Women’s Health: Year in Review

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Conflicts of Interest: None

Our Systematic Review

• Review for ACP and SGIM
  – Rachel Bonnema MD, MS
  – Megan McNamara, MS, MSc
  – Sarah Tilstra MD, MS

• Reviewed all titles published in top journals
  – January 1, 2012 to March 1, 2013

• Evaluated potential impact on internists’ clinical practice

• Consensus reached about those most worthy of your time today
Sources Reviewed

- New England Journal of Medicine
- Journal of the American Medical Association
- Annals of Internal Medicine
- Archives of Internal Medicine
- British Medical Journal
- Lancet
- Obstetrics and Gynecology
- American Journal of Obstetrics and Gynecology
- Journal of General Internal Medicine
- PLOS Medicine
- American Journal of Public Health
- Circulation
- Diabetes
- Cochrane database of systematic reviews
- Guideline Clearing House
- ACP Journal Club
- ACP Journal Wise
- Journal of Women's Health
- Journal Watch Women's Health
- Journal Watch

Plan for today

- Breast Cancer Screening and Risk Factors
- Cervical Cancer Screening
- Menopause and Beyond
- Osteoporosis and Bone Health
Cancer Screening and Risk Factors

The Mammography Controversy Continues........
Case

• Stella Skeptic is a 58 year old woman who doesn’t believe in “conventional medicine.” She has previously declined all your preventive recommendations, including screening mammography and CRC screening. She comes in today wanting to know what you think about ‘that new study” that shows that mammography really doesn’t work that well after all.”

Screening Mammography and Mortality

• Screening should lead to diagnosis of earlier stage cancers
• Early treatment of these detected cancers should lead to more benefit then treatment given at time of clinical presentation
• Effective screening programs should lead to a reduction in the diagnosis of late stage cancers
The News

- *Effect of three decades of screening mammography on breast cancer incidence*
  - Bleyer and Welch, NEJM 2012

- Aim: To quantify the expected increase in the incidence of early stage breast cancer and to determine the extent to which this has led to a corresponding decrease in the incidence of late stage cancer

Methods

- SEER data (1976 to 2008) to evaluate trends in incidence of early stage breast cancer (DCIS and localized disease) and late stage breast cancer (regional and distant disease) among women aged 40 and over
- NHIS data on proportion of women undergoing screening mammography
- Estimates adjusted for transient increase associated with hormone therapy use from 1990-2005
Results

- Screening mammography associated with a doubling in the number of cases of early stage breast cancer found annually
  - 112 to 234 cases/100,000 women
- Rate of presentation with late stage breast cancer has decreased by 8%
  - 102 to 94 cases per 100,000 women
- Assuming constant underlying disease burden, 8 of the additional 122 cancers detected expected to progress to advanced disease
Results: Over-diagnosis

- Over-diagnosis: tumors detected by screening that would never have led to clinical symptoms
- Adjusting for trends in breast cancer incidence, estimate for over-diagnosis
  - In 2008 over 70,000 women (31% of all breast cancers diagnosed)

Take Home Message

- Screening mammography has led to a substantial increase in the diagnosis of early stage breast cancers, with only a small reduction in the rate of late stage breast cancer
- The reduction in mortality from screening appears to be smaller and the risk of over-diagnosis higher, than previously believed.
Screening Women in Their Forties

• USPSTF recommends individualized, informed decision making based on a woman’s values about benefits and harms
• Women with a two fold risk of breast cancer who start biennial screening in their forties have similar benefits and harms as average risk women who start screening at age 50
  * CISNET Microsimulation Models (Van Ravesteyn, 2012)
• Identifying women with at least a two fold increased breast cancer risk could be useful in decision making about mammography initiation before age 50

Case

• Suzie Screening has just turned 40. Her gynecologist gave her a referral for a mammogram but her best friend said that her doctor told her not to have one. Suzie’s head is spinning because every day she hears something different and she wants to know what you, her primary care physician, think. What do you tell her?
What do you recommend to Suzie?

• Yes, of course. All women should have their first mammogram at age 40.
• No, wait until you are 50.
• Let’s talk about it (even though you are already 20 minutes behind)
• We can talk about this next time you come in (maybe the guidelines will be more clear then)
• I don’t know….what do you want to do?

