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Can Population-based and Personalized Screening Coexist?

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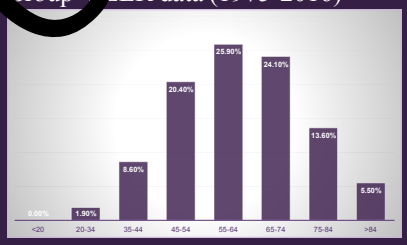
Breast Cancer Incidence and Screening

Female invasive breast cancer cases estimated to reach 268,600 in 2019
Estimated 41,760 deaths from the disease

Death rate has decreased by 37% since mid 1980s, largely attributable to screening

Falling on average 1.8% each year (2006-2015)

Percent of New Breast Cancer Cases by Age Group- SEER data (1975-2016)



RCTs Evaluating Mammography Screening

	of Initiation	Duration	Follow-up
HIP Trial		4 years	18 years
CNBSS-1 and CNBSS-2	*1980*	*4.5 years*	*25 years*
Age trial	1991	9 years	17.5 years
Stockholm trial	1981	4.8 years	11.4 years
Malmö trial	1976-1978	≥ 10 years	11-15.5 years
Gothenburg trial	1982	9 years	12 years
Swedish Two-County Trial	1977	7 years	20 years

Reduction in breast cancer deaths of **15-30%** in women 40-74 years of age invited to screening

Statistically significant mortality reductions of 15–18% for women who were 40–49 years old at invitation

Mortality Reduction with Long-term Follow-Up for Women Aged 40-49

Trial	Follow-up (years)	Mortality Reduction (%)
All 8 RCTs	10.5-18.0	15-18
7 RCTs (excluding CNBSS-1)	7.0-18.0	24
5 Swedish Trials	11.4-15.2	29
Gothenburg, Sweden	12.0	45
Malmö, Sweden	12.7	36

Recreated from: Ray KM, et al. Evidence to Support Screening Women in Their 40s. Radiol Clin N Am 2017; 55: 429-439.

RCTs and Mortality Reduction

Swedish trials-

- Gothenburg (after 12–14 years of follow-up) reported 45% mortality reductions for women 39–49 years old at time of randomization
- Malmö- (12.7 years of follow up) 36% for women who were 45–49 years old

CNBSS-1 (Canadian trial) only RCT that did not find a reduction in mortality for those 40-49 however flaws with the trial are well documented

- Poor quality mammograms, untrained radiologists, study design (contamination of control group, nonblinded randomization)

Observational Studies

- **Observational Studies** are ones in which the independent variable is not under the control of the investigators – researchers cannot assign participants to groups within the experiment. Information is collected without investigator intervention. More prone to selection bias than RCTs, but still very important studies
- Large-scale, population-based studies (Europe, Canada, Australia and New Zealand) have demonstrated **38-49% decrease in mortality**
  - **Tabar -** 20 year follow up of mortality effect from breast canc[illegible]creening: 48% reduction in deaths for those 40-49 exposed to screening
  - **Hellquist -** Sweden service screening: median 16 year follow-[illegible] mortality rates 26% lower for 40-49 age group for those invited to sc[illegible]

Tabar, L., Ming-Fang, Y., Vitak, B., Chen, H. T.-A. et. e (2000). Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. The Lancet, 351(9087), 1458-10.

[illegible] B. N., Duffy, S. W., Abdsalah, S., [illegible] Yen, L. and Jonsson, H. (2011), Effective [illegible] ation-based service screening with [illegible] for women ages 40 to 49 years. Ca[illegible] 9-252.

Observational Studies

Coldman - seven provincial service screening programs in Canada, 44% mortality reduction among screened women 40–49

Breast Cancer Surveillance Consortium longitudinal study - seven regions of US- tumors in women 45–49 years old behaved similarly to those in women 50–59; concluded these groups should be screened similarly

Coldman, A., Phillips, N., Wilson, C., Decker, K., Chiarelli, A. M., Brisson, J., ... & Ahmad, R. (2014). Pan-Canadian study of mammography screening and mortality from breast cancer. JNCI: Journal of the National Cancer Institute, 106(11).

