killer in the US population younger than 85 years

CA Cancer J Clin 2011; 61: 212-236



Trends in prevalence of cigarette smoking among US men aged 18 years or older and age-adjusted lung cancer mortality rate

Chest 1997; 111: 1414-1416



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Chest 1997; 111: 1414-1416

Once cancer is diagnosed…

- For patients with metastatic cancer, even the most advanced treatment methods often do not save their lives.

- In patients with less advanced cancer, treatment extracts a high morbidity and causes tremendous social and economic devastation.

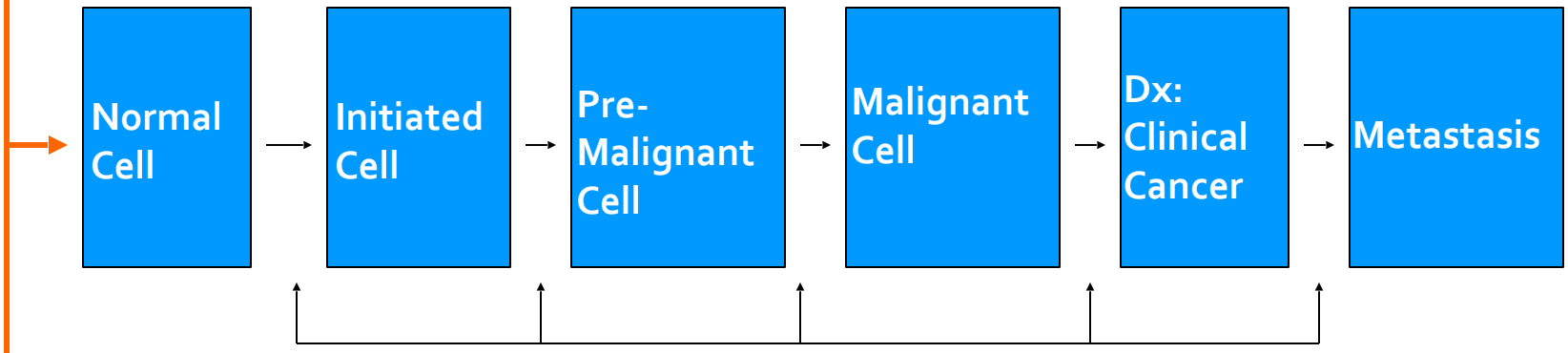
Cancer cells are extremely difficult to eliminate

- Unlimited replicative potential
- Self sufficiency in growth signals
- Insensitivity to anti-growth signals
- Evading apoptosis
- Sustained angiogenesis
- Tissue invasion and metastasis

Carcinogenesis

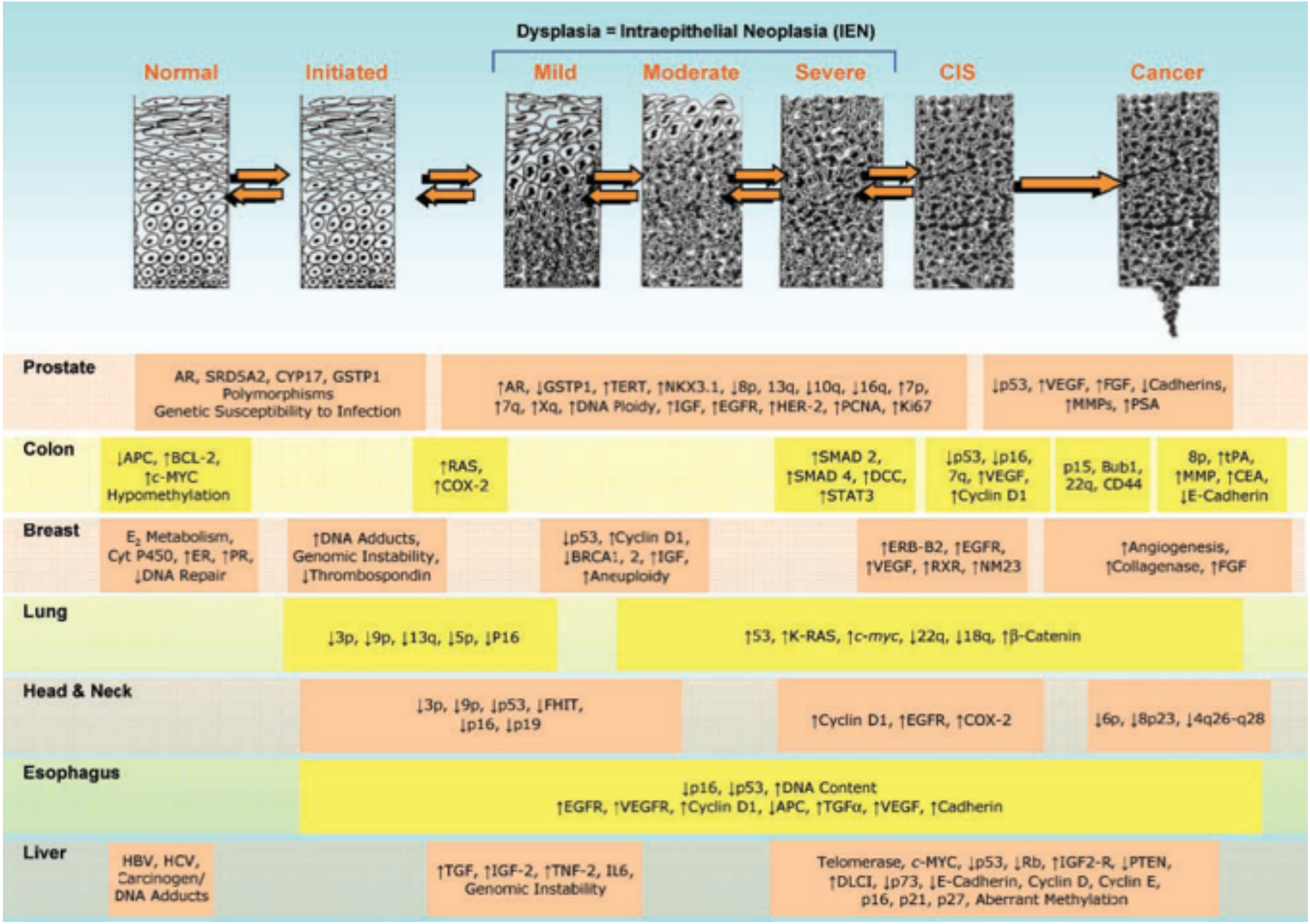
Clonal selection and expansion (multiyear, multistage and multipath)

Chemicals
Radiation
Biological agents
Random



Genetic Changes

Activation of protooncogenes
Inactivation of tumor suppressor genes
Disturbance of proliferation and apoptosis



