

Epithelial atypia in biopsies performed for microcalcifications. Practical considerations about 2,833 serially sectioned surgical biopsies with a long follow-up

Isabelle de Mascarel · Gaëtan MacGrogan ·
Simone Mathoulin-Pélissier · Anne Vincent-Salomon ·
Isabelle Soubeyran · Véronique Picot ·
Jean-Michel Coindre · Louis Mauriac

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Abstract This study analyzes the occurrence of epithelial atypia in 2,833 serially sectioned surgical breast biopsies (SB) performed for microcalcifications (median number of blocks per SB:26) and the occurrence of subsequent cancer after an initial diagnosis of epithelial atypia (median follow-up 160 months). Epithelial atypia (flat epithelial atypia, atypical ductal hyperplasia, and lobular neoplasia) were found in 971 SB, with and without a concomitant cancer in 301 (31%) and 670 (69%) SB, respectively. Thus, isolated epithelial atypia were found in 670 out of the 2,833 SB (23%). Concomitant cancers corresponded to ductal carcinomas in situ and micro-invasive (77%), invasive ductal carcinomas not otherwise specified (15%), invasive lobular carcinomas (4%), and tubular carcinomas (4%). Fifteen out

of the 443 patients with isolated epithelial atypia developed a subsequent ipsilateral ($n=14$) and contralateral ($n=1$) invasive cancer. The high slide rating might explain the high percentages of epithelial atypia and concomitant cancers and the low percentage of subsequent cancer after a diagnosis of epithelial atypia as a single lesion. Epithelial atypia could be more a risk marker of concomitant than subsequent cancer.

Keywords Breast · Epithelial atypia · Lobular neoplasia · Atypical ductal hyperplasia · Cancer

Introduction

Breast biopsies for infraclinical lesions are more frequent with mammographic screening programs, but the distribution of the corresponding histological lesions and their associations are still imprecise. Difficulties encountered in following up patients without cancer account for the fact that the clinical significance of certain non-malignant lesions and the management of patients are still debated. Moreover, the problem of surgical biopsy sampling has never been fully investigated and has added additional confusion in appreciating the distribution and clinical significance of such lesions. In 1981, breast epithelial atypia were hardly mentioned and not clearly defined in the World Health Organization/International Union Against Cancer (WHO/UICC) histologic classification of breast tumors [73]. The histologic classification of noncancerous lesions has been mainly based on studies analyzing for each lesion the associated risk of subsequent cancer. These studies were initiated by the survival studies of Dupont and

I. de Mascarel (✉) · G. MacGrogan · I. Soubeyran ·
J.-M. Coindre
Department of Pathology, Institut Bergonié,
Regional Cancer Center,
Bordeaux, France
e-mail: mascarel@bergonie.org

S. Mathoulin-Pélissier
Department of Biostatistics, Institut Bergonié,
Regional Cancer Center,
Bordeaux, France

A. Vincent-Salomon · V. Picot
Department of Pathology, Institut Curie,
Regional Cancer Center,
Paris, France

L. Mauriac
Department of Medical Oncology, Institut Bergonié,
Regional Cancer Center,
Bordeaux, France

Page [15, 46] based on lesions discovered by palpation before the era of mammography. Thereafter, further studies [6, 9, 17, 24, 31, 51, 62, 67] substantiated these results, which were ratified in 2003 by the new American Joint Committee on Cancer (AJCC)/UICC classification of breast tumors [70]. Schematically, this classification differentiates benign epithelial lesions (usual ductal hyperplasia and other lesions) from atypical lesions of ductal or lobular type. Although this historical classification is challenged by a new classification [68], it remains the most widely used in practice. Interestingly, the occurrence of epithelial atypia was low in Page's study [46] and has increased with mammographic screening programs [60, 66] and with the development of percutaneous large core needle biopsy (CNB) methods using stereotactic mammography or ultrasound guidance. At present, CNB is frequently used for the initial evaluation of clinically occult breast lesions, thus generating dilemma for the subsequent management of certain noncancerous lesions. At our institution, surgical biopsies (SB) have always been managed in the same way, and most patients with atypical and malignant lesions have been followed. The objectives of our work were to analyze the occurrence of epithelial atypia and their association with a concomitant cancer in a large series of SB performed for microcalcifications without a palpable tumor and to assess the subsequent cancer probability in the group of patients with an initial diagnosis of epithelial atypia. Finally, we provide some practical considerations for the management of patients with epithelial atypia in this era of mammographic screening and CNB.