Miglioretti, D. L., Zhu, W., Kerlikowske, K., Sprague, [illegible]ega, T., Bolte[illegible] ... & Smith, R. A. (2015). Breast tumor prognostic cha[illegible]s and biennial vs annual mammography, age, and menopausal status. JA[illegible]Ogy, 2(9), 1069-[illegible]

[illegible]bar 2011 – Longest Running Study

Long-term (29-year) effect of mammographic screening on breast cancer mortality in terms of both relative and absolute effects

Invitation to mammographic screening results in a highly significant decrease in breast cancer–specific mortality

At 29 years of follow-up, the number of women needed to undergo screening for 7 years to prevent one breast cancer death was 519

The estimated years of life saved from the consensus data was 34 per 1000 women invited to screening

"Had two-view mammography and a shorter interval been used in our trial, the impact on breast cancer mortality would have been even greater"

Tabár, László, et al. "Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades." Radiology 260.3 (2011): 658-663.

Bene[illegible]s of Scre[illegible]ing- Mortality and Survival

Relative risk of [illegible]om breast cancer 20% less in women invited to screening compared with those not invited to screening

Each missed year of mammography screening has been shown to be associated with a decline in overall survival

- 2.3 fold increased chance of death, compared with those undergoing yearly mammography

Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. Lancet. 2012;380:1778-1786.
Andersson I, Lars J. Reduced Breast Cancer Mortality in Women Under Age 50: Updated Results From the Malmö Mammographic Screening Program. J Natl Cancer Inst Monogr. 1997; 1997(22):63-67.

Mammography Screening- Mortality and Life Years Gained

	Mortality Reduction	Deaths Averted	Life Years Gained (LYG)	# Needed to Screen/death averted	# Needed to Screen/LYG
Annual Screening beginning age 40	39.6%	11.9	189	84	5.3
Annual screening 45-54, biennial 55-79	30.8%	9.25	149	108	6.7
Biennial 50-74	23.2%	6.95	110	144	9.1

Recreated from: Arleo EK, et al. Comparison of Recommendations for Screening Mammography Using CISNET Models. Cancer 2017; 123:3673-80.

Benefits of Population-Based Screening

Detection of small tumors at an earlier stage
- Important as stage at diagnosis is one of the most important factors in survival

5-year relative survival rates:
- stage I: 100%
- stage II: 86.2%
- stage III: 57.2%
- stage IV: 19.9%

Plecha D, Salem N, Kremer M, Pham R, Downs-Holmes C, Sattar A, Lyons J. Neglecting to Screen Women Between 40 and 49 Years Old With Mammography: What Is the Impact on Treatment Morbidity and Potential Risk Reduction? Am J Roentgenol 2014;202:2, 282-288.

Benefits of Population-Based Screening

Detection of smaller tumors, with less nodal metastasis, lower stage
- less likely to need chemotherapy, radiation and other extreme treatments
- the benefit of detecting cancer at an earlier stage leads to less-toxic and better tolerated treatments

Recurrence also less likely when a cancer is found and treated at an early stage

Ongoing Screening Controversy

Despite the benefits, there remains ongoing controversy over the optimal approach to breast cancer screening

Led to discordant professional society recommendations, particularly in women age 40 to 49 years

Mammography is not a Perfect Test

Though the decreased mortality benefit is clear for the general population, *there are specific populations of women for whom mammography is not as successful*
- For women with extensive family history or personal history
- Genetic predisposition
- Dense breast tissue
- Personal history of breast cancer

Personalized, risk-based screening

Risk-Based Screening: An Alternative to Population Based Screening?

A woman's risk of developing breast cancer is influenced by many factors, but breast cancer screening recommendations are based primarily on age

Decisions around the starting age, stopping age, frequency, and modality of screening are based on individual risk to maximize the early detection of aggressive cancers and minimize the harms of screening through optimal resource utilization – Shieh 2017

Shieh, Yiwey, et al. "Breast cancer screening in the precision medicine era: risk-based screening in a population-based trial." *Journal of the National Cancer*

Risk-Based Screening in a Population-Based Trial

Novel approach to risk-based screening that integrates clinical risk factors, breast density, a polygenic risk score representing the cumulative effects of genetic variants, and sequencing for moderate- and high-penetrance germline mutations

