Update in Women’s Health

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Immediate Past Chair, ACP Board of Regents
Topics

- Heart Disease
- Menopause
- Breast Cancer
- Cervical Cancer Screening
Case #1

- 68 year old woman comes to the clinic with a 1 year history of worsening fatigue and shortness of breath. Was previously seen in urgent/express care clinics and told her symptoms were due to obesity and inactivity. Symptoms getting progressively worse. Used to be able to walk 3 miles without shortness of breath, now can only go 1-2 blocks.
Scope of problem

- One woman dies every minute from CAD in the US
- Leading cause of death in women beginning at age 45 years onward
- Women are roughly 10 years older than men when they present
- Young women who develop CAD have a worse prognosis
Scope of problem continued

- Women are referred less often for testing and treatment
- Women with MI are more likely to have complications and increased mortality
- Fewer women have been included in studies so less data
- Awareness is still lacking
  - Whites 65%
  - African Americans 36%
  - Latinas 34%
Awareness

What warning signs would associate with having a heart attack?

<table>
<thead>
<tr>
<th></th>
<th>1997</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>67</td>
<td>56*</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>18*</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>33</td>
<td>38*</td>
</tr>
<tr>
<td>Shoulder/arm pain</td>
<td>NA</td>
<td>60</td>
</tr>
</tbody>
</table>

Mosca L et al, Circulation 2013; 127
Symptoms in Women with MI

- Chest pain absent in 43% (vs. 31% of men)
  - Younger women without chest pain at greatest risk of death
- Most common symptoms
  - Shortness of breath 58%
  - Weakness 55%
  - Fatigue 43%
- Prodrome
  - Fatigue 71%
  - Sleep disturbances 48%
Women without chest pain

- Later presentation
- More NSTEMI
- Less timely therapies
- Less antiplatelets, heparin, beta blockers
- Higher mortality (14.6% vs. 10.3%)

Canto et al JAMA 2012
<table>
<thead>
<tr>
<th>Response (Unaided)</th>
<th>Overall, 2012</th>
<th>Racial/Ethnic Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>White (a)</td>
</tr>
<tr>
<td>If you thought you were experiencing signs of a heart attack, what is the first thing you would do?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Call 9-1-1</td>
<td>65</td>
<td>63</td>
</tr>
<tr>
<td>Take an aspirin</td>
<td>20</td>
<td>22&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Go to the hospital</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Call a family member</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Call your doctor</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>If you thought someone else was experiencing signs of a heart attack, what is the first thing you would do?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Call 9-1-1</td>
<td>81</td>
<td>80</td>
</tr>
<tr>
<td>Advise him/her to take an aspirin</td>
<td>11</td>
<td>13&lt;sup&gt;c,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Take him/her to the hospital</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tell him/her to call the doctor</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Call his/her spouse or family member</td>
<td>—</td>
<td>…</td>
</tr>
</tbody>
</table>

All values are weighted percentages among telephone respondents. Letters denote significant differences in columns for racial/ethnic and age groups at $P<0.05$. Dash indicates small base sample <100; ..., empty cell.
Women can present differently, and do worse when they do

Women are referred less often for appropriate testing

Women are often do not receive appropriate care

Awareness is important

- Patient awareness
- Physician/clinician awareness
Case 2

- 56 year woman comes in to clinic for advice regarding her menopausal symptoms. She has not had a period in 3 years, but is having severe hot flashes and night sweats that significantly impair her sleep. She travels for business and the hot flashes interfere with her concentration and presentations. She is tired and irritable. Relationships with husband and adult children are strained as well.
Diagnosis – S/O

- **Hot flashes** — The most common symptom during the menopausal transition and menopause
  - occur in **up to 80 percent** of women in some cultures.
  - only about **20 to 30 percent of women** seek **medical attention** for treatment.
  - Some women first develop hot flashes that cluster around menses during their late reproductive years, but symptoms are typically mild and do not require treatment.
• **Sleep disturbance** — women experience sleep disturbances *even in the absence of hot flashes.*
• The estimated prevalence of difficulty sleeping based upon two longitudinal cohort studies was 32 to 46%.
• **Anxiety and depression** symptoms may also contribute to sleep disturbances; in one study, they were predictive of subjective sleep disturbances.
• In addition, perimenopausal women with hot flashes are more likely to be depressed. Primary sleep disorders are also common in this population.
• **Depression** — A number of reports indicate that there is a **significant increased risk of new onset depression** in women during the menopausal transition compared with their premenopausal years. The **risk then decreases in the early postmenopause**.

• In a study to determine risk factors for depressive disorders, a diagnosis of **depression was 2.5 times more likely to occur** in the menopausal transition compared with when the woman was premenopausal (odds ratio [OR] 2.50; 95% CI 1.25-5.02).
I'll have the cafe mocha vodka xanax latte to go, please.

