Absolute Risk of Endometrial Carcinoma During 20-Year Follow-Up Among Women With Endometrial Hyperplasia

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ABSTRACT

Purpose

The severity of endometrial hyperplasia (EH)—simple (SH), complex (CH), or atypical (AH)—influences clinical management, but valid estimates of absolute risk of clinical progression to carcinoma are lacking.

Materials and Methods

We conducted a case-control study nested in a cohort of 7,947 women diagnosed with EH (1970-2002) at one prepaid health plan who remained at risk for at least 1 year. Patient cases (N = 138) were diagnosed with carcinoma, on average, 6 years later (range, 1 to 24 years). Patient controls (N = 241) were matched to patient cases on age at EH, date of EH, and duration of follow-up, and they were counter-matched to patient cases on EH severity. After we independently reviewed original slides and medical records of patient controls and patient cases, we combined progression relative risks (AH v SH, CH, or disordered proliferative endometrium [ie, equivocal EH]) from the case-control analysis with clinical censoring information (ie, hysterectomy, death, or left the health plan) on all cohort members to estimate interval-specific (ie, 1 to 4, 5 to 9, and 10 to 19 years) and cumulative (ie, through 4, 9, and 19 years) progression risks.

Results

For nonatypical EH, cumulative progression risk increased from 1.2% (95% CI, 0.6% to 1.9%) through 4 years to 1.9% (95% CI, 1.2% to 2.6%) through 9 years to 4.6% (95% CI, 3.3% to 5.8%) through 19 years after EH diagnosis. For AH, cumulative risk increased from 8.2% (95% CI, 1.3% to 14.6%) through 4 years to 12.4% (95% CI, 3.0% to 20.8%) through 9 years to 27.5% (95% CI, 8.6% to 42.5%) through 19 years after AH.

Conclusion

Cumulative 20-year progression risk among women who remain at risk for at least 1 year is less than 5% for nonatypical EH but is 28% for AH.

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INTRODUCTION

The severity of an endometrial hyperplasia (EH) diagnosis guides clinical management and reflects risk of concurrent or future endometrial carcinoma.¹⁻³ The WHO classification categorizes EH as simple (SH), complex (CH), simple atypical (SAH), or complex atypical (CAH) on the basis of architectural crowding and nuclear atypia.⁴ The term atypical hyperplasia (AH) often encompasses CAH or SAH, because SAH is so rare.⁵

Hysterectomy is generally recommended for AH,⁶ because up to 50% of women whose endometrial biopsies are classified as AH in fact have carcinoma.^{5,7-9} Optimal clinical management strategies for women with nonatypical EH (ie, SH or CH), who far outnumber women with AH, are unclear.^{1,3} One third of women with nonatypical

EH undergo hysterectomy, but overtreatment among this group is likely.³ Little is known about progression risk among women with AH who opt for nonsurgical (ie, hormonal) treatment to preserve fertility or to avoid hysterectomy, and evidence-based treatment guidelines are lacking.^{5,10} Current estimates of progression risk are limited to crude and imprecise percentages (eg, 0% to 27% for nonatypical EH, and 20% to 100% for AH^{5,11-15}) during unspecified follow-up intervals from small case series that lacked controls and used suboptimal statistical analyses.

We recently completed a nested case-control EH progression study, which had carefully matched controls and complete follow-up and treatment data over 34 years.¹⁶ Women with AH were 14 times more likely (relative risk [RR], 14) than women with nonatypical EH to subsequently develop carcinoma.

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Because RRs are insufficient for quantifying progression risk during specific time intervals or for predicting which patients will experience progression,¹⁷ we utilized our population-based design to directly estimate absolute risk of progression from EH to carcinoma. Our objective was to generate accurate and precise estimates of risk of progression for nonatypical EH versus AH.

