

# Cancer Prevention

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# Multidisciplinary Cancer Management Course

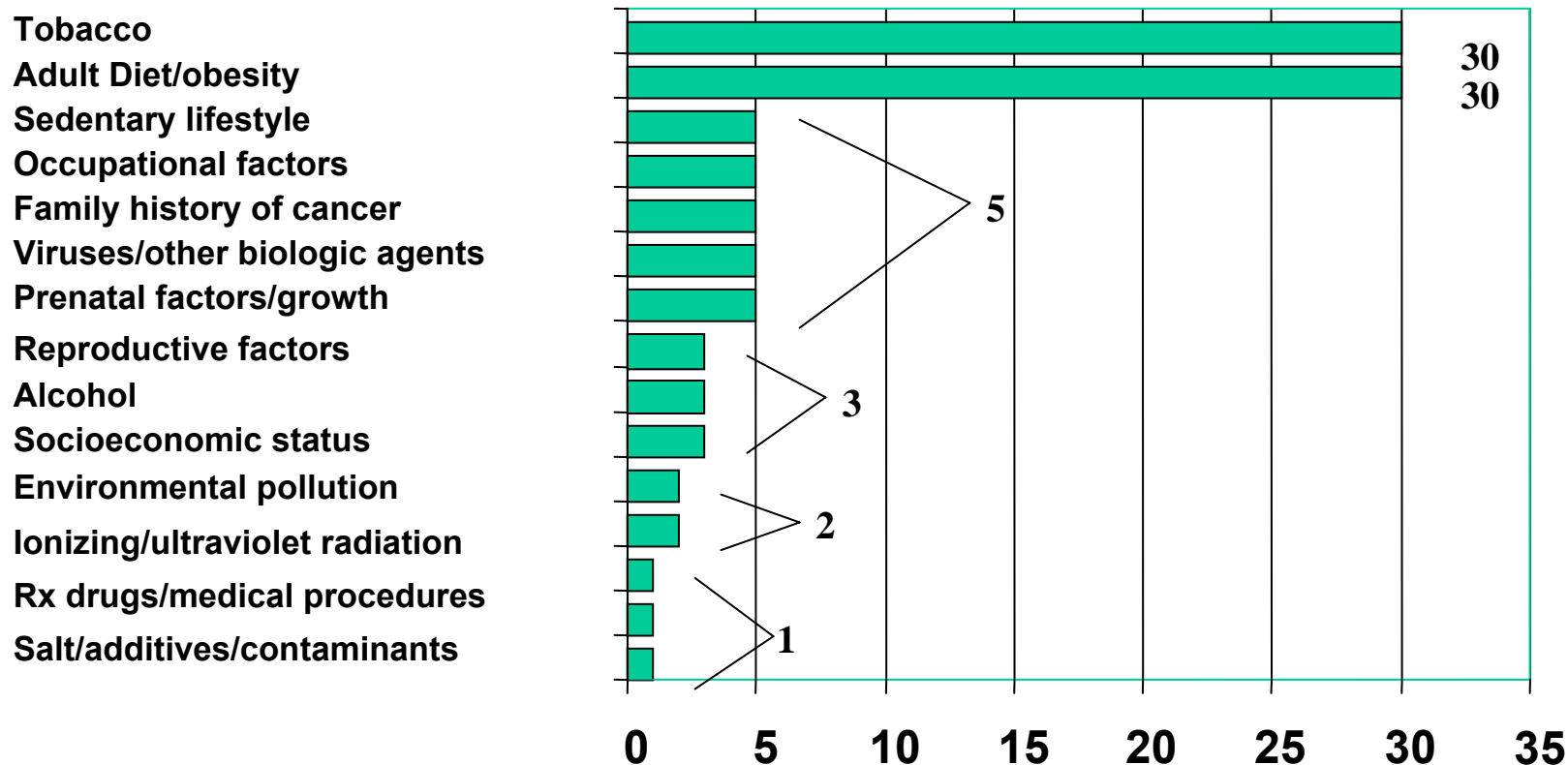
## Global Cancer Burden (World Health Organization [WHO])

	2000	2020
New cases of cancer	10 million	20 million
No. of cancer-related deaths	6 million	12 million
Percentage of new cases in developing countries	50%	70%

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## Causes of Cancer: Review of the Evidence

Estimated percentage of total cancer deaths attributable to established causes of cancer



Harvard Center for Cancer Prevention. *Cancer Causes Control*. 1996;7(suppl 1).

