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Cancer Screening: Controversial Topics

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Outline

- Case review
- Introduction
- Why this matters
- Breast Cancer
- Prostate Cancer
- Conclusion

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Case

- 75 year old female w/ O2 dependent COPD
- Symptoms of constipation, weight loss, decreased appetite, “hemorrhoid flare”
- Empiric cortisone with no improvement
- Referred for 1st colonoscopy (refused in past)
  - Found to have a frieable anal and distal rectal mass
  - Biopsy proven squamous cell carcinoma

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Case

- Further history in my office – patient had rectal bleeding for > 1 year, fecal incontinence, and severe pain on BM.
- Exam showed a > 5 cm circumferential anal canal mass extending into the distal rectum, + left inguinal node

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Case

- Locally advanced anal canal cancer
- Treatment was planned for definitive chemoradiation – curative intent
- Patient passed away within days of my initial evaluation

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Case

- If your patient has symptoms, you are not screening – you need prompt diagnostic test
- If you don't ask the question (or do the exam) you will not know
- Properly performed rectal, Gyn breast exams take time but can save lives
- Screening has implications for the population and also for your individual patient

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Introduction

- Cancer screening seeks to detect cancer before a person has any symptoms.
- Screening can mean:
  - History and Physical Exam
  - Laboratory Test
  - Imaging
  - Invasive Procedure
  - Genetic Screening

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Introduction

- Screening tests have risks.
  - Some screening tests can cause serious problems.
  - False-positive test results are possible.
  - False-negative test results are possible.
  - Finding the cancer may not improve the person's health or help the person live longer.

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Introduction

Certain factors may cause disease-specific outcomes to look like they are getting disproportionately better with screening when they are not.

- Lead Time bias
- Length time bias
- Overdiagnosis

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Introduction

Ideal Cancer Screening Tests:

- Screen for a cancer that is easier to treat and cure when found early.
- Has few false negative results
- Has few false positive results.
- Decreases the chance of dying from cancer.
- Is cost effective for the healthcare delivery system

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Why is this important?

	Common Types of Cancer	Estimated New Cases 2015	Estimated Deaths 2015
1.	**Breast Cancer (Female)**	**231,840**	**40,290**
2.	Lung and Bronchus Cancer	221,200	158,040
3.	Prostate Cancer	220,800	27,540
4.	Colon and Rectum Cancer	132,700	49,700
5.	Bladder Cancer	74,000	16,000
6.	Melanoma of the Skin	73,870	9,940
7.	Non-Hodgkin Lymphoma	71,850	19,790
8.	Thyroid Cancer	62,450	1,950
9.	Kidney and Renal Pelvis Cancer	61,560	14,080
10.	Endometrial Cancer	54,870	10,170

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A Brief word

"The Tyranny of Randomized Controlled Trials"

- ***Equipoise*** – feasible in principle but difficult in practice – leads to crossover
- Careful patient selection may mean results are not generalizable to population
- Participating centers may not represent hospitals nationally – experience
- Systematic bias of study design (funding source)

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Breast Cancer

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Why screen for Breast Cancer?

Breast cancer is easier to treat when found early

- Pillars of breast cancer treatment are surgery, systemic therapy, and radiotherapy
- Surgery: Lumpectomy vs Mastectomy, ALND vs SLN bx
- Systemic therapy: need for chemotherapy vs not
- Radiotherapy: breast only radiation vs RT regional lymphatics
- Detecting breast cancer earlier can and does lead to decreased physical and psychosocial side effects for the patient.

- Source : NCCN guidelines

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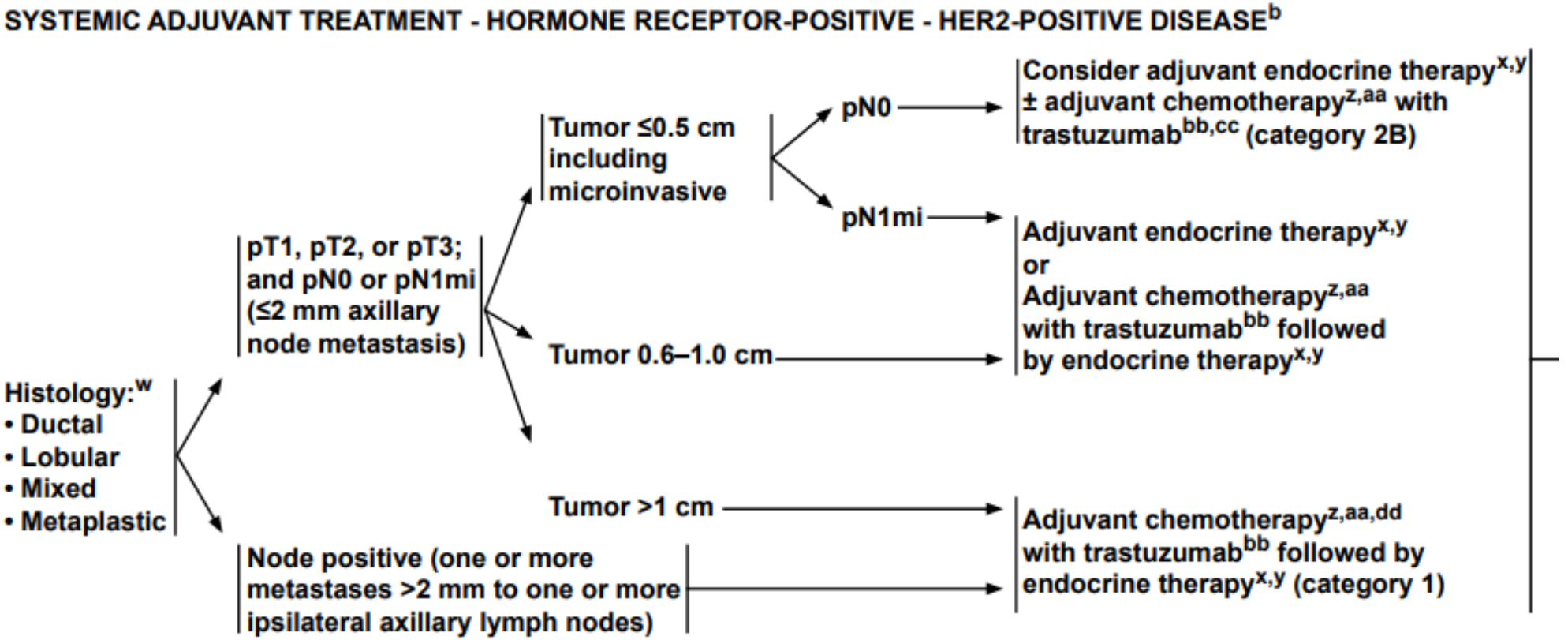
Is breast cancer easier to treat when found early?



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Is breast cancer easier to treat when found early?