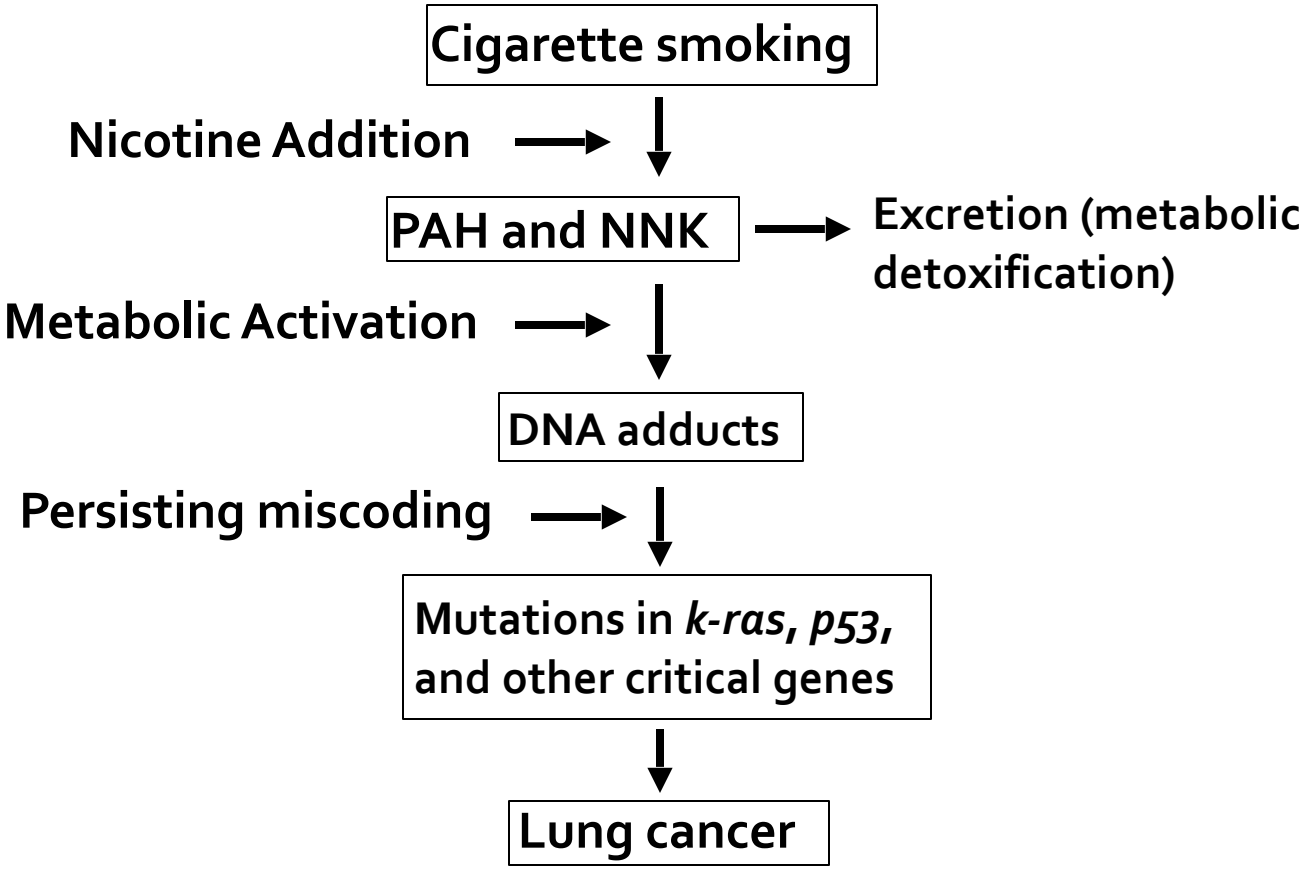
Clin Cancer Res 2006; 12: 3661-3697

Cancer Can Be Prevented

Cancer-causing factors:

- **What you eat: carcinogen-contaminated foods.**
- **What you drink: alcohol, carcinogen-contaminated water.**
- **What you inhale: tobacco smoke, polluted air.**
- **Sunshine: UVA and UVB.**
- **Medicine: certain drugs, radiation therapy.**
- **Infection: hepatitis B and C virus, human papillomavirus, Epstein-Barr virus, *Helicabecter pylori*, *Shistosoma Haematobium*.**
- **Germline mutations.**
- **Random mutations during DNA replication in stem cells.**

Someone who has smoked all their life has a lung-cancer risk 20-30 times greater than a non-smoker



PAH, polynuclear aromatic hydrocarbons

NNK, 4-(methylnitrosamino-1-(3-pyridil)-1-butanone

Effects of Smoking Cessation on Lung Cancer Risk

Time since stopping	Relative risk	
	Men	Women
Current smokers	1.00	1.00
2-9 years	0.66*	0.41*
10-19 years	0.27*	0.19*
20-29 years	0.17*	0.08*
>30 years	0.08*	0.13*
Non-smokers	0.04*	0.11*

* $p<0.05$

Tyczynski et al., Lancet Oncology 4, 45-55, 2003

In addition to avoiding exposure to carcinogens, cancer risk can be reduced by employing intervention measures.

Human Papillomavirus (HPV) Vaccine Prevents Cervical Cancer

N Engl J Med 2007;356:1915-1927.

Background and Study Design: HPV types 16 and 18 cause approximately 70% of cervical cancers. In a randomized, double-blinded trial involving women of 15-26 years of age (without prior HPV infection), a quadrivalent vaccine against HPV types 6, 11, 16 and 18, was administered at day 1, month 2, month 6, and subjects were then followed for 3 years.

Cervical Intraepithelial Neoplasia or Adenocarcinoma *In Situ* Associated with HPV-16 or HPV-18

Vaccine Group		Placebo Group	
Total Subjects	No. of Cases	Total Subjects	No. of Cases
5305	1	5260	42

The Prostate Cancer Prevention Trial (PCPT)

The Finasteride Prevents Prostate Cancer Trial

N Engl J Med 2013;369:603-610

Background: Androgens are involved in prostate cancer development. Finasteride, an inhibitor of 5α-reductase, inhibits the conversion of testosterone to dihydrotestosterone, the main androgen in the prostate.

Design: Finasteride (5 mg/day) was given to men ≥55 years for 7 years.

Prostate Cancer			
Finasteride Group		Placebo Group	
Total Subjects	No. of Cases	Total Subjects	No. of Cases
9423	989	9457	1412

Finasteride reduces prostate cancer incidence by 30% (P<0.01), but high-grade cancer (Gleason score, 7-10) is more common in the finasteride group (relative risk, 1.17; P=0.05). This study cost over $70m.

