Cancer in Primary Care

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Disclosure

I have no financial interests or relationships to disclose.

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CANCER IN PRIMARY CARE

A. The war on cancer

B. Cancer screening

C. Cancer prevention

D. Cancer survivorship

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WAR ON CANCER

President Richard Nixon signs the National Cancer Act on December 23, **1971**

4

WAR ON CANCER

President Joe Biden announces Cancer Moonshot on February 3, **2022**

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BURDEN OF DISEASE: PRE-COVID19

Morbidity and mortality

Disease	*World*	*High-income*
Circulatory	1	1
Infections	2	6
Mental, behavioral	3	3
Neonatal	4	7
Cancers	**5**	**2**
Musculoskeletal	6	4
Injuries	7	5

IMHE, Seattle, 10/20

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PEOPLE WITH CANCER, 2024

US: excluding non-melanoma skin cancer

2,001,140 people newly diagnosed (2024 est.)

35% diagnosed less than 5 years ago

17,113,494 people living with cancer (2023 est.)

5-year survival: **70%** (was **50%** in 1975)

611,720 people die from cancer (2024 est.)

ACS, SEER

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CANCER, DIAGNOSES AND DEATHS, 2024

Cases

Estimated New Cases

Male			Female		
Prostate	299,010	29%	Breast	310,720	32%
Lung & bronchus	116,310	11%	Lung & bronchus	118,270	12%
Colon & rectum	81,540	8%	Colon & rectum	71,270	7%
Urinary bladder	63,070	6%	Uterine corpus	67,880	7%
Melanoma of the skin	59,170	6%	Melanoma of the skin	41,470	4%
Kidney & renal pelvis	52,380	5%	Non-Hodgkin lymphoma	36,030	4%
Non-Hodgkin lymphoma	44,590	4%	Pancreas	31,910	3%
Oral cavity & pharynx	41,510	4%	Thyroid	31,520	3%
Leukemia	36,450	4%	Kidney & renal pelvis	29,230	3%
Pancreas	34,530	3%	Leukemia	26,320	3%
All sites	**1,029,080**		**All sites**	**972,060**	

Estimated Deaths

Male			Female		
Lung & bronchus	65,790	20%	Lung & bronchus	59,280	21%
Prostate	35,250	11%	Breast	42,250	15%
Colon & rectum	28,700	9%	Pancreas	24,480	8%
Pancreas	27,270	8%	Colon & rectum	24,310	8%
Liver & intrahepatic bile duct	19,120	6%	Uterine corpus	13,250	5%
Leukemia	13,640	4%	Ovary	12,740	4%
Esophagus	12,880	4%	Liver & intrahepatic bile duct	10,720	4%
Urinary bladder	12,290	4%	Leukemia	10,030	3%
Non-Hodgkin lymphoma	11,780	4%	Non-Hodgkin lymphoma	8,360	3%
Brain & other nervous system	10,690	3%	Brain & other nervous system	8,070	3%
All sites	**322,800**		**All sites**	**288,920**	

Deaths

ACS

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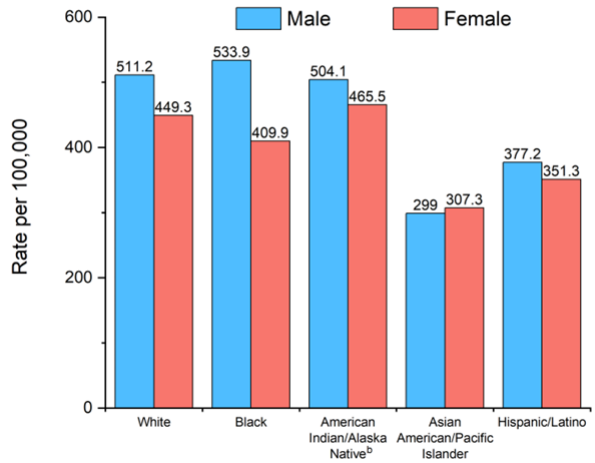
CANCER INCIDENCE IN DIFFERENT GROUPS



ACS, SEER

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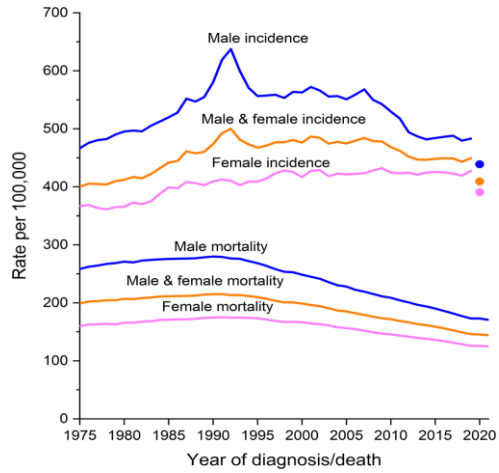
CANCER INCIDENCE SINCE 1975



