Learning Objectives

1. Discuss what is known about risk factors for common malignancies
2. Discuss methods of screening for cancer in women
3. Review risk factors for breast cancer used in the Gail model
4. Review the significance of BRCA mutations in causing breast cancer

1. All of the following women would be at increased risk for uterine cancer, based on the information provided, EXCEPT

A. A 35-year-old with a BMI of 32 kg/m²
B. A 39-year-old with polycystic ovarian syndrome
C. A 46-year-old who has had 6 children and breastfed all of them
D. A 47-year-old who experienced menarche at age 10 and has never been pregnant
E. A 59-year-old with hereditary nonpolyposis colon cancer

Endometrial Cancer

- Most common gynecologic malignancy in the USA (Adenocarcinoma)
  - Affects 2/100,000 women (SEER)
  - 75% occurs in postmenopausal women
- Best overall survival of all gyn cancers
  - 5-year survival is 84-90%
- Strongest association with reduced risk: Combined hormonal contraception use

Endometrial Cancer

- Believed to be caused by overexposure to unopposed estrogen stimulation of the endometrium (Endogenous and/or exogenous)
  - Lethaby et al. Cochrane 2006
  - Users of unopposed exogenous estrogens for at least 2 years develop endometrial cancer 2-20 times more frequently than nonusers
Endometrial Cancer

Risk and Protective Factors

- **Risk**
  - Advancing age
  - Obesity
  - Nulliparity
  - Early menarche
  - Late menopause
  - Chronic anovulation
  - Unopposed exogenous estrogen use
  - Tamoxifen
  - Diabetes

- **Protective**
  - Progesterone
  - OCPs
  - Cigarette smoking
  - Multiparity
  - Breastfeeding
  - Physical Activity

* Obesity leads to increased estrogen levels from peripheral conversion of androstenedione. The presence of DM and HTN as risk factors may simply reflect the high incidence of obesity in patients with these disorders.
† All reduce exposure to unopposed estrogens.

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Hereditary Non-polyposis Colorectal Cancer (HNPCC) Lynch Syndrome

- Autosomal dominant
  - Mutations that impair DNA mismatch repair
- High risk of cancers
  - Colon (80% lifetime risk) – accounts for about 3-7% of cases diagnosed in US each year; average age 44
  - Endometrium (80% lifetime risk)
    - Average age of diagnosis – 46
  - Ovary
  - Stomach, Small intestine, Hepatobiliary tract
  - Upper urinary tract; Brain; Skin

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SERMs and Endometrial Cancer

- Although raloxifene has estrogen-like effects on the uterus, it has NOT been shown to increase the risk of endometrial cancer (SOR A)
- Tamoxifen is a selective estrogen receptor modulator that has estrogen-like effects. While it has a protective effect on breast tissue, its effect on the uterus INCREASES the risk of endometrial cancer (SOR A)

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Abnormal Uterine Bleeding and Endometrial Cancer

- Endometrial cancer is the cause in < 10%
  - Most bleeding is due to benign endometrial abnormalities: atrophy, polyps, and fibroids
    - (Buyuk et al. Acta OG Scand. 1999;78.)
  - Abnormal uterine bleeding is the presenting sign in 85% of women with endometrial cancer
    - Increases chance of survival from early detection

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2. Which of the following statements is most accurate regarding endometrial cancer?

A. The ACS does not recommend screening for women who have no identified risk factors
B. There are rarely alerting symptoms for endometrial cancer
C. The majority of bleeding in postmenopausal women is the result of endometrial cancer
D. Office endometrial samplers have a low sensitivity for detection of endometrial cancer
Endometrial Cancer

**Screening**

- ACS 2001 – No indication that screening for endometrial cancer is warranted for women who have no identified risk factors
  - Early diagnosis usually results from the presence of alerting symptoms (bleeding) – at the onset of menopause, inform women of risks/symptoms; encourage to report any unexpected bleeding/spotting