Celecoxib Reduces Colon Cancer Risk

Background: Cox-2 is involved in colon cancer development. Celecoxib is a selective Cox-2 inhibitor.

Design: Celecoxib was given at 16 mg/kg daily for 3 months to children of ages 10-14 years with APC gene mutations and/or colorectal adenomas with a family history of familial adenomatous polyposis (FAP).

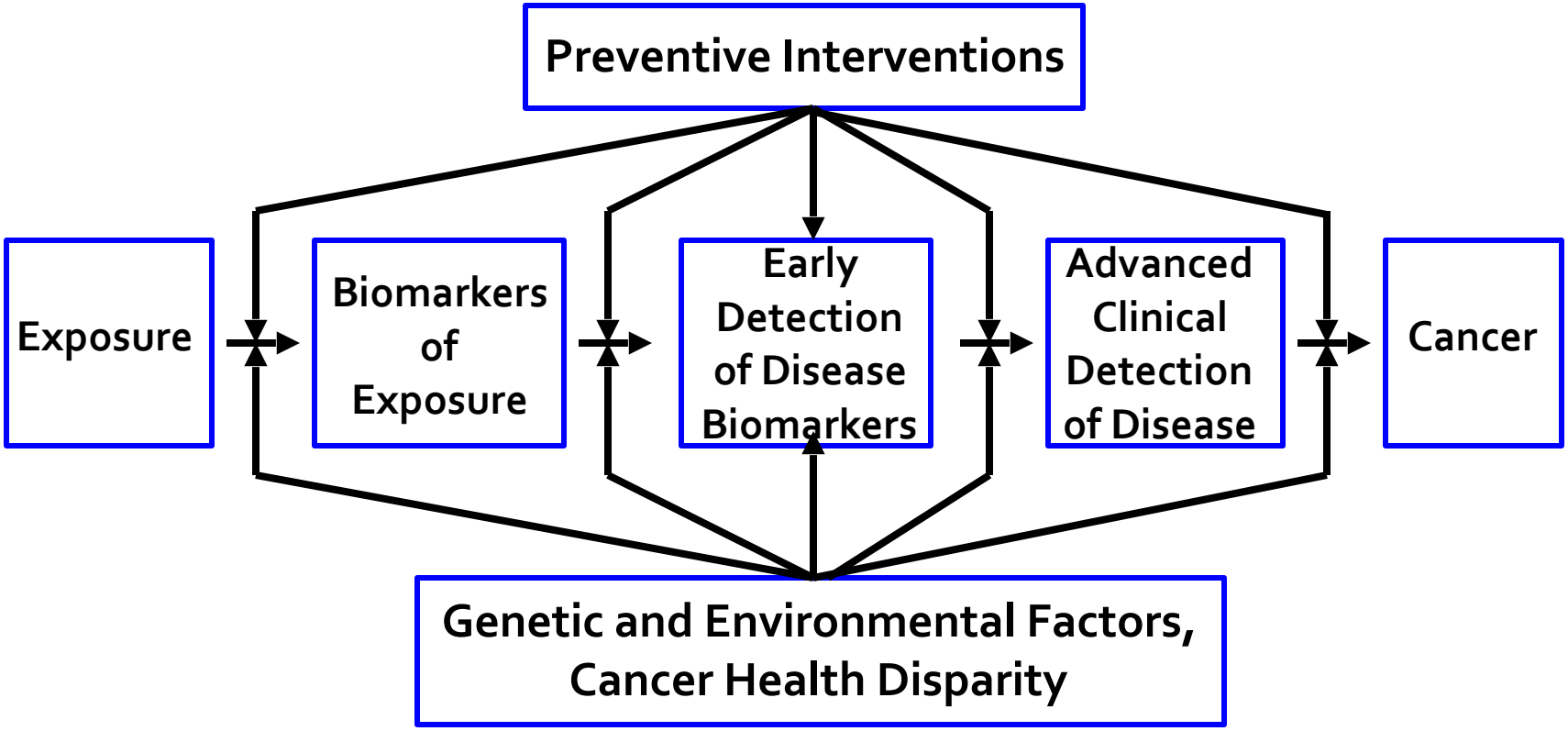
No. of polyps median (range)	Placebo	Celecoxib
Baseline	40 (21-68)	43 (8 to 68)
End of study	65 (26-122)	16.5 (6 to 38)
Change in polyp number	17.5 (-5 to 63)	-17.5 (-2 to -48)
Percent change in polyp number	39.1 (-16.1 to 300)	-44.2* (-70.6 to -25.0)

6-4 patients/group. Celecoxib was well tolerated. *P = 0.01.

Am J Gastroenterol 2010;105:1437-1443

Several other studies show celecoxib or asperin prevents colon cancer, .e.g., *Cancer Preven Res 2009;2:310-321.* J Natl Cancer Inst 2009;101:256-266.

