

# Nipple Adenoma: Systematic Review of Literature

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**Background:** Nipple adenomas (NAs) are rare benign proliferative tumors presenting as palpable nodules, erosive lesions, or nipple discharge, mimicking other conditions. This systematic review categorizes cases into sole NA (ONA) or co-diagnoses with other conditions (CONA) to enhance clinical recognition, diagnosis, and treatment efficacy.

**Methods:** Following PRISMA guidelines, a PubMed search was conducted for NA. Inclusion criteria covered original research, excluding reviews or other breast diseases. Bias risk was assessed through a thorough search, authors independently evaluated studies, and data were synthesized using varied measures. Subgroups ONA and CONA were formed. Analyses were conducted in Excel and R, complemented by a qualitative review due to case report predominance. Biases in case reports were transparently addressed.

**Results:** Of the 86 studies, 387 cases were analyzed, showing 10.34% with co-diagnoses of malignant or premalignant conditions. Mean age was 44, with a female predominance (97%). ONA (347 cases) and CONA (40 cases) subgroups exhibited variations in symptoms, physical findings, and imaging. Treatment modalities included excision (51.39%), biopsy alone (11.1%), and mastectomy (8.6%). Mean follow-up of 56.73 months revealed recurrence (2.87%) and malignancy development (1.79%), notably in CONA cases (33.33%).

**Conclusions:** This study provides insights into the broader age range of NA and its associations. Higher co-diagnosis rates were correlated with older age, highlighting the necessity for thorough investigation, with excision as the primary treatment. Follow-up emphasizes the significance of identifying and monitoring CONA cases, which pose a higher malignancy risk. Recurrence is presumed to be linked to proper lesion excision and co-diagnosis. (*Plast Reconstr Surg Glob Open* 2024; 12:e5827; doi: 10.1097/GOX.0000000000005827; Published online 24 May 2024.)

## INTRODUCTION

Nipple adenomas (NAs) are rare and benign proliferative processes originating from the lactiferous ducts of the nipple.<sup>1</sup> Histopathologically, they are defined as the proliferation of tubules lined by epithelial and myoepithelial cells, with or without proliferation of the epithelium around the nipple collecting ducts.<sup>1,2</sup> They are also known by various subtypes such as “erosive adenomas,” “sub-areolar adenomas,” “syringomatous adenomas,” “erosive adenomatosis of the nipple,” or “florid papillomatosis of the nipple.” They were initially described in 1962 and are predominantly observed in middle-aged women.<sup>3,4</sup>

Clinically, NAs often manifest as a palpable nipple nodule, an erosive nipple lesion, and/or discharge from the surface of the nipple.<sup>3</sup> Due to their clinical presentation, NAs can easily be mistaken for mammary Paget disease or even nipple squamous cell carcinoma. A small percentage of NAs may also coexist with precancerous and cancerous lesions of the breast.<sup>5</sup> Accurate diagnosis of breast diseases is crucial for effective treatment planning and prognosis. NAs are likely underrecognized among patients presenting with abnormalities in the nipple/areolar region.<sup>3</sup>

The existing literature on NAs primarily consists of numerous case reports and case series. This article aims to systematically present a comprehensive review of available data, providing insights for healthcare providers assessing patients with breast skin conditions. Given that a co-diagnosis of malignant or premalignant conditions necessitates a different treatment plan and potentially

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has different outcomes,<sup>5</sup> the article also aims to categorize cases between a diagnosis of NA only (ONA) and a co-diagnosis with another condition (CONA). This division aims to better understand the characteristics of each group and identify factors that may pose greater risks to patients. Our objective is to enhance clinical recognition, diagnosis, and treatment of patients with NAs.

## METHODS

During January 2024, a literature search was conducted using the PubMed database with the keywords “nipple adenoma” OR “nipple florid papillomatosis” OR “nipple florid subareolar” OR “nipple florid adenomatosis,” OR “nipple erosive adenomatosis.” Given the limited available literature, no restrictions were imposed on the publication year or language. This review adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. The research, consisting of a systematic review of existing literature, did not need a Helsinki approval.

