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INCIDENCE OF ENDOMETRIAL HYPERPLASIA

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Abstract

Objective—Estimate age-specific incidence of endometrial hyperplasia: simple, complex, and atypical, in order of increasing likelihood of progression to carcinoma.

Study design—Women ages 18–90 years with endometrial pathology specimens (1985–2003) at a large integrated health plan were identified using automated data. Incidence rates were obtained by dividing the number of cases by the estimated number of female health plan enrollees who retained a uterus.

Results—Endometrial hyperplasia peak incidence was: simple-142/100,000 woman-years, complex-213/100,000 woman-years, both in the early 50s; and atypical-56/100,000 woman-years in the early 60s. Age-adjusted incidence decreased over the study period, especially for atypical hyperplasia.

Conclusions—Endometrial hyperplasia incidence without and with atypia peaks in the early postmenopausal years and in the early 60s, respectively. Given that some cases of endometrial hyperplasia likely go undiagnosed, the figures provided should be viewed as minimum estimates of the true incidence.

Keywords

atypical endometrial hyperplasia; complex endometrial hyperplasia; incidence; simple endometrial hyperplasia

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Introduction

Endometrial hyperplasia has been classified into 3 main types: simple hyperplasia, characterized by minimal endometrial glandular crowding and with low risk of progression to endometrial carcinoma; complex hyperplasia, characterized by greater endometrial glandular crowding and intermediate risk of progression; and atypical hyperplasia, comprised of endometrium with complex glandular crowding and/or cytologic atypia and the greatest risk of endometrial carcinoma progression.^{1–3} Despite the fact that endometrial carcinoma is the most common gynecologic cancer in the U.S, with an incidence of 23.2/100,000 women,⁴ very little is known about the incidence of endometrial hyperplasia. Endometrial hyperplasia not only predisposes to endometrial carcinoma, its presenting clinical symptoms, menorrhagia and menometrorrhagia, often lead to emergency and outpatient evaluations.^{5–7} In addition, patients and the health care system bear the cost and burden of diagnostic evaluations and surgical and medical treatment (including endometrial biopsy, dilatation and curettage, hysterectomy, and potential prolonged progestogen therapy).^{6, 8–9}

There are no routine screening procedures available for the detection of endometrial cancer or its antecedent lesions. Endometrial neoplasia usually is detected following the investigation of symptoms of abnormal uterine bleeding.^{10–11} Any estimates of the incidence of endometrial hyperplasia must take into consideration that diagnoses of endometrial hyperplasia are made only among women who have had endometrial sampling. Due to the invasive nature of endometrial sampling, very few studies have performed routine endometrial biopsies on asymptomatic women.^{12–13} The findings from these studies suggest that among women with normal bleeding patterns the prevalence of simple and complex hyperplasia is 0.5–5% and the prevalence of atypical endometrial hyperplasia or carcinoma is less than 1%. Further complicating the assessment of the incidence of endometrial hyperplasia is the poor reproducibility of the histopathologic classifications of normal and abnormal endometrial tissues into the various accepted diagnostic categories.^{2–3, 14}

The objective of this study was to estimate the age-specific incidence of the three main types of endometrial hyperplasia (simple, complex, atypical) as diagnosed by community pathologists in a population of women in a large integrated health plan, as well as the temporal trends in that incidence.

Materials and Methods

Study Population

The study was conducted among the membership of Group Health (GH), an integrated health plan with over 530,000 enrollees in Washington State. Automated pathology, enrollment, inpatient and outpatient databases were linked for data on all female enrollees 18 and over from January 1, 1985 through December 31, 2003. The study was approved by the Group Health Institutional Review Board.

Data Collection

The GH SAS databases are linked through the unique medical history number (consumer number) assigned to each enrollee when s/he first joins GH, and reassigned upon each subsequent enrollment. Disenrollment of subjects during the study period was ascertained by computerized membership files that are updated monthly. The pathology database, established in 1977, includes the specimen date and all result reports entered as text fields. Outpatient and inpatient databases contain all visit-related ICD-9 diagnostic codes since 1972. Codes for endometrial hyperplasia included 620.3, 620.30, 620.31, 620.32, and 620.33.