Paradigm of Cancer Prevention Research



Genetic and Environmental factors vs. cancer risk/prognosis

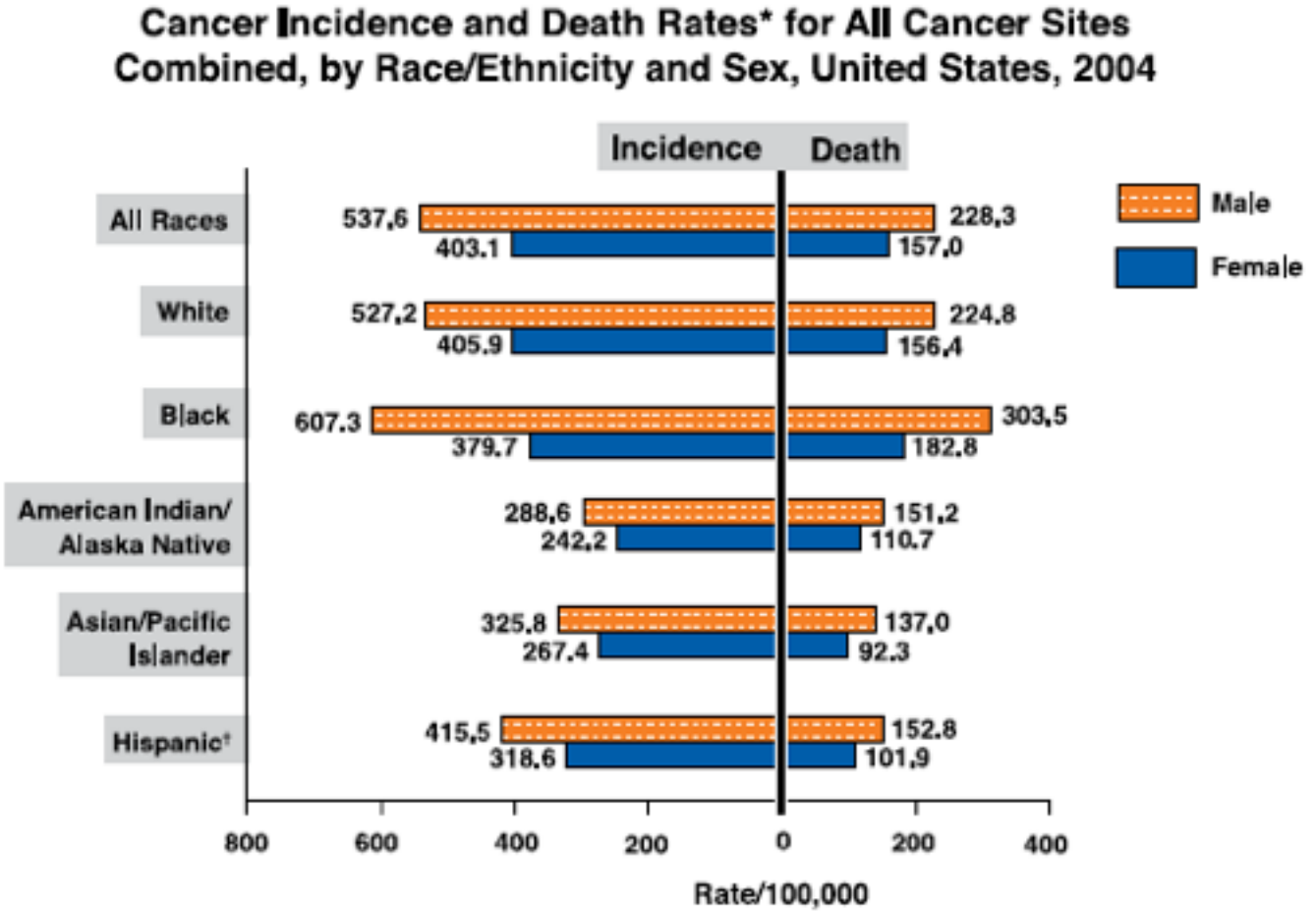
1. Genetic Changes: Analysis of SNP, haplotype or whole genome.

2. Environmental Factors: carcinogens, anticarcinogens, nutritional factors.

3. Gene and Environment Interaction.

Cancer Health Disparity Research

To identify and understand the factors that contribute to the disparities in cancer incidence, mortality or survival in relation to race/ethnicity.



United States Cancer Statistic: 2004 Incidence and Mortality

Factors that Contribute to Health Disparities in Cancer

1. Socioeconomic status (education, income, employment).
2. Access to and utilization of health care services (e.g., cancer screening, timely cancer diagnosis and treatment).
3. Behaviors (physical activity, diet, tobacco use).
4. Social environment (educational and economic opportunities, racial discrimination, neighborhood, and working conditions).
5. Exposure to carcinogens.

Detection

Exposure Biomarkers: **endogenous or exogenous agents and their metabolites or adducts in tissues or body products (e.g., carcinogen-DNA adducts).**

Susceptibility Biomarkers: **an indicator of a heritable ability of an individual to respond to the challenge of carcinogenic agent(s) or event(s) (e.g., GST-null and APC mutation).**

Cancer Biomarkers: **predict future cancer development or suggest a potential presence of cancer.**

Phenotypic biomarkers **(e.g., colorectal adenomas and actinic keratosis).**

Molecular biomarkers **(e.g., CA125, PSA).**

Cell-free DNA in blood and other specimens: **In 2014, FDA approved Cologuard, the first stool-based test that detects the presence of red blood cells and certain DNA mutations associated with colorectal cancer.**

Some of the American Cancer Society Guidelines for the Early Detection of Certain Cancers

Breast Cancer: Yearly mammogram at age ≥40; clinical breast exam about every 3 years at age ≥20 and every year at age ≥40.

Colon and Rectal Cancer: At age ≥50, flexible sigmoidoscopy every 5 years, colonoscopy every 10 years, yearly fecal occult blood test.

Cervical Cancer: Pap test every 3 years at age 21-29, Pap test every 5 years at age 30-65 plus HPV test.

Prostate Cancer: Used to be yearly PSA and digital rectal examination of the prostate at age ≥50, and men at higher risk (e.g., African-American) should begin testing at age ≥45. But now, "ACS believes that men should not be tested without learning about what we know and don't know about the risks and possible benefits of testing and treatment."

Preventive Interventions

- Vaccination.
- Weight Control.
- Life style change (physical excise, eating healthy and others).
- Chemoprevention.

Weight Control

68.5% of American adults and 31.8% of children/adolescents were overweight or obese (BMI ≥ 25-29.9 kg/m^2) in 2012-2012.

34.9% of American adults and 16.9% of children/adolescents were obese (BMI ≥ 30 kg/m^2) 2011-2012.

Overall, no significant changes in obesity prevalence in youth or adults between 2003-2004 and 2011-2012.

In 2001, experts concluded that cancers of the colon, breast, endometrium, esophagus, kidney and thyroid are associated with obesity.

Studies have also shown links between obesity and cancers of the gallbladder, ovaries, and pancreas.

Possible mechanisms include alterations of levels of sex hormones, sex-hormone binding globulin, and insulin and IGF-1.

JAMA 2014;311:806-814

Life Style Change – The Success Story of the New York State Smokers' Quitline (1-866-NY-Quits)

Established in January 2000 at RPCI

The Quitline received its millionth call in 2008.

The Quitline provided support to more than 75,000 smokers in 2013 alone.

There are approximately 2.4 million adult smokers in New York.

