9:45 – 10:45 am

Reduced Cancer Mortality: Screening and Risk Reduction as a Strategy

SPEAKER
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Presenter Disclosure Information

The following relationships exist related to this presentation:

- Lowell E. Schnipper, MD: Advisory Board for Eviti, Inc. Co-editor-in-chief of oncology for UpToDate.

Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Cancer Screening for the Primary Care Physician

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Objectives

- Review the evidence behind screening recommendations
- Differentiate between screening and diagnostic work-up
- Use appropriate guidelines in implementing screening in clinical practice

Cancer Screening: A Good Investment

- Health economists generally agree that an intervention is cost effective if it can save 1 year of life for less than $50,000.
- Screening for colorectal, breast, and cervical cancers is indisputably cost effective:
  - Screening for colorectal cancer extends life at a cost of $11,890 to $29,725 per year of life saved.
  - A mammogram every 2 years extends life for women aged 65 or older at a cost of about $36,924 per year of life saved.
  - Pap screening every 3 years extends life at a cost of about $5,392 per year of life saved.

When is Screening for Cancer Efficacious?

- **Early detection is possible (prior to symptoms developing)**
- **Evidence supporting improved outcome with early treatment**
- **Decrease in cause-specific mortality (*not survival rates-lead time bias*)**

When is Screening for Cancer Efficacious-how to evaluate them?

- **sensitivity**-is the chance that a person with cancer has a positive test
- **specificity**-the chance a person without cancer has a negative test
- **positive-predictive values (PPV)**-PPV is the chance that a person with a positive test has cancer
- **negative-predictive values (NPV)**- the chance that a person with a negative test does not have cancer

Rationale for Screening

Mutation rate of cancers 10^{-6}
Smaller tumor burden = lower likelihood of cells with metastatic potential
Cancer with small tumor burden is more likely to be curable

Screening Tests That Save Lives

- **CRC: Colonoscopy, sigmoidoscopy, and high-sensitivity fecal occult blood tests (FOBTs)**
- **Lung Cancer: Low-dose helical computed tomography** among heavy smokers ages 55 to 74
- **Breast Cancer: Mammography**
- **Cervical Cancer: Pap test and human papillomavirus (HPV) testing**

Other Screening Tests: *less well validated-not proven to save lives*

- AFP-liver cancer
- MRI-breast cancer
- Breast Self Exam or provider exams
- CA 125 – Ovarian Cancer
- Transvaginal US
- Skin Exams
- PSA

Prostate Cancer

▸Case for Discussion

•53 yo African American male
•Initial annual visit
•Father died of prostate cancer *(states that "they got it late");* paternal uncle has prostate cancer
•Married, sexually active; no significant co-morbidities
•No urinary or urological symptoms
•PE: mild hypertension; negative DRE
•**WHAT ARE YOUR RECOMMENDATIONS REGARDING PSA BASED TESTING?**

Courtesy, M. Garnick

▸ What are your recommendations? ?

1. Order a PSA test as part of the routine annual bloods, along with lipid panel, glucose, and CBC (patient not informed)
2. Given the lack of symptoms and PE, do not bring PSA issue up, but document your decision in the medical record
3. Briefly discuss controversies about PSA testing and have patient make decision (and document)
4. Briefly discuss controversies about PSA testing and recommend the test (and document)
5. Briefly discuss controversies about PSA testing and do NOT recommend the test (and document)

▸ For the same patient with prostate cancer, the options range from

Radical Treatment_____No Treatment

so how can we decide?

▼

Now-- Should testing that led to the prostate cancer Dx even be offered?