Study Outcomes

We first searched ICD codes for endometrial hyperplasia. Then to improve case ascertainment we utilized the pathology databases. Pathology reports were classified according to the Standard International Society of Gynecological Pathologists and World Health Organization criteria.^{2–3} This classification, based on the schema developed by Kurman,¹ divides hyperplasia into four categories: simple with and without atypia, and complex with and without atypia. Often, and as adapted in our study, simple hyperplasia with atypia and complex hyperplasia with atypia were combined into a single category, hyperplasia with atypia (or atypical hyperplasia).

We developed a method to evaluate pathology text reports that combined computerized text searches with programmed text matching using PERL (a specific programming language for text processing) for initial classification of all reports. Among age-eligible women, we identified reports with full text fields indicating endometrial tissue in the GH pathology database. We loaded these data into a Microsoft SQL Server database (a relational database management system). The initial computerized classification was then refined with visual review of the pathology text reports by an investigator (SR) to confirm or reclassify the designation assigned by the computerized text search. An iterative process was created, refining text searches and repeating the review, to arrive at the final classification of the pathology report.

Specifically, we constructed regular expressions based on phrase sets compiled by the investigators and then matched the phrase sets to the text fields of the pathology reports stored on the SQL server using PERL scripts. The presence and/or absence of specific flags set by the PERL scripts classified reports into the diagnostic categories of interest: “simple hyperplasia” (cystic), “complex hyperplasia” (adenomatous), “hyperplasia with atypia”, “FIGO grade I endometrial carcinoma” (well differentiated), and “FIGO grade 2–3 endometrial carcinoma” (moderately to poorly differentiated). Multiple phrase sets designated the absence of atypia: “without atypia”, “no cytologic atypia”, “no significant atypia”, “without diagnostic atypia”, “no cellular atypia”, and “no significant cytologic atypia”. In addition, reports were classified as quantity insufficient for diagnosis or “QNS”, “pregnancy tissue”, and “normal endometrium”. We scrubbed the text fields by removing extra spaces, punctuation, and extraneous characters and then searched for each set of phrases by matching the regular expressions that we had constructed for that phrase set with the pathology report text. The regular expressions in the PERL scripts were refined during the review process to improve the accuracy of the matching of the phrase sets. For example, we added to the regular expressions common abbreviations used by GH pathologists and frequent misspellings. The database for the search results was constructed as a set of flags, one for each of the regular expressions used to indicate a match to the phrase set in the report’s text fields. Examples of the text searches that classified women with hyperplasia or carcinoma are shown in Appendix A.

We were inclusive rather than exclusive when assigning final diagnoses. Any text diagnoses with a possible diagnosis of endometrial hyperplasia or endometrial carcinoma were included. Pathology reports in which the diagnosis was ambiguous were classified in the more severe abnormal category. For example, a pathology diagnosis of “cannot rule-out atypia” was classified as “atypia” and a pathology diagnosis of “simple and complex hyperplasia” was classified as “complex”. Initially we searched for biopsy/specimen type that contained endometrial tissue using the words: “endometrial biopsy”; “embx”; “endometrium”, “biopsy”; “endometrium”, “curettage”; “EMC”; “endometrial bx”; “dilatation and curettage”; “D&C”; “hysterectomy”; “uterus”, and “endometrial”. We excluded specimens that had only endocervical tissue with no endometrial tissue diagnosis in the same specimen. Cervical hyperplasias were excluded by text searches for the phrases “microglandular hyperplasia” or “endocervical hyperplasia” without any of the above phrases also being present. Breast and

colonic hyperplasias were excluded by text searches for the phrases “breast hyperplasia” or “colonic hyperplasia” without any of the above phrases also being present.

The first search of the pathology database for reports using the terms “adeno” and “endo” identified 121,842 specimens. Searching on words that indicated a tissue source that was not endometrium (breast, colon, endocervical) left 64,874 potential endometrial or uterine pathology specimens. We then excluded 1,156 because they were ectopic or intrauterine pregnancy tissue and 30 with non-endometrial tissue, leaving 63, 688 endometrial specimens. Ultimately, all reports of simple, complex, and atypical hyperplasias, all endometrial carcinomas and 10% of all reports assigned as normal endometrium by computerized searches were reviewed (SR).

Analyses

For purposes of this analysis, age-eligible women in the GH population were allowed to achieve a given outcome, a diagnosis of endometrial hyperplasia (simple, complex or atypical hyperplasia) or endometrial carcinoma (FIGO grade 1 or FIGO grade 2/3), only once. However, each woman remained eligible for ascertainment of a subsequent more severe outcome.

