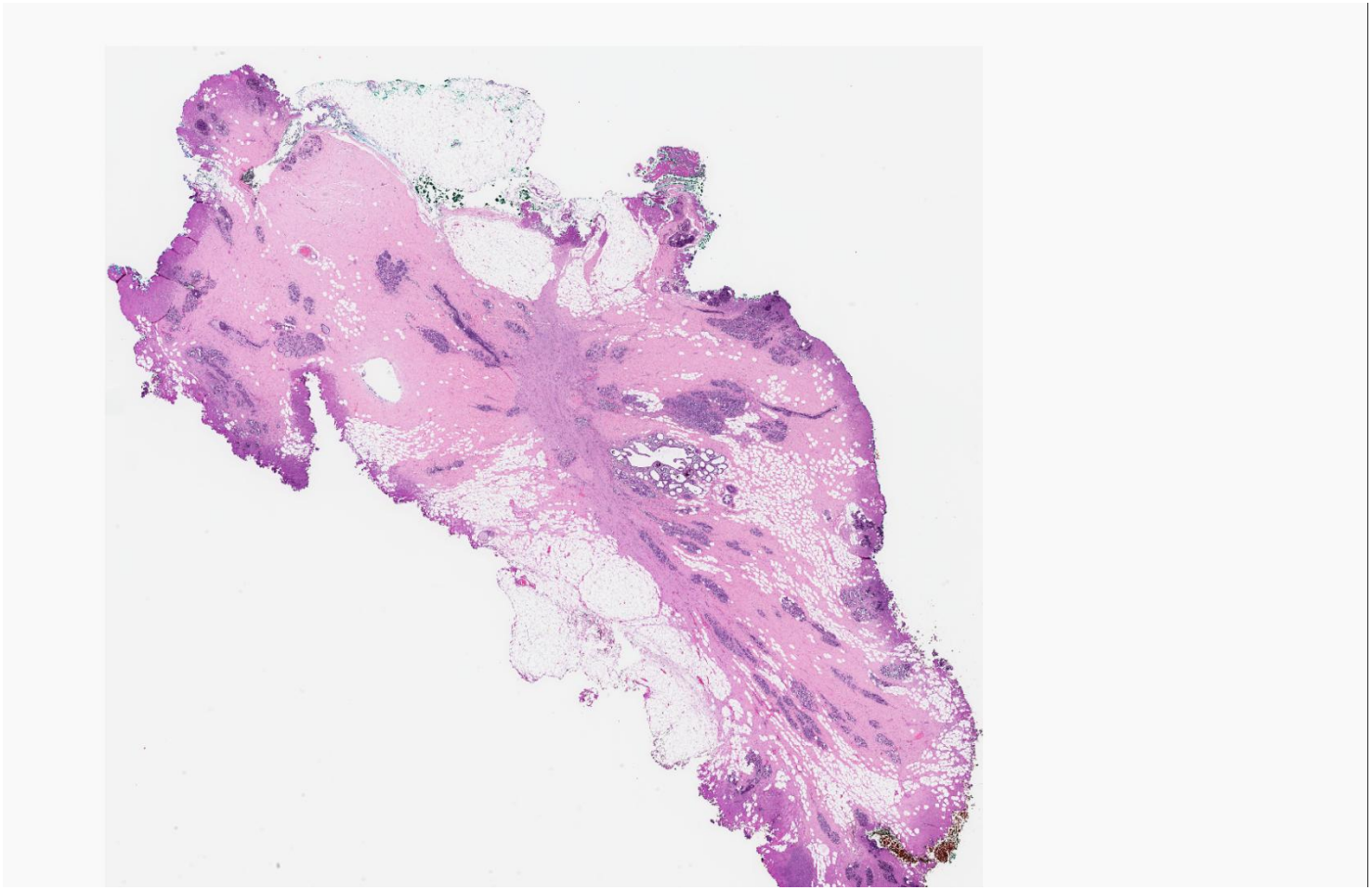
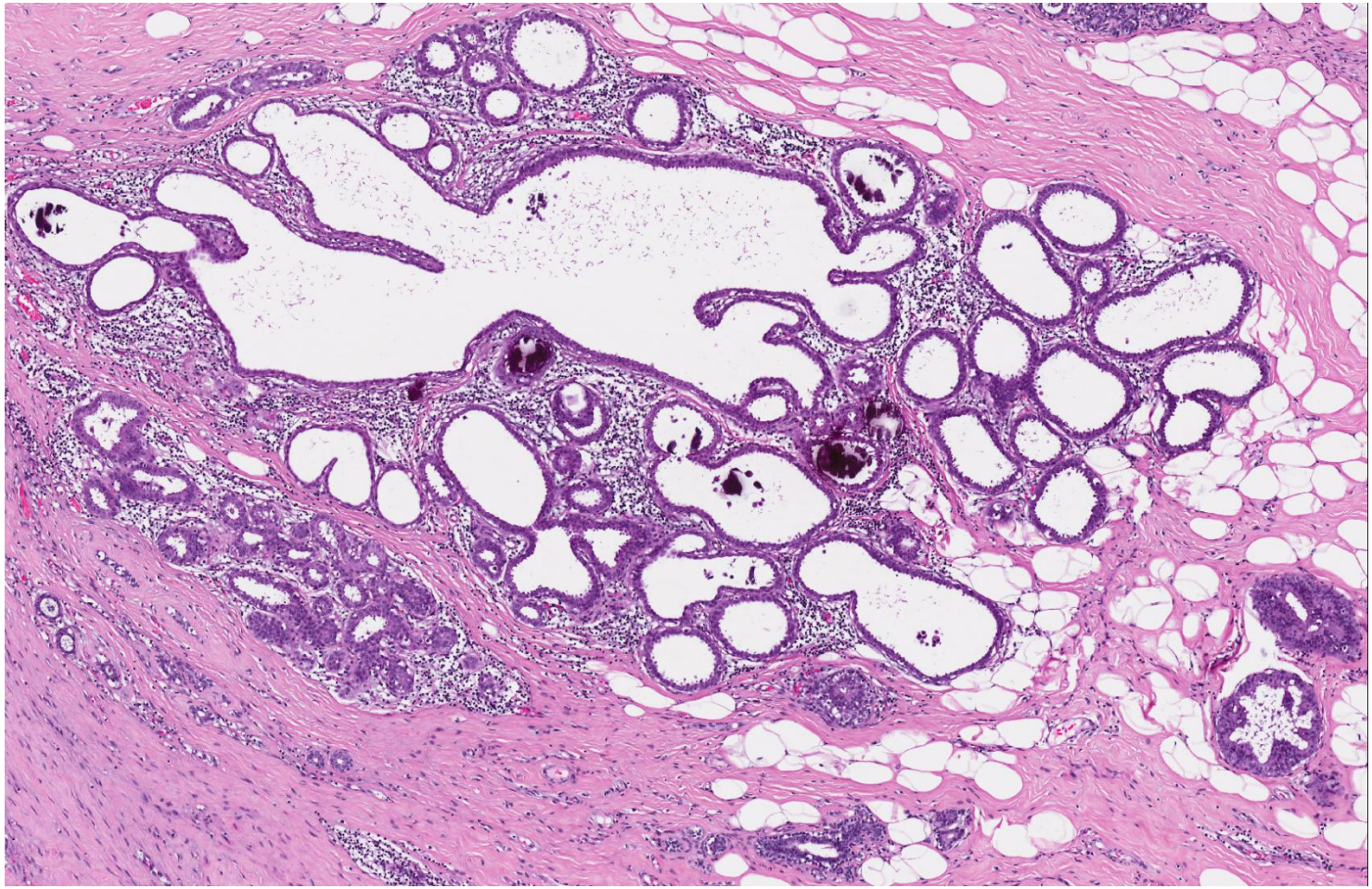
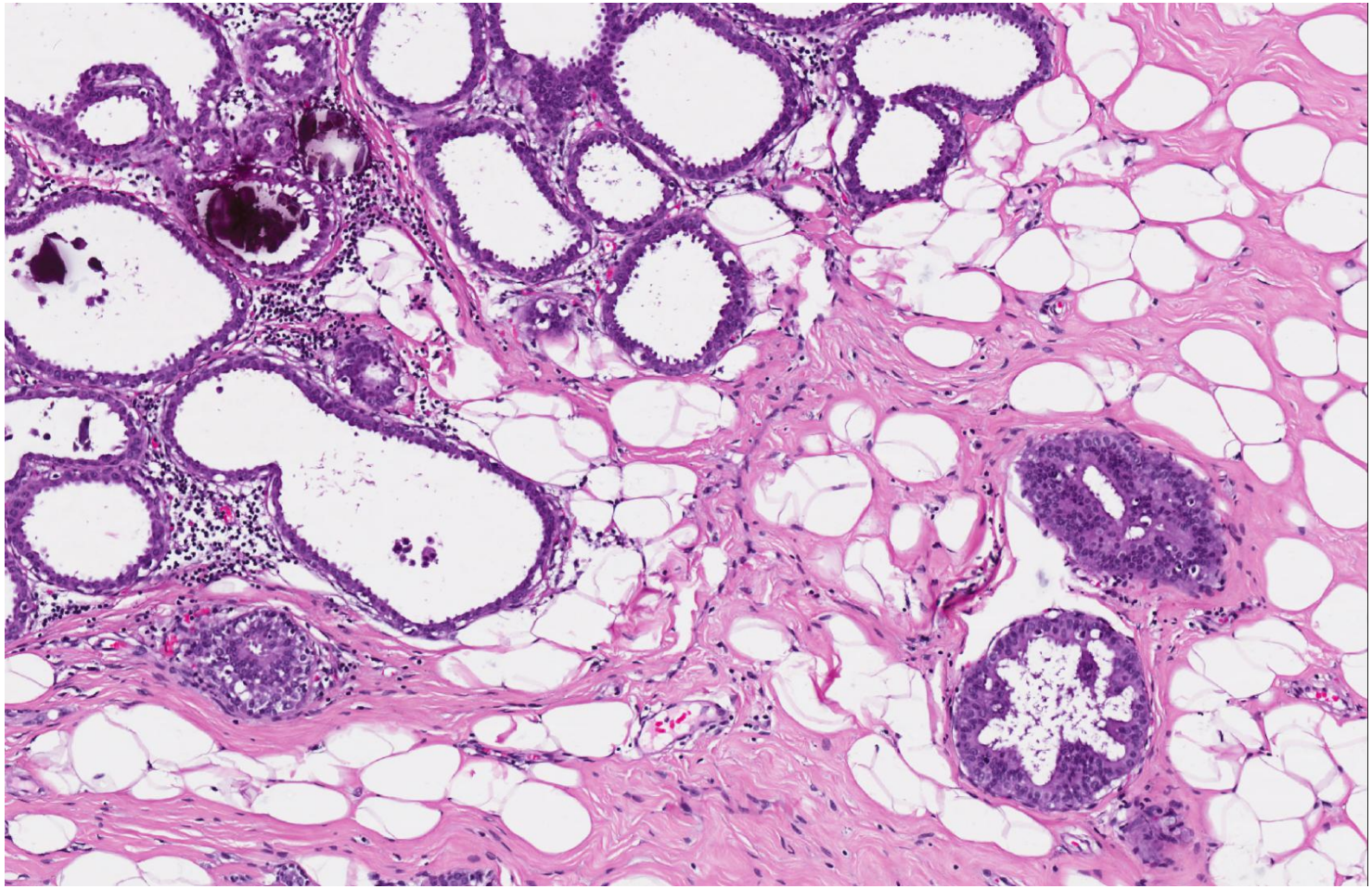
