Detection of and Screening for Endometrial Cancer

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Endometrial cancer occurs more than twice as frequently as cervical cancer. The main risk factors are age, estrogen use, and obesity. Increasing life expectancy and more liberal use of estrogen to prevent postmenopausal bone loss will probably increase the magnitude of the problem. Endometrial cancer is a heterogeneous disease. Good prognosis is associated with obesity and estrogen use and with carcinomas preceded by precancerous hyperplasia. A bad prognosis may be found in women without major risk factors and is associated with a normal or atrophic endometrium.

Because of a high prevalence of asymptomatic disease (6.9 per 1,000) and because the group with a poor prognosis is usually asymptomatic, all postmenopausal women should be screened at least one time. For screening, the use of one of the cytologic instruments is recommended; these instruments are safe, easy to handle, and can be used in the office setting without anesthesia. Yields are comparable to dilation and curettage. Family physicians are encouraged to familiarize themselves with cytologic instruments and to use them for screening postmenopausal women in their office.

The incidence of endometrial cancer in the United States increased sharply in the early 1970s to reach a peak of 32.4 per 100,000 among the white population in 1975.[1,2] In 1976 the incidence began to decline[3] and has remained constant since 1979.[4,5] Endometrial cancer is twice as common as cervical cancer, with 36,000 new cases reported for 1986 as opposed to 14,000 for cervical cancer.[6] Mortality from endometrial cancer, however, is lower than that of cervical cancer[6] because most of these uterine cancers have not metastasized at the time of initial diagnosis. At presentation 75 to 80 percent of patients with endometrial cancer are in stage I, which has a five-year survival of 80 percent, and a relative survival* of 92 percent.[7] Yet, endometrial cancer is the sixth most common cause of cancer death among women, with a peak incidence in the sixth and seventh decades.

* *Relative survival is defined as the ratio of observed survival to expected survival of the same group in the general population.*

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RISK FACTORS

Age is the most potent risk factor with a relative risk of 5.2 for women aged over 60 years.[8] Retrospective studies incriminating estrogen as a risk factor have been criticized for containing three kinds of biases[9]: methodological bias (selection of a case group that is distorted in favor of exposed individuals), choice of proof bias (lack of randomization with respect to other known risk factors), and the interpretation of anatomopathologic sections bias (overdiagnosis by incorrectly reading atypical hyperplasia as endometrial cancer). Still there is general consensus derived from retrospective studies that incriminates estrogen as a major risk factor. The risk increases with dose[10] and duration[11] and remains present for up to ten years after discontinuing estrogen.[12] The increased risk of endometrial cancer in patients with the polycystic ovary syndrome is further support of an estrogen effect. The preliminary results of a recent prospective study from Sweden, however, show that estrogen increases the risk of developing endometrial premalignant lesions but does not increase the risk of developing endometrial cancer.[13]

There is increasing evidence that progesterone decreases the risk of endometrial carcinoma by preventing hyperplasia of the endometrium. The incidence of endometrial cancer in postmenopausal women treated with estrogen and an added progestogen is even lower than that observed in the general population of nonhormonally treated post-

menopausal women.[13,14] Data from the completed cancer and steroid hormone study from the Centers for Disease Control demonstrate that combination oral contraceptive use for 12 months or longer conferred protection against endometrial cancer, a protection that persisted for at least 15 years after the cessation of oral contraceptive use.[15] Evidence that obesity (probably related to high endogenous estrogen level) and late menopause are risk factors is controversial,[8,16] and support for nulliparity, diabetes, and hypertension as additional risk factors is poor.

Pelvic irradiation for benign conditions and a history of breast cancer have also been cited as risk factors.[17] Adenomatous hyperplasia and atypical hyperplasia (or endometrial carcinoma in situ) are considered precancerous lesions[18] with risk factors, mainly endogenous and exogenous estrogen exposure, similar to those of endometrial cancer.[19]

PATHOGENESIS AND PROGNOSIS

Endometrial hyperplasia had long been considered the precursor to all endometrial cancers, but Koss et al[16] challenged this concept. Their data demonstrate a low ratio (1.5) of hyperplasia to cancer, and they suggest two types of endometrial cancer. One occurs in association with generalized hyperplasia in long-term estrogen users, causes symptoms, and is discovered early in the course of the disease. The other develops as a focal event either in an atrophic or focally hyperplastic endometrium and frequently remains asymptomatic until after invasion or metastasis. The same conclusion was reached when endometrial cancers associated with adenomatous hyperplasia were found to be more differentiated and less invasive than those not associated with adenomatous hyperplasia. The latter also included, besides adenocarcinoma, clear cell, papillary, and anaplastic giant cell tumors.[20] An analysis of estrogen and progesterone tumor receptors also showed that receptor-negative cancers are less differentiated, more invasive, and more associated with rare histologic forms (papillary, serous, clear cell, and solid cancer types) than receptor-positive types.[8] The prognosis of receptor-negative cases was, irrespective of the state of the disease, worse than receptor-positive cases, with 80 percent mortality at two years. The receptor-poor and receptor-negative cases were a minority (17.3 percent of the sample were totally receptor negative). Receptor-positive disease occurred most frequently in obese women and in women that reported long-term estrogen usage.