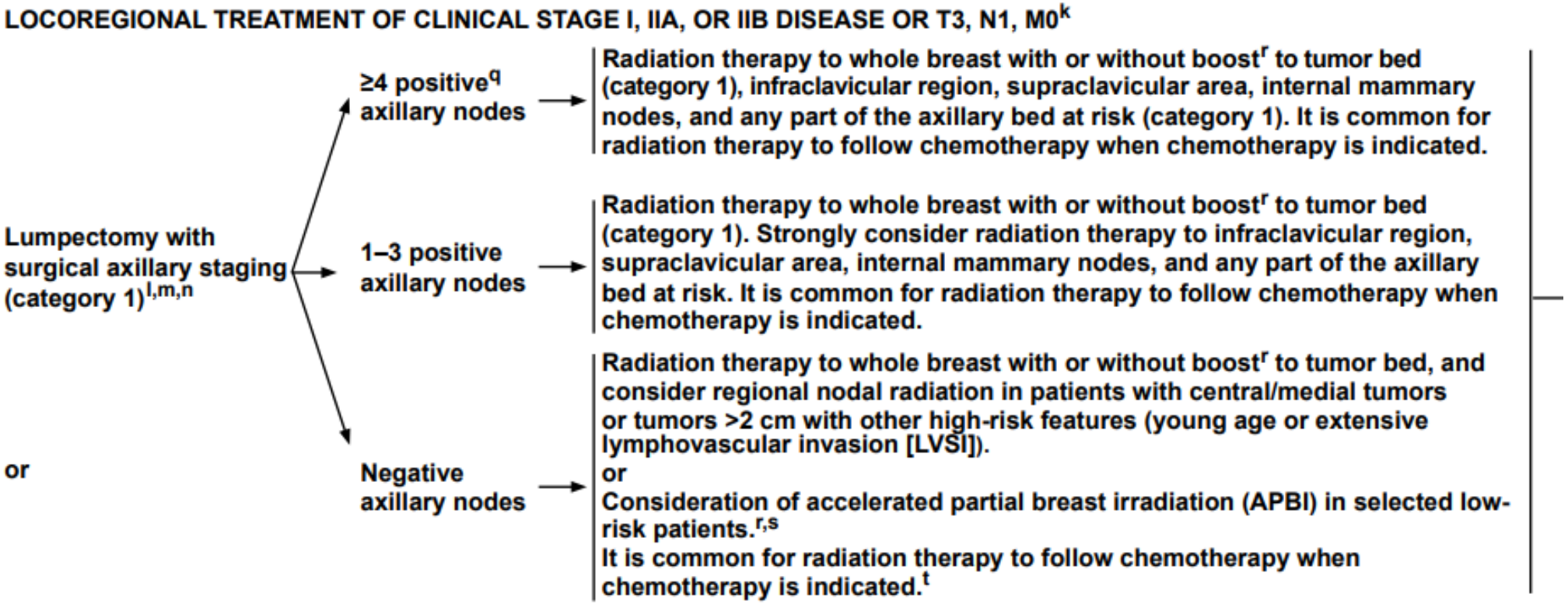

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Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging System For Breast Cancer

Primary Tumor (T) The T classification of the primary tumor is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cutoff for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cutoff. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2.0 cm. Designation should be made with the subscript "c" or "p" modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements, respectively. In general, pathologic determination should take precedence over clinical determination of T size.

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted
T1	Tumor ≤20 mm or less in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules).

Note: Invasion of the dermis alone does not qualify as T4

T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

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Table 1 (continued)

Pathologic (pN) *(continued)*

pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***
pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4–9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN3	Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected*** ; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in ten or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes

*** "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

**** "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

Distant Metastasis (M)

M0	No clinical or radiographic evidence of distant metastases
cM0(I+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Table 1 (continued)

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0	**Stage IIIA**	T0	N2	M0
Stage IA	T1*	N0	M0		T1*	N2	M0
Stage IB	T0	N1mi	M0		T2	N2	M0
	T1*	N1mi	M0		T3	N1	M0
Stage IIA	T0	N1**	M0		T3	N2	M0
	T1*	N1**	M0	**Stage IIIB**	T4	N0	M0
	T2	N0	M0		T4	N1	M0
Stage IIB	T2	N1	M0		T4	N2	M0
	T3	N0	M0	**Stage IIIC**	Any T	N3	M0
				Stage IV	Any T	Any N	M1

* T1 includes T1mi

** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

- M0 includes M0(i+).
- The designation pM0 is not valid; any M0 should be clinical.
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
- Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.
- Postneoadjuvant therapy is designated with "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

HISTOLOGIC GRADE (G)

All invasive breast carcinomas should be graded. The Nottingham combined histologic grade (Elston-Ellis modification of Scarff–Bloom–Richardson grading system) is recommended.[1,2] The grade for a tumor is determined by assessing morphologic features (tubule formation, nuclear pleomorphism, and mitotic count), assigning a value of 1 (favorable) to 3 (unfavorable) for each feature, and adding together the scores for all three categories. A combined score of 3–5 points is designated as grade 1; a combined score of 6–7 points is grade 2; a combined score of 8–9 points is grade 3.

HISTOLOGIC GRADE (NOTTINGHAM COMBINED HISTOLOGIC GRADE IS RECOMMENDED)

GX	Grade cannot be assessed
G1	Low combined histologic grade (favorable)
G2	Intermediate combined histologic grade (moderately favorable)
G3	High combined histologic grade (unfavorable)

HISTOPATHOLOGIC TYPE

The histopathologic types are the following:

In situ Carcinomas

NOS (not otherwise specified)

Intraductal

Paget's disease and intraductal

Invasive Carcinomas

NOS

Ductal

Inflammatory

Medullary, NOS

Medullary with lymphoid stroma

Mucinous

Papillary (predominantly micropapillary pattern)

Tubular

Lobular

Paget's disease and infiltrating

Undifferentiated

Squamous cell

Adenoid cystic

Secretory

Cribriform

[1]Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol 2007;25:5287–312.

[2]Singletary SE, Allred C, Ashley P, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol 2002;20:3628–36.

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Breast Cancer

- Screening Guideline first introduced in 1976
- Dissemination of screening at a population level has had an unprecendented impact on breast cancer detection
- Since the mid 1980s, as breast cancer screening has gained traction, breast cancer related death has dropped > 30% in the USA.
- Guidelines are basis for quality metrics, pay-for-performance, and other healthcare delivery policies
- Controversies remain regarding relative benefit and harm

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Guidelines

Remember, these guidelines are for average risk women.

- No symptoms
- No history of breast cancer / DCIS/LCIS/atypia
- No family history of breast cancer
- No suggestion of a hereditary syndrome
- no history of childhood malignancy / previous radiation

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Before 1980

Pre 1980	Breast self-exam (BSE)	Start during high school years	Monthly
	Clinical breast exam (CBE)	20 and over	"Periodically"
	Mammogram (starting in 1976)	35 - 39	Only if personal history of breast cancer
		40 - 49	May have mammogram if they or their mother or sisters had breast cancer
		50 and over	May have mammograms yearly

Today

Population	Recommendation	Grade (What's This?)
Women, Age 50-74 Years	The USPSTF recommends biennial screening mammography for women 50-74 years.	B
Women, Before the Age of 50 Years	The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account, including the patient's values regarding specific benefits and harms.	C
Women, 75 Years and Older	The USPSTF concludes that the current evidence is insufficient to assess the benefits and harms of screening mammography in women 75 years and older. Go to the Clinical Considerations section for information on risk assessment and suggestions for practice regarding the I statement.	I
All Women	The USPSTF recommends against *teaching* breast self-examination (BSE).	D
Women, 40 Years and Older	The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of clinical breast examination (CBE) beyond screening mammography in women 40 years or older. Go to the Clinical Considerations section for information on risk assessment and suggestions for practice regarding the I statement.	I

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Self Breast Exam

Very little research has been done

- Huge numbers of patients needed – funding issue
- Crossover issue
- long time interval may be needed to detect mortality differece

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Self Breast Exam – Shanghai JNCI

- > 130,000 patients taught BSE with medically supervised refresher every 6 months vs 130,000 patients not taught
- No overall survival or mortality benefit
- # of patients **diagnosed** with breast cancer ~**3%** (in both groups) was detected **by self exam – <u>crossover</u>**
- slight (2%) increase in mastectomy rate in pts not taught BSE
- Ratio of biopsy to cancer diagnosis 1:3 for control and 1:4 for BSE (difference highest in first 6 months of trial, down with time)

Thomas DB, Gao DL, Ray RM, et al. Randomized trial of breast self-examination in Shanghai: final results. J Natl Cancer Inst. 2002;94(19):1445–1457

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Clinical Breast Exam -CNBSS2 JNCI

- Canadian trial randomizing CBE ± mammography (40k patients)
- Trial was planned with a fixed sample to evaluate whether CBE led to a 40% reduction in breast cancer mortality !
- The trial was designed to test if mammography added benefit to breast exam
- This is behind the USPSTF “insufficient evidence” statement