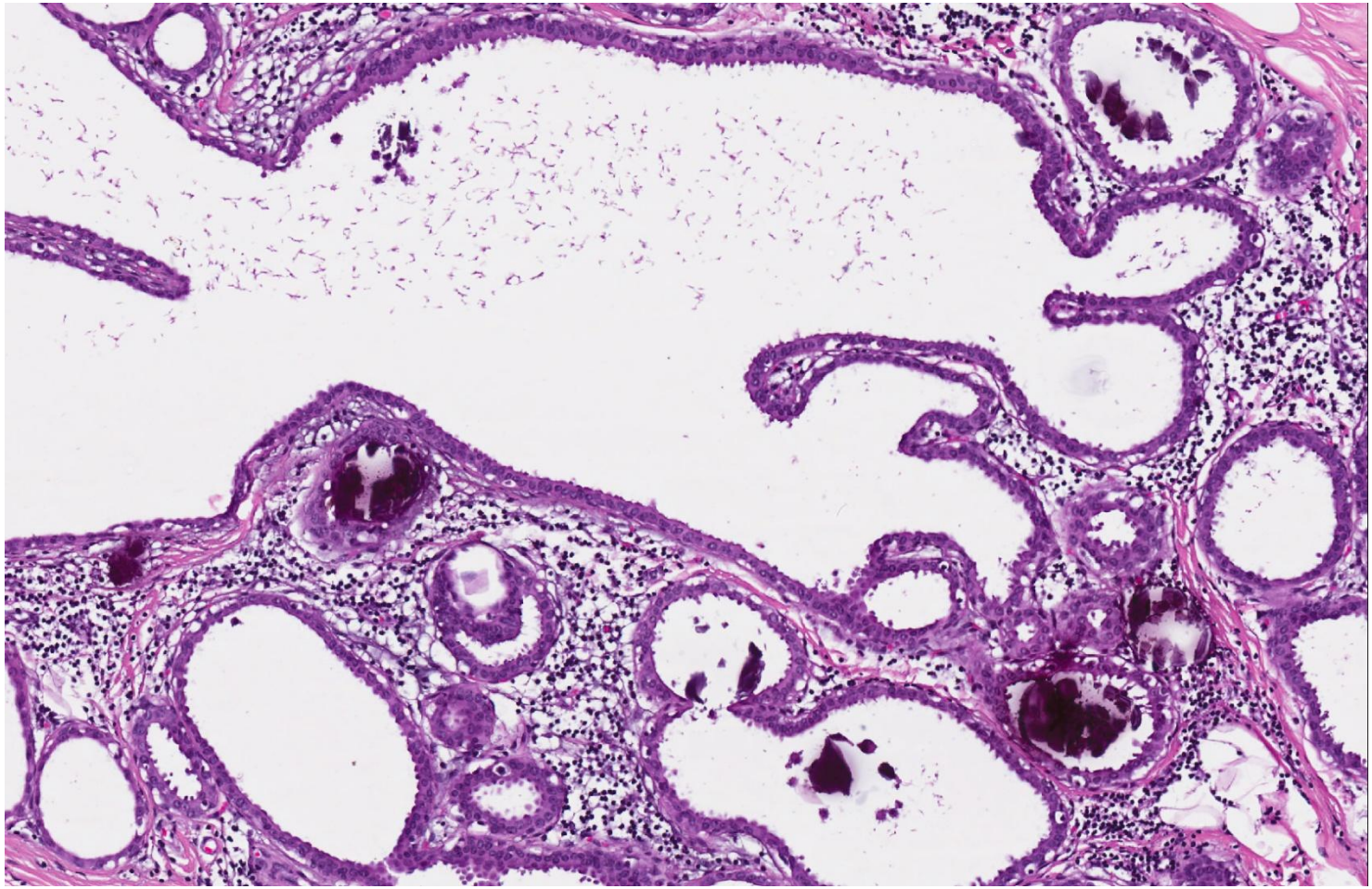
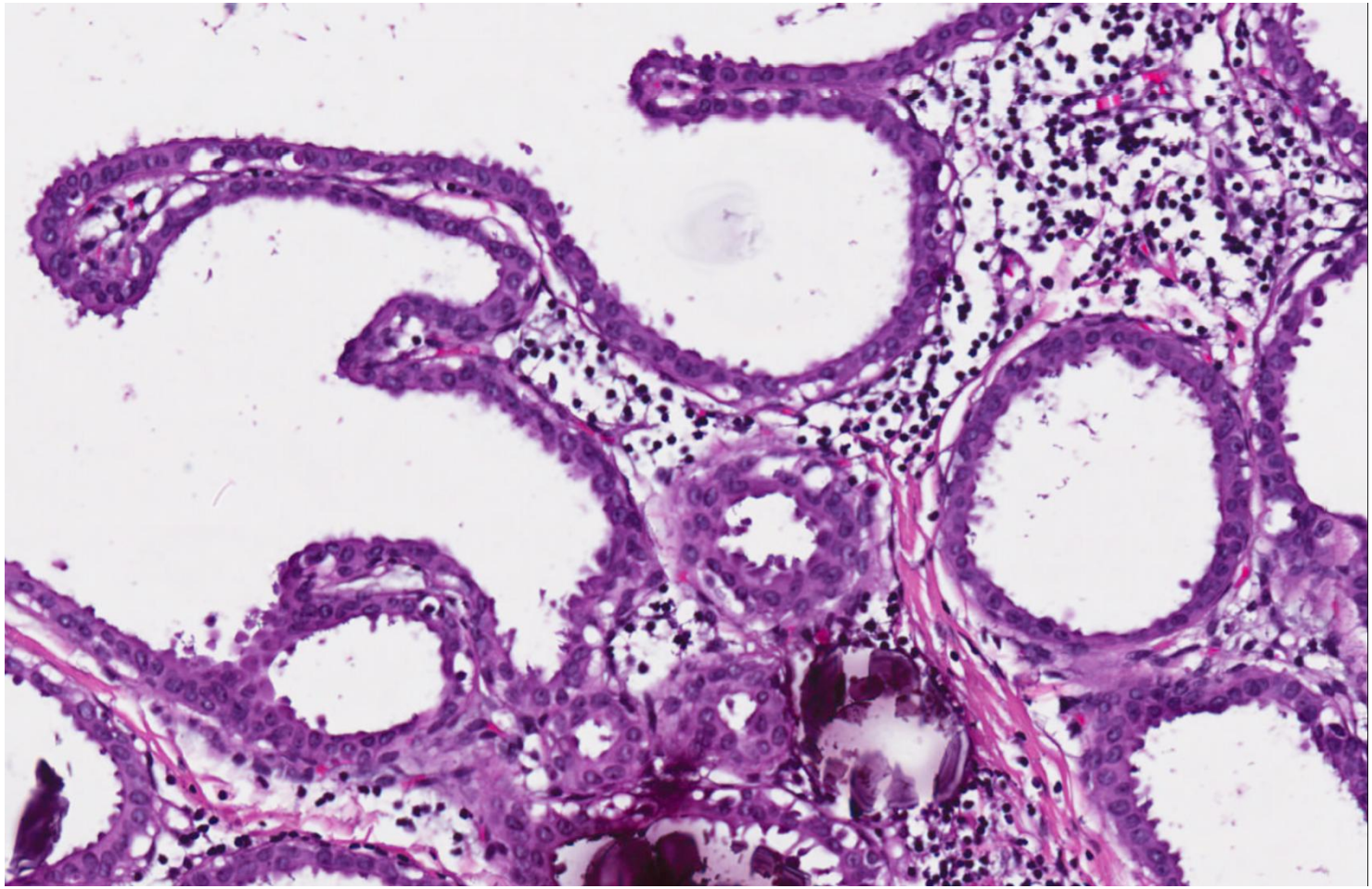
- Set B.2
- 42 year old Chinese female underwent hookwire localisation excision biopsy of screen detected calcifications in the left breast.