Inclusion criteria encompassed all publications presenting original research on NA, whereas exclusion criteria excluded review articles or publications on other breast diseases. After the search, two authors independently evaluated all articles based on predefined study criteria. In case of disagreement between authors, the article was discussed among all authors and a joint decision was made. Publications that were excluded were categorized as missing source, retracted article, other breast disease, and review article.

Data extracted included year of publication, study design, country of publication, number of patients, mean age, age range, gender distribution, breast lesion laterality, symptoms and duration, physical examination findings, imaging results, co-existing malignant or premalignant diagnoses, treatment modalities, follow-up, and outcomes.

The data were divided into two subgroups: those with only NA diagnosis (ONA) and those with a pathological concurrent diagnosis with NA (CONA). Data specifically assigned to subgroups was included; otherwise, it was omitted from the subgroups and added only to the general total cases group.

Descriptive statistics were used to outline demographic, clinical, and pathologic features across all selected studies. Continuous variables, including duration and age, were presented as means with SD. Categorical variables, encompassing symptoms, physical and imaging findings, pathology diagnosis, demographics, treatment, recurrence, and malignancy development, were expressed as proportions. Statistical analysis was conducted using Microsoft Excel 2021.

Inferential statistical tests (including chi-square for symptoms, physical findings, and treatments, *t* test for mean age, mean symptom duration and follow-up duration, and exact Fisher for imaging findings and outcomes) were applied. Odds ratios compared findings between subgroups, and logistic regression assessed the relationship between patient age and co-diagnosis. Analyses were

## Takeaways

**Question:** Nipple adenomas, rare benign breast tumors, pose a challenge in management and risk understanding due to their uncommon occurrence. This study aims to establish and disseminate knowledge about this rare entity.

**Findings:** In this systematic review of 387 cases, 10.34% presented with a co-diagnosis, most commonly invasive ductal carcinoma, highlighting the increased risk of adverse outcomes such as recurrence or malignancy development in this subgroup.

**Meaning:** Despite being benign and rare, nipple adenomas demand attention for their potential recurrence and malignancy. The study emphasizes the importance of complete resection for effective management.

conducted using R statistical software version 4.3.2, with a significance level set at a *P* value less than 0.05.

Our analysis primarily comprises case reports and series. To enhance robustness, we conducted a thorough qualitative analysis, acknowledging constraints arising from limited case reports and potential generalizability limitations. To address inherent biases like publication bias, we transparently outlined inclusion criteria and the search strategy. We also acknowledged the potential impact of publication bias on findings interpretation. When assessing certainty in the body of evidence, we contextualized discussions within the limitations of case reports, emphasizing their descriptive and exploratory nature.

## RESULTS

Out of 162 identified studies, 86 publications met inclusion criteria, spanning from 1955 to 2023. Among these, 73% were case reports, 26% were case series, and 1% was a retrospective cohort study (Fig. 1). (See appendix, Supplemental Digital Content 1, which displays the references of the publications in the systematic review. <http://links.lww.com/PRSGO/D248>.) (See appendix, Supplemental Digital Content 2, which displays the collected data. <http://links.lww.com/PRSGO/D249>.)

Among 387 patients, 347 were in the ONA subgroup, and 40 (10.34% of the total) were in the CONA subgroup. Patient characteristics, physical and imaging findings, and pathological co-diagnoses are summarized in Supplemental Digital Content 3 and Table 1. (See appendix, Supplemental Digital Content 3, which displays demographic characteristics, findings, treatments, and follow-up. <http://links.lww.com/PRSGO/D250>.) Logistic regression revealed age as a significant predictor of co-diagnosis (estimate = 0.0398, *P* = 0.014), indicating an increased likelihood of co-diagnosis with age.