NEW!
THE MENOPAUSE SPECIAL
Hormone Replacement Therapy
Hormone replacement therapy (HRT) is used in the United States, especially for:

- treatment of menopausal symptoms
- prevention and treatment of osteoporosis
- prevention of dementia
- prevention of colon cancer
What Do We Know?

- HRT relieves symptoms of menopause
- Decreases LDL, increases HDL, decreases lipoprotein(a), but increases TG’s
- Increases bone mineral density, decreases fracture risk
- Prevents but does not reverse memory loss
Pretreatment Assessment for HRT

- Cancer risk (breast, endometrial, colon)
- Unexplained vaginal bleeding
- Thrombosis risk (DVT, PE, smoking)
- Liver Disease
- Cholelithiasis risk
- CAD risk (HLP, HTN, DM)
- Osteoporosis risk
- Dementia risk
Continued

- Should also include
  - assessment of current menopausal symptoms
  - assessment of patient’s beliefs about prevention
  - assessment of likelihood that patient will tolerate the potential side effects
Lowest dose
for least amount of time
Other Options

- Anti-depressants
- Anti-epileptics
- Anti-hypertensives
- Herbals
- Other
Anti-depressants

- **SSRI’s**
  - Paroxetine (only one with FDA approval for use for treatment of hot flashes)
  - 60-65% effective

- **SNRI’s**
  - Venlafaxine
  - 60-70% effective

- Note: Placebo 50-75% effective
Anti-epileptics

- Gabapentin
  - 60-70% effective at moderate doses
  - 70-80% effective at high doses
  - Combining with paroxetine does not improve efficacy
  - Side effects often limit ability to tolerate

Anti-hypertensives

- Clonidine
  - 40-50% efficacy
Herbals

- Black cohosh
- Red clover
- Soy
- Flaxseed
- Dong quai
- Wild yam
- Ginseng
- Evening primrose

- NO Benefit over placebo
Other

- Exercise
- Acupuncture
- Hypnosis
- Cognitive behavioral therapy
- Guided imagery
Take Home Points Menopause

- Individualized treatment based on severity of symptoms, impact on quality of life, and risk factors
- HRT most effective in symptom management
- Other pharmacologic options available and may be slightly more effective than placebo
- Herbals not regulated and not effective
- Non-pharmacologic treatments promising
Carol found her own way of coping with the hot flushes.
Breast cancer
Case 3

- 51 year old woman with 3 sisters who have had premenopausal breast cancer and a mother who died from ovarian cancer at age 48 comes in to discuss cancer screening and cancer prevention options.
### Screening for average risk

<table>
<thead>
<tr>
<th>Cancer Prevention Group</th>
<th>Age 40-44</th>
<th>Age 45-54</th>
<th>&gt;50-55</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Cancer Society</td>
<td>Individualized decision</td>
<td>Annual</td>
<td>Switch to every 2 years or continue annually</td>
</tr>
<tr>
<td>USPSTF</td>
<td>Individualized decision</td>
<td>Individualized decision</td>
<td>Every 2 years (50-74)</td>
</tr>
</tbody>
</table>
Screening: Why the controversy?

Is 40 too early?

- Modest benefits of screening in the 40s
- Does not significantly decrease breast cancer mortality (RR 0.92, 95% CI 0.75-1.02)
- Does not reduce risk of advanced breast cancer (RR 0.98, 95% CI 0.74-1.37)
- False positives, biopsies, costs and psychological stress
Screening - Controversy

Why over 50?

- Studies show a significant RR for breast cancer mortality
  - 50 to 59 years (RR 0.86, 95% CI 0.68-0.97)
  - 60 to 69 years (RR 0.67, 95% CI 0.54-0.83)
- Reduced risk of advanced breast cancer in > 50 (RR 0.62, 95% CI 0.46-0.83)

Annual vs Biennial?

10-year cumulative false-positive mammography rates
- Annual 61%
- Biennial 42%
Increased risk populations

- Lifetime risk of > 20% (models such as Tyrer-Cuzick, BRCAPRO)
- Prior h/o breast cancer
- h/o thoracic RT under the age of 30 yo
- 5 year risk of Invasive disease $\geq 1.66\%$ in women $\geq 35$ (Gail model)
  https://www.cancer.gov/bcrisktool/
- Diagnosis of atypical hyperplasia, LCIS (DCIS)
How common is hereditary breast cancer?

Familial, 15-20%

Hereditary, 5-10%

Sporadic 70-80%

BRCA1 and BRCA2 are the most common causes of hereditary breast and hereditary ovarian cancer.

**Breast Cancer**
- 12% of women in the general population will develop breast cancer
- 50-65% of women who inherit the BRCA1 gene will develop breast cancer

**Ovarian Cancer**
- 1.3% of women in the general population will develop ovarian cancer
- 39% of women who inherit the BRCA1 gene will develop ovarian cancer
Who should have genetic testing?