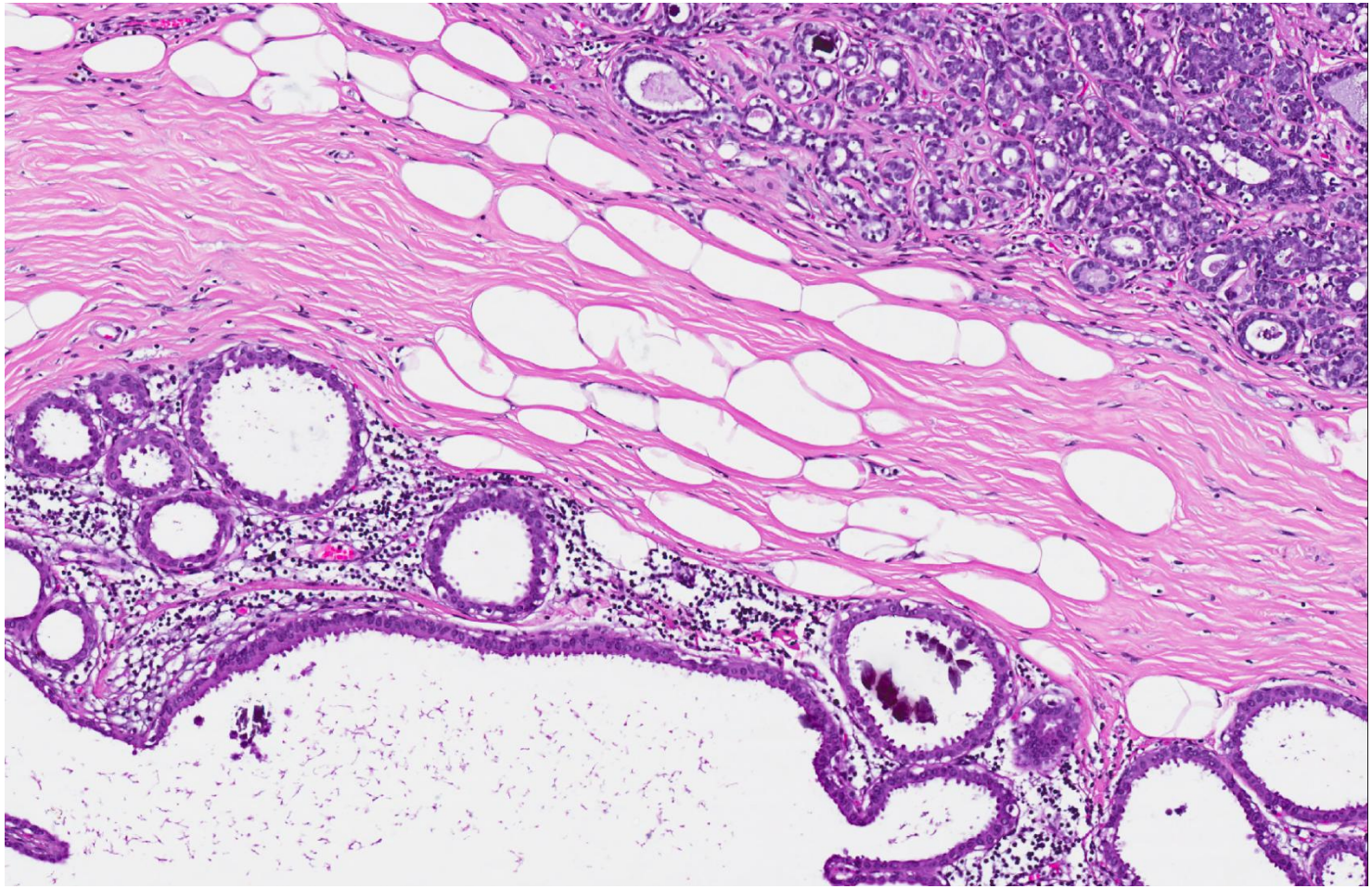


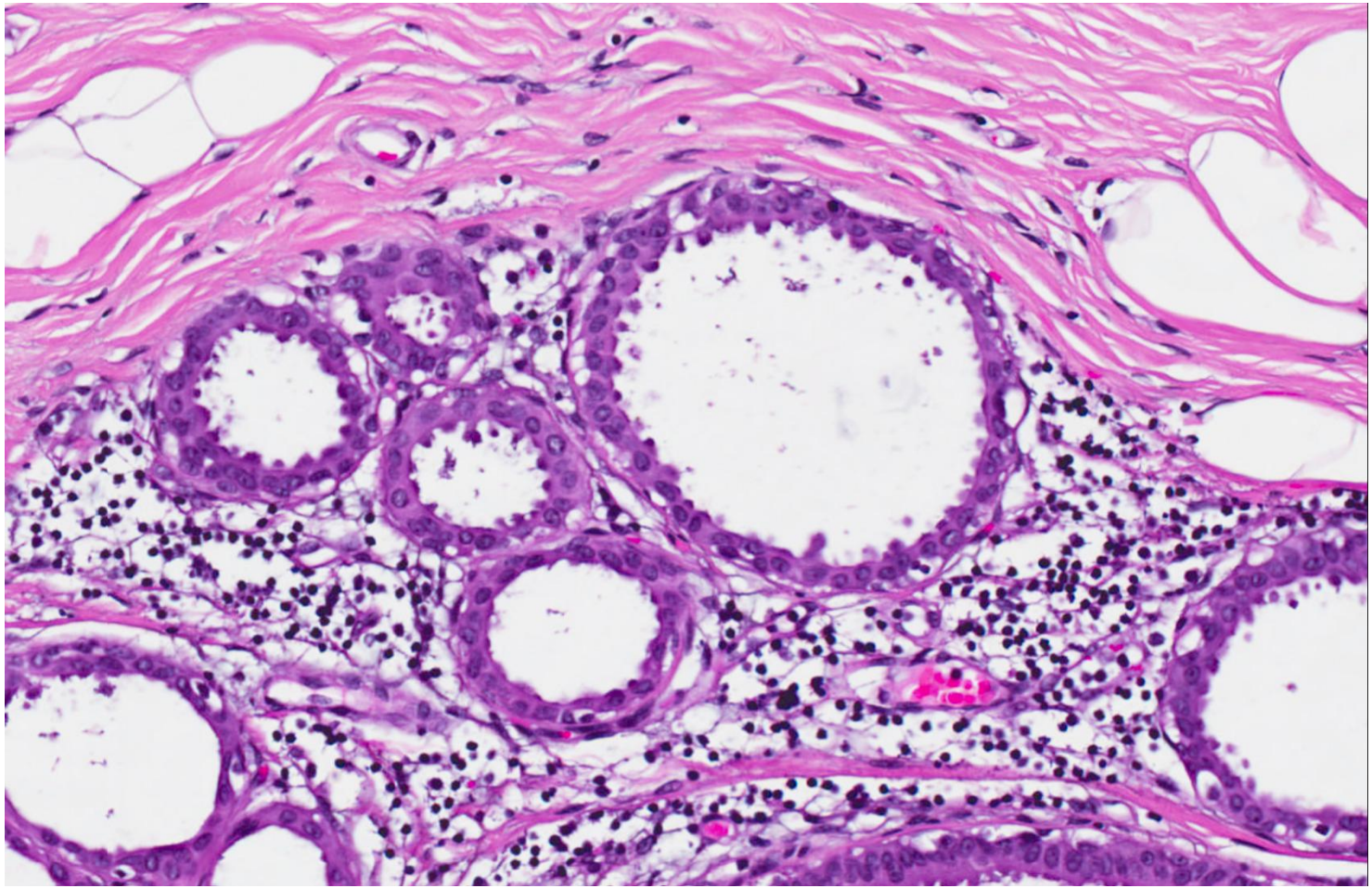


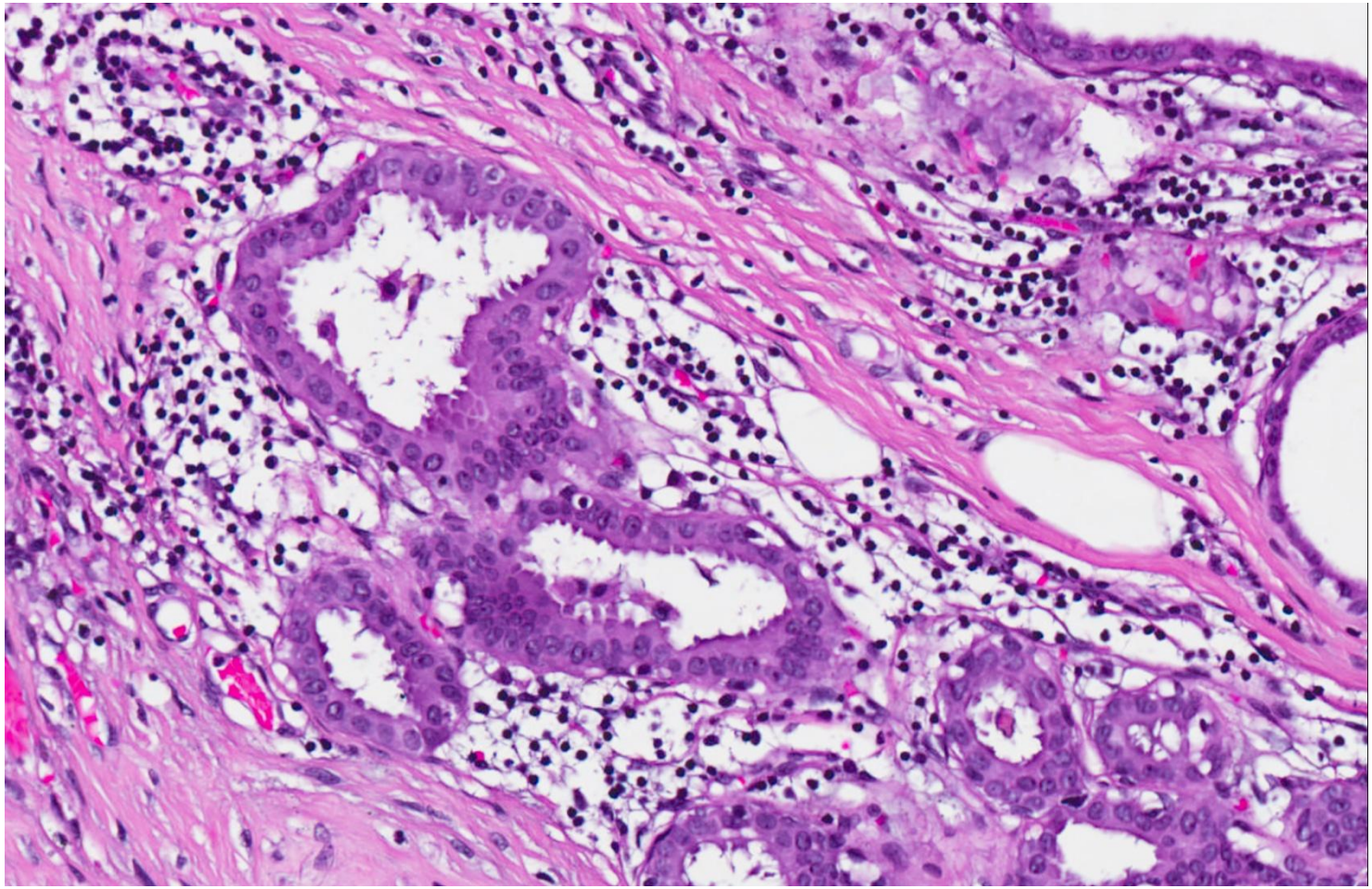


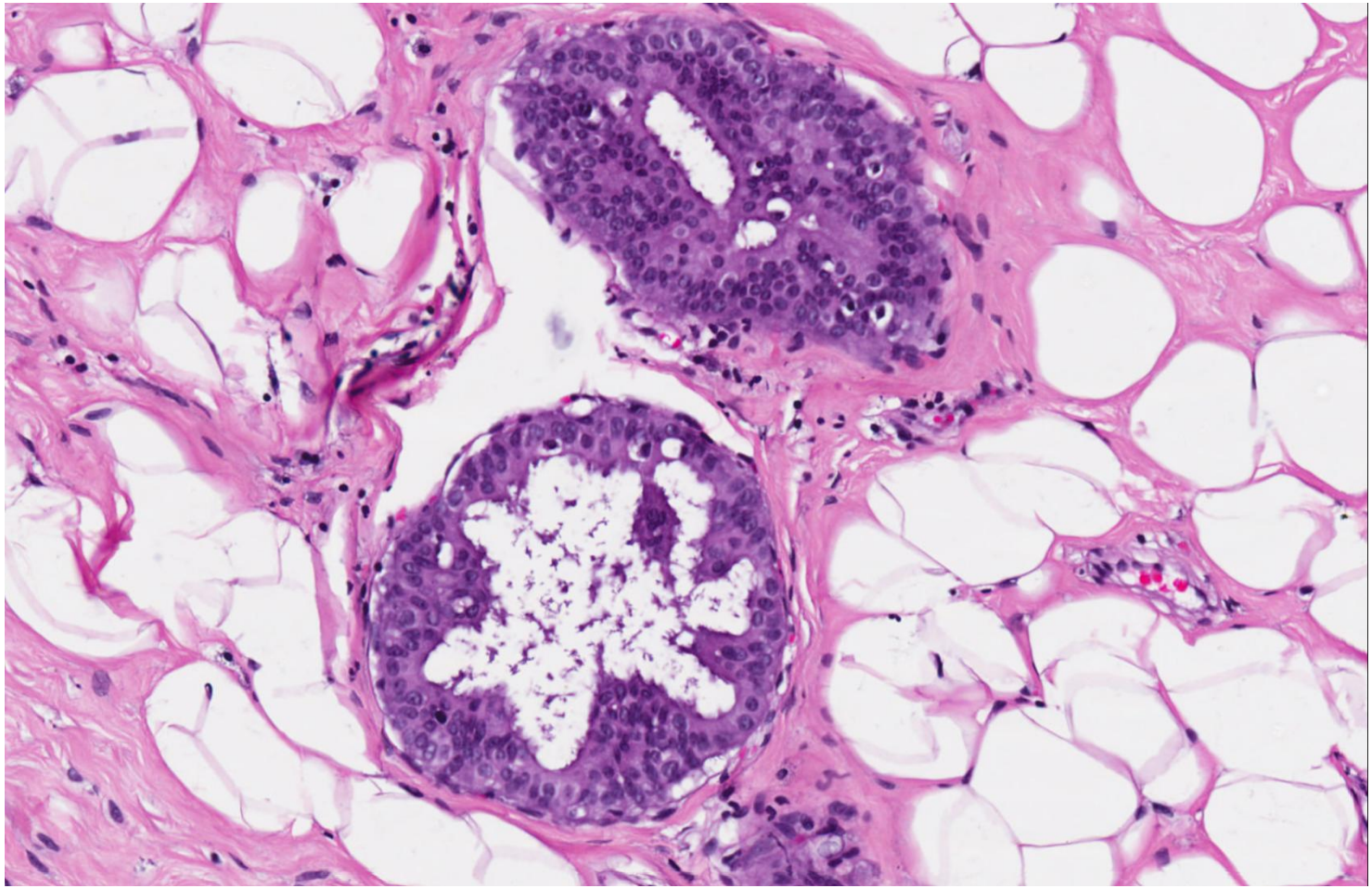


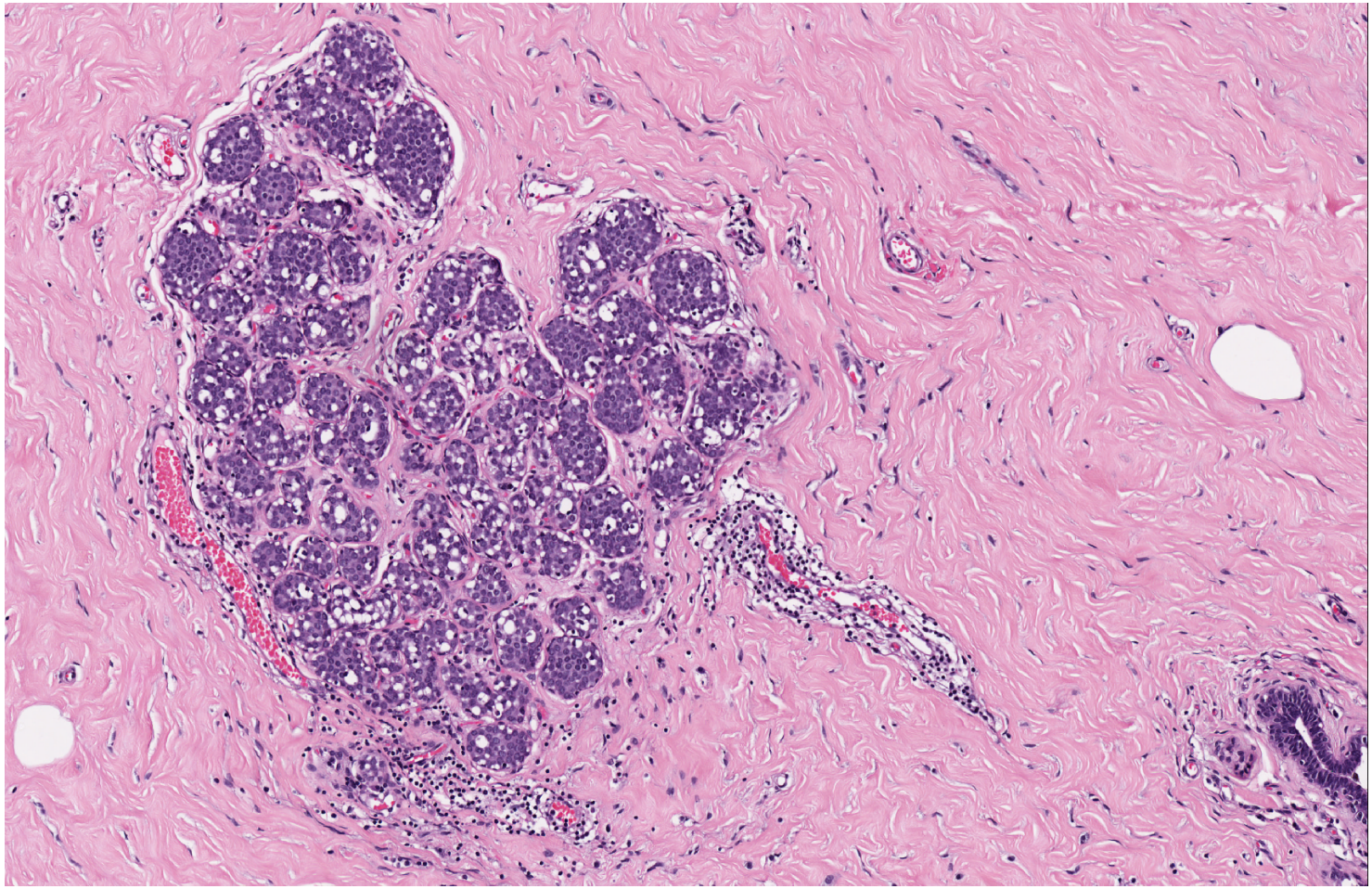


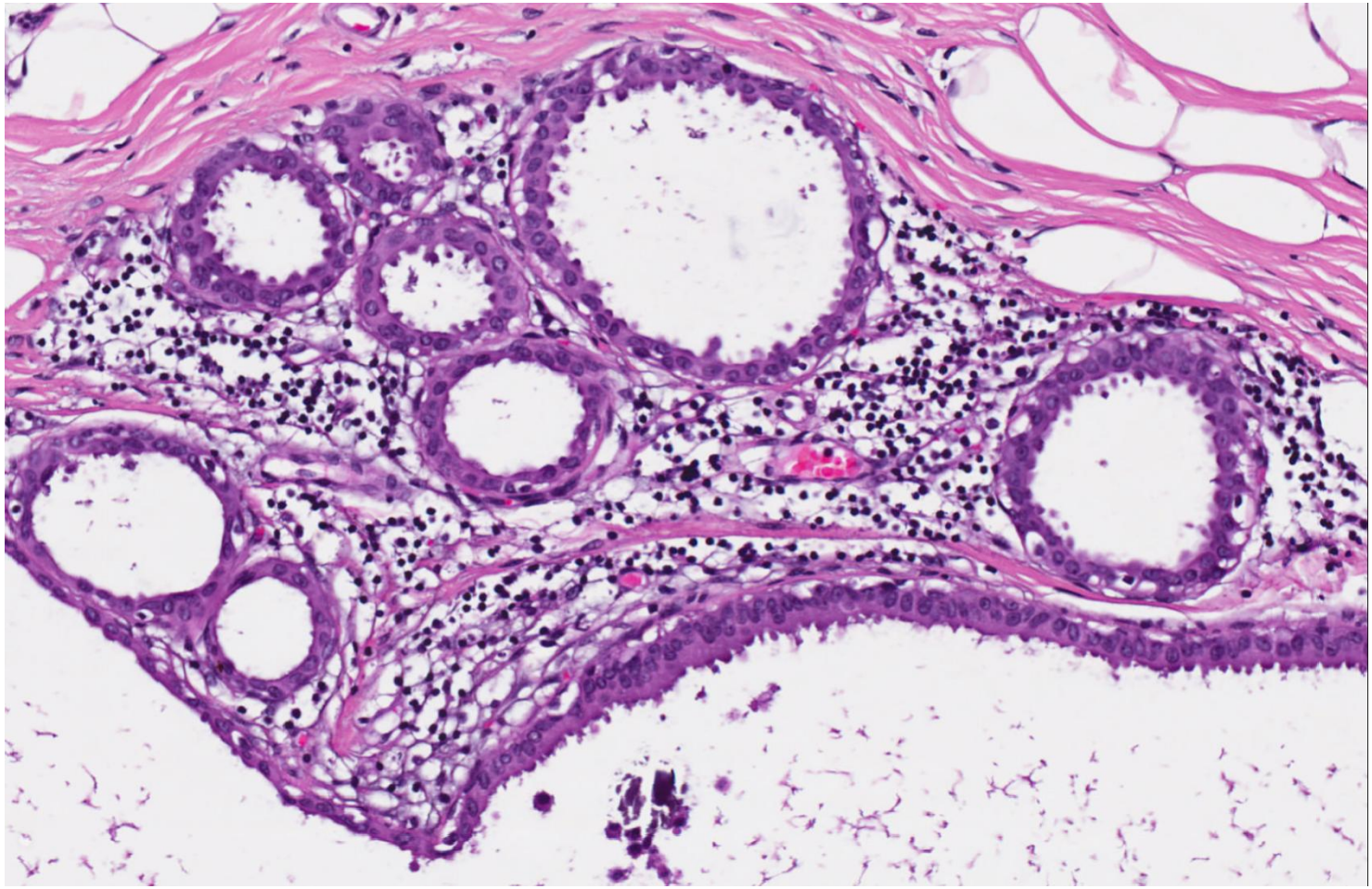


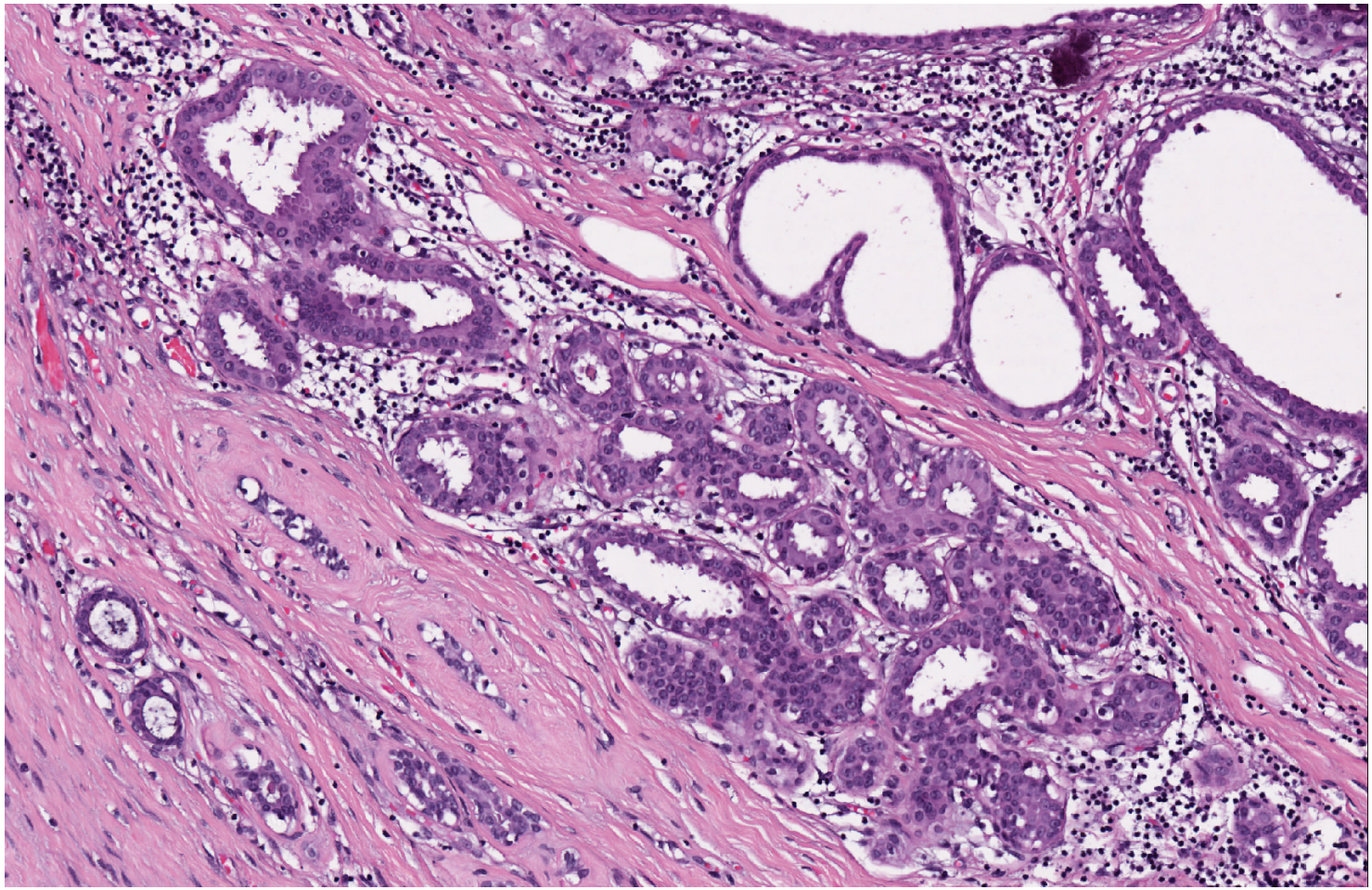












- Columnar cell lesion with flat epithelial atypia (FEA) and multifocal atypical lobular hyperplasia (ALH).

Flat epithelial atypia

- Presumably neoplastic intraductal alteration characterised by replacement of native epithelial cells by a single or 3 to 5 layers of mildly atypical cells.

  (*World Health Organisation 2003*)

Terminology

- Atypical lobule type A (Wellings et al, 1975).
- “clinging carcinoma” (Azzopardi, 1979).
- Small ectatic ducts lined by atypical ductal cells with apocrine snouts (Goldstein & O’Malley, 1997).
- Columnar alteration with prominent apical snouts and secretions (CAPSS) (Fraser et al, 1998).
- Atypical cystic lobules (Oyama et al, 1999).
- Atypical cystic duct (Kusama et al, 2000).
- Ductal intraepithelial neoplasia 1-flat type (Tavassoli).
- Enlarged lobular units with columnar alteration (ELUCA, 2004).