- Smith et al. CA Cancer J Clin 2001;51:38-75

Endometrial Cancer

**Methods of Detection**

- Endometrial Biopsy (EMB)
  - Office endometrial samplers are highly sensitive (97.5% or more) for detection of endometrial cancer
  - Women with endometrial cancer were tested
  - Misses polyps and submucous fibroids
  - May fail to adequately sample the atrophic endometrium
  - Insufficiency rate = 15% (atrophy)
  - Samples by “shear” rather than curettage

3. Which of the following statements is true when evaluating postmenopausal women with vaginal bleeding?

- An endometrial stripe on TVUS > 3mm should be evaluated by endometrial biopsy
- TVUS is adequately sensitive to use as the only test for evaluation
- Endometrial hyperplasia on histologic evaluation is a cancer precursor
- Cytologic atypia is the single most important histologic finding

48%  
23%  
2%  
28%  
48%

Abnormal Bleeding

**Who Needs Endometrial Biopsy?**

- Women
  - > age 35 with suspected anovulatory bleeding
    - ACOG 2000; No. 14
  - Between 19 and 35 years who do not respond to medical therapy OR have prolonged periods of anovulation
    - ACOG 2000; No. 14
  - Using tamoxifen
    - ACOG 2002; No. 39

What Are We Looking for on the Biopsy?

- Cytologic atypia is the SINGLE most important histologic finding
- Only ATYPICAL hyperplasia has a significant risk of developing into endometrial cancer
  - 29% progresses to invasion
  - Need to rule out cancer if atypia is present
- Endometrial hyperplasia is a BENIGN condition, not a cancer precursor
Triage Guidelines

Reproductive Age Women
- No cytologic atypia
  - Simple EMHP with abnormal bleeding
    - Progestin withdrawal for 6 months then rebiopsy
  - Complex (adenomatous) EMHP
    - Progestin withdrawal then rebiopsy
- Cytologic atypia
  - High dose progestins, Megace, or Depo-Provera for 3 months then rebiopsy

Postmenopausal Women
- No cytologic atypia
  - Progestins for 6 months then rebiopsy
  - TAH for recurrent EMHP or bleeding
- Cytologic atypia (substantial risk of deeply invasive or poorly differentiated cancer)
  - Hysterectomy

Use of Transvaginal Ultrasound (TVUS) in Postmenopausal Women

<table>
<thead>
<tr>
<th>Undiagnosed Vaginal Bleeding</th>
<th>&lt;4-5 mm</th>
<th>&gt; 5mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial Biopsy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Can the “content” of the endometrial stripe be reliably assessed by TVUS?

TVUS for Endometrial Cancer: Meta-analysis
- Tabor et al. Obstet Gynecol 2002;99
- Not sensitive enough to use as the only test in postmenopausal women with abnormal uterine bleeding
  - 50% false positive rate
  - Hyperplasia associated with the thickest endometrium, but not most serious disease
  - 4% of cancers missed even when liberal guidelines for referral to D&C are used
  - Cut-off should be ≤4mm if women at high risk
- Conclusion: Obtain histologic sample if possible

Endometrial Cancer Treatment
- Prognosis is directly related to the stage of disease and grade of neoplasm
- Standard surgical therapy is total abdominal hysterectomy and bilateral salpingo-oophorectomy
  - Surgical staging with pelvic and para-aortic lymphadenectomy for “all” or only high-risk patients...?
  - Radiotherapy vs. chemotherapy – No RCTs

Endometrial Cancer Prevention
- OCPs (combined hormonal contraception) lead to a decreased incidence of Endometrial cancer
  - 50% reduction in risk
  - Protection for 10-15 years after discontinuation
- Likely the result of increasing the duration of endometrial exposure to progestins
- Pregnancy

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4. Which of the following is true regarding Ovarian Cancer?

