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Detection of Occult Endometrial Carcinoma

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Abstract Endometrial carcinoma is commonly diagnosed as a consequence of abnormal uterine bleeding. In a study published in 1962, it was documented that endometrial cancer may be detected by vaginal pool smears in asymptomatic postmenopausal women.

As a consequence of these observations, a systematic search for occult endometrial carcinoma was initiated in 1979, supported by a contract from the National Cancer Institute. The techniques used in this study and the problems encountered in the diagnosis of occult endometrial carcinoma will be discussed.

Within 3½ years of this study encompassing 2,586 peri- or postmenopausal women, 16 occult endometrial carcinomas were discovered by direct endometrial sampling. Two carcinomas, missed on initial screening, were subsequently documented in this cohort, for a prevalence rate of 6.96 per 1,000. The incidence data based on follow-up examinations of 1,754 women was 1.71 per 1,000 woman-years. An elaborate epidemiologic questionnaire was evaluated. Contrary to some prevailing views, obesity, hypertension, and diabetes failed to reach statistical significance as risk factors. The only risk factor of statistical value was delay in the onset of menopause past age 49, observed in about 50% of the cohort. It was noted that the administration of estrogens to women in Quetelet Index groups below mean was more likely to be associated with carcinoma than in women in higher Quetelet groups but, again, the difference was not statistically significant.

It was noted that in spite of an active search for endometrial hyperplasias, the rate of these lesions was nearly identical to the prevalence and incidence rates for carcinoma. It was postulated that some, or perhaps most, endometrial carcinomas in postmenopausal women are not preceded by hyperplasia but originate *ab initio* in the endometrium.

Key words: Carcinoma, detection, endometrium

THE PROJECT

Between January 1979 and June 30, 1982, a study of 2,586 asymptomatic peri- and postmenopausal women was conducted in this institution to document whether occult endometrial carcinoma could be diagnosed by direct endometrial sampling [1].

The women were referred by physicians who were providing their general care within the framework of the Montefiore Medical Group or recruited by mailings of pamphlets, personal appeals to organizations of women, and for a few months, by an announcement aired on a local radio station. The recommendations of satisfied examinees to their friends and acquaintances proved to be an important source of new patients.

The age distribution of the initial cohort is shown in Table I. Notably, 61 women were between the ages of 40 and 44, hence below the eligible age of 45. Most of them initially misrepresented their age, and a few could not be rejected for reasons of hospital policy. This group represents 2.36% of the sample, and its inclusion

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had no bearing on statistical evaluation of results. The racial distribution of the sample was as follows: 78.54% White, 14.11% Black, 4.18% Hispanic, and 3.17% others. Although all the women were asymptomatic at the time of their examination, some of them, in the past, may have had some abnormal bleeding or vaginal discharge that they either considered unimportant or concealed from the interviewer.

There were 525 (20.3%) premenopausal and 2,061 (79.7%) postmenopausal women. The peak years for the onset of menopause were between the ages of 50 and 55. Sixty-two women who experienced the onset of menopause between the ages of 56 and 59 were closely queried as to the accuracy of their statement. All confirmed the initial information; all were asymptomatic when seen.

An elaborate informed written consent form listing possible dangers of sampling by an endometrial device was presented and explained to each woman who had to sign it before admission to the program.

An epidemiologic questionnaire coded for processing by computer was comprised of 80 questions pertaining to age, weight, menstrual and obstetric history, use of contraceptives or hormones, general medical and surgical history, other forms of medication, and family history. The questionnaire was completed by the patient and subsequently reviewed with her by an experienced interviewer.

The questionnaire failed in one important respect, namely, the precise identification of the type and duration of estrogen administration.

There were 1,567 women who returned for a second examination (60.6% of the original cohort). The age distribution of the returnees was similar to that of the primary examinees, except that the participation of women between the ages of 50 and 69 was somewhat enhanced (Table I). One hundred and eighty-seven of the earliest participants were recalled for a third annual examination, which was offered before the termination of the study.

