Histological Detection of High-Risk Benign Breast Lesions from Whole Slide Images

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1. ABSTRACT

- Accurate diagnosis of high-risk benign breast lesions is **crucial** since they are associated with an increased risk of invasive breast cancer development.
- Since it is not yet possible to identify the occult cancer patients without surgery, this limitation leads to retrospectively **unnecessary surgeries**.
- Here, we present a computational pathology pipeline for histological diagnosis of high-risk benign breast lesions from whole slide images (WSIs).
- Our computational pathology pipeline includes:
  - WSI stain color normalization,
  - Ductal regions of interest (ROIs) segmentation, and
  - Cytological and Architectural feature extraction to classify ductal ROIs into triaged high-risk benign lesions.
- We curated 93 WSIs of breast tissues containing high-risk benign lesions.
- Ground truth annotations collected from 3 pathologists.
- Our method has comparable performance to expert pathologists.

2. BACKGROUND

- Benign breast lesions remain a critical source of **disagreement and uncertainty** for breast pathologists [1].
- These benign lesions include; atypical hyperplasias, which include atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH), are found in 12-17% of biopsies performed; and flat epithelial atypia (FEA), which is an alteration of the breast lobules, all with long term **breast cancer risks**.

  On the other hand, columnar cell change (CCC) is a relatively common, non-atypical proliferative lesion that has very low risk despite morphological similarity to FEA (Figure 2).
- Diagnostic criteria exist but rely on **atypia**, which is a subjective feature that may lack reproducibility (%52 misdiagnosis among 115 pathologists [1]).
- **Computational pathology** tools aid in minimizing diagnostic discordance and providing quantitative measurements for differential diagnosis of proliferative breast lesions.
- An end-to-end system for detecting ductal carcinoma in situ (DCIS) was proposed by [2], in which ROIs from WSIs were delineated and classified into benign vs. DCIS.
- No such tool exist for **high-risk benign breast lesions**, since discordance makes the cases difficult to identify.

3. DATA

- **46 ADH cases** from Magee Womens Hospital of UPMC.
- **93 WSIs** were selected by Dr. Fine as containing at least one high-risk benign lesion.
- **1759 ROIs** were derived using method in Figure 1(B).
- 1009 ROIs are labeled by Dr. Fine, forming the training set, and 750 ROIs labeled by all three pathologists.
- Labeling options include : “ADH”, “FEA”, “CCC”, “Normal”, “Don't know”, and “Other”.
- ROIs in which all three pathologists disagreed were discarded.
- “ADH” and “FEA” are grouped in “high-risk”, and “CCC” and “Normal duct” are grouped in “low-risk”.
- In total, we observe 251 “high-risk” and 588 “low-risk” in the training set and 71 “high-risk” and 537 “low-risk” in the test.
- The overall Fleiss' kappa score is .55, indicating a moderate agreement between the pathologists.
- Pathologist agree on ADH for only 9% of the time.