**BRCA testing**
- Individuals from families with known BRCA
- Personal history of breast cancer with multiple family members with breast and/or ovarian cancer
- Ashkenazi Jewish descent
- Young age at diagnosis (≤ 45 y or ≤ 50 with other factors*)
- Triple negative cancer age <60
- Personal history of ovarian cancer
- At any age if FH of ovarian cancer or male breast cancer

**Multigene/ Panel testing**
- There are other cancer types in the family
- One or more rare syndromes in the differential, and/or
- The results would influence medical management

* >= 1 relative (first, second, third on the same side of the family) at any age with breast cancer, pancreatic cancer or prostate cancer. Also if has an additional breast primary
Screening in increased risk populations

- Clinical encounter at least annually
- Annual screening mammogram: begin 10 years prior to youngest affected family member (but at > 25yo)
- Some may need screening breast MRIs
Who should get a screening MRI

Recommend Annual MRI Screening

- BRCA mutation
  - First-degree relative of *BRCA* carrier
    - Lifetime risk $\sim 20\text{--}25\%$ or greater
  - Radiation prior to age 30
Risk reduction in high risk patients

- Risk reduction surgeries: In patients with a genetic mutation

- Endocrine therapy: tamoxifen, raloxifene, or aromatase inhibitor for 5 years
  - Prevents HR+ breast cancer by 50%, does not prevent HR- cancer
  - Most notable benefit is seen in Atypical hyperplasia
  - No known survival benefit
  - Absolute benefit is small

- Consider sending these patients to an oncologist for further evaluation and management
Cervical cancer screening
Case 4

- 35yo woman comes in for a pap smear
- She has been in a monogamous relationship for 7 years
- She hopes to become pregnant and plans to discontinue condom use
- Her last Pap smear was 1 year ago and was normal. She has had annual Pap smears for the past 15 years. All have been normal.
2018 USPSTF Cervical Cancer Screening Recommendations for Average-Risk Women

<table>
<thead>
<tr>
<th>Population*</th>
<th>Recommendation</th>
<th>Recommendation Grade†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women aged &lt;21 years</td>
<td>No screening</td>
<td>D</td>
</tr>
<tr>
<td>Women aged 21 – 29 years</td>
<td>Cervical cytology alone every 3 years</td>
<td>A</td>
</tr>
<tr>
<td>Women aged 30 – 65 years</td>
<td>Cervical cytology alone every 3 years</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hrHPV testing† alone every 5 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Co-testing (hrHPV testing† and cervical cytology) every 5 years</td>
<td></td>
</tr>
<tr>
<td>Women aged &gt;65 years with adequate</td>
<td>No screening</td>
<td>D</td>
</tr>
<tr>
<td>prior screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women who have had a hysterectomy</td>
<td>No screening</td>
<td>D</td>
</tr>
<tr>
<td>with removal of the cervix and do not</td>
<td></td>
<td></td>
</tr>
<tr>
<td>have a history of a high-grade cervical precancerous lesion or cervical cancer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Why NO HPV testing in patients younger than 30?

- HPV co-testing is not recommended for women under 30 years of age, since most infections in this age group are transient.
HPV Test Result Outcomes

- A single HPV-positive test result in women 30 years of age or older provides a marker of increased risk for cervical cancer development. However, the positive predictive value of a single test is around 20% for pre-cancer and even less for cancer.
- HPV-negative test results offer greater assurance of protection from pre-cancer or cancer than normal cytology.
- HPV-negative co-testing offers protection for about 3 to 6 years.
- HPV-negative alone offers protection for about 3 years.
- Negative Pap testing offers protection for about 3 years.
<table>
<thead>
<tr>
<th>Test Combination Outcomes</th>
<th>Risk for Cancer</th>
<th>What to Do Next</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Pap Negative HPV</td>
<td>Very low risk for CIN3 or cancer in next 3+ years.</td>
<td>Rescreen in 5 years.</td>
</tr>
</tbody>
</table>
| Normal Pap Positive HPV   | Risk of cervical intraepithelial neoplasia (CIN) 3 or cancer within 10 years:  
  • 13.5% in younger (22 to 32 year-old) women  
  • 21.2% in older (40 to 50 year-old) women | Repeat co-testing in 1 year or triage immediately based on the HPV DNA typing result. HPV DNA typing tests for the specific type of HPV (16, 18) present, rather than just the presence of any high-risk HPV. If 16/18 negative, repeat co-test in 1 year. If 16/18 positive, go to colposcopy. |
Is screening needed after HPV vaccination?

- Yes!

- Cervical cancer cytology screening recommendations remain unchanged for women who have been vaccinated for HPV because 10% to 30% of cervical cancer is caused by HPV types not included in the vaccine, and sexually active women could have been infected prior to vaccination.
“I had a miraculous dream in which our list of questions all had answers.”