SCREENING

Koss et al[16] screened a cohort of 2,586 asymptomatic women for endometrial cancer and found an incidence of 6.9 per 1,000. They concluded that the frequency of occult endometrial cancer warrants screening and proposed screening all women aged 50 years or more at least once, as most occult lesions were discovered at the initial screening. The incidence rate of 1.71 per 1,000 found on follow-up of one to three years was too small to justify the expense of a second screening. Others suggest screening every two to three years following a negative sample.[17]

The American Cancer Society recommends screening only "high-risk women," defined as women with a history of infertility, failure of ovulation, obesity, and prolonged estrogen therapy. Yet patients with no known risk factors are more likely to be asymptomatic and to carry a poor prognosis. If the morbidity and mortality from endometrial cancer are to be decreased, screening of asymptomatic patients is needed.

Screening Methods: Histology vs Cytology

Although the Papanicolaou smear is an excellent screening tool for cervical cancer, it is ineffective for endometrial cancer screening. The incidental presence of endometrial cells in the smear, whether normal or abnormal, is, however, indicative of possible endometrial pathology and requires further evaluation. The sensitivity of such a finding is low (40 to 75 percent), and its specificity, even if improved by scoring the endometrial cells, is lower (24.6 percent).[21] The diagnosis of endometrial cancer has, for a long time, relied on dilation and curettage, which was also used as a screening method for high-risk patients. Dilation and curettage however, usually requires hospitalization and general anesthesia, and although the risk is small, is not devoid of complications. In 1983 approximately 210,000 dilation and curettage procedures were done for both diagnostic and screening purposes in women aged more than 45 years[22] at an estimated cost of $400 million. Because of this need for hospitalization with its attendant high costs, other procedures that can be performed in an office for both screening and diagnosis are attractive.

The office procedures that have been used can be divided into two groups: those that rely on histology (endometrial biopsy curettes, the Vabra Aspirator, Vakutage and Karman cannula), and those that rely on cytology (the Gravlee Jet-Washer, the Isaacs Cell Sampler, the Endo-Pap Sampler, the Mi-Mark, the Accurette Endometrial Brush, the Endocyte Endometrial Brush, and the Endoscann). Both the histologic and cyctologic methods have their advocates, and although the cytologic ones are emphasized in this review, the debate on which method is best for screening is far from settled.

The advantages of cytologic methods are higher yield of adequate samples from the atrophic endometrium of postmenopausal women,[23,24] less pain,[25] and presumably better acceptance by the patient. The ease of insertion of

TABLE 1. COMPARISON OF CYTOLOGIC INSTRUMENTS: EASE OF USE AND ADEQUATE SAMPLES RETRIEVED

Brand	Diameter	Percent Successful Insertion	Histology	Percent With Adequate Samples
Mi-Mark	3.5 mm	90.4 (75 without tenaculum)[28]	+	89.4[16] 90.0[26] 96.3[20]
Endocyte	2.6 mm	95.0 (20 without tenaculum)[32]	+	92.0[32]
Endoscann	3.0 mm	92.0 + 5.0 after dilation with a sound[34]	+	100.0 premenopausal[34] 92.0 postmenopausal[34]
Acurette	4.0 mm	No more difficult than IUD[24] 87.5[35]	+	96.0[24] 88.5[35]
Endo-Pap	2.0 mm	90.0 (without tenaculum)[36]	+	89.5[36] 92.0[33]
Isaacs	1.9 mm	90.8 (75 without tenaculum)[28] 98.0[37] 94.0[30]	+	92.3[16] 96.0[37] 93.0 premenopausal[23] 90.0 postmenopausal[23] 91.0[38] 97.0[30]

these instruments has been compared to that of intrauterine devices (IUD). The processing is simple, as the sample recovered is fixed on a slide and sent for routine Papanicolaou staining. The average cost of cytologic screening is lower than that for histologic screening ($13 vs $78). Finally, cytologic examination occasionally detects ovarian malignancies.[23,26] Two shortcomings reported are a lower yield of both endometrial polyps[24,26] and endometrial hyperplasia.[23] The first is unimportant when screening for cancer. The second, however, cannot be ignored because adenomatous and atypical hyperplasia are considered precancerous lesions,[18] and can be missed if they are focal and deep in the endometrium.[23] In addition, endometrial smears are more difficult to interpret than cervical smears,[27] and there is a lack of uniform morphologic criteria that define hyperplasia.[20] The validity of cytologic screening, therefore, is directly related to the experience of the cytologist. Care in the preparation of thin, well-spread smears that are rapidly fixed facilitates interpretation.