We estimated the number of women enrolled in GH who were at risk of endometrial hyperplasia by age and year using automated enrollment data. The number of women 18 to 90 years of age who were enrolled each year in GH as of December 1, 1985 through 2003 was tabulated by five-year age groups using automated enrollment data. Person-years for each age group were computed by summing enrollment over all years by five-year age group. We used data from women randomly selected as controls for a study of risk factors for endometrial hyperplasia¹¹ and determined the proportion with prior hysterectomy by age. We then ascertained the total number of women enrolled in GH from 1985–2003 by age and excluded from this group the fraction estimated to have had a prior hysterectomy, arriving at an estimate of the number of women at risk for endometrial hyperplasia to be used in our incidence calculations.

The incidences of simple hyperplasia, complex hyperplasia, and atypical hyperplasia, both overall and within 5-year age groups were calculated. We also assessed temporal trends comparing incidence rates by 5-year calendar periods.

The accuracy of our automated case detection methodology was also assessed. We found that queries using ICD-9 codes performed poorly, being both less sensitive and less specific than pathology text searches (data not shown). We calculated the sensitivity and specificity of our automated diagnosis assignments based on the flags created by the final form of the PERL regular expressions and SQL program without referring to classifications due to reassignment by the investigator. The gold standard for the classifications was a pathology text review by the investigator. The diagnostic classifications made by the investigator were compared with those derived by the text searches, with sensitivity and specificity.. Queries using text strings alone varied in sensitivity from a low of 75% for atypical hyperplasia to a high of 99% for normal endometrium.

Results

The endometrial pathology reports were classified as shown in Figure 1 (24,812 women had one endometrial specimen; 8,269 had two specimens; 3,194 had three; 1,299 had four; 553 had five; 269 had six; 103 had seven; 61 had eight; 33 had nine; and 28 women had ten or more). We excluded 12 women over the age of 90 years and 111 women who were not enrolled in GH on the date the specimen was obtained, leaving 3,735 incident diagnoses of endometrial hyperplasia from 1985 through 2003.

Among women 18–90 years, the incidence of simple hyperplasia was 58 per 100,000 woman-years. The corresponding rates for complex hyperplasia and atypical hyperplasia were 63 per 100,000 and 17 per 100,000, respectively. The age-specific incidences of simple hyperplasia, complex hyperplasia, and atypical hyperplasia are shown in Table 1. The incidences of simple and complex hyperplasia were highest in women ages 50–54 years (142 and 212 per 100,000 woman-years, respectively). The incidence of atypical hyperplasia was highest in women ages 60–64 years (54 per 100,000 woman-years). Overall, the incidence of any type of hyperplasia was highest in women ages 50–54 (386 per 100,000 woman-years) and was rare in women under age 30 (6 per 100,000 woman-years) and increased steadily in each 5-year interval between 30 and 54 years.

Age-adjusted temporal trends in simple, complex and atypical hyperplasia incidence are shown in Figure 2. Rates in 2000–2003 generally were lower than in earlier years, substantially so for atypical hyperplasia and possibly complex hyperplasia as well.

Comment

In our study, among women 18–90 years the overall incidence of endometrial hyperplasia was 133 per 100,000 woman-years, was most common in women ages 50–54, and was rarely observed in women under 30. Simple and complex hyperplasia incidences peaked in women ages 50–54. The incidence of atypical hyperplasia was greatest in 60–64 year old women, and was similar to the peak age-specific incidence of endometrial carcinoma.⁴ Decreases in the incidence of endometrial hyperplasia over time were observed, particularly for atypical endometrial hyperplasia.

Given the known increasing prevalence of obesity and the known association of obesity with endometrial hyperplasia,¹¹ one might have expected increases in endometrial hyperplasia toward the end of the study period. It is possible that our finding of a diminishing incidence could be explained by decreasing use of unopposed estrogen therapies in women with a uterus, but no data to support this supposition are available within GH. In theory, the greatest impact of changes in practice regarding unopposed estrogen use would have occurred in the 1980s shortly after publications demonstrating increased endometrial carcinoma risk with unopposed estrogen in the 1970s¹⁵ with a persistent slow decline over the ensuing years. Therefore this theory may partially, but probably does not fully explain the steady decline in atypical hyperplasia incidence observed from 1985 through 2003.

