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Complex Hyperplasia With and Without Atypia: Clinical Outcomes and Implications of Progestin Therapy

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Abstract

Objective—Limited data exist to inform clinicians and patients as to the likelihood of long-term endometrial hyperplasia response to progestin therapy, especially for atypical hyperplasia. We evaluated women with complex and atypical endometrial hyperplasia, comparing those prescribed progestin to those not prescribed progestin.

Methods—This retrospective cohort study was conducted in 1985–2005 among women aged 18–88 years at an integrated health plan in Washington State. Women were ineligible if they achieved an outcome (endometrial carcinoma, hysterectomy, or both) within 8 weeks of hyperplasia diagnosis. Exposure was progestin use for at least 14 days, by duration and recency. Outcomes included rate of: 1) endometrial carcinoma; and/or 2) hysterectomy. Analyses performed included Kaplan Meier, incident rate ratios, and Cox proportional hazard ratios.

Results—One thousand four hundred forty-three eligible women were identified. One thousand two hundred one had complex (n=164 no progestin) and 242 had atypical hyperplasia (n=62 no progestin). During follow-up, median 5.3 years (range 8 weeks to 20.8 years), 71 women were diagnosed with endometrial carcinoma (35 complex, 36 atypia) and 323 underwent hysterectomy (216 complex, 107 atypia). Among women with complex and atypical hyperplasia, rates of endometrial carcinoma among progestin users were 3.6 and 20.5 per 1,000 woman-years, respectively (compared with without progestin, 10.8 and 101.4). Among women with complex and atypical hyperplasia, rates of hysterectomy among progestin users were 23.3 and 61.4 per 1,000 woman-years, respectively (compared with without progestin, 55.1 and 297.3).

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Conclusion—Endometrial carcinoma risk is diminished approximately 3- to 5-fold in women diagnosed with complex or atypical endometrial hyperplasia and dispensed progestin; hysterectomy risk is also decreased.

Introduction

Endometrial hyperplasia, a noninvasive proliferation of the endometrial epithelium, is generally classified as simple (non-neoplastic) or complex (sometimes neoplastic), with or without atypia (neoplastic), based on architectural complexity and nuclear cytology and is a precursor to endometrial carcinoma. (1) Endometrial hyperplasia with atypia is the least common type of hyperplasia, but is the type most likely to progress to type 1 endometrial carcinoma (1-3) which accounts for 97% of uterine cancers, whereas simple hyperplasia rarely progresses to carcinoma. (1;4) Known risk factors for endometrial hyperplasia are related to an excess of estrogen relative to progesterone; (5;6) therefore progestin is used to treat endometrial hyperplasia.

There are no large population-based studies describing the incidence of progression of endometrial hyperplasia among women treated and not treated with progestin. In 1985, Kurman et al (1) described an increased risk of progression to carcinoma among lesions classified as complex hyperplasia with atypia (23%), in contrast to lesions classified as hyperplasia without atypia (2%), within a mean follow-up of 13.4 years. A recent large study has confirmed the higher risk of progression associated with atypical endometrial hyperplasia. (3) However, these studies combined women treated and not treated with progestin. Data from women who developed endometrial hyperplasia while using postmenopausal hormone therapy have confirmed that progestins uniformly result in regression of endometrial hyperplasia without atypia. (7;8) Others have described regression of atypical endometrial hyperplasia and/or well-differentiated carcinoma with various forms of progestin, although these reports lacked controls. (9-12) Despite this, there are limited data regarding long-term outcomes for women with endometrial hyperplasia treated with progestin therapy. Consequently, endometrial hyperplasia, especially hyperplasia with atypia, is commonly treated with hysterectomy because of fear of progression to endometrial carcinoma and/or concern that unsampled carcinoma may already be present. (13-15)

The objective of this study was to estimate the incidence of endometrial carcinoma and/or hysterectomy associated with complex or atypical endometrial hyperplasia, comparing progestin users to non-users, among women who did not have a hysterectomy and/or a diagnosis of endometrial carcinoma within 8 weeks of endometrial hyperplasia diagnosis.