A. Risk peaks between ages 65 and 75
B. Most women are genetically predisposed
C. Stromal ovarian is the most common type
D. The pelvic exam is rarely normal

A. Risk peaks between ages 65 and 75
B. Most women are genetically predisposed
C. Stromal ovarian is the most common type
D. The pelvic exam is rarely normal

Ovarian Cancer

- The most lethal of the gynecologic malignancies
  - Epithelial ovarian is the most common type (85-95%)
  - Risk peaks between ages 65 and 75
  - <5% of women are genetically predisposed
- There are very few warning signs until disease is far advanced
  - Pelvic exam may be normal
  - Various symptoms of bloating, increased abdominal girth in the year prior to diagnosis (Goff et al., JAMA 2004;291)
  - A palpable postmenopausal ovary warrants investigation

Ovarian Cancer

Risk Factors

- Majority have no identifiable risk factors (90%)
- Highest risk factor: genetic predisposition
  - 90% are inherited mutations in either BRCA1/2 genes
    - Among ALL women who present with ovarian cancer - ~ 8% have a BRCA mutation
    - Among Ashkenazi women who present with ovarian cancer - ~ 40% have a BRCA mutation
  - Ethnic Groups
    - Ashkenazi Jews
    - French Canadians
    - Icelanders

5. Which of the following best characterizes the USPSTF recommendation on screening asymptomatic women for ovarian cancer?

A. Screening is recommended for all women over age 18
B. Screening is recommended for postmenopausal women
C. Screening is recommended for women with a family history of ovarian cancer
D. No screening is recommended

A. Screening is recommended for all women over age 18
B. Screening is recommended for postmenopausal women
C. Screening is recommended for women with a family history of ovarian cancer
D. No screening is recommended
USPSTF – 1996, 2004

- Recommended against routine screening of asymptomatic women
- Cited “fair evidence” that screening could lead to harmful outcomes and that this risk outweighed the potential benefit of screening
  - 98% of women with a positive screening test will not have ovarian cancer
- USPSTF rating of “D”

Ovarian Cancer Screening Tests

- There are no screening tests (CA-125, TVUS) of sufficient sensitivity, specificity or PPV to recommend use in the general population (ACS, ACOG).
  - It is unknown if women at risk for the hereditary ovarian cancer syndrome would benefit from screening – not yet sufficient evidence
  - CA-125 has low sensitivity and is inadequate for screening for early-stage cancers
  - Significant false-positive rate
  - TVUS has low specificity and has limited value

Genetic Risk Assessment and BRCA Mutation Testing

USPSTF 2005

- Recommends AGAINST routine referral for genetic counseling or routine BRCA testing for women whose family history is not associated with increased risk of BRCA 1/2 mutations
- Fair evidence to recommend genetic counseling and evaluation for BRCA testing in women with family history of BRCA 1/2 mutations.

Ovarian Cancer Treatment

- Primary treatment is surgical removal of as much tumor as possible – “debulking”
  - Following surgery – cisplatin and paclitaxel for patients with stages >1A or 1B who are at risk of recurrence
  - Pelvic radiation not useful as primary therapy
- Assess response by serial Ca-125 levels
  - 90% correlation with disease progression
- Most women have persistent or recurrent disease

6. Which of the following has been associated with prevention of ovarian cancer?

A. Breastfeeding
B. Folic acid supplementation in the reproductive-age years
C. Greater than one full-term pregnancy after the age of 35
D. No more than 1 sexual partner

6. Which of the following has been associated with prevention of ovarian cancer?

- Breastfeeding: 65%
- Folic acid supplementation in the reproductive-age years: 4%
- Greater than one full-term pregnancy after the age of 35: 28%
- No more than 1 sexual partner: 4%
Ovarian Cancer

Prevention

- OCPs and a decreased incidence
  - 40% reduction among all users
  - 50% reduction with use ≥ 5 years
  - Up to 80% reduction with use ≥ 10 years
  - Protective effect persists up to 15 years after discontinuation
- Breastfeeding
  - Each month of breastfeeding results in a 1-2% decrease
- Tubal sterilization
  - Decreases risk by ~18-40%; mechanism for the protective effect is unknown; some experts theorize it stops carcinogens from reaching the ovaries after they enter the body via the vagina
- Avoid talc powders in genital hygiene
- Greater than one full-term pregnancy prior to age 35
- Prophylactic oophorectomy

Risk Factors Summary

Increased Risk
- Delayed childbearing
- Early menarche
- Endometriosis
- ERT>5 years
- Family history suggesting genetic predisposition
- Genetic syndromes
- High-fat diet
- Late menopause
- Low parity

