

Cancer Screening

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MCMC Objectives:

- **Screening and prevention**
- **Diagnosis**
- **Staging**
- **Multidisciplinary treatment**
- **Follow up**
- **Rehabilitation**

Screening

- Defined as the detection of risk; the identification of risk or disease in asymptomatic individuals or populations
- May be assessment of genetic, dietary, or environmental factors
- May be individualized or based on populations

Early Detection

- Defined as the discovery of lesions that are either pretransformed or transformed and can be removed
- Decision to remove lesion depends on risk-benefit—the risk to the patient of undergoing a procedure versus the likelihood of future transformation and invasion of a premalignant lesion
- Concept of ablation using local means is more compelling for transformed lesions

Screening Principles

- Disease should be an important health problem
- Disease should have a detectable preclinical phase
- Natural history of the lesion identified by screening should be known

Screening Principles (cont.)

- Effective treatment should be available
- Screening test should be accessible, simple, noninvasive, and safe
- Cost of screening test should be balanced against the benefit
- Age at which death from cancer causes most years of life lost is important

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Does Early Detection Reduce Mortality?

Several scientific reasons why the early detection of cancer does not automatically guarantee a reduction in cancer-related mortality

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Is Cancer Screening Effective?

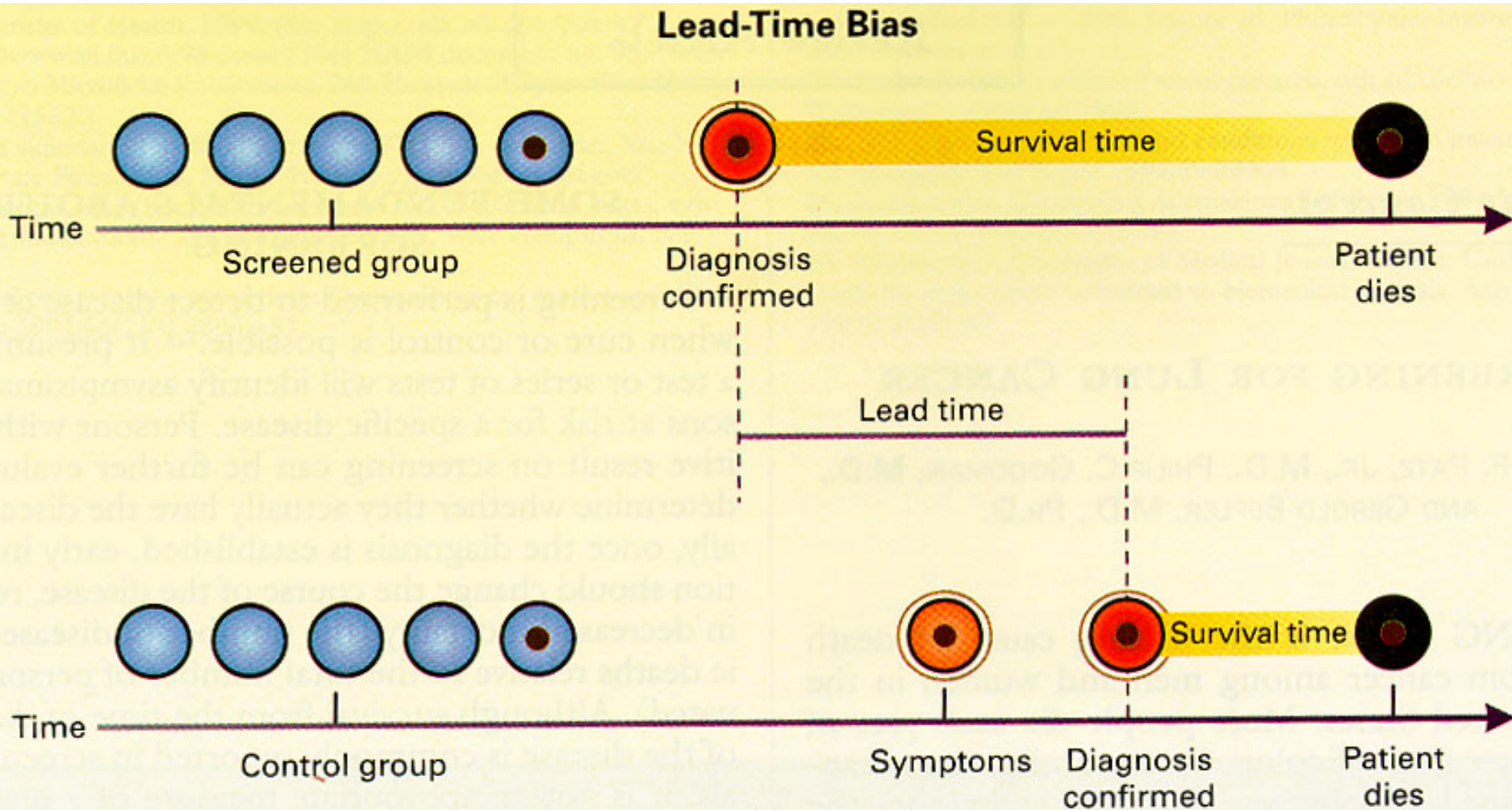
Conventional Endpoints

Survival—years

Death rate (mortality rate)—deaths/1,000/year

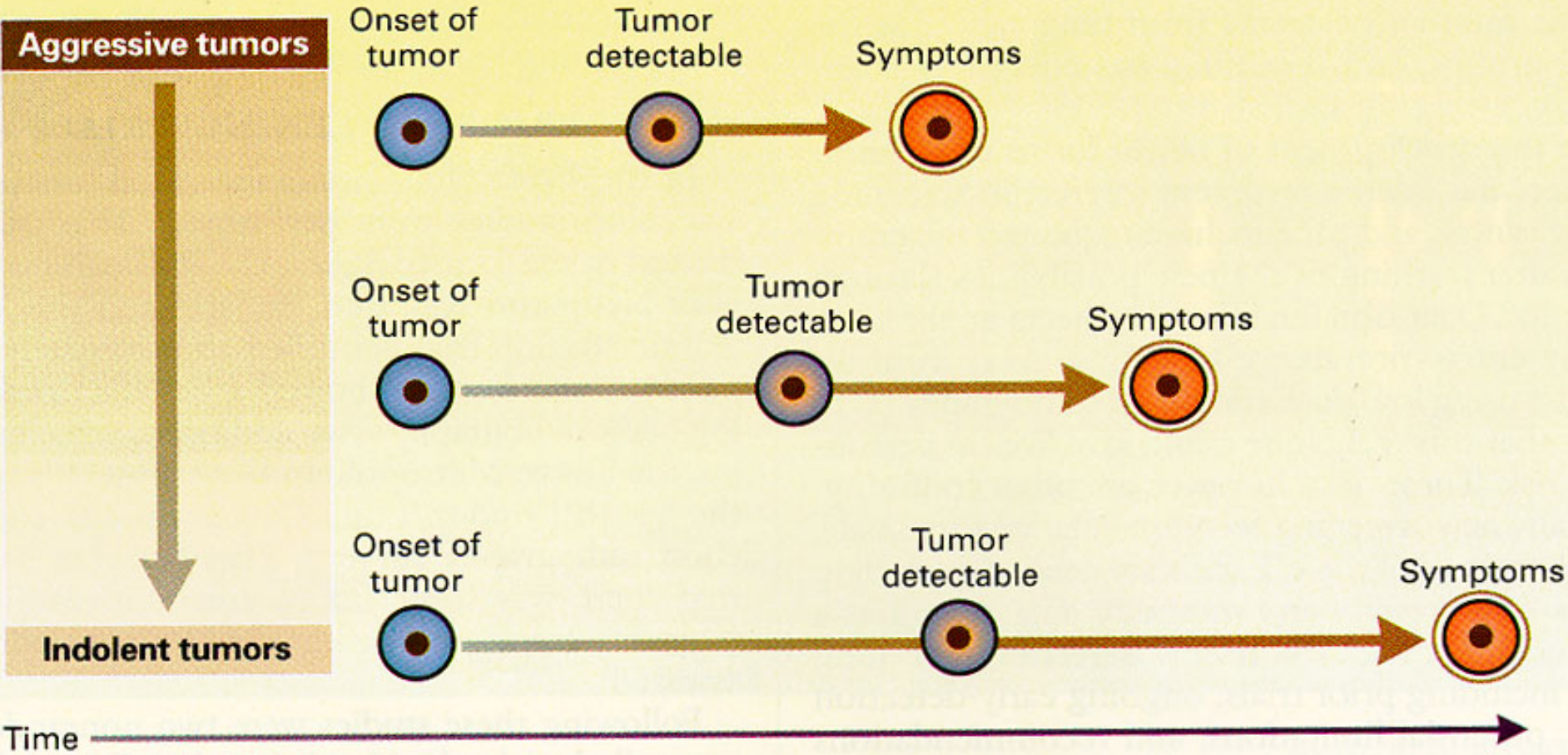
Use of death rate as an endpoint completely avoids lead-time and length-time bias