Miller AB, To T, Baines CJ, et al. Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women aged 50-59 years. J Natl Cancer Inst. 2000;92(18):1490-1499

Mammogaphy

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Mammography Guidelines

Age	USPSTF	ACS	ACOG
40-44	Personal Decision	Personal Decision	Yearly
45-49	Personal Decision	Yearly	Yearly
50-55	Biennial	Yearly	Yearly
55-74	Biennial	Biennial	Yearly
>75			Yearly

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Areas of disagreement

- Screening for women 40-49
- Time interval for screening mammography
- Screening >75

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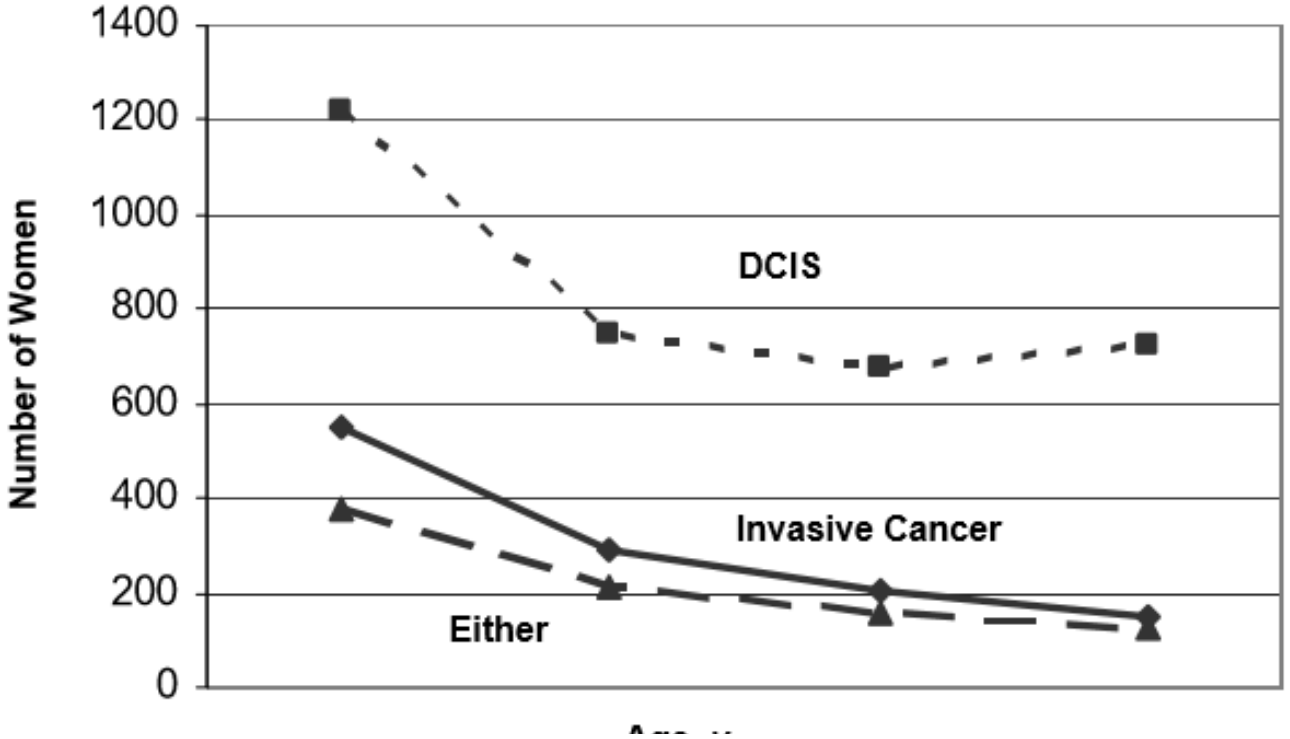

	40-49	50-59	60-69	70+
Invasive	556	294	200	148
DCIS	1,250	769	667	690
Either	385	213	154	122

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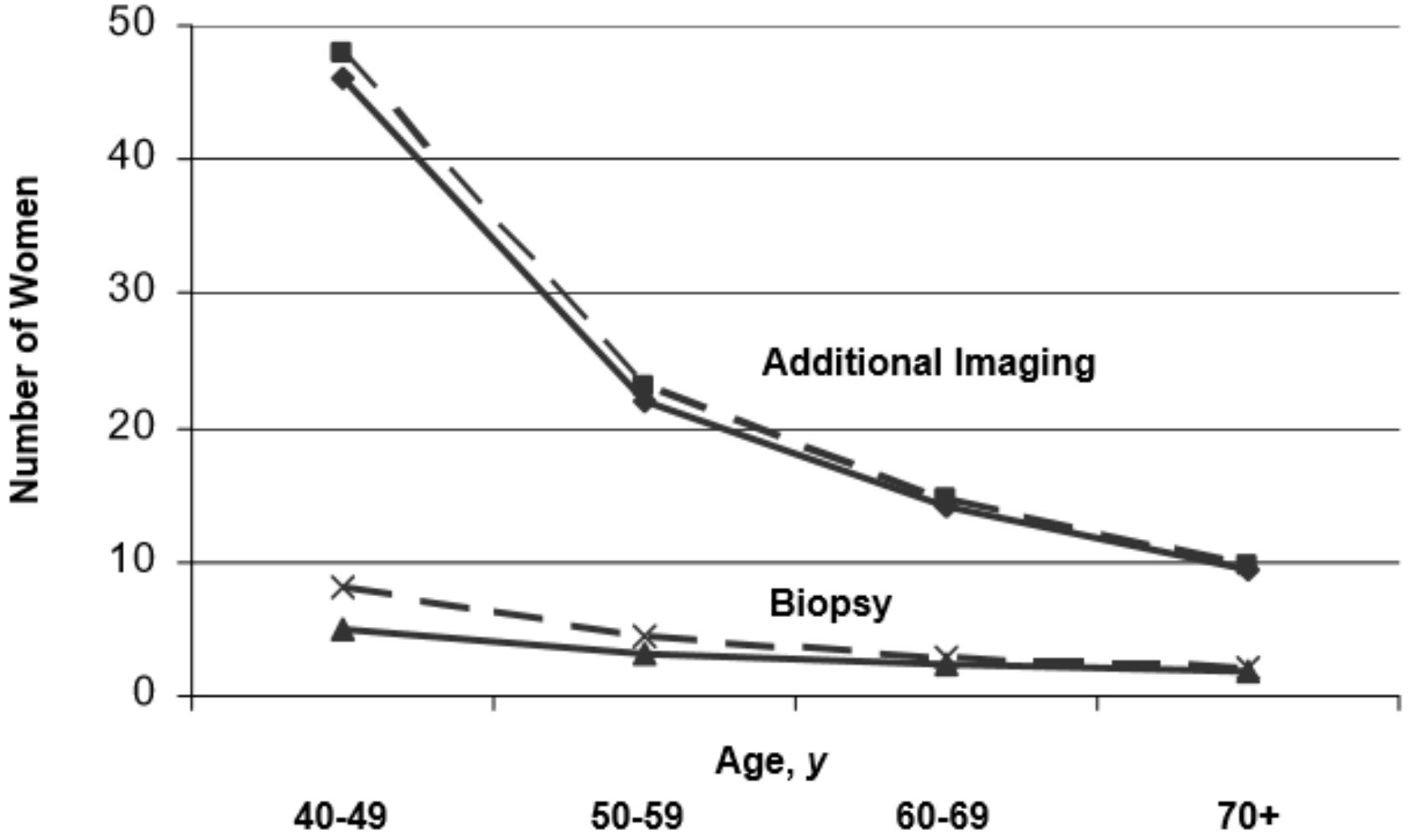

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Table 12. Age-Specific Screening Outcomes per Screening Round

