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Evaluating final pathology results in patients operated for intraductal papilloma

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Abstract

Introduction: Intraductal papilloma is a breast lesion caused by abnormal epithelial proliferation of ducts.
Objectives: The aim of this study was to evaluate the final pathology reports of intraductal papilloma.
Patients and Methods: This cross-sectional study was conducted in Isfahan, containing 101 cases initially diagnosed with intraductal papilloma. We reviewed the medical documents and pathology reports of all cases with the following information of age, consumption of oral contraceptive pills, hormone replacement therapy, age of menarche, age of menopause and familial history of breast, ovarian, or endometrial cancers, and the pathology reports from tissue biopsy. The statistical analysis utilized chi-square test for qualitative variables and analysis of variance for quantitative variables.
Results: The frequency distribution of pathology results showed that in 37.4% (n = 35) of cases, intra-ductal papilloma were observed, and in 30.7% (n = 31) of them, benign lesions were reported. Additionally, 29.7% (n = 30) had pre-malignant lesions, and 5% (n = 5) had malignant lesions. Among the factors, only age was related to the type of lesion, with the mean age of people with pre-malignant or malignant lesions being significantly higher than those with benign lesions (P = 0.014).
Conclusion: Complete excision and pathological evaluation of intraductal papilloma could reveal significant findings. Special attention should be given to older patients with intraductal papilloma.

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Introduction

Intraductal papilloma is a breast lesion caused by abnormal epithelial proliferation of ducts (1). Epidemiologic data suggest that intraductal papilloma can be detected at any age, with the most common age range being 30-77 years. It has been reported that this type of tumor is observed in less than 10% of benign breast lesions and less than 1% of malignant breast tumors (2). The most common risk factors for this tumor include the consumption of oral contraceptive pills, hormone replacement therapy, lifetime estrogen exposure, and a positive family history (3).

These lesions can develop in the central ducts, where they are usually single and large, with the tumor located behind the nipple (4). They can also occur in peripheral ducts, where they are usually smaller but numerous, and in such cases, the tumor can be located in any quadrant of the breast (3). Multiple papillomas are more associated with cancer, although this increased risk is attributed to the association with atypical epithelial hyperplasia (5). This lesion diagnosed on core needle biopsy have upgrade rates of 7.14% to carcinoma and 3.57% to high-risk breast lesions (6).

This lesion attaches to the duct wall with a stem. Histologically, it features a fibro-vascular nucleus covered with myoepithelial and epithelial layers (7). The covering epithelium comprises two types of cells, cuboidal and columnar. Pathological changes that may accompany intraductal papilloma include sclerosis, epithelial or myoepithelial hyperplasia, atypical proliferation, squamous or apocrine metaplasia (8). Additionally, it can be associated with occult carcinoma, atypical epithelial hyperplasia, and ductal carcinoma in situ (DCIS) (5).

Multiple intraductal papillomas usually originate in the terminal duct lobular unit and present as a palpable mass with less nipple discharge. The diagnosis of this lesion is made through imaging and sampling, and for a definitive diagnosis, radiological and pathological findings must be coordinated (9). In some cases, this lesion may remain

Key point

This study was conducted from March 2016 to March 2020 in Isfahan on 101 cases with initial diagnosis of intraductal papilloma. We reviewed medical documents and pathology reports of all cases and collected the following information from the records; age of patients, consumption of oral contraceptive pills, hormone replacement therapies, age of menarche, age of menopause, familial history of breast or ovarian or endometrial cancer and the pathology reports from tissue biopsy. At this study, we showed that in 37.4% (n = 35) of cases, intra-ductal papilloma was observed; since, in 30.7% (n = 31) of them, benign lesions were reported. About 29.7% (n = 30) had pre-malignant lesions and 5% (n = 5) had malignant lesions. Among the factors, only age was related to the type of lesion, while the mean age of people with pre-malignant or malignant lesions was significantly higher than those with benign lesions ($P = 0.014$). Complete excision and pathological evaluation of intraductal papilloma could reveal significant findings. Special attentions should be given to older patients with intraductal papilloma.

mammographically obscured, but it could be associated with microcalcification. If the mammogram reveals a round or oval mass with a definite or indistinct margin, it raises suspicion for this lesion (10).