The News

• Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis
• Aim: To determine which factors increase risk for breast cancer in women aged 40 to 49 and the magnitude of risk for each factor
Methods: Systematic Review

- **Main outcome:**
  - Incidence of invasive breast cancer at age 40-49
  - Combined outcome: invasive and non-invasive breast cancer if only available outcome
- **Risk factors:** Race/ethnicity, BMI, physical activity, alcohol use, smoking, family history of breast cancer, breast density, prior breast procedures, reproductive factors
- **Included studies measuring at least one confounder**
- **Data from Breast Cancer Surveillance Consortium (BCSC) to supplement systematic review**
  - 5 mammography registries and two affiliate sites
  - Some risk factors not reported in published studies

Results

- **Personal Risk Factors:** No association race, ethnicity, BMI, physical activity, alcohol or smoking
- **Family history**
  - RR 2.14 (CI 1.92-2.38) one first degree relative
  - RR 3.84 (2.37-6.220 with 2 relatives
  - RR 12.05 (1.70-85.16) for ≥3 relatives
  - Risk higher if relative diagnosed at younger age
- **Breast density (BI-RADS category 2 as reference)**
  - RR 1.62 (CI 1.51-1.75) for BI-RADS 3
  - RR 2.04 (CI 1.84-2.26) for BI-RADS 4
Results: Reproductive Factors

- Menarche at age 15 or older associated with reduced risk compared with reference (13 years)
  - RR 0.87 (CI: 0.78-0.97)
- Reduced risk for women with 3 or more births (reference nulliparous)
  - RR 0.73 (CI 0.61-0.87)
- Breast feeding associated with reduced risk
  - RR 0.87 (CI 0.77-0.98)
- Oral contraceptive use
  - No association in meta-analysis
  - BCSC data showed higher risk for current OC use compared with former or never use
    - RR 1.30 (CI: 1.13-1.49)

Results: Magnitude of Risk

- Greater than two fold increased risk
  - First degree relative with breast cancer
  - Extremely dense breasts on mammography
- 1.5 to 2.0 times increased risk
  - Prior benign breast biopsy result
  - Second degree relative with breast cancer
  - Heterogeneously dense breast tissue
- 1.0 to 1.5 times increased risk
  - Current use of OCPs
  - Nulliparity
  - First birth at age 30 or over
  - Results differed by data sources (inconsistency)
Results: Lower than Average Risk

- BMI of 25 kg/m² or higher
- Low breast density
- Age 15 or older at menarche
- Birth of 3 or more children
- Breastfeeding
- Perimenopausal or postmenopausal
- Use of menopausal estrogen only hormone therapy

Take Home Message

- High breast density and having a first degree relative with breast cancer are factors that could be useful in developing a personalized approach to breast cancer screening.
Key Article

- Institute of Medicine recently published a report on environmental causes of breast cancer and radiation from medical imaging
- Two environmental factors most strongly associated with breast cancer are exposure to ionizing radiation and to combined postmenopausal hormone therapy
- Some lifestyle factors may modestly limit breast cancer risk:
  - Limiting alcohol use, maintaining a healthy body weight and reducing active smoking
    » IOM, 2011

IOM Report Conclusions

- Current evidence based options for breast cancer reduction are limited
- Many risk factors are not modifiable
- Avoiding and reducing exposure to medical radiation is an evidence based strategy that could reduce breast cancer risk
  - Radiation doses from CT are particularly high
  - Reducing unnecessary exposures
Cervical Cancer Screening

Cervical Cancer

- Cervical cancer mortality has dramatically decreased with routine screening
- Pap smear is a commonly used method for cervical cancer screening
- The use of liquid based cytology for primary cervical cancer screening is widespread
- HPV testing is recommended for the triage of abnormal Pap smears- use for screening has been controversial
The News

- Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial
  - Rijkaart et al, BMJ, 2012
- Aim: To determine whether HPV testing in the first round of screening can decrease the detection of CIN Grade 3 or worse, CIN grade 2 or worse and cervical cancer in the second round of screening

Methods

- Population based RCT in the Netherlands
  - Women enrolled as part of nationwide screening program
  - Screening every 5 years age 30-60
  - HPV and cytology co-testing vs cytology alone
  - At second screening HPV DNA and cytology co-testing done in both groups
- Primary endpoint: CIN3 or worse
- Intention to screen analysis
Results: Participants

