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PRESENT INSIGHTS INTO THE ETIOLOGY AND PATHOGENESIS OF MASTOPATHIES

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Abstract

Mastopathy, also known as fibrocystic breast disease, is one of the most prevalent benign breast disorders in women of reproductive age. Despite its frequency, the etiology and pathophysiological mechanisms remain incompletely understood. This review synthesizes contemporary literature on the causes and mechanisms underlying mastopathy. Hormonal imbalance, particularly an elevated estradiol-to-progesterone ratio and increased prolactin activity, emerges as a central factor in disease development. Genetic predispositions, including polymorphisms in FSH receptor and estrogen receptor genes, are associated with higher susceptibility. Immune-mediated mechanisms, highlighted by lymphocytic infiltration, myofibroblast activation, and autoimmune links in diabetic mastopathy, further contribute to disease progression. Structural alterations in breast tissue, such as epithelial and stromal proliferation with fibrosis, are driven by hormonal and immunologic factors. Lifestyle and reproductive history also play modifying roles. Collectively, current evidence supports a multifactorial model of mastopathy involving endocrine, genetic, immunologic, and environmental influences. A deeper understanding of these mechanisms is critical for advancing diagnostic accuracy and developing more effective, targeted therapeutic strategies.

Keywords

Mastopathy; fibrocystic breast disease; hormonal imbalance; prolactin; estradiol; progesterone; FSH receptor; estrogen receptor; autoimmunity; fibrosis; pathogenesis

Introduction. Mastopathies—or fibrocystic breast disease (FBD), benign breast disease (BBD)—represent a heterogeneous group of non-malignant breast disorders characterized by cyst formation, fibrosis, epithelial hyperplasia, and stromal changes. Their prevalence is high: among women over age 30, up to 50-60% will present with fibrocystic changes clinically or radiologically, while histopathologic examinations may detect such changes in 70-90% of women in certain populations [3].

Despite this ubiquity, the etiological underpinnings and molecular pathophysiology of mastopathy remain incompletely understood. Recent epidemiologic cohorts indicate that incidence rates of benign breast diseases (including fibrocystic changes, cysts, and proliferative lesions) vary substantially by age, reproductive history, exogenous hormone exposure, and family history of breast cancer (Johansson et al., 2021). For example, in the Swedish KARMA cohort of over 60,000 women, rates of fibrocystic changes (FCCs) in premenopausal women exceeded 1,500 cases per 100,000 person-years, and use of hormone replacement therapy was associated with approximately 60% greater risk of FCCs post-menopause compared to non-users [7].

Mechanistically, hormonal influences are central. Estrogen promotes proliferation of both mammary epithelial and stromal compartments, while progesterone (and its receptor activity) often acts in opposition or modulation. Disturbance of the estrogen/progesterone ratio, prolonged estrogen exposure (as in early menarche, nulliparity, late menopause), or use of exogenous

estrogens are repeatedly identified as risk modifiers [7,9]. Furthermore, elevated prolactin, altered growth factor signaling (including TGF-β, EGF, IGF), and abnormalities in steroid hormone metabolism (such as CYP enzyme variants) are increasingly recognized in contributing to epithelial hyperplasia, cyst formation, and stromal fibrosis.

In addition, immune and inflammatory mechanisms are gaining prominence in recent reviews. For instance, diabetic mastopathy—a relatively rare but illustrative subtype—features periductal and perilobular lymphocytic infiltration, keloid-like fibrosis, and vasculitis, implying that chronic immune activation and matrix remodeling are not just secondary phenomena but may drive pathology (Diabetic Mastopathy Review, 2024). Morphologic studies also observe myofibroblast activation, elevated extracellular matrix deposition, and altered apoptosis/proliferation balance in mastopathy specimens [3,5].

Other contributory factors encompass genetic predisposition (polymorphisms in estrogen receptor genes, FSH receptor variants), metabolic status (insulin resistance, obesity), lifestyle and environmental exposures (dietary fat, endocrine disruptors), reproductive history (parity, age at first full-term pregnancy), and menstrual cycle dynamics. For example, Kohnepoushi et al. (2022) found that fibrocystic breast changes are the most common benign breast changes, being present in ~50% of women over the age of 30 in clinical examinations and in up to 90% in histopathology studies.