Materials and methods

Selection of patients

At Institut Bergonié, from January 1975 to December 2002, 3,166 breast biopsies for diagnostic purposes, 2,833 SB and 333 CNB, were performed for microcalcifications without any palpable mass in 2,708 patients (mean age 51.8 years, range 19.7–81 years). Among them, 248 (9%) had several biopsies in the same or contralateral breast. Since 1998, microcalcifications have been classified according to the classifications of the American College of Radiology [2]. SB for diagnostic purposes were defined before 1998 by the absence of a preoperative diagnosis based on the clinical–mammographic–cytologic triplet and by the absence of a positive frozen section and, since 1998, by the presence of epithelial atypia on CNB. Excluded from this study were 132 cancers and 139 non-atypical benign lesions diagnosed on CNB as well as 49 re-excisions performed elsewhere than in our center. Thus, 2,833 SB in 2,375 patients were available for analysis, among which 13 corresponded to re-

excision after a CNB with epithelial atypia. Since 1989, needle localization, intraoperative specimen radiography, and post-excisional biopsy mammography have been performed in most cases.

Surgical biopsies and tissue sampling: serial macroscopic sectioning

SB was removed in one fragment and measured more than 3 cm in 94% of the cases (mean size 60 mm, 5–250 mm). For SB margin assessment, either the surface of the specimen was inked or the surgeon during the same operation removed additional tissue in the remaining cavity after excision of the specimen (surgical margins). After fixation in Holland Bouin, SB and margin specimens were serially sectioned in their entirety into numbered slices every 2 mm [12]. In most cases (89%), careful macroscopic examination of the specimen failed to reveal any lesion. Each numbered slice was put in as many numbered separate cassettes as necessary and paraffin-embedded in sequence. The median number of blocks per SB was 26 (from 2 to 180) and 8 (from 1 to 44) for surgical margins. Each block was examined on one hematoxylin–eosin–safran stained slide.

Classification of lesions and review of slides

Since 1975, all patients have been prospectively included in our clinical, histologic, and biologic database by senior pathologists (IM, GMG, IS, JMC). For each SB and each lesion, we prospectively entered in our pathologic database morphological descriptive criteria by using 65 pathological items for noncancerous lesions and 181 for cancers. Definitions and terminologies given in the literature were used to report columnar cell lesions (CCL), non-atypical ductal hyperplasia, atypical ductal hyperplasia, ductal carcinoma in situ (DCIS), and lobular carcinoma in situ (LCIS) [1, 4, 7, 10, 17, 19, 21–28, 38, 43–45, 47, 49, 50, 56, 59, 61, 69, 72, 74, 75]. The interest of our database was to collect morphological descriptive criteria of nearly all the breast lesions without labeling them. In fact, labels and definitions of breast lesions have varied throughout the past 30 years, while neither lesions nor their corresponding descriptive criteria (i.e., size, type, architecture, cellular and nuclear features, etc...) have changed. The only changes during this period were the definitions and/or the names given to these lesions. As we have listed for each lesion all the corresponding descriptive criteria among the 236 available items, we have been able to reclassify each lesion according to the “new” criteria recommended by referent authorities for a new definition, by selecting in our database the “new” correspondent descriptive criteria corresponding to this new definition. Consequently, this provided a

homogeneous approach to the pathological lesions at the time of our study. For example, low-grade DCIS ≤ 2 mm have been reclassified as atypical ductal hyperplasia/ductal intraepithelial neoplasia (ADH/DIN) 1B ($n=30$) according to the new AJCC/UICC classification of breast tumors [70], and lesions that we used to term before 1997 [71] as clinging carcinoma of the monomorphic type [4] have been reclassified as flat epithelial atypia (FEA)/DIN 1A or columnar cell change (CCC) with atypia ($n=84$) [61]. About half of these 114 cases have been systematically reviewed by one (IM) or two senior pathologists (IM and GMG or IS), and there was a complete concordance between the second review and the initial descriptive criteria listed in the database. Similarly, lesions that we used to name LCIS before 1997 have been renamed lobular neoplasia (LN) since 1997, corresponding either to atypical lobular hyperplasia (ALH) or to LCIS. On the contrary, all the cases with micropapillary lesions were reviewed ($n=155$) because there was no item corresponding to precise descriptive criteria of micropapillations (number, topography around the duct, type).