References
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4. METHOD

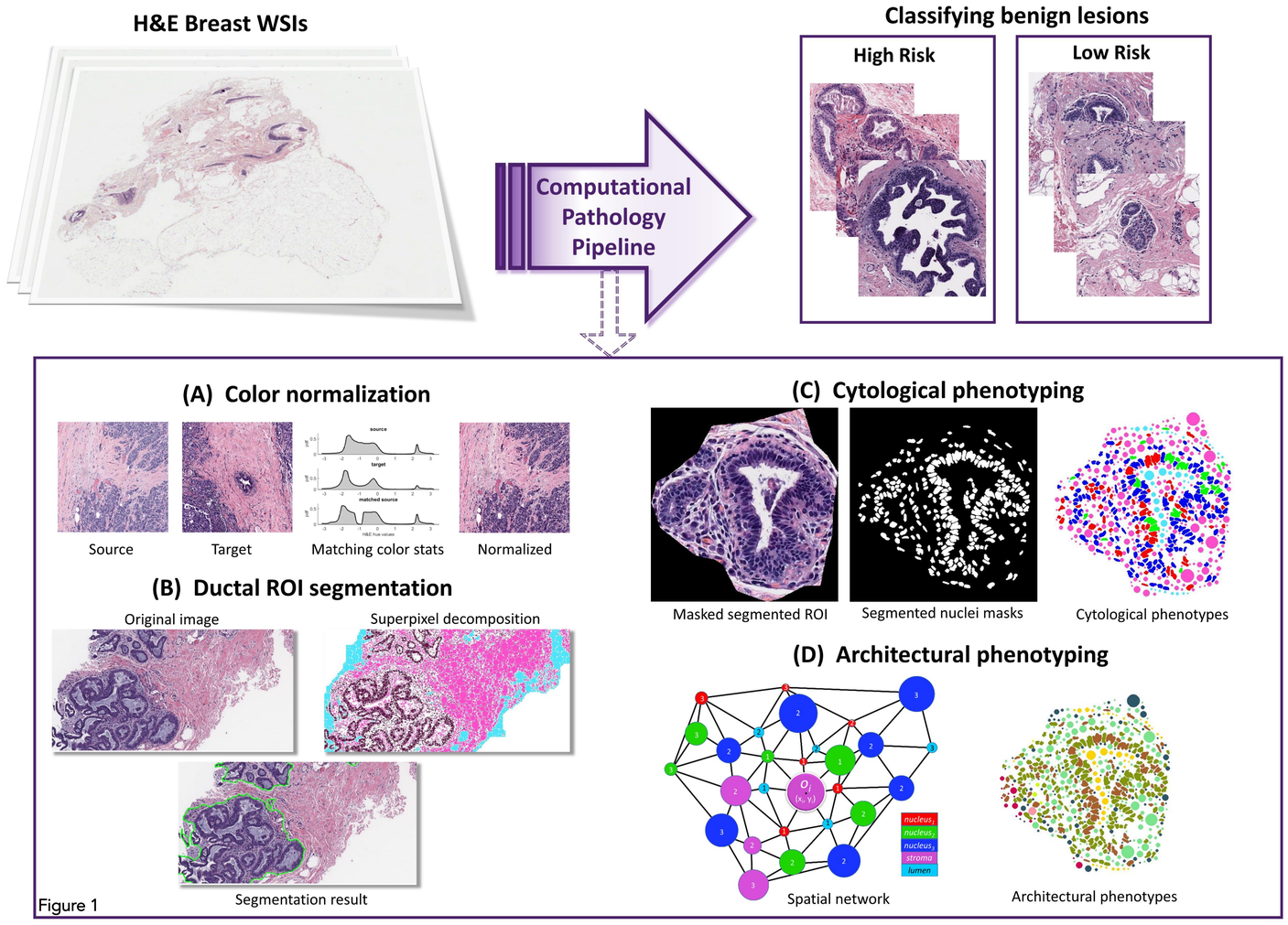

Figure 1

(A) Color normalization

- A scalable color normalization method based on opponent color spaces is used [3].
- This color space is angular, the stains are separated using a mixture of von Mises distributions.
- This method is scaled to work with large WSIs (single core ~90secs per slide).

(B) Ductal ROI segmentation

- The spatial density of epithelial nuclei used to segment ducts from breast WSIs.
- WSI is decomposed into superpixels to approximately denote the nuclei, stroma, and lumen components of the tissue [4].
- Delaunay triangulation is performed on superpixel centers for a neighborhood graph [4].
- Neighboring superpixels are connected by an edge if their physical distance is below the median distance between pairs of neighboring nuclei.
- Greedy connected component analysis is run to cluster the superpixels into ROIs.

(C) Cytological phenotyping

- A more precise set of nuclei masks are generated for each ductal ROI using Fiji.
- 196 features computed for each nuclei including morphological features, intensity features, and texture features.
- Three dominant phenotypes (nuclei$_1$, nuclei$_2$, nuclei$_3$) discovered, after k-means clustering; a consequence of normal, atypical, and pleomorphic nuclei in high-risk benign breast lesions.