Decreased Risk
- Breastfeeding ≥ 18 months
- Early menopause
- Multiparity (risk decreases with each additional pregnancy)
- Hysterectomy
- Late menarche
- Low-fat diet
- OCP use
- Tubal ligation

Cervical Cancer

- HPV is the causative agent
- The squamocolumnar junction (SCJ) is where the majority of cancer arises

7. A 56 yo female presents for a health maintenance examination. She has a history of a total hysterectomy for benign disease 4 years ago. You are able to document that the hysterectomy pathology was benign and that she has had normal Pap tests for 10 years. The patient asks about regular Pap smears. Which one of the following would be the most appropriate recommendation?

A. Routine Pap smears should be continued until age 70
B. A pap smear should be done every three years
C. A pap smear is not indicated
D. A pap smear should be done yearly for 3 years and only if indicated thereafter
### Cervical Cancer Screening Guidelines—United States

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>When to start</td>
<td>~3 y after onset of vaginal intercourse, but no later than 21 years</td>
<td>Within 3 y of onset of sexual activity or age 21 years, whichever comes first</td>
<td>Age 21</td>
</tr>
<tr>
<td>Intervals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional</td>
<td>Annually, every 2-3 years for women aged &gt;30 years with three negative cytology tests</td>
<td>At least every 3 years</td>
<td>Every 2 years for women aged ≥21-30; once every 3 years for women aged &gt;30 years with three consecutive negative cytology tests.</td>
</tr>
<tr>
<td>Liquid-based</td>
<td>Every 2 years; every 2-3 years for women aged &gt;30 years with three negative cytology tests</td>
<td>Insufficient evidence</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>HPV testing used as an adjunct to cytology</td>
<td>Every 3 years if HPV negative, cytology negative</td>
<td>Insufficient evidence</td>
<td>Every 3 years if HPV negative, cytology negative</td>
</tr>
</tbody>
</table>

### Draft Recommendation Statement

- **USPSTF, ACS, ASCCP, ASCP 19 October 2011**
- **Grade A Recommendation**
  - Screen for cervical cancer with cytology every 3 years in women ages 21-65 who have had intercourse and have a cervix (upper limit of 65 selected with adequate screening and not otherwise at high risk)
- **Grade D Recommendations**
  - Screening in women <21, regardless of sexual history
  - Screening in women with total hysterectomy for benign disease
  - Screening using Cytology + HPV in women <30
- **Grade I Recommendation**
  - HPV + Cytology in women >30
  - If both (-) – rescreen every 3-5 years.

### Annual Counts, Age-Adjusted Incidence Rates, and Median Age at Diagnosis of Invasive Cervical Carcinoma: United States, 1998-2003

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Average Annual Incidence Count (95% CI)</th>
<th>Percent Incidence Rate</th>
<th>Median Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Ages</td>
<td>10,846</td>
<td>8.9 (8.8-8.9)</td>
<td>100</td>
</tr>
<tr>
<td>0-14</td>
<td>0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>15-19</td>
<td>14</td>
<td>0.2 (0.1-0.2)</td>
<td>0.7</td>
</tr>
<tr>
<td>20-24</td>
<td>123</td>
<td>1.1 (1.0-1.2)</td>
<td>1.1</td>
</tr>
<tr>
<td>25-29</td>
<td>543</td>
<td>5.9 (5.7-6.1)</td>
<td>5.0</td>
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<tr>
<td>30-34</td>
<td>1045</td>
<td>12.3 (12.0-12.6)</td>
<td>9.6</td>
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<tr>
<td>35-39</td>
<td>1350</td>
<td>14.6 (14.3-14.9)</td>
<td>12.5</td>
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<td>40-44</td>
<td>1834</td>
<td>16.3 (15.9-16.6)</td>
<td>14.1</td>
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<tr>
<td>45-49</td>
<td>1323</td>
<td>15.4 (15.0-15.7)</td>
<td>12.2</td>
</tr>
<tr>
<td>50-54</td>
<td>1958</td>
<td>14.5 (14.2-14.7)</td>
<td>18.0</td>
</tr>
<tr>
<td>55-59</td>
<td>1352</td>
<td>14.8 (14.5-15.1)</td>
<td>12.5</td>
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<tr>
<td>60-69</td>
<td>1008</td>
<td>12.9 (12.6-13.3)</td>
<td>9.3</td>
</tr>
<tr>
<td>70-79</td>
<td>595</td>
<td>11.2 (10.9-11.6)</td>
<td>5.5</td>
</tr>
</tbody>
</table>