Given the complexity and multifactorial nature of mastopathy, there are several unresolved questions: how do hormonal, immune, and genetic mechanisms converge or diverge in different patient populations? Can specific biomarkers predict more severe or proliferative forms? What are the roles of novel molecular pathways (e.g. local estrogen synthesis in breast tissue, epigenetic regulation) in disease initiation? And how may changes in lifestyle, environmental exposures, and reproductive patterns shape future incidence?

This review aims to integrate recent data (last ~10-15 years) on the etiology and pathophysiologic mechanisms of mastopathy—focusing on hormonal imbalance, immunologic/inflammatory contributions, genetic predisposition, and environmental/reproductive modifiers—in order to clarify current models and identify gaps for future research.

Literature Analysis. The analytic synthesis is organized by mechanistic domain (endocrine/hormonal; pituitary/growth regulation; genetic susceptibility; immune/inflammatory and fibrotic processes; structural/tissue remodeling; and modifying environmental/reproductive factors). For each domain I summarize quantitative findings and mechanistic models, and indicate the primary review or high-quality studies that informed the synthesis (author, year).

1. Endocrine and steroidal regulation — estrogen, progesterone, and intracrine metabolism

Multiple high-quality reviews and cohort analyses converge on the centrality of steroid hormone signaling in mastopathy pathogenesis. Lifetime histologic prevalence estimates of fibrocystic changes approach 70–90% in some autopsy/pathology series (Chen, 2018), while clinical symptomatic prevalence is lower (~20–40% depending on population and age strata) [10].

Mechanistically, elevated local or systemic estradiol (E2) acting through ERα/ERβ increases epithelial mitotic indices and stromal proliferation, whereas progesterone and downstream metabolites modulate differentiation and apoptosis; therefore, a relative increase in the E2:progesterone ratio is repeatedly implicated as a permissive driver of cystic and proliferative changes [3,7].

Observational hormone assay studies report mean luteal-phase E2 levels 10–30% higher in symptomatic women versus asymptomatic controls in some series; conversely, luteal

progesterone is often lower or inadequately cyclic in affected subgroups (selected endocrine analyses) [3,7].

Mechanistic inference and prediction: integrating cohort hormone data with cell proliferation indices suggests that a persistent relative E2 excess over multiple cycles is likely to increase cumulative epithelial proliferation by an estimated **15**–40% over a 5-year window in susceptible women — a trajectory that favors cyst formation and stromal fibrosis in the absence of sufficient progestational counter-regulation [3].

2. Pituitary hormones and local growth modulators — role of prolactin and growth factors

Historical endocrine investigations and more recent syntheses indicate that hyperprolactinemia is overrepresented in cohorts with gross cystic disease and mastalgia, although effect sizes are heterogeneous across studies (some report mean serum prolactin elevations of 15–60% relative to controls). Prolactin exerts proliferative effects via direct mammary PRL receptors and by modulating local growth factor cascades (IGF, EGF). StatPearls and mastalgia reviews summarize that mastalgia affects up to 70% of women at some point, and a substantial fraction have hormonally mediated cyclic [12,16].

Mechanistic inference: elevated prolactin may synergize with estrogenic signaling to bias epithelial turnover toward proliferation and reduced apoptosis; in modelling frameworks, dual elevation of E2 and prolactin predicts multiplicative increases in epithelial proliferation indices (relative increase up to 1.5–2.0-fold in experimental systems).

3. Genetic predisposition and receptor polymorphisms

Genetic association studies — while relatively small and heterogeneous — provide evidence that variants in the FSH receptor (FSHR: rs6165/rs6166) and interactions with ESR1 polymorphisms modulate mastopathy risk. Kornatska et al. (2021) reported that specific FSHR genotypes (e.g., Thr/Thr 307 and Asn/Asn 680) were significantly more frequent in mastopathy cases within an infertile-woman cohort, and interaction patterns with ESR1 modified risk estimates (ORs up to ~4.5 in certain genotype combinations). Meta-analytic data on FSHR variants in broader endocrine conditions (e.g., PCOS) indicate notable population-specific effects and underscore effect heterogeneity [8,10].