## Tobacco as a Cause of Death

- Tobacco smoking remains the greatest single avoidable cause of premature death in the world
- Tobacco is the most known carcinogen in humans: 25-30% of all cancers are tobacco related
- **According to WHO, the annual mortality related to tobacco is 3 million**

## Tobacco and Cancer

The International Union Against Cancer (UICC) recommends the following strategies to deal with the tobacco problem:

- Education
- Ban on all advertising and promotion of tobacco products
- Effective government health warnings on all tobacco products
- Policy on low tar and nicotine
- Tax, pricing, and alternative economic policies

## Tobacco and Cancer (cont.)

- Policies to protect young people from tobacco promotion and sales
- Policies to protect the right of nonsmokers and establish in law the right to smoke-free common environment, including the workplace
- Policies to prohibit new methods of nicotine delivery and block future industry marketing strategies
- Policies to ensure the wide availability of help for tobacco users who wish to stop

## Alcohol and Cancer

Epidemiologic data have identified chronic alcohol consumption as a significant risk factor for upper alimentary tract cancer, including cancer of the oropharynx, larynx, and esophagus, as well as the liver

## Alcohol, Tobacco, and Cancer

The carcinogenic effects of both alcohol and tobacco were found to be multiplicative on the relative risk scale in a meta-analysis

## Lifestyle and Cancer

### Western lifestyle

- Diet high in calories, animal fat, refined carbohydrates, and animal protein
- Low level of physical activity

### Consequences

- Greater adult body weight, obesity
- Cardiovascular disease, diabetes, hypertension
- Early menarche
- Cancer

## Obesity and Cancer

- Obesity found to be responsible for 14% of all cancers in a study of 900,000 people, conducted by the American Cancer Society
- Excess body mass accounts for 5% of all cancers in the European Union

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## Reduction of Cancer Risk with Weight Control and Adequate Physical Activity

Type of Cancer	Level of Evidence of Reduced Cancer Risk (population attributable risk %)
Colon	Convincing (13-14%)
Breast	Convincing (11%)
Endometrium	Accumulating consistent results (11%)
Prostate	Inconsistent and problematic
Lung	Limited information, possible risk reduction
Ovary	Limited information – an increase?

IARC. *Weight Control and Physical Activity*. 2002

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## Population Attributable Risk of Cancer Associated with Body Mass Index (BMI) and Physical Inactivity

Type of Cancer	BMI ( $\geq 25$ vs. $< 25$ )	Physical Inactivity
Colon	11%	13-14%
Breast	9%	11%
Endometrium	39%	11%*
Esophagus (adenocarcinoma)	37%	No data
Kidney	25%	Limited information

IARC. *Weight Control and Physical Activity*. 2002

## What about Diet?

- “Five a day” remains best recommendation
- Diet is complex mixture of known and unknown substances
- Genetics and diet interactions are likely to be important

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TABLE 5

American Cancer Society Grades for Benefit Versus Harm (2001)*									
Nutritional Factor	Colorectal Cancer	Breast Cancer	Prostate Cancer	Lung Cancer	Esophageal, Oral Cancer	Stomach Cancer	Pancreatic Cancer	Bladder Cancer	Endometrial Cancer
Increasing vegetable and fruit intake	A2	A3	A3	A2	A2	A2	A3	A3	A3
Limiting intake of red meat	A2	B	A3	B	B	C	A3	C	B
Increasing physical activity	A1	A1	B	B	B	B	B	B	A2
Avoiding overweight	A1	A1	C	B	A2	C	A3 <sup>•</sup>	C	A1
Limiting alcohol intake	A3	A2	C	B	A1	C	A3	C	B
Consuming soy foods	B	B	B	B	B	B	B	B	B
Taking beta-carotene supplements	B	B	C	D	B	B	B	B	B
Taking vitamin E supplements	B	B	A3	C	B	B	B	B	B
Taking vitamin C supplements	B	B	B	B	B	B	B	B	B
Taking folic acid supplements	A3	A3	B	B	B	B	B	B	B
Taking selenium supplements	A3	B	A3	A3	B	B	B	B	B

\*Note: Group met in 2001 and recommendations were adopted by the American Cancer Society Board of Directors in November, 2001.