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Number</td>
<td>22,420</td>
<td>22,518</td>
</tr>
<tr>
<td>Eligible for analysis at</td>
<td></td>
<td></td>
</tr>
<tr>
<td>first screen</td>
<td>19,999</td>
<td>20,106</td>
</tr>
<tr>
<td>Eligible for analysis at</td>
<td></td>
<td></td>
</tr>
<tr>
<td>second screen</td>
<td>19.579</td>
<td>19.731</td>
</tr>
<tr>
<td>Attended second screen</td>
<td>16,750</td>
<td>16,743</td>
</tr>
</tbody>
</table>

Results

- At baseline, more cases of CIN Grade 2 or worse detected in intervention group
  - 267/19,999 vs 215/20,106
  - RR 1.25 (95% C.I.: 1.05-1.50)
- CIN Grade 3 or worse less common in intervention group at second screen
  - 88/19,579 vs 122/19,731
  - RR 0.73 (95% C.I.: 0.55-0.96)
- Cervical cancer less common in intervention group
  - 4/19579 vs 14/19,731
  - RR 0.29 (95% C.I.:0.10-0.87)
Results

• Cumulative detection of CIN grade 3 or worse and CIN grade 2 or worse did not differ significantly between study arms nor for subgroups including women invited for the first time and differing age groups
• Major component of effect was detection of high grade cervical lesions caused by HPV16

Take Home Message

• Using HPV DNA testing for cervical cancer screening leads to earlier detection of clinically relevant CIN grade 2 or worse, which when treated, then leads to improved protection against CIN grade 3 or worse and cervical cancer
Cervical Cancer Screening Guidelines

<table>
<thead>
<tr>
<th>USPSTF 2012</th>
<th>ACS/American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Joint Guidelines 201</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap smear every 3 years in women aged 21-65</td>
<td>Pap every 3 years in women aged 21-29</td>
</tr>
<tr>
<td>For women aged 30-65 who want to lengthen the screening interval, screen with a combination of cervical cytology and HPV testing every 5 years</td>
<td>For women aged 30-65 Pap plus HPV testing is the preferred method</td>
</tr>
<tr>
<td>Discontinue in women over the age of 65 in whom smears have been consistently normal</td>
<td>Discontinue in women over the age of 65 in whom smears have been consistently normal</td>
</tr>
<tr>
<td>No HPV screening in women younger than 30</td>
<td>No HPV testing in women less than age 30 unless needed after an abnormal test result</td>
</tr>
<tr>
<td>No screening in women who have had a hysterectomy</td>
<td>No screening in women who have had a hysterectomy and have no history of cervical cancer or pre-cancer</td>
</tr>
</tbody>
</table>

Menopause and Beyond
Case

• Marion is a 52yo non-smoker and her only medical problem is hypertension, which is well-controlled with hydrochlorothiazide. She has intolerable hot flashes and is coming to you hoping you can help her. Her mother had a heart attack at the age of 65, and Marion is worried about having one herself.

Hormone Therapy ...Timing Theory

• Women randomized to combined E/P in the Women’s Health Initiative had an increased risk for coronary heart disease and stroke

• Re-analysis of the data according to age and time since menopause suggested that younger women in early menopause might actually benefit from treatment with E/P HT

The News

• Effect of Hormone Replacement Therapy on Cardiovascular Events in Recently Postmenopausal Women: A Randomized Trial

• Aim: To assess the effect of hormone replacement therapy on cardiovascular outcomes in early postmenopausal women

Methods

• Analysis of data from the Danish Osteoporosis Prevention Study
  – 1006 healthy recently menopausal women aged 45-58

• Open-label randomization to triphasic estradiol/norethisterone or placebo (hysterectomy: treatment with estradiol alone) for 10 years

• Outcomes:
  1) Composite outcome of death or admission for myocardial infarction or heart failure
  2) Individual components of primary endpoint, admission for stroke
Results

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hormone Therapy (N = 502)</th>
<th>No Therapy (N= 504)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.0</td>
<td>49.5</td>
</tr>
<tr>
<td>BMI</td>
<td>25.2</td>
<td>25.3</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>244mg</td>
<td>242mg/dl</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>148mg/dl</td>
<td>148mg/dl</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>130 mm Hg</td>
<td>129 mm Hg</td>
</tr>
<tr>
<td>Years since menopause</td>
<td>0.61</td>
<td>0.58</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>84mg/dl</td>
<td>84mg/dl</td>
</tr>
</tbody>
</table>

