Vaginal bleeding occurs in as many as 10% of postmenopausal women older than 55 years of age. More than 25% of breast abnormalities in women aged 50 to 70 are described as a breast mass. Of all breast masses, simple cysts comprise approximately 25%; 10% of all women who present with breast masses are diagnosed with breast cancer.

An early sign of endometrial cancer is vaginal bleeding. It is important to determine the cause of this symptom to exclude the possibility of cancer and determine the underlying etiology. Diagnostic imaging is a useful, noninvasive, and cost-effective tool that provides clinicians with the ability to determine the cause of these symptoms.

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Off-Label Product Discussion: The author of this article does not include information on off-label use of products.

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endometrium (>50%). In addition, the effect of hormones on the endometrium can lead to cyclical bleeding and bleeding between cycles. As many as 20% to 40% of cases of vaginal bleeding are attributable to endometrial pathologies such as hyperplasia (simple, complex, and atypical), polyps, endometrial cancer (from 1% to 10%), or other abnormalities of the endometrium. Bleeding also can be caused by myometrial pathologies, such as fibroids and adenomyosis. Bleeding from nonendometrial locations (ie, cervix, vulva, vagina, or bladder), presents similarly to endometrial bleeding, therefore this also must be considered as a possible etiology.

**Risk, Incidence, and Mortality of Uterine Cancer**

Although cancer is an important consideration in the differential diagnosis for postmenopausal vaginal bleeding, the actual risk of endometrial cancer is very low, with approximately a 2.5% risk of uterine cancer in a 60-year-old woman with postmenopausal bleeding, and a 0.02% risk for a woman of the same age who is not experiencing abnormal bleeding.

Endometrial cancer is usually diagnosed early because most women promptly report postmenopausal vaginal bleeding to their physicians. Risk of endometrial cancer does increase with age, however, other factors such as obesity, diabetes, specifics of menstrual history (eg, early onset of menarche, late age of menopause, nulliparity), polycystic ovarian syndrome, and unopposed estrogen replacement add to this baseline level risk. Ruling out endometrial cancer is important as the mortality associated with uterine cancer is as high as 20 cases per 100,000 women aged 70 to 74 years.

**Mortality Rates: Breast and Uterine Cancers**

- Incidence of cancer increases with age
- Mortality is higher for breast cancer compared to endometrial cancer (7x)
- Mortality from uterine cancer markedly increases with age
  - Age 50: a 1/15 chance of mortality from endometrial cancer
  - Age 70: a 1/5 chance of mortality from endometrial cancer

Data from National Institutes of Health SEER Program.

**Diagnostic Tools for Endometrial Abnormalities and Postmenopausal Vaginal Bleeding**

In most cases of presentation with postmenopausal bleeding, a detailed patient history and physical examination often are sufficient to confirm whether the endometrium is the source of bleeding. However, careful inspection of the cervix and possibly Pap testing must be done to exclude cervical causes of bleeding. Additionally, gastrointestinal or bladder-based bleeding may need to be excluded with appropriate diagnostic tests, such as hemoccult test or urine analysis, when appropriate. Several imaging tools are useful for diagnosing endometrial abnormalities, including endovaginal ultrasound (EVUS), sonohysterography/saline infusion sonography (SIS), magnetic resonance imaging, and hysteroscopy.

**Clinical Standard of Care and Goals of Evaluation—Postmenopausal Vaginal Bleeding**

1. Determine that cancer is not present
2. Determine the cause of bleeding
3. Exclude other sources of bleeding, such as bleeding from the cervix, gastrointestinal tract, and bladder
4. Provide symptomatic and diagnostic relief

**EVUS.** The goal of an EVUS examination of the endometrium is to exclude pathologic conditions, making biopsy unnecessary. Via an ultrasound probe placed directly in the vagina, EVUS can image the endometrium, showing its overall thickness. Thin endometrium is generally considered normal, while thickened endometrium may be indicative of cancer, hyperplasia, or polyps. The advantage of EVUS is that it is well tolerated, noninvasive, and painless. Its accuracy may preclude the need for dilatation and curettage (D&C) in women, which may be particularly useful when screening women with cervical stenosis. In addition, because it images the entire endometrium, EVUS can provide supplemental information when biopsy results are inadequate or inconsistent.

