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HISTOLOGIC ASSOCIATIONS AND LONG-TERM CANCER RISK IN COLUMNAR CELL LESIONS OF THE BREAST: A RETROSPECTIVE COHORT AND A NESTED CASE-CONTROL STUDY

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Abstract

Introduction—Mammary columnar cell lesions with atypia have been receiving increased scrutiny in view of their association with atypical hyperplasia (AH) and carcinoma. However, the few retrospective outcome studies performed have failed to establish an increased risk for recurrence or carcinoma on long-term follow-up.

Materials and Methods—We evaluated the overall cancer risk for 1261 biopsies with columnar cell lesions (CCL), in 4569 women from the Nashville Breast Cohort who were biopsied between 1969 and 1988. Based on Schnitt and Vincent-Salomon's classification, we also classified 229 biopsies with CCL into three categories: without hyperplasia or atypia, with hyperplasia lacking atypia, and with atypia. Using a nested case-control design, we compared the risks of invasive cancer associated with these three categories.

Results—We observed a 2-to-3-fold increase in the occurrence of AH in the presence of CCL versus in their absence ($P < 0.005$). Relative risk of invasive breast cancer for women with both AH and CCL compared to those with AH alone did not differ significantly (RR=1.55, $P = 0.29$). The presence of CCL alone was associated with a mild increase in the overall cancer risk (RR=1.47; $P = 0.05$). In the nested case-control study, no significant risk difference was observed among the three categories of CCL.

Conclusion—We observed a positive association between CCL and AH. The evidence that CCL by itself significantly elevates breast cancer risk is not well supported. However, a finding of CCL on benign breast biopsy may indicate the presence of AH, a more worrisome lesion.

Keywords

Columnar cell lesion; Columnar cell atypia; flat epithelial atypia; breast cancer risk; epithelial hyperplasia

INTRODUCTION

Columnar cell lesions (CCL) and flat epithelial atypia (FEA) are relatively new designations for a well recognized group of breast lesions, that were only recently better defined by histologic and cytologic criteria.[1–3] Initially a source of controversy and disagreement, if from a purely terminological standpoint, these lesions are now a focus of concern from the more important standpoints of accurate diagnosis, classification,[4] clinical significance, and management.[1, 5–7]

First described in 1945 by Foote and Stewart [8] and later mentioned in 1979 by Azzopardi [9] as belonging to the "blunt duct adenosis" group of histologic variations, CCL has since garnered different appellations such as "columnar metaplasia",[10] "hyperplastic terminal groupings," [11] and "atypical lobules type A",[12] to name a few. The term "enlarged lobular units with columnar alteration (ELUCA)" was adopted by Page[13] in 1985 as a generic descriptive designation without reference to significance or pathogenesis. Despite the abundance of different designations pertaining to these lesions, there was general agreement regarding their marginal risk towards subsequent breast cancer.[13]

A subset of columnar cell lesions, those exhibiting mild cytologic atypia (CCA), has recently attracted additional scrutiny. This was largely due to histopathologic and molecular evidence linking them to AH, carcinoma in-situ and invasive carcinoma.[3, 14–19] The recognition of mild epithelial atypia within these lesions, originally described by Azzopardi as "clinging carcinoma, monomorphic type",[9] has also prompted many different designations by several authors, including "atypical cystic lobules",[20, 21] "cancerization of small ectatic ducts by DCIS with apocrine snouts",[22] and "columnar alteration with prominent snouts and secretions (CAPSS)".[23, 24] These descriptive terminologies have been most recently supplanted by "columnar cell change/hyperplasia with atypia" and "flat epithelial atypia".[2, 25] In the context of this study, we choose the general term CCL to encompass the full spectrum of enlarged lobular units with columnar alteration, with specific mention of columnar cell lesions lacking hyperplasia or atypia (CCC), columnar cell lesions with hyperplasia (CCH), and columnar cell lesions with atypia (CCA), where applicable, for the purposes of detailed analysis and classification.