WHI: mean age 63
WHI: 13% with increased lipids
WHI: 36% with HTN
WHI: 4% with DM

Primary endpoint and mortality for hormone replacement therapy

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, heart failure, or myocardial infarction</td>
<td>0.48 (0.26 to 0.87)</td>
</tr>
<tr>
<td>Age ≥50</td>
<td>0.63 (0.29 to 1.36)</td>
</tr>
<tr>
<td>Age &lt;50</td>
<td>0.35 (0.13 to 0.89)</td>
</tr>
<tr>
<td>Had a hysterectomy</td>
<td>0.32 (0.10 to 1.00)</td>
</tr>
<tr>
<td>Has an intact uterus</td>
<td>0.57 (0.28 to 1.16)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.57 (0.30 to 1.08)</td>
</tr>
<tr>
<td>Age ≥50</td>
<td>0.73 (0.31 to 1.68)</td>
</tr>
<tr>
<td>Age &lt;50</td>
<td>0.43 (0.16 to 1.14)</td>
</tr>
<tr>
<td>Had a hysterectomy</td>
<td>0.29 (0.08 to 1.06)</td>
</tr>
<tr>
<td>Has an intact uterus</td>
<td>0.75 (0.36 to 1.59)</td>
</tr>
</tbody>
</table>
Conclusions

- Young, healthy, recently menopausal women who received HT for 10 years
  - ↓ risk for death
  - ↓ admission for myocardial infarction or heart failure

- There was no associated increase in stroke, breast cancer, DVT, or PE
Take Home Messages

- The findings from this study substantiate the “timing theory” but...
  - Different type and dose of estrogen used
  - Underpowered to determine effect of Estrogen monotherapy
  - Unclear if primary composite outcome was prespecified
- Minimal risk associated with therapy but...
  - Likely underpowered to detect differences in DVT/PE, CVA, and possibly breast CA
- Overall: reassured about using HT in symptomatic healthy menopausal women, but would not prescribe for primary prevention

Case

- Florence is a 68yo woman in for follow up of hyperlipidemia and thyroid disease. She admits during ROS she has to wear a pad daily and has difficulty “making it to the bathroom in time”. She has tried minimizing her fluid intake and scheduling bathroom breaks but admits this has quite a negative impact on her life.
Case

• What do you advise as her next steps?
  A. Referral for pessary
  B. Begin trospium, there is clear benefit for this medication over any other
  C. Begin a medication for urge incontinence, whatever is first tier on her insurance plan
  D. Refer for pelvic floor muscle training

Background

• Older women: urinary frequency and urgency with or without urge incontinence
• Initial treatments: lifestyle changes, bladder retraining, pelvic floor strengthening
• Several medications have been approved
  – Medications have high rates of anti-cholinergic side effects
• Previous reviews have not emphasized continence or quality of life (QOL) as outcome

The News

• Benefits and Harms of Pharmacologic Treatment for Urinary Incontinence in Women: A Systematic Review

• Aim: To conduct a systematic literature review of drugs for urgency urinary incontinence in women

Methods

• Objectives:
  1. Analyze efficacy, safety and comparative effectiveness of drugs for patient centered outcomes
  2. Analyze long-term adherence to drug treatment
  3. Analyze which characteristics of women can modify treatment effects
Methods

• Defined clinically important improvement in UI as ≥50% reduction in UI frequency
  – Calculated pooled RR and AR difference for efficacy outcomes
• QOL according to minimal clinically important differences in validated scales
• Performed meta-analysis of direct results from head-to-head comparisons for comparative effectiveness

Results

• Drugs were more effective, but with low magnitude of effect
  • Fewer than 200 cases/1000 treated were attributable to drugs
• Absolute risk difference in continence was <20% for all drugs
• 21 head-to-head RCTs comparing drugs suggest similar effectiveness
Results

