Take 3 – Practical Practice Pointers© September 16, 2019 Edition

BRCA Testing, Meds to Reduce Breast CA Risk, Breast CA Screening

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From the USPSTF

1) BRCA-related Cancer in Women

Potentially harmful mutations of the *BRCA1/*2 genes are associated with increased risk for breast, ovarian, fallopian tube, and peritoneal cancer. For women in the US, breast cancer is the most common cancer after nonmelanoma skin cancer and the second leading cause of cancer death. In the general population, *BRCA1/2* mutations occur in an estimated 1 in 300 to 500 women and account for 5% to 10% of breast cancer cases and 15% of ovarian cancer cases. A woman's risk for breast cancer increases if she has clinically significant mutations in the *BRCA1/2* genes. Mutations in the *BRCA1/2* genes increase breast cancer risk by 45% to 65% by age 70 years. Risk of ovarian, fallopian tube, or peritoneal cancer increases to 39% for *BRCA1* mutations and 10% to 17% for *BRCA2* mutations.

The USPSTF recently updated their 2013 recommendation regarding screening for BRCA-related cancer in woman. Recommendations include:

- Recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with breast cancer susceptibility 1 and 2 (*BRCA1/2)* gene mutations with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing. (**B** Recommendation)
- Recommends <u>against</u> routine risk assessment, genetic counseling, or genetic testing for women whose personal or family history or ancestry is not associated with potentially harmful *BRCA1/2* gene mutations. (**D** Recommendation)

Mutations in the *BRCA1/2* genes cluster in families, showing an autosomal dominant pattern of inheritance in either the mother's or father's family. When taking medical and family history information from patients, primary care clinicians should ask about specific types of cancer, primary cancer sites, which family members were affected, and whether relatives had multiple types of primary cancer. Clinicians should also inquire about the age at diagnosis, age at death, and sex of affected family members, both immediate (ie, parents and siblings) as well as more distant (ie, aunts, uncles, grandparents, and cousins).

For women who have family members with breast, ovarian, tubal, or peritoneal cancer or have a personal history of these types of cancer, primary care clinicians may use appropriate brief familial risk assessment tools to determine the need for in-depth genetic counseling. Tools evaluated by the USPSTF were multiple, and included brief versions of BRCAPRO (BRCAPRO-LYTE). Each of these tools has been validated and accurately estimate the likelihood of carrying a harmful *BRCA1/2* mutation. They can be used to guide referrals to genetic counseling for more definitive risk assessment. General breast cancer risk assessment models (eg, the National Cancer Institute Breast

Cancer Risk Assessment Tool, which is based on the Gail model – See Pointer 2) are not designed to identify *BRCA*-related cancer risk and should not be used for this.

In general, these brief familial risk assessment tools include factors associated with increased likelihood of potentially harmful *BRCA1/2* mutations. These include breast cancer diagnosis before age 50 years, bilateral breast cancer, presence of both breast and ovarian cancer in one individual, male family members with breast cancer, multiple cases of breast cancer in the family, 1 or more family members with 2 primary types of *BRCA*-related cancer (such as ovarian cancer), and Ashkenazi Jewish ancestry. The USPSTF recognizes that each risk assessment tool has advantages and limitations and found insufficient evidence to recommend one over another.

My Comment:
With the onset of "direct to consumer" genetic testing (including BRCA testing), this recommendation update is quite timely. There was not enough evidence for the Task Force to make a recommendation concerning these over-the-counter tests.

One concern that was raised in some of the commentary regarding this recommendation is the specific guidance that every woman with a high risk based on her risk assessment should then see a genetic counselor before testing. With limited access to such counselors in many communities, this step could limit access to testing, and the recommendation provides no guidance for the primary care clinician and high-risk woman if these resources are not readily available.

Genetic screening in general has become the "wild west" of health care testing, and I'll take that up in a future edition of Take 3 – when I get up the courage ....

References

- USPSTF August 2019: BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing. Link
- Nelson HD, et al. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women. JAMA. 2019 Aug 20;322(7):666-685. Article

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Another from the USPSTF

2) Medication Use to Reduce Breast Cancer (CA) Risk

Breast cancer is the most common nonskin CA among women in the US and the second leading cause of CA death. The median age at diagnosis is 62, and an estimated 1 in 8 women will develop breast CA at some point in their lifetime. African American women are more likely to die of breast cancer compared with other races.