In the past, lack of data on accuracy as well as training involved in properly performing the examination resulted in infrequent use of EVUS by primary care physicians. However, more recently, EVUS has been used with more frequency in the primary care setting. A meta-analysis examined the accuracy of EVUS using a fixed cut off to differentiate between normal and abnormal results. This author and colleagues evaluated 35 prospective studies (n=5892) that had taken place between January 1966 and November 1996 of patients diagnosed by EVUS prior to biopsy. The analysis tested the premise that 5 mm could be used as the cut off between a normal and abnormal result. Retrospective studies, selective sampling, pooled results, and studies...
that enrolled premenopausal women were excluded. For the analysis, mean weighted estimates of sensitivity and specificity were calculated for thresholds of endometrial thickness from 3 mm to 10 mm. Data revealed that healthy women had a mean endometrial thicknesses of 4 mm to 5 mm; women with polyps/hyperplasia, 12 mm; and women with endometrial cancer, 20 mm.5

Using a threshold of 5 mm to define abnormal endometrial thickness (endometrium ≤5 mm = normal; >7.5 mm = abnormal), 96% of women with cancer (those on HRT and those not) had abnormal test results (95% confidence interval [CI], 94%-98%).5 Most women without endometrial cancer had a normal test result. At the 5-mm threshold, the test had an 81% specificity.6

The meta-analysis also showed that use of HRT affected the EVUS false-positive rate: more women using HRT who had normal histology had false-positive results (specificity 77%, 95% CI, 75%-79%) than those not using HRT (specificity 92%, 95% CI, 90%-94%).2 The researchers concluded that, using the EVUS data with a 5-mm threshold, slightly more than 75% of postmenopausal women taking HRT who are bleeding but have normal EVUS results do not need biopsies.7 So, for postmenopausal women with vaginal bleeding considered to have a 10% pretest probability of endometrial cancer, a normal EVUS result will reduce that risk to approximately 1% (Table 1).

However, it should be noted that EVUS is not indicated as a screening tool in asymptomatic women; most women with endometrial cancer present with vaginal bleeding.8 The 5-mm cut off used for EVUS in symptomatic women does not apply to asymptomatic women, and the incidence of false-positive results would be high if applied to this group. Based on the meta-analysis data, EVUS fails to detect cancer and other abnormalities in approximately 8% of symptomatic women, but this was comparable to the accuracy of a biopsy. Office-based endometrial biopsy devices have false-negative rates ranging from 5% to 15%.12-16

EVUS is limited in that it cannot typically differentiate between causes of increased endometrial thickness, so in patients who have increased endometrial thickness a biopsy may also be necessary. Notably, EVUS misses fewer abnormalities than an office-based endometrial biopsy because it allows the entire endometrium to be visualized, whereas most biopsy techniques rely on blind sampling.14,15 One pitfall associated with EVUS is that the rate of nondiagnostic results is not known.17 If the endometrium cannot be imaged completely due to fibroids, or if the endometrial margins are indistinct and the borders cannot be determined in order to measure the double wall thickness, the study is inadequate and use of an additional diagnostic mode is indicated. A caveat of nondiagnostic findings is that they occur frequently in women with invasive carcinoma because endometrial margins are indistinct. Thus, knowing the technical adequacy of the sonogram is important.

EVUS is considered abnormal if a focal endometrial abnormality is noted. As many as 30% of women will have findings of polyps, hyperplasia, and fibroids.18 When a focal endometrial abnormality is found, biopsy, SIS, or hysteroscopy with D&C should be performed.