Interpretation of any estimates of the incidence of the various forms of endometrial hyperplasia must take into account the known diagnostic challenges for endometrial tissues and the controversy regarding the pathologic classification of endometrial hyperplasia and well-differentiated endometrial cancer.^{16–21} Inaccuracies in the histopathologic diagnoses of endometrial hyperplasia have been well described, as well as concerns for concomitant endometrial carcinoma.¹⁴ The pathologic diagnosis of the different types of endometrial hyperplasia and well-differentiated carcinoma is only moderately reproducible with an intra-observer reproducibility of kappa (k)=0.4–0.8 and inter-observer reproducibility of k =0.9 for carcinoma, k =0.6 for simple, k =0.4 for complex, k =0.5 for complex with atypia and k =0.2 for simple with atypia.^{18, 22–23} Diagnostic challenges are compounded by the fact that endometrial biopsies are done blindly, randomly sampling the endometrial cavity in the majority of cases and potentially missing smaller lesions. Improved accuracy is observed with hysterectomy specimens.²⁴ In our study, 7.5% of the diagnoses of incident simple, complex or atypical hyperplasia were from hysterectomy specimens (10.5%, 5.1% and 6.3%, respectively).

Several endometrial hyperplasia classification schemes have been introduced over the years.^{1–3} Our study used WHO diagnostic criteria modified by Kurman¹ in 1985 and revised in 1994.² Using this scheme, Kurman¹ reported progression to carcinoma in 1% of cases with simple, 3% of cases with complex and 22% of cases with atypical hyperplasia. A newer classification scheme defines 2 endometrial hyperplasia groups: 1) benign polyclonal hyperplastic lesions (simple and some complex hyperplasia) and 2) monoclonal precancerous endometrial epithelial neoplasias or EIN (some complex and most atypical hyperplasias).^{26–27} Others have reclassified endometrial hyperplasia specimens originally categorized by the WHO criteria, using the new EIN classification scheme²⁸ and showed that the exact reclassification to EIN from WHO does not always hold true (for example, some specimens originally classified as simple hyperplasia were reclassified as EIN). In addition, both EIN and atypical hyperplasia were found to have similar risks of progression to carcinoma.

We acknowledge the additional inherent biases that must be taken into account in the interpretation of the findings reported here. 1) Because not all women in the study population had endometrial biopsies, but rather only those that presented with bleeding or a problem, our methodology would have missed some women with asymptomatic endometrial hyperplasia. Previous studies^{12–13} would suggest that the prevalence of women with asymptomatic endometrial neoplasia is relatively low, however. One of the studies reported on 556 asymptomatic postmenopausal women and 4.8% had simple or complex hyperplasia and 0.54% had atypical hyperplasia.¹² The other study reported that of 2964 asymptomatic women with a mean age of 52 years, only 0.64% had simple hyperplasia. None of the women had complex or atypical hyperplasia.¹³ 2) By including possible diagnoses (i.e. “cannot rule-out complex hyperplasia” classified as complex hyperplasia) we may have inflated our incidence figures of endometrial hyperplasia. 3) In addition, to calculate incidence among women at risk, we were unable to fully assess the numbers of women within the population who had had a hysterectomy, but we estimated these numbers utilizing data from our previous work.¹¹ These estimates are very similar to the age-specific prevalence reported nationally.²⁵ 4) Not all reports classified as normal endometrial tissue were reviewed (only 10%), thus contributing to a small underestimation of the incidence rates; two specimens with simple, seven with complex, one with atypical hyperplasia were identified among the 5493 “normal” specimens reviewed. 5) Interpretation of temporal trends must take into account any changes in the criteria that GH pathologists used to classify endometrial pathology over this period of time.

In summary, to the best of our knowledge, this is the first population-based study to estimate the age-specific incidence of the various forms of endometrial hyperplasia. Although women in the GH population are less likely to be very poor or very wealthy, women in this cohort are similar to women residing in Western Washington state and have been described;¹¹ our findings are generalizable to similar populations. Given that some cases of endometrial hyperplasia likely go undiagnosed, the figures provided should be viewed as minimum estimates of the true incidence.