	Age, *yr*				
	40-49	**50-59**	**60-69**	**70-79**	**80-89**
Women screened, *n*	113,770	127,958	94,507	50,204	18,752
Invasive breast cancer cases, *n*	349	574	651	427	154
DCIS cases, *n*	191	246	208	120	43
Outcomes, *n per 1,000 women screened*					
False-positive mammography result	121.2	93.2	80.8	69.6	65.2
False-negative mammography result	1.0	1.1	1.2	1.5	1.3
Additional imaging recommended†	124.9	98.5	88.7	79.0	74.5
Biopsy recommended†	16.4	15.9	16.5	17.5	15.6
Screen-detected invasive cancer	2.2	3.5	5.8	7.2	7.1
Screen-detected DCIS	1.6	1.8	2.1	2.3	2.1
Number Needed to Screen, *n*					
Women undergoing mammography to diagnose 1 case of invasive breast cancer	464	285	172	139	141
Women recommended for additional imaging to diagnose 1 case of invasive breast cancer	58	28	15	11	11
Women recommended for biopsy to diagnose 1 case of invasive breast cancer	10	6	3	3	3

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Pooled Relative Risk for Breast Cancer Mortality from Mammography

Age, *y*	Trials Included, *n* *	RR for Breast Cancer Mortality (95% CrI)	NNI to Prevent 1 Breast Cancer Death (95% CrI)
39-49	8	0.85 (0.75-0.96)	1,904 (929-6,378)
50-59	6	0.86 (0.75-0.99)	1,339 (322-7,455)
60-69	2	0.68 (0.54-0.87)	377 (230-1,050)
70-74	1	1.12 (0.73-1.72)	Not available

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NNS to diagnose 1 Breast cancer

Source	No. needed to screen	Follow-up period (years)
UK review (2012)	180*	25
USPSTF, depending on age (2009)	377-1904†	~ 15
EUROSCREEN (2012)	111*	30

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Mammography

USPSTF may be overestimating risks of mammography relative to benefits in comparison to our European colleagues

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Mammography – what are the risks?

- Risk of False Positive
- Overtreatment?
- Radiation Exposure

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Risk of False Positive - Recall

- False Positive probability: ~15% at first mammogram, ~10% subsequently
- False Positive leading to biopsy recommendation: 2.5% first mammogram, ~1% subsequently (cumulative ~ 7% @ 10 yrs)
- Availability of comparison mammograms halved the odds of a false-positive recall
- A non–statistically significant increase in the proportion of late-stage cancers was observed with biennial compared with annual screening

Hubbard RA, Kerlikowske K, Flowers CI, Yankaskas BC, Zhu W, Miglioretti DL. Cumulative probability of false-positive recall or biopsy recommendation after 10 years of screening mammography: a cohort study. Ann Intern Med. 2011;155(8):481-92.

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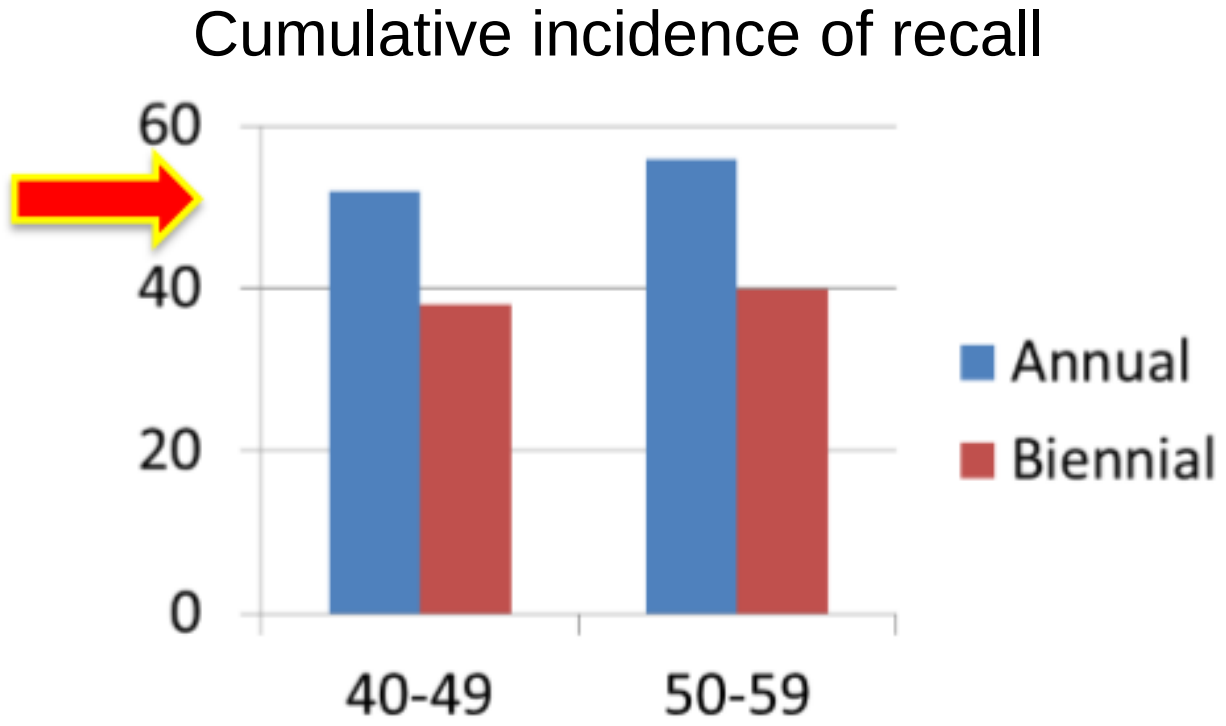
Risk of False Positive - Recall



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Risk of False Positive - Recall

A significant increase in the proportion of late-stage cancers was observed with biennial compared with annual screening

Hubbard RA, Kerlikowske K, Flowers CI, Yankaskas BC, Zhu W, Miglioretti DL. Cumulative probability of false-positive recall or biopsy recommendation after 10 years of screening mammography: a cohort study. Ann Intern Med. 2011;155(8):481-92.

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Risk of False Positive - Psychosocial

- Survey of > 1000 patients who participated in a screening trial
- Increased short-term anxiety
- No change in long-term anxiety
- No measurable health utility decrement.
- False-positive mammograms increased women's intention to undergo future cancer screening

Tosteson AN, Fryback DG, Hammond CS, et al. Consequences of false-positive screening mammograms. JAMA Intern Med. 2014;174(6):954-61..