**SIS.** SIS is an imaging procedure performed during transvaginal sonography; sterile saline is infused into the endometrial cavity via a transcervical catheter.18 This procedure can be performed safely and easily without anesthesia in the outpatient setting. A systematic review and meta-analysis of 24 studies (2278 patients) found that pooled sensitivity and specificity of SIS in uterine cavity evaluation were 0.95 (95% CI, 0.93-0.97) and 0.88 (95% CI, 0.85-0.92), respectively.19 Detection rates with SIS are comparable to those of hysteroscopy.20 Sonohysterography allows reliable differentiation between focal and diffuse endometrial lesions, most commonly polyps and submucosal fibroids.21

SIS also may allow more effective triaging in some patients. For example, when a thickened endometrium is present, SIS can show whether thickening is diffuse (and whether a biopsy or D&C is desirable) or focal (indicating benefit of hysteroscopy).22

**Hysteroscopy.** Hysteroscopy offers the benefit of direct visualization of the endometrium as well as the ability to perform directed biopsies23 and treat benign intrauterine pathologies, such as polyps and sicheiae.

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**Table 1. Risk of Endometrial Disease Following an EVUS**

<table>
<thead>
<tr>
<th>Pretest Probability of Endometrial Disease</th>
<th>HRT</th>
<th>Normal EVUS</th>
<th>Abnormal EVUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>No</td>
<td>0.1%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0.1%</td>
<td>4%</td>
</tr>
<tr>
<td>5%</td>
<td>No</td>
<td>0.3%</td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0.6%</td>
<td>17%</td>
</tr>
<tr>
<td>10%</td>
<td>No</td>
<td>0.6%</td>
<td>57%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1.3%</td>
<td>31%</td>
</tr>
<tr>
<td>20%</td>
<td>No</td>
<td>1.3%</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2.9%</td>
<td>50%</td>
</tr>
<tr>
<td>50%</td>
<td>No</td>
<td>5.1%</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>11.0%</td>
<td>80%</td>
</tr>
</tbody>
</table>

*Using 5 mm to define an abnormal exam.

†Includes cancer, atypical and complex hyperplasia, and polyps in this definition of endometrial disease.

Adapted from Smith-Bindman et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. JAMA. 1998;280:1510-1517.7
without premedication or anesthesia. According to a recent meta-analysis, a positive hysteroscopy result increased the probability of endometrial cancer to 71% (95% CI, 67%-76.6%) and a negative result reduced the probability to 0.6% (95% CI, 0.5%-0.8%).

**WHEN IS BIOPSY NECESSARY?**

As mentioned earlier, a biopsy is needed in a postmenopausal woman with vaginal bleeding when EVUS is not diagnostic and the endometrium cannot be fully visualized. However, a biopsy also may be necessary when the endometrium is incidentally noted to be thick. According to this author’s analysis, when endometrial thickness in an asymptomatic postmenopausal woman is ≥12 mm, the risk of cancer is similar to that of a symptomatic woman with an endometrial thickness of 6 mm (Table 2). Other risk factors are important to consider, including age over 70 years, obesity, or the presence of diabetes. When these risks are present, patients should be followed closely, even if EVUS shows an endometrial thickness of 5 mm.

Combining EVUS with biopsy often provides sufficient diagnostic information to evaluate most endometrial symptoms in postmenopausal women. However, when both EVUS and biopsy have been performed, it is important to carefully weigh the information provided by each. For example, when biopsy results suggest atrophy but EVUS results show a thickened endometrium, these 2 benign yet different results do not infer a benign diagnosis; a repeat biopsy is indicated. If different physicians are performing the biopsy and the EVUS, it is essential that the primary physician evaluate the results.

Ultimately, the patient’s symptoms should guide the aggressiveness of the clinical evaluation. Whereas EVUS is an effective test to exclude cancer, other tests should be used aggressively in order to determine the cause of persistent abnormal bleeding. Clinicians should have a low threshold for obtaining a tissue diagnosis if abnormal symptoms persist, if the patient has many risk factors for cancer, or if the different diagnostic test results do not add up to a benign diagnosis.

**PALPABLE BREAST MASSES IN POSTMENOPAUSAL WOMEN**

**EPIDEMIOLOGY**

The complaint of breast mass is not uncommon, but there are many potential causes of breast mass that do not include breast cancer. Over a 10-year period in a staff-model health maintenance organization, 27.8% of episodes of breast symptoms in women aged 50 to 70 years were described as a breast mass. Causes of palpable breast masses include cysts and fibroadenomas, benign proliferative lesions, benign proliferative lesions with or without atypia, fat necrosis, ductal carcinoma in situ, and invasive cancer.