Materials and Methods

Following institutional review board approval from the Group Health Research Institute, this retrospective cohort study was conducted among female enrollees at Group Health (GH), a mixed-model integrated health plan with over 500,000 enrollees in Washington State. Automated pathology, enrollment, pharmacy, inpatient and outpatient databases were linked for data on all women over age 18, diagnosed with complex and/or atypical endometrial hyperplasia, between January 1, 1985 and April 1, 2005. Women were followed from the time of hyperplasia diagnosis until an outcome occurred (endometrial carcinoma and/or hysterectomy), disenrollment, death, or until September 30, 2005. Eligibility criteria included no prior diagnosis of endometrial carcinoma and an intact uterus. Because the most commonly recommended progestin treatment duration for endometrial hyperplasia is at least 8 weeks, (16-18) women who had outcomes prior to 8 weeks were excluded. In addition, women who took primarily unopposed estrogen for greater than 6 months at any time during the study period or who left GH for over 2 months during the study period were excluded.

Automated databases were linked through a unique identifier assigned to each woman when she first joined GH, and reassigned upon each subsequent enrollment. Disenrollment was ascertained by computerized membership files.

The pathology database includes unique pathology accession numbers, specimen collection dates, and test results, entered as text fields. Text searches indicating possible diagnoses of complex or atypical hyperplasia were conducted to identify women with the conditions of interest. Details of this methodology have been previously described. (19) The primary goal of this study was to answer the question, "in a given population of women with a clinical diagnosis of either complex or atypical endometrial hyperplasia, what is the risk of endometrial carcinoma or hysterectomy occurring at least 8 weeks after the endometrial hyperplasia diagnosis, with and without progestin exposure?"

A diagnosis of endometrial carcinoma was ascertained from linkage with records of the Cancer Surveillance System of Western Washington, a population-based cancer registry that participates in the Surveillance Epidemiology and End Results (SEER) cancer registry. Hysterectomy, including date, was determined during review of the medical record (yes/no) and was confirmed by the presence of a uterine specimen in the pathology record.

The exposure of interest, progestin prescriptions, was ascertained from the GH pharmacy database. GH pharmacy databases capture all medications dispensed to enrollees through GH pharmacies including the specific drug, drug class, date and amount dispensed, and dosing instructions. Surveys among female GH members aged 50-80 years have shown that 97% of HT prescriptions are filled at GH pharmacies. (20)

All progestin dispensings from one week before the index biopsy up until the outcome or censoring date were identified. Women were classified as progestin "ever users" if they were dispensed at least 15 days of progestin and as "never users" if they had ≤ 14 days of progestin dispensed. Duration of exposure (<56 days and ≥ 56 days of progestin dispensed) was evaluated in sub-analyses.

For time-dependent analyses, days of use was calculated from the time of the index biopsy to the outcome or censoring, within 6-month blocks. Women were classified as progestin "ever users" or as "never users" as described above, within each 6-month block. We created progestin and estrogen exposure variables for each time period that reflected exposure in the previous 6 month period.

Progestins were categorized by type - megesterol acetate, medroxyprogesterone acetate, and norethindrone acetate. Women who were given oral contraceptives were included in the progestin user group as all of these formulations are progestin dominant. We classified women as unopposed progestin users (PT) if they were dispensed progestin without an estrogen or if the number of estrogen pills dispensed was less than 1/3 the number of progestin pills dispensed. Women were classified as estrogen plus progestin users (EPT) if the number of estrogen pills dispensed was at least 1/3 of the number of progestin pills dispensed. We classified women as unopposed estrogen users (ET) if they were dispensed estrogen alone or if the number of progestin pills dispensed was less than 1/3 of the estrogen pills dispensed.

Three trained abstractors reviewed archived paper charts and the electronic medical records. Variables ascertained included: medical and family history; demographic, reproductive, and physical characteristics, including height and weight at the time of the index biopsy; bleeding patterns preceding the biopsy; ultrasound findings; age at menopause; race; parity; history of breast, colon, or ovarian cancer; diabetes; hypertension; and smoking status. Indications for hysterectomy and endometrial biopsies were recorded. Last clinical contact date (including

date of death) and if deceased, whether death was related to endometrial carcinoma, were assessed.