THE CLINICAL PROCEDURE

The physical examination was confined to palpation of the breasts and the abdomen, and an inspection and bimanual gynecologic examination administered by an experienced gynecologist.

From each eligible woman the following cytologic samples were obtained: (1) a scrape smear of the lateral vaginal wall to determine the level

TABLE I. Age Distribution of 2,586 Primary Examinees and 1,567 Returnees [1]

	Primary examinees		Returnees	
Age	Number of patients	Percent of sample	Number of patients	Percent of sample
40–44	61	2.36	8	0.51
45–49	532	20.57	277	17.68
50–54	574	22.19	384	24.51
55–59	535	20.69	338	21.57
60–64	388	15.00	229	14.61
65–69	248	9.59	173	11.04
70–74	167	6.46	101	6.45
75–79	64	2.47	41	2.62
80–90	17	0.66	16	1.02
Total	2,586	100.00	1,567	100.00

of maturation of the squamous cells (estrogen index), (2) a vaginal pool smear, and (3) a cervical smear obtained with a plastic scraper. All smears were immediately fixed in bottles with 95% ethanol. Endometrial samples were obtained either with the Mi-Mark Helix (Simpson-Bayse, Inc., Wilmington, DE) or the Isaacs cannula (Isaacs-Curity, Kendall Corp., Boston, MA), assigned by a computer program to ensure random application of the two devices.

The approach to endometrial sampling has been described in detail [2]. Briefly, the procedure was first demonstrated on an anatomic model, and the women were forewarned of possible discomfort. On most examinees the endometrial sampling could be performed without the use of a tenaculum, after bimanual palpation of the uterus.

Processing of the Endometrial Samples

Upon withdrawal of the endometrial sampling device, the project nurse immediately prepared one or two smears by quickly passing the instrument on the surface of clean glass slides, attempting to spread the material as evenly and as thinly as possible. The smears were immediately fixed in bottles with 95% ethanol. Thereafter, the devices were inspected visually, and all fragments of tissue still attached were removed by a fine forceps and placed in a small bottle with Bouin's fixative. Subsequently, the tips of the instruments were placed in the same bottle and vigorously shaken to free all residual fragments of tissue that may have remained attached to the sampler. The Isaacs device was also rinsed with the fixative. After fixation, the material in the Bouin's fixative was spun down in a centrifuge and processed for embedding in paraffin as a cell block or a mini-biopsy [2]. These proved to be quite useful in interpreting the endometrial samples.

Statistical Definitions

For the purposes of the present study, "prevalence" of lesions was arbitrarily defined as all endometrial lesions detected on first screening or diagnosed because of symptoms within one year of the first screening. All lesions subsequently discovered were classified as "incidence" lesions. The calculation of incidence was based on woman-years. We were aware that some of the incidence lesions were probably present and missed at the time of first screening and thus the definitions are not fully accurate from the epidemiologic point of view. The definitions represent a compromise necessary for statistical evaluation. True incidence of lesions could have been elicited only by continuing follow-up of the cohort for several additional years if funding had been available.

Summary data have been presented in terms of the numbers and percentages of patients in particular categories or with certain characteristics. Comparisons of rates across patient groups were carried out using the χ^2 test or Fisher exact test for contingency tables, as appropriate. The results were declared statistically significant if $p < 0.05$.

The risk of endometrial carcinoma in one group of subjects relative to another was evaluated using the odds ratio [3]. The odds ratio represents the rate of disease in a group of subjects exposed to a certain factor, divided by the rate for a group of unexposed individuals. An odds ratio of one indicates equivalent risk in each group. The significance of the odds ratio is tested via the χ^2 or Fisher exact test applied to the contingency table from which the data are derived.