CA Journal, 1/2024

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CANCER 5-YEAR SURVIVAL
SINCE 1975

Site	1975-77	1995-97	2013-2019
All sites	49	63	69
Breast (female)	75	87	91
Colon & rectum	50	61	64
Leukemia	34	48	67
Liver & intrahepatic bile duct	3	7	22
Lung & bronchus	12	15	25
Melanoma of the skin	82	91	94
Non-Hodgkin lymphoma	47	56	74
Ovary	36	43	51
Pancreas	3	4	13
Prostate	68	97	97
Uterine cervix	69	73	67
Uterine corpus	87	84	81

ACS/SEER

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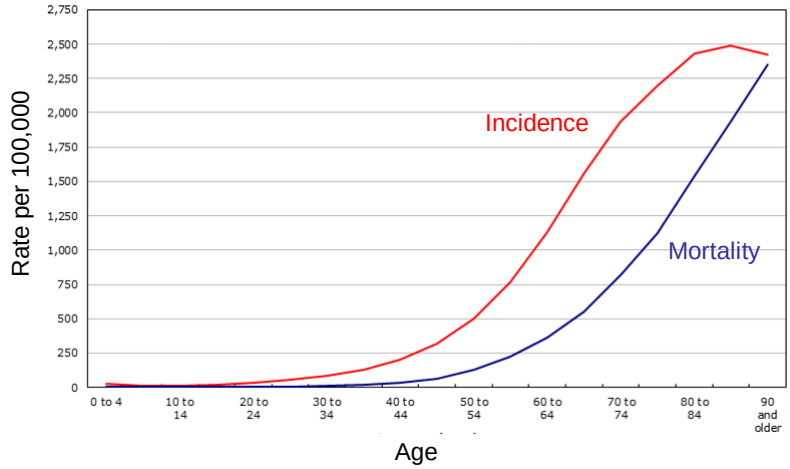
AGE AND CANCER



Cancer Is a Disease of Older People

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LIFETIME PROBABILITY FOR CANCER

(Excluding non-melanoma skin cancer)

Males

Site	Risk
All sites*	1 in 3
Prostate	1 in 9
Lung & bronchus	1 in 15
Colon & rectum	1 in 23
Urinary bladder†	1 in 27
Melanoma of the skin‡	1 in 27
Non-Hodgkin lymphoma	1 in 42
Kidney & renal pelvis	1 in 47
Leukemia	1 in 56
Oral cavity & pharynx	1 in 61
Pancreas	1 in 62

Females

Site	Risk
All sites*	1 in 3
Breast	1 in 8
Lung & bronchus	1 in 17
Colon & rectum	1 in 25
Uterine corpus	1 in 35
Melanoma of the skin†	1 in 40
Non-Hodgkin lymphoma	1 in 54
Thyroid	1 in 55
Pancreas	1 in 65
Ovary	1 in 79
Leukemia	1 in 80

- *Incidence about **40%***
- *Risk of dying from cancer: **25%***

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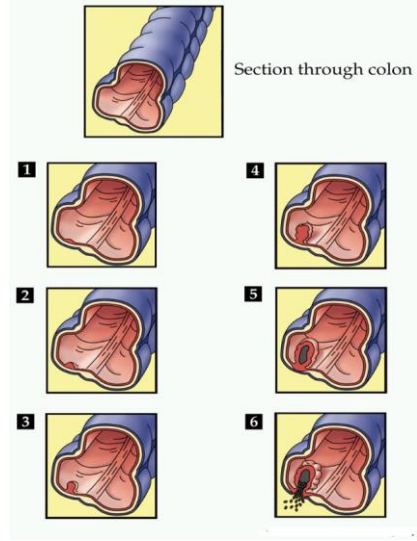
AGE AND CANCER: MOLEC. BIOGRAPHY



Polyp

Precancerous lesion

Adenoma

Carcinoma

Metastatic tumor

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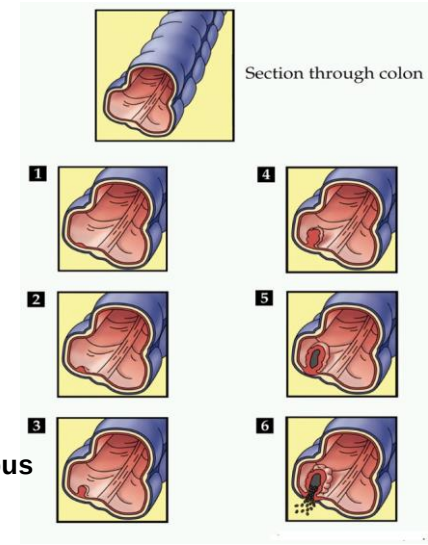
AGE AND CANCER: MOLEC. BIOGRAPHY