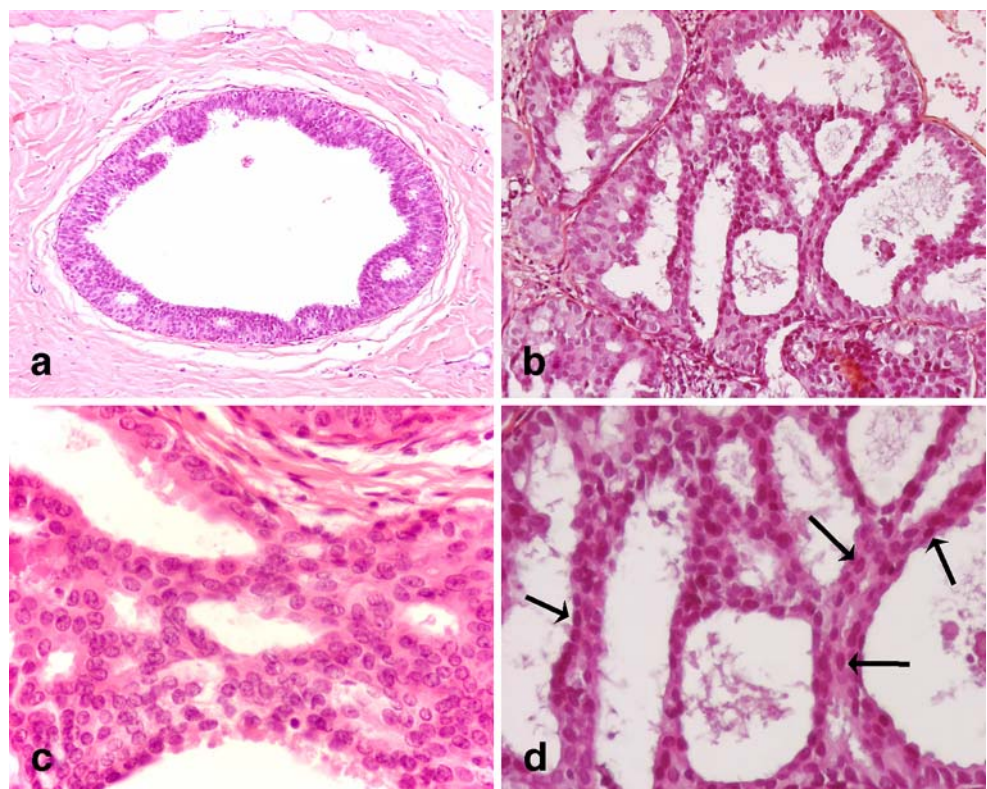
Atypical ductal hyperplasia: definition and sizing

Among the group of ADH/DIN 1B, we individualized two morphologic types of ADH. Neither had any high-grade cytological atypia or necrosis.

ADH “mimicking DCIS” (Fig. 1). In this type, architectural atypia were qualitatively insufficient to allow a diagnosis of DCIS, therefore this “mimicking” DCIS lesion was classified as ADH whatever its size. Tufts and short micropapillations formed by cells had a broad base and were cohesive. There was no polarization of cells, i.e., no true cribriform spaces. Pseudo-cribriform patterns comprised irregular or relatively round microlumina with incomplete polarization of surrounding epithelial cells. Cellular bridges were wavy without any cellular polarization. Cells corresponded either to columnar cells with uniform ovoid to elongated nuclei or to cells with a slight increase in the nuclear/cytoplasmic ratio with more or less distinct cell borders and round or ovoid nuclei. These cells were sometimes admixed in the same lesion displaying a morphological gradient, but there was no regular arrangement. Nuclear chromatin was evenly dispersed, homogeneous, or slightly marginated, and nucleoli were inconspicuous. Apical snouts, intraluminal secretions, and psammoma-type calcifications were frequently present.

ADH corresponding to “mini DCIS” (Fig. 2). In this type, architectural and cytologic atypia corresponded to a low-grade DCIS but were quantitatively insufficient to allow a diagnosis of DCIS, therefore this “mini” DCIS lesion was classified as ADH when ≤ 2 mm. Tufts and short micropapillations had a tight base, were present on over all the periphery of the duct, and were non-cohesive with small

Fig. 1 a–d. ADH “mimicking DCIS.” **a** Tufts and short micropapillations with a broad base. **b** Pseudo-cribriform spaces. **c** Microlumen with incomplete polarization of surrounding epithelial cells. **d** Cellular bridges without cellular polarization. Cells are parallel to the axes (*arrows*)