Framing the Problem

- We screen **older men** who are **unlikely to die** from a screen detected cancer
- We practice **widespread overtreatment** of low risk disease
- **Surgical complications** are proportional to skill and volume of surgeon, yet most surgeons perform three or fewer prostatectomies per year. (Vickers cancer letter interview 10/10/14
- **Cost to prevent one death** from prostate cancer with PSA screening=$5.2MM

M. Garnick, personal comm.

Know Harms Associated with PSA Screening and Rx

- **Bleeding**
- **Infection**
- **Incontinence**
- **Erectile dysfunction**
- **False positive rates**
- **Overdiagnosis**
- **Death**

Two Key Studies that Address Screening

ERSPC: no survival benefit; small ca specific survival advantage DOI:
http://dx.doi.org/10.1016/S0140-6736(14)60525-0

PLCO: no survival or ca specific survival benefit

25% of screened patients had LUTS/BPH
JNCI 2012, 104:125

Know Key Guidelines

- **USPSTF: "Recommends against PSA-based screening for prostate cancer"**
  http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/prostate-cancer-screening
- **American Urological Association**
  https://www.auanet.org/education/guidelines/prostate-cancer-detection.cfm
  American College of Physicians
- **Canadian Task Force on Preventive Health Care**
  CMAJ November 4, 2014 vol. 186 no. 16 First published October 27, 2014, doi: 10.1503/cmaj.140703

▸ Recent Guidelines – ACP

I: Inform patients of possible benefits and significant harms of PSA testing. No testing for those who do not express a clear preference for screening

II: NO PSA testing for those <50; >69; or LE of <10-15 years

Talking points provided

Ann Int Med 2012, 157:120

▸ Recent Guidelines - AUA

I: NO PSA testing under age 40

II: PSA not recommended 40-54

III: 55-69: prevent mortality in 1/1000 men over 10 years; PSA testing undergo shared decision making, based upon values and preferences

IV: for those screened, every two years

V: NO PSA testing for men >70 with less than 10-15 years of life expectancy

CTF PHC

Men <55 and ≥70

Strong recommendation against screening

"Clinicians should not routinely discuss screening … unless the topic is raised by the patient"

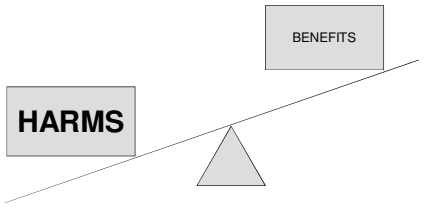
CTF PHC

- **Men 55-69**
- Weak recommendation against screening

- Risks and benefits discussed
- Those who place a high value on a small potential reduction in mortality and are less concerned with undesirable consequences may choose to be screened"

(doi/10.1503/CMAJ.141252)

▸ After weighing ALL the evidence…



Approaches to Screening for Cervical Cancer

- **Cytology**
- **VIA/VIL**
- **DNA based**

USPTF: Cervical Cancer Screening

Summary of Recommendations and Evidence
Population Recommendation: Grade A
Women 21 to 65 (Pap Smear) or 30-65 (in combo with HPV testing)

- The USPSTF recommends screening for cervical cancer in women age 21 to 65 years with cytology (Pap smear) every 3 years or,
- For women age 30 to 65 years who want to lengthen the screening interval, screening with a combination of cytology and human papillomavirus (HPV) testing every 5 years

Ann Intern Med. 2011;155:687-697

USPTF: Cervical Cancer Screening

Recommendation Summary
Summary of Recommendations and Evidence
Population Recommendation

•Women younger than 30 years, HPV testing:The USPSTF recommends **against** screening for cervical cancer with HPV testing, alone or in combination with cytology—**likely no benefit**

•Women younger than 21: The USPSTF recommends against screening for cervical cancer in women younger than age 21 years. Recommendation: **against screening**

•Women Older than 65, who have had adequate prior screening The USPSTF **recommends against**

•Women who have had a hysterectomy: The USPSTF **recommends against** screening for cervical cancer in women who have had a hysterectomy with removal of the cervix

Ann Intern Med. 2011;155:687-697

Colorectal Cancer

Screening CRC: Average Risk

- Average Risk
- Asymptomatic
- Age over 50
- No personal or family history adenoma or CRC