### Rationale for Screening after Hysterectomy?
- Anticipated ID of early-stage vaginal disease or cervical pathology from residual cervical tissue
- Missed opportunity for performing other screening/preventive services
  - Limited data suggesting performance of pap/increased likelihood of mammogram (Murata et al. JFP, 1992)
- Missed cancer/Delay in Diagnosis

### ACS Guidelines

**Screening Interval – Special Considerations**

- **HIV**
  - Pap smear recommended twice a year after diagnosis of HIV, then annually if cytology normal
- **DES exposure in utero**
- **Cervical cancer history**
  - Annual screening as long as patient is in good health and no life-threatening condition exists

### 8. According to the 2006 Consensus Guidelines for the Management of Women with Cervical Cytologic Abnormalities, by the ASCCP, which of the following statements is correct (based on the 2001 Bethesda System of reporting Pap smears)?

- **A. ASC-US can be followed up with a repeat Pap smear in 1 year if the reflex test for HPV is negative**
- **B. ASC-H should be followed with a repeat Pap smear in 6 months**
- **C. LGSIL requires testing for HPV prior to a decision on colposcopy**
- **D. HGSIL requires confirmation on a repeat Pap prior to proceeding with colposcopy**
8. According to the 2006 Consensus Guidelines for the Management of Women with Cervical Cytologic Abnormalities, by the ASCCP, which of the following statements is correct (based on the 2001 Bethesda System of reporting Pap smears)?

- **A.** ASC-US can be followed up with a repeat Pap smear in 1 year if the reflex test for HPV is negative
- **B.** ASC-H should be followed with a repeat Pap smear in 6 months
- **C.** LSIL requires testing for HPV prior to a decision on colposcopy
- **D.** HGSIL requires confirmation on a repeat Pap prior to proceeding with colposcopy

9. A 39 yo female with no past history of abnormal PAP smear receives a report indicating the presence of “atypical glandular cells.”

**Appropriate management would include:**
- HPV DNA testing, and if negative, a repeat Pap test in 4-6 months
- Colposcopy with endocervical sampling and an endometrial biopsy
- An endometrial biopsy
- Referral for dilatation and curettage

**Atypical Glandular Cells (AGC)**

**Initial Management**
- Women with ALL subcategories of AGC should undergo colposcopy
- Additionally –
  - Endometrial sampling in women > age 35 years
  - Endometrial sampling in women < 35 with risk factors for endometrial neoplasia (e.g. unexplained vaginal bleeding, anovulation)
  - HPV DNA testing (new)
- Repeat cytology or HPV testing ALONE as initial management of AGC is unacceptable

**2006 ASCCP Consensus Guidelines – What’s New?**

- Adolescent guidelines for ASC-US, LSIL, HSIL; CIN 1, CIN 2, 3
  - Adolescent defined as < 20 years
  - Very conservative management
- Management of CIN 1
  - Observation is preferred for all ages
- Use of HPV DNA testing
  - ASC-US, AGC, follow-up CIN 2, 3 treatment

**AGC**

**Subsequent Management**

<table>
<thead>
<tr>
<th>HPV Status</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV (+)</td>
<td>Repeat HPV testing in 6 months; referral to colposcopy if &gt; ASC or HPV(+)</td>
</tr>
<tr>
<td>HPV(-)</td>
<td>Repeat HPV testing at 12 months</td>
</tr>
</tbody>
</table>
AGC – Favor Neoplasia or AIS

**Initial Management**

- If no invasion
  - Diagnostic excision
- If AIS
  - Hysterectomy preferred
  - If childbearing desired, conservative management with colposcopy, cytology, and HPV testing at 6 months