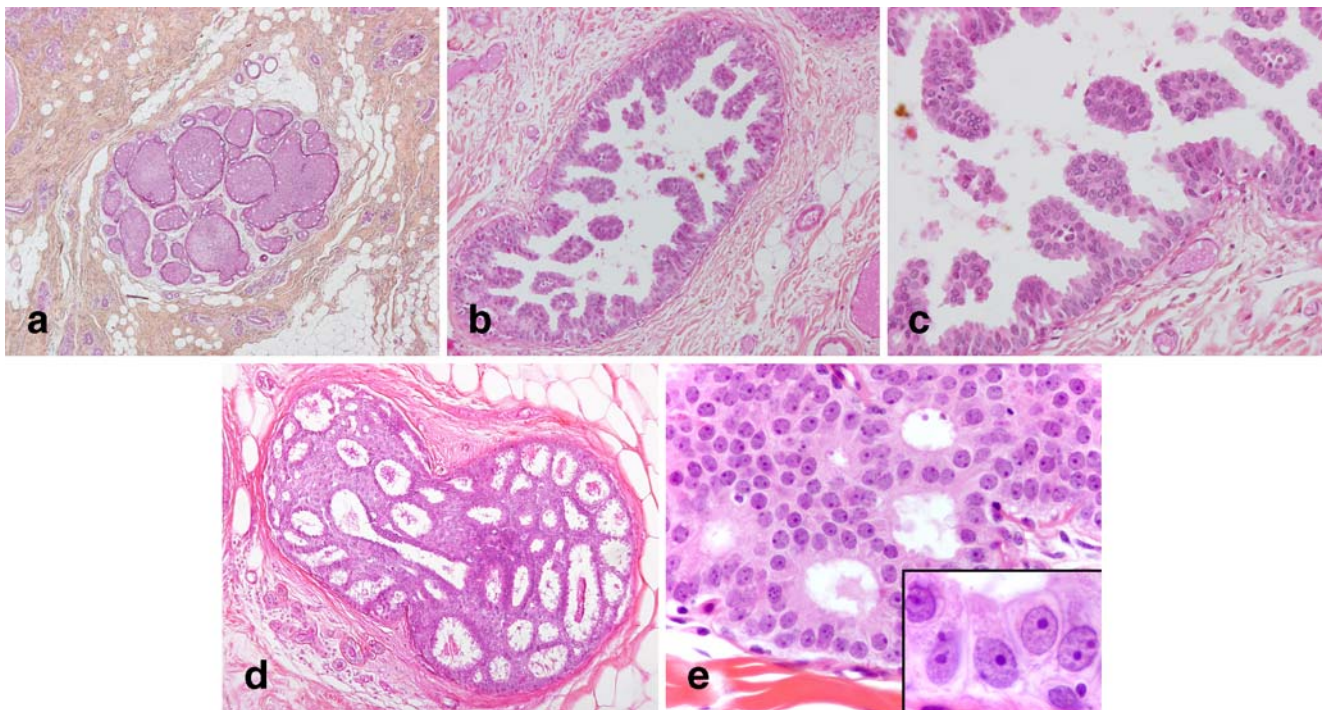


Fig. 2 a–e. ADH corresponding to “mini DCIS.” **a** A solid mini DCIS focus measuring less than 2 mm in one TDLU. **b** Tufts and short micropapillations over the entire periphery of the duct with small

free papillary tufts in the lumen. **c** Short micropapillations with a tight base. **d** True cribriform spaces. **e** Microlumen with complete polarization of surrounding epithelial cells

free papillary tufts in the lumen. There were true cribriform patterns with a polar organization of cells around glandular spaces and/or variants of cribriform patterns (i.e., trabecular bars, cartwheel formations, and Roman bridges, Fig. 3) with polarized cells arranged perpendicular to the axes. Some solid areas with regular arrangement of cells were also present. Cells were often small, monomorphic, sometimes without a columnar change, with a distinct cytoplasmic membrane and a spaced regular round nucleus with uniformly dispersed chromatin without prominent nucleoli. Intraluminal secretions and calcifications (amorphous or psammoma-type) were also frequently present (Fig. 4). When one mini DCIS focus was found in one

partially or completely involved duct/ductular cross-sections in one terminal ductal lobular unit (TDLU), it was classified as ADH when it measured ≤ 2 mm and as DCIS when it measured >2 mm. When there were several foci of “mini” DCIS in close duct/ductular cross-sections in the same TDLU or in TDLUs located in the same field at low power magnification (2.5), the lesion was classified as ADH when its size, i.e., its largest diameter, was ≤ 2 mm and as DCIS when >2 mm. When there were several foci of “mini” DCIS in distant duct/ductular cross-sections in the same TDLU or in close TDLUs, the size of each focus was assessed separately. FEA, rare and scattered single micropapillations, and cribriform variants