Analyses were performed separately for complex and atypical hyperplasia. We computed the proportion of women with each type of hyperplasia (complex; atypical) who subsequently had a diagnosis of endometrial carcinoma and/or a hysterectomy. We calculated the adjusted rates of endometrial carcinoma and hysterectomy by computing the number of events by person years at risk for "ever users versus "never users" and by duration of progestin use (< 56 days, ≥ 56 days). Absolute risk differences were calculated. Time to event was estimated using Kaplan Meier survival functions. We computed adjusted Cox proportional hazard ratios with progestin exposure as a time-dependent variable. The time between index and censoring was divided into 6 month periods. Only cohort members who had been followed for one year or more were included in the analyses using time-dependent variables.

We considered and evaluated confounding factors and adjusted for variables that influenced the risk estimates associated with progestin dispensing by more than 10%, specifically, age (<50, ≥50 years) and body mass index (BMI) (<30, ≥ 30 kg/m^2). Analyses were performed using STATA 9.2 (STATA Corporation, College Station, Texas). All reported p-values are 2-sided.

Results

A total of 2030 potentially eligible women, ages 18-88 years, (1544 complex; 486 atypia) were identified from the automated pathology database (Figure 1). Of these, 315 were ineligible (204 complex; 111 atypia) and an additional 272 women (139 complex; 133 atypia) were excluded; 74 had a diagnosis of endometrial carcinoma within 8 weeks of index diagnosis (6 complex, 68 atypia) and 67 took unopposed estrogen during the study period (59 complex, 8 atypia). The remaining 1443 women (1201 complex, 242 atypia) were followed for a median of 5.3 years (range 8 weeks - 20.8 years).

Cohort characteristics (Table 1) did not differ by progestin exposure (ever versus never) with the exception that those women dispensed progestin were more likely to have been dispensed ET or EPT in the 6 months prior to index diagnosis. During follow-up, 42% (45% complex; 25% atypia) were dispensed EPT for at least one 6 month period and 24% (25% complex; 15% atypia) were dispensed EPT during at least 50% of their follow-up period. Among women dispensed EPT or PT, 80% used medroxyprogesterone acetate (>80% of the time), 11.5% used megesterol acetate (> 80% of the time), and 8.5% used other progestins or combinations of progestins such that there was no predominant type used.

Among women with complex and atypical hyperplasia, the rate of hysterectomy in progestin users was less than that in non-users; 23.3 and 61.4 per 1,000 woman-years, respectively (vs. without progestin, 55.1 and 297.3) (Table 2). Adjusted relative rates associated with the use of a progestin were aIRR = 0.47 (95%CI 0.33-0.67) for complex and aIRR =0.23 (95% CI 0.16-0.34) for atypical hyperplasia. Absolute rate differences between progestin users and non-users were 7.2 and 80.9 per 1,000 women years for women with complex and atypical hyperplasia, respectively. Adjusted relative rates associated with the use of a progestin were aIRR = 0.35 (95% CI 0.16-0.78) for complex and aIRR = 0.23 (95% CI 0.12-0.44) for atypical hyperplasia.

Among women with complex and atypical hyperplasia, the rate of hysterectomy in progestin users was less than that in non-users; aIRR = 0.47 (95%CI 0.33-0.67) and aIRR =0.23 (95% CI 0.16-0.34), respectively.

There were 1159 women remaining in the cohort after 1 year (Figure 2). There were too few women with atypical hyperplasia (n=150) to assess the impact of duration or recency of progestin use on risk for endometrial carcinoma or hysterectomy among women who remained in the cohort at 1 year. However, among the 1009 women with complex hyperplasia who remained in the cohort at 1 year, the risk of endometrial carcinoma was decreased among women who used progestin ≥ 56 days, RR = 0.29 (95% CI 0.12-0.68) [data not shown], and among recent users, HR = 0.42 (95% CI 0.18-1.01) [data not shown]. The incidence of hysterectomy was not decreased among women with complex hyperplasia who used progestin who remained in the cohort at 1 year, either for ≥ 56 days, RR = 0.66 (95% CI 0.37-1.14) or among recent users, HR = 1.08 (95% CI 0.74-1.58) [data not shown].