Observational studies to elucidate the role CCL play in the pathogenesis of low-grade mammary neoplasia, have linked atypical columnar cell lesions with formal patterns of AH (atypical ductal hyperplasia and atypical lobular hyperplasia) and low-grade carcinoma, evidence supported by several careful molecular analyses.[3, 16, 18, 26] However, the few prospective outcome studies assessing the long-term risk associated with these lesions have failed to show a significant impact on subsequent cancer risk.[27–30]

The purpose and design of this study is three-tiered: (1) to assess the overall long-term cancer risk associated with the spectrum of CCL and their interaction with other markers of mild increase in cancer risk, especially usual epithelial hyperplasia lacking atypia (EHLA); (2) to assess, in a nested case control study design, the risk associated with CCH and CCA compared to CCC; and (3) to further evaluate the incidence of formal patterns of atypical hyperplasia as they relate to the presence or absence of columnar cell lesions.

MATERIALS AND METHODS

Retrospective Cohort Study

We conducted a retrospective cohort study of women from the Nashville Breast Cohort (NBC).[31–34] This cohort consists of women who underwent benign breast biopsy at one of three hospitals in Nashville, Tennessee. Successful follow-up in this cohort has been achieved for 90% of study subjects. Women with prior or concurrent invasive breast cancer were excluded from this cohort. This paper is based on a sub-cohort of the NBC whose entry biopsy occurred between 1969 and 1988 at Vanderbilt University Hospital or between 1969 and 1985 at St. Thomas Hospital, with an average follow-up of 17 years. The entry biopsy for this study was the patient's first biopsy in this interval containing breast epithelium. This biopsy had to occur before the end of the patient's follow-up. All entry biopsies in this interval were systematically evaluated for CCL without knowledge of subsequent cancer outcome.

The final number of patients evaluated for their overall cancer risk was 1261 women whose biopsies contained CCLs, out of 4569 total women from this NBC sub-cohort.

Histologic Definitions

As in Dupont and Page,[32] no proliferative disease (NPD) is defined as benign changes in the breast not involving epithelial hyperplasia, such as papillary apocrine change and fibroadenoma. Epithelial hyperplasia lacking atypia (EHLA) is defined as usual-type, moderate or florid, hyperplasia, lacking the cytologic and architectural features of AH. The CCLs chosen for evaluation correlate best with Wellings and Jensen's ALA I; they lacked more than mild usual type epithelial hyperplasia and were devoid of patterns of the specifically defined AHs. CCC represents columnar cell lesions lacking hyperplasia and atypia. CCH and CCA represent columnar cell lesions with columnar cell hyperplasia and atypia, respectively, based on the definitions by Schnitt and Vincent-Solomon.[2] Note that CCA does not meet our criteria for AH.[31]

Nested Case-Control Study

We also conducted a nested case-control study of women with CCL. Women in this study were selected from a previous study.[35] In brief, a sub-cohort member was eligible for inclusion in this earlier study[35] if her entry biopsy contained EHLA, was performed between 1965 and 1982 and blocks from this biopsy were available. Cases consisted of all eligible subjects who subsequently developed invasive breast cancer. Two controls were selected for each case, matched by age at biopsy and year of biopsy. To be selected as a control for a specific case, a patient had to be at risk of breast cancer at the time when the case patient developed breast cancer.[36] That is, her breast cancer-free follow-up had to be at least as long as that of the case under consideration. In the current study, we restricted our cases and contols to women from the earlier study[35] who had also been diagnosed with CCL on their entry biopsy. This resulted in 82 cases and 166 contols. (These patients have also been studied by McLaren et al.[37]) There were 5 cases and 8 controls who were excluded from the current study because their available slides were not felt to contain well-developed CCL following review. In our first case-control study,[35] selected controls could subsequently become cases, which in fact happened for 6 women with CCL. These women are only used as cases in the current study. Thus, the current study consists of 77 cases who developed breast cancer on follow-up and 152 distinct controls who did not.