Several methods for tissue sampling exist, including core needle biopsy, vacuum-assist biopsy, and open tissue biopsy. The first two are preferred over fine needle aspiration as they provide more tissue for examinations (11). Open tissue biopsy is not preferred due to its surgical nature, increased invasiveness, and potential to cause chronic pain, which may contribute to heightened levels of depression and anxiety in patients (12, 13).

Objectives

It is important to note that intraductal papilloma is a benign breast tumor, however there appears to be a link between this type of tumor and malignant and pre-malignant lesions. Furthermore, this lesion itself could increase the chance of malignancy by 0.5 to 4 times (14). Considering that breast cancer is not only the most common cancer among women but also the second leading cause of cancer death in females, and given that a statistical study of the association of this lesion with malignant and pre-malignant breast lesions in Iran has not been conducted so far, it is necessary to investigate this connection and evaluate the degree of association between malignant and pre-malignant lesions with intraductal papilloma.

Patients and Methods

Study design

This cross-sectional study was conducted from March 2016 to March 2020. The study included 101 patients initially diagnosed with intraductal papilloma which referred to the breast cancer centers of Isfahan for surgical operation. The inclusion criteria comprised women with intraductal papilloma, confirmed by pathology reports from pre-operative biopsies, who underwent surgical operations at the referral breast cancer centers of Isfahan. Participants needed to have complete medical documents and provide written informed consent to participate in the study. The exclusion criteria involved a diagnosis of cancer in the pre-operative biopsy and more than 20% missing data.

The sampling method employed in this study was a census, where in all eligible cases meeting the criteria were included. We systematically reviewed the medical documents and pathology reports of all cases, extracting the following information from the records; age of patients, consumption of oral contraceptive pills, hormone replacement therapy, age of menarche, age of menopause, familial history of breast, ovarian, or endometrial cancer, and the pathology reports from tissue biopsy.

It is important to note that the pathology samples underwent a thorough review by two expert pathologists to ensure accurate diagnosis.

Statistical analysis

The collected data were entered into the Statistical Package for Social Sciences (SPSS) (version 24, SPSS Inc., Chicago, IL). Quantitative data were presented as mean ± standard deviation, while qualitative data were reported as frequency distribution (percentage). The analysis of the data involved the use of independent T-test and chi-square test. A significance threshold of P value < 0.05 was considered for statistical significance.

Results

In the current study, data from 101 patients were analyzed. The mean age of the population was 45.15 ± 11.7 years, with a mean age of menarche at 11.26 ± 2.2 years. The mean age of the first pregnancy was 23.99 ± 4.6 years, and the mean age of menopause was 51.55 ± 3.2 years.

Further analysis of demographic data revealed that out of all 101 patients, 59 (58.9%) had a lesion in the right breast, 7 patients (6.9%) had histories of oral contraceptive pill use and 11 patients (10.9%) had a positive family history of breast cancer, while none of them had a positive family history for ovarian or endometrial cancer. None of the patients were using hormone replacement therapy.

The frequency distribution of pathology results indicated that in 34.6% (n = 35) of cases, intra-ductal papilloma was observed, since in 30.7% (n = 31) of them, benign lesions were reported. Furthermore, 29.7% (n = 30) had pre-malignant lesions, and 5% (n = 5) had malignant lesions.

The frequency distribution of pathology results by the type of pathology is depicted in Figure 1. The comparison of pathology results based on the characteristics of the subjects is depicted in Table 1. Among the factors assessed, only age demonstrated a correlation with the type of lesion. Specifically, the mean age of individuals with pre-malignant or malignant lesions was significantly higher than that of individuals with benign lesions ($P = 0.014$).

