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Extent of Atypical Hyperplasia Stratifies Breast Cancer Risk in Two Independent Cohorts of Women

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Abstract

Background—Women with atypical hyperplasia (AH) on breast biopsy have a substantially increased risk of breast cancer (BC). Here we report BC risk with AH extent and subtype in two separate cohorts.

Methods—All samples containing AH were included from two cohorts of benign breast disease, Mayo Clinic and Nashville. Histology review quantified the number of foci of atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH). BC risk was stratified for number of AH foci within AH subtypes.

Results—The study included 708 Mayo and 466 Nashville AH subjects. In the Mayo Cohort, increasing foci of AH was associated with a significant increase in risk of BC, both for ADH (RR's of 2.61, 5.21, and 6.36 for 1, 2, and 3+ foci, $p=0.006$ for linear trend) and for ALH (RR's of 2.56, 3.50, and 6.79 for 1, 2, and 3+ foci, $p=0.001$ for linear trend). In the Nashville Cohort, RR's of BC for ADH were 2.70, 5.17, and 15.06 for 1, 2, and 3+ foci respectively ($p<0.001$ for linear trend); for ALH, RR's also increased but not significantly (2.61, 3.48, and 4.02, $p=0.148$). Combining both Mayo and Nashville samples, risk increased significantly for 1, 2, and 3+ foci: RR's of 2.65, 5.19, and 8.94 for ADH ($p<0.001$), and 2.58, 3.49, and 4.97 for ALH ($p=0.001$).

Conclusions—In two independent cohort studies of benign breast disease, extent of atypia stratifies long-term breast cancer risk for ADH and ALH.

Keywords

breast cancer; risk; atypical hyperplasia; atypical ductal hyperplasia; atypical lobular hyperplasia

Introduction

Women with atypical hyperplasia (AH) have been recognized since 1985 as a group at increased risk of breast cancer (BC), after the seminal report by Dupont and Page.¹ Subsequent independent studies have confirmed that as a group, women with AH have an approximate four-fold increase in BC risk,^{2–4} and recent reports with long-term follow-up demonstrate that absolute risk of BC is in the range of 1–2% per year.^{5, 6} Several prevention medications can reduce BC risk in women with AH, but they are underutilized due to concerns of side effects and also the lack of ability to predict an individual woman's risk, which is a critical element in decision-making.

Unfortunately, standard BC risk prediction tools do not perform well when estimating risk for individual women with AH. Two commonly used models in these women are the BC Risk Assessment Tool (BCRAT) and the IBIS (Tyrer-Cuzick) model; neither model performs better than chance alone for women with AH, as evidenced by c-statistics of 0.50 and 0.54 respectively.^{7, 8} In 2007, we reported a novel histologic feature that offers improved risk stratification in women with AH- namely, the number of foci of AH present within the benign biopsy tissue.⁹ In 331 women with AH from the Mayo Clinic Benign Breast Disease Cohort in that 2007 report, BC risk increased in a stepwise fashion for women with one, two, and three or more foci of AH. Recently we confirmed this finding in our expanded cohort.⁶ The goals of the current study were: 1) to investigate if the number of foci of atypia validates as a risk stratification feature in an independent group of women with AH, and 2) to determine if this association is present for both histologic phenotypes of AH [atypical ductal hyperplasia (ADH), and atypical lobular hyperplasia (ALH)]. To meet these goals we collaborated with the Nashville Breast Cohort of benign breast disease.

Materials and Methods

Mayo BBD Cohort

The Mayo Clinic Benign Breast Disease study has been described previously^{3, 9} and currently comprises 13,538 women ages 18 to 85 who underwent a benign breast biopsy between 1967 and 2001 at Mayo Clinic in Rochester, MN. Follow-up for BC events (including both invasive cancer and DCIS) and risk factor information were identified from medical records and questionnaires and was available for 91.4% of women who met study inclusion criteria.³

Nashville Breast Cohort

The Nashville benign breast disease study has also been described previously^{1, 10–12} and comprises 12,702 women ages 20 to 91 who underwent a benign breast biopsy at Vanderbilt, St. Thomas or Baptist hospitals in Nashville, Tennessee between 1950 and 1991. Follow-up was obtained for 87% of women meeting entry criteria. BC diagnoses were confirmed by review of histologic slides or medical records. The median length of follow-up was 20 years. Tissue specimens for all women were reviewed for histologic features, and all samples with AH were included in this study.