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Length-Time Bias



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Use of Biomarker as detection test for screening

Biologic event that takes place between “health” exposure and the subsequent development of a disease



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Role of a Biomarkers

- Risk assessment
- Prevention
- Early detection
- Prognosis
- Therapeutic effect

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Key Concepts in Validating Biomarkers

- Sensitivity
- Specificity
- Positive predictive value
- Negative predictive value

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Key Concepts in Validating Biomarkers (cont.)

Sensitivity and **specificity** test the validity of a diagnostic test in terms of its ability to accurately assess the presence or absence of a target condition

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Key Concepts in Validating Biomarkers (cont.)

Sensitivity = True Positives / True Positives + False Negatives

- How well does the test find people with a target condition?
- Proportion of individuals who have positive findings for a condition out of all who actually have the condition

Specificity = True Negatives / True Negatives + False Positives

- How well does the test find people without a target condition?
- Proportion of individuals who have negative findings for a condition out of all who really do not have the condition

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Key Concepts in Validating Biomarkers (cont.)

Positive predictive value and **negative predictive value** evaluate the usefulness of a test by determining if it yields a sufficient number of accurate responses to predict a clinical outcome

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Key Concepts in Validating Biomarkers (cont.)

Positive Predictive Value =

$\text{True Positives} / (\text{True Positives} + \text{False Positives})$

- The likelihood that a person who has positive results actually has the condition

Negative Predictive Value =

$\text{True Negatives} / (\text{True Negatives} + \text{False Negatives})$

- The likelihood that a person who has negative findings actually does not have the condition

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Establishing Value of Screening

- A cancer screening method should be accepted as standard of care **only** when its value has been demonstrated in randomized controlled trials
- National priorities should be considered

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Levels of Scientific Evidence about Therapeutic Interventions

Level I Evidence

Randomized controlled trials that are large enough to yield positive results with small risk of false-positive conclusion

Meta-analyses of randomized controlled trials

Level II Evidence

Randomized controlled trials that are too small, showing either

Positive trends that are not statistically significant, with large risk of false-positive conclusions

No impressive trends, but large risk of false-negative conclusions

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Levels of Scientific Evidence about Therapeutic Interventions (cont.)

Level III Evidence

Formal comparisons with nonrandomized contemporaneous controls

Level IV Evidence

Formal comparisons with historic controls

Level V Evidence

Case series, descriptive studies, clinical experience, reports from expert committees

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Debate on Mammography to Detect Breast Cancer in Women 40-49 Years Old

1977

National Cancer Institute (NCI) and American Cancer Society (ACS) recommend that mammography be done yearly only for high-risk women 40-49 years old

1980

ACS recommends one-time mammography for women 35-40 years old, to establish a baseline for future testing

1983

ACS recommends mammography every 1-2 years for symptom-free women 40-49 years old

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Debate on Mammography to Detect Breast Cancer in Women 40-49 Years Old (cont.)

1993

NCI changes recommendation, stating, "Experts do not agree on the value of routine screening mammography for women ages 40-49."

ACS and 20 other organizations state that there is value to routine screening

1998

National Institutes of Health (NIH) consensus conference agrees to 1993 recommendation