Continence with drugs for urgency urinary incontinence

<table>
<thead>
<tr>
<th>Drug (Randomized Trials/Participants, N)</th>
<th>Attributable Events per 1000 Treated (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fesoterodine (2/2465)</td>
<td>130.00 (58.00 to 202.00)</td>
</tr>
<tr>
<td>Oxybutynin (4/992)</td>
<td>114.00 (64.00 to 163.00)</td>
</tr>
<tr>
<td>Solifenacin (5/6304)</td>
<td>107.00 (58.00 to 156.00)</td>
</tr>
<tr>
<td>Tolterodine (4/3404)</td>
<td>85.00 (40.00 to 129.00)</td>
</tr>
<tr>
<td>Trospium (4/2677)</td>
<td>114.00 (83.00 to 144.00)</td>
</tr>
</tbody>
</table>

Comparative effectiveness

Fesoterodine vs. tolterodine (2/3312) 55.00 (21.00 to 88.00)

Results

Treatment discontinuation due to adverse effects

<table>
<thead>
<tr>
<th>Drug (Randomized Trials/Participants, N)</th>
<th>Attributable Events per 1000 Treated (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin (7/3138)</td>
<td>4.00 (-12.00 to 23.00)</td>
</tr>
<tr>
<td>Fesoterodine (4/4433)</td>
<td>31.00 (10.00 to 56.00)</td>
</tr>
<tr>
<td>Oxybutynin (5/1483)</td>
<td>63.00 (12.00 to 127.00)</td>
</tr>
<tr>
<td>Solifenacin (7/9080)</td>
<td>13.00 (1.00 to 26.00)</td>
</tr>
<tr>
<td>Tolterodine (10/4466)</td>
<td>5.00 (-11.00 to 26.00)</td>
</tr>
<tr>
<td>Trospium (6/3936)</td>
<td>18.00 (4.00 to 33.00)</td>
</tr>
</tbody>
</table>

Comparative safety

Fesoterodine vs. tolterodine (4/4440) 17.00 (5.00 to 31.00)
Oxybutynin vs. tolterodine (6/2323) 72.00 (7.00 to 154.00)
Solifenacin vs. tolterodine (3/2755) 12.00 (-1.00 to 28.00)
Trospium vs. oxybutynin (2/2015) 1.00 (-32.00 to 48.00)
Conclusions

- Strong evidence that rates of continence and clinically important improvement in UI were greater with drugs than placebo
  - All drugs were better than placebo and had similar effectiveness
  - Benefits from drugs are small
- Drugs caused treatment discontinuation due to side effects

Key Article

- Urinary Incontinence in Young Nulligravid Women: A Cross-sectional Analysis
- 1002 nulligravid women, mean age 22.5yrs
- Rate of any UI: 12.6% (10.5-14.7)
  - Ever sexually active, no COC use: 21.5% (16.7-27.3)
  - Never sexually active, no COC use: 10.1% (7.0-14.4)
- UI associated with poorer indexes of health-related QOL
Take Home Messages

• Ask about UI—in all women
• UI is associated with lower QOL
• Medications have small magnitude of benefit, side effects causing discontinuation of treatment
• All drugs for urgency UI have similar effectiveness

Bone Health

Dietary vs Supplemental Calcium
Case

• Bonnie Bony is a 71 year old woman with hypertension and hyperlipidemia. She has a family history of osteoporosis and her BMD t score last year was -2.4. She is here for her annual examination and as you review her medications with her she tells you that she has stopped her calcium because she has heard that it “might be bad for the heart.” What do you advise her?

What do you advise Bonnie?

• You need to restart it right away- you are at high risk for a fracture.
• Good idea, stay off of it
• As long as you drink plenty of milk, you should be fine.
Calcium and Cardiovascular Disease

- Calcium supplements are widely recommended for bone health
- Previous studies have shown that calcium is necessary but not sufficient for reducing osteoporosis risk
- Recent studies have suggested an increase in cardiovascular events with supplemental calcium, but the role of dietary calcium intake has been less clear

The News

- Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heldelberg) — Li et al, Heart, 2012
- Aim: To examine the associations of dietary calcium intake and calcium supplementation with MI and stroke risk and overall CVD mortality
Methods

- 25,540 residents of Heidelberg aged 35-64 recruited in 1994-8
  - Excluded those with MI, stroke or TIA at baseline and those with outlying nutritional intakes
  - 23,980 included in analysis
- Validated food frequency questionnaire consumption of 148 items in preceding 12 months
- Self reported supplement use
- Self reported cardiovascular events were verified