PREVALENCE AND INCIDENCE OF ENDOMETRIAL CARCINOMA AND HYPERPLASIA

Table II summarizes the findings defined as prevalence, *i.e.*, occult carcinomas found on first screening and in those women who became symptomatic within one year after initial screening. It may be noted that the prevalence rate of carcinoma as defined was 6.96/1,000 women after inclusion of two small carcinomas that were missed on first screening. The last two patients had episodes of vaginal spotting within four and eight months, respectively, after a negative examination, and their disease was diagnosed by curettage. The prevalence rate of hyperplasia, including polyps, was only slightly higher (8.1 in 1,000). It must be noted that there were only four patients with adenomatous hyperplasia. The remaining women had relatively slight endometrial abnormalities ranging from focal atypia of glands to focal cystic and proliferative hyperplasia.

TABLE II. Prevalence and Incidence Rates of *Histologically Proven Endometrial Carcinoma and Hyperplasia [1]*

	Prevalence per 1,000 women	Incidence per 1,000 woman-years
Number of examinees	2,586	1,754*
Occult carcinomas	16+	1
Missed carcinomas	2++	2++
Total carcinomas	**18**	**3**
Rate	**6.96**	**1.71**
Hyperplasia	17	3
Polyps with hyperplasia	4	0
Total hyperplasias	**21**	**3**
Rate	**8.12**	**1.71**

* Second and subsequent annual clinical visits. Additional follow-up through doctor's office was obtained in about 20 additional women. + One patient was diagnosed on second screening. On review the original material was suspicious. ++ See text.

The incidence of endometrial carcinoma was calculated as 1.71 per 1,000 woman-years and was based on findings recorded on the second and subsequent annual visits to the program (Table II). One small superficial adenocanthoma was diagnosed on the third clinic visit. The two missed cases occurred in patients previously screened with negative results, who became symptomatic. One woman who developed vaginal spotting 14 months after screening had a carcinoma *in situ* in hyperplastic endometrium observed only by curettage. The other woman had an episode of vaginal bleeding 17 months after negative examination. The disease, which was diagnosed on a vaginal smear, was a small adenoacanthoma in a myomatous uterus. There were but three incidence cases of mild, focal endometrial hyperplasia.

EFFICACY OF THE SAMPLING PROCEDURES IN OCCULT ENDOMETRIAL CARCINOMA

There were 17 occult endometrial carcinomas classified as either prevalence or incidence cases. In 16 of them, the diagnosis was established or suggested on the endometrial sample, with either the smear (one case), the cell block (one case), or both (14 cases) showing abnormalities. Nine carcinomas were diagnosed with the Isaacs and seven with the Mi-Mark instrument. The 17th case was diagnosed on a vaginal pool smear in a 71 year-old woman whose endometrial sampling failed because of a stenotic os. Interestingly, the vaginal pool smear was positive in four other patients with occult endometrial carcinoma. Thus, the use of the vaginal smear alone would have led to further investigation of the endometrium in almost one-third of the patients.

PATHOLOGIC FINDINGS

The pathologic findings in occult endometrial carcinoma are summarized in Table III. Several points are of interest. With two exceptions, the uteri were of normal size. A markedly enlarged uterus was observed in a patient with ten-year therapy with unopposed conjugated estrogens and extensive, severe endometrial hyperplasia with focal carcinoma. In the other patient, the enlargement was due to leiomyomata. Eight of the 17 occult carcinomas had a squamous component and were classified as adenocanthomas. The lesions were well-differentiated (grade 1) in six pa-

TABLE III. Pathologic Findings in 17 Patients* With Occult Carcinoma of Endometrium [1]

Uterus of normal size	14	Myometrial invasion	17
Enlarged	2	None	5
Size unknown (radiotherapy only)	1	Superficial+	3
		Deep	4
Histologic type of tumor		Unknown (radiotherapy alone or before	
Adenocarcinoma (9) Adenocanthoma (8)		hysterectomy)	5
Grade 1	6		
Grade 2	8	Accompanying hyperplasia	
Grade 3	1	Focal Extensive	5
Too scanty to grade	2	Extensive	1

* 16 prevalence, 1 incidence, + one with identical carcinoma in left ovary.