- Colonoscopy every 10 years, or
- Annual FOBT with or w/o Sigmoidoscopy every 5 years
- Air contrast BE every 5 years
- ? Virtual colonoscopy

https://www.rmf.harvard.edu/~/media/Files/_Global/KC/PDFs/RMFCRC.pdf

Moderate Risk Algorithm

- Personal history CRC
  - •Colonoscopy 1 year after resection, then at 3 years, then 3-5 years
- Polyps
  - •If <1cm--repeat every 5 years
  - •If large, or many, repeat at 3 years
- Family History: first degree relatives
  - •Screen at age 40 or 10 years < earliest case

https://www.rmf.harvard.edu/~/media/Files/_Global/KC/PDFs/RMFCRC.pdf

Hi Risk--Hereditary Nonpolyposis coli (HNPCC)

•Amsterdam Criteria
- 3 relatives with CRC
- 1 is first degree
- 2 successive generations

•Bethesda
- CRC < 50
- 2 CRC' s in same person
- CRC w/ MSI
- Relative w/CRC related cancer (ovarian, gastric, small bowel, GU, pancreas, brain

•Gene Test +: Mismatch repair genes

- Start screening age 20-25
- High risk clinic if available
- Repeat screening every 1-2 years

https://www.rmf.harvard.edu/~/media/Files/_Global/KC/PDFs/RMFCRC.pdf

High Risk: FAP

FAP

- **Individuals with more than 100 colonic adenomas**
- **Multiple adenomas and a relative with known FAP**
- **Finding 10-100 adenomas on colonoscopy**
- **High risk clinic referral**
- **Flex. Sig in children beginning age 12, if negative**
- **Repeat annually until age 40**
- **Prophylactic colectomy**

https://www.rmf.harvard.edu/~/media/Files/_Global/KC/PDFs/RMFCRC.pdf

High Risk: Inflammatory Bowel Disease

Universal ulcerative colitis or Crohn's Disease > 8-10 years	Colonoscopy every 1-2 years, with random biopsies
Left sided ulcerative colitis > 15 years	Colonoscopy every 1-2 years with random biopsies

https://www.rmf.harvard.edu/~/media/Files/_Global/KC/PDFs/RMFCRC.pdf

Screening Modalities

Modality	Advantages	Disadvantage
FOBT	Safe, easy, inexpensive, 33% decrease. mortality	Annual, low sensitivity. specificity
Flex. Sig	Safe, decreased mortality by 60-70%	Does not visualize entire colon, requires prep
Colonoscopy	Optimal procedure; entire colon visualized, permits polyp removal; most sensitive; 50-72% reduction	Costly, time consuming, prep, requires escort
Barium Enema	Reasonably sensitive; safe, sensitiviety 83%	Bowel prep., misses polyps; cannot get tissue
Virtual Colonoscopy	Rapid, more acceptable, no sedation; as sensitive as colonoscopy	Cannot get tissue, not yet widely accepted, not reimbursed
Fecal DNA	Non-invasive, better than FOBT, k-ras, methyl-vimentin, APC	availability

Lung Cancer

Summary of Recommendation and Evidence: USPTF: screening for lung cancer

Recommendation Grade B
Adults Aged 55-80, with a History of Smoking

- Annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years.
- Discontinue after 15 years off tobacco
  There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.

http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/lung-cancer-screening

Breast Cancer Screening

to screen, if so, whom, when, and with what modality?

CRICO's Breast Cancer Diagnosis-Related Cases

29 cases asserted 2008–2012;
$27.2 million total incurred losses
(i.e., aggregate of expenses, reserves, and payments on open and closed cases).

A Clinical Case: What is Your Advice?

A 38 year old woman initiates care with you and presents for a routine history and physical. As a teenager she was found to have a mediastinal mass that proved top be Hodgkins Disease that required treatment with chemotherapy and radiation therapy to a mantle port. She is without any symptoms and her exam is normal.

She asks you for advice about how best to remain well and cancer free. Your recommendation(s) are?