Mutation in APC gene: **Polyp**

Mutation in DCC gene: **Adenoma**

Mutation in p53 gene: **Carcinoma**

Mutation in ras gene: **Precancerous lesion**

Mutation in anti-metastasis genes: **Metastatic tumor**

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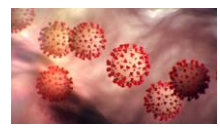
IMPACT OF COVID19 PANDEMIC ON CANCER

COVID19 Pandemic	Early Detection	Diagnosis	Treatment
Reduced access to care	*Delayed screening*	*Later stage diagnosis*	*Delayed treatment*

2020: 17% fewer breast cancer patients diagnosed



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CANCER IN PRIMARY CARE

A. The war on cancer

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D. Cancer survivorship

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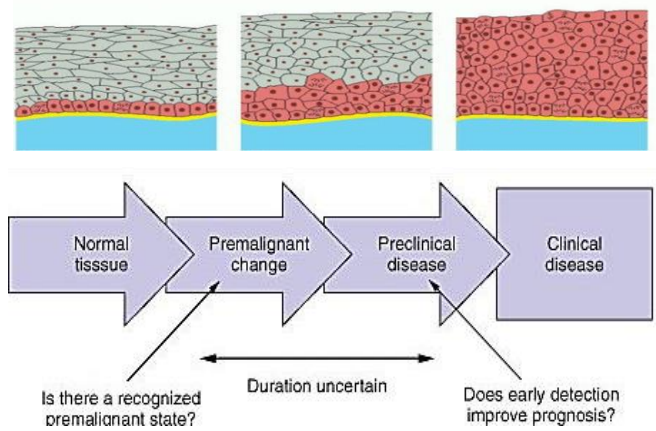
THE LOGIC OF SCREENING



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THE LOGIC OF SCREENING

Benefit: Reduced mortality

Costs: Expense
Morbidity
Acceptability

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HOW GOOD IS A SCREENING TEST?

Reliability: Repeatable with same result.

Validity: Is the test an indicator of disease?

Sensitivity: Proportion of people *with* the disease who test positive

False negative: burden on patient

Specificity: Proportion of people *without* the disease who test negative

False positive: burden on providers

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CANCER SCREENING IN PRIMARY CARE

Screening tests detect disease before it is harmful:

Success: A good test widely applied

- Cervical cancer screening is very successful
- Breast cancer screening is successful
- Colon cancer screening is successful
- Prostate cancer screening is partially successful
- Lung cancer screening is partially successful

Endpoint issue: Does detection result in improved survival?

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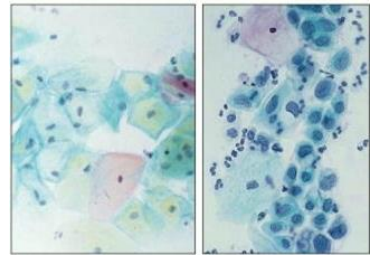
CERVICAL CANCER SCREENING: PAP SMEAR

G. Papanicolaou
1928-1943



Normal Precancerous

This test is being replaced with HPV DNA testing of the cervical sample

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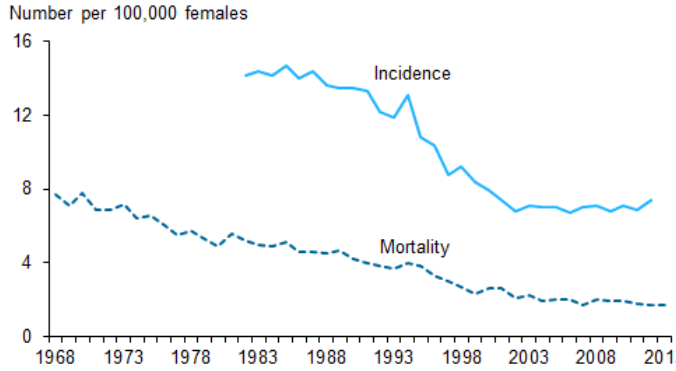
CERVICAL CANCER USA



Over lifetime, with no screening incidence is 5%
with screening, incidence is 0.5%

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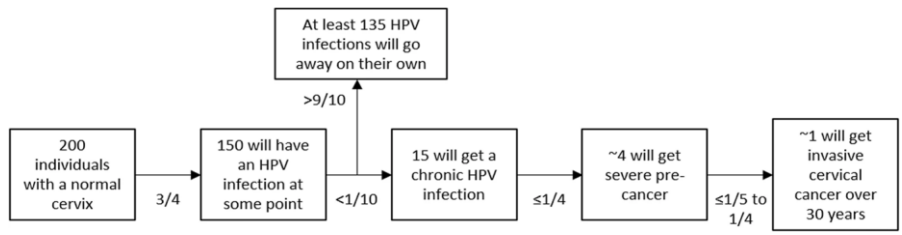
CERVICAL CANCER AND HPV