MATERIALS AND METHODS

We previously described this study¹⁶ in detail. All participants were members of the Kaiser Permanente Northwest (KPNW; Portland, OR) prepaid health plan,¹⁸ which has linked and computerized administrative, pathology, tumor registry, and pharmacy databases. The Kaiser Permanente Center for Health Research Subjects Protection Office and the National Cancer Institute Special Studies institutional review board approved this study.

Study Participants

From 1970 to 2003, 10,273 female KPNW members were diagnosed with incident EH (Table 1) via biopsy or (occasionally) curettage. We referred to this first diagnosis of EH as the index biopsy. Because EH is often diagnosed concurrently with or shortly before carcinoma,^{5,7-9} we limited our progression study to the 7,947 KPNW women with EH who remained at risk for at least 1 year after their index biopsies. We excluded 2,326 women (23%) with EH who were diagnosed with endometrial carcinoma ($n = 308$), underwent hysterectomy ($n = 1,379$), or left the health plan ($n = 639$) less than 1 year after their index biopsies, and we excluded 112 women with EH who had been diagnosed with endometrial carcinoma before their index biopsies. Censoring information for the complete cohort was available through the linked KPNW databases.

From the remaining 7,835 women, we identified 228 potential patient cases who were diagnosed with endometrial carcinoma at least 1 year after their index biopsies.¹⁶ We retrieved original pathology reports and diagnostic slides for all their endometrial procedures, including hysterectomies. Three gynecologic pathologists independently reviewed the slides to assign a panel WHO diagnosis (ie, normal, disordered proliferative endometrium [DPEM; ie, equivocal EH^{2,5,19}], SH, CH, AH [either SAH or CAH], or carcinoma). Each slide received a panel diagnosis, which was based on a standard algorithm.¹⁶ After that pathology panel review, 138 (60.5%) of the 228 potential patient cases were eligible, because their index biopsies panel WHO diagnoses were

DPEM ($n = 33$), SH ($n = 42$), CH ($n = 21$), or AH ($n = 42$). These 138 patient cases were all diagnosed with endometrial carcinoma at least 1 year later, and they represent the progression end points for this analysis. The other 90 potential case patients (39.5%) were ineligible because the panel WHO diagnoses of their index biopsies were normal ($n = 55$) or carcinoma ($n = 13$) or because their original EH or carcinoma diagnoses had been miscoded or were missing ($n = 22$).

For each case patient, we identified all control patients in the cohort who were individually matched to case patients on age and date of index biopsy (both within 1 year) and who did not experience progression to carcinoma but remained at risk for a follow-up interval at least as long as the progression interval of the patient case to whom she was matched. The absence of both a uterine cancer diagnosis in the tumor registry and a hysterectomy in the pathology databases, plus a confirmed date of last active membership in the health plan, confirmed at risk status for controls. We found, on average, 43 potential controls per patient case.

We used (Lacey JV Jr et al, submitted for publication) batch-quota sampling and counter-matching²⁰ to select three potential controls per patient case ($N = 413$ for controls).¹⁶ For 413 potential control patients, original KPNW WHO diagnoses were SH ($n = 129$; 31%), CH ($n = 153$; 37%), or AH ($n = 131$; 32%). Our pathology panel reviewed and classified all original diagnostic slides for the index biopsies of these control patients. After excluding control patients for whom the panel WHO diagnoses of their index biopsies were normal ($n = 160$), carcinoma ($n = 3$), or missing ($n = 9$), 241 eligible control patients had index biopsies with panel WHO diagnoses of DPEM ($n = 97$), SH ($n = 67$), CH ($n = 43$), or AH ($n = 34$).

RRs

We previously generated RRs for the association between panel WHO diagnosis and risk of carcinoma.¹⁶ The RRs were statistically weighted to account for the study design and the counter-matched control group, as described elsewhere (Lacey JV Jr et al, submitted for publication). Compared with DPEM as the reference group, neither SH (unadjusted RR, 1.9; 95% CI, 0.96 to 3.9) nor CH (RR, 2.2; 95% CI, 0.91 to 5.3) was strongly associated with endometrial carcinoma. AH was strongly associated (RR, 9.9; 95% CI, 4.3 to 23.1),¹⁶ so we used that dichotomy—with a revised RR of 6.9 (95% CI, 3.3 to 14.6) for AH versus DPEM or nonatypical EH—to calculate absolute risks of endometrial carcinoma.