A total of 71 women were diagnosed with endometrial carcinoma (35 complex, 36 atypia) during follow-up (Figure 2, Table 3) and 30 of these were diagnosed in the first year (8 complex, 22 atypia). Median interval between index biopsy and carcinoma diagnosis was 1.3 years (range 8 weeks – 11.6 years). Of the women who developed carcinoma, 49 (67.1%) had at least 14 days of progestin treatment. Median time to diagnosis of endometrial carcinoma among women diagnosed 1 year after index diagnosis of endometrial hyperplasia was longer for women with complex (5.1, range 1.1 – 11.6 years) than for women with atypical hyperplasia (2.5, range 1.01 – 7.9 years).

There were 131 deaths during follow up including 11 in women with endometrial carcinoma. Of these 11 women, 4 died with documented complications related to endometrial carcinoma; 2 had stage 1 grade 2 endometrial carcinoma, one of whom was considered too high risk for surgery due to multiple comorbidities; 2 had either a type 2 endometrial carcinoma (serous carcinoma) or a poorly differentiated adenocarcinoma (both with normal BMI). Of the 4 women who died from their disease, 2 had a family history of breast or endometrial carcinoma.

Discussion

In this cohort study, among women who did not have a diagnosis of carcinoma and/or hysterectomy within 8 weeks of hyperplasia diagnosis, 2.9% of women with complex hyperplasia and 14.9% of women with atypical hyperplasia were subsequently diagnosed with endometrial carcinoma during a median follow-up of 5.5 years. Of the 71 women who developed endometrial carcinoma, 30 were diagnosed between 8 weeks and one year after the endometrial hyperplasia diagnosis, suggesting they may have had concomitant carcinoma at the time of index biopsy; the majority of these cases (73.3%) had atypical endometrial hyperplasia at index. Whereas, among the remaining endometrial carcinomas diagnosed at least one year after index, the majority (65.9%) had complex hyperplasia at index. Any use of progestin decreased the risk of endometrial carcinoma by approximately 65% and 77% in women with complex or atypical hyperplasia, respectively. Four women (0.3%) died from endometrial carcinoma.

Although endometrial carcinoma is undoubtedly the most important outcome, the rates of hysterectomy in our study were considerable and thus have significant societal and economic impact. Others estimate that hysterectomy is performed in 75-80% of women with atypical hyperplasia. (21) Progestin therapy decreased the risk of hysterectomy in our study by 53% and 77% in women with complex and atypical hyperplasia, respectively. It should be noted that among those women excluded from this study, a larger proportion of women with atypia had hysterectomy within 8 weeks of index hyperplasia diagnosis (119/376, 31.7%) than women with complex hyperplasia (56/1340, 4.2%).

For women with complex hyperplasia, a low risk of progression to endometrial carcinoma supports current clinical standards for non-surgical treatment. (17) Findings from earlier

studies using the current WHO classification scheme for endometrial hyperplasia (4) also support this management strategy for complex hyperplasia. (1;7;22-25) However, only one of these studies compared women with complex hyperplasia treated with progestin to those untreated, and women were followed for only a median of 4.8 months. (22) Among 208 women with complex hyperplasia treated with progestin for 3-5 months, 2 (1%) were diagnosed with endometrial carcinoma, whereas 6 (3.3%) out of 182 not treated with progestin developed endometrial carcinoma.

More controversial is whether clinicians should use non–surgical approaches to treat women with atypical endometrial hyperplasia. Currently, in the United States, hysterectomy is commonly recommended for atypical hyperplasia rather than a trial of hormonal therapy, due to concern for development of carcinoma or concurrent carcinoma (13;16) although many clinicians do treat and follow women who desire fertility conservation. There are no other studies with substantial numbers of women with atypical hyperplasia treated with progestin versus untreated to comment on endometrial cancer risk. Our data suggest that among women who did not have a hysterectomy and/or a diagnosis of endometrial carcinoma within 8 weeks of their atypical hyperplasia diagnosis, the risk of endometrial carcinoma in women treated with progestin was 4-5 fold lower than in women not treated with progestin. The majority of these women were diagnosed with carcinoma in the year following their atypical hyperplasia diagnosis and none of those women died from complications related to their disease. Therefore, our data suggest that with close follow-up, progestin therapy may be safely used to treat atypical endometrial hyperplasia in select patients.