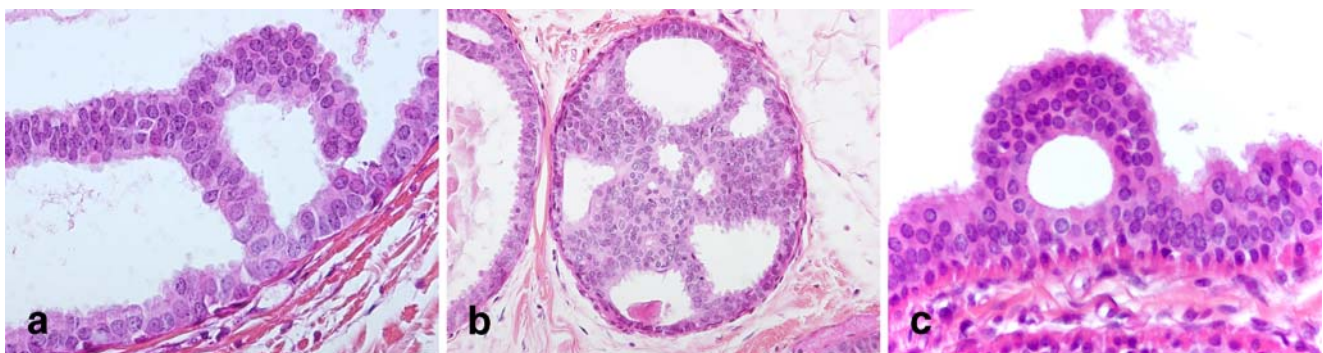
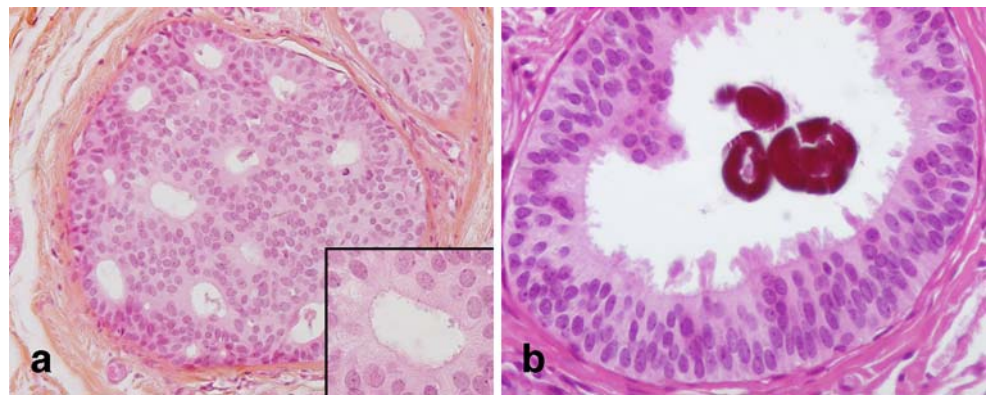


Fig. 3 a–c. Variants of cribriform patterns. Polarized cells arranged perpendicular to the axes. **a** Trabecular bars. **b** Cartwheel formations. **c** Roman bridges

Fig. 4 **a** and **b**. **a** Mild cytologic atypia. **b** Columnar cells with uniform ovoid nuclei, intraluminal calcifications



were not taken into consideration for sizing, even if located in the same TDLU.

FEA were present either as a single lesion or in association with ADH in the same TDLU and since 1997 have been included in the ADH group. The distinction of FEA from columnar change without atypia was based on the criteria given by the WHO for the definition of FEA. Furthermore, columnar change without atypia was characterized by one or two layers of columnar cells without nuclear atypia, i.e., no increase in the nuclear/cytoplasmic ratio, no prominent nucleoli. Nevertheless, some cases of columnar change with progesterone impregnation, especially in the second part of the cycle, might display a lobular distension with a secretory material and large nuclei with prominent nucleoli. In such cases, myoepithelial cells displayed the same alterations with clarified cytoplasm, thus facilitating the diagnosis. The distinction of ADH mimicking DCIS from usual hyperplasia (UDH) was based on morphological criteria. Architectural pattern and cytologic criteria of usual ductal hyperplasia were easy to identify in most cases. UDH corresponded to a proliferation of epithelial cells in solid or fenestrated areas without any polarization of surrounding cells. Cells were haphazardly arranged with overlapping nuclei or were parallel with characteristic streamings. They were elongated or pseudo epithelioid, but there was no columnar metaplasia. Cytoplasm was more or less abundant with indistinct borders. Nuclei had irregular size and shape and sometimes contained a prominent eosinophilic inclusion. In some rare cases, immunohistochemical staining with cytokeratin 5/6 [41] was used and was negative in ADH mimicking DCIS and strongly positive in UDH. In some lesions, differential diagnosis between ADH and low-grade DCIS was all the more difficult because there were intermediate and intricate morphological aspects in the same TDLU. In practice, diagnosis of micropapillary lesions was often difficult. Extensive micropapillary lesions were classified as DCIS when quantitative and qualitative criteria were simultaneously present, i.e., lesion sizing more than 2 mm

corresponding to micropapillations with a tight base over the entire periphery of the ducts. Additional sections could be useful for demonstrating more or less qualitative or quantitative diagnostic criteria. When malignancy remained equivocal, the case was classified as ADH. When a concomitant cancer was diagnosed, histologic size was assessed, and in DCIS, the percentage of blocks with cancer (“positive blocks”) was specified [13]. Presence and topography of microcalcifications were also assessed. Lastly, when FEA and/or “mimicking” DCIS foci were found on excision margins of a SB with DCIS, a further surgical resection was not performed.