## Infection and Cancer

- Infectious agents cause as much as 23% of cancers in developing countries and approximately 8% in developed countries
- Hepatitis B virus causes liver cancer; can be prevented with vaccine
- Human papillomavirus (HPV) causes cervical cancer, anal cancer; can be prevented with use of condoms and with vaccine (in the future)
- Other infectious agents include *Helicobacter pylori*, schistosomiasis, human T cell lymphotropic virus, and Epstein-Barr virus

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## Main Sources of Exposure to Agents Known to Be Carcinogenic to Humans

<u>Source of Exposure</u>	<u>Number of Carcinogens</u>
Environmental/Occupational	25
Biologic	10
Medical	20
Radiation	13
Lifestyle related	6

## Cancer Prevention through Control of Environmental Exposure to Carcinogens

Most prevalent carcinogens

- Asbestos
- Tobacco smoke (passive)
- Chlorinated drinking water
- Arsenic-contaminated water

## Target Organs of Environmental Carcinogens

<u>Organ</u>	<u>No. of Carcinogens</u>
Lung	19
Bladder	7
Skin	7
Nose	4
Blood (leukemia)	3
Larynx	2
Liver	1
Pleura	1

# Second Cancers Among Long-Term Survivors of Cancer

- As the prevalence of cancer survivors increases, second, third, and higher-order cancers are increasing, now consistently representing more than 13% of cancers in the United States
- The risk of cancer is double that of the healthy population

## Childhood Cancers

- Overall cure rate for cancer in children now exceeds 70% and is projected to reach 85% by the year 2010
- Estimated that early in the new millennium, 1 in every 1,000 young adults (20-29 years) will have been treated earlier in life for cancer

## Childhood Cancer Survivor Study

- Mortality was 10.8 times greater than that of the general U.S. population
- Causes: recurrence of original disease, subsequent cancer, cardiomyopathy, ischemic heart disease, pulmonary fibrosis
- Cancer screening among survivors was below optimal level

# Genetics and the Management of Women at High Risk for Breast Cancer

- Estimated that 5-10% of all breast cancers in women are associated with hereditary susceptibility as a result of mutations in autosomal dominant genes, such as *BRCA1*, *BRCA2*, and others

# Genetics and the Management of Women at High Risk for Breast Cancer (cont.)

- 15-20% of female breast cancers occur in women with a family history but without an apparent autosomal dominant inheritance pattern
- 7-10% of ovarian cancers occur in women with hereditary susceptibility, primarily secondary to mutations in *BRCA1* and *BRCA2*

## Reducing Breast Cancer Incidence in Familial Breast Cancer

- Prophylactic surgery
  - Mastectomy
  - Oophorectomy
- Chemoprevention
  - Tamoxifen
  - Aromatase inhibitors

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### Occurrence of Breast Cancer among Women Having Bilateral Prophylactic Mastectomy

Study, Year	No. of Breast Cancer Cases	Mean Follow-Up (Yrs.)
Hartmann et al., 1999	37 of 425 expected (Gail model); 4 occurred	14
Rebbeck et al., 2004	2 (1.9%) of 105 pts.; 184 (48.7%) of 378 matched controls	6.4

## Prevention of Breast Cancer

- Tamoxifen
  - 70% reduction in estrogen receptor-positive contralateral breast cancer and a 30-40% reduction of all breast cancer in high-risk population
  - Risk of thromboembolic and endometrial cancers are increased about twofold

## Prevention of Breast Cancer (cont.)

- Anastrozole
  - ATAC trial showed that anastrozole is more effective than tamoxifen in reducing recurrence or preventing new contralateral tumors
- Raloxifene
  - MORE trial demonstrated that raloxifene reduces the risk of both in situ and invasive breast cancer by 65%