Cohort-Based Absolute Risks

To convert these RRs into absolute risks, we needed to know the panel WHO diagnoses for all 7,719 potential controls (ie, 7,947 minus 228), not just for the 413 controls whom we selected via counter-matching and for whom the slides were reviewed by our pathology panel. Fortunately, the distribution of panel WHO diagnoses within each original WHO diagnosis category among the selected controls is representative of the distributions of panel WHO diagnoses within each original WHO diagnosis category among all potential controls.¹⁶ By using the sampling weights, we generated an unbiased distribution of panel WHO diagnoses among all 7,719 potential controls on the basis of the panel WHO diagnoses of the 413 counter-matched controls.

We combined the RR from our nested case-control data, the estimated distribution of panel WHO diagnoses among all potential controls, and censoring data for those controls to calculate the absolute risk of endometrial carcinoma for each of the study WHO diagnoses (ie, DPEM, SH, CH, and AH) via generalized Kaplan-Meier survival curve estimation, as described elsewhere.²¹ This allowed us to estimate, without bias, the contribution of all members of the cohort to the RR at the time each patient case was diagnosed with endometrial carcinoma and to calculate a true risk (ie, number of cancers divided by number at risk) for each study WHO diagnosis during specific follow-up intervals of 1 to 4 years, 5 to 9 years, and 10 to 19 years.

RESULTS

Figure 1 and Table 2 show discrete risks over time for each EH type. For women with DPEM or nonatypical EH, risks were 1.2% (95%

Table 1. Clinical and Censoring Outcomes of Female KPNW Members Diagnosed With EH Between 1970 and 2003 ($N = 10,273$)

Variable	Time From EH to Event (years)				Total	
	< 1		≥ 1			
	No.	%	No.	%	No.	%
Alive and at risk through December 31, 2004	—	—	3,299	100	3,299	32
Endometrial cancer	308	57	228	43	536	5
Hysterectomy for reasons other than endometrial cancer*	1,379	56	1,077	44	2,456	24
Left the KPNW health plan†	639	16	3,343	84	3,982	39
Total	2,326	23	7,947	77	10,273	100

NOTE. The 228 potential case patients and 413 potential control patients in the nested case-control study of EH progression were selected from these 7,947 women who had at least 1 year of follow-up.¹⁶

Abbreviations: KPNW, Kaiser Permanente Northwest; EH, endometrial hyperplasia.

*Includes 110 women diagnosed with ovarian cancer.

†Includes 31 women who died within 1 year of their EH diagnosis and 794 women who died 1 or more year after their EH diagnosis.

Fig 1. Absolute risk of subsequent endometrial carcinoma by endometrial hyperplasia (EH) type at index biopsy over intervals of 1 to 4, 5 to 9, and 10 to 19 years. Vertical bars indicate 95% CIs. Data points are plotted at the mean time to diagnosis within each time interval. Size of data points is proportional to the number of case patients diagnosed with endometrial carcinoma during that time interval. AH, atypical hyperplasia; DPEM, disordered proliferative endometrium.

Fig 2. Cumulative risk of subsequent endometrial carcinoma by endometrial hyperplasia (EH) type at index biopsy. Vertical bars indicate 95% CIs. Data points are plotted at the mean time to diagnosis within each time interval. Size of data points is proportional to the number of case patients diagnosed with endometrial carcinoma during that time interval. AH, atypical hyperplasia; DPEM, disordered proliferative endometrium.

CI, 0.6% to 1.9%) at 1 to 4 years, 0.7% (95% CI, 0.3% to 1.0%) at 5 to 9 years, and 2.7% (95% CI, 1.7% to 3.7%) at 10 to 19 years after index biopsy. For women with AH, risks were 8.2% (95% CI, 1.3% to 14.6%) at 1 to 4 years, 4.5% (95% CI, 0.7% to 8.2%) at 5 to 9 years, and 17.3% (95% CI, 4.4% to 28.4%) at 10 to 19 years after index biopsy.