Cancer Chemoprevention

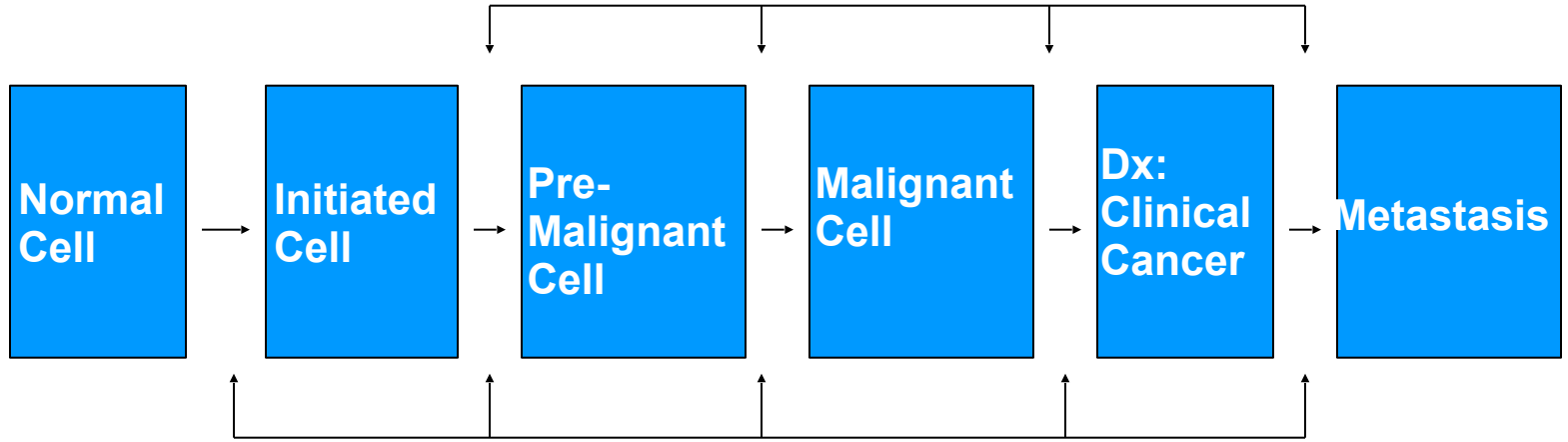
Interventions with pharmaceuticals, vitamins, minerals, biologics, or other chemicals to retard, block, or reverse the carcinogenic process - *Chemotherapy of Carcinogenesis, or to prevent cancer recurrence.*

'Preemptive Strike against Cancer'

Carcinogenesis Offers Many Opportunities for Intervention

Chemicals
Radiation
Biological agents
Random

Clonal selection and expansion
(multiyear, multistage and multipath)



Genetic Changes

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Examples of Chemopreventive Targets

- Carcinogen-activating enzymes (Cytochrome P450s)
- Carcinogen-detoxifying enzymes (e.g., GST)
- Estrogen receptor
- Androgen receptor
- 5-α Reductase
- Cyclooxygenase-2
- Retinoic acid receptor (RAR) and retinoic X receptor (RXR)
- Aromatase
- Thymidine synthetase
- Viruses

Some of the Agents That Have Shown Chemopreventive Activity in Clinical Trials

Finasteride – Prostate Cancer

Tamoxifen, Raloxifene – Breast Cancer

Aspirin, Celecoxib, Sulindac – Colorectal Cancer

13-*cis*-Retinoic acid – Head and Neck Cancer

Vitamin A, Fluorouracil – Skin Cancer

Bacillus Calmette-Guérin (BCG) – Bladder Cancer

HPV Vaccine – Cervical Cancer and Other Cancers

Photodynamic therapy (PDT) with Photofrin – Barrett Esophagus

FDA-Approved Agents for Treating Precancerous Lesions or Reducing Cancer Risk

Tamoxifen, Raloxifene – Breast Cancer

Celecoxib – Adenomatous Colorectal Polyps

Fluorouracil – Actinic Keratosis

BCG – Bladder Cancer

HPV Vaccine – Cervical Cancer and Other Cancers

PDT with Photofrin – Barrett Esophagus

Clin Chem 2013;59:94-101

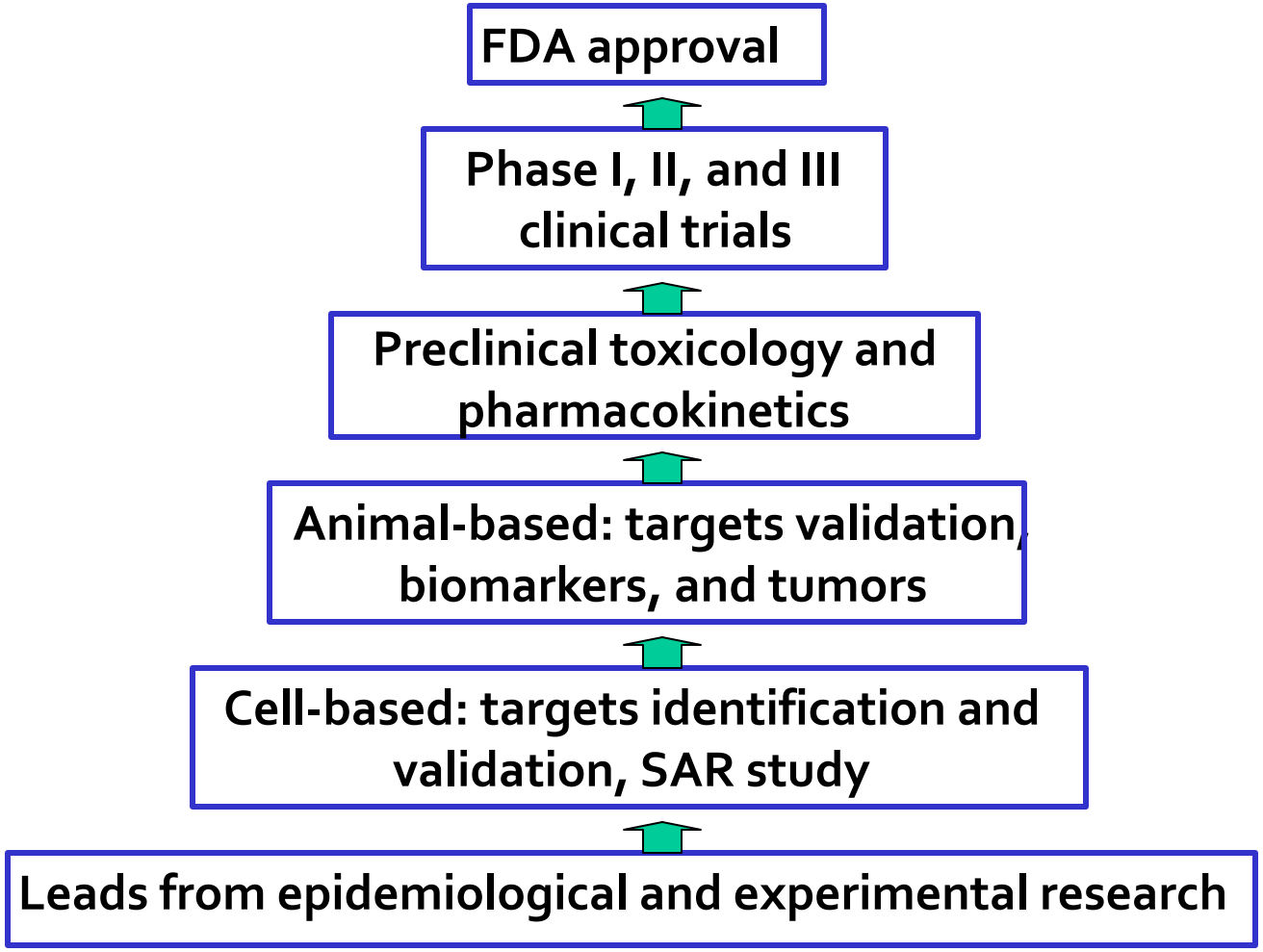
Examples of over 400 Agents That Are at Certain Stages of Evaluation for Cancer Chemopreventive Activities

Vitamins and Minerals: Folic acid, vitamin A, vitamin C, vitamin E, vitamin D, selenium, calcium.