### Symptoms

The mean symptom duration upon presentation for all cases (total 387) was 24 months. In the ONA subgroup (total 211), the average duration was 25.84 months,

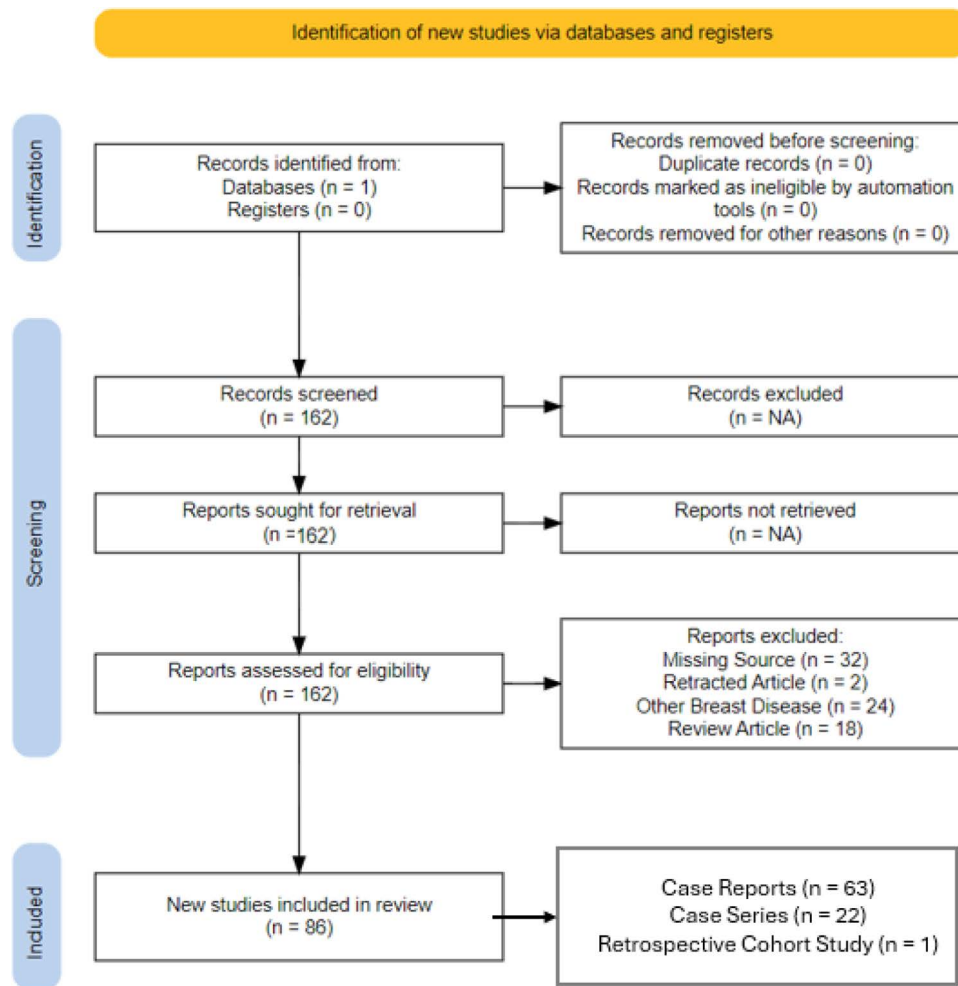


Fig. 1. Flow chart of the review process.

Table 1. Concurrent Diagnoses and Their Prevalence

| Concurrent Diagnoses                       | No. Cases (%) |
|--|---------------|
| Total                                      | 40 (10.34)    |
| Invasive ductal carcinoma (IDC)            | 21 (5.43)     |
| Breast carcinoma (mucinous, adenosquamous) | 6 (1.55)      |
| Ductal carcinoma in situ (DCIS)            | 4 (1.03)      |
| Metaplastic tumors                         | 3 (0.78)      |
| Lobular carcinoma in situ (LCIS)           | 3 (0.78)      |
| Invasive lobular carcinoma (ILC)           | 2 (0.52)      |
| Paget disease                              | 1 (0.26)      |

whereas the CONA subgroup showed a mean duration of 33.36 months (total seven), with no significant difference in mean symptom duration between subgroups ( $t = 0.65$ ,  $P = 0.515$ ).