Thresholds of absolute risk estimates generated for use to stratify women into different screening strategies (biennial mammography, annual mammography, annual mammography with adjunctive magnetic resonance imaging, defer screening at this time) while informing the starting age of screening for women age 40 to 49 years

WISDOM Trial

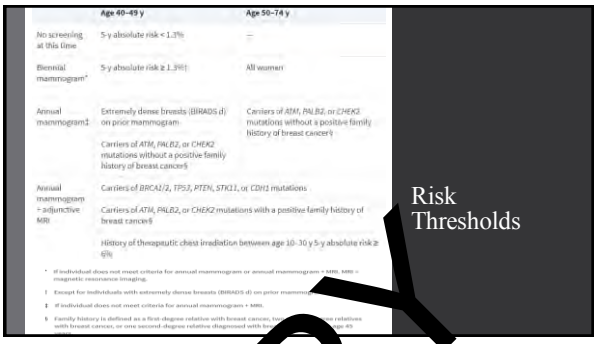
A randomized controlled trial of annual vs personalized screening

Preference-tolerant design to encourage women to participate - women can elect to be randomly assigned or request to be assigned to the risk-based or annual screening groups

Risk-based arm will undergo risk stratification using the BCSC model, a polygenic risk score, and genetic testing with a nine-gene panel, and the participants randomly assigned to this arm will be screened based on the thresholds described (next slide)

Goal to test the hypothesis that risk-based screening will decrease mammography usage without an increase in diagnosis of late-stage breast cancers

Shieh Y, et al. on behalf of the Athena Breast Health Network Investigators. Breast Cancer Screening in the Precision Medicine Era: Risk-Based Screening in a Population-Based Trial. *JNCI: Journal of the National Cancer Institute*, Volume 109, Issue 5, May 2017, djw290.



	Age 40–49 y	Age 50–74 y
No screening at this time	5-y absolute risk < 1.3%	–
Biennial mammogram*	5-y absolute risk ≥ 1.3%†	All women
Annual mammogram‡	Extremely dense breasts (BIRADS d) on prior mammogram Carriers of *ATM*, *PALB2*, or *CHEK2* mutations without a positive family history of breast cancer§	Carriers of *ATM*, *PALB2*, or *CHEK2* mutations without a positive family history of breast cancer§
Annual mammogram + adjunctive MRI	Carriers of *BRCA1/2*, *TP53*, *PTEN*, *STK11*, or *CDH1* mutations Carriers of *ATM*, *PALB2*, or *CHEK2* mutations with a positive family history of breast cancer§ History of therapeutic chest irradiation between age 10–30 y 5-y absolute risk ≥ 6%	

* If individual does not meet criteria for annual mammogram or annual mammogram + MRI, MRI = magnetic resonance imaging.

† Except for individuals with extremely dense breasts (BIRADS d) on prior mammo

‡ If individual does not meet criteria for annual mammogram + MRI.

§ Family history is defined as a first-degree relative with breast cancer, tw relatives with breast cancer, or one second-degree relative diagnosed with bre age 45

Risk Thresholds

WISDOM Trial Pitfalls

Using risk assessments and genetic testing investigators will identify those with predetermined risk factors (familial history, genes known to increase risk) to determine the commencement and frequency of screening

Authors of the study predict this method would have 75% of women aged 40-49 defer screening to 50 and 91% of women 50-74 receive biennial mammography screening

Authors claim less mammography usage in these "low-risk" populations will decrease the likelihood of a woman experiencing a supposed harm – false positives, anxiety of recall etc.

Hsia JS. The Complexity of Achieving the Promise of Pre ast Cancer Screening. *JNCI: Journal of the National Cancer Institute*, Volume 109, May 2017, djw301.