Of concern to patients and clinicians is a concomitant endometrial carcinoma at the time of diagnosis of atypical endometrial hyperplasia. Of women who had a hysterectomy performed within 12 weeks of atypical endometrial hyperplasia diagnosis with no intervening therapy, up to 46% had concomitant endometrial carcinoma. (14;21;26-32) A second related concern is the reliability of the pathologist's diagnosis of atypical hyperplasia versus well-differentiated carcinoma. (3;14;15;33-36) In studies by Kurman (1) and others, (3) the presence of cytologic atypia has been associated with the highest risk of developing carcinoma; hence the current WHO terminology divides endometrial hyperplasia into typical (simple and complex hyperplasia) and atypical hyperplasia. (4) Regrettably, others have shown that the diagnosis of atypical hyperplasia is one of the least reproducible in the current WHO scheme. (14;15; 33-36)

More important than diagnostic accuracy may be the ability to predict therapeutic response to progestin therapy. Multiple studies have assessed progestin treatment of atypical hyperplasia and well-differentiated endometrial carcinoma. (9-12) A literature review of women diagnosed with endometrial carcinoma showed an overall histologic response of 76% in 81 patients at a median time of 12 weeks; 15 of the women who had an initial response (24%) recurred at a median of 19 months. No patients died of their disease. (10)

There are limitations to our study. We were unable to control for unmeasured factors related to whether a patient and her physician opted for progestin therapy and those related to the incidence of carcinoma or hysterectomy. In addition, the study was designed to only include those women who did not undergo hysterectomy or have a diagnosis of endometrial carcinoma within 8 weeks of their endometrial hyperplasia diagnosis. The challenges with standardization of diagnostics in endometrial tissues are well established. (33) We could not control for the method of endometrial sampling. The number of women included in our study limited our ability to fully assess the possible impact of progestin duration, dose and type on the likelihood of progression to endometrial carcinoma, particularly for women with atypical hyperplasia. Finally, we were unable to assess compliance and a central pathology review was not utilized for these analyses.

Several study strengths bear mentioning. Few studies have compared risks of endometrial carcinoma among women treated and untreated with progestin and the number of women in our cohort is much greater than has been previously studied. The pharmacy data has been shown to be reliable at our institution (20) and the methods used for case and outcome identification were rigorous. (19) We had extensive data on multiple potential covariates and controlled for age, BMI, ET use during the study, and prior HT exposure.

In summary, the decision whether or not to attempt hormonal therapy with progestins or to proceed immediately to hysterectomy is influenced by the perceived risk of progression to invasive carcinoma that each histology-based diagnosis carries. Our work would suggest that among women with a diagnosis of complex or atypical hyperplasia who do not choose immediate hysterectomy, a 3-month trial of progestin with strict surveillance for recurrence is relatively safe with regard to risk of endometrial carcinoma. This strategy does not completely negate endometrial carcinoma risk. Whether women with endometrial hyperplasia need continued ongoing progestin therapy for a number of years remains unanswered.

PRECIS

Endometrial carcinoma risk is diminished 3- to 5-fold in women diagnosed with complex or atypical endometrial hyperplasia and prescribed progestin; hysterectomy risk is also decreased.