Phytochemicals: *Phytoestrogens* (*e.g.*, genistein, lignans), *carotenoids* (*e.g.*, *b*-carotene, lycopene), *glucosinolates-derived* (*e.g.*, sulforaphane), allium organosulfur compounds (*e.g.*, diallyl sulfide), flavonoids (*e.g.*, quercetin, catechins), phenolics (e.g., curcumin), terpenoids (*e.g.*, *d*-limonene, perillyl alcohol), dietary fiber (*e.g.*, chlorophyll, chlorophyllin).

Synthetic Chemicals: Nonsteroid anti-inflammatory drugs (NSAIDS, *e.g.*, aspirin, celecoxib), dithiolethiones (*e.g.*, oltipraz), modulators of estrogen receptor signaling (*e.g.*, tamoxifen, raloxifene). Vitamin A and D analogs (*e.g.*,13-*cis*-retinoic acid, calcitriol), 5α-reductase inhibitors (*e.g.*, finasteride), ornithine decarboxylase inhibitor (*e.g.*, difluoromethyl ornithine).

Paradigm for Development of Chemopreventive Agents



Because chemopreventive agents are used in "healthy" people (high-risk subjects and even the general population), and require chronic administration, it is widely suggested that none or minimal drug toxicity is allowed. But, in reality, FDA has approved drugs for cancer chemoprevention, which have significant toxicities.

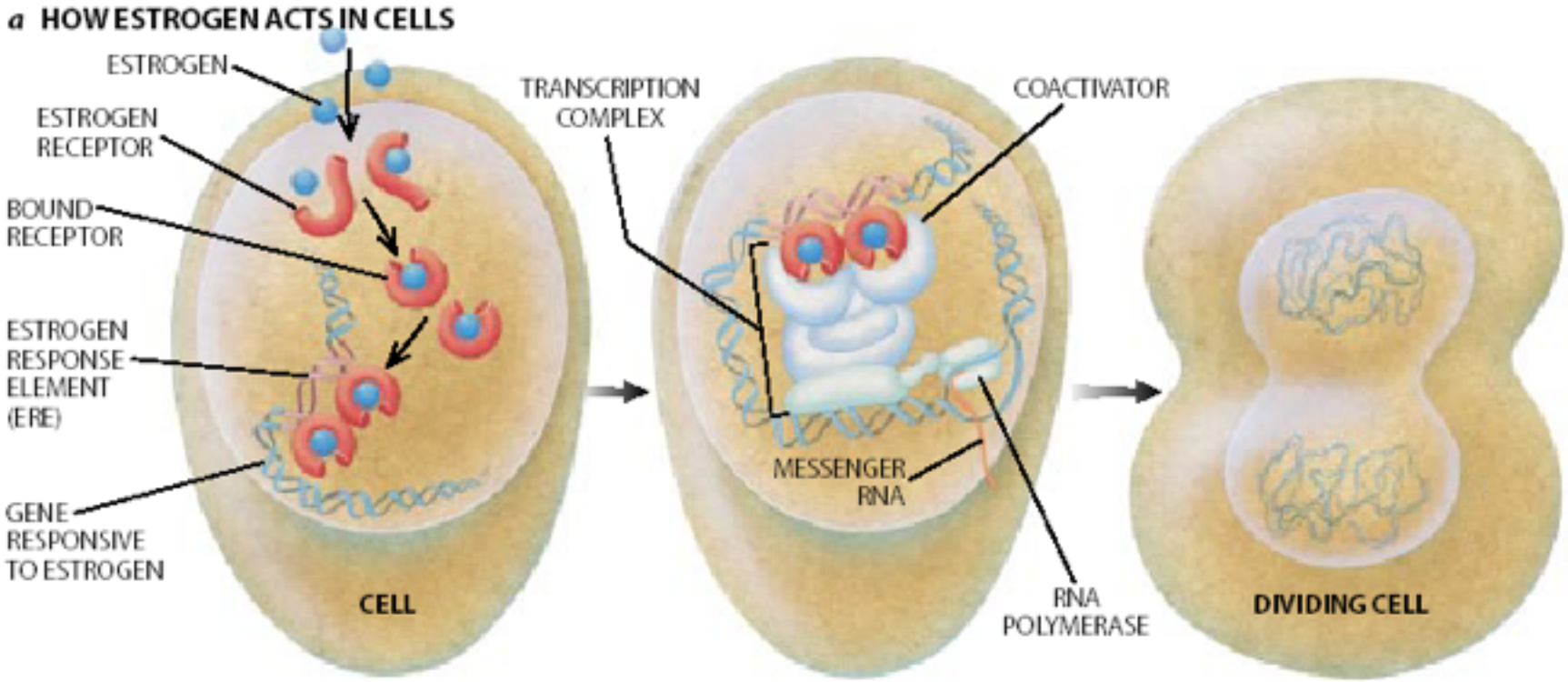
The Case of Tamoxifen

Tamoxifen was discovered as an anti-estrogen compound in 1962 by ICI Pharmaceuticals.

Tamoxifen has been used for over 30 years in patients with early stage breast cancer as adjuvant therapy to prevent breast cancer recurrence, and in those with metastatic breast cancer to slow the growth of cancer.