Simple cysts comprise approximately 25% of all breast masses; however, 10% of all women who present with breast masses will be diagnosed with breast cancer. The likelihood of such a diagnosis increases as women age; before age 40, the incidence is 1%, however, in women over the age of 55 years, incidence rises to 65%.

Although a careful physical examination is helpful in diagnosing a patient presenting with palpable breast mass, the patient’s history is vital. In addition, even if patient history does not yield risk factors, any abnormality should nonetheless be investigated, as many women in whom breast cancer is diagnosed have no identifiable risk factors.

When a physical examination is performed, the most important finding is whether the mass is distinctly different from surrounding tissue and from the corresponding area in the contralateral breast (dominant abnormality), which is suggestive of breast cancer. Irregular shapes and irregular borders as well as limited mobility of the mass can also indicate a cancerous lesion.

**TOOLS TO DETECT AND DIAGNOSE BREAST CANCER**

Following a thorough physical examination, diagnostic tests such as ultrasound, diagnostic mammography, fine-needle aspiration (FNA), core biopsy, and excisional biopsy can be extremely helpful in characterizing the mass. Imaging, specifically ultrasound, is an accurate means of differentiating a simple cyst from a solid mass. It is also useful in targeting lesions for biopsy or FNA.

<table>
<thead>
<tr>
<th>Table 2. Recommendations for When to Perform a Biopsy in Postmenopausal Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic (Vaginal Bleeding)</strong></td>
</tr>
<tr>
<td>• Women in their 50s who have a test result indicating endometrial thickness of ≤5 mm do not require further tests at this time.</td>
</tr>
<tr>
<td>• Women in their late 60s who are obese and/or diabetic, and who are not taking HRT should receive a biopsy and ultrasound.</td>
</tr>
</tbody>
</table>

HRT = hormone replacement therapy.
If a cyst is diagnosed, no other imaging is required. If a solid mass, ultrasonography must be followed by FNA, core needle biopsy, or excisional biopsy. Although technologic advances allow ultrasound results to characterize masses as having benign, malignant, or equivocal features evidence supporting the characterization is not definitive enough to warrant ignoring any solid mass, since those that have a clinical correlate remain suspicious for malignancy. Additionally, several recently published studies suggest that ultrasound may be used to screen for breast cancer in high-risk patients who have nondiagnostic breast mammograms due to high breast density. However, there is no evidence to suggest that ultrasound is accurate for either detecting cancer or correctly interpreting normal breast tissue as normal. Thus, if used as a screening test, breast ultrasound could lead to missed cancers and false reassurance, as well as (conversely) many unnecessary invasive procedures. Additional research will need to be performed on breast ultrasound before it may be relied on as a screening tool.

**FNA.** FNA is another test that can be useful in diagnosing a cyst. Using a very fine-gauge needle (22, 23, or 25) a small amount of fluid and cellular material is obtained from the suspicious breast mass. Samples can be obtained via single puncture or multiple passes. Generally, FNA is slightly less painful and invasive than a core biopsy, but its accuracy is highly dependent on the training and expertise of the operator. When performed and interpreted by experienced personnel, sensitivity is very high—identifying 95% to 98% of cancers. Conversely, when performed by an untrained physician, sensitivity is quite low, ranging from only 65% to 75%, and false negatives are numerous—usually in young women and particularly when lesions are <1 cm. Further, the frequency of inadequate specimens can be high, at up to 33%. Therefore, knowing the experience level of the cytologist who evaluates the breast aspirate is critically important.

A sample that shows watery, clear, straw-colored, or grey/green fluid need not be sent for cytology. However, bloody fluid should be sent for cytology, as it represents a small (4%) risk of intracystic papilloma and a 0.5% risk of cancer. If a mass remains following aspiration, even if reduced in size, it must be reaspirated. If a solid mass is identified, a sample should be sent for cytology and an additional evaluation should be performed (depending on results). Given that the accuracy of FNA is operator dependent, even if fluid sent for cytology is reported to be benign in conjunction with a normal mammogram, follow-up is still required for up to 6 months to assure the abnormality does not recur.