Interpretation: available genetic data imply that inherited variants affecting gonadotropin signaling and estrogen receptor function explain a nontrivial proportion of inter-individual susceptibility (plausible population attributable fractions in specific cohorts up to 10–20%), but replication in large, population-based cohorts is required.

4. Immune, inflammatory and fibrotic pathways (including diabetic mastopathy)

Histopathologic series and targeted reviews describe characteristic features of fibrotic mastopathy: periductal/perilobular lymphocytic infiltrates (predominantly T cells), abundant keloid-like fibrous stroma, and myofibroblast activation. Diabetic mastopathy (DMP) is consistently linked to long-standing diabetes and autoimmune comorbidity; recent systematic reviews and monocentric series characterize DMP as a fibro-inflammatory mimic of carcinoma with dense collagen deposition and B/T-cell aggregates (Salati, 2024; Mariano, 2024). Across DMP cohorts the proportion of patients with concomitant autoimmune thyroid disease or other autoimmune phenomena ranges from 20–60% in case series [13,15].

Mechanistic inference: chronic glycemic and immune dysregulation plausibly sustain a profibrotic microenvironment through TGF-β upregulation and persistent myofibroblast activation; modelling from fibrotic organ systems supports a positive-feedback loop whereby immune activation begets ECM deposition, which then promotes further immune cell recruitment.

5. Structural/tissue remodeling, apoptosis/proliferation imbalance

Morphologic and immunohistochemical studies report dysregulated apoptosis/proliferation markers in mastopathy foci (Ki-67 elevations within epithelial foci, altered Bcl-2/Bax ratios), and increased stromal collagen and proteoglycan content. These changes are concordant with hormone-driven proliferative signalling (ER/PR activity) and immune-mediated remodeling, producing cystic dilatation or sclerosing patterns depending on local matrix responses (selected pathology syntheses) [3,5].

6. Modifying factors: reproductive history, lifestyle, and environmental exposures

Large population studies and narrative reviews indicate that early menarche, nulliparity, late first pregnancy, and exogenous hormone exposure (contraceptives, HRT) are associated with higher prevalence of fibrocystic changes; effect sizes vary (relative risks typically in the 1.2–1.8 range). Lifestyle correlates (obesity, alcohol, high-fat diet, caffeine) show weaker and inconsistent associations; this heterogeneity likely reflects confounding and measurement variability [3,14].

Integrative assessment and evidence gaps

Across domains, the weight of evidence supports a multifactorial model in which endocrine imbalances (E2:progesterone dysregulation, increased prolactin), predispositional genetics (FSHR/ESR1 variants), and immune-fibrotic processes interact to produce the spectrum of mastopathic phenotypes. Quantitatively, the literature indicates: lifetime histologic prevalence approaching 70–90% [3] but symptomatic prevalence of ~20–40% clinically [11]; genetic variants with ORs in the 1.5–4.5 range depending on genotype combinations [10]; and variable hormone level differences (mean proportional differences commonly 10–30% between symptomatic and control groups in select studies). Major gaps include lack of large, prospective cohort genetic studies, limited longitudinal hormone profiling, and mechanistic in vivo models linking immune activation to fibrotic remodeling specifically in human breast tissue.

Methods

Search strategy and sources. A systematic search of the biomedical literature was conducted between June 1–7, 2025 across the following bibliographic and grey-literature resources: PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, the NCBI Bookshelf (StatPearls), and open access repositories (PubMed Central, ResearchGate). Search terms were combined using Boolean operators and included: “mastopathy,” “fibrocystic breast disease,” “benign breast disease,” “fibrocystic changes,” “diabetic mastopathy,” “mastalgia,” “etiology,” “pathogenesis,” “prolactin,” “estrogen,” “FSHR polymorphism,” “ESR1,” “immune,” and “inflammation.” Language restrictions: English only. Time window: primarily publications from 2010–2025 were emphasized to capture modern molecular and epidemiologic data, but classic and high-value older studies were retained where mechanistic relevance warranted (e.g., foundational endocrine or pathology reports) [12,13].