Discussion

In the present study, we assessed the pathological results of intraductal papilloma and their correlation with patients'

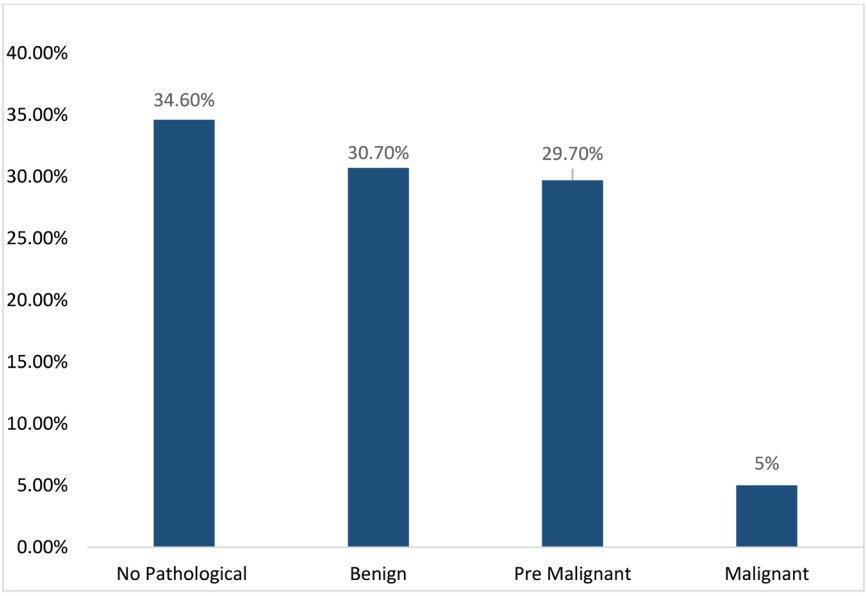

Figure 1. Frequency distribution of pathology results. Benign (Fibrocystic change, ductal hyperplasia without atypia, sclerosing adenosis, florid ductal hyperplasia, intraductal papilloma). Premalignant (Ductal carcinoma insitu, ductal hyperplasia with atypia). Malignant (Invasive ductal carcinoma).

characteristics. Our results revealed that nearly one-third of the reports showed intra-ductal papilloma, another one-third had benign lesions, and the remaining cases presented with pre-malignant lesions. Malignant lesions were observed in only 5% of cases. Importantly, we found no significant differences between the demographic and clinical data of patients and pathology reports, except for a higher age observed in patients with pre-malignant and malignant lesions compared to others.

In previous studies, such as the study conducted by Nakhlis et al on 119 intraductal papilloma samples, 21.3% of cases exhibited atypia in the excision specimen, and the malignancy rate was 2.7%. The study indicated no statistically significant differences in family history of breast cancer, indication for core needle biopsy, mammographic findings, or location of papilloma when comparing patients with benign or atypical findings (15). Another study by Limberg and others, which evaluated 175 intraductal papilloma samples, found that 4% of samples had malignant lesions, and this was more prevalent in older patients (16).

These findings align with the results of the current study, where only 5% of cases had malignant lesions, but pre-malignant lesions were observed in 29.7% of patients. Additionally, our study reported higher rates of pre-malignant and malignant lesions in older patients, consistent with the trends observed in the aforementioned studies. The results underscore the significance of pathological studies in patients with this lesion particularly emphasizing the need for heightened attention to older patients. Consistent with previous studies (2,17,18), it is evident that this lesion of the breast warrants comprehensive investigation due to the notable occurrence of malignant or pre-malignant lesions.