Follow-up of patients with epithelial atypia as a single lesion

There were 443 patients with epithelial atypia in one or several SB, without any previous or synchronous carcinoma in the same or contralateral breast and treated by biopsy alone (median follow-up 160 months, 7 to 315). Only 28/443 (6%) were lost to follow-up. Among the 415 other patients, 180 were monitored at our institute and 235 outside by correspondent specialists working in close relationship with our institute. All patients received a clinical examination and mammography once a year. When a new biopsy was necessary, it was performed at our institute.

Statistical analyses

Comparison of clinical and histologic characteristics was conducted by using the chi-square test. For women with epithelial atypia, the probability of developing in situ or invasive cancer was calculated from the date of the first biopsy to the earliest event: breast cancer (ipsi- or contralateral), death, or last contact (last consultation for the group monitored at our institute and checkpoint date, i.e., 1 March 2004, for the others). Probabilities were calculated according to the Kaplan–Meier method (SPSSv11).

Results

Occurrence of epithelial atypia in the 2,833 surgical biopsies

Epithelial atypia were recorded in 971/2,833 SB (34%). They were found with and without a concomitant cancer in 301/971 (31%) and 670/971 (69%) of the cases, respectively. Thus, isolated epithelial atypia were found in 23% of the cases (670 out of the 2,833 SB). Calcifications were present at histologic examination in 98.6% of SB with cancer and were located in benign, cancerous, and both lesions in 10, 39, and 51% of the cases, respectively. In several cases, cancerous foci without any microcalcifications were located at points distant from those with calcifications detected by needle localization.

Types of epithelial atypia

Among the 971 SB with epithelial atypia, there were 101 SB with FEA as a single lesion (11%), 342 (35%) with ADH, 223 (23%) with LN, and 305 (31%) with ADH and LN. Thus, ADH was encountered in 647/971 SB (66%).

Types of cancers associated with epithelial atypia

Cancers associated with epithelial atypia corresponded to DCIS and micro-invasive carcinoma (DCIS-MI) in 233 cases (77%). Among invasive carcinomas ($n=68$), there were 13 (9%) lobular and 11 (6%) tubular carcinomas (Table 1). Cancers were small (≤ 5 mm in 46% of invasive carcinomas, fewer than half of the blocks positive in 76% of DCIS). They were non-high grade in 78 and 67% of DCIS and invasive carcinoma, respectively. In most cases, ADH and cancer were situated close to each other. FEA alone were less frequently associated with a concomitant cancer than ADH and/or LN ($p=5 \times 10^{-4}$).

Cancers without epithelial atypia (malignancy alone)

There were 821 malignant SB without epithelial atypia [590 micro-invasive carcinomas, 206 infiltrating ductal carcinomas (IDC), and 25 infiltrating lobular carcinomas (ILC)].

Subsequent cancer in patients with an initial diagnosis of epithelial atypia as a single lesion

At 5 and 10 years, the probabilities of developing invasive breast cancer in the group of 443 patients with epithelial atypia were 2.8% [95%CI=1.4 to 5.5] and 5.5% [95%CI=3.3 to 9.9], respectively (Fig. 5). Among the 18 subsequent carcinomas, 15 were invasive (11 IDC and 4 ILC), and 3 corresponded to DCIS. Most subsequent carcinomas were encountered in the homolateral breast ($n=14$) and before 10 years ($n=16$). Seven carcinomas occurred in the group of patients with an initial diagnosis of LN, in the same ($n=5$) or contralateral ($n=2$) breast. They corresponded to infiltrating ductal ($n=6$) or lobular ($n=1$) carcinomas. The interval of development was 4, 5, 6 ($n=2$), 9, and 12 ($n=2$) years. Seven carcinomas occurred in the group of patients with an initial diagnosis of ADH, in the same ($n=3$) or contralateral ($n=4$) breast. They corresponded to DCIS ($n=2$) and to infiltrating ductal ($n=4$) or lobular ($n=1$) carcinomas. The interval of development was 1, 2, 3 ($n=3$), 9, and 12 years. Four carcinomas occurred in the group of patients with an initial diagnosis of ADH associated with LN, in the same ($n=3$) or contralateral ($n=1$) breast. They corresponded to DCIS ($n=1$) and to infiltrating ductal ($n=2$) or lobular ($n=1$) carcinomas. In the four cases, the interval of development was 4 years. There was no subsequent carcinoma in the group of patients with FEA.