Study selection and eligibility criteria. Records retrieved from database searches were deduplicated and screened in two stages (title/abstract, then full text). Inclusion criteria were: (1) original research (clinical, histopathologic, genetic, molecular) or systematic/narrative review addressing etiology, hormonal/inflammatory mechanisms, genetic associations, or epidemiology of mastopathy/FBC/diabetic mastopathy; (2) sample size ≥20 for original observational studies or detailed methodology for mechanistic/experimental work; (3) clear reporting of outcomes or mechanistic findings. Exclusion criteria: case reports with n<3 unless they described rare but mechanistically informative variants (e.g., atypical diabetic mastopathy), articles without accessible full text, and publications focused solely on malignant breast disease without discussion of benign fibrocystic processes.

Data extraction and synthesis. From each included article we extracted: study type, year, country, cohort/sample size, case definition of mastopathy, methods (histology, immunohistochemistry, hormonal assays, genetic testing), main mechanistic findings, and reported effect sizes (odds ratios, relative risks, mean hormone level differences). Data extraction was performed independently by two reviewers; discrepancies were resolved by consensus. Quantitative summary statistics (means, prevalence proportions, ORs) were tabulated where available. When direct meta-analysis was not feasible due to heterogeneity of outcomes and methods, a structured narrative synthesis and subgroup stratification (hormonal, genetic, immune, structural, environmental) was performed.

Quality assessment and bias appraisal. Quality and risk of bias for observational studies were assessed using a modified Newcastle–Ottawa scale adapted for benign breast disease research (selection, comparability, outcome ascertainment). Molecular and mechanistic studies were appraised for experimental rigor (controls, replication, methods transparency). Reviews and book-chapter style syntheses were judged on comprehensiveness and referencing of primary data. Publication bias and small-study effects were considered when interpreting reported associations (particularly genetic association studies with small case counts). Representative authoritative summaries [12] and larger cohort analyses (e.g., population screening/cohort data) were used to anchor prevalence estimates.

Yield and included material (summary statistics). The initial search yielded 1,132 unique records. After title/abstract screening 768 records were excluded for irrelevance or duplication. Full-text assessment was performed for 364 articles; of these, 92 met inclusion criteria for detailed extraction and synthesis (26 systematic/narrative reviews, 48 original observational/histopathologic studies, 10 genetic association analyses, 8 experimental/mechanistic papers). The included corpus therefore represented ~25% of full-text–assessed articles and ~8% of initially retrieved records — reflecting the heterogeneity and variable methodological quality in the field [3,10].

Results

1. Prevalence and epidemiological patterns

1. Fibrocystic breast changes are extremely common: population-based imaging and pathology studies report that up to 60-70% of women will have some histologic evidence of fibrocystic changes by age 50, even if they remain asymptomatic [3].
2. Clinically, symptomatic benign breast disease (mastopathy, fibrocystic mastalgia, palpable nodules) is less frequent, affecting roughly 20-40% of women in various cohorts [3,12].
3. Diabetic mastopathy (DMP), though rare among benign breast lesions overall (<1%), shows markedly higher prevalence in long-standing type I diabetic women: reported ranges are 0.6% to 13% in such populations [6,15]. In unselected diabetic cohorts, even 7–9% prevalence has been reported when imaging and biopsy screening are used [13,15].

2. Hormonal alterations

1. In a large cross-sectional study of general female populations, higher body fat percentage (PBF) was associated with increased odds of fibrocystic breast change (FBC) (OR ≈ 2.45, 95% CI 1.52-3.94) for women in the highest quartile of PBF vs lowest (Chen, 2018). Meanwhile, total lean mass (TLM) was inversely associated: women with higher lean mass had reduced risk (OR ≈ 0.28, 95% CI 0.17-0.46) [3].
2. Late luteal phase estradiol/progesterone (E2/P) ratio has been documented to remain elevated in women who develop more severe or symptomatic fibrocystic changes; in one study, E2/P did not decline as expected in the luteal late days in affected women vs controls (Brkić, 2018).

3. Hormone panel studies in benign breast disease patients (n≈134) found that ≈73.9% showed abnormal levels in at least one hormone: estrogen elevated in ~9.7%, prolactin also in ~8.9%, FSH elevated ~8.9%, lowered testosterone ~20.8% [4].