- *Flat epithelial atypia, recently adopted by the WHO working group on breast tumours (2003).*

Columnar cell lesions: *Pathologic classification*

- Lack of uniform terminology.
- Schnitt & Vincent-Salomon:
  - Columnar cell change.
  - Columnar cell hyperplasia.
  - Columnar cell change with atypia.
  - Columnar cell hyperplasia with atypia.

} ***Flat epithelial atypia***

- Flat epithelial atypia:
  - *Distinguished from atypical ductal hyperplasia by absence of architectural atypia.*
  - *Lacks micropapillary tufts, Roman bridges and rigid arcades.*

Flat epithelial atypia: *an early neoplastic transformation?*

- Morphologic evidence:
  - Association with lobular neoplasia, low grade DCIS, tubular carcinoma.
  - 14 of 32 (43.7%) cases of invasive tubular carcinoma associated with "small ectatic ducts lined by atypical ductal cells with apocrine snouts". *Goldstein & O'Malley, AJCP 1997; 107: 561-6.*
  - Associated with DCIS with shared cytological characteristics. *Oyama et al, Virchows Arch 1999; 435: 413-21.*

Flat epithelial atypia:
an early neoplastic transformation?

- Immunophenotypic and molecular genetic evidence:
  - Similar immunohistochemical profile with low grade DCIS: CK19, ER, PR, cyclin D1 positive.