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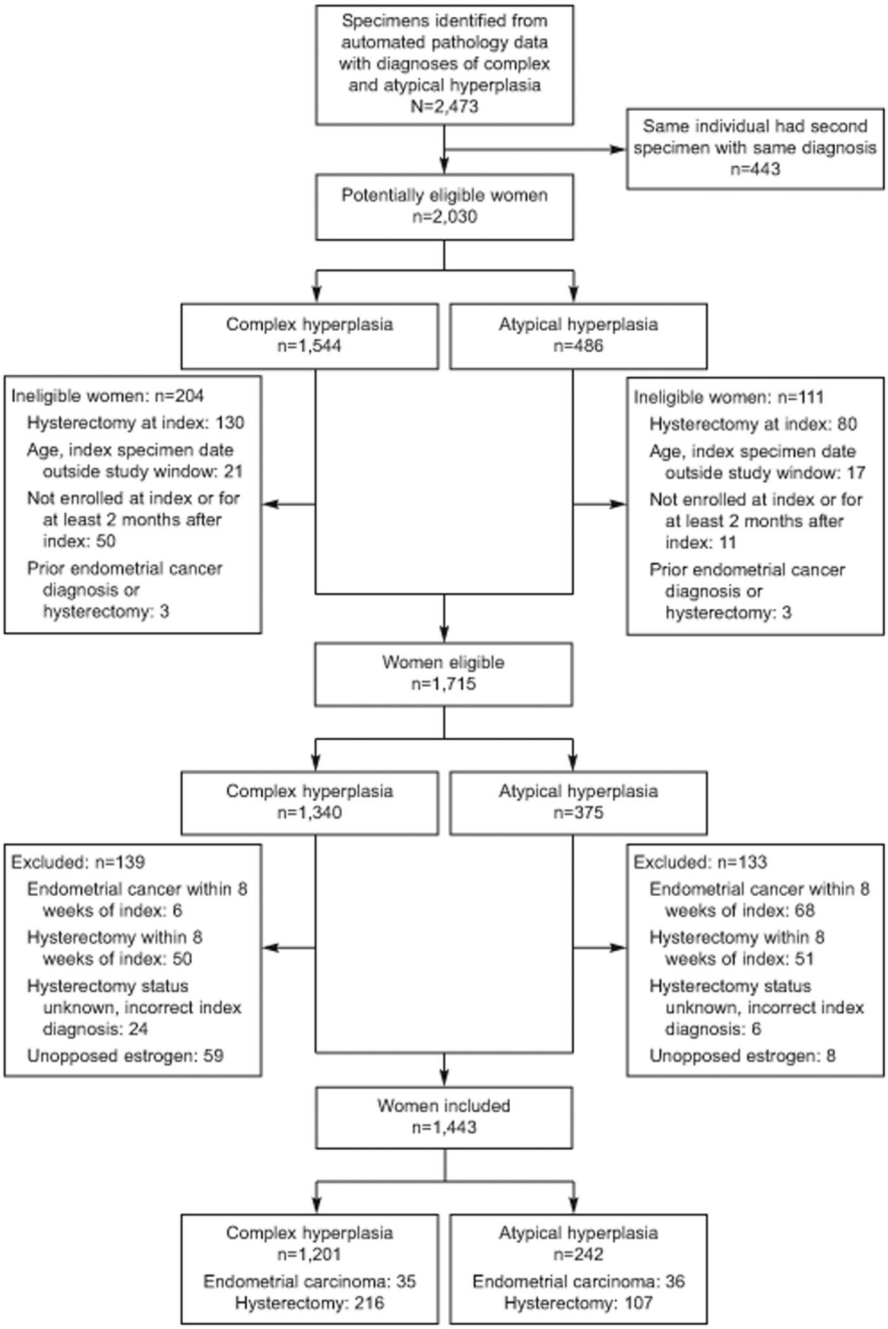

Figure 1.

Study design – ineligibility and exclusions. Numbers of women ineligible and excluded are mutually exclusive and were determined in the order shown. “Unopposed estrogen” use was defined as at least 6 months of unopposed estrogen or combined estrogen and progestin use where progestin was used less than 1/3 of the time. Women using unopposed estrogen prior to index date were not excluded.