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USPSTF:US PREVENTIVE SERVICES TASK FORCE, 2024

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Michael Silverstein (pediatrics)
James Stevermer, MD, MPH (prev)
Sandra Underwood, RN, PhD (health disp)
John Ruiz, PhD (psychology)

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CERVICAL CANCER SCREENING: USPSTF 2018

Population	Recommendation	Evidence for screening
< 21 years	No screening	D
21-29 years	Cyt. every 3 years	A
30-65 years	Cyt. every 5 years or HPV every 5 years	A
>65 years	No screening	D
Hysterectomy with no prior lesion	No screening	D

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CERVICAL CANCER SCREENING: PRIMARY CARE ISSUES

< 21 years	**No screening**

Primary care surveys: 19 % (2 million) females age 15-20 annual Pap smear
Mostly unnecessary

30-65 years	**Cyt. every 5 years or HPV every 5 years**

Cohort study of cyt .vs. HPV: HPV testing is 2x more sensitive in detecting neoplasia (2018)

>65 years **No screening**

California study (2023): 17% of cervical cancer diagnoses were in women >65; generally advanced disease with poor outcome.
Why stop screening?

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CERVICAL CANCER SCREENING: ACS 2023

Population	Recommendation	Evidence for screening
< 25 years	No screening	D
25-65 years	HPV every 5 years	A
25-65 years	Cyt. every 3 years with HPV every 5 years	A
>65 years	No screening	D
Hysterectomy with no prior lesion	No screening	D

Transition from cytology to HPV
Issue: Local availability of HPV testing vs cytology

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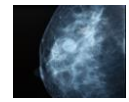
BREAST CANCER SCREENING

- Breast self-examination

- Clinical breast exam

- Mammogram



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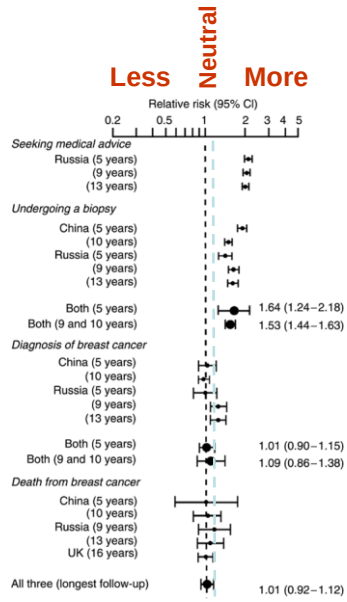
BREAST CANCER SCREENING: SELF EXAM



More *doctor visits*

More *biopsies for cancer*

No change *in breast cancer diagnosis*

No change *in breast cancer deaths*

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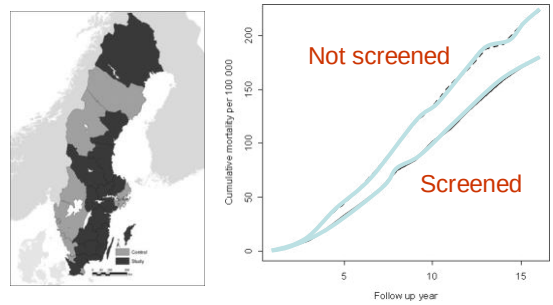
MAMMOGRAPHY SCREENING SWEDEN: 1986-2005



Reduction in deaths in screened group

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BREAST CANCER SCREENING RECOMMENDATION 2024 USPSTF

Population	***Recommendation for mammography***	***Evidence for screening***
< 40 years	No screening unless genetic risk	D
40-74 years	Biennial	B
>75 years	No screening	I: insufficient evidence for benefit

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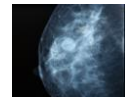
BREAST CANCER SCREENING ARTIFICIAL INTELLIGENCE

Can AI improve radiology screening?

40,000 women screened med. age 54 mammo. in Sweden
20,000 mammo. read by two radiologists
20,000 mammo. read by two radiologists plus AI
Results: Screening only: 203 breast cancer
Screening plus AI: 244 breast cancer (20% increase)

Lancet Oncol. 8/1/23



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SCREENING FOR BREAST CANCER SUSCEPTIBILITY: MUTATIONS

Clinical case:
22-year-old female
Mother: breast cancer age 35
Grandmother: breast cancer age 38

Analysis:
DNA sequencing for 23 genes implicated in breast cancer: *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, DICER, EPCAM, MLH1, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, RECQL, SMARCA4, STK11, TP53*

- Patient: Change behavior to lower risk factors
- Physician: Advise preventive care, increase screening

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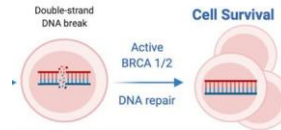
SCREENING FOR BREAST CANCER SUSCEPTIBILITY: MUTATIONS