**Who Gets a Cone?**

**5 Classic Indications**

- Inability to see the extent of the lesion at colposcopy
- Cervical biopsy demonstrating microinvasion
- Positive endocervical curettage
- Inadequate colposcopy
- Discrepancy between Pap smear and biopsy
  - e.g. HGSIL Pap smear and normal biopsy or biopsy with minimal atypia – in which case you have not explained the Pap smear findings and need to continue the evaluation

**Breast Cancer**

- 2nd most common cause of cancer in women and the 2nd leading cause of cancer death
  - 1/8 women will develop breast cancer
  - 1/30 will die
- Presence of dominant inherited cancer susceptibility genes (BRCA 1 and BRCA 2) occurs in about 1/300-500 of general population
  - Screening for inherited risk (AHRQ, 10/2006)
    - Assessment of risk for significant BRCA mutations
    - Genetic testing of high-risk women

**Breast Cancer Screening Methods**

- Breast self-examination (BSE)
  - Studies have not clearly demonstrated BSE as beneficial for cancer screening
  - Any benefits must be balanced against potential harms – such as excessive invasive procedures performed as a result of the discovery of noncancerous lesions
- Clinical Breast Exam (CBE)
  - Insufficient evidence to recommend it as a singular screening modality
  - RCTs demonstrate varying detection rates of 3-57%
  - Most advocates have supported CBE as a complementary technique to mammography
  - About 5% of screening-detected cancers are found using CBE alone
Breast Cancer 
Screening Methods

• Mammography
  – ACS – Monthly BSE (Age 20), CBE every three years (20-39); annual screening mammography starting at age 40
  – AAFP – Screening mammography and CBE every 1-2 years from ages 50-69; counsel women between ages 40 to 49 about potential benefits of mammography and CBE; support teaching BSE

Berry DA et al. NEJM 2005;353:1784-92
15% reduction in death rate from breast cancer

Screening for Breast Cancer 
USPSTF 2009

• Biennial screening mammography for women aged 50-74 (Grade B)
• Biennial screening before age 50 should be an individual decision and take patient context into account (Grade C)
• > 75 years of age – insufficient evidence to assess additional benefits and harms from mammogram (Grade I)
• Recommends against teaching BSE (Grade D)
• CBE in women > 40 ? (Grade I)
• Digital mammography or MRU (Grade I)

Decision Analysis 
Reduction of Mortality

• Biennial Screening

<table>
<thead>
<tr>
<th>Age</th>
<th>Reduction in Mortality (compared with no screening) [Range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-69</td>
<td>17% [15-23%]</td>
</tr>
<tr>
<td>40-69</td>
<td>20% (considered a minor improvement)</td>
</tr>
<tr>
<td>50-79</td>
<td>24% (additional 7%)</td>
</tr>
</tbody>
</table>

Extending the age range produced only minor improvements – additional 3% reduction starting at age 40 years and 7% extending to age 79 years

Preventive Medications 
USPSTF 2007

• Recommends against routine use of tamoxifen or raloxifene for primary prevention of breast cancer in women at low or average risk for breast cancer (Grade D)
• Discuss chemoprevention with women at high risk for breast cancer and low risk for adverse effects of medication (Grade B)

10. Significant risk factors for the development of breast cancer include all of the following EXCEPT:

A. Age older than 50
B. Female gender
C. Prior therapeutic abortion
D. 35 years at delivery of the first child

10. Significant risk factors for the development of breast cancer include all of the following EXCEPT:

A. Age older than 50
2%
B. Female gender
1%
C. Prior therapeutic abortion
74%
D. 35 years at delivery of the first child
23%
What Is My Risk of Getting Breast Cancer?
- Institute of Medicine – 2004
  - Identified individual risk assessment as essential to improving early detection of breast cancer

The Breast Cancer Risk Assessment Tool—Gail Model
- Six predictors to identify women who may be at risk:
  - Current age
    - One of the strongest predictors
    - Most breast cancers occur in women > 50 years
  - Age at menarche
    - Early onset of menses (<12) – Increased RR -1.2
    - Age at first live birth
      - Nulliparous and first live birth age 25-29 – RR 1.6
      - First live birth > 30 = RR 1.9