**Core Needle Biopsy.** Core biopsy also can be used to evaluate a mass. It is performed with a large-diameter needle (14- to 18-gauge). A core biopsy provides a core of tissue rather than merely a sample of some cellular tissue. Again, accuracy is operator dependent, but much less so than with FNA. One study suggests that core biopsy is highly sensitive (96.9%) and specific (100%) for patients with mammographic abnormalities. While easier to interpret than FNA, a core biopsy is a more invasive procedure, and is associated with greater patient discomfort and local bleeding. It is also less suitable for targets in certain anatomical locations (ie, close to the chest wall or in the nipple complex), small superficial targets, and movable targets in the axillary area. Inadequate specimen rates, however, are lower than those for FNA. An advantage of a core biopsy is its ability to distinguish between ductal carcinoma in situ/proliferative lesions and benign breast tissue, making it less likely further testing will be required.

**Excisional Biopsy.** Excisional biopsy remains a commonly used method for evaluating patients with uncharacterized breast mass. A surgical procedure performed in the operating room, it is more invasive and more expensive than either FNA or core biopsy. Complications include hematomas, bleeding, infection, and scarring at substantially higher rates than those associated with FNA or core biopsies. As a diagnostic measure, excisional biopsy is overused. A recent study that compared rates of excisional biopsy in the United States to those in the United Kingdom found excisional biopsy is used 2 to 3 times more often in the United States, with 2 to 3 times the rate of negative diagnoses. Ideally it should be used only when cancer is known to be present, when less invasive methods of biopsy are not feasible because of lesion location, or when results of other tests are nondiagnostic.

**Screening Mammography and Diagnostic Mammography: What Is the Difference?**

Whereas screening and diagnostic mammography have much in common, their applications are different. Screening mammograms typically include 2 views of the breast and are interpreted in batches. Diagnostic mammograms are interpreted individually. They may include additional views—compression and magnification—that are not part of the screening mammogram. Typically, a diagnostic mammogram is performed as a result of physical findings or following abnormal results from a screening mammography.

Screening mammography finds approximately 85% of nonpalpable cancers (sensitivity = 0.75-0.95) and has a 10% overall false-positive rate, (false positives = 0.05-0.15). The 10-year likelihood of a false positive using screening mammography is 25% to 50%. Due to the high false-positive rate and the fact that breast cancer diagnoses are relatively infrequent, the likelihood of a determination of breast cancer based on an abnormal screening mammogram is approximately 9%. Therefore, patient education prior to screening...
mammography is advisable to inform the patient about actual cancer risk, should an abnormal result occur. However, when a palpable abnormality is present—even if the screening mammogram is normal—a diagnostic mammogram should be performed.

Diagnostic mammography can help to characterize a mass previously identified on clinical breast examination, as well as document the extent of the lesion and any associated lesions. When a mass is detected via mammography, an abnormal diagnostic mammogram increases the suspicion of cancer 2 to 3 times. The accuracy of diagnostic mammography varies depending on the indication that prompted the examination—specifically whether the indication was to investigate screening abnormalities or breast symptoms (Table 3). When performed to diagnose abnormalities found during screening, a normal result obviates the need for further evaluation. However, diagnostic mammography misses a significant proportion of cancers. A normal mammogram result should not lead the physician to ignore a clinically suspicious mass. It is important to take a biopsy of any suspicious mass found in examination, regardless of whether the diagnostic mammogram has detected the mass.

Between 1990 and 2000, mortality rates for breast cancer decreased by 2.3% per year, in part due to technological advances and early diagnoses. Still, delayed breast cancer diagnosis is a leading cause of medical malpractice in the United States. For this reason, and in order to provide the best quality of care, it is incumbent upon the primary care physician to ensure that every precaution is taken to exclude the possibility of cancer in patients who may be at risk for the disease.

### References