Clinical case: DNA sequencing:

Mutation in BRCA1: c211 A to G (very rare variant)

Result: aberrant splicing of pre-mRNA leading to premature stop codon and truncated, non-functional protein

BRCA1 normal role: DNA damage repair; tumor suppressor



Risk for breast cancer by age 70: 60% (normally 12%)

Patient may choose prophylactic mastectomy

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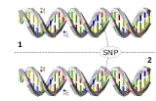
SCREENING FOR BREAST CANCER SUSCEPTIBILITY: POLYGENIC SCORE

***Polygenic risk score**:* 377 SNP's in DNA



- Tested on 94K breast cancer patients and 75K controls

Polygenic risk score	***Breast cancer risk by age 80***
1-5%	0.05
40-60%	0.10
>99%	0.33

For an individual with a high risk score:

- Patient: Change behavior to lower risk factors
- Physician: Advise preventive care, increase screening

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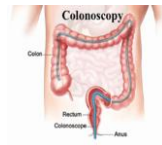
COLON CANCER SCREENING

- **Fecal tests**:
  FOBT: blood in stool
  FIT: immuno. blood in stool
  FIT-DNA: Tumor DNA

- **Sigmoidoscopy**
  (distal colon)

- **Colonoscopy**



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COLON CANCER LIVES SAVED BY SCREENING

	Screening interval age 45-75	CRC lives saved / 1000 screened
FOBT	Annual	26
FIT	Annual	26
FIT-DNA	Annual	26
Sigmoid.	5 yr	26
Colonoscopy	10 yr	27

USPSTF

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COLON CANCER SCREENING

Clinical case: 65-year-old man

No history of bowel abnormalities

Mother died of colon cancer age 85

Declined primary care practitioner's recommendation for colonoscopy

Test: FIT home test positive

Follow-up: colonoscopy revealed multiple adenomatous polyps: removed; then chemotherapy
DNA analysis: No germline mutations (not inherited)

Treated with surgery, chemotherapy

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COLON CANCER SCREENING RECOMMENDATION 2021 USPSTF

Population	***Recommendation for screening***	***Evidence for screening***
45-49 years	Screening as below	B
45-75 years	*Stool:* FOBT: annual FIT: annual FIT-DNA: 1-3 yr	A
45-75 years	*Direct visualization:* Sigmoid: every 5 yr Colonoscopy: every 10 yr	A
>75 years	Selectively offer screening	C: low evidence of benefit

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COLON CANCER SCREENING: NEW MOLECULAR TESTS

Multitarget stool DNA / RNA

- Detects abnormal DNA markers in advanced colon cancer: e.g., *BMP4, NDRG4* methyl., *KRAS* mutation
- Sensitivity 92% for advanced, but 42% precancerous
- Specificity 80%: many false positives – follow up colonoscopy

Blood test circulating DNA*: "* liquid biopsy"

- Detects abnormal DNA methylation - 50 cancers
- Sensitivity for colon cancer: 40%, specificity >95%
- Large clinical trials underway
- Over 15 other tests underway, including sequencing

So far, data on cancer detection but not yet on mortality

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PROSTATE CANCER SCREENING

- *Digital exam*: Sensitivity 51%
  Specificity 59%

- *Prostate specific antigen* blood test (PSA)
  Sensitivity 21%
  Specificity 91%
  (at 4 ng/ml)

SEER: 45% of prostate cancers "over-diagnosed": would not increase morbidity or mortality after treatment

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PROSTATE CANCER SCREENING: PSA

The Great Prostate Mistake
RICHARD J. ABLIN

EACH year some 30 million American men undergo testing for prostate-specific antigen, an enzyme made by the prostate. Approved by the Food and Drug Administration in 1994, the P.S.A. test is the most commonly used tool for detecting prostate cancer. The test's popularity has led to a hugely expensive public health disaster. It's an issue I am painfully familiar with — I discovered P.S.A. in 1970.

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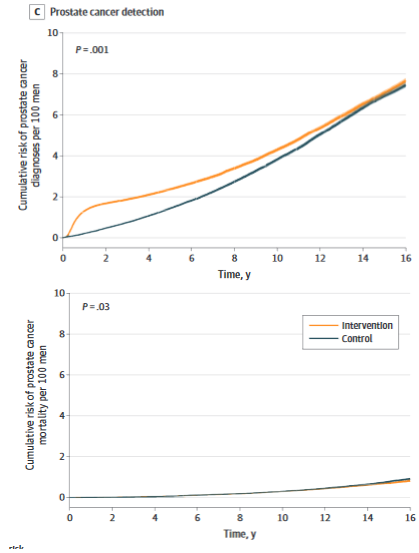
PSA SCREENING AND PROSTATE CANCER: UK



JAMA 4/6/24

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PROSTATE CANCER SCREENING RECOMMENDATION 2018 USPSTF

Population	*Recommendation for PSA screening*	*Evidence for screening*
< 55 years	No screening	D
55-69 years	Discuss: small benefit vs. harm by additional testing, over-diagnosis, treatment side effects	C
>70 years	No screening	D

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OTHER WAYS TO SCREEN FOR PROSTATE CANCER?