The USPSTF recently updated their 2013 recommendation regarding medication use to reduce breast cancer risk. This recommendation applies to asymptomatic women 35 years and older, including women with previous benign breast lesions on biopsy (such as atypical ductal or lobular hyperplasia and lobular carcinoma in situ). This recommendation does not apply to women who have a current or previous diagnosis of breast cancer or ductal carcinoma in situ. The updated recommendation is consistent with the previous recommendation, and includes:

- Recommends that clinicians offer to prescribe risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors, to women who are at increased risk for breast cancer and at low risk for adverse medication effects. (**B**)
- Recommends against the routine use of risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors, in women who are not at increased risk for breast cancer. (**D**)

Numerous risk assessment tools, such as the National Cancer Institute (NCI) Breast Cancer Risk Assessment Tool (Gail Model), estimate a woman's risk of developing breast cancer over the next 5 years. There is no single cutoff for defining increased risk for all women. Women at greater risk, such as those with at least a 3% risk for breast cancer in the next 5 years, are likely to derive more benefit than harm from risk-reducing medications and should be offered these medications if their risk of harms is low.

Alternatively, clinicians may use combinations of risk factors (including some risk factors not included in risk assessment tools but that would have permitted enrollment in some of the risk reduction trials) to identify women at increased risk. Some examples of combinations of multiple risk factors in women at increased risk include (but are not limited to) age 65 years or older with 1 first-degree relative with breast cancer; 45 years or older with more than 1 first-degree relative with breast cancer or 1 first-degree relative who developed breast cancer before age 50 years; 40 years or older with a first-degree relative with bilateral breast cancer; presence of atypical ductal or lobular hyperplasia or lobular carcinoma in situ on a prior biopsy.

Although evidence on the best interval at which to reassess risk and indications for risk-reducing medications is not available, a pragmatic approach would be to repeat risk assessment when there is a significant change in breast cancer risk factors, for instance when a family member is diagnosed with breast cancer or when there is a new diagnosis of atypical hyperplasia or lobular carcinoma in situ on breast biopsy.

My Comment:
This Pointer as well as the first highlighted for me how poorly a family history I take on most patients. I also reminded me how little many patients know about their family medical history, particularly the extended family history. As genetic testing and more sophisticated risk assessment as well as proactive intervention become more mainstream, the ability to have a more accurate family medical history will become even more essential in order to provide better context for the results.

References:

- USPSTF September 2019: Breast Cancer: Medication Use to Reduce Risk**: Link**
- Owens DK et al. Medication Use to Reduce Risk of Breast Cancer: USPSTF Recommendation Statement. JAMA. 2019 Sep 3;322(9):857-867. Article
- NCI Breast Cancer Risk Assessment Tool (Gail Model): Link

From the American College of Physicians

3) Screening for Breast Cancer ACP Guidance Statement

Recommendations for breast cancer screening in asymptomatic average-risk women vary regarding frequency, age to start and stop, and whether clinical breast examination

(CBE) is useful. This past April, the American College of Physicians (ACP) Clinical Guidelines Committee published recommendations for breast cancer screening for asymptomatic women with average risk for breast cancer. To develop this guidance statement, the ACP Clinical Guidelines Committee reviewed seven relevant guidelines from U.S. and Canadian professional organizations and the WHO. Guidance Statements included:

- In average-risk women aged 40 to 49 years, clinicians should discuss whether to screen for breast cancer with mammography before age 50 years. Discussion should include the potential benefits and harms and a woman's preferences. The potential harms outweigh the benefits in most women aged 40 to 49 years.
- In average-risk women aged 50 to 74 years, clinicians should offer screening for breast cancer with biennial mammography.
- In average-risk women aged 75 years or older or in women with a life expectancy of 10 years or less, clinicians should discontinue screening for breast cancer.
- In average-risk women of all ages, clinicians should not use clinical breast examination to screen for breast cancer.

The committee noted that, in general, the magnitude of reduction in breast cancer mortality associated with mammography screening is small, a point it believes most guidelines do not emphasize. The guidance statement also points out that most guidelines did not demonstrate any mortality reduction among women aged 39 to 49. Screening in this age group also did not reduce the incidence of advanced breast cancer. Regardless of women's age, mammography did not reduce all-cause mortality. In most women aged 40 to 49, screening's harms (overdiagnosis, overtreatment, false-positive results, unnecessary diagnostic testing and biopsies) outweighed its benefits. More-frequent screening was associated with greater harm, and outcomes of annual mammography did not clearly differ from those of longer intervals.