(D) Architectural phenotyping

- Tissue is represented by 5 different objects: three cytologically phenotyped nuclei (nuclei$_1$, nuclei$_2$, nuclei$_3$) and two superpixel based components (stroma and lumen).
- A spatial network is constructed by breadth-first traversal from each object [5].
- Neighborhood statistics collected and clustered using k-means.
- Each image is then represented by the relative proportion of q architectural patterns, which covers 95% of the input variance.

5. RESULTS & CONCLUSIONS

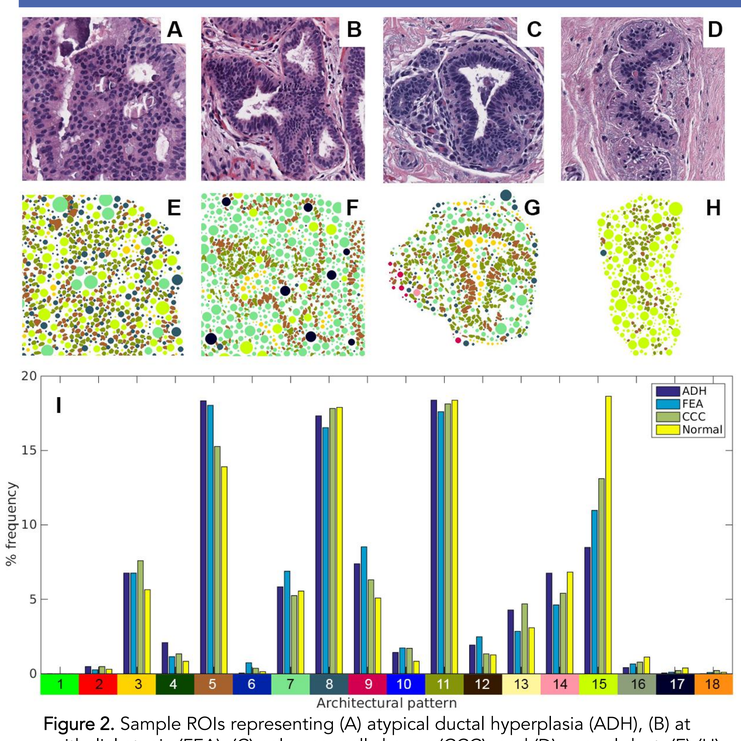

Figure 2. Sample ROIs representing (A) atypical ductal hyperplasia (ADH), (B) at epithelial atypia (FEA), (C) columnar cell change (CCC), and (D) normal duct. (E)-(H) Visualization of architectural patterns discovered in ROIs. Patterns are derived from a combination of cytological and architectural features and visualized by color coded objects (see x-axis of panel (I)).

- In **Figure 2**, note the overexpression of pattern #5 in ADH, #7 in FEA, and #15 in normal ducts (E)-(H). This observation is further supported by the histogram in panel (I), where we measure relative proportions of architectural patterns separately in each one of the categories: ADH, FEA, CCC, and normal.
- We tested classification with Naive Bayes, Decision Tree, SVM, and Logistic Regression (which performed the best).
- Below is the performance of our models using Color Architectural Features (AF-C), Nuclei Architectural Features (AF-N), Combined Architectural Features (AF-CN), Cytological Features (CF).

	Majority	Expert	AF-C	AF-N	AF-CN	CF
Recall (High-Risk)	0.00	0.77	0.65	0.65	0.65	0.69
F-measure (Weighted)	0.83	0.78	0.62	0.71	0.76	0.83

- It took ~24 minutes per WSI end-to-end processing on a single core machine.
- We built the first end-to-end computational pipeline for histological diagnoses of high-risk vs. low-risk benign breast lesions.
- Results highlight the challenge of diagnosing atypical breast lesions.
- The key contribution is in encoding morphometric properties of nuclear atypia (cytological) and combining them with the spatial distribution of nuclei in relationship to stroma and lumen (architectural).

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