Histologic Examination

The study breast pathologist (DWV) performed histologic review of archived hematoxylin-and-eosin (H&E) slides from the benign biopsies of all women in the Mayo BBD cohort, and for AH biopsies in the Nashville Breast Cohort to confirm the diagnosis. A diagnosis of atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia (ALH) was based on the criteria of Page et al.^{10, 13}

For each sample with AH, the number of separate foci of ADH and ALH were recorded, and the number of slides evaluated per subject. Separate foci of AH were defined as involving separate terminal duct lobular units with clear separation by mammary stroma between lobules.

Statistical Methods

Data were summarized using frequencies and percents for categorical variables, and medians and ranges for continuous variables. Associations of number of atypical foci with demographic and clinical variables were assessed using chi-square tests of significance or Kruskal-Wallis tests as appropriate. We calculated standardized incidence ratios (SIRs), overall and within subgroups defined by number of atypical foci and type of AH, by dividing the observed numbers of incident BCs by the population-based expected counts. We used cumulative incidence curves to visually display BC risk by type and extent of AH, accounting for death as a competing risk. To reduce the possibility of including women with subclinical BC at benign biopsy, the first six months post-biopsy were excluded from person-years of observation. More details can be found in the supplementary material.

Results

Characteristics of study population

A total of 1174 women with pathologically confirmed AH (708 from the Mayo cohort and 466 from the Nashville cohort) were included in the study. The mean number of slides reviewed per subject was 4.1 in the Mayo cohort and 5.6 in the Nashville cohort ($p < 0.001$); medians were 3.0 in both cohorts, range 1–48 (Mayo) and 1–51 (Nashville). Cohort-specific distributions of demographic and clinical variables are presented in Table 1. Overall, the clinical and histologic characteristics were similar for women in the two cohorts, with a few caveats. Compared to the Nashville cohort, the Mayo cohort is more recent, with slightly older subjects, some core needle biopsies, a higher proportion of ADH, and a lower proportion multiple foci.

Associations between number of foci of AH and demographic and clinical characteristics (Table 2)

The number of foci of AH was not associated with age at biopsy in either cohort. In both cohorts, duration of follow-up was shorter in women with more than one focus of AH compared to women with just one focus, but this difference disappeared when stratifying by BC status ($p > 0.05$ for each). An association was observed between the number of AH foci and more recent year of biopsy in the Nashville cohort, but not in the Mayo cohort. Number of foci was not significantly associated with biopsy type. In both cohorts women with ALH were more likely to have 3+ foci compared to women with ADH.

Association of number of foci and BC risk

In the Mayo cohort, 143 BC's were observed over a median follow-up of 13.5 years: 11 in women with synchronous ADH and ALH at initial biopsy and 132 in women with ADH only or ALH only. Including all women with AH (ADH, ALH, or both), we observed a strong dose-response association between number of foci of AH and BC risk, similar to that reported previously:⁹ SIR=2.86 (95% CI 2.20–3.66) for 1 focus; 5.15 (95% CI 3.77–6.87) for 2 foci; 5.88 (95% CI 4.07–8.21) for 3+ foci (test for heterogeneity in SIRs < 0.001). Analyzing the women who had only ADH or only ALH (excluding the 7% who had both), the number of foci of AH remained significantly associated with BC risk for both subtypes

of AH. For ADH, SIRs were 2.61, 5.21 and 6.36 for women with 1, 2 and 3+ foci respectively ($p=0.006$), and for ALH SIRs were 2.56, 3.50 and 6.79 ($p=0.001$), Table 3.

In the Nashville cohort, a total of 115 BC events were observed (12 in women with synchronous ADH and ALH and 103 in women with ADH only or ALH only) over a median follow-up of 17.0 years. As with the Mayo cohort, we observed a dose-response association between number of foci and risk of BC including all women with AH: SIR=2.66 (95% CI 1.95–3.55) for 1 focus; 4.28 (95% CI 2.89–6.11) for 2 foci; 4.80 (95% CI 3.42–6.57) for 3+ foci (test for heterogeneity in SIRs=0.005). This association was especially strong in the ADH subgroup (SIRs=2.70, 5.17 and 15.06 for women with 1, 2 and 3+ foci respectively, $p<0.001$, Table 3). Although still trending in the same direction, the dose-response association within the Nashville ALH group failed to reach statistical significance (SIRs 2.61, 3.48, 4.02, $p=0.148$).