WISDOM Trial Pitfalls

This approach could be troublesome for multiple reasons:

- Majority of breast cancers are spontaneous – no known genetic or familial risk factors can be identified
- Younger women tend to be diagnosed with more aggressive forms of breast cancer that will not be identified before causing symptoms
- Level of testing required to identify proper risk score is not widely available in most offices – implementation may be cumbersome and not cost effective
- Lack of proper identification due to limitations of available genetic testing could lead to lack of screening adherence and missing women who belong to a higher risk group
- Physicians will need access to the proper tools and communication aids to effectively counsel women based on risk – currently many physicians feel unprepared for this conversation
- Areas with lower levels of funding and resources would have a difficult time implementing the proper tools for risk assessment and genetic testing which could lead to health care disparities for women of differing economic levels

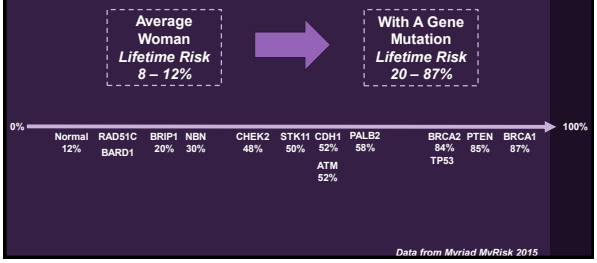
How do We Identify those at Higher Risk?

Risk prediction models
Gail, BRCAPRO, Tyrer-Cuzick, Claus, Myriad

Models take into account wide range of breast cancer risk factors
- Hereditary
- Hormonal
- Environmental

Models measure:
- Risk of BRCA 1 or 2 mutation
- Risk of developing breast cancer
- Timeframe of risk: 5-year, 10-year, Lifetime

Breast Cancer Risk Spectrum

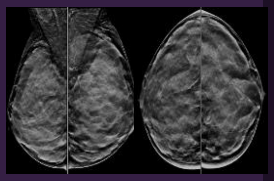


Data from Myriad MyRisk 2015

Inclusion of Breast Density in Risk Assessment

Women with dense tissue have a 3 to 5 times greater risk of developing breast cancer in comparison to women with fatty tissue

Nearly half of the general screening population has heterogeneously dense or extremely dense breasts



O'Neil SC, et al. Mammographic Breast Density as a Risk Factor for Breast Cancer: Awareness in a Recently Screened Clinical Sample. 2014

Should Personal History be Included as a Risk Factor?

- **Not an indication for MRI screening in most recommendations**
- 2018 ACR guidelines update (JACR 2018)
  - Now recommend that women with personal history of breast cancer and dense tissue, or diagnosed under age 50, be screened with MRI
- Studies have demonstrated that MRI can detect otherwise occult carcinoma in this population - Patients with PH are at similar risk level as those with PH and FH in the development of subsequent breast cancer and therefore benefit from screening breast MRI (Destounis 2016, Tadros 2017, Park 2018)

Monticciolo, [illegible] 9:406-414.
Destounis, S., Arieno, [illegible] Personal history of premenopausal breast cancer as a risk factor for referral to [illegible] and MRI. Academic radiology, 23(3), 383-387.
[illegible] et al. Utility of surveillance MRI in [illegible] with a personal history of breast cancer. [illegible] 2017; 46: 33-38.
[illegible] Yigean, et al. BMC cancer 18.1 [illegible]

Destounis et al. 2016

- EWBC study comparing results from high risk MRI exams in patients with a personal history (PH) of premenopausal breast cancer to patients with a personal history and family history (PHFH) of breast cancer

	# of Patients	# of Exams	Diagnosed Cancers
PH	52	146	7
PHFH	79	235	8

- Average time between diagnosis was 7.1 years in PH group and 6.9 years in PHFH group
- Patients with PH are at similar risk level as those with PH and FH in the development of subsequent breast cancer and therefore benefit from screening breast MRI

Destounis et al. Academic Radiology, [illegible] Issue 3

Management Guidelines – Who Is Currently Identified for Adjunctive Screening?