1999

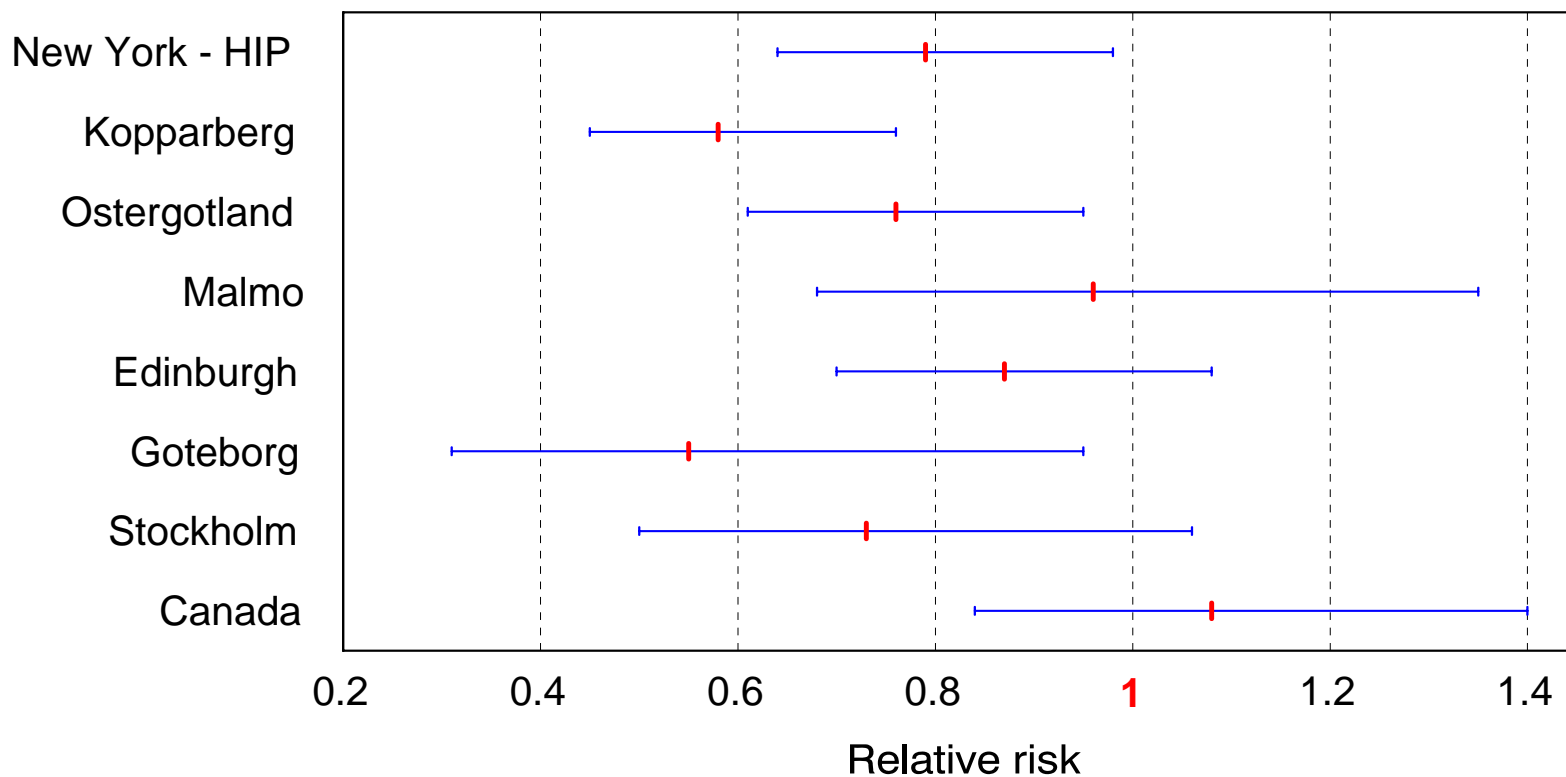
ACS and NIH recommend annual mammography for women 40-49 years old

Screening for Breast Cancer

- Mammography led to 30% reduction in breast cancer-related mortality in a 1970 trial
- Mammography every year or every other year for women older than 50 years led to improved survival in eight subsequent randomized controlled trials and meta-analyses

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Relative risk of death from breast cancer in screening mammography trials



Screening for Colorectal Cancer

Guidelines for average-risk individuals beginning at age 50 years:

- Fecal occult blood test every year
- Colonoscopy every 10 years
- Fecal occult blood test every year and flexible sigmoidoscopy every 5 years
- Flexible sigmoidoscopy every 5 years
- Double-contrast barium enema every 5 years

Evidence for Colorectal Screening

- Fecal occult blood testing: randomized trials have demonstrated a significant reduction in mortality (approx. 30% at 5 years)
- Colonoscopy: case-control study
- Virtual colonoscopy: investigational studies

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Screening for Cervical Cancer

- Pap smear every year beginning 3 years after the start of sexual activity (and no later than age 21)
 - Pap smear every 2-3 years beginning at age 30 for women who have had normal results on 3 consecutive Pap smears
 - Pap smear every year for women with risk factors
- Human papillomavirus (HPV) testing can be done with the Pap smear for women over 30 years old

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Screening for Lung Cancer

- Trial reported by Henschke et al.
 - Screening performed for 25,000 individuals
 - Positive findings for 13%
 - Cancer detected in 1.2% (79 patients)
 - Stage 1 disease in more than 80%
- ACS stated: Findings are encouraging, but policymakers need to be persuaded by classically definitive studies

Screening for Lung Cancer (cont.)