TABLE IV. Assessment of Risk Factors [1]

Factor	No. of women	No. of carcinomas	Rate per 1,000	Odds ratio	p value
Race					
White	2,031	18	8.8		
				1.65:1	NS
Non-white	555	3	5.4		
Parity					
Nulliparity	204	2	9.8		
				1.07:1	NS
Parous	2,382	19	8.0		
Onset of menopause					
≤ 49 years	969	5	5.1		
50–55 years	1,030	14	13.5		p < 0.04
≥ 56 years	62	2	32.2		
Obesity					
Quetelet Index > 3.4	1,422	12	8.4		
Quetelet Index ≤ 3.4	1,157	9	7.7	1.09:1	NS
Quetelet Index > 4.4	301	3	9.9		
Quetelet Index ≥ 4.4	2,278	18	7.9	1.26:1	NS
Estrogen					
Yes	565	6	10.6		
				1.31:1	NS
No	2,021	15	7.4		

* p value, Mantel-Haenszel test for "onset of menopause" Mantel's extension procedure.
NS = not signficant

tients, moderately well-differentiated (grade 2) in eight patients, and poorly differentiated (grade 3) in one patient. Two patients, diagnosed elsewhere, had biopsy specimens too small for grading.

The level of invasion could be assessed in 12 uteri. The disease was confined to the endometrium in five patients. Invasion confined to the inner one-third of the myometrium was observed in three patients, invasion to the middle one-third in three patients, and to the outer one-third in one. In five patients the depth of invasion could not be determined because of prior radiotherapy. It is of interest that one patient

with superficial invasion had a focus of carcinoma of endometrial type in the left ovary. It could not be determined whether the histologically identical tumor was a metastasis or a primary endometroid ovarian carcinoma.

In the present study, the authors compared race, age, parity, onset of menopause, obesity index, and estrogen intake in the entire cohort of 2,586 women with the same factors in 21 women with occult endometrial carcinoma diagnosed in the present study. The essential epidemiologic data for the cohort are shown in Table IV.

The state of obesity for the population was calculated by the Quetelet Index based on the following formula:

$$[\text{weight}/\text{height}^2] \times 100$$

This index may be calculated in pounds and inches or in kilograms and centimeters. Although the values differ according to the measurement system used, they are convertible. In Figure 1, the index was calculated using pounds and inches as provided in the epidemiologic questionnaire and verified on a sample of 250 women as being within ± 2% of actual height and weight. The mean index value for the authors' population was 3.6 ± 0.6.

The analysis of other risk factors is shown in Table IV. It may be noted that the only factor showing a valid trend, evaluated by Mantel's extension procedure [4,5], was the onset of menopause: women with early menopause appear to be at a lower risk for endometrial carcinoma than women with late menopause. Race, parity, obesity (as measured by Quetelet Index), or estrogen medication had no significant association with endometrial carcinoma in this prospective study of asymptomatic women. Although not shown in Table IV, hypertension, diabetes, and past history of other cancers had no statistically significant association with endometrial cancer.

The relationship of estrogen intake to the Quetelet Index values was also examined. Among the 1,157 women with Quetelet Index ≤ 3.4, there were 302 estrogen users, four of whom developed endometrial carcinoma, for a rate of 13.25 per 1,000. Among the 1,422 women with Quetelet Index > 3.4, there were 263 estrogen users, one of whom developed endometrial carcinoma, for a rate of 3.80 per 1,000. One carcinoma patient with questionable exposure to estrogens was included among nonusers. The rate of endometrial carcinoma among nonusers of estrogen was 5.88 per 1,000 for women with Quetelet Index < 3.4, and 9.54 per 1,000 for women with Quetelet Index > 3.4. These differences, while not statistically significant, show an interesting trend suggesting that women of below average weight may be at a greater risk