3. Genetic associations

1. Polymorphisms in FSHR and ESR1 have been repeatedly identified in reviews as risk modifiers: combinations of certain alleles confer odds ratios of ~3-5 for mastopathy vs non-affected women in infertile or endocrine-clinic based populations [10].
2. However, effect sizes are heterogeneous, with many studies showing modest ORs ~1.5-2.5, depending on population ethnicity, phenotype (proliferative vs nonproliferative), and hormone levels [10].

4. Immune, inflammatory, and fibrotic findings

1. Diabetic mastopathy is characterized by dense fibrosis, lobular atrophy, and periductal & perivascular lymphocytic infiltrates. In the review by Salati (2024), among DMP patients, 20-60% had associated autoimmune thyroid disease or other autoimmune comorbidity [15].
2. The clinical presentation is often of long-standing type I diabetes, often with mean duration ≈15-25 years before manifestation of DMP lesions [6,12].
3. Bilaterality or recurrence in DMP is common. In classic cases series (e.g., Camuto et al.), ~63% of lesions are bilateral or recurrent or both over a follow-up period of ~3-4 years [2,6].

5. Structural and tissue remodeling: proliferation/apoptosis imbalance

1. Immunohistochemical markers such as Ki-67 (for proliferation) are elevated in epithelial components in many fibrocystic lesions compared to non-affected tissues. Reviews such as Chen (2018) report roughly 1.5- to 2-fold elevations in Ki-67 index in proliferative mastopathy vs normal tissue.
2. Apoptotic regulators (Bcl-2/Bax ratio) are shifted in favor of survival (i.e. increased Bcl-2, reduced Bax) in many studies of mastopathy [3], hence favouring accumulation of epithelial and stromal cells.
3. Stromal changes include increased collagen density, hyalinization, and extracellular matrix (ECM) alterations. In DMP, fibrosis is often keloid-like, with thick bands of collagen and reduced interstitial adipose tissue [6].

6. Modifying factors: reproductive, anthropometric, and environmental

1. Early menarche (before age 12), nulliparity (no full term pregnancies), and late first pregnancy are repeatedly correlated with higher risk of fibrocystic changes; effect sizes generally RR or OR ~1.3-1.8 in large epidemiologic reviews [3,12].
2. Obesity and high body fat percentage (PBF) are strongly associated: in Chen (2018), highest quartile PBF had OR ≈2.45 (95% CI 1.52-3.94) for FBC vs lowest quartile. Higher lean mass (lean body composition) had a protective effect.
3. Environmental or exogenous hormone exposure (HRT, exogenous estrogens) in postmenopausal women increases symptomatic fibrocystic breast changes; some cohorts observe increases of 30-60% in symptom rates for women on combined hormone therapy vs none [12].

Predictions based on current trends

a. If obesity prevalence continues to rise globally (projected increase from ~15% to ~30% among women in certain regions over next 10-15 years), the prevalence of symptomatic mastopathy may increase by ~10-25%, particularly in pre- and peri-menopausal cohorts.

b. Genetic studies are likely to refine risk stratification: with larger GWAS, polygenic risk scores might be able to predict subsets of women with odds ratios >5 for severe or proliferative mastopathy forms, enabling preventive interventions.
c. The role of immune dysregulation (autoimmunity, chronic low-grade inflammation) is likely to be established as more than just a secondary process — in some individuals, immune activation may precede or potentiate hormonal effects; future longitudinal mechanistic studies may show immune markers (e.g. specific cytokines, HLA class II variants) rising prior to detectable tissue changes.
d. Diagnostic imaging modalities combined with molecular or hormone assays (e.g. serum E2/P ratio, prolactin, FSHR genotype) may allow non-invasive early detection of higher risk mastopathy, potentially reducing invasive biopsies.

Discussion. The findings of the present review reinforce the understanding that **m**astopathy (fibrocystic breast disease, benign breast disease) is far from a monolithic condition; instead, it is a multifactorial syndrome in which endocrine, genetic, immunologic, structural, and environmental factors interact. Several salient points emerge, along with implications and directions for future research.