U.S. Preventive Services Task Force, 2004 Update

Current data do not support screening asymptomatic individuals for lung cancer (using chest x-ray, low-dose computerized tomography, sputum cytology, or a combination of these tests)

Screening for Ovarian Cancer

- Transvaginal ultrasonography and tumor marker CA-125 every year
- Transabdominal ultrasonography every year
- Positive-predictive value of each test, 1.4%

Screening for Gastric Cancer

- In Japan, 3 million radiographs with barium contrast were performed between 1960 and 1988; results were positive for 10%
- Positive predictive value of 1.7%
- No randomized trials to confirm value of screening have been reported
- *Helicobacter pylori* associated with lymphoma and gastric cancer

Screening for Prostate Cancer

- Common disease but often indolent, with no symptoms
- Digital rectal examination is subjective and lacks sensitivity
- Prostate-specific antigen (PSA) testing has good sensitivity
- Randomized trials demonstrating reduction in mortality are not yet available

Evidence for Prostate Cancer Screening

Insufficient evidence to establish whether a decrease in mortality from prostate cancer occurs with screening by digital rectal examination, transrectal ultrasonography, or serum markers, including prostate-specific antigen

Level of Evidence: V

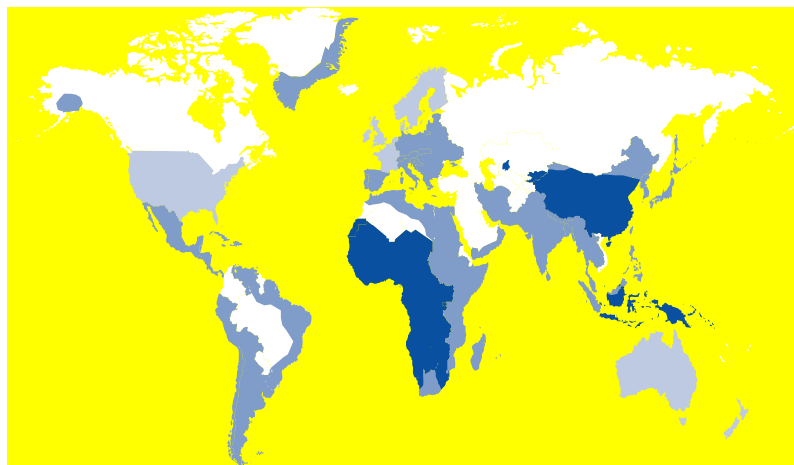
Opinions of respected authorities based on case series, descriptive studies, clinical experience, or reports of expert committees

Expense of Prostate Cancer Screening

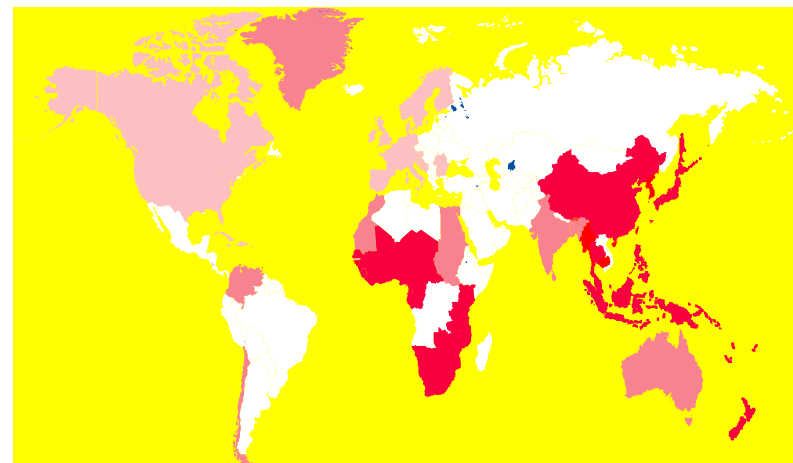
- Screening of 1994 Swedish men randomly selected from a group of 9,025 men led to a diagnosis of 13 cases of prostate cancer at a cost of \$3,750 for each case detected
- In the United States, the first year of screening would cost \$12-28 billion
- Despite the cost, screening should be done for men with a family history of prostate cancer