The Breast Cancer Risk Assessment Tool—Gail Model
- Number of first-degree relatives with breast cancer (mother, sister, daughter)
  - One first-degree relative – RR 2.1
  - Two first-degree relatives – RR 3.6
- Number of previous breast biopsies
  - The more times a woman requires a bx, the greater her risk
  - At least one breast biopsy with atypical hyperplasia
    - RR of 2.0 for hyperplasia
    - RR 5.0 if atypical hyperplasia

Challenges with the Gail Model
- J Nat Ca Institute 2006;98:1673
- Risk factors are widely prevalent and are neither highly sensitive nor highly specific
- A risk factor must be strongly associated with a disease (RR of about 200) to be effective for screening
- Most risk factors for breast cancer are relatively weak
  - “Strong” risk factors such as older age are associated with RR < 10
  - BRCA 1 mutations may be exception

11. Which one of the following statements about BRCA testing is true?

A. BRCA genes occur in pairs and exhibit cancer-suppressive activity
B. BRCA mutations affect almost 15% of the U.S. population
C. Almost every woman with a first-degree relative with breast cancer will carry a BRCA mutation
D. A new $50 blood test can easily identify BRCA mutations
BRCA 1 and BRCA 2

- If one of the inherited pair is defective, and the normal copy mutates over time, the patient is at greater risk for developing cancer.
  - Mutations are rare – affecting only 0.1% of the population
- BRCA mutations constitute only a small proportion of women with a family member with breast cancer; they comprise the majority of women with genetically related breast cancer.

Genetic Risk Assessment and BRCA Mutation Testing for Breast Cancer and Ovarian Cancer Susceptibility

- Family history is NOT associated with increased risk for mutations in BRCA 1 or BRCA 2
  - Recommends against routine referral for genetic counseling or BRCA testing
- Family history is associated with increased risk for BRCA 1 and 2 mutations
  - Recommends referral for genetic counseling and evaluation for BRCA testing
- Prophylactic therapy
  - Decreases incidence of breast and ovarian cancer
  - Inadequate evidence for mortality benefits

Family History Patterns Associated with Increased Risk of BRCA 1 and 2 Gene Mutations **USPSTF 2007**

- Non-Ashkenazi Jewish Women
  - 2 first-degree relatives with breast cancer (1 diagnosed ≤ age 50)
  - ≥ 3 first- or second-degree relatives with breast cancer regardless of age
  - Both breast and ovarian in first- and second-degree relatives
  - First-degree relative with bilateral breast cancer
  - History of breast cancer in male relative

- Ashkenazi Jewish Women
  - Any first-degree relative (or 2 second-degree relatives on the same side of family) with breast OR ovarian cancer

BRCA 1 or 2 Mutation

- Can be considered for prophylactic oophorectomy and mastectomy
- **Cancer Genetics Studies Consortium Recommendations for Screening**
  - Monthly BSE – age 21
  - CBE q 6-12 m starting at age 25-35 years
  - Annual mammograms starting at age 25-35 years
  - Ovarian cancer screening (US, CA-125 levels) q 6-12 months starting at age 25-35 years

Chemoprevention of Breast Cancer—**USPSTF 2002**

- Fair evidence that treatment tamoxifen significantly reduces risk for invasive estrogen-receptor (+) breast cancer in women with BRCA 1/2 mutations
- Good Evidence:
  - Tamoxifen and raloxifene increase risk of thromboembolism
  - Tamoxifen (NOT raloxifene) increases the risk of endometrial cancer
Tamoxifen for Early Breast Cancer

• Cochrane 2006
  – Tamoxifen has not been reliably shown to be effective in women with ER(-) tumors
  – Adjuvant tamoxifen treatment significantly improves the 10-year survival of women with ER(+) tumors or unknown ER status
    • Highly significant effect with longer treatment
    • 12-26% reduced mortality rates
    • Proportional reductions in contralateral breast cancer

Answers
1. C
2. A
3. D
4. A
5. D
6. A
7. C
8. A
9. B
10. C
11. A