  - Downregulation of 14-3-3 sigma protein.
  - LOH of 11q and 16q.

Columnar cell lesions: *Molecular studies*

- Morphologic classification mirrors level of genetic instability observed by CGH.

  Simpson et al. Am J Surg Pathol 2005; 29: 734-746.

- Columnar cell change (CCC), 1.6
- Columnar cell hyperplasia (CCH), 2.8
- CCH with architectural atypia, 3.8
- CCH with cytologic atypia, 3.8
- CCH with cytologic and architectural atypia, 4.4
- CCC with atypia, 1.9

Histologic mimics

TABLE 1 Summary of salient histological features of flat epithelial atypia and its mimics

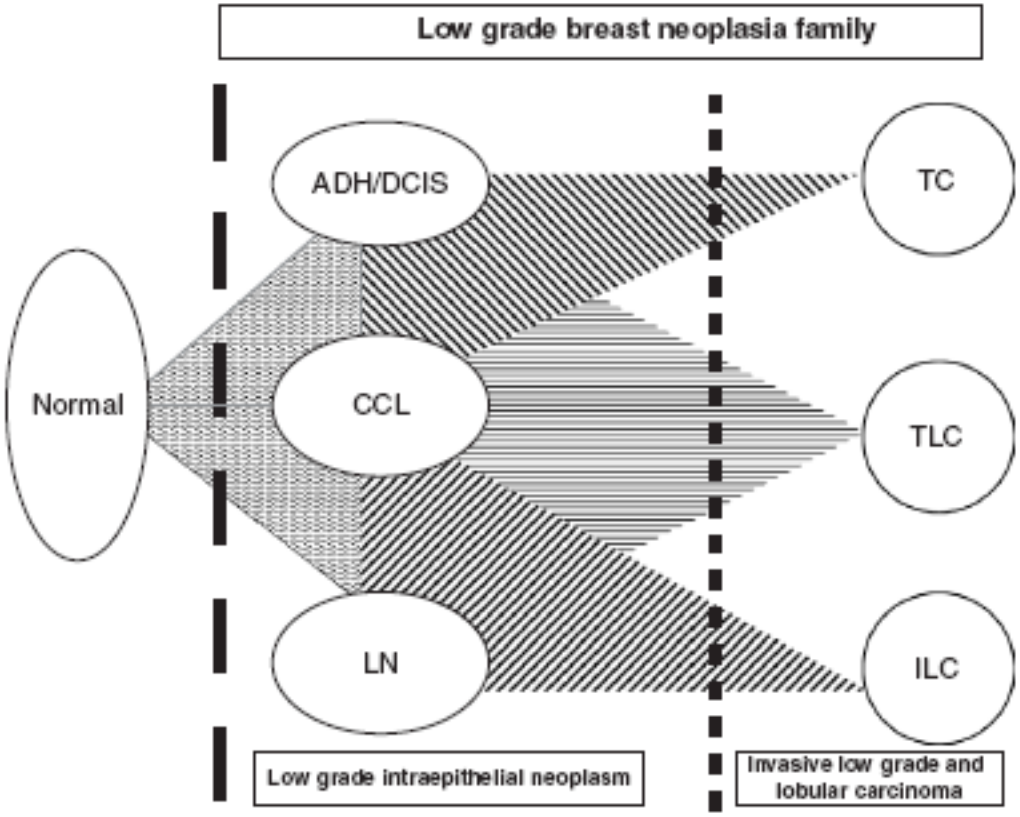
Lesion	Architecture	Cytology	Remarks
FEA	Single layer or stratified; loss of cellular polarity may be evident; no architectural complexity	Monomorphic with mild atypia; nuclear-cytoplasmic ratio increased compared with CCC/CCH; nuclei tend to be ovoid to rounded, and may show nucleoli	A potentially challenging diagnosis to make since no single feature is specific; need to exclude areas of complex architectural formation, especially in extensive lesions
CCC	Single to two layers of cells oriented perpendicular to basement membrane; no architectural complexity	Some degree of cellular variation seen, nuclei elongated and oriented perpendicular to basement membrane; small cytoplasmic snouts	Devoid of cytological atypia; assessment of atypia may be tricky and arguable in certain instances
CCH	More than two cell layers (stratified) oriented perpendicular to basement membrane; small tufts or mounds may form but no architectural complexity seen	Some degree of cellular variation seen, nuclei elongated and oriented perpendicular to basement membrane; apical cytoplasmic snouts more exaggerated than in CCC	Devoid of cytological atypia
Apocrine metaplasia	Usually single layer without stratification; no architectural complexity	Abundant pink cytoplasm; nuclear-cytoplasmic ratio much lower than CCC, CCH or FEA; nuclei generally round and may show small nucleoli	Abundant eosinophilic cytoplasm is a useful distinguishing feature
Low-grade DCIS	Architectural complexity present in the form of Roman bridges or rigid arcades with cells polarised towards lumina	Monomorphic with mild nuclear atypia, cells polarised towards lumina	Architectural atypia localised to a single duct space; may be considered atypical ductal hyperplasia