The most prevalent symptom, encompassing enlargement, nodule, or mass, occurred in 35.4% of all cases. Notably, this symptom was significantly more pronounced in the CONA subgroup, with a prevalence of 80%, compared with the ONA subgroup, where it occurred in 41.76% of cases ( $\chi^2 = 1058.45$ ,  $P < 0.05$ ). Other symptoms were also significantly different between subgroups

(Supplemental Digital Content 3, <http://links.lww.com/PRSGO/D250>).

### Physical Examination

The systematic review highlighted 10 common findings in physical examination. The most prevalent discovery was the presence of papule or nodules, noted in 37.54% (145) of cases. Within the ONA subgroup, the ratio was 26.77%, whereas in the CONA, it reached 30.77% ( $\chi^2 = 744.54$ ,  $P < 0.05$ ). All other physical findings' prevalences were also significantly different between subgroups (Supplemental Digital Content 3, <http://links.lww.com/PRSGO/D250>).

### Imaging

Among all patients, 91 (23.51%) underwent ultrasound examinations. Specifically, 85 individuals had ultrasound examinations in the ONA subgroup (24.5%), and six in the CONA subgroup (15%). Of all cases, 65 (16.8%) underwent mammography, with 61 (17.58%) in the ONA subgroup and four (10%) in the CONA subgroup. Of the 387 patients, 20 (5.17%) underwent magnetic resonance imaging examinations, with 5.19% in the ONA subgroup and 5.0% in the CONA subgroup. Lesions/nodules were

the most common finding in ultrasound, whereas masses were the predominant finding in mammograph and magnetic resonance imaging examinations. All other findings are also described in Supplemental Digital Content 3 (<http://links.lww.com/PRSGO/D250>).

### Treatment

Treatment modalities were documented for 254 cases (65.63%), with 133 patients (34.37%) lacking specific information. Excision was the predominant treatment, accounting for 51.39% (199 cases), significantly more common in the ONA subgroup ( $\chi^2 = 22.804$ ,  $P < 0.001$ , 95% CI 27.75%-66.89%). Biopsy-only showed no significant difference between groups ( $\chi^2 = 0.183$ ,  $P = 0.669$ , CI95% -7.96%-17.70%). Mastectomy was more frequent in the CONA subgroup ( $\chi^2 = 75.167$ ,  $P < 0.001$ , CI95% -80.65% to -40.40%). Additionally, exclusive treatments observed in the ONA subgroup included lumpectomy, Mohs surgery, Cryosurgery, and 5-aminolevulinic acid-induced photodynamic therapy.

### Follow-up and Outcomes

Postoperative follow-up was conducted for 279 patients (72.09%), with mean durations of  $56.73 \pm 28.2$  months (Range 0.5-283 months). Follow-up details were available for 15 cases (37.5%) in the CONA subgroup and 252 cases (72.62%) in the ONA subgroup. The mean follow-up duration was significantly longer in ONA ( $57.71 \pm 36.6$  months) compared with CONA ( $27.58 \pm 10.7$  months) ( $t = -6.10$ ,  $P < 0.05$ ).

Adverse effects were documented in 13 cases (4.66%), with eight cases (2.87%) of recurrence (four after excision and four after biopsy alone,  $P = 0.035$ ) and five cases (1.79%) of malignancy development. Adverse effects were more associated with CONA ( $P < 0.05$ ), with malignancy and mortality due to malignancy observed exclusively in the CONA subgroup ( $P < 0.05$ ).