Combining women in the two cohorts, BC risk was significantly higher with increasing number of foci of AH, with SIR of 8.94 (95% CI 5.48–14.59) for women with 3+ foci of ADH, and SIR of 4.97 (95% CI 3.74–6.62) for women with 3+ foci of ALH (Table 3). Sensitivity analyses subsetting to only invasive BC events (i.e. excluding cases of DCIS) yielded similar results (Supplemental Table 1). Risk did not differ by biopsy type (Supplemental Table 2).

Cumulative incidence plots for the combined Mayo and Vanderbilt groups, by strata of AH subtype and number of foci of AH, are provided in Figure 1.

DISCUSSION

In this study, we report results from two different cohorts on the long-term BC risk associated with increasing extent of AH. To our knowledge, there are no other similar size cohorts of women with AH with central pathology review. We found that in both the Mayo and Nashville cohorts that the risk of BC increases with increasing number of foci of AH found at the time of benign biopsy. Furthermore, the risk stratification associated with extent of AH is present in both ADH and ALH subtypes. These findings are relevant for the clinical management of women diagnosed with AH (approximately 100,000 in the United States every year).

Clinical trials of several prevention medications have proven effective for reducing BC risk, with ~50% reduction in BC risk across most high risk women,^{14–16} and even greater benefit (~70% risk reduction) in women with AH.^{14–17} Despite these proven benefits, uptake has generally remained low,^{18, 19} often due to concerns regarding side effects.²⁰ Our hope is that providing more accurate risk estimates will help to increase utilization of proven prevention medications in women at high risk who are in a position to benefit from them. Unfortunately, accurate risk estimation for women with AH has been elusive and is the main reason that risk stratification for AH is clinically important.

In 2007, we reported the association of number of foci of AH and long-term BC risk in a group of 331 women. Relative risk of BC was noted to be 3.9 for all women with AH, and was similar for both subtypes of AH: 3.8 for ADH and 3.7 for ALH. A notable finding was

that the number of foci of AH significantly stratified long-term risk: relative risks were 2.3, 5.3, and 8.0 for women with 1, 2, and 3 or more foci of AH, respectively.⁹ This finding was important because it provided a major step towards the possibility of personalizing the clinical management of women with AH. In 2015, data on an expanded cohort of 698 women with AH confirmed the risk-stratifying effect of the number of foci of AH, with relative risks of 3.2, 5.5, and 7.6 for 1, 2, and 3+ foci.⁶ In addition, figures summarizing the cumulative incidence of BC in women based upon extent of AH provided important estimates of absolute risk, showing 25 year risk of 30% for the group as a whole, but significantly higher risk (47%) in the minority of women with multiple foci of AH. Furthermore, risk was fairly constant over time, with averaged annual risks of ~1%, ~1.5%, and ~2% for increasing number of foci of AH. Although these risk estimates may seem high, in fact they are lower than risk estimates seen in an electronically-derived independent cohort. Coopey et al reported on a retrospective cohort of 2938 women with high risk lesions (ADH, ALH, LCIS, and severe ADH) based upon electronic search of pathology reports within the Partners Healthcare System from 1987–2010.²¹ They evaluated BC events (DCIS or invasive) and estimated BC risk at 10 years for each entity: risk at 10 years was 17% for women with ADH, 21% for ALH, 24% for LCIS, and 26% for women with severe ADH.²¹ In this dataset, Kaplan-Meier plots showed a similar rate of BC events beyond 10 years, corroborating the persistent increased long-term risk observed in the Mayo and Nashville cohorts for women with AH.