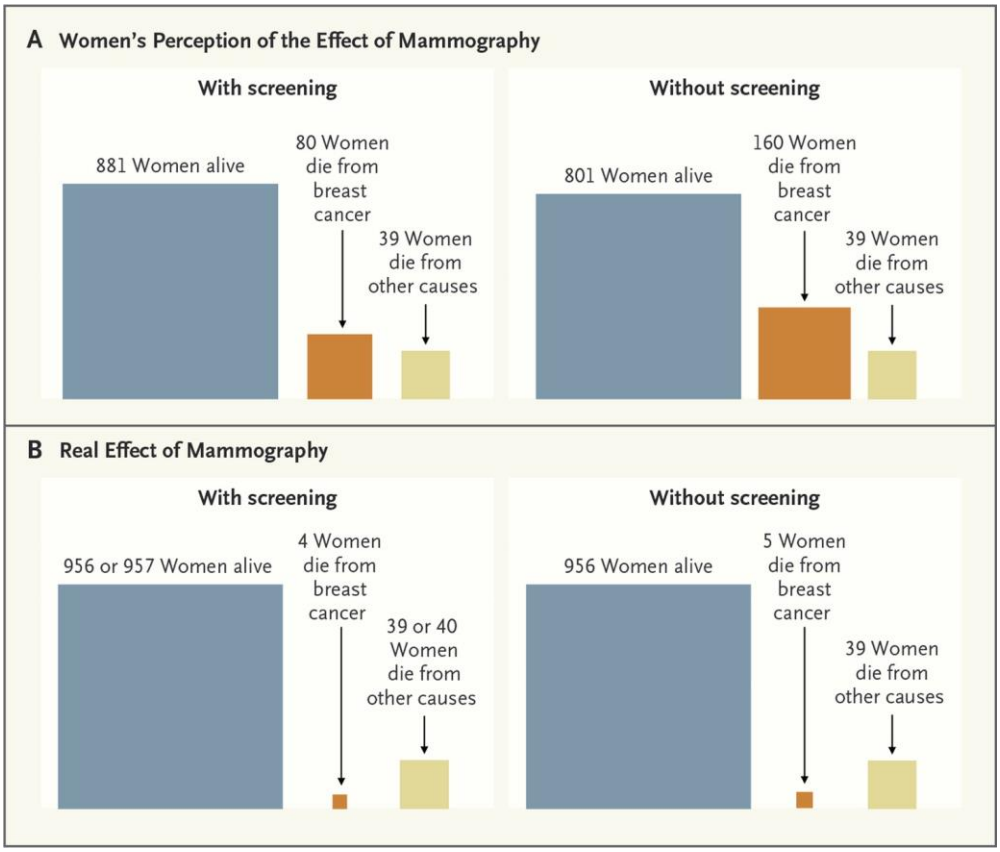
My Comment:
Patients (and many clinicians) greatly overestimate the impact of mammography on breast cancer mortality. This is not “news,” as there are many studies highlighting misperception of risk by both patients and clinicians in multiple areas of medicine (and life). **Below** is a graph from the NEJM that very starkly demonstrates this gap. Panel A shows the views of 50-year-old women in the US regarding the effect of mammography <u>every 2 years</u> on the 10-year risk of death from breast cancer (at left), as compared with no screening (at right). The areas of the squares are proportional to the numbers of women per 1000 who would be alive (blue), die from breast cancer (orange), or die from other causes (yellow). Panel B shows the actual effect of mammography screening on breast-cancer deaths.

For every breast cancer death prevented over a 10-year course of annual screening beginning at 50 years of age, 490 to 670 women are likely to have a false positive mammogram with repeat examination; 70 to 100, an unnecessary biopsy; and 3 to 14, an overdiagnosed breast cancer that would never have become clinically apparent.

This highlights yet once again the dynamic tension that exists as we implement any screening test. If the goal is to detect all breast cancer at any cost, then the false positives and “overdiagnosis” of cancers that would never have been of consequence is an acceptable if regrettable “side effect” of screening. If, however, the goal is to

decrease breast cancer and overall morbidity and mortality, the evidence such as this provides stark contrast for reflection.

I am reminded with such debates that the practice of medicine (or life) is never a purely "cognitive" nor rational exercise. A tenant that I have tried to live in my own medical practice was articulated well by Sir William Osler, who is considered one of the "grandparents" of modern medicine. He said, "Good clinical medicine will always combine the science of probability with the art of uncertainty." For both our medical culture and our western culture at large, we in general are still not very comfortable with either. I'm not holding my breath that this will change any time soon, and so in the meantime, we will likely continue to "error" on the side of more, rather than less, screening, which, rightly or wrongly, seems to reflect the values of our dominant culture both within and outside of medicine.



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- Qaseem A, et al. Screening for Breast CA in Average-risk Women: A Guideline Statement From the ACP. Ann Intern Med 16 April 2019;170:547-560. Article
- Biller-Andorno, N and Juni P. Abolishing Mammography Screening Programs? A View from the Swiss Medical Board. NEJM May 22, 2014;370(21): 1965-67. Link

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