- *Prostate Health Index (PHI):* free PSA, total PSA, 2pro-PSA variant

- *MRI:* After a positive PSA screen or symptoms, MRI can detect whether prostate cancer is present: reduce need for biopsy or guide for biopsy

- *Exosomes:* Membrane-bound vesicles released from cancer cells to urine; levels of mRNA for PCA3 and two other genes correlate with aggressive PCa: reduce need for biopsy

- *MyProstateScore:* mRNA transcripts of 18 genes in urine indicate probability of aggressive tumor (Gleason >7)

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LUNG CANCER SCREENING

5-year survival for breast cancer >90%

" colorectal 65%

" prostate >95%

Screening detects cancers when localized

" lung 23%

5-year survival for lung cancer after diagnosis:

Localized: 60% (25% of patients)
Regional: 30% (20% of patients)
Distant spread: 10% (55% of patients)

Need test to detect localized disease

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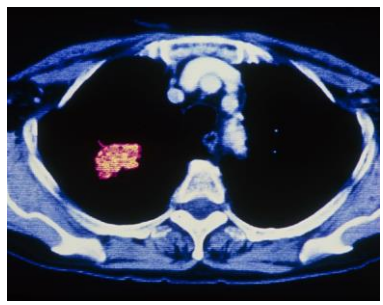
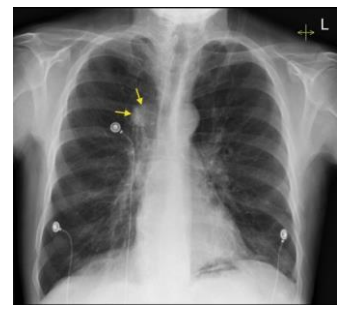
LUNG CANCER SCREENING





Low-dose CT scan:

Sensitivity 94%
Specificity 95%

X-ray:

Sensitivity 73%
Specificity 91%

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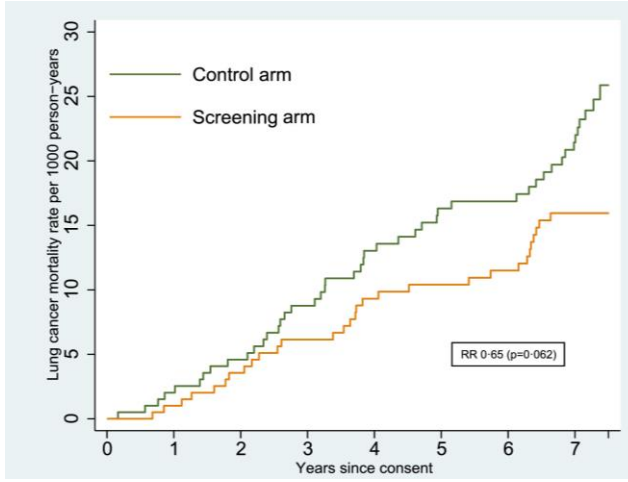
LUNG CANCER SCREENING: MORTALITY



Lancet Regional Health Europe, 2021

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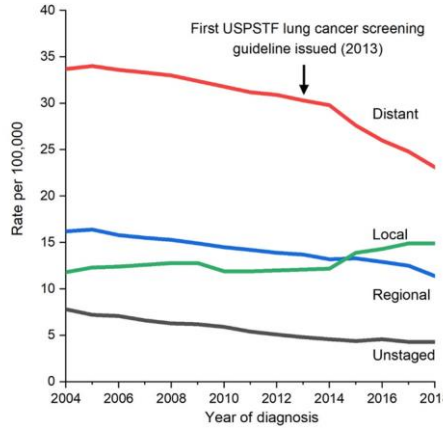
LUNG CANCER SCREENING USA



Only 10% participation by those eligible: 14.5 million

ACS, 2024

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LUNG CANCER SCREENING RECOMMENDATION 2023 USPSTF

Population	*Recommendation for low-dose CT screening*	*Evidence for screening*
50-80 years	Current smokers and past smokers; annual screen	B

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CANCER IN PRIMARY CARE

A. The war on cancer

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CAUSES OF CANCER

Nevada test site: 100 explosions, 1951-62

Filming site: St. George, Utah, downwind from Nevada test site

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CAUSES OF CANCER

Dick Powell, dir.
Lung cancer

Pedro Armendariz
Kidney cancer

Susan Hayward
Brain cancer

Agnes Moorhead
Uterine cancer

John Hoyt
Lung cancer

John Wayne
Stomach cancer

Radiation cause? But they were smokers.