The current study deepens our understanding of the natural history of AH by defining how the extent of AH stratifies risk within subtypes of ADH and ALH. In the Mayo Cohort, the number of foci of AH was significantly associated with BC risk and had similar stepwise increases for separate subgroups of ADH and ALH. In the Nashville cohort, increasing number of foci of ADH and ALH showed increasing BC risk, although significant only in the ADH subgroup. In a recent case-control study from the Nurses' Health Study (124 cases and 192 controls, nested within women diagnosed with AH), the observed BC risk increased with increasing number of foci of any type of AH although this trend did not reach statistical significance.²² Risk was not increased for women with multifocal ADH; in women with ALH, relative risk was 8.0 for those with 3+ foci (but again not statistically significant compared to women with 1 or 2 foci of ALH). They concluded that any apparent association of atypia extent and risk is driven by the greater risk observed in ALH. Interestingly, this contrasts with the Mayo cohort findings where the effect is significant for both ADH and ALH, as well as with the Nashville cohort findings, where the association was strongest in ADH.

Although the findings of Collins et al. and those of the Mayo and Nashville studies are discordant, it is plausible that these discrepancies are due to limited statistical power in the smaller Nurses' Health Study study, or due to different designs. Variability may also exist in how the number of foci were identified. These factors may also contribute to the finding that the proportion of women with 3+ foci in the NHS study (43%) was substantially higher than that observed in the Mayo (17%) and Nashville (27%) cohorts. Collins et al suggest that the Mayo cohort has a smaller proportion of women with 3+ foci due to fewer slides (a surrogate of less tissue) reviewed per subject. This is one possible explanation; another is that more cases of unifocal AH may have been detected in the Mayo cohort by systematic

re-review of all benign biopsies by a single pathologist. Although the volume of tissue removed may impact the number of foci of AH identified (especially ALH which is known to be multifocal and multicentric), we observed similar breast cancer risk in women with core biopsies compared to excisional biopsies, suggesting that the number of foci of AH is a fairly robust risk indicator despite some variation in tissue sample size, and that this finding is valid when obtained from a breast biopsy within usual clinical practice. Moreover, if fewer cases of multifocal atypia were detected in the Mayo cohort due to fewer slides/less tissue evaluated, that would tend to bias results toward the null hypothesis; despite that fact we still detect a significant association with risk among the women with 3+ foci. In addition, the general agreement between the Mayo and Nashville results regarding extent of atypia and BC risk increases the likelihood that our findings are valid.

It is plausible that more extensive AH correlates with a greater degree of long-term BC risk. Previous studies have shown that AH reflects increased constitutional BC predisposition across the entire field of breast tissue, as demonstrated by elevated risk for subsequent BC in both breasts (albeit an ipsilateral predominance) in women with AH.^{5, 10, 11} Some cases of AH, however, likely represent direct precursors, since about 60% of patients develop cancer on the same side as their AH (both for ADH and ALH),^{5, 11} and AH is often observed in the tissues adjacent to breast carcinomas. In addition, gene expression profiling of adjacent AH, DCIS, and invasive cancer shows that alterations in the invasive tumors are to a large degree present in the preinvasive disease.²³ AH multifocality would logically be present in patients with a greater degree or more penetrant field effect cancerization as well as in patients with more advanced localized degree of premalignant changes. Either scenario would be associated with a tendency for greater generation and growth of abnormal cell populations. The clinically occult nature of AH (whereby it is detectable only with tissue biopsy) limits our ability to explore these relationships in BC. However, a relationship between increased burden of premalignant disease and subsequent cancer diagnosis is well described for other tumor systems (eg colorectal neoplasia).²⁴

There are several notable strengths of this study. The Mayo and Nashville cohorts include sizable numbers of women with AH, with excellent and systematic long-term follow-up on BC events. A major strength in the study is the fact that findings were similar in these independently developed cohorts of women from two different geographic areas. All specimens were reviewed histologically by the same breast pathologist who was blinded to later cancer outcomes, so there was consistency in interpretation of the number of foci present within the biopsy tissues. Reproducibility of this measure across pathologists will be important for clinical practice. In our initial report demonstrating increased risk with greater foci of AH, multifocality was agreed upon by two study pathologists.⁹ To confirm the reliability of pathologists to assess this feature independently, a separate study is underway to evaluate pathologists' concordance in determining the number of foci of AH in breast biopsies.