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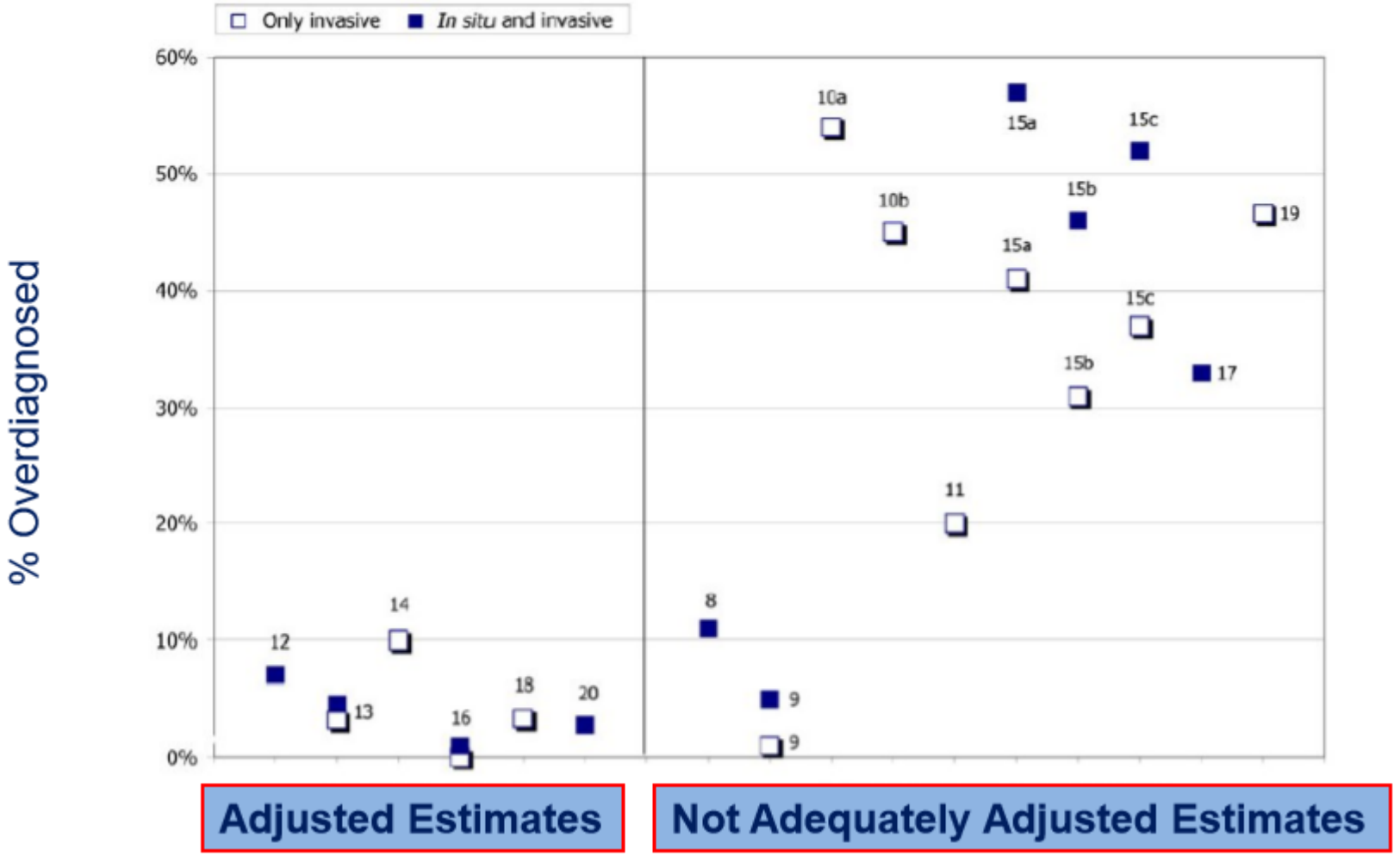
Risk of Overdiagnosis



Source: Puliti, et al. JMS 2012;19(1)

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Risk of Radiation exposure

Mammography exposes people to 0.4 mSv of additional radiation above background

- A flight from Los Angeles to New York is 0.04 mSv
- Average annual dose from food is 0.3 mSv
- Average yearly background dose is 3.1mSv

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Risk of Radiation exposure

Adult X-ray Exam	Average Effective Dose (mSv)	Lifetime Risk of Cancer Death
Bilateral Mammography*	0.48	age 70: 1 in 500,000*
		age 60: 1 in 250,000*
		age 50: 1 in 125,000*
		age 40: 1 in 70,000*

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Shared Decision Making

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Breast Screening Decisions

A mammogram decision aid for women ages 40-49

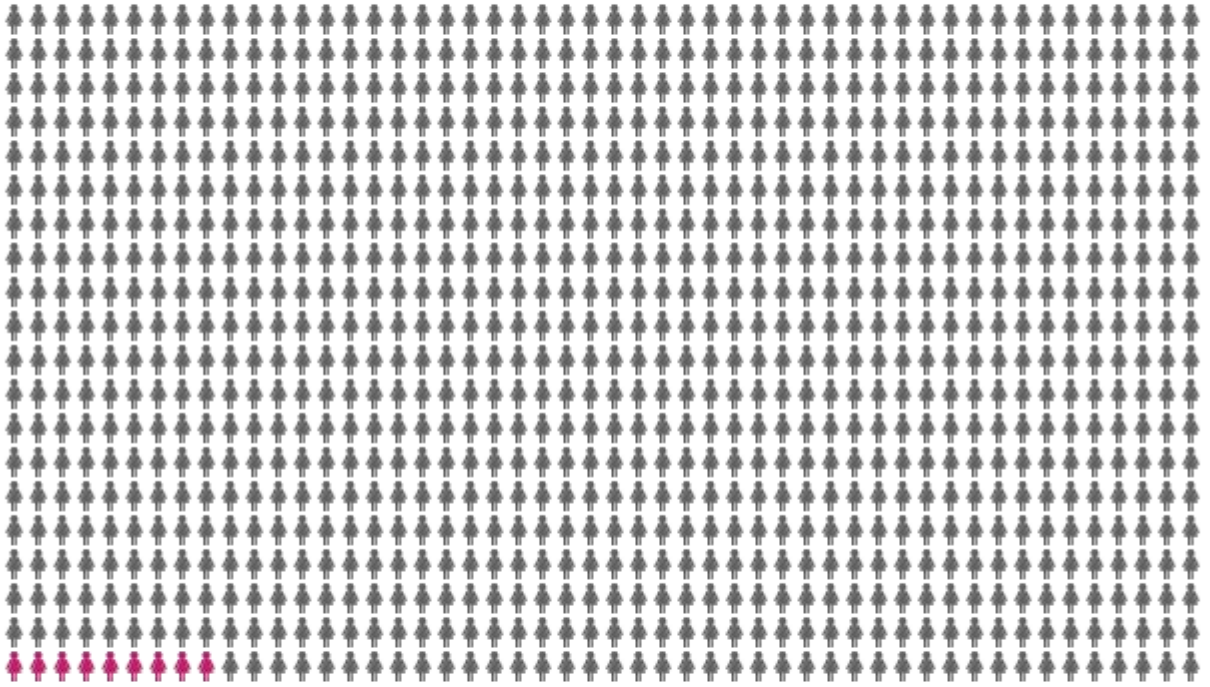
Your risk in the next 5 years

Based on your responses, your chance of developing breast cancer in the next 5 years is 0.9%. That means that out of 1000 women like you, 9 of them will develop breast cancer in the next 5 years.

Of 1,000 women like you:

In the next 5 years, **991** will not get breast cancer

In the next 5 years, **9** will get breast cancer



How did we calculate this?

Other things to know

There are other factors such as breast feeding, alcohol intake, body weight, and physical activity that may affect your breast cancer risk. Just how much they affect that risk is not certain. To learn more about strategies for reducing your breast cancer risk, click here.

Now that you know your breast cancer risk, let's talk about mammograms.