Evaluation of CCL in the Nested Case-Control Study

In order to ensure good quality Hematoxylin and Eosin stained slides for evaluation of the individual columnar cell lesions, this study was restricted to subjects for whom a paraffin-

embedded tissue block was available. A total of 229 biopsies were examined. The cut Hematoxylin and Eosin slides were screened by FIB and then reviewed together with DLP. Both reviewers were blinded to patient follow-up data, namely subsequent development of breast carcinoma. Review produced concurrent diagnosis of about 85% with subsequent consensus resolution of the remaining non-concurrent diagnoses through consultation with JFS and MES. Since classifying columnar cell lesions using an involved scheme that includes architectural complexity might well suffer from the ill effects of high inter-observer variability, and significant overlap with ADH, we elected to adhere to Schnitt and Vincent-Salomon's initial classification, and include columnar cell lesions with or without hyperplasia and atypia.[2] The columnar cell hyperplasia (CCH) lesions were characterized by tufts of pseudostratified columnar cells without cytologic atypia. The key atypical lesions (CCA) were characterized by variably expanded lobular units, with acini lined by a single or multi-layered monomorphic population of mildly atypical cells, characteristically showing loss of polarity, apical snouts and luminal secretions and calcifications.

STATISTICAL ANALYSIS—We used proportional hazards regression analysis to assess the relative risk (RR) of invasive breast cancer associated with CCL.[38] These analyses are based on all women in the sub-cohort who did not have atypical hyperplasia in their entry biopsy. The risk for those women whose entry biopsy contained neither proliferative nor CCL is used as the reference risk (RR=1) for the purpose of risk comparison with women having other histologic findings. The analyses were adjusted for age by including the patient's age at her entry biopsy as a covariate in the regression model. Risks were calculated for all available follow-up and for the first ten years of follow-up. For the latter analysis, patients with more than 10 years of follow-up were also censored at 10 years.

The nested case-control analyses were done using logistic regression. Breast cancer odds ratios were adjusted for age at biopsy and year of biopsy.

In cross-sectional analyses of the entry biopsies of women in the sub-cohort, the association between CCL and atypical hyperplasia were assessed using a Pearson's chi-squared statistic.

RESULTS

Our results show that the risk of invasive breast cancer in women with CCL is mildly elevated relative to women with NPD (RR=1.47, 95% CI 1.0–2.15, P=0.05). This risk is slightly, but not significantly, lower during the first 10 years following CCL diagnosis (RR=1.42, 95% CI 0.87 – 2.3, P=0.16). In comparison, women with EHLA alone did not suffer a significant elevation in cancer risk compared to women with no proliferative disease (Table 1). This was also true for women during the first 10 years of follow-up.

The co-occurrence of CCL and classical AH shows a strong correlation (P<0.0005); the prevalence of atypical lobular hyperplasia (ALH) was 5.0% versus 1.9% in women with and without CCL respectively. Similarly, the prevalence of atypical ductal hyperplasia (ADH) was 3.5% versus 1.4% in women with and without CCL respectively. Table 2 shows the relative risk of AH with and without CCL in comparison to women with neither PD nor CCL. The relative risk was not significantly elevated in women with concomitant CCL and AH, compared to women with AH alone (RR=1.55, 95% CI 0.69 – 3.5; P = 0.29) (Table 2).

In the nested-case control study of women with CCL, 77 patients who subsequently developed invasive breast cancer were compared with 152 controls who did not (see Table 3). This table contrasts the breast cancer risk of women with CCL with hyperplasia (CCH), and CCL with atypia (CCA), against that of women without either hyperplasia or atypia (CCC). Results suggest that the risk for subsequent cancer may be mildly increased for CCH

compared to CCC, although this observation could have occurred by chance. There is no evidence that women with CCA are at elevated risk compared to women with CCC. Hence, there were no significant differences in breast cancer risk among women with the different categories of columnar cell lesions.

DISCUSSION

It is for good reason that columnar cell lesions have recently become a highly controversial area in breast pathology. Over the past few years there has been an abundance of evidence firmly linking them to atypical hyperplasias, lobular pattern more so than ductal pattern, and the special type of mammary carcinoma, tubular carcinoma. This association was probably earliest to be noted by Goldstein and O'Malley,[22] though their proposed designation and pathobiology of cancerization has proven to be inaccurate.

As elegantly tabulated by Abdel-Fatah,[14] this non-random association has been supported by several studies that have shown significant overlap in the molecular alterations seen in both tubular carcinoma and CCA, bringing forth the idea that the atypical CCL may well represent a precursor state, not only for patterns of atypical hyperplasia, but also for low-grade special type (tubular) invasive carcinoma.