Cumulative risks (Fig 2) for DPEM or nonatypical EH were 1.2% (95% CI, 0.6% to 1.9%) at 4 years, 1.9% (95% CI, 1.2% to 2.6%) at 9 years, and 4.6% (95% CI, 3.3% to 5.8%) at 19 years after index biopsy. For AH, cumulative risk steadily increased to 27.5% (95% CI, 8.6% to 42.5%) at 19 years after index biopsy. Neither the discrete nor cumulative risks differed when stratified by age at index biopsy of less than 50 years versus 50 years or older (eg, cumulative risk for AH, 25%; 95% CI, 6.5% to 39.9% among

women < 50 years old at index biopsy v cumulative risk for AH, 30%; 95% CI, 8.1% to 46.7% among women 50 years or older at index biopsy).

Case patients and control patients received generally similar hormonal treatment for EH (eg, medroxyprogesterone acetate) and follow-up biopsies.¹⁶ Among case patients with AH who were diagnosed with carcinoma 5 or more years after index biopsy, all received hormonal treatment, and 89% received at least one follow-up biopsy. Similar clinical follow-up was observed for case patients with non-atypical EH (data not shown).

DISCUSSION

Among 7,947 women with incident EH who remained at risk for at least 1 year and who were treated and observed according to community standards, fewer than one in 20 women with DPEM, SH, or CH developed carcinoma during 20 years. In contrast, one in eight women with AH developed carcinoma within 10 years, and one in three developed carcinoma within 20 years.

Fifty-year old women in the United States have a 1.3% probability of being diagnosed with endometrial cancer before age 70 years.²² In this study, the average age at EH was 52 years, and the 20-year cumulative risk among women with nonatypical EH was 4.6%. Therefore, endometrial carcinoma risk among women with nonatypical EH, who represent the majority of all EH diagnoses, is three times higher than the average population risk. Risk among women with AH (27.5%) is 21 times higher than the average population risk.

The hypothesis¹ that nonatypical EH among older, postmenopausal women has substantial progression risk, and therefore warrants hysterectomy, has not been rigorously tested. In one report, 30% of women with nonatypical EH underwent hysterectomy; fear of progression motivated half of those surgeries.³ On the basis of the 5% cumulative progression risk in our data, hysterectomy as primary treatment for 30% of women with nonatypical EH might represent

Table 2. Discrete Risks Over Time for Each EH Type

Variable	Time From Diagnosis of EH to Diagnosis of Carcinoma (years)		
	1-4	5-9	10-19
No. of carcinomas			
AH	24	9	10
DPEM or non-atypical EH	33	19	43
Mean time to carcinoma, years			
AH	3.0	7.7	12.4
DPEM or non-atypical EH	2.9	7.2	14.5
Women with hormonal treatment, %			
AH	83	100	100
DPEM or non-atypical EH	85	89	88
Median no. of follow-up biopsies			
AH	2	3	3
DPEM or non-atypical EH	2	1	3

Abbreviations: EH, endometrial hyperplasia; DPEM, disordered proliferative endometrium; AH, atypical EH.

overly aggressive management,³ but numerous factors could influence individual risk thresholds for patients and their gynecologic health care providers.

Previous estimates of EH progression risk come from limited case series with no controls and few clinical end points.^{11-14,23} The reported percentages of women who developed carcinoma (eg, 0% to 27% of women with nonatypical EH, and 20% to 100% of women with AH) are imprecise, assumed to be constant with time, and suffer from biased losses-to-follow-up and end point ascertainment. In one of the larger studies, the 52% progression risk for AH after 22 months was likely biased by occult carcinoma among women diagnosed with carcinoma in the first few months after their AH diagnosis.¹⁵ In a widely cited 1985 case series of 13 cancers among 170 patients with EH, diagnosed between 1940 and 1970 and observed for at least 1 year and for an average of 13 years, two (2%) of 122 women with nonatypical EH and 11 (23%) of 48 women with AH developed carcinoma.²³ Kurman et al²³ advocated conservative treatment for nonatypical EH and hysterectomy for AH, especially among perimenopausal or postmenopausal women. This analysis showed that cumulative risks are slightly higher and increase three-fold in the 20 years after index biopsy.