Cytological Instruments

The Gravlee Jet-Washer will not be discussed. It has been discontinued because of difficulties in use and in processing of specimens.

Six cytologic instruments will be discussed: Mi-Mark,[25,28,29] Isaacs,[30] Accurette,[31] Endocyte,[25,32] Endo-Pap,[33] and Endoscann.[34] Of these, only the Endocyte (Gyneco, Inc, Branchberg, NJ), Endo-Pap (Sherwood Medical, St. Louis, Mo), Isaacs (Kendall, Boston, Mass), and Mi-Mark (Simpson Bayse, Inc, Wilmington, Del) are available in the United States.

Comparison of the several cytologic instruments by reviews of the different studies should be considered in light of differences in number of samples taken, different patient age groups studied, different proportions of postmenopausal women, and different ratios of symptomatic to asymptomatic women. With these reservations, findings from several reported studies are compared in Table 1 and Table 2.

The instrument diameters, success rate of insertion, and the percentage of adequate samples obtained are compared in Table 1. Although primarily designed for cytologic purposes, all these instruments can also remove tissue suitable for histologic examination. The main advantage of the Accurette is its ability to obtain tissue in a high proportion of patients (79 percent[24] to 86 percent[35]). The number of patients in these two studies, however, was low (92 and 40).

A small instrument diameter is important because insertion is facilitated in postmenopausal women, who are a primary target group. The Isaacs sampler has the smallest diameter and could be inserted in 75 percent of patients without a tenaculum,[28] thereby eliminating another source of discomfort. In the initial study by Isaacs,[30] insertion in a group of postmenopausal women was successful in 150 out of 160 (94 percent). The Endo-Pap, which has nearly the same diameter as the Isaacs, was successfully introduced without a tenaculum in 90 percent of all patients (353).[36]

The Endocyte, with the next larger diameter, has a high success rate of insertion; 95 percent in a study of 200 women.[32] A tenaculum, however, had to be used in 80 percent of cases, probably because the less-rigid plastic material requires stabilization of the cervix before insertion.

Adequate samples are obtained in more than 90 percent of patients with any of the cytologic instruments, comparing favorably with a 10 percent rate of inadequate

TABLE 2. COMPARISON OF CYTOLOGIC INSTRUMENTS: ACCEPTABILITY, SAFETY, AND YIELD

Brand	Pain	Complications*	Percent Yield Compared With Dilation and Curettage
Mi-Mark	None or mild[16,26,29]	None	93.3 for cancer[26**] 100.0 for cancer[29**] 69.2 for hyperplasia[26**] 96.7 for hyperplasia[29]
Isaacs	None or mild[16]	None	100.0 for cancer[30] 100.0 for cancer[23***] 100.0 for hyperplasia[37**] 96.3 cumulative[38]
Accurette	Mild to moderate[35]	None	89.0 for hyperplasia[24] 100.0 for hyperplasia and cancer[35]
Endocyte	None or mild[32]	None	100.0 for cancer[32]† 80.5 for hyperplasia[32]†
Endoscann	Slightly more painful than Isaacs[23]	None	91.0 for cancer (low percentage due to sampling failure)[34] 40.0 for hyperplasia[34]
Endo-Pap	None or mild[33,36]	None	75.0 for cancer (missed cancers read as adenomatous and atypical hyperplasia)[36] 95.0 for cancer[33] 46.5 for hyperplasia[36] 31.0 for hyperplasia[33]

** Perforations and infections only*
*** Comparison with Vabra Aspirator; with both dilation and curettage and Vabra[29]*
**** In the same study, the authors mention that focal adenomatous hyperplasia deep in the endometrium was missed but that all cases of adenomatous hyperplasia with atypia were confirmed*
† Comparison with Kevorkian Curette

samples with the Kevorkian Curette[32] and a 15 percent rate of method failure and up to a 23 percent rate of unsatisfactory specimens with the Vabra Aspirator.[37] Even dilation and curettage has a 1.3 to 10.0 percent rate of inadequate samples,[39] the higher figure reflecting difficulty in obtaining tissue from the atrophic endometria of elderly women.