Frequency of 21 Endometrial Carcinomas in Quetelet Groups in 2,579 Women Screened Through June, 1982 [1]

Quetelet group	Number of patients	Percent	Carcinoma rate per group
< 2.5 to 2.9	259	10.40	11.58/1000
3.0 to 3.4	898	34.62	6.68/1000
3.5 to 3.9	766	29.70	7.85/1000
4.0 to 4.4	355	13.76	8.45/1000
4.5 and above	301	11.66	9.97/1000

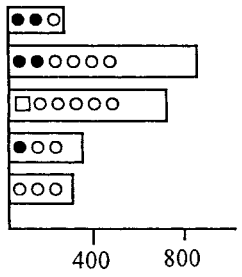

Fig. 1. Index of obesity (Quetelet Index) calculated as [weight (lbs)/height^2 (in)] x 100. ● = women with estrogen intake; ○ = women without estrogen intake; □ = women with questionable estrogen intake.

for endometrial carcinoma when exposed to estrogens than women of average and above average weight. Because the data on estrogen medication in the authors' cohort are not completely reliable, this observation warrants further study.

Findings Not Related to Endometrium

In the cohort of 2,586 women, several other cancers and precancerous conditions were observed. Four cases of mammary carcinoma were diagnosed by palpation, two cases of ovarian and one tubal carcinoma were diagnosed by cytology. One ovarian lesion was identified in the endometrial sampling, one ovarian cancer in a vaginal pool smear, and the tubal lesion in both. One patient with ovarian carcinoma died of her disease. The other one and the patient with tubal carcinoma were alive and well three years after surgery followed by radiotherapy.

There were also 24 patients with various grades of cervical intraepithelial neoplasia, including carcinoma *in situ*, discovered in cervical smears (22 on first screening, 2 on second screening). All were treated under colposcopic control, and all were free of disease for a period of three years.

DISCUSSION

The assessment of efficacy of any cancer detection system must be considered from several points of view. (1) Is the disease sufficiently frequent in an occult state in a population to justify the cost and time involved in a screening project? (2) Does the disease have occult precursor stages that could be identified and effectively treated, thus preventing the occurrence of the disease? (3) Are there means of disease detection that are reliable and reproducible? (4) Can a high-risk group of examinees be identified to reduce the cost of screening to society?

The ideal example of cancer detection is carcinoma of the uterine cervix. By means of a cervical smear, the precursor stages of the disease can be identified with resulting decreases in morbidity and mortality. In reference to endometrial carcinoma, the objective answers to those questions are less evident.

In reference to precursor stages of endometrial cancer, the study was disappointing. At the onset of the study it was assumed that endometrial hyperplasia, commonly assumed to be a precursor lesion of endometrial cancer, would be observed with a significantly greater frequency than endometrial carcinoma. Based on data provided by Gusberg and Kaplan [6], who observed a progression of about 12% of atypical hyperplasia to carcinoma, the author expected to observe at least eight times more cases of hyperplasia than carcinoma. The observed ratio was at most 1.5 to 1, even if the one diffuse and five focal hyperplasias observed in cancerous uteri are included. Although it may be conjectured that the detection system performed poorly in identifying endometrial hyperplasia, all women with abnormal endometrial samples were carefully followed by tissue sampling or repeat endometrial procedure. Whereas endometrial lesions were uncovered in some of them as described, the remainder failed to show any disease within the period of the present study. It is difficult to relate the low hyperplasia-to-carcinoma ratio to poor screening performance alone. Thus, another explanation is presumably in order. Most women who develop endometrial hyperplasia become symptomatic and receive care. These women, some of whom are undoubtedly candidates for endometrial cancer, constitute but one population at risk. The possibility that estrogen-induced endometrial proliferation leads to the early discovery of endometrial carcinoma was suggested by Horwitz and Feinstein [7].