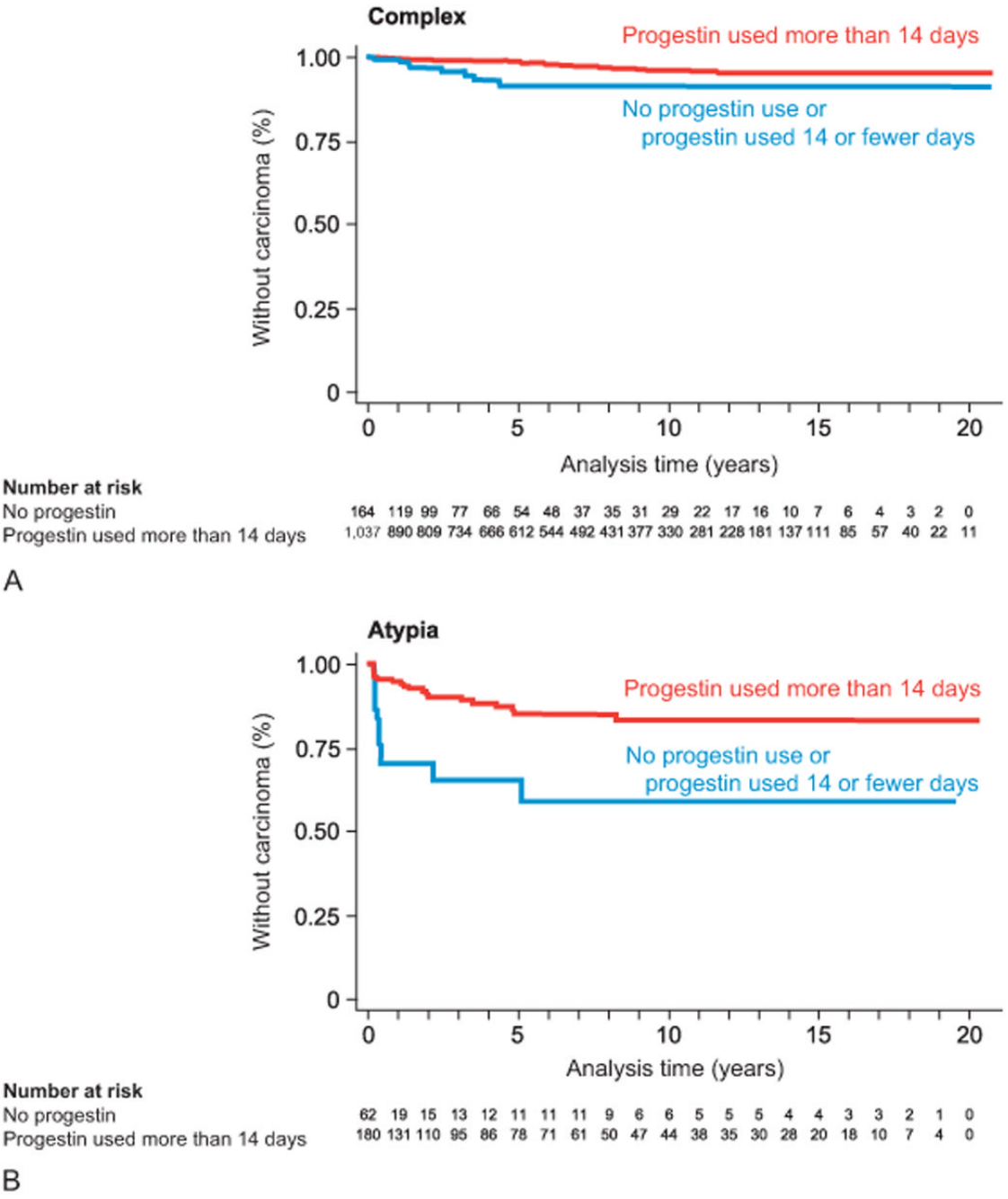

Figure 2.

Time from index diagnosis of complex (A) and atypical (B) hyperplasia to endometrial carcinoma diagnosis, by progestin exposure. Women who were diagnosed with endometrial carcinoma within 8 weeks of index endometrial hyperplasia diagnosis were excluded (6 complex, 68 atypia).

Table 1

Baseline characteristics of 1443 women with complex hyperplasia with and without atypia by progestin exposure during the study

	Complex N=1201		Atypia N=242	
	No Progestin N=164	**Progestin > 14d N=1037**	**No Progestin N=62**	**Progestin > 14d N=180**
Age (years)				
<39	17(10.4)	79(7.6)	4(6.5)	13(7.2)
40-49	50(30.5)	314(30.3)	16(25.8)	35(19.4)
50-59	59(36.0)	415(40.0)	16(25.8)	64(35.6)
60-69	23(14.0)	145(14.0)	15(24.2)	43(23.9)
≥70	15(9.1)	84(8.1)	11(17.7)	25(13.9)
Caucasian[1]	128(82.1)	907(89.3)	55(90.2)	156(90.2)
Diabetes[1]	13(8.3)	82(8.1)	6(9.8)	21(12.1)
Breast/Colon Cancer[1]	15(9.1)	23(2.2)	3(4.8)	13(7.2)
Current Smoker[1]	12(8.3)	117(12.1)	9(15.5)	21(12.6)
BMI (kg/m2)[1]				
<25	42(27.5)	329(33.1)	19(31.2)	56(32.2)
25 – 29.9	32(20.9)	260(26.2)	14(23.0)	39(22.4)
≥30	79(51.6)	404(40.7)	28(45.8)	79(45.4)
Nulliparous[1]	32(20.5)	158(15.6)	13(21.3)	32(18.5)
Oral contraceptive[2]	4(2.4)	13(1.3)	1(1.6)	1(0.6)
Estrogen + Progestin[2,3]	0(0)	165(15.9)	4(6.5)	24(13.3)
Unopposed Estrogen[2,4]	6(3.7)	143(13.8)	7(11.3)	28(15.6)
Progestin only[2]	0(0)	11(1.1)	0(0)	4(2.2)
Index biopsy year				
1985 – 1989	32(19.5)	233(22.5)	19(30.7)	56(31.1)
1990 – 1994	37(22.6)	364(35.1)	14(22.6)	52(28.9)
1995 – 1999	46(28.0)	291(28.0)	19(30.7)	42(23.3)
2000 – 2005	49(29.9)	149(14.4)	10(16.1)	30(16.7)