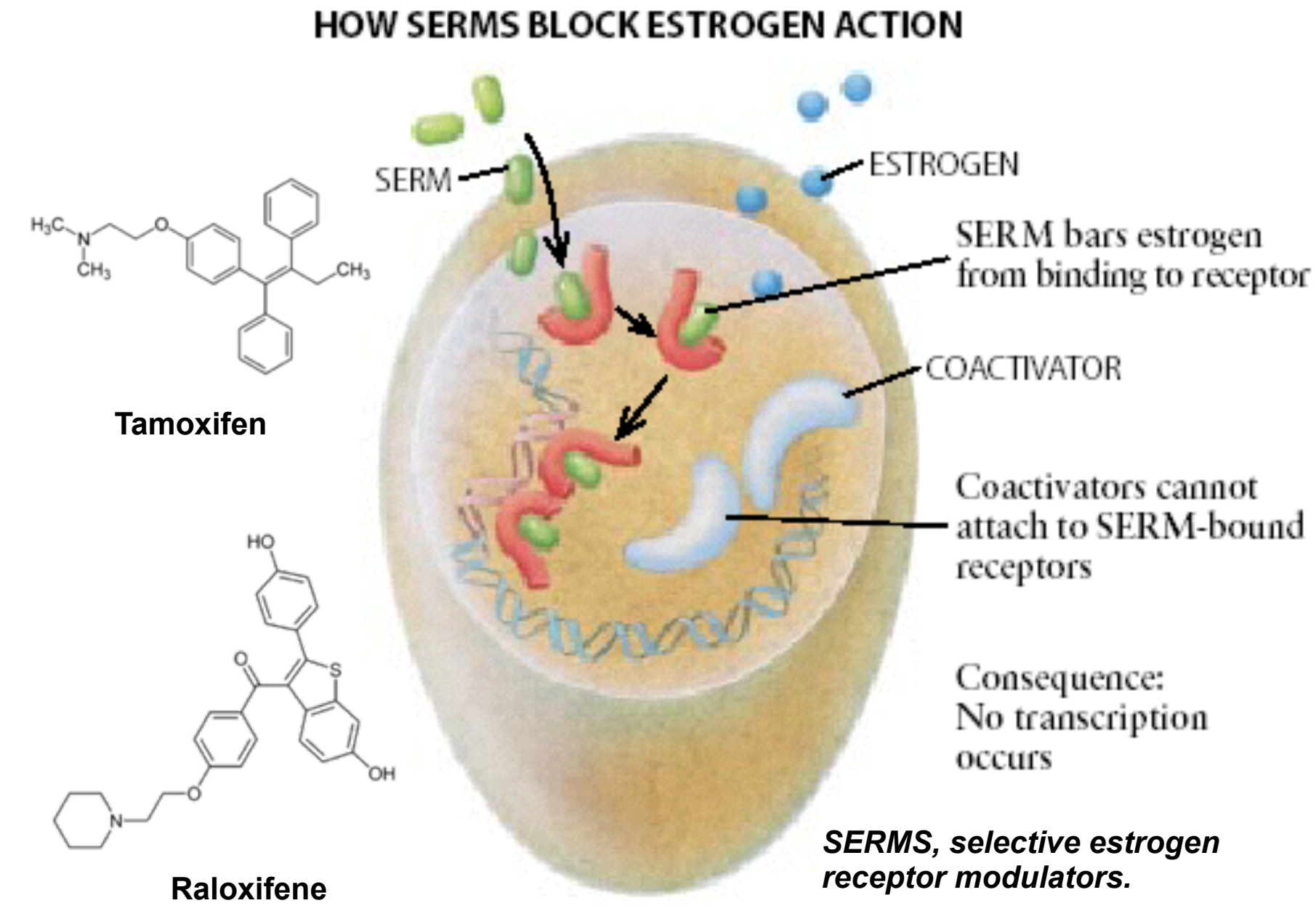
An NCI-sponsored breast cancer chemoprevention study of tamoxifen was initiated in early 1990s based on its clinical efficacy as an ER-positive breast cancer therapeutic agent.

Example 1: Targeting Estrogen Receptor



1. **Estrogen binds to its receptor, which then binds to certain genes**
2. **A transcription complex forms and activates gene transcription**
3. **Cell behavior changes**

Jordon, Scientific American, October, 1998, 60-67



SERMS, selective estrogen receptor modulators.

The Breat Cancer Prevention Trial (BCPT)

Study design

Question: Does Tamoxifen (20 mg daily) reduce the risk of developing breast cancer in a high risk population of women?

Protocol: Double blind; Placebo controlled

13,388 Women: enrolled April 1992 to Sept. 1997
35 years or older
300 Centers in U.S. and Canada

Exclusion criteria: blood clots; steroid replacement or oral contraceptives; pregnancy or contemplated pregnancy; prior breast cancer

Cost: $30-50 million, NCI-sponsored

The Tamoxifen Trial Result

Reduced:

Invasive Breast Cancer (45%)
Ductal Carcinoma (48%)
Bone Fractures (34%),

Increased:

Endometrial Carcinoma (2.4-fold)
Pulmonary Embolism (2.8-fold)
Deep Vein Thrombosis (1.6-fold)

Other Adverse Effects:

Menopause-like symptoms (hot flashes, vaginal dryness, joint pain, and lag cramps), cataracts, stroke, uterine sarcoma.

Fisher et al., Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J. Natl. Cancer Inst. 90:1371-1388, 1998.

Tamoxifen also inhibits the development of 7,12-dimethylbenz(a)-anthracene (DMBA)-induced rat mammary carcinoma

2 wk, pretreatment — **4 wk, oral DMBA, 5 mg/wk** — **10 wk, experiment stopped**

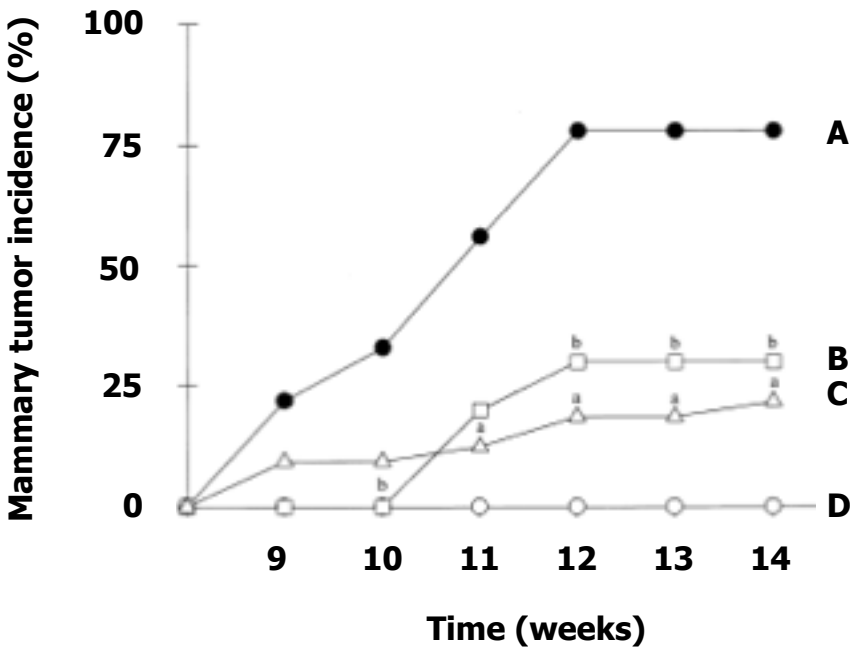
A, placebo

B, subcutaneous leuprolide (chemical castration)

C, subcutaneous tamoxifen (10 mg/kg/wk)

D, oophorectomy (sugical castration)

Leuprolide and tamoxifen began two weeks prior to DMBA and ended one week after DMBA.