In most asymptomatic women with endometrial cancer, the disease usually does not develop in diffuse hyperplasia, but rather as a focal event either in an essentially atrophic or focally hyperplastic endometrium. Several lines of reasoning may be cited in support of this hypothesis. Only one of the patients with occult carcinoma had extensive endometrial hyperplasia in an enlarged uterus; she received exogenous estrogens for ten years. Although asymptomatic at the time of the examination, this woman concealed from the interviewer a history of spotting that was elicited on close questioning. Thus, she was not truly asymptomatic. In the 14 remaining women who did not receive radiotherapy and whose uteri could be examined, focal hyperplasia was observed in six, but the

remaining endometrium was either cancerous or atrophic. Further support of this thesis comes from a report by Horwitz *et al.* [8], who observed unsuspected endometrial carcinoma in 24 autopsied women dying of unrelated causes for a rate of 2.2 per 1,000 at Yale-New Haven Hospital and 3.1 in 1,000 at Massachusetts General Hospital. None of the 24 patients had any history of vaginal bleeding. Whereas the rate of cancer in the authors' examinees was substantially higher, there are reasons to believe that at least some of those with advanced disease would have become symptomatic, as did the four missed cases, thus reducing the pool of women with asymptomatic cancers dying of other causes to the levels reported by Horwitz *et al.* [8].

Still further support for this view is provided by Greene *et al.* [9] and Horwitz *et al.* [10]. Greene *et al.* [9], reviewing the pathologic findings in 120 patients with endometrial carcinoma treated by hysterectomy, found accompanying hyperplasia in only ten patients. These authors expressed this view: "... some (and probably the minority) of endometrial carcinomas are preceded by or possibly induced in or developed from areas of endometrial hyperplasia." These observations are particularly valuable because they were published in 1959, before widespread use of estrogens obscured endometrial pathology. In 1981, Horwitz *et al.* [10] reported on the status of peripheral endometrium in a case-control study of 233 postmenopausal women, of whom 112 had endometrial carcinoma. Peripheral hyperplasia was more commonly observed with grade 1 cancer among estrogen users than in cancer of higher grades among nonusers of estrogen. Among 74 women with endometrial cancer who were nonusers of estrogen, only 33 had some evidence of endometrial proliferation, including hyperplasia. The authors concluded their report by stating that "... it was likely that many otherwise asymptomatic tumors might have remained undetected except for the manifestations of the estrogen-related comorbid condition."

The means of detecting occult endometrial carcinoma are only moderately reliable. Despite many years of experience [11], the authors found the endometrial smears difficult to interpret. Any thought that the endometrial smear is just another Papanicolaou smear is not based on a realistic assessment of the level of diagnostic difficulty. The use of the cell block was helpful. It is the author's impression that the physical characteristics of the device used to secure a sample of endometrial cells matter little, provided that it is acceptable to the patients, that the entire endometrium is sampled, and that the sample is adequately interpreted. About one-third of the endometrial cancers would have been discovered by the much-neglected vaginal pool smear, the original genital cancer detection tool described by Papanicolaou and Traut [12]. However, the failure to detect four cases of carcinoma over a period of three years of follow-up indicates that there is no foolproof system of endometrial cancer detection.

In reference to screening an identified high-risk population, the present study suggested that all women past the age of 50 should be screened at least once. The bulk of the occult lesions was discovered on the first screening. The incidence rate based on a follow-up of one to three years appears rather small and may not justify the expense of a second screening.

Is there a high-risk group for women? This study discloses trends that suggest that late onset of menopause, and possibly unopposed estrogen medication in nonobese women, may constitute risk factors. On the other hand, menopause before the age of 49 appears to reduce the risk somewhat. Yet the data generated in the present study failed to uncover a group significantly free of risk because some occult endometrial cancers have been observed in all of the groups.

The results of this study may have some implications in reference to chemoprevention trials of endometrial carcinoma.

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