Guidelines currently incorporate some level of risk-based management – to recommend <u>additional screening</u>

Ex. Intensive screening with annual mammography and adjunctive MRI is recommended for several high-risk groups according to guidelines by the NCCN

NCCN, ACR, ACS and ACOG all have versions of recommendations for MRI

- >20% lifetime risk
- Mutation carrier (self, or family member)
- History of chest radiation therapy <30
- *Women with personal history of breast cancer and dense breast tissue, or diagnosed before age 50 (newest rec per ACR)*

Prov[illegible] Performance with Screening MRI in Diff[illegible]nt Risk Levels (Sippo 2019)

Evaluated screening breast MRI performance across women with different elevated breast cancer risk indications

- BRCA mutation carrier or history of chest radiation (BRCA/RT group)
- Family history of breast cancer (FH group)
- Personal history of breast cancer (PH group)
- History of high-risk lesion (HRL group)

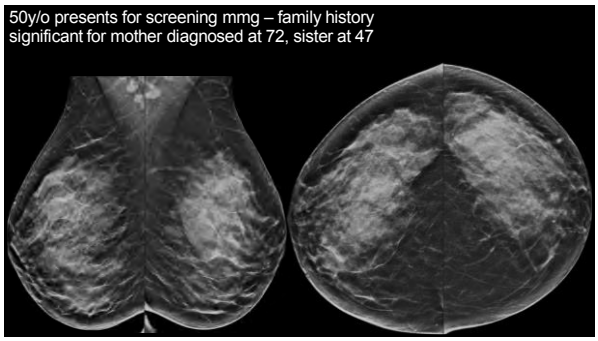
5170 screening exams in 2637 women; 67 breast cancers detected

Sippo, Dorothy A., et al. "Performance of Screening Breast MRI across Women with Different Elevated Breast Cancer Risk Indications." Radiology (2019): 181136.

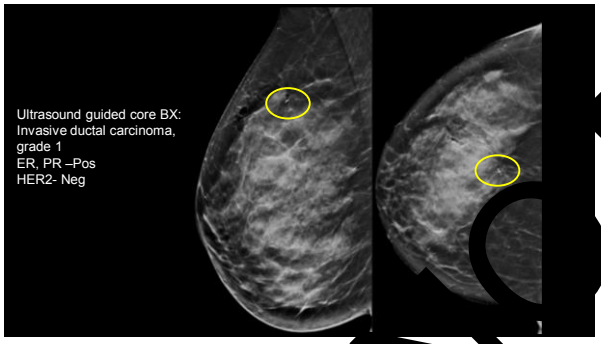
Sippo: Screening MRI

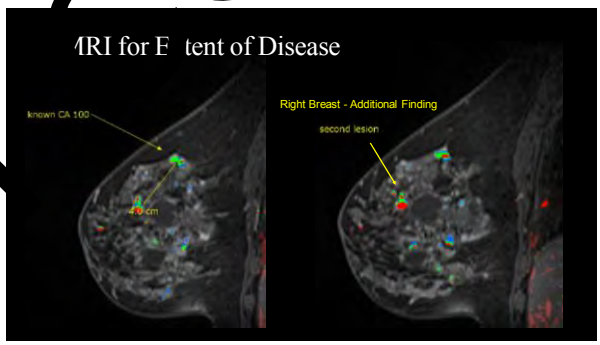
- **<u>PH outperformed FH in all categories</u>**, and was more comparable to the metrics for the BRCA/RT group
- For FH group the PPV2 (for biopsy recommendations) and PPV3 (for biopsies performed) fell below BI-RADS MRI screening benchmarks
- These results support expanding screening MRI indications to include PH, which would also possibly include HRL

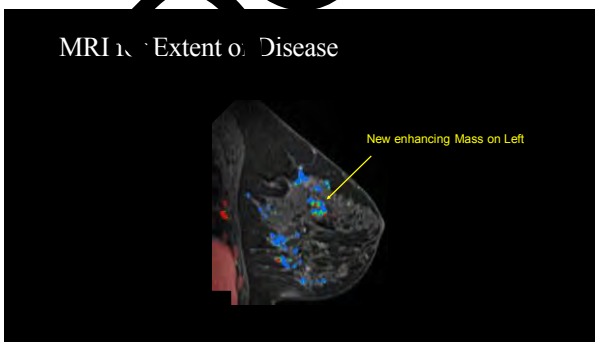
	BRCA/RT	PH	HRL	FH
CDR (#/1000 exams)	26	12	15	8
PPV_3	25	19	15	8
Sensitivity	84	88	75	77
Specificity	92	95	92	91