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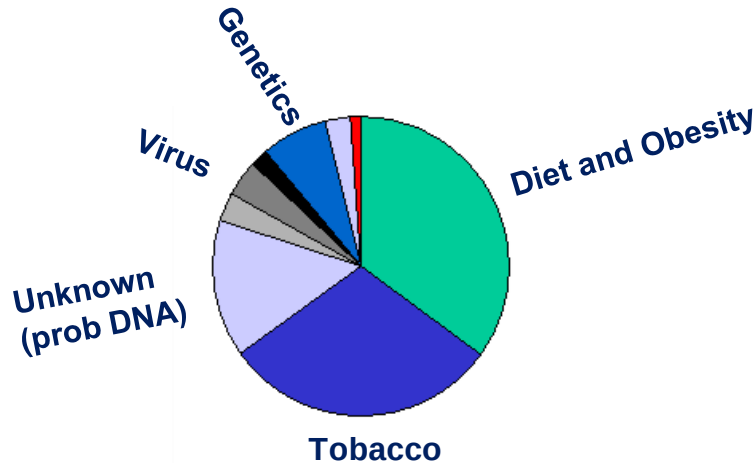
CAUSES OF CANCER



How do we know this?

- *Epidemiology*

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RISK ANALYSIS

***Hazard identification*:** Does it cause cancer?

***Dose response*:** How much cancer can it cause at what dose?

***Exposure assessment*:** How much of it gets into people?

***Risk characterization*:** Is the exposure worth the benefits?

Discussions in the primary care setting

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CANCER PREVENTION: AVOIDING CARCINOGENS

Tobacco smoking causes 180K cancer deaths US/ yr (+ 300K from stroke, cardiovascular, lung diseases)

Tobacco smoke has over 7000 identifiable chemicals, of which 70 are known carcinogens: *not nicotine*

e.g., Benzpyrene binds to DNA, causes mutations in G bases

US Adults: 2022: 11% smokers US (2005: 21% and1965: 42%)
- more smokers among those with less education, less income

Role of primary care physicians: ***prevent*** *(adolescents);* ***stop*** *(adults)*

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CANCER PREVENTION: SMOKING: ADULTS

Method	**Effectiveness: reduction after 1 year**
None (self)	0.1%
Physician counseling	5%
Nicotine patch, gum, inhaler	10-16%
Bupropion (Wellbutrin)	15-23%
Varenicline (Chantix)	23-30%

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CANCER PREVENTION: TOBACCO SMOKING: ADOLESCENTS

90% of smokers began before age 21

2% of middle school students smoke tobacco non-electronic
down from 4% 10 years ago

5% of high school students smoke tobacco non-electronic
down from 16% 10 years ago

USPSTF: recommend counseling by primary care physicians for adolescents who have not begun smoking (B evidence)

Public health: *ads:* what works: conspiracies
laws to make smoking an "outlaw activity"
CDC

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CANCER PREVENTION: VAPING

Many flavors: pods; online purchase

2023: 18% age 18-24 vaping

Most flavored vapes no longer sold

Must be 18 to purchase and possess

Low but significant levels of some carcinogens; irritants; bronchitis

CDC cautions against vaping in adolescents and non-smokers

Does vaping lead to cigarette smoking in nonsmokers?
Does vaping reduce cancer in smokers?

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CANCER PREVENTION: VAPING

Does vaping reduce cancer in smokers?

Surrogate end point: Does vaping reduce tobacco smoking in smokers?

China: 1060 smokers (10/day)

	Quit after 6 months
Electronic cigarettes	16%
Varenicline	14%
Nicotine gum	8%

Switzerland 1246 smokers (5/day)

	Quit after 6 months
Electronic cigarettes + counseling	29%
Counseling only control	16%

JAMA Int Med. 184: 291 (2024)
NEJM 390: 601 (2024)

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TOBACCO SMOKING CESSATION ADULTS: RECOMMENDATIONS 2021 USPSTF

Population	***Recommendation***	***Evidence***
Non-pregnant	Clinician counseling; FDA approved drugs	A
Pregnant	Clinician counseling; no drugs	A
All	E-cigarettes	I: insufficient evidence for benefit

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HUMAN TUMOR VIRUSES

Virus	*Cancer*
Epstein-Barr virus	Lymphoma
Papilloma virus	Cervical cancer
Hepatitis B virus	Liver cancer
Human T-cell leukemia	T-cell leukemia virus
Herpes virus 8	Kaposi sarcoma
Polyoma virus	Merkel carcinoma

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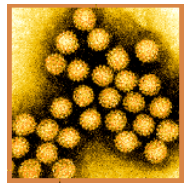
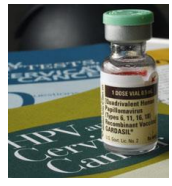
HPV AND CERVICAL CANCER