In this study, almost one third of women with AH who did not undergo hysterectomy were diagnosed with carcinoma within 20 years. The approximate doubling of cumulative risk after 10 years—from 12% to 28%—may help inform decision making regarding how long patients might wish to rely on hormonal treatment and repeat assessment if hysterectomy is not performed within the first year after a diagnosis of AH.

For patients who undergo hysterectomy within the first 3 months after a diagnosis of AH, the recent data from Trimble et al⁷ provide the best estimate of prevalence of occult carcinoma (43%) at the time of AH diagnosis. Patients at KPNW who had similar experiences as those in that Gynecologic Oncology Group (GOG) study were not eligible for this analysis, because we required all of our case patients and control patients to remain at risk for at least 1 year after index biopsy. These two studies together describe both a high short-term risk of having an occult carcinoma when AH is diagnosed and a high long-term risk of being diagnosed with carcinoma years after the initial AH diagnosis.

This large, population-based study included a full range of EH, complete follow-up, independent pathology panel review, and absolute risks and RRs unbiased by age, calendar period, or follow-up time.¹⁶ Some risk estimates were based on small numbers, but our sample size exceeds what previous studies reported. Our risks are based on our pathology panel's interpretation and application of the current WHO classification criteria,⁴ which have inherent limitations¹⁰ but which remain widely used. Our panel downgraded many of the case patient and control patient index biopsies that were initially classified as EH by the pathologists at KPNW.²⁴ This probably reflects overdiagnosis of EH severity among community pathologists.⁵ That overdiagnosis of less-than-EH lesions implies that the progression risks for groups of women with community-based EH diagnoses would be lower than what we observed. Regardless of how EH diagnoses are assigned, better tools to identify characteristics of high-risk EH in endometrial biopsy specimens are needed.

Limitations of this analysis warrant discussion. Our AH risk estimates had wide CIs, because patients with AH who remain at risk

(ie, did not undergo hysterectomy) for long intervals are rare. We employed counter matching to maximize the number of patients with AH, but those stratified sampling methods reduce overall analytic precision. Nonetheless, the CIs for nonatypical EH versus for AH only overlapped in the first 1 to 4 years after index biopsy. For both nonatypical EH and AH, the discrete risks were higher 1 to 4 years after index biopsy than 5 to 9 years after index biopsy. This may reflect occult carcinomas that went undetected in the first year after index biopsy but were diagnosed in years 2 to 4, especially among women with AH.⁵ Although missed occult carcinoma at index biopsy doesn't alone explain the high progression risk with AH,¹⁶ it could artificially inflate short-term risks. Even with this potential misclassification, cumulative risks for both nonatypical EH and AH more than doubled after 10 years. Our results are not generalizable to women whose endometrial biopsies show or are strongly suspicious for carcinoma, because our analysis excluded carcinomas diagnosed within 1 year of an index biopsy. Our study in the KPNW health plan included primarily white women, so our results might be less generalizable to other ethnic groups.

In conclusion, our rigorous, population-based study of women with EH who remained at risk for at least 1 year indicates that the overall progression risk for EH is three times higher than the average population risk of endometrial carcinoma. Fewer than 5% of women with nonatypical EH will experience progression to carcinoma, but 28% of women with AH progress to carcinoma during 20 years. The lower risks for women with nonatypical EH than AH can assist decision making for nonsurgical clinical management of EH, whereas the higher risks of AH progressing to carcinoma warrant consideration of appropriately aggressive approaches.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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