# Cancer Risk for Male Carriers of Germline Mutations of *BRCA1* and *BRCA2*

- Increased risk of prostate and breast cancer
- Evidence supporting increased susceptibility to colon cancer is limited
- *BRCA2* mutation is more important—susceptibility for breast, prostate, and pancreatic cancer, as well as risk of gastric cancer and melanoma
- Further studies are needed

## Colorectal Cancer

Colorectal cancer is the second leading cause of death overall and the first leading cause among individuals age older than 75 years

## Colorectal Cancer (cont.)

Recommendations to reduce the risk of adenomatous polyps and colorectal cancer

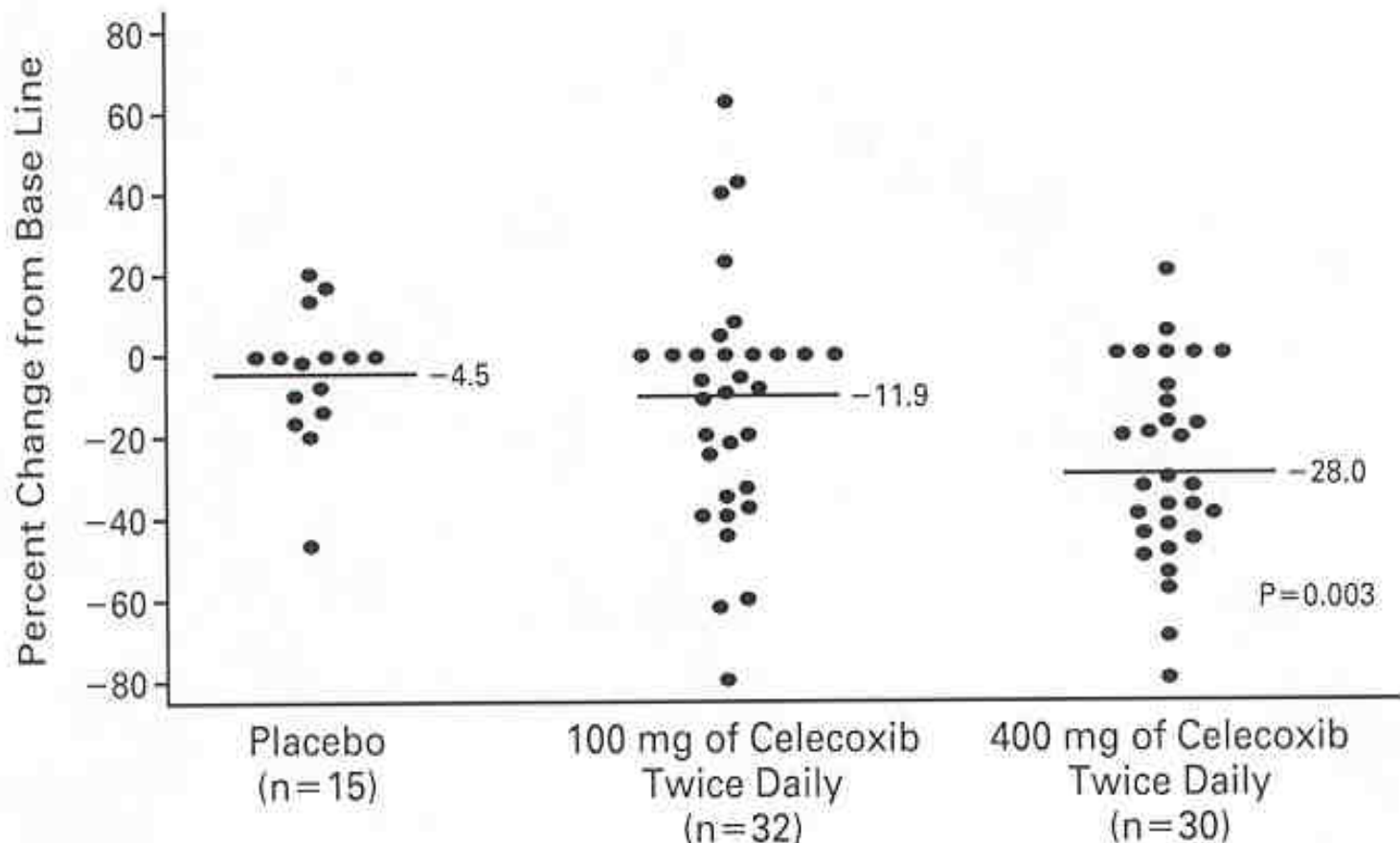
- Follow diet low in red meat and alcohol and high in fruits and vegetables
- Avoid smoking
- Maintain normal body weight
- Increase physical activity