Conclusions

In summary, the critical findings of this report are that the association of number of foci of AH and long-term BC risk 1) is validated in the Nashville cohort, and 2) applies to both

ADH and ALH subgroups. The similarities of results in the Mayo and Nashville cohorts further underscores the strength of the findings. We believe that this information will be helpful in estimating BC risk for women with atypical hyperplasia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Cumulative incidence of BC (both invasive cancer and DCIS) in women with atypical hyperplasia, by type and extent of AH. Results are based on the combined Mayo and Nashville cohorts. Extent of AH is defined by number of atypical foci (1, 2 or 3+). Expected cumulative incidence curves, calculated by applying age- and year-stratified person-years of follow-up to the appropriate population-based incidence rates (Iowa SEER for the Mayo cohort and Atlanta SEER for the Nashville cohort), are provided for comparison.

Table 1

Clinical and histologic characteristics among women with atypical hyperplasia in the Mayo and Nashville Cohorts.

	Mayo (N=708)	Nashville (N=466)	Total (N=1174)
Characteristic	N (%)	N (%)	N (%)
Vital Status			
Alive	522 (73.7)	367 (78.8)	889 (75.7)
Deceased	186 (26.3)	99 (21.2)	285 (24.3)
Breast Cancer Status			
Unaffected	565 (79.8)	351 (75.3)	916 (78.0)
Any Invasive BC	115 (16.2)	94 (20.2)	209 (17.8)
DCIS only	22 (3.1)	21 (4.5)	43 (3.7)
BC- Type Unknown	6 (0.8)	–	6 (0.5)
Year of Biopsy			
< 1967	–	188 (40.3)	188 (16.0)
1967–1981	106 (15.0)	177 (38.0)	283 (24.1)
1982–1991	237 (33.5)	101 (21.7)	338 (28.8)
1992–2001	365 (51.6)	–	365 (31.1)
Age at Atypia Biopsy			
N	708	466	1174
Median	56.0	48.0	52.0
Q1, Q3	48.0, 67.0	44.0, 55.0	46.0, 64.0
Range	(25.0–84.0)	(19.0–85.0)	(19.0–85.0)
Age at Atypia Biopsy			
<45	94 (13.3)	142 (30.5)	236 (20.1)
45–55	241 (34.0)	208 (44.6)	449 (38.2)
55+	373 (52.7)	116 (24.9)	489 (41.7)
Duration of Follow-up (years)			
N	708	466	1174
Median	13.5	17.0	14.2
Q1, Q3	8.4, 17.9	8.8, 28.8	8.6, 20.7
Range	(0.5–39.8)	(1.0–43.9)	(0.5–43.9)
Type of Atypia			
ADH only	324 (45.8)	176 (37.8)	500 (42.6)
ALH only	340 (48.0)	254 (54.5)	594 (50.6)
ADH and ALH	44 (6.2)	36 (7.7)	80 (6.8)
Type of Biopsy			
Excisional	558 (78.8)	466 (100.0)	1024 (87.2)
Core plus excision	49 (6.9)	0	49 (4.2)
Core biopsy only	101 (14.3)	0	101 (8.6)
Number of atypical foci			

	Mayo (N=708)	Nashville (N=466)	Total (N=1174)
Characteristic	N (%)	N (%)	N (%)
1	405 (57.2)	236 (50.6)	641 (54.6)
2	184 (26.0)	104 (22.3)	288 (24.5)
3+	119 (16.8)	126 (27.0)	245 (20.9)

Table 2

Clinical and Histologic Characteristics by Number of Foci of AH.