Reported findings on the instruments' yield compared with histologic yield from dilation and curettage, the amount of pain, and complications are displayed in Table 2. The quoted studies, however, used different histologic methods, although the sensitivity of the Kevorkian Curette and the Vabra Aspirator approaches that of dilation and curettage in detecting precancerous and cancerous lesions whenever adequate tissues are obtained.[17,40,41] For most of the cytologic instruments the sensitivity for detecting cancer is excellent, approaching 100 percent. Their sensitivity for detecting hyperplasia, however, is more variable, but it compares favorably with the sensitivity of the Papanicolaou smear for detecting cervical intraepithelial neoplasia (CIN), which averages 80 percent. The two exceptions are the Endo-Pap and the Endoscann. The Endo-Pap has a consistently low sensitivity[33,36] but the low yield reported for the Endoscann in detecting hyperplasia[27] could be due to the low number (five) of specimens with detected hyperplasia found in the group of 200 women studied. There were, however, 23 cancers identified, 21 of which were diagnosed with the Endoscann. The Isaacs sampler had an excellent rate for the detection of hyperplasia (100 percent); nevertheless, the number in that study, too, was low (100).[29] The same rate (100 percent) for hyperplasia detection was obtained with the Accurette,[35] but again the number of patients was low (40).

The specificity of these instruments for detecting hyperplasia is also variable and was not reported in all studies: 96 percent for the Mi-Mark[26,29] 92 percent for the Endoscann,[23] and 97 to 99 percent for the Endo-Pap.[33,36]

Patients rated pain from cytologic sampling as none, mild, moderate, or severe. The Accurette is relatively more painful than the others because of its large diameter. Ninety percent of 200 patients screened with the Endocyte[32] reported no or mild pain, and more than 85 percent of 1,293 women screened with the Isaacs[16] reported no or mild pain.

These instruments appear to be quite safe; major complications such as perforations or infections were absent in all reported studies. Even minor complications are few. Koss et al,[16] in their large prospective study comprising 2,586 asymptomatic women in which they used both the Mi-Mark and Isaacs samplers, reported a 1 percent incidence for pain lasting more than 48 hours and a 2 percent incidence for bleeding lasting more than 24 hours.

FAMILY PHYSICIANS' ROLE IN ENDOMETRIAL CANCER SCREENING

The American Cancer Society recommends screening all "high-risk" women. The evidence for two different pathogenetic mechanisms, each with a different prognosis, prompted Koss et al[16] to recommend screening all postmenopausal women older than 50 years. In fact, screening will improve the already good survival rate of endometrial cancer only if there is a subset of patients with a bad prognosis. Thus limiting screening to one time only seems reasonable. Limited resources should be directed at the prevention of lung cancer (41,100 deaths in 1986) and at screening for breast cancer (39,900 deaths in 1986) and cervical cancer (6,800 deaths in 1986).[6] Use of cytologic instruments would result in a considerable monetary saving by decreasing the number of dilation and curettages. In Norway, Iversen and Segadal[23] used endometrial cytology as the first diagnostic procedure to assess postmenopausal bleeding and have reduced curettage by 60 to 70 percent. They claim they will raise this figure to 80 to 90 percent if cytologic examination replaces all diagnostic curettings as a first-step examination. In the United States approximately 210,000 dilation and curettages are done both for postmenopausal bleeding and screening of menopausal and postmenopausal women. With a dilation and curettage cost of $1,925, a 70 percent reduction of dilation and curettages rates will save $283 million of medical care costs.

Family physicians can and should play an important role in both increasing the available experience with these instruments and confirming their sensitivity by using them to screen patients for endometrial cancer. The recent demonstration that calcium supplements alone will not retard postmenopausal bone loss could lead to an increase in the use of estrogens and therefore an increased need for endometrial sampling at the primary care level.[42,43] A previous knowledge of intrauterine device insertion is all that is required; in fact, cytologic sampling instruments have a smaller diameter and should be easier to use than instruments for inserting intrauterine devices. Furthermore, the success rate as measured by adequate sample rates is unrelated to experience.[23] The lack of major complications (not a single case of perforation reported) reflects the safety of these instruments.

In a previous review of the different methods of screening for endometrial cancer, Boone et al[25] encouraged family physicians to use the new cytologic screening methods in view of their good yield, low cost, ease of use, and absence of major complications. In their review, the Endocyte and Accurette samplers were found most appropriate for use by the family physician. The Isaacs sampler was not mentioned. Based on the present review, family physicians are encouraged to become familiar with the use of either the Endocyte or Isaacs sampler.

At the present time (while further experience accumulates), a conservative approach is suggested. It consists of screening all asymptomatic postmenopausal women on a single occasion. Patients whose results are positive for hyperplasia or cancer, whose samples are inadequate, or in whom the insertion is not feasible should have a dilation and curettage or uterine biopsy. Until further experience confirms the sensitivity of the Isaacs and Endocyte samplers, and until future studies delineate their specificity, the group of symptomatic women, that is, women with perimenopausal or postmenopausal bleeding, should be referred for a dilation and curettage or uterine biopsy.

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