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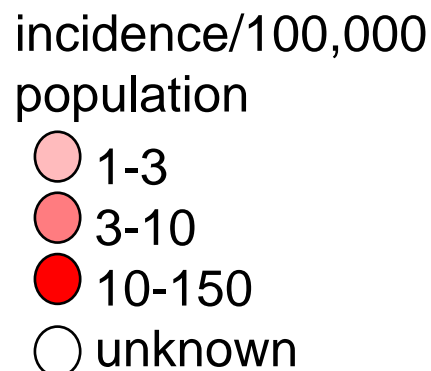
Screening HBV carriers for early detection of HCC



Prevalence of HBV carriers



Annual incidence of hepatoma

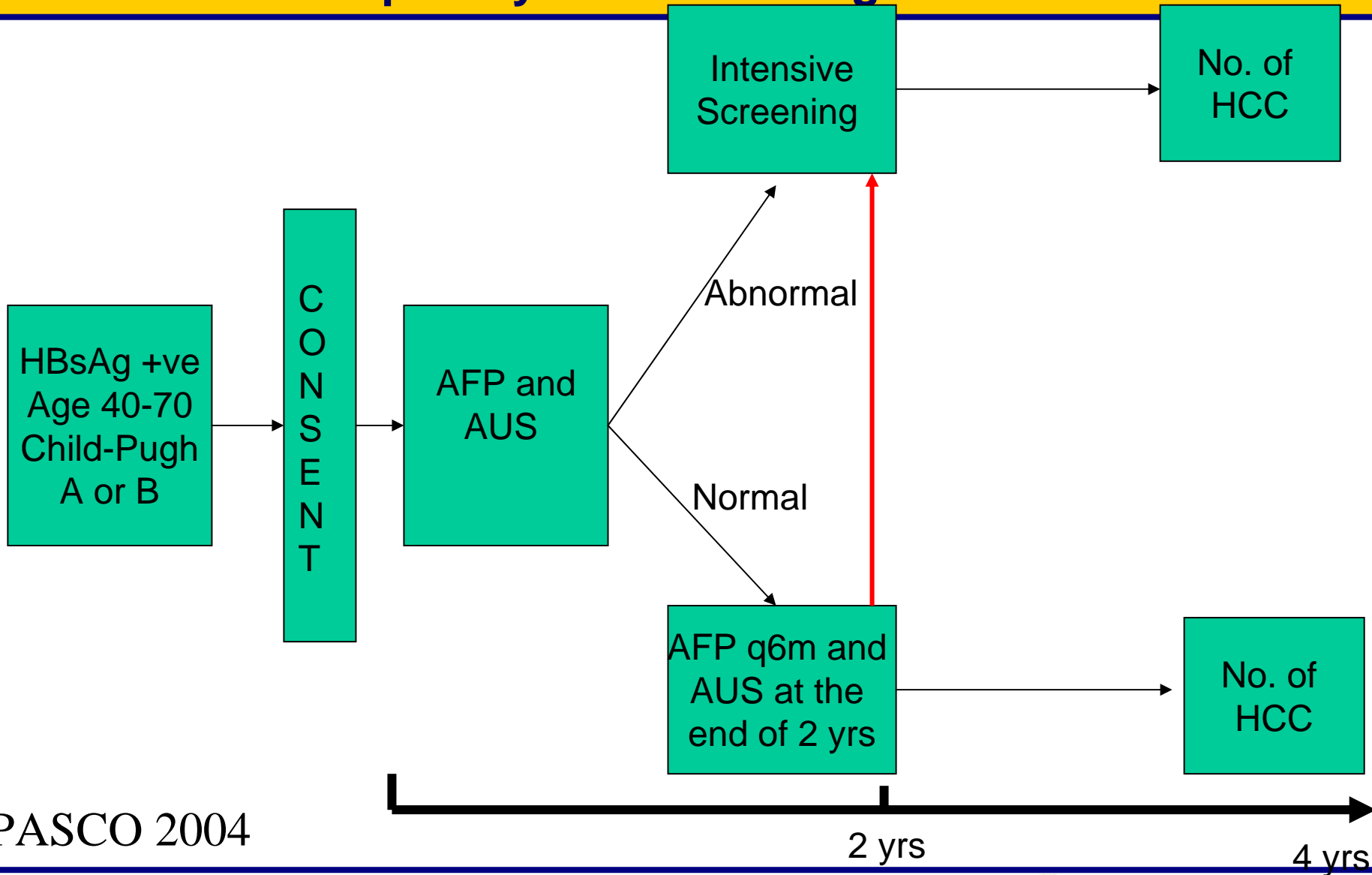


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Author	Sample size	Detection test	Confirmatory test	Number of HCC	Resection rate	Survival
McMahon (Alaska, HBV)	1487	AFP	AUS or CT	32 (2.2%)	68.7%	5 YS: 42%
Sherman* (Canada HBV)	1069	AFP versus AFP plus AUS	Histology	14 (1.3%)	50%	NA