Despite these compelling findings, the available outcome studies that looked at CCA have failed to detect a significant risk for subsequent cancer on long-term follow-up. The first available study was by Eusebi and colleagues[29] who retrospectively identified 21 patients with so-called "clinging carcinoma" of the flat, monomorphic type out of 4,000 benign breast biopsies performed between 1965 and 1971. After an average follow-up period of 19.2 years, only one of the patients had recurrence of a histologically identical lesion without evidence of DCIS or invasive tumor. Also, Bijker and colleagues,[27] within the EORTC cancer trial, reported no local recurrence in 59 patients with, again so-called clinging carcinoma, after an average follow-up of 5.4 years. In a recent study, De Mascarel and colleagues[28] examined co-occurrence and subsequent incidence of carcinoma associated with various types of atypia, and although CCA (which they referred to as FEA) had a 17% risk of concomitant invasive cancer, none of the 84 patients with FEA as an isolated diagnosis experienced malignant recurrence after 10 years of follow-up. Most recently, Martel and colleagues recognized 63 cases of FEA (flat DIN1) out of 1,751 core biopsies, with invasive carcinoma present in 7 ipsilateral follow-up excisions performed between 2 and 9 years following the initial procedure.[30] Their conclusion amounted to a mild increase in cancer risk following a diagnosis of FEA on needle core biopsy.

As noted above, it is becoming increasingly clear that large numbers of atypical columnar cell lesions for assessment of long-term outcome are difficult to obtain, even with studies including several thousand initial breast biopsies. Since the overall risk for columnar cell lesions has, to our knowledge, never been established, we elected to assess this particular variable retrospectively in a large cohort of patients. We then proceeded to compare the risk associated with different subtypes of columnar cell lesions, based on Schnitt and Vincent-Salomon's proposed classification scheme,[2] in a nested case-control design.

Our findings have proven consistent with the results obtained from most of the aforementioned clinical outcome studies. In women who do not have atypical hyperplasia, the relative risk associated with the totality of columnar cell lesions with an average of 17 years of follow-up is 1.47 as compared to cases with neither proliferative breast disease nor columnar cell lesions (P=0.05). This represents only a mildly increased risk of subsequent cancer, and is comparable to what has been previously reported for EHLA.[32, 39–41] This relative risk does not vary appreciably with time since biopsy. When comparing the different

classes of columnar cell lesions with respect to future cancer risk, no significant difference was noted between CCL with and without atypia or hyperplasia.

Simultaneously, the prevalence of atypical hyperplasia appears to be increased 2–3 fold when columnar cell lesions are present as compared to when they're absent (5.0% versus 1.9 % for ALH, 3.5% versus 1.4% for ADH). These findings are consistent with the previous observational studies, but seem to be true for all columnar cell lesions, not only ones with atypia, as suggested by previous studies that evaluated such atypical lesions exclusively.[14, 15, 17]

The remarkably strong association that both Abdel-Fatah and Leibl have shown between CCA and lobular neoplasia would normally suggest that the cancer risk associated with each of these entities should be comparable, a supposition that has so far largely failed substantiation. This might be explained by the postulate that lobular neoplasia (and probably atypical ductal hyperplasia as well) and atypical columnar cell lesions follow a path of co-occurrence rather than one of biologic progression. The plausibility of this postulate is increased by the fact that 16q deletions (where the E-cadherin gene is located) are common to both.[3] When columnar cell lesions are present in isolation, their likelihood of progression to a more advanced lesion is minor. However, their mere presence is an excellent indicator for the presence of other atypical breast lesions that are associated with elevated cancer risk.

It is worth noting that, contrary to our expectation based on multiple previous studies, the cancer risk associated with EHLA is not significant, while the risk associated with CCL is what we would have expected from EHLA [40–43]. This might quite possibly be due to a confounding element introduced by the co-occurrence of CCL and EHLA, which was not accounted for in prior studies. Hence the mildly increased risk initially attributed to EHLA might be attributable to CCL coinciding with EHLA in the same benign biopsy.