Hormonal imbalance: central but heterogeneous driver. Our synthesis confirms that dysregulated steroid hormone signaling remains the most consistent etiological signal. Specifically, literature [3] documents that up to 70-90% of women show histologic signs of fibrocystic changes by middle age; however, only about 20-40% manifest clinically significant symptoms[3,12]. This suggests that hormonal imbalance (notably elevated estradiol / progesterone ratio, or prolonged estrogen exposure) is necessary but not sufficient for symptomatic disease.

We observed that elevated progesterone during luteal phases can be protective; in cohorts with normalized progesterone, the odds of fibrocystic changes decrease by ~30-50% relative to women with persistently low luteal progesterone [3,7]. Similarly, prolactin elevations (15-60% above control group means in some studies) are associated with more severe cystic or mastalgic presentations [12]. But effect sizes are variable, reflecting differences in assay techniques, cycle timing, patient selection, and ethnic/genetic background.

Interpretation: These data suggest a model in which individual sensitivity to hormone fluctuations (e.g. via receptor density or local intracrine metabolism) modulates the threshold at which structural and symptomatic changes appear. Hormonal imbalance seems to act in concert with other risk modifiers rather than alone.

Genetic predisposition: moderate risk amplifiers. Genetic association studies (e.g., FSHR, ESR1 polymorphisms) show odds ratios in the range of ~1.5 to ~4.5 depending on genotype combinations, especially in endocrine or infertility-clinic-based populations [10]. These moderate to strong associations suggest that individuals possessing unfavorable allele combinations may have considerably higher risk of developing more proliferative or fibrotic phenotypes, especially when exposed to hormonal imbalances.

However, the literature also reveals substantial heterogeneity: for many women with "high-risk" genotypes but favorable hormone profiles (balanced E2/P, low prolactin, good metabolic health), symptomatic mastopathy does not develop. This supports a gene–environment/hormone interaction model. Furthermore, current genetic studies are limited by relatively small sample sizes, lack of longitudinal follow-up, and often recruitment of convenience or clinic-based samples, which may overestimate effect sizes.

Immune and fibrotic mechanisms: beyond secondary responses. A major insight is the prominence of immune and fibrotic pathways, particularly in subtypes such as diabetic

mastopathy. The reviewed studies [15] document that 20-60% of DMP patients have autoimmune comorbidities, dense fibrosis, periductal lymphocytic infiltrates, and myofibroblast activation. These processes may not merely be reactive but may precede overt fibrotic tissue and cystic lesion formation in some individuals, especially those with long-standing metabolic or hormonal dysregulation.

Additionally, apoptosis/proliferation imbalance demonstrated via upregulation of proliferation markers (Ki-67, etc.) and altered Bcl-2/Bax ratios suggests that epithelial and stromal cell turnover regulation is skewed towards accumulation and reduced programmed cell death. These changes in tissue architecture promote cystic dilatation, ductal ectasia, and fibrotic remodeling.

Modifying factors: reproduction, obesity, environment. The evidence underscores that reproductive history (earlier menarche, nulliparity, later first pregnancy) confers relative risks of ~1.3-1.8 in many cohorts [3,12]. Obesity, especially high percent body fat, is another strong modifier: in some studies, highest quartile body fat had OR ≈2.45 vs lowest quartile [3], with lean mass being protective. Environmental/lifestyle exposures (diet, exogenous hormones) show weaker but still meaningful associations.

A particularly important finding is the temporal trend: in populations undergoing secular changes in reproductive patterns (e.g. delayed childbearing, fewer births), increasing obesity, greater exposure to endocrine disruptors, one can expect elevated incidence of symptomatic mastopathy. This raises public health implications, especially in urbanizing regions and developing countries.

Limitations and heterogeneity. While the evidence base is robust in many respects, several limitations must be acknowledged:

1. **Measurement variability** — Hormone levels, imaging definitions, histologic criteria vary across studies, making cross-study comparisons difficult. For instance, timing of sampling in the menstrual cycle or definition of “proliferative” vs “non-proliferative” changes differ, leading to divergent risk estimates.
2. **Cross-sectional vs longitudinal studies** — Many associations are derived from cross-sectional data, limiting causal inferences. Longitudinal cohort data with repeated hormone/genetic/immunologic measurements are relatively scarce.
3. **Population bias** — Many genetic studies are among women with infertility or in specific clinical settings, who may not represent the general population. Similarly, ethnic and geographic diversity is limited in many datasets.
4. **Symptom reporting bias** — Symptomatic mastopathy is subject to subjective reporting and may be underdiagnosed or underreported; asymptomatic histologic changes are often only detected incidentally or via imaging/autopsy, which may bias prevalence estimates.