FEA, flat epithelial atypia; CCC, columnar cell change; CCH, columnar cell hyperplasia; DCIS, ductal carcinoma *in situ*.

Natural history of flat epithelial atypia

- Limited information.
- Indolent behaviour.

- 2 distinct low-grade and high-grade pathways of progression.
- Blurring the boundary between ductal and lobular routes of breast carcinogenesis.



Tarek et al. Am J Surg Pathol 2007; 31: 417-426

Columnar cell lesions: *Practical considerations*

- If CCL are identified in the absence of cytologic or architectural atypia, no further action is needed.
- If a CCL is associated with cytologic (FEA) and/or architectural (ADH) atypia:
  - Open biopsy: follow-up.
  - Core biopsy: follow with open biopsy.
  - Need for radiologic-pathologic correlation.

Table 1: Correlation of CCL on core biopsy with their subsequent excision biopsy.

	Core biopsy	Excision biopsy						
	CCL diagnosis	Invasive CA	DCIS	Lobular neoplasia	ADH	FEA	No atypia	Additional comments
Martel, et al, 2007 (abstract)[11]	Flat DIN 1 (FEA): (n=24)	9 (14.3%)	7 (11.1%)					Excision 15 days to 10 years after (n=24)
	Flat DIN 1 (FEA): (n=5)	0	0					Excision 3 months after
Labbe-Devilliers, et al, 2006 (abstract)[45]	CCH with atypia (n=25); CC with atypia (n=15)	4 (10%)	3 (8%)		6 (15%)	19 (48%)	9 (23%)	All carcinomas within CCH with atypia; No cancer when CCA is <10mm on core.
Lim, et al, 2006[40]	ADH (n=15)	0	6 (40%)	0	8 (53.3%)		1 (6.7%)	
	CCL with nuclear atypia (n=5)	0	1 (20%)	0	3 (60%)		1 (20%)	
	CCL with ALH (n=3)	0	1 (20%)	1	1		0	
Kunju, et al, 2006[35]	Pure FEA (n=12)	3 (21%)*		5 (36%)	1 (8%)		3 (21%)	Most common pattern of ADH: cribriform (57%), micropapillary (28%)
	Pure ADH (n=7)	3 (38%)*		0	2 (25%)		2 (25%)	
	FEA+ADH (n=31)	4 (11%)*		6 (16%)	2 (5%)		19 (50%)	
Guerra-Wallace, et al, 2004[25]	CAPSS without atypical features (n=6)	0	1 (17%)†					No statistical difference between the 3 categories (ADH, CAPSS with atypical features, CAPSS with atypical features (P=0.621)
	CAPSS with atypical features (n=31)	1 (3%)	3 (10%)†					
	ADH	1 (3%)	8 (22%)†					
Bonnet, et al, 2003[41]	Columnar alteration with atypia (n=9)	2 (22%)*			3 (33%)		4 (44%)	

*DCIS/invasive carcinoma
† In situ carcinomas (DCIS/LCIS)

Table 5 Histological correlations between stereotactic vacuum-assisted core biopsy and surgical excision in columnar cell lesions group

		Number	*Histology at surgery*			*Radiological FU (months)*
			Benign	*Atypia (LIN/ADH/FEA)*	*Malignancy (DCIS/IC)*	*Mean 38 ± 6.8*
B2	CCL without atypia	68	5 (7%)	–	–	63 (93%)
B3	FEA	38	13 (34%)	20 (53%)	–	5 (13%)
	CCL without atypia and papilloma	1	–	–	–	1 (100%)
	CCL without atypia or FEA with LIN	11	2 (18%)	5 (45%)	1 (9%)	3 (27%)
	CCL without atypia or FEA with ADH	2	1 (50%)	1 (50%)	–	–
B4	Extensive FEA	3	1 (33%)	2 (67%)	–	–
B5	CCL without atypia and DCIS	4	–	–	4 (100%)	–
	FEA and DCIS	9	–	1 (11%)	8 (89%)	–
	CCL without atypia with IC	1	–	–	1 (100%)	–

CCL: columnar cell lesions; FEA: flat epithelial atypia; LIN: lobular intraepithelial neoplasia; ADH: atypical ductal hyperplasia; DCIS: ductal carcinoma *in situ*; IC: invasive carcinoma; FU: follow up.

Senetta et al. Mod Pathol 2009; 22: 762-769

'FEA, as the only histological finding on vacuum assisted core biopsies, was never associated with malignancy at surgery'

TABLE 1. Findings on Surgical Excision After Core Needle Biopsy Diagnosis of Pure FEA or FEA+ADH

		Diagnosis on Surgical Excision					
		CDIS	CRINV	FEA	FEA + LN	FEA + ADH	No Lesions
Diagnosis on CNB	FEA	0	0	10	5	1	4
	FEA + ADH	2	1	2	0	3	2

ADH indicates atypical ductal hyperplasia; CNB, core needle biopsy; CDIS, ductal carcinoma in situ; CRINV, invasive carcinoma; FEA, flat epithelial atypia; LN, lobular neoplasia.

Piubello et al. Am J Surg Pathol 2009; 33: 1078-1084

'….patients with an 11-gauge vacuum-assisted CNB diagnosis of pure FEA (esp if related to a small radiologic target, completely or almost completely removed…….) could be spared surgical excision and managed with close radiologic follow-up.'

Columnar cell lesions: *Practical considerations*

- To look for associated lesions when FEA is present:
  - Lobular neoplasia.
  - ADH/DCIS.
  - Tubular/tubulolobular carcinoma.
  - Invasive lobular carcinoma.

Columnar cell lesions: *Practical considerations*

- Possibility of follow-up without need for open surgery if FEA is the most advanced lesion found on core biopsy, especially if the entire radiologic lesion is removed.

Conclusions

- Flat epithelial atypia is an evolving lesion.
- More information is required about the true biology of this lesion in order for better understanding and management.

Learning points

- Criteria for FEA.
- Coexistence of FEA and ALH.
- Recuts show ALH within FEA.
- Recognition of previous biopsy site.
- Approach to management of FEA on excision biopsy.