Breast Cancer Risk Assessment

- Known genetic predisposition-BRCA1,2 or other
- Personal history: invasive CA or DCIS
- Family history (maternal or paternal) of breast or ovarian cancer
- History of thoracic radiation age <30
- Lobular carcinoma in situ (LCIS), atypical ductal hyperplasia or atypical lobular hyperplasia on breast biopsy
- Prior breast biopsy
- Hormonal risk factors: early age at menarche, nulliparity, later age at first birth, late menopause and >5 years of combined estrogen/progesterone hormone replacement therapy

Screening for Breast Cancer

- Breast Self Exam ☒
- Clinical Breast Exam ☒
- Ultrasound ☒
- Mammography ☑
- MRI ☑

Breast Self Exam

- Randomized controlled trials have shown no benefit to BSE in decreasing mortality
- Of cancers detected on palpation women do often discover their mass-- but not on routine BSE
- BSE does lead to the discovery of more benign masses

Ann Intern Med. 2009;151(10):716, CTFPHC CMAJ. 2011;183(17):1991

Clinical Breast Exam

- Lack of standardized technique
- Include visual inspection, node exam
- Systematic palpation
- High degrees of variability
- Not a useful screening tool (USPTF &CTFPHC)

Ann Intern Med. 2009;151(10):716
CMAJ. 2011;183(17):1991.

Digital vs. Film – Is one better?

- **DMIST trial (N Engl J Med; 353;17:1773-1783, 2005)**
- **For entire population – no difference**
- **Costlier**
- **BUT digital better for**
  - **Under age 50**
  - **Heterogeneously dense or very dense breasts**
  - **Pre- or peri-menopausal**

Mammogram Findings

- Results assigned a BIRADS score
  - BIRADS 0: assessment incomplete, additional imaging or comparison to prior film needed
  - BIRADS 1: normal, continue routine screening
  - BIRADS 2: benign findings
  - BIRADS 3: probably benign, short interval follow-up (cancer risk ~2%)
  - BIRADS 4: suspicious- biopsy should be considered (cancer risk a: <15%, b: 15-60%, c: 60-95%)
  - BIRADS 5: highly suspicious (cancer risk>95%)
  - BIRADS 6: known biopsy proven cancer
- Work-up based on radiologist's recommendations

Tomosynthesis "3D" Mammography

- Approved by the FDA in 2011 using tomosynthesis as well as standard 2D views
- 2X More radiation
- Clinical outcomes not shown to be better than standard mammography
  - May have benefit in same patients that may benefit from digital over film screen

JAMA. 2014;311(24):2499-2507. doi:10.1001/jama.2014.6095

MRI

- Gadolinium contrast shows areas of increased blood flow
- Considerable overlap between benign and cancerous areas
- Ductal Carcinoma in Situ and cancers without much increase in vascularity may not show up as well
- Small nonrandomized studies of high risk patients show better sensitivity than mammography but specificity remains a problem
- No evidence of a decrease in mortality
- High cost, longer exam, claustrophobia a problem
- USPTF: recommends against for routine screening

Ann Intern Med. 2009;151(10):716

Dueling Screening Recommendations Normal Risk (1)

- USPSTF: against teaching BSE, insufficient evidence for CBE, Digital mammography over film, MRI
  - Age 39-49: against routine mammography, assess individual risk and discuss benefits/harms
  - Age 50-74: biennial mammography
  - Age $\geq$75: insufficient evidence to assess
- CTFPHC: against routine screening with BSE, CBE, MRI
  - Age 40-49: no routine screening
  - Age 50-69: mammography every 2-3 years.
  - Age 70-74: mammography every 2-3 years

Dueling Screening Recommendations Normal Risk (2)

- ACS: CBE at least every 3 years age 20-39, annual mammogram + CBE age 40 on, discuss BSE as an option but women should know their breasts and report changes, MR if >20% risk (ACSGuidelines@cancer.org.)
- NCCN:
  - Age 20-39: CBE every 1-3 years, "Breast awareness"
  - Age $\geq$ 40: Annual CBE, annual mammogram, "Breast awareness"