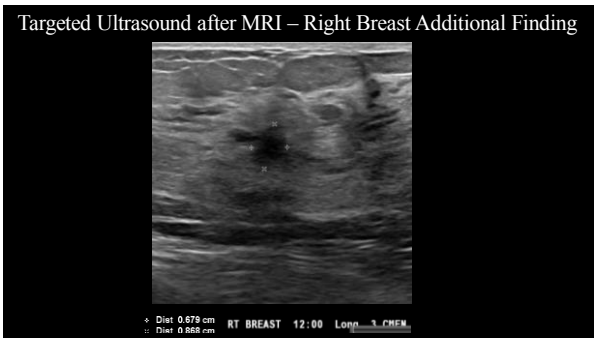

50y/o presents for screening mmg – family history significant for mother diagnosed at 72, sister at 47


Patient requested screening US due to extremely dense tissue
RT BREAST 1:00
Dist 0.941 cm

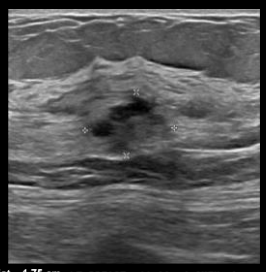

Ultrasound guided core BX:
Invasive ductal carcinoma, grade 1
ER, PR –Pos
HER2- Neg


MRI for E tent of Disease
known CA 100
Right Breast - Additional Finding
second lesion

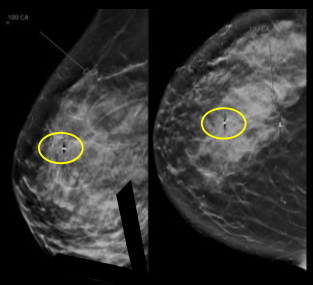

MRI f Extent o Disease
New enhancing Mass on Left


Targeted Ultrasound after MRI – Right Breast Additional Finding
Dist 0.679 cm
RT BREAST 12:00

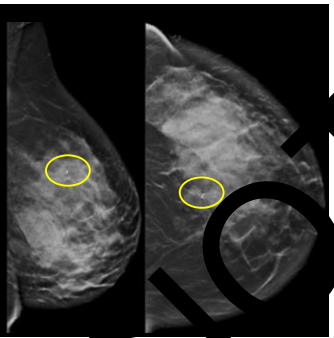
Targeted Ultrasound – MRI detected Left Breast Lesion



Right 12:00 core biopsy:
Invasive ductal carcinoma, morphologically similar to previous R1:00



Left 11:00 core biopsy:
Invasive ductal carcinoma, grade 1
ER, PR – Pos
HER2 - Neg



Why is this Important?

Three malignancies diagnosed that were occult on mammography due to the patient's dense breast tissue

Patient had dense breast tissue, but also strong family history of breast cancer – due to >20% lifetime risk, patient would qualify for screening MRI, which could have potentially led to earlier diagnosis

Patient went on to have bilateral mastectomy

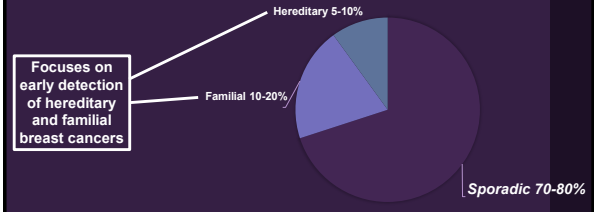
What a Change in Screening Could Mean

Hendrick & Helvie screening mammography shows greatest benefit—a 39.6% mortality reduction—from annual screening of women 40–84 years old

- This screening regimen saves 71% more lives than the USPSTF-recommended regimen of biennial screening of women 50–74 years old, which had a 23.2% mortality reduction
- For U.S. women 30–39, annual screening mammography from 40–84 years would save 99,829 more lives than USPSTF recommendations if all women comply, and 64,889 more lives with the current 65% compliance rate

Hendrick, R. E., & Helvie, M. A. (2011). United States preventive services task force screening mammography recommendations: science ignored. American Journal of Roentgenology, 196(2), W112-W116.