Table 1 Types of concomitant cancers ($n=301$) in the 971 surgical biopsies with epithelial atypia

Epithelial atypia	FEA ($n=101$)		ADH ($n=342$)		LN ($n=223$)		ADH+LN ($n=305$)	
	No. of cases (%)		No. of cases (%)		No. of cases (%)		No. of cases (%)	
Without cancer	84	83	220	64	139	62	227	74
With cancer	17	17	122	36	84	38	78	26
DCIS/DCIS-MI	12	12	103	30	58	26	60	20
IDC/NOS	–	–	16	4.7	17	8	11	3
ILC	1	1	1	0.3	6	3	5	2
TC	4	4	2	1	3	1	2	1

FEA Flat epithelial atypia; ADH atypical ductal hyperplasia; LN lobular neoplasia; DCIS ductal carcinoma in situ; DCIS-MI DCIS with micro-invasion; IDC infiltrating ductal carcinoma; ILC infiltrating lobular carcinoma; TC tubular carcinoma

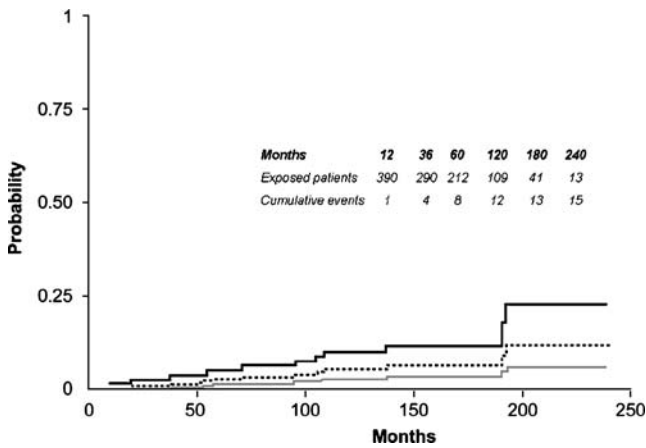


Fig. 5 Probability of developing subsequent invasive breast cancer in the group of 415 patients with epithelial atypia (dotted line: confidence interval 95%)

Discussion

Application of the WHO classification: practical considerations

For a long time, DCIS was diagnosed even if the characteristic features were found in only one ductal space [6]. Thereafter, some authors introduced quantitative criteria for distinguishing between ADH and DCIS [46, 67], while others [23] rejected them. More recently, Rosen [57–59] and Schnitt and Vincent-Salomon [61] described CCL comprising CCC and columnar cell hyperplasia (CCH)

with and without atypia. Nasser [40] challenged this classification based on columnar shape and limited the group of lesions to proliferations characterized by a low-grade atypicity, “atypical columnar cell lesions,” (ACCL) rather by a columnar cell configuration. In the WHO classification, ADH includes various not clearly defined types of lesions (Table 2). On one hand, there are lesions with arcades, moundings, and micropapillary formations, but without any true cribriform/complex architectural patterns [34]. This type of ADH corresponds to the CCH with atypia of Schnitt and Vincent-Salomon [61] termed category 3 in Simpson’s study [51], to the definition of ADH by Koerner [34] and to ADH “mimicking” DCIS in our study. On the other hand, there are lesions displaying architectural and cytologic atypia. This type of ADH corresponds to the complex architectural pattern with cytologic and architectural atypia of Schnitt and Vincent-Salomon [61] termed category 5 in Simpson’s study [64], to the definition of “microfocus of DCIS” by Koerner [34] and to “mini DCIS” in our study. In Simpson’s study, the ADH/category 5 contained chromosomal changes and the same total mean number of changes to that observed in DCIS/DIN IC, unlike the other CCL. Lastly, because there is still no consensus for measuring ADH, there is no clear-cut distinction between ADH and DCIS, and the cut-off at 2 or 3 [52] mm or at two completely involved spaces [70] seems arbitrary. While awaiting a definitive molecular classification, the simplest attitude could be recommended in routine

Table 2 Terminologies used for intraductal proliferative lesions with low-grade cytologic atypia, so-called atypical columnar cell lesions

Spectrum of lesions	1, 3–5 Layers Occasional mounding No or rare arcades and micropapillary formations	No polarization* Mounding, arcades Cohesive micropapillary tufts with a broad base	With polarization Cribriform spaces and their variants Non-cohesive micropapillary tufts with a tight base
[70]	Flat epithelial atypia/DIN 1A	ADH/DIN 1B ≤ 2 mm; or in two spaces	DCIS/DIN 1C
[59, 61]	Columnar cell hyperplasia with atypia Columnar cell change (CCC) with cytologic atypia		ADH if not extensive = Complex structures with architectural and cytologic atypia
[34]	Columnar cell lesions + ADH		Microscopic focus of DCIS DCIS
Institut Bergonié	Ex-clinging carcinoma of monomorphic type	ADH “mimicking” DCIS	ADH corresponding to “mini” DCIS ≤ 2 mm DCIS
[64]	CCC with cytologic atypia Or CCH with cytologic atypia	CCH with architectural atypia	CCH with architectural atypia And Cytologic atypia DCIS
Regrouping?	DIN 1A	ADH/DIN 1B Not measured	ADH/DIN 1C Measured: ≤ 3 mm > 3 mm DCIS/DIN 1C

*Or incomplete polarization

practice. Only mini foci of ADH obviously similar to low-grade DCIS foci could be measured and classified as ADH when equal to or less than 2–3 mm [52] and as DCIS when more than 3 mm. Although the mode of measurement in our study is not under consensus, it is simple and can be routinely applied.