CRICO/RMF

http://www.rmf.harvard.edu

- Breast Care Management Algorithm
- Screening recommendations by age per NCCN guidelines:
  - Women ages 40-69: annual screening
  - Women ages 70 and over: screening every 1-2 years with consideration of overall quality of life
- Screening applies only to asymptomatic women
- Breast symptoms requires a Diagnostic Work-up

High Risk Screening Guidelines NCCN

- Women ≥ age 35 with 5 yr risk ≥ 1.7%: Annual mammogram, CBE every 6-12 months, breast awareness, consider risk reduction
- Lifetime risk >20% based on models largely dependent on family history: Annual mammogram and CBE every 6-12 months starting age 30, breast awareness, consider risk reduction, consider annual MRI age 30 on
- Prior Thoracic Radiation
  - Age <25: Annual CBE and "Breast awareness"
  - Age ≥25: Annual mammogram, CBE every 6-12 months 8-10 years following radiation or age 25 (whichever LAST), annual MRI, "breast awareness"

NCCN High Risk Screening Guidelines: Hereditary Predisposition (HBOC)

- Women
  - Breast awareness
  - CBE every 6-12 months starting age 25
  - Mammography and MRI annually starting age 25 (or depending on earliest onset in family)
  - Consider risk reduction
- Men
  - Breast awareness
  - CBE every 6-12 months starting age 35
  - Consider baseline mammogram age 40, then annually if gynecomastia or dense glandular tissue

Breast Cancer Follow-up NCCN

- Interval H&P every 4-6 months for 5 years then annually
- Annual mammography
- Annual gyn exam if on Tamoxifen and uterus in place
- Monitor bone density in women on aromatase inhibitors or made postmenopausal by therapy
- Assess and encourage adherence to endocrine therapy
- Encourage active lifestyle achieving and maintaining BMI of 20-25

Diagnosis- Principles

- Want least invasive method to make an accurate diagnosis
- In most cases in USA core needle biopsy should be the procedure of choice
- If pathology results do not correlate with clinical suspicion, surgical biopsy should be performed
- Core needle biopsies with pathology revealing LCIS, atypia, papillary lesions or radial scar should be referred for possible surgical excision

Image Guided Biopsies

- Ultrasound guided core needle biopsy
  - limited by mobility of target, proximity to skin or chest wall
- Stereotaxic core needle biopsy
  - limited by faintness of calcifications, location adjacent to chest wall or superficial, depth of breast tissue on compression
- Wire localization and biopsy
  - relies on accurate placement of wire, careful removal of tissue around wire

A Clinical Case: what is your advice?

A 38 year old woman initiates care with you and presents for a routine history and physical. As a teenager she was found to have a mediastinal mass that proved top be Hodgkins Disease that required treatment with chemotherapy and radiation therapy to a mantle port. She is without any symptoms and her exam is normal.

She asks you for advice about how best to remain well and cancer free. Your recommendation(s) are?

Mantle Radiation 25 years earlier: what advice for screening?

And, if she did not have radiation, but had a strong family hx breast ca, and, affected relatives were BRCA 1,2 negative?

Screening studies that have not been shown to reduce mortality

- AFP
- CA 125
- MRI breast
- Virtual colonsocopy
- Transvaginal US
- Skin exams

Take Home Messages (all screening)

- Stay current: screening recommendations can change fairly frequently.
- Document screening guidelines you are following and when not following, document why.
- Make sure patients know you are listening to their concerns and taking them seriously
- Work-up of a breast problem should follow recommended guidelines, if not document why
- All hand-offs should be clear between practitioners and documented in the medical record
- Relationships are very important.

Reference Links

- CRICO/Risk Management Foundation
  - http://www.rmf.harvard.edu
  - Click on Guidelines/Algorithms and then Breast Cancer
- National Comprehensive Cancer Network
  - http://www.nccn.org
- National Cancer Institute nci.gov