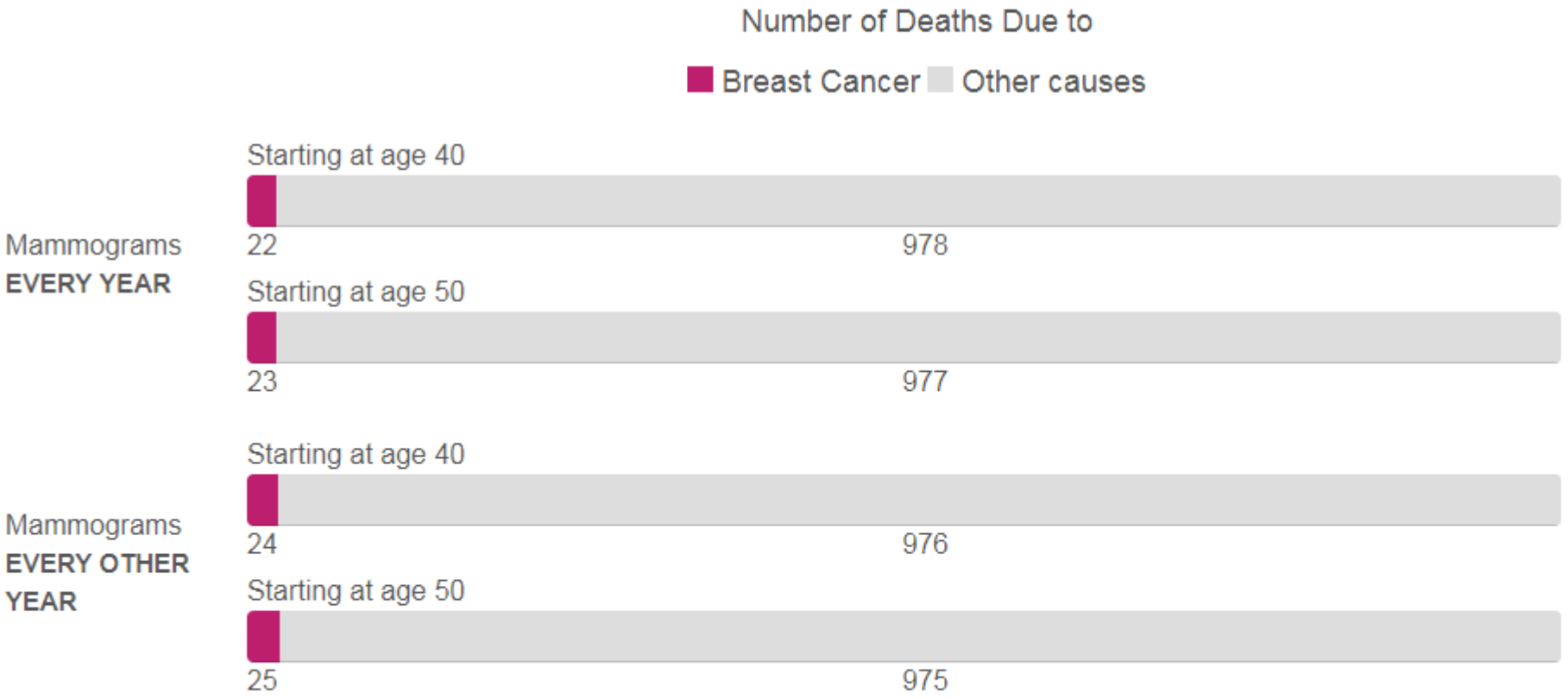
Summarizing so far

Save My Progress

You are at low to average risk of developing breast cancer.

Your chance of developing breast cancer in the next 5 years is about 0.9%. This means that out of 1,000 women like you, 9 of them will develop breast cancer in the next 5 years and 991 will not.

Of 1000 women like you at low to average risk who have screening mammograms, over their lifetime:



But your decision about having a screening mammogram is not just about the numbers. In the next section, we'll explore your personal values and concerns about breast cancer and screening mammograms.

Gaps in the evidence

Evidence Gaps in Population-Based Personalized Breast Cancer Screening

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- Benefits and harms of screening in women aged ≥75 y.
- Optimal approaches for risk assessment, risk communication, and shared decision-making.
- Performance of breast MRI for subgroups of women, over time, and by indication.
- Appropriate performance measures to optimize the screening process.
- Comparative assessment of tomosynthesis.
- Understanding risk of DCIS progression to invasive cancer.
- Methods for measuring overdiagnosis.
- Process measures validated for efficient, high-quality screening.
- Refined breast cancer risk models including factors such as breast density, genetic markers, and prior imaging results.

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Conclusions - Breast

- Breast cancer screening is a highly charged topic
- There is very little evidence regarding self exam and clinical breast exam – 3% of patients are diagnosed by self exam regardless of if they are taught or not
- Mammography decreases breast cancer mortality
- The risks of mammography decline with age and with ability to compare to previous mammograms
- The risk /benefit ratio for mammography in women 40-50 is slightly less favorable – this must be weighed against the aggressive nature of breast cancers in young patients on an individual basis

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Prostate Cancer

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Why screen for prostate cancer?

Prostate cancer is easier to treat when found early.

- Surgery – Need to LND, need for adjuvant RT/ADT
- Systemic therapy: need for ADT and/or chemotherapy
- Radiotherapy: prostate alone vs prostate + pelvic nodes, one time radiation implant vs 40 external treatments.

-

Source : NCCN guidelines

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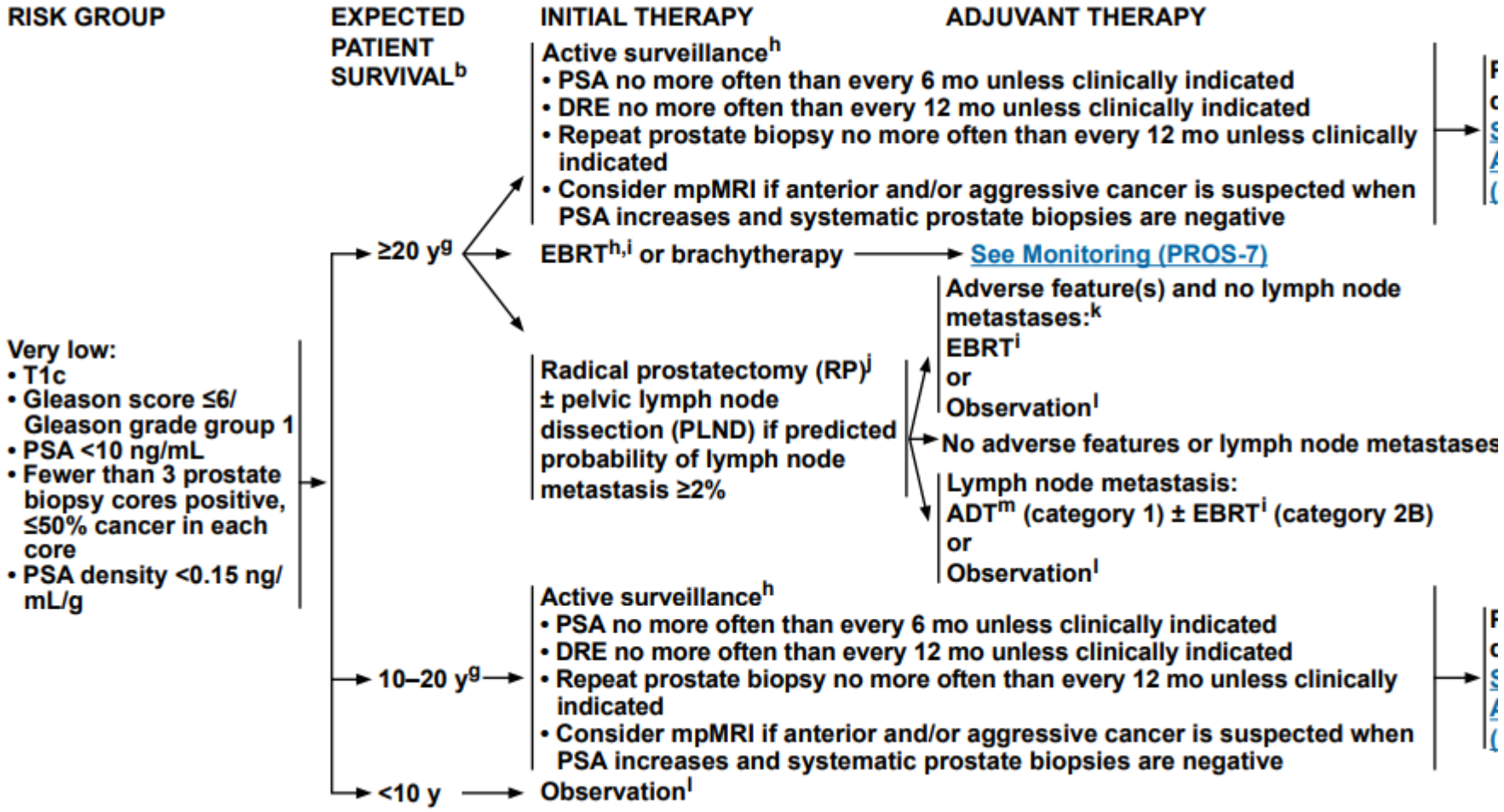
Is prostate cancer easier to treat when found early?