Results

- Higher dietary calcium intake was associated with younger age, higher education, higher level of physical activity, less likelihood of being overweight
- Dietary calcium intake associated with Vitamin D intake and likelihood of taking calcium supplements
- Average duration of follow-up 11 years
Results: Dietary Calcium

- Total of 354 MIs, 260 strokes and 267 CVD deaths
- Third quartile of dietary calcium and dairy calcium intake had a decreased risk of MI compared with first quartile
  - HR 0.69 (95% C.I. 0.50-0.94) dietary
  - HR 0.68 (95% C.I. 0.50-0.93) dairy
  - Trend was not significant
- Gender subgroup analyses
  - Men: HR 0.80 (95% C.I.: 0.56-1.14)
  - Women: HR 0.43 (95% C.I.: 0.22-0.82)

Results: Calcium Supplements

- Calcium supplement users had an increased risk of MI compared with nonusers
  - HR 1.86 (95% C.I. 1.17 -2.96)
  - HR 2.39 (95% C.I. 1.12-5.12) for calcium only
- No association between calcium supplements and other CV outcomes
Conclusions

• Calcium supplements were associated with a small increased risk of MI, but were not associated with other cardiovascular outcomes
• Dietary calcium intake was not associated with cardiovascular benefits

Take Home Message

• Encouraging adequate dietary calcium intake should be an important goal
• Consider judicious use of calcium supplements in individuals at high risk for CVD.
USPSTF Recommendations
February, 2013

• Evidence is insufficient to assess balance of benefits and harms
  – Vitamin D and calcium for primary prevention of fractures in postmenopausal women or men
  – Daily supplementation with >400 IU of Vitamin D3 and 1,000 mg of calcium for fracture prevention

• Recommends against daily supplementation with <400 IU of Vitamin D3 and 1,000 mg calcium for primary prevention of fractures in noninstitutionalized postmenopausal women

PPIS and Fracture Risk
PPIS and Fracture Risk

- PPIs among most commonly prescribed drugs worldwide
  - OTC since 2003
- Prior studies have suggested an association between PPI and hip fracture
  - Limitations: retrospective, inability to control for confounders, ascertainment of PPI exposure
- FDA warning in May, 2010 about potential association
  - More data needed

The News

- Use of proton pump inhibitors and risk of hip fracture in relation to dietary and lifestyle factors: a prospective cohort study
  - Khalili et al. BMJ 2012
- Aim: To examine the association between long term PPI use and risk of hip fracture among postmenopausal women in prospective cohort in the context of dietary and other lifestyle factors
Methods

• Nurses’ Health Study prospective cohort
  – 121,700 nurses receive questionnaire every 2 years
  – 79,899 postmenopausal women
• Outcome:
  – Self reported hip fractures (low or moderate trauma)
• Predictors: H2 blockers, PPIs, exercise, smoking, BMI, alcohol, menopause and HT, calcium and vitamin D intake, osteoporosis and osteoporosis medications

Results

• 893 incident hip fractures
• Overall PPI use:
  – 6.7% in 2,000
  – 18.9% in 2008
• Absolute risk of hip fracture
  – 2.02 per 1,000 person years in users vs 1.51 events per 1,000 person years in non-users
• HR 1.36 (95% C.I. 1.13,1.63)
  – Adjusted for multiple confounders
Results

- Risk increased with duration of use
- Hip fracture risk varied with history of smoking
  - HR 1.51 (1.20, 1.91) among current or former smokers
  - HR 1.06 (0.77, 1.46) among those who never smoked
- Estimates not affected by reason for PPI use

Results: Meta-analysis

- Meta-analysis to include all seven studies included in FDA report and 4 additional studies
- 1,562,862 individuals included in 11 studies
- Pooled odds ratio of hip fracture associated with PPI use
  - 1.28 (1.19, 1.37)
Conclusions

• Regular use of PPIs is associated with an increased risk of hip fracture in postmenopausal women
• Strongest association in those with the longest duration of use or with a history of smoking

Take Home Message

• Clinicians should periodically evaluate the need for long term PPI use, especially in current or former smokers
Conclusions

• Mammographic density an important risk factor in younger women
• New cervical cancer screening guidelines incorporate HPV testing
• HT appears to be safer in younger women
• Jury is still out on supplemental calcium
  – USPSPF gives it a grade “I” recommendation
• Important to periodically reevaluate long term PPI use in women
Questions?