Implications and precise predictions. Based on the data analyzed:

1. Prediction 1: Over the next decade, the prevalence of clinically significant mastopathy is likely to increase by 10-25% in populations with rising obesity and delayed childbearing, particularly in peri- and post-menopausal women receiving hormone replacement therapy.
2. Prediction 2: With larger and more diverse genome-wide association studies (GWAS), polygenic risk scores (PRS) for mastopathy severity are expected to emerge. These PRS may be able to stratify women into low, moderate, and high risk with odds ratios for high risk vs low risk exceeding ~5 in some settings.

3. Prediction 3: Early markers of immune activation (for example, specific cytokine profiles, presence of autoantibodies) will be validated as pre-clinical biomarkers. If so, intervention trials targeting anti-fibrotic or immunomodulatory pathways may emerge, perhaps resulting in therapies that reduce fibrotic progression by ~30-50% in high-risk populations.
4. Prediction 4: Non-invasive diagnostics combining imaging (advanced ultrasound, elastography), serum hormonal panels (estradiol/progesterone ratio, prolactin), and genetic markers may reduce the rate of unnecessary biopsies by more than 20–30% while maintaining sensitivity for detecting proliferative or atypical changes.

Integration with recent diagnostics and treatments. The narrative review by Nori et al. (2025) emphasizes that diagnostic improvements (mammography, ultrasound, bioinformatics tools) and lifestyle interventions remain central to management [24]. This complements our etiologic findings: since hormonal and immune/fibrotic factors are modifiable to some extent, therapeutic strategies that target them are rational. For example, the use of metformin in benign breast disease (as small trials suggest) may act via modulation of metabolic/hormonal pathways and fibrosis [12]. Combination therapies (hormonal balancing agents + immunomodulators) deserve rigorous testing.

The current literature strongly supports a multifactorial etiological model of mastopathy in which endocrine imbalance, genetic predisposition, immune/fibrotic activation, and modifying environmental/reproductive factors synergize. While many associations have been robustly demonstrated, the field would benefit from more longitudinal, ethnic-diverse cohort studies, standardization of definitions, and mechanistic investigations into immune-fibrotic pathways. Predictive tools integrating genetics, hormone panels, and imaging are plausible in the near future, and may reshape early diagnosis, risk stratification, and personalized therapeutic approaches.

Conclusion. Mastopathies represent a multifactorial pathological process with complex etiological origins and diverse pathogenetic mechanisms. The synthesis of current evidence highlights that hormonal dysregulation, particularly imbalances in estrogen and progesterone, remains the central factor in disease development [22]. Additional contributors such as prolactin hypersecretion, thyroid dysfunction, and insulin resistance significantly potentiate the risk (Petrakis, 2020). Epidemiological data demonstrate that mastopathies affect approximately 30–70% of women of reproductive age, with incidence peaking between 35 and 50 years [17].

Lifestyle-related risk factors, including obesity, alcohol consumption, and low physical activity, have been consistently linked to increased mastopathy prevalence [23]. Genetic susceptibility, as indicated by family clustering and BRCA gene involvement, further underscores the interplay between hereditary and environmental determinants [19]. Moreover, the growing recognition of oxidative stress, chronic inflammation, and epigenetic modifications expands the understanding of the disease beyond purely hormonal frameworks [18].

Taken together, the findings suggest that mastopathies are not merely benign breast disorders but rather a complex systemic manifestation of endocrine-metabolic imbalance with significant public health implications. Predictive models indicate that if current epidemiological trends persist, the global burden of mastopathies will rise by 20–25% over the next two decades, particularly in developing regions where lifestyle-related risk factors are increasing [20]. Therefore, future strategies must focus on early detection, hormonal and metabolic regulation, and preventive lifestyle interventions.

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