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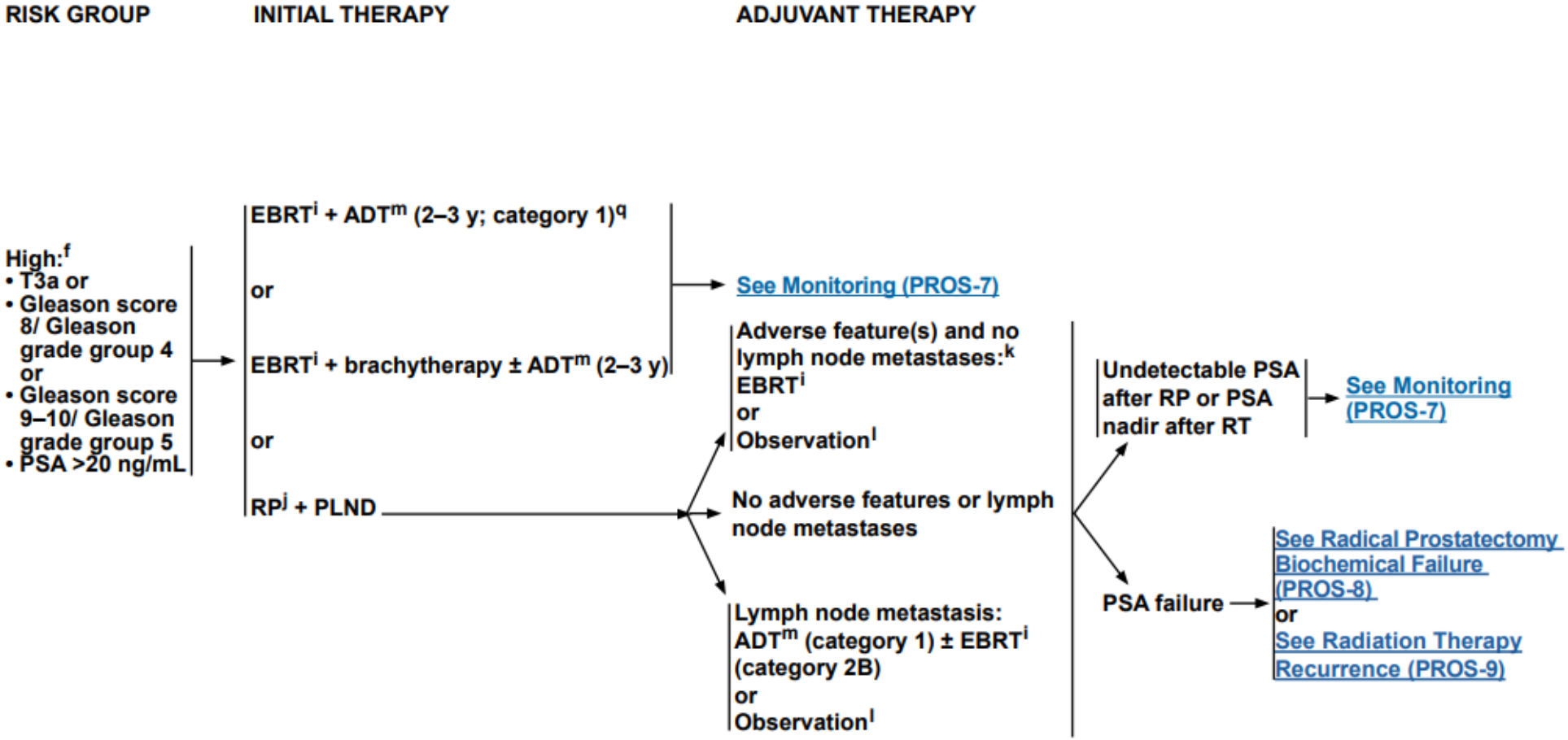
Is prostate cancer easier to treat when found early?



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Prostate Cancer

- Prostate cancer is a clinically heterogenous disease, affecting > 200,000 men per year, > 30,000 of whom die from disease
- 40% low risk, ~ 40% intermediate risk, ~ 20% high risk
- associated with high fat diet, # sexual partners, tobacco use, **insulin resistance**
- Risk for prostate cancer significantly higher in AA vs Caucasian M
- In the 1970s-1980s, prostate cancer mortality rates were approximately 30/100k and steadily increasing

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Prostate Cancer

- PSA screening became available in in the early 1990s and widespread screening was available by the late 1990s
- Based on SEER analysis, since the early 1990s, prostate cancer related mortality has decreased 40%
- The incidence of metastatic disease at presentation has declined by approximately three-fourths in the US since the advent of PSA screening.

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Prostate Screening: Guidelines

- Concern for overdiagnosis of clinically irrelevant cancers
- At the same time, the risk factors for development of the disease are increasing
- The long term effect of reduced screening on a population basis is not known

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Prostate Screening: Guidelines

Modeling studies show:

- PSA screening yields survival benefits that have contributed, to some extent, to the dramatic and sustained drop in prostate cancer death rates in this country.
- Second, PSA screening advances prostate cancer diagnosis by five to six years on average.
- Approximately one in four screen-detected cases reflects overdiagnosis.

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Prostate Screening: Guidelines

What risk groups do the guidelines not address?

- Family History
  - consider number of relatives and age at diagnosis
  - Family history of breast/ovarian (potential BRCA carrier) or colorectral, endometrial, gastric pancreatic (possible Lynch)
- African American ethnicity

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Prostate Screening: Guidelines

- USPSTF
  - recommends against PSA screening
- AUA
  - men 40-55 at high risk should be offered screening
  - Screening men > 55 should be offered screening if life expectancy > 15 years
  - Interval of screening should be individualized based on baseline PSA

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Prostate Screening: Basis of guidelines

	PLCO ("US")	ERSPC ("European")	Goteberg ("Swedish")
No. Men	76,693	162,388	20,000
Age Range	55-74	55-69	50-64
Screening group	PSA q1yr x6, DRE qyr x4	PSA q4yr	invitation to PSA q2 yrs
Control group	'usual' care	no screening	no screening
Med f/u (years)	13	13	14 yrs
Indication for biopsy	PSA>4 or abnormal DRE	PSA>3	PSA>2.5-3.4 (dep on yr)
Intervention arm compliance	85% PSA, 86% DRE	82% screened ≥once Avg. 2.27 per subject	76% of invited had ≥1 PSA
PrCa detection (scr/cont)	11.1% vs 9.9%	9.6% vs 6.0%	12.7% vs 8.2%
PrCa deaths (scr/cont)	158 vs 145	299 vs 462	44 vs 78
RR of PrCa death	1.09 (0.87-1.36)	0.79 (0.69-0.91)	0.56 (0.39-0.82)
NNI (Invite)/ NND (Diagnose)	na	781/27	293/12
Notes	44% prescreened in both arms	Low/Int risk: 84.8% (scr) vs 68.4% (cont)	Younger men, less prescreening
	Up to 52% of cont. arm screened	PPV 24.1%	lower PSA threshold

Andriole et al., , JNCI 2012; Schroder et al., Lancet 2014; Hugosson et al., Lancet 2010

Prostate Screening: Risks of screening

Biopsy related side effects

Overtreatment

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Prostate Screening: Risks of screening

Biopsy related side effects: hematuria, hematochezia, hematospermia, dysuria and retention, pain and infection.

- Hematuria 14% to 50% of the time
- Hematospermia 10% to 70% of patients

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Prostate Screening: Reducing Risk

- Strategies that screen less frequently than every year, and even less frequently for men with low PSA levels, are likely to be of value in reducing costs and harms while preserving most of the potential benefit of PSA-based screening
- Risk stratificaiton
- Novel biomarkers?

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Prostate Screening: Reducing Risk

- Rotterdam Prostate Cancer Risk Calculator
  - ERSPC data- based on a population aged 55-74 yr. The analyses are based on the biopsy outcomes of 3616 men screened for the first time, 24.5% of whom had prostate cancer detected.
  - Has not specifically been validated in the US population
  - Risk < 12.5% - no biopsy recommended
  - 12.5-20% - consider biopsy based on comorbidity
  - 20% or more – biopsy recommended

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Future Risk Calculator*

Time = 0 (Now)

Age (years) 50

PSA (ng/ml) 5

DRE (•) Abnormal ( ) Normal

Family history * (•) Yes ( ) No

DRE volume class (cc) 25

Previous neg. biopsy (•) Yes ( ) No

Calculate

Time = 4 (4 years later)

Probability of NO Prostate Cancer: **89.5%**

Probability of potential LOW RISK Prostate Cancer: **5.3%**

Probability of potential AGGRESSIVE Prostate Cancer[2]: **5.2%**

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* Has your father or brother has prostate cancer?