Colombo (Italy, HCV/ HBV/ETOH))	447	AFP plus AUS	Histology	59 (13.2%)	29% (20.3% resected)	Med Sur 25 Months
Izzo (Italy, HCV/HBV)	1125	AFP plus AUS	Histology	67 (6%)	35.8%	Med Sur 26 months
Yang* (China, HBV)	18,816	AFP+AUS Vs Nil	CT scan or MRI	86 (1.0%) vs 41 (0.4%)	71% vs 0%	Mortality OR 0.81

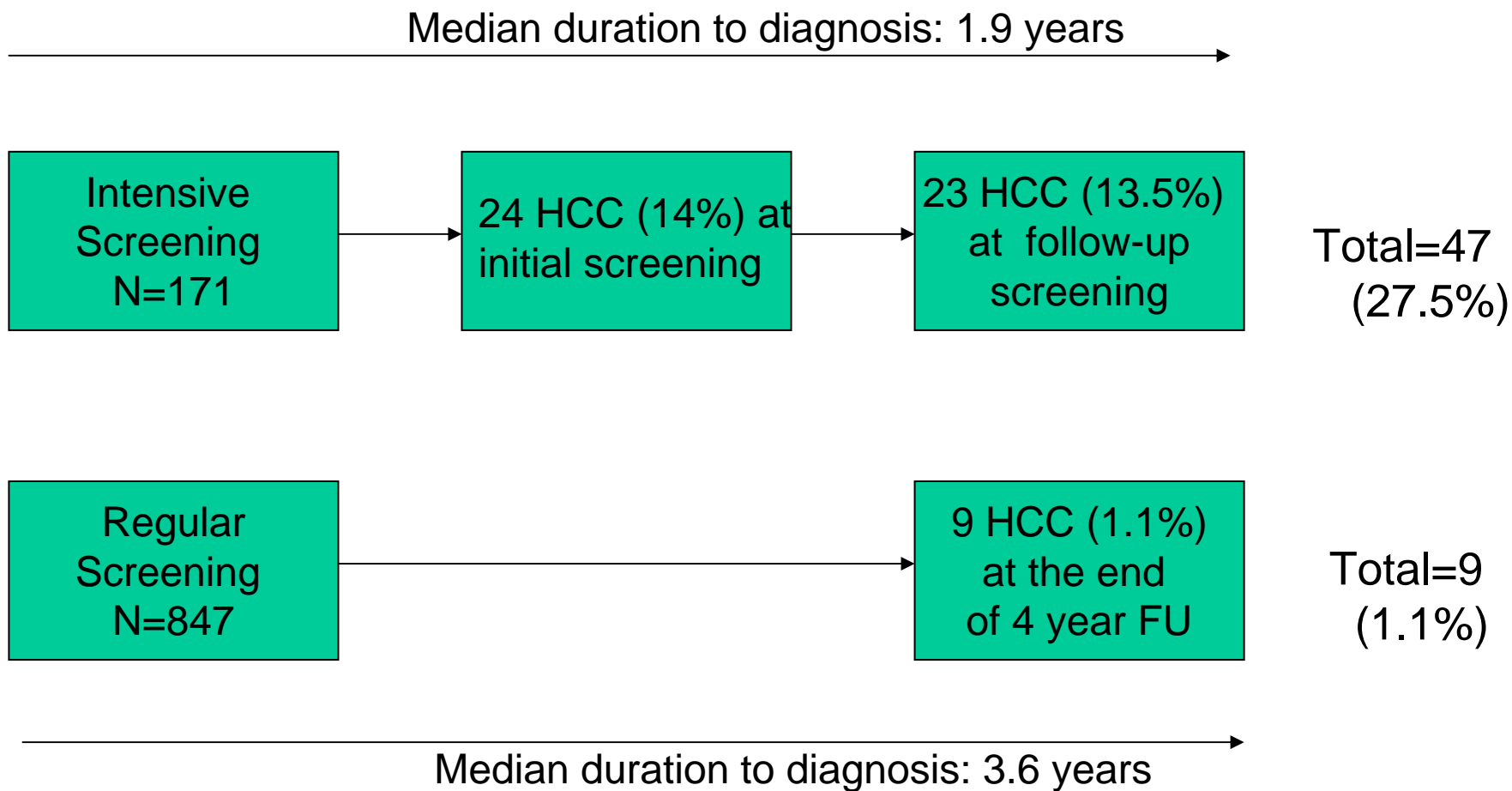
Hepatology 32:842,00; Hepatology 22:432,95; NEJM 325:675,91; Annals of Surg 227:513,98; J Cancer Res Clin Oncol 123:357, 1997