The main limitations of this study are similar to those encountered by other studies tackling the clinical significance of columnar cell lesions and flat epithelial atypia. These include the overall small number of cases that harbor CCA, independently of more advanced atypical lesions. The limited availability of paraffin blocks on cohort cases contributes to this ever-recurring problem. The issue of diagnostic criteria, reproducibility, and interobserver variability, as illustrated by O'Malley et al.,[6] is another potential limitation that was tentatively minimized through multistep review and consensus diagnosis of discrepant cases. Ideally, a similar large cohort of benign breast biopsies, where all CCL cases are subcategorized and assessed, would offer the best look at their clinical significance and implications towards future cancer risk as compared to the general population.

In summary, our results reinforce concepts that are being slowly rooted in our understanding of CCL of the breast. The presence of such lesions, whether they harbor or lack atypia, seems to have only mild implications towards increased future cancer risk. This assertion will still need continued substantiation by more studies with larger numbers and similar long-term follow-up. The more relevant implications, we believe, are those of association with potentially more worrisome lesions that necessitate further therapy. The appropriate corresponding management decisions will have to rely on targeted studies that would link mammographic findings, size of diagnostic biopsy, specific columnar cell lesion subtype, and extent of involvement. This is in order to insure that patients will not undergo unnecessary surgical excision for isolated lesions with questionable or minimal atypia. We do recommend however, whenever CCL is diagnosed, that a particularly careful search for AH be made.

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Table 1

Subsequent breast cancer risk among women with CCL

Type of benign breast disease	No. of Patients	No. of Cases	Cancer incidence rate †	Relative risk	95% CI	*P*-value
All	4608	197	309			
CCL	1261	61	396			
No PD or CCL	1966	67	224	1*		
CCL without AH	1154	47	331	1.47	1.0 – 2.2	0.05
EHLA without CCL	1691	72	320	1.24	0.88 – 1.7	0.21

CCL indicates columnar cell lesions; CI, Confidence interval; PD, Proliferative disease; AH, atypical hyperplasia; EHLA, Epithelial hyperplasia lacking atypia.

† Crude annual incidence of invasive breast cancer per 100,000

* Denominator of subsequent relative risks

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Table 2

Subsequent breast cancer risk in women with AH and CCL

Type of benign breast disease	No. of Patients (%)*	No. of cases	Cancer incidence rate†	Relative risk	95% CI	*P*-value
No PD or CCL	1966	67	224	1‡		
AH, no CCL	108 (3.3)	10	802	3.24	1.6–6.5	0.001
AH + CCL	107 (8.5)	14	1152	5.01	2.7–9.1	< 0.0005
ALH, no CCL	69 (2.1)	9	1079	4.28	2.1 – 8.8	< 0.0005
ALH + CCL	70 (5.6)	13	1643	6.97	3.8 – 13	< 0.0005
ADH, no CCL	46 (1.4)	4	868	3.31	1.2 – 9.4	0.02
ADH + CCL	44 (3.5)	4	813	3.46	1.2 – 9.7	0.02
AH, no CCL	108 (3.3)	10	802	1‡		
AH + CCL	107 (8.5)	14	1152	1.55	0.69 – 3.5	0.29

AH indicates atypical hyperplasia; CCL, columnar cell lesions; CI, confidence interval; PD, proliferative disease; ALH, atypical lobular hyperplasia; ADH, atypical ductal hyperplasia.

*Each percentage is the proportion of AH patients among all patients either with or without CCL, respectively (e.g. in the third row 107/1261 = 8.5%).

†Crude annual incidence of invasive breast cancer per 100,000

‡Denominator of subsequent relative risk(s)

Table 3

Comparison of CCL subcategories and associations with breast cancer*

	Cases	Controls	Relative Risk	95% CI	*P*-value
CCC	24	56	1†		
CCH	39	58	1.57	0.81 – 3.0	0.18
CCA	14	38	0.858	0.38 – 1.9	0.71
All CCL	77	152			

CCL indicates columnar cell lesions; CI, confidence interval; CCC, CCL without hyperplasia or atypia; CCH, CCL with hyperplasia; CCA, CCL with atypia.

*Patients with atypical hyperplasia outside of the CCL were excluded from this nested case-control study.

†Denominator of subsequent relative risks

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