Previous research has identified certain risk factors associated with malignant lesions in intraductal papilloma, including age over 35 years, non-menstrual breast pain, breast duct ectasia, lesion distance from the nipple >2 cm,

Table 1. Evaluation of demographic information in patients undergoing intraductal papilloma surgery

Variable		Intraductal papilloma		Benign lesions		Pre-malignant or malignant lesions		*P* value
Location of lesion	Right	20	33.9	17	28.8	22	37.3	0.919
	Left	15	35.7	13	31	14	33.3	
Oral contraceptive pill use	Yes	4	57.1	2	28.6	1	14.3	0.356
	No	31	33	28	29.8	35	37.2	
Family history	Positive	5	45.5	3	27.3	3	17.2	0.711
	Negative	30	33.3	27	30	33	36.7	
Age		45.20	10.7	40.56	10.9	48.94	12.5	0.014
Menarche age		11.22	2.3	11.7	2.4	10.91	1.9	0.378
First pregnancy age		24.04	4.6	24.57	4.5	23.52	4.7	0.731
Menopause age		53.50	2.8	50.75	4.1	50.70	2.8	0.218

and lesion size >10 mm as observed using ultrasonography (19). These findings align with our results to some extent. However, we did not identify significant differences between patients with benign or malignant lesions regarding other patients' characteristics. Further research and attention to specific risk factors can contribute to a more comprehensive understanding of the implications of this lesion in different patient populations. Indeed, variations in study populations and patient characteristics can contribute to differences in study outcomes. The study conducted by Sack and colleagues in the United States, who assessed 416 biopsies of intraductal papilloma, reported a higher rate of malignancy at 11.3% [including DCIS and invasive cancer] compared to our study. Their findings indicated that the risks of developing cancerous lesions were elevated in patients with concurrent ipsilateral breast cancer, larger imaging size, less than 50% excised with biopsy, and atypia involving intraductal papilloma. However, age, clinical presentation, and concurrent contralateral cancer were not significantly associated with an upgrade to malignancy (20).

These differing results emphasize the complexity of intraductal papilloma and the need for further research to better understand the factors influencing its pathology and potential progression to malignancy. It also underscores the importance of considering regional and population-specific variations when interpreting study findings.

The study has its limitations, including a restricted study population and the absence of an evaluation of imaging examinations for the patients. Despite these limitations, the results of our study have revealed significant findings. It is recommended that future research continues to focus on the pathology properties of this lesion, considering a broader and more diverse study population and incorporating the evaluation of imaging examinations for a more comprehensive understanding of this condition.

Conclusion

Indeed, the recommendation for complete excision and thorough pathological evaluation of intraductal papilloma aligns with the importance of understanding the potential risks associated with this condition. Your suggestion to prioritize pathological studies of these lesions in older patients due to a higher prevalence of pre-malignant or malignant lesions is valuable. It underscores the need for tailored approaches to diagnosis, monitoring, and potential intervention, especially in populations where certain risk factors may be more pronounced. Further research and clinical attention in this direction can contribute to improved management and outcomes for individuals with this lesion.

Limitations of the study

The sample size was small, as the research was conducted at a single center with a limited number of patients. It is recommended that future studies in this field utilize a larger sample size. It is also suggested that future studies validate these results through the use of the IHC method.

Authors' contribution

Conceptualization: Reza Eshraghi Samani.
Data curation: Kian Dolatshahi.
Formal analysis: Kian Dolatshahi.
Investigation: Masumeh Safaee.
Methodology: Kian Dolatshahi.
Project administration: Reza Eshraghi Samani.
Resources: Kian Dolatshahi.
Software: Masumeh Safaee.
Supervision: Kamran Dolatshahi.
Validation: Reza Eshraghi Samani.
Visualization: Kian Dolatshahi.
Writing–review & editing: Masumeh Safaee.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Isfahan University of Medical Sciences (Ethical code #IR.MUI.MED.REC.1399.674). Prior to any intervention, all participants provided written informed consent. The study was extracted from the thesis of Reza Eshraghi Samani (Thesis #199378) in the department of surgery at this university. The authors have fully complied with ethical issues, such as plagiarism, data fabrication, and double publication.

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