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PASCO 2004

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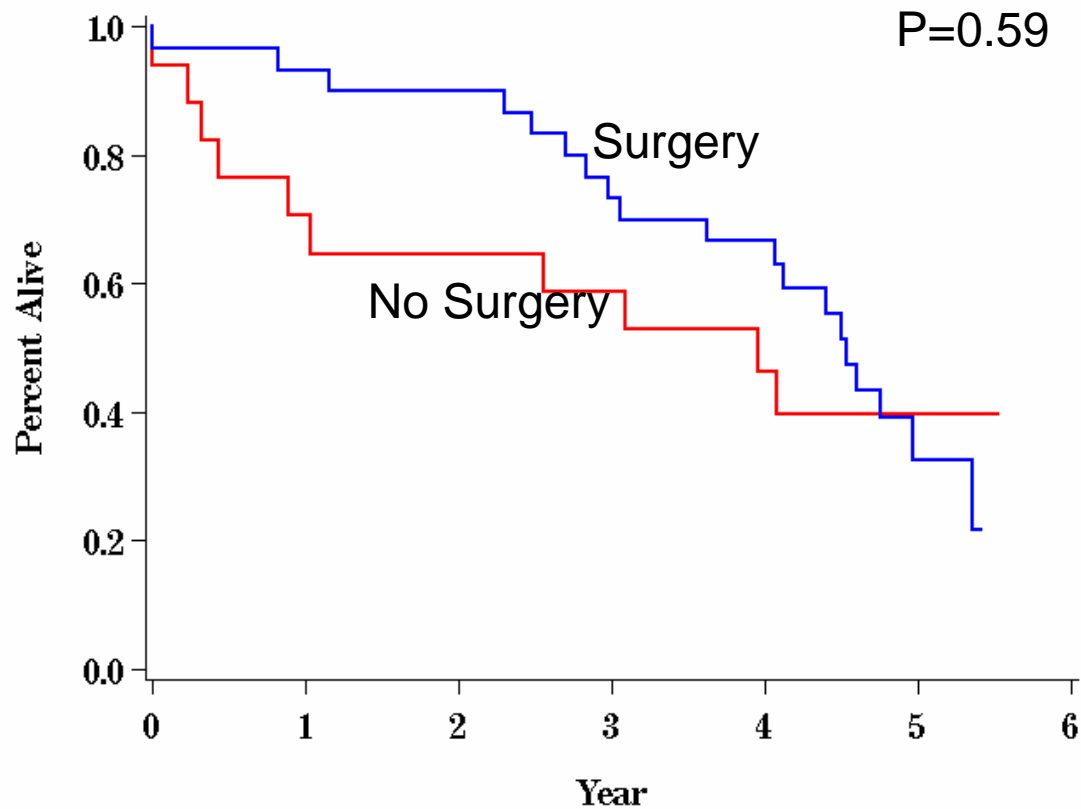
Intensive Screening

	Initial Screening (N=23)	Follow-up Screening (N=24)	Total (N=47)
Surgical resection	9 (39%)	8 (33.3%)	17 (36%)
No surgery	14 (61%)	16 (66.6%)	30 (64%)

Regular Screening: 5 out of 9 had surgery (55.6%)

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Survival: surgical vs non-surgical



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Simple, Noninvasive Screening
Tests Confirmed by
Randomized Controlled Trials

Type of Cancer

Breast

Colon

Rectum

Cervix

Test

X-ray

Sigmoidoscopy

Fecal occult blood testing

Pap smear

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Simple, Noninvasive Screening Tests with No Randomized Controlled Trials Available

Type of Cancer

Prostate

Melanoma

Ovary

Testis

Bladder

Endometrium

Lung

Hepatoma

Test

Prostate-specific antigen

Visual examination

Ultrasonography/CA-125

Self-examination

Hematuria testing

Ultrasonography

Low-dose computerized tomography

AFP and Abdominal US