## Prevention of Colorectal Cancer

- Knowledge to identify patients at high risk
- Much evidence to suggest an inverse relationship between use of nonsteroidal anti-inflammatory drugs (NSAIDs) and incidence of colorectal cancer
- Cyclo-oxygenase (COX)-2 inhibitors have similar effect to that of NSAIDs but fewer side effects

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## Prevention of Colorectal Cancer with Celecoxib



Reprinted with permission from Steinbach et al. *N Engl J Med.* 2000;342:1946-1952.

# Preventive Management for Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

- Colonoscopy surveillance every year starting at the age of 25 is recommended for individuals who test positive for HNPCC mutations
- Prophylactic colectomy is a reasonable alternative to lifetime colonoscopy surveillance for the prevention of colorectal cancer

## Finasteride and Prostate Cancer

- Preventive treatment with finasteride shown, in large randomized study, to reduce prevalence of prostate cancer prevalence by 25%
- Increase in high-grade prostate cancer
- Cost burden is substantial while survival benefit is small and only realized many years later

# Counseling for Prevention of Skin Cancer

Recommendations and Rationale of the U.S. Preventive Services Task Force (October 17, 2003):

- Insufficient evidence to recommend for or against routine counseling by primary care clinicians to prevent skin cancer
- Counseling of parents may increase children's use of sunscreen
- Little evidence to determine the effects of counseling on adults' sun protection behaviors (protective clothing, reducing excessive sun exposure, avoiding sun lamps and tanning beds, self-examination of skin)

## Chemoprevention

- Defined as intervention with pharmaceutical agents, vitamins, minerals, or other chemicals to reduce the incidence of cancer
- Currently more than 50 chemopreventive drugs in clinical development and in clinical trials

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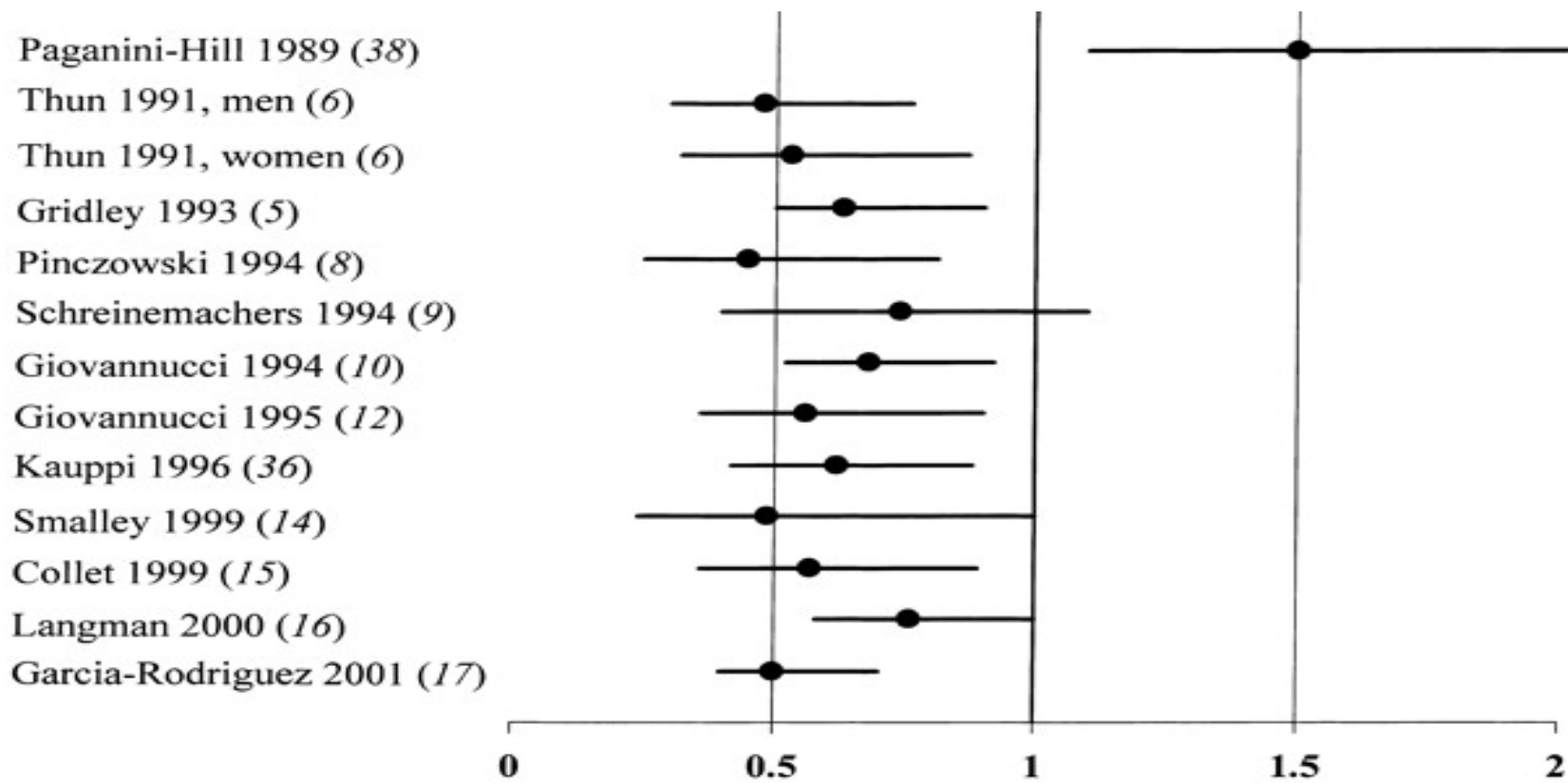
## Phase III Chemoprevention Trials