Characteristic	Mayo Cohort			Nashville Cohort			p-value
	1 (N=405)	2 (N=184)	3+ (N=119)	1 (N=236)	2 (N=104)	3+ (N=126)	
Age of BBD							0.092 ¹
<45	57 (60.6)	22 (23.4)	15 (16.0)	82 (57.7)	32 (22.5)	28 (19.7)	
45–55	130 (53.9)	70 (29.0)	41 (17.0)	104 (50.0)	46 (22.1)	58 (27.9)	
55+	218 (58.4)	92 (24.7)	63 (16.9)	50 (43.1)	26 (22.4)	40 (34.5)	
Year of Biopsy							0.004 ¹
< 1967	–	–	–	114 (60.6)	38 (20.2)	36 (19.1)	
1967–1981	61 (57.5)	32 (30.2)	13 (12.3)	76 (42.9)	46 (26.0)	55 (31.1)	
1982–1991	141 (59.5)	55 (23.2)	41 (17.3)	46 (45.5)	20 (19.8)	35 (34.7)	
1992–2001	203 (55.6)	97 (26.6)	65 (17.8)	–	–	–	
Duration of Follow-up (years)							0.035 ²
N	405	184	119	236	104	126	
Median	14.1	12.4	12.0	18.6	15.4	16.3	
Q1, Q3	9.2, 18.3	7.9, 17.3	7.6, 17.3	9.8, 29.8	9.2, 28.9	7.9, 24.9	
Range	(0.9–37.3)	(0.5–38.4)	(0.8–39.8)	(1.0–43.5)	(1.0–40.9)	(1.0–43.9)	
Type of Atypia							<0.001 ¹
ADH only	220 (67.9)	80 (24.7)	24 (7.4)	133 (75.6)	29 (16.5)	14 (8.0)	
ALH only	185 (54.4)	92 (27.1)	63 (18.5)	103 (40.6)	63 (24.8)	88 (34.6)	
ADH and ALH	–	12 (27.3)	32 (72.7)	–	12 (33.3)	24 (66.7)	
Type of Biopsy							NA
Excisional biopsy ³	339 (55.8)	163 (26.9)	105 (17.3)	236 (50.6)	104 (22.3)	126 (27.0)	
Core biopsy only	66 (65.3)	21 (20.8)	14 (13.9)	–	–	–	

Values presented as number (percent) unless otherwise indicated.

¹ Chi-Square test

² Kruskal Wallis test

³ includes individuals undergoing an excisional biopsy only or a core biopsy followed by an excisional biopsy.

Table 3

Breast Cancer Risk Stratified by Number of Foci of AH for Histologic Subtypes of AH

ADH					ALH			Linear trend p-value [/]
No. Women	Observed Events	Expected Events	SIR (95% CI)	Linear trend p-value [/]	No. Women	Observed Events	Expected Events	SIR (95% CI)
Mayo Cohort								
Overall	324	62	18.12	3.42 (2.62, 4.39)	340	70	19.98	3.50 (2.73, 4.43)
Number of atypical foci				0.006	0.001			
1	220	34	13.02	2.61 (1.81, 3.65)	185	29	11.32	2.56 (1.71, 3.68)
2	80	20	3.84	5.21 (3.18, 8.05)	92	19	5.42	3.50 (2.11, 5.47)
3+	24	8	1.26	6.36 (2.75, 12.53)	63	22	3.24	6.79 (4.25, 10.28)
Nashville Cohort								
Overall	176	42	11.72	3.58 (2.58, 4.85)	254	61	18.47	3.30 (2.53, 4.24)
Number of atypical foci				<.001	0.148			
1	133	26	9.64	2.70 (1.76, 3.95)	103	20	7.66	2.61 (1.59, 4.03)
2	29	8	1.55	5.17 (2.23, 10.17)	63	16	4.60	3.48 (1.99, 5.65)
3+	14	8	0.53	15.06 (6.50, 29.64)	88	25	6.21	4.02 (2.60, 5.94)
Mayo and Nashville combined								
Overall	500	104	29.84	3.49 (2.88, 4.22)	594	131	38.45	3.41 (2.87, 4.04)
Number of atypical foci				<.001	0.001			
1	353	60	22.66	2.65 (2.06, 3.41)	288	49	18.98	2.58 (1.95, 3.42)
2	109	28	5.39	5.19 (3.59, 7.52)	155	35	10.02	3.49 (2.51, 4.86)
3+	38	16	1.79	8.94 (5.48, 14.59)	151	47	9.45	4.97 (3.74, 6.62)

Standardized incidence ratios and corresponding 95% confidence intervals, comparing the observed number of BC events to those expected based on incidence rates from Iowa SEER (for the Mayo cohort) and Atlanta SEER (for the Nashville cohort) data. Analyses account for the effects of age and calendar period. To facilitate comparisons across AH subtypes, women with synchronous ADH and ALH were excluded from these analyses.

[/]Linear trend p-value for test in heterogeneity in SIRs across number of foci within AH subtype.