[1] Missing data. d = days. BMI = body mass index.

[2] Dispensed for at least 2 months in the 6 months preceding diagnosis of endometrial hyperplasia.

[3] Estrogen + progestin = postmenopausal hormone therapy (the progestin was dispensed for at least 1/3 of the time that the estrogen was dispensed).

[4] Unopposed Estrogen = postmenopausal hormone therapy (estrogen alone or estrogen plus progestin where progestin was dispensed less than 1/3 of the time that estrogen was dispensed).

Table 2

Incidence rate ratios for endometrial cancer and hysterectomy among women diagnosed with complex and atypical hyperplasia

		CARCINOMA			HYSTERECTOMY		
Progestin Exposure	**Person years**	**Cases**	**Rate[1]**	**aIRR (95%CI)[2]**	**Cases**	**Rate[1]**	**aIRR (95%CI)[2]**
COMPLEX							
None	744	8	10.75	1.0	41	55.11	1.0
P >14 d	7524	27	3.59	0.35(.16-.78)	175	23.26	0.47 (.33-.67)
P 15-56d	530	3	5.66	0.39 (.08-2.02)	32	60.38	1.13 (.70-1.82)
P >56 d	6994	24	3.43	0.35 (.16-.77)	143	20.45	0.42(.29-.60)
Total	8268	35	4.23		216	26.12	
ATYPIA							
None	148	15	101.35	1.0	44	297.30	1.0
P >14 d	1026	21	20.47	0.23 (.12-.44)	63	61.40	0.23 (.16-.34)
P 15-56d	68	9	132.35	1.61(.71-3.64)	18	264.71	0.98 (.58-1.66)
P >56 d	958	12	12.53	0.15(.07-.31)	45	46.97	0.19 (.12-.28)
Total	1174	36	30.66		107	91.14	

[1] Per 1000 person years

[2] Adjusted for age (<50, 50+ years) and body mass index (<30, 30+ kilograms per meter squared)

aIRR = adjusted Incidence Rate Ratio

CI = Confidence Interval

P = Progestin

d = days

Table 3

Incidence of endometrial carcinoma (stage, grade and type), by time since diagnosis and type of hyperplasia

	Outcome >8 weeks < 1 yr n=1443		Outcome ≥ 1 yr n=1159	
	Complex N=1201	**Atypia N=242**	**Complex N=1009**	**Atypia N= 150**
Type 1 (endometrioid)				
St 1Gr 1	3	8	5	2
St 1 Gr 2	2	6	10 ††	7
St 1 Gr 3	1	1	2	4
St 1 unk Gr	1	4	4	0
St 2 Gr 1	0	1	0	0
St 2 Gr 2	0	0	2	0
St 2 Gr 3	0	0	2 †	0
St unk Gr2	0	0	2	0
Type 2 (papillary serous)				
St 1	1	2	0	0
St 4	0	0	0	1 †
Total Endometrial carcinomas	**8**	**22**	**27**	**14**

* 6 women with an index diagnosis of complex and 68 women with an index diagnosis of atypical hyperplasia with subsequent diagnosis of endometrial carcinoma between index date and 8 weeks were excluded from the analyses.

† Death from endometrial carcinoma.