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Appendix

Appendix A

Text searches to identify women with simple hyperplasia, complex hyperplasia, hyperplasia with atypia, well differentiated carcinoma and moderately-poorly differentiated endometrial carcinomas

Text Search	
<i>Simple Hyperplasia</i> *	Simple or cystic hyperplasia
<i>Complex Hyperplasia</i> *	Complex or adenomatous hyperplasia
<i>Hyperplasia with Atypia</i> †	Atypical or Atyp or Atypia
<i>Endometrial Carcinoma Grade 1</i> **	FIGO I FIGO grade 1 Well differentiated Low grade (FIGO grade 1) Well diff Wel dif
<i>Endometrial Carcinoma Grade 2–3</i> **	FIGO 2–3 FIGO grade 2–3 Moderate to poorly differentiated High grade (FIGO grade 2–3) Mod diff

Text Search	
Poor diff	
Possible	Pregnancy tissue – excluded
Cannot R/O	Pregnancy
Possible	Pregnancy-related
PsbI	Products of conception
Suspicious	POC
Suspicious for	Products
Cannot exclude	Villi
Worrisome for	Chorionic villi
Versus	Villus
Probable	Chorionic villus
Highly suspicious	Placenta
Cannot ruleout	Placent
Features of	Placental
Feats of	Trophoblast
Unspecified hyperplasia	Trophoblastic
	Gestational endometrium
	Gestational
	Fetal
	Fetus
Tissue quantity insufficient to make diagnosis in specimen identified as endometrium	
Insuf for diag	Adequate endometrial tissue not identified
Insuff mat 4 evaluation	Adequate endometrial tissue is not identified
Insufficient for diagnosis	Q.N.S.
Insufficient	QNS
Insuff for dx	Quantity not sufficient
Insuff for evaluation	Insufficient material for evaluation
Insufficient	No endom present
Tissue insufficient for endometrial diagnosis	No endometrial tissue present for evaluation
Tissue insufficient for diagnosis	No intact endometrial tissue is recognized
TX insuffic for dx	Nondx fragmented endom
Tx insuff for dx	Nondx epithelial particles
Scant nondx endom particles	Diagnostic endometrial tissue not identified
Scant nondiagnostic material	Frag nondx particles of endom glands
Scant nondx particles of superficial endom	

Without atypia, With No cytologic atypia, Without diagnostic atypia, With No significant atypia, With No atypia, With No significant cellular atypia, Without cytologic atypia, With No significant cytologic atypia, Does Not show significant cytologic atypia, Negative for dysplasia or malignancy, No malignancy or significant cellular atypia

[†] Simple or complex

^{**} Adenocarcinoma or adenoca or carcinoma or malignancy or malign:

Figure 1.
Endometrial Specimens from 1985–2003, Group Health, Seattle, Washington.

Figure 2. Temporal Trends from 1985–2003 of Incidence of Simple, Complex and Atypical Endometrial Hyperplasia, Group Health, Seattle, Washington. The x-axis shows time from 1985–2003 for the 3 different types of endometrial hyperplasia (simple, complex and atypia). The y-axis defines incidence per 100,000 women years.

Table 1
Age specific incidence of simple, complex and atypical endometrial hyperplasia, 1985–2003

Ages	Adjusted person years Denominator*	SIMPLE		COMPLEX		ATYPIA		TOTAL	
		Cases	Rate per 100,000 person yr	Cases	Rate per 100,000 person yr	Cases	Rate per 100,000 person yr	Rate per 100,000 person yr	
18–29	549,242	17	3.10	11	2.00	6	1.09	6.19	
30–34	253,722	28	11.04	28	11.04	4	1.58	23.25	
35–39	258,672	78	30.15	73	28.22	18	6.96	63.01	
40–44	290,315	170	58.55	140	48.22	28	9.65	114.36	
45–49	223,667	272	121.61	302	135.02	46	20.57	270.04	
50–54	165,432	235	142.05	352	212.78	69	41.71	386.26	
55–59	127,754	133	104.11	175	136.98	59	46.18	270.05	
60–64	96,708	98	101.34	111	114.78	52	53.77	256.44	
65–69	88,344	105	118.85	99	112.06	40	45.28	262.61	
70–74	80,606	74	91.80	56	69.47	29	35.98	187.33	
75+	135,369	107	79.04	77	56.88	31	22.90	149.22	
Total	2,269,831	1317	58.02	1424	62.74	382	16.83	132.57	

* Adjusted for estimated prevalence of hysterectomy in each age group.