Breast Cancer Research and Treatment 47, 63-70, 1998

Tamoxifen was approved by FDA in 1998 for reducing the incidence of breast cancer in women at high risk for developing breast cancer

Some of the Significant Risk Factors of Breast Cancer

A history of breast cancer: 3-4-fold increased risk of developing a new breast cancer, not a recurrence.

Having one first degree relative with breast cancer, the risk doubles; having two first degree relatives with breast cancer, the risk is 5-fold higher.

Carrying an inherited alteration in BRCA1 or BRCA2: Up to 80% chance of developing breast cancer.

A previous history of atypical hyperplasia: 4-5 fold higher risk.

The Case of Raloxifene

Background: In studies to evaluate its ability to reduce the risk of bone fracture of older women with osteoporosis, raloxifene was found to prevent breast cancer

Design: A study of tamoxifen and raloxifene for breast cancer prevention (STAR) in nearly 20,000 postmenopausal women

Intervention: Tamoxifen at 20 mg/d or Raloxifene at 60 mg/d over 4 years, beginning 1999.

Result: raloxifene is as effective as tamoxifen, both reducing the risk of invasive breast cancer by about 50%. But the raloxifene-treated women had 36% fewer uterine cancers and 29% fewer blood clots than the tamoxifen-treated women.

JAMA 2007;295:2727-2741

Outcome: FDA approval of raloxifene in 2007 in postmenopausal women at high risk for invasive breast cancer.

Longer-term Analysis of STAR (about 7 years): Raloxifene is 76% as effective as tamoxifen in preventing invasive disease.

Cancer Prev Res 2010;3:696-706

Alternative Strategies in Breast Cancer Prevention

1. Estrogen receptor down regulators, e.g., fulvestrant.

2. Aromatase inhibitors, e.g., exemestane, letrozole.

In post-menopausal women, estrogen is no longer produced by the ovaries, but is converted from androgen by aromatase.

Cancer Control 4, 217-221, 2004.
J Clin Oncol 22, 1605-1613, 2004.
N Engl J Med 364, 2381-2391, 2011.

Breast Cancer Subtypes

Type 1 (luminal A, 40%): ER positive and PR positive, likely to benefit from hormone therapy.

Type 2 (luminal B, 20%): ER positive, PR negative and HER-2 positive; may benefit from hormone therapy.

Type 3 (HER-2 positive, 15-20%): ER negative and PR negative, but HER-2 positive, likely to have no benefit from hormone therapy.

Type 4 (basal-like, 10-15%): ER negative, PR negative and HER2 negative, also known as triple-negative, likely to have no benefit from hormone therapy.

Effect of Selenium and Vitamin E on Risk of Prostate Cancer

The selenium and vitamin E cancer prevention trial (SELECT)

JAMA 2009;301:39-51

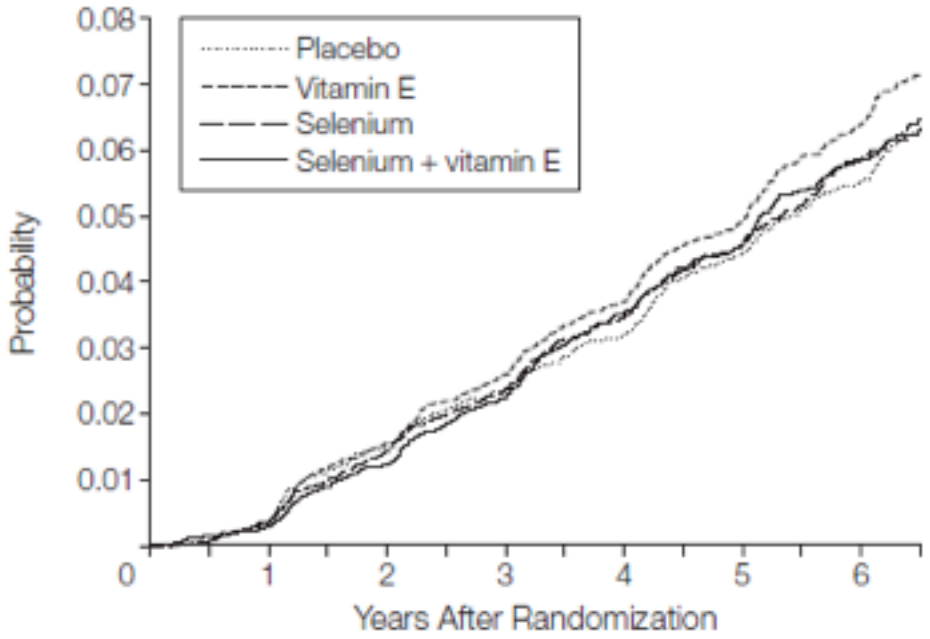
Design: **A randomized, placebo-controlled trial of 35,533 men from 427 participating sites, double-blinded, ≥50 years of age, no prostate cancer (serum PSA ≤4 ng/ml).**

Intervention: **Oral selenium (200 μg/d from *L*-selenomethionine) and matched vitamin E placebo, vitamin E (400 IU/d of all rac-α-tocopheryl acetate) and matched selenium placebo, selenium + vitamin E, or placebo + placebo; 7-12 years.**

Main endpoint: **Prostate cancer.**

Supported by epidemiological and preclinical data: J Urol 1999,161:1651-1654; Cancer Res 2000,60:2882-2886; Cancer Res 2001,61:3061-3070; CEBP 2000,9:1171-1182; Cancer Lett 1998,125:103-110; JNCI 1998,90:1184-1185; JNCI 1998,90:1219-1224; Cancer Res 2001,61:7071-7078.

Cumulative Incidence of Prostate Cancer Detected Each Year by Intervention Group



No. at risk							
Placebo	8689	8553	8328	8039	7389	4892	2516
Vitamin E	8732	8610	8373	8098	7401	4867	2537
Selenium	8750	8597	8341	8083	7393	4848	2558
Selenium + vitamin E	8700	8585	8371	8097	7428	4894	2580

Compared with placebo, there was a statistically nonsignificant increase in prostate cancer in the vitamin E group (P=.06) and not in the selenium + vitamin E group (P=.52) or the selenium group (P=.62).