Authors	Start of Study	No. of Subj.	Durat. of Study (Yrs.)	Treatment	Endpoint	Outcome
Duffield-Lillico, et al.	1983	1,312	4.5	Selenium (yeast) vs. placebo	Non-melanoma skin cancer	No reduction in skin cancer, secondary analysis: reduced incidence of prostate, lung, total cancers
Taylor et al.	1986	29,584	5.25	Retinol, zinc, riboflavin, niacin, selenium (yeast), $\alpha$ -tocopherol, $\beta$ -carotene (2x4 factorial)	Cancer incidence	Reduced incidence of gastric and esophageal cancer in $\alpha$ -tocopherol, $\beta$ -carotene arm
Albanes et al.	1985	29,133	6.1	$\alpha$ -tocopherol, $\alpha$ -tocopherol+, $\beta$ -carotene, $\beta$ -carotene, placebo	Lung cancer	18% increase in $\beta$ -carotene treated population
Omenn et al.	1985	18,314	4.0	$\beta$ -carotene and retinol vs. Placebo	Lung cancer	26% increase in treatment arm
Lang et al.	1982	22,071	12	$\beta$ -carotene vs. placebo (+ aspirin up to 12 years)	Cancer incidence	No change in incidence including smokers, all cancer or cancer-specific
Dunn and Ford	1992	13,388	6	Tamoxifen vs. placebo	Breast cancer	49% reduction of breast cancer risk

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## Epidemiologic Data: Aspirin and Colon Cancer

Risk of Development of Colon Cancer Taking Aspirin vs. Not Taking Aspirin



## Cancer and Aspirin

- Almost 7 million Americans take aspirin daily to prevent heart attack
- Should aspirin be taken to prevent cancer?

Answer remains elusive but the consensus is that it is too early to make such a recommendation

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## Summary

- Tobacco, alcohol, and obesity are significant risk factors for a variety of cancers
- Infectious agents cause as much as 23% of cancers in developing countries and approximately 8% in developed countries
- The risk of second cancers for long-term cancer survivors is double that of the healthy population

## Summary (cont.)

- Tamoxifen, anastrozole, and raloxifene have been shown to reduce the risk of breast cancer
- Currently more than 50 chemopreventive drugs are in clinical development and in clinical trials