## DISCUSSION

NAs are rare and benign breast tumors. On average, a breast pathology unit encounters only one case per year,<sup>2,6,7</sup> a yearly incidence rate of 0.0025%,<sup>8</sup> or a diagnosis rate of 0.45% among all benign cases.<sup>9</sup> This rarity might be attributed to the historical challenge in pathologically distinguishing NA from other nipple neoplasms.<sup>6</sup> Advancements in immunohistochemistry have addressed this challenge, but no current estimation of its incidence was found.<sup>10</sup> Reports on NA are scarce, with most being described in case reports,<sup>2</sup> as supported by the results of our systematic review. We present one of the largest studies conducted on this subject, encompassing 387 patients. As mentioned, most patients are female, with the average age presentation ranging from 36 to 47 years-old.<sup>2</sup> In our study, the average age is 44, but the range is broader, including congenital cases and those in older patients. We did not observe a preference in laterality between right and left nipples, contrary to some previous works.<sup>2</sup>

NA and breast carcinoma, when concurrently observed, usually appear as independent lesions in

distinct locations. Although a recognized association exists, the definitive link between NA and subsequent breast cancer development or a direct causal relationship for NA transforming into breast cancer has not been established but cannot be ruled out.<sup>1,2,6</sup> In our study, 10.34% of cases presented with a malignant or premalignant co-diagnosis, a statistically significant occurrence. All cases of malignant disease during follow-up were identified in the co-diagnosis group. The duration of symptoms at presentation did not differ between the ONA and CONA groups. However, there was a variation in the average age of patients, with the likelihood of co-diagnosis increasing with age, potentially explaining the higher rate of malignancy. Interestingly, we didn't observe a significant difference in rate of co-diagnosis between genders.

Previous studies reported diverse clinical presentations, including skin growth, rash, nipple discharge, erosive lesion, or other symptoms.<sup>2,6</sup> Our findings highlight a nodule or mass as the predominant clinical symptom, occurring more frequently in the co-diagnosis group. Symptoms like erythema, pain, and nipple deformity were more prevalent in the CONA, whereas ulceration and discharge were more common in the ONA group. Symptomatic duration varied widely, ranging from months to years.<sup>1</sup> The mean duration upon presentation was 24 months, with no significant difference between subgroups.

Nodules emerged as the most prevalent physical findings, aligning with the overall clinical symptoms profile. In cases of ONA, the presentation commonly featured erosion or ulceration, along with crust or scale. Conversely, findings more closely associated with CONA included papule or nodule, swelling, any form of discharge, retraction or inversion, and enlargement of axillary lymph nodes. These distinctive CONA-related findings can act as red flags, signaling the importance of a thorough investigation for concurrent conditions and obtaining clear margins in an aesthetically reasonable result.

While imaging has a limited role in diagnosis, if used, common modalities include ultrasound and mammography, aligning with our study findings. Among all modalities and findings, only masses and calcifications on mammography exams demonstrated a significant association with CONA. However, the restricted number of exams conducted in the CONA subgroup limits our ability to draw insights regarding a potential profile for imaging characteristics.

Excision remains the predominant treatment,<sup>1,2,6</sup> with more than half of the patients undergoing local excision. Notably, local excision demonstrated a local recurrence rate of 2.01%. Biopsy as an exclusive treatment, the second most common modality, carries a risk of 11.63% for recurrence or future malignant transformation and should be avoided as a sole treatment.<sup>1</sup>

NAs seldom require mastectomy, and it should only be considered when the adenoma poses a local issue necessitating extensive excision. Cases where nipple adenoma coincides with other breast pathologies are managed

according to the appropriate protocols for each condition. It is imperative to diagnose nipple adenoma through biopsy and then pursue treatment through complete excision, aiming for minimal tissue removal to maintain cosmetic outcomes and reduce morbidity. Techniques such as Mohs technique or the use of frozen sections can be used in this regard.

Limited case reports have documented alternative treatment modalities for NA. One case reported the use of 5-aminolevulinic acid, with no reported adverse effects during follow-up.<sup>7</sup> Additionally, two separate case reports explored cryosurgery, both demonstrating no adverse effects.<sup>11,12</sup> Despite the aesthetic advantages of these approaches, minimizing damage to surrounding healthy tissue, they do not guarantee clean, uninvolved margins. Moreover, the risk of recurrence is not refuted from such a small cohort.