* Future risk implies 4 years after assessment of predictors and is based on a screening algorithm using a lateral sextant biopsy indication based on a PSA >= 3.0 ng/ml cut-off

[2] A prostate cancer with a clinical stage > T2b or Gleason score >= 7 or PSA > 10.0 ng/ml

Select Risk Calculator:

Your Risk Calculators
(for non-medical people)

1 2

Risk Calculator 6

Predicting cancer in the future

This prototype looks at a man's future risk over a four year period - a promising tool in reducing uncertainty, unnecessary testing, and overdiagnosis with regard to prostate cancer. This individualized multivariate model includes age, prostate-specific antigen, digital rectal examination, family history, prostate volume, and previous biopsy status.

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Prostate Cancer: New Biomarkers

4Kscore (OPKO Laboratory, Nashville, TN, USA)	Blood	Panel of 4 kallikrein proteins: total PSA, free PSA, intact (single-chain PSA) and human kallikrein 2	Likelihood that a patient will have high-grade pathology (Gleason ≥7) on needle biopsy	CLIA-certified. Not covered by insurance. $395
Prostate Health Index (Beckman Coulter, Brea, CA, USA)	Blood	Combines PSA, free PSA and p2PSA via a formula	Likelihood of finding prostate cancer on a repeat biopsy	FDA-cleared for use in men >50 years who have a PSA of 4–10 ng/mL and a negative DRE. Covered by Medicare and most insurance. $80–100
PCA3/Progensa (Hologic, Bedford, MA, USA)	Urine	Nucleic acid amplification test measuring the concentration of PCA3 and PSA RNA in post-DRE specimens	Scores <25 are associated with lower likelihood of positive biopsy; those ≥25 are associated with a higher likelihood of positive biopsy	FDA-cleared for use in men ≥50 years considering repeat biopsy after ≥1 previous negative biopsies. $385, covered by most insurance
ConfirmMDx (MDxHealth, Irvine, CA, USA)	Biopsy tissue	Quantifies DNA hypermethylation of three associated with prostate cancer; methylation of these genes is believed to occur even in non-malignant cells that are continuous with cancerous tissue, leading to a field effect	When performed on a patient's previous negative prostate biopsy, DNA changes can suggest the presence of cancer nearby that may have been missed, thus warranting a repeat biopsy	CLIA-certified. $3300, with limited Medicare coverage

Prostate Screening: Reducing Risk

- Prostate Health Index
  - It predicts the likelihood of finding prostate cancer on a subsequent biopsy.
  - The basis of the PHI lies in the identification of the free PSA precursor isoform [-2]proPSA, which forms 25–95% of the fPSA fraction in men with prostate cancer, compared with just 6–19% in biopsy-negative men
  - Higher PHI values were associated with a higher percentage of positive biopsies, as well as with a higher percentage of high-grade cancer (Gleason score of ≥7).

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Prostate Screening: Risks of screening

Overtreatment

- Estimates of overdiagnosis vary widely
- Less than 5% to more than 75%
- Lead times of 5 to 15 years
- Overdiagnosis estimates are not portable across geographic settings because they depend not only on the screening and biopsy protocol, and compliance with biopsy referral under screening, but also on practice patterns and disease incidence in the absence of screening.

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Prostate Screening: Overtreatment?

Overtreatment

- Our best estimates for the fraction of screen-detected cases overdiagnosed in the US in the 1990's is approximately one in four, but the likelihood of overdiagnosis is highly age dependent.

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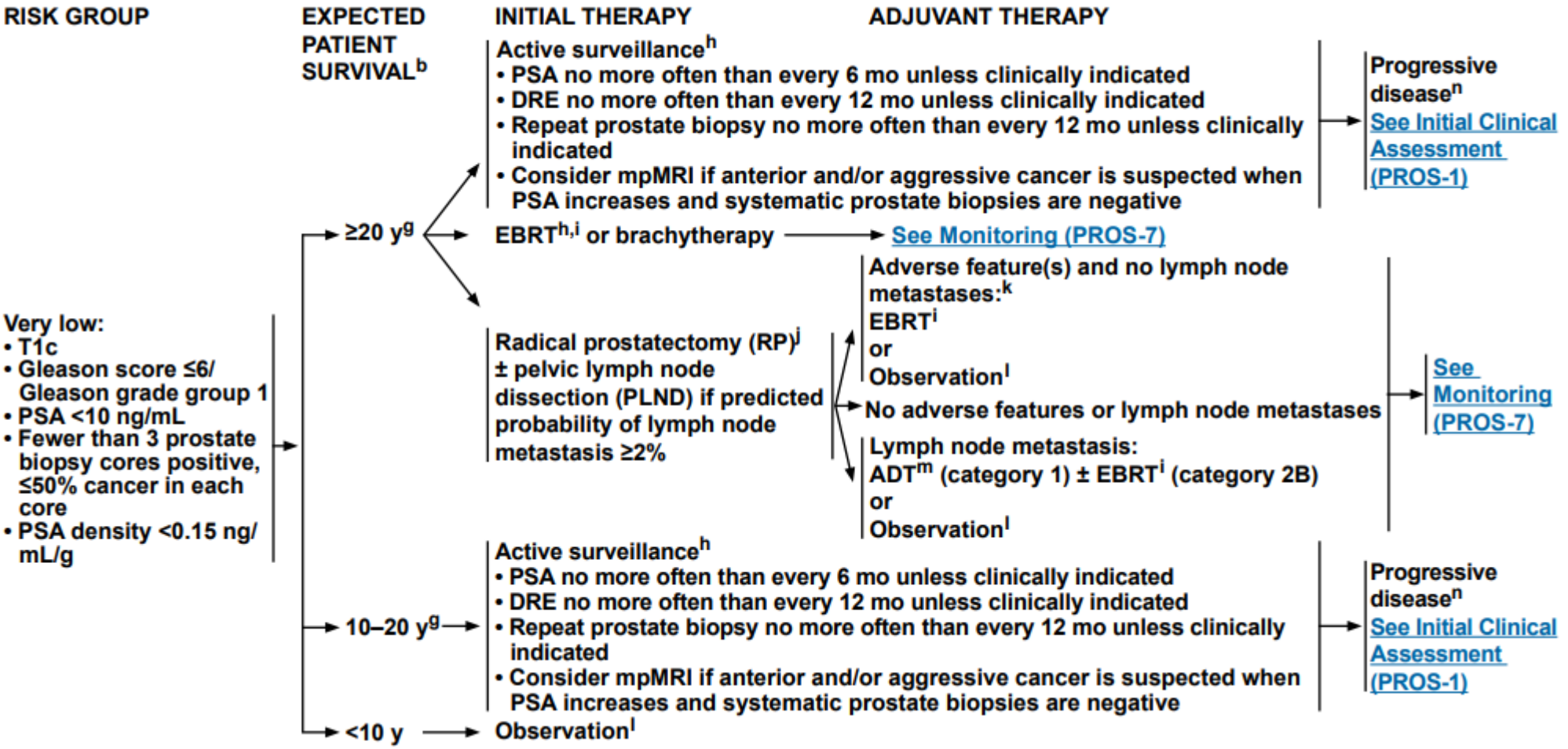
Prostate Screening: Observation



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Prostate Screening: Conclusions

- Prostate cancer mortality has significantly decreased since initiation of PSA screening
- PSA screening for African American men, or men with family history of prostate cancer / genetic syndrome, should be strongly considered
- Screening average risk men with long life expectancies is reasonable
- Predictive tools and novel biomarkers may aid in shared decision making

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Thank you!

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