Occurrence of epithelial atypia and their association with a concomitant cancer: practical considerations

In our study, the proportion of epithelial atypia is high (23%), a result difficult to compare to others in the literature, as the methodologies used by teams are different. In the Page and Dupont case-control studies [15, 46], ADH and ALH were found in 2.1 and 1.6% of the cases, respectively. In mammographic screening programs, epithelial atypia and cancers increase as the number of biopsies performed for microcalcifications increases, especially as ACR4/ACR5 lesions are more often excised than ACR3. However, as underlined by Page [46], “the most direct relationship of epithelial atypia incidence is to slide rating.” The number of slides per SB in our study (median 26) was higher than in the other studies on benign breast lesions: 1–5 in 93% of the cases in the study of Page et al. [46] ($n=283$), 3 (range 1–25, $n=674$) in the study of Shaaban et al. [62], and a mean of 1.6 slides per cm of tissue ($n=199$) in the study of Tavassoli and Norris [67]. In a recent study conducted in the south west of France in women aged between 50 and 75 with mammographically detected non-palpable breast lesions, a similar proportion of atypical lesions were found when biopsies were serially sectioned [39]. Furthermore, this high slide rating allowed the detection of small concomitant cancers in the vicinity of epithelial atypia in 31% of our cases, with a skew towards low-grade lesions (high proportions of DCIS and low-grade invasive carcinomas, especially tubular carcinomas). Our results strengthen the hypothesis that FEA and ADH are risk markers of low-grade cancers. This has been confirmed by the study of Simpson et al. [64] on molecular genetic profiles of CCL. In some of them, there are both a morphological and a molecular continuum in the degree of proliferation and atypia, supporting the hypothesis that “CCL are a non-obligate, intermediary step in the development of some forms of low grade in situ and invasive carcinoma.” The association of epithelial atypia with a concomitant cancer in nearly one third of the cases in our study parallels previous findings concerning the frequency of cancers found in SB performed for atypia in CNB. Thus, approximately 30% [20, 29] and 15 to 21% [5, 8, 14, 18, 35, 45, 53, 63, 76] of excisions after CNB with ADH and LN, respectively, were proven to have cancer. Consequently, excision is recommended [45] for all patients in whom ADH is identified on CNB and may be justified in patients

with FEA, as they are included in the spectrum of ACCL. Excision remains a controversial issue in patients with LN. Some authors have advocated it [3, 18, 33, 63], while others have rebutted it [55], especially when LN is an incidental non-extensive finding [48] with no radiologic–pathologic discordance [18] and without any synchronous mass lesion [37]. SB corresponding to re-excision should be processed in its entirety by serial macroscopic sectioning [32, 65]. When pathologic examination is exclusively focused on mammographic calcifications, the risk is to underestimate the DCIS size/extension because cancerous foci without any calcification (10% in our study vs 6% in Owing’s study) [42] may be located at points distant from those with benign breast tissue containing calcifications.

Subsequent cancer after an initial diagnostic of epithelial atypia as a single lesion: practical considerations

In the literature, 4 to 22% (average interval 8.3 years follow-up) [6, 42, 67] and 15 to 20% [16, 30, 56] of patients developed invasive carcinomas after a diagnosis of ADH and LN, respectively. The risk of developing cancer increases with extended follow-up, but many cancers after a diagnosis of LN have a good prognosis and a low mortality [36]. These results are difficult to compare to ours because the methodologies are different. The low probabilities of subsequent invasive cancer in our study could be due to the high slide rating, allowing the detection of small concomitant cancer that might have been missed with a low slide rating and inadequate patient management [11, 54].

In conclusion, when epithelial atypia are present, they are associated in nearly one third of the cases with a concomitant close cancer and are found as isolated lesions in nearly 23% of SB performed for microcalcifications. In practice, ADH should be more clearly defined with simple guidelines for measuring lesions. When malignancy remains equivocal and/or when sizing is difficult, it is better to classify the lesion as ADH. Epithelial atypia could be more a “risk factor” of a concomitant geographically small close cancer than a risk marker for a subsequent cancer, as they form part of a spectrum of lesions [64].

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