On the other hand, Mohs surgery is particularly useful, as NA arises in a functionally and aesthetically sensitive location. Mohs ensures complete lesion removal while minimizing functional and aesthetic harm,<sup>1</sup> with no reported adverse effects, making it suitable therapy, especially when breast feeding continuation is desired.

Follow-up data were available for most patients in the ONA group, and a minority in CONA. Instances of malignancy development and death due to malignancy were exclusively observed in the CONA patients. This notable finding emphasizes the importance of identifying and closely monitoring this subgroup, as NA poses a risk for serious consequences. Recurrence rates were related to proper surgical excision, as well as the presence of other diagnoses, marking both properties as related to recurrence.

Although our systematic review based on case reports offers valuable insights into individual patient experiences, its retrospective and anecdotal nature introduces limitations. Relying on case reports may lead to selection bias, potentially skewing understanding towards atypical cases. The retrospective design lacks controls and standardized methodologies found in prospective studies, limiting the ability to establish causal relationships or draw definitive conclusions about NA incidence, prevalence, and outcomes. Heterogeneity among case reports in demographics and clinical characteristics may impact generalizability. Despite these constraints, our review highlights repeated findings between cases and serves as a starting point for further research.

Although NA is a benign condition, it necessitates treatment due to its potential to cause damage to the nipple and its associated risk of malignancy. Given the unneglectable rate of concurrent premalignant and malignant diagnoses, we advocate for a comprehensive evaluation for each case. In instances where the diagnosis is solely nipple adenoma, Mohs surgery is deemed advantageous. While a systematic review of case reports may not be sufficient for developing a comprehensive diagnosis and treatment algorithm, we have devised a preliminary algorithm using the available data, as shown in Figure 2.

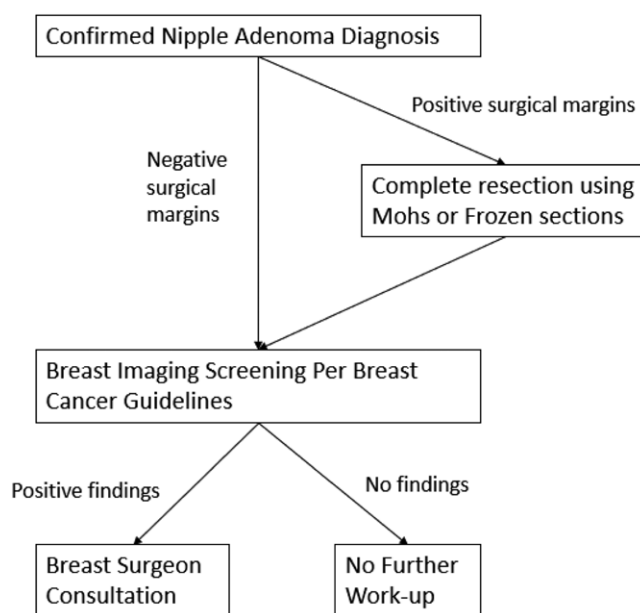


Fig. 2. A diagnosis and treatment algorithm.

## CONCLUSIONS

Our review of 387 cases sheds light on NA. Although typically seen in middle-aged women, our study reveals a broader age range, encompassing congenital cases and cases in older patients. Symptom duration did not influence whether a patient was presented with a sole diagnosis or concurrent diagnoses. Comprehensive follow-up data, more prevalent in ONA cases, reveal higher recurrence rates and exclusive malignancy development in CONA, underscoring the significance of timely identification of the CONA subgroup. Age is a risk factor for developing CONA, characterized by distinctive features such as swelling, discharge, and enlarged axillary lymph nodes or masses on imaging. Avoiding improper surgical excision is crucial to reduce recurrence risk, advocating for Mohs surgery to minimize functional and aesthetic damage to the nipple while ensuring clear surgical margins. Our study highlights the importance of a thorough investigation for concurrent conditions and obtaining clear margins, particularly in older individuals, emphasizing the need for ongoing research in this domain.

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## DISCLOSURE

*The authors have no financial interest to declare in relation to the content of this article.*

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