Remember: Majority of Breast Cancers Diagnosed are Sporadic



Focuses on early detection of hereditary and familial breast cancers

Risk Based Screening Women 40-49 (Price 2015)

Determined the prevalence of very strong family history and extremely dense breasts in women 40-49 with breast cancer detected on screening
- Patients with personal history were excluded

Family History evaluation:
- Patients with one first-degree relative with breast cancer diagnosed at 50 or older were considered to have strong family history
- Patients with at least two first-degree relatives with breast cancer, or one first-degree relative with breast cancer diagnosed younger than 50 were considered to have very strong family history
- Remaining patients were not considered to have relevant family history

Price ER, et al. AJR 2015; 205:1360-1364.

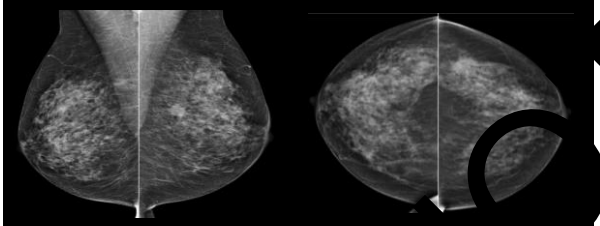
Price: Risk Based Screening

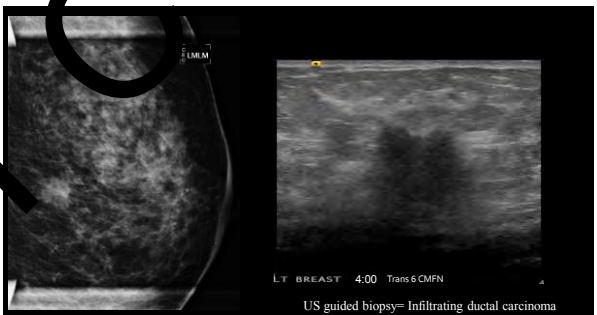
Very strong family history was absent in 88% of the study population
- Extremely dense breast tissue absent in 86%

76% of patients had neither very strong family history nor dense breast tissue, including 79% of the invasive cancer cases
- 25% had axillary nodal involvement and 89% were ER positive

These results show that reducing the number of women screened in this age group using this risk-based approach would lead to reduction in screen-detected cancers, ultimately precluding the benefit of mortality reduction

44 year old patient presents for screening; prior mammograms normal- no family history





US guided biopsy= Infiltrating ductal carcinoma

What Women Want in Screening

Survey evaluated willingness of women to change breast cancer screening practices if given personalized recommendations based on risk factors such as breast density, family history and lifestyle

54.6% of women are definitely or probably willing to reduce their frequency vs **81.9%** are definitely or probably willing to increase screening

Most cited disadvantage for reduced screening: delayed detection of breast cancer 77%

Most cited advantage for increased screening: earlier detection 82%

92.3% women are willing to change their type of screening; most would want additional screening

W Cohn, W Novicoff, McKinney M Dean, T Gulerbock, D Reerdde, C Eggleston, J Harvey and W Kraus Are Women Willing to Change Breast Cancer Screening Guidelines? Cancer Epidemiol Biomarkers. 2014; 23(1)

How do Women View Risk Based Screening?

Study explored women's views and personal acceptability of a potential risk-based mammography screening paradigm

Some women accepted the idea that early cancer detection with traditional screening was beneficial—although many also reported hearing inconsistent recommendations

Some familiar with risk-based screening paradigm and thought matching screening mammography frequency to personal risk made sense
- But personal acceptability of risk-based screening was mixed - some believed it could reduce the harms of false positives and overdiagnosis - others thought screening less often might result in missing a dangerous diagnosis
- Many expressed concerns about the feasibility of risk-based screening and questioned whether breast cancer risk estimates could be accurate

He X, et al. How Do Women View Risk-Based Mammography Screening? A Qualitative Study. Journal of General Internal Medicine. 2018; 33(11):1905–1912.

Summary

- Annual Mammography beginning at 40 has been proven to save lives
- Risk assessment is important- women at higher risk need to be identified as management options will be different
- Target increased surveillance and other interventions specifically to individuals with known increased risk
- Significantly improve outcomes and reduce medical costs through earlier diagnosis and treatment of cancer, should it develop
- New techniques and technologies to increase access to screening for those at an elevated risk are continuing to be developed and should be further investigated for broad scale utilization

Thank You

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