Harald zur Hausen, MD
Nobel Prize, 12/2008



HPV vaccine ages 15-26:
- lowers HPV by >85%
- lowers CIN by 99% at 5 yr follow-up

Issue: participation two doses
By age 26: Australia 80%; USA 60%

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CANCER AND NUTRITION

EPIC: European Prospective Investigation into Cancer and Nutrition

520,000 people enrolled 1992-2009

Baseline:
Diet, nutrition, lifestyle environment

Follow-up:
Medical history annually
9 million blood samples stored

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EPIC: European Prospective Investigation into Cancer and Nutrition

- Obesity: Increased breast, colon cancer
- Mediterranean diet: No effect on cancer
- Vitamin supplements: No effect on cancer
- Alcohol: Slight increase in liver and breast cancer
- Dietary fiber: Less colon cancer
- Cured meats: More colon cancer

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CANCER CHEMOPREVENTION CLINICAL TRIALS

Natural substances

Vitamins A, E: Colon cancer in post-menopausal women
Result: *No change*
Beta-carotene and vitamin A: Lung cancer in smokers
Result: *Increased cancer*

Drugs

Finasteride: Prostate cancer in men over 55 **at risk**
Result: *25% reduction*
Tamoxifen, raloxifene: Breast cancer in women **at risk**
Result: *50% reduction*

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CANCER IN PRIMARY CARE

A. The war on cancer

B. Cancer screening

C. Cancer prevention

D. Cancer survivorship

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CANCER SURVIVORSHIP

Clinical vignette:

- Primary care clinic: 62-year-old man has episodic abdominal pain and diarrhea
- Loss of appetite and weight loss
- Rapid fecal occult blood test is positive for hemoglobin
- Referred for colonoscopy: polyps, biopsy shows adenocarcinoma
- Referred for oncology; treated with surgery, chemotherapy
- ***Six months later, patient is back in the primary care clinic***

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CANCER SURVIVORSHIP

*Survivorship**: Interval after treatment up to cure, recurrence, or death*

There are 18.1 million cancer survivors in the US

By 2030, there will be a 25% increase in cancer survivors

In 2024: 70% of people live 5 years after diagnosis
50% " " " 10 " " "
20% " " " 20 " " "

70% of survivors have functional limitations

This is a significant issue for primary care practitioners

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CANCER SURVIVORSHIP

Primary care practitioners: Screening

Oncologists, etc.: Diagnosis, treatment

Primary care practitioners: Survivorship

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CANCER TREATMENT

The primary care practitioner is a gatekeeper for where a cancer patient is treated

National Cancer Inst. Cancer Centers: 71 in 36 states

- Typically, academic centers, research, clin. trials
- Treat about 25% of all cancer patients
- 75% treated in local cancer centers

Two major trends re primary care referral:

- NCI centers buying out local cancer centers
- NCI centers PR campaign

CANCERCARE IS DIFFERENT

CANCER PATIENTS BILL OF RIGHTS

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CANCER SURVIVORSHIP

From a patient:

"The lack of guidelines and providers who understand the long-term needs of cancer survivors in an unmet need. My cancer was diagnosed 30 years ago, when I was 13. I have not found a provider who understands both sides of my current needs. (Primary care practitioners) do not understand my cancer and oncologists do not understand my non-cancer health maintenance needs, such a monitoring cholesterol and blood pressure."

JNCI monographs, 40

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CANCER SURVIVORSHIP CARE

A typical cancer survivorship plan for the primary care practitioner:

- **Surveillance**: recurrence of primary; secondary cancers (8% of survivors)
- **Management** of late effects of treatment: fatigue, neuropathy, etc. (up to 80% have some disability); chronic pain (35%)
- **Psycho-social** implications of survivorship: mood disorders (20%), family, etc.
- **Coordination of care:** PCP and oncology team
- **Treatment plan:** Adapted to EHR

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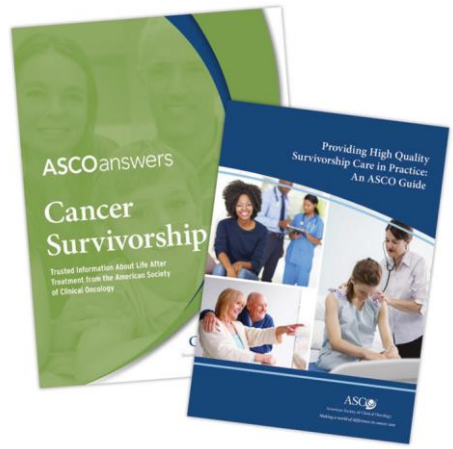
CANCER SURVIVORSHIP CARE

Patients



Practitioners

American Society of Clinical Oncology

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CANCER